

# Disease Prevention & Health Promotion

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## GENERAL APPROACH TO THE PATIENT

The medical interview serves several functions. It is used to collect information to assist in diagnosis (the “history” of the present illness), to understand patient values, to assess and communicate prognosis, to establish a therapeutic relationship, and to reach agreement with the patient about further diagnostic procedures and therapeutic options. It also serves as an opportunity to influence patient behavior, such as in motivational discussions about smoking cessation or medication adherence. Interviewing techniques that avoid domination by the clinician increase patient involvement in care and patient satisfaction. Effective clinician-patient communication and increased patient involvement can improve health outcomes.

### Patient Adherence

For many illnesses, successful prevention and treatment depends on difficult fundamental behavioral changes, including altering diet, taking up exercise, giving up smoking, cutting down drinking, wearing masks to prevent infection, and adhering to medication regimens that are often complex. Adherence is a problem in every practice; up to 50% of patients fail to achieve full adherence, and one-third never take their medicines. Many patients with medical problems, even those with access to care, do not seek appropriate care or may drop out of care prematurely. Adherence rates for short-term, self-administered therapies are higher than for long-term therapies and are inversely correlated with the number of interventions, their complexity and cost, and the patient’s perception of overmedication.

As an example, in HIV-infected patients, adherence to antiretroviral therapy is a crucial determinant of treatment success. Studies have unequivocally demonstrated a close relationship between patient adherence and plasma HIV RNA levels, CD4 cell counts, and mortality. Adherence levels of more than 95% are needed to maintain virologic suppression. However, studies show that 40% of patients

are less than 90% adherent and that adherence tends to decrease over time.

Patient reasons for suboptimal adherence include simple forgetfulness, being away from home, being busy, and changing daily routine. Other reasons include psychiatric disorders (depression or substance misuse), uncertainty about the effectiveness of treatment, lack of knowledge about the consequences of poor adherence, regimen complexity, and treatment side effects. The rising costs of medications, including generic drugs, and the increase in patient cost-sharing burden, have made adherence even more difficult, particularly for those with lower incomes.

Patients seem better able to take prescribed medications than to adhere to recommendations to change their diet, exercise habits, or alcohol intake or to perform various self-care activities (such as monitoring blood glucose levels at home). For short-term regimens, adherence to medications can be improved by giving clear instructions. Writing out advice to patients, including changes in medication, may be helpful. Because low functional health literacy is common (almost half of English-speaking US patients are unable to read and understand standard health education materials), other forms of communication—such as illustrated simple text, videotapes, or oral instructions—may be more effective. For non-English-speaking patients, clinicians and health care delivery systems can work to provide culturally and linguistically appropriate health services.

To help improve adherence to long-term regimens, clinicians can work with patients to reach agreement on the goals for therapy, provide information about the regimen, ensure understanding by using the “teach-back” method, counsel about the importance of adherence and how to organize medication-taking, reinforce self-monitoring, provide more convenient care, prescribe a simple dosage regimen for all medications (preferably one or two doses daily), suggest ways to help in remembering to take doses (time of day, mealtime, alarms) and to keep appointments, and provide ways to simplify dosing (medication boxes). Single-unit doses supplied in foil wrappers can increase adherence but should be avoided for patients who have difficulty opening them. Medication boxes with compartments (eg, Medisets) that are filled weekly are useful. Microelectronic devices can provide feedback to show

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patients whether they have taken doses as scheduled or to notify patients within a day if doses are skipped. Reminders, including cell phone text messages, are another effective means of encouraging adherence. The clinician can also enlist social support from family and friends, recruit an adherence monitor, provide a more convenient care environment, and provide rewards and recognition for the patient's efforts to follow the regimen. Collaborative programs in which pharmacists help ensure adherence are also effective. Motivational interviewing techniques can be helpful when patients are ambivalent about their therapy.

Adherence is also improved when a trusting doctor-patient relationship has been established and when patients actively participate in their care. Clinicians can improve patient adherence by inquiring specifically about the behaviors in question. When asked, many patients admit to incomplete adherence with medication regimens, with advice about giving up cigarettes, or with engaging only in "safer sex" practices. Although difficult, sufficient time must be made available for communication of health messages.

Medication adherence can be assessed generally with a single question: "In the past month, how often did you take your medications as the doctor prescribed?" Other ways of assessing medication adherence include pill counts and refill records; monitoring serum, urine, or saliva levels of drugs or metabolites; watching for appointment nonattendance and treatment nonresponse; and assessing predictable drug effects, such as weight changes with diuretics or bradycardia from beta-blockers. In some conditions, even partial adherence, as with drug treatment of hypertension and diabetes mellitus, improves outcomes compared with nonadherence; in other cases, such as HIV antiretroviral therapy or tuberculosis treatment, partial adherence may be worse than complete nonadherence.

## ► Guiding Principles of Care

Ethical decisions are often called for in medical practice, at both the "micro" level of the individual patient-clinician relationship and at the "macro" level of the allocation of resources. Ethical principles that guide the successful approach to diagnosis and treatment are honesty, beneficence, justice, avoidance of conflict of interest, and the pledge to do no harm. Increasingly, Western medicine involves patients in important decisions about medical care, eg, which colorectal screening test to obtain or which modality of therapy for breast cancer or how far to proceed with treatment of patients who have terminal illnesses (see Chapter 5).

The clinician's role does not end with diagnosis and treatment. The importance of the empathetic clinician in helping patients and their families bear the burden of serious illness and death cannot be overemphasized. "To cure sometimes, to relieve often, and to comfort always" is a French saying as apt today as it was five centuries ago—as is Francis Peabody's admonition: "The secret of the care of the patient is in caring for the patient." Training to improve mindfulness and enhance patient-centered communication increases patient satisfaction and may also improve clinician satisfaction.

- Cutler RL et al. Economic impact of medication non-adherence by disease groups: a systematic review. *BMJ Open*. 2018; 8:e016982. [PMID: 29358417]
- Daliri S et al. Medication-related interventions delivered both in hospital and following discharge: a systematic review and meta-analysis. *BMJ Qual Saf*. 2021;30:146. [PMID: 32434936]
- Kini V et al. Interventions to improve medication adherence: a review. *JAMA*. 2018;320:2461. [PMID: 30561486]
- Spaen P et al. Psychosocial interventions enhance HIV medication adherence: a systematic review and meta-analysis. *J Health Psychol*. 2020;25:1326. [PMID: 29417851]

## HEALTH MAINTENANCE & DISEASE PREVENTION

Preventive medicine can be categorized as primary, secondary, or tertiary. Primary prevention aims to remove or reduce disease risk factors (eg, immunization, giving up or not starting smoking). Secondary prevention techniques promote early detection of disease or precursor states (eg, routine cervical Papanicolaou screening to detect carcinoma or dysplasia of the cervix). Tertiary prevention measures are aimed at limiting the impact of established disease (eg, partial mastectomy and radiation therapy to remove and control localized breast cancer).

Tables 1–1 and 1–2 give leading causes of death in the United States and estimates of deaths from preventable causes. Recent data suggest increased mortality rates, driven by increases in suicide and substance misuse and its sequelae. Unintentional injuries, including deaths from opioid-related overdoses, have become the third leading cause of death in the United States. Non-Hispanic Whites with a high school education or less have suffered disproportionately.

Many effective preventive services are underutilized, and few adults receive all of the most strongly recommended services. Several methods, including the use of

**Table 1–1.** Leading causes of death in the United States, 2018.

| Category  | Estimate  |
|---|-----------|
| All causes                                      | 2,839,205 |
| 1. Diseases of the heart                        | 655,381   |
| 2. Malignant neoplasms                          | 599,274   |
| 3. Unintentional injuries                       | 167,127   |
| 4. Chronic lower respiratory diseases           | 159,486   |
| 5. Cerebrovascular diseases                     | 147,810   |
| 6. Alzheimer disease                            | 122,019   |
| 7. Diabetes mellitus                            | 84,946    |
| 8. Influenza and pneumonia                      | 59,120    |
| 9. Nephritis, nephrotic syndrome, and nephrosis | 51,386    |
| 10. Intentional self-harm (suicide)             | 48,344    |

Data from National Center for Health Statistics 2020.

**Table 1–2.** Leading preventable causes of death in the United States, 2017.

| Category                     | Estimate |
|------------------------------|----------|
| Dietary risks                | 503,390  |
| High systolic blood pressure | 454,346  |
| Tobacco                      | 437,706  |
| High fasting plasma glucose  | 420,192  |
| High BMI                     | 408,831  |
| High LDL cholesterol         | 221,557  |
| Impaired kidney function     | 173,378  |
| Air pollution                | 107,506  |
| Alcohol use                  | 104,536  |
| Drug use                     | 104,440  |
| Low physical activity        | 70,844   |
| Occupational risks           | 63,580   |

BMI, body mass index; LDL, low-density lipoprotein.  
Data from the US Burden of Disease Collaborators, 2019.

provider or patient reminder systems (including interactive patient health records), reorganization of care environments, and possibly provision of financial incentives to clinicians (though this remains controversial), can increase utilization of preventive services, but such methods have not been widely adopted.

Borsky A et al. Few Americans receive all high-priority, appropriate clinical preventive services. *Health Aff.* (Millwood). 2018;37:925. [PMID: 29863918]

Levine DM et al. Quality and experience of outpatient care in the United States for adults with or without primary care. *JAMA Intern Med.* 2019;179:363. [PMID: 30688977]

US Burden of Disease Collaborators. The state of US health, 1990–2016: burden of diseases, injuries, and risk factors among US states. *JAMA.* 2018;319:1444. [PMID: 29634829]

Woolf SH et al. Life expectancy and mortality rates in the United States, 1959–2017. *JAMA.* 2019;322:1996. [PMID: 31769830]

Xu JQ et al. Mortality in the United States, 2018. NCHS Data Brief, no 355. Hyattsville, MD: National Center for Health Statistics. 2020.

## PREVENTION OF INFECTIOUS DISEASES

Much of the decline in the incidence and fatality rates of infectious diseases is attributable to public health measures—especially immunization, improved sanitation, and better nutrition.

**Immunization** remains the best means of preventing many infectious diseases. Recommended immunization schedules for children and adolescents can be found online at <http://www.cdc.gov/vaccines/schedules/hcp-child-adolescent.html>, and the schedule for adults is at <http://www.cdc.gov/vaccines/schedules/hcp/adult.html> (see also Chapter 30). Substantial morbidity and mortality from vaccine-preventable diseases, such as hepatitis A, hepatitis B, influenza, and pneumococcal infections, continue to occur among adults. Increases in the number of

vaccine-preventable diseases in the United States (eg, regional epidemics) highlight the need to understand the association of vaccine refusal and disease epidemiology.

Evidence suggests annual **influenza vaccination** is safe and effective with potential benefit in all age groups, and the Advisory Committee on Immunization Practices (ACIP) recommends routine influenza vaccination for all persons aged 6 months and older, including all adults. An alternative high-dose inactivated vaccine is available for adults 65 years and older.

Routine use of **23-valent pneumococcal polysaccharide vaccine (PPSV23)** is recommended for adults aged 65 and older. If PPSV23 was administered prior to age 65 years, administer one dose PPSV23 at least 5 years after previous dose. A shared clinical decision-making approach is recommended for use of 13-valent pneumococcal conjugate vaccine (PCV13) in average-risk individuals aged 65 and older.

The ACIP recommends routine use of a single dose of **tetanus, diphtheria, and five-component acellular pertussis vaccine (Tdap)** for adults aged 19–64 years to replace the next booster dose of **tetanus and diphtheria toxoids vaccine (Td)**.

Hepatitis B vaccine administered as a three-dose series is recommended for all children aged 0–18 years and high-risk individuals (ie, health care workers, injection drug users, people with end-stage renal disease). The ACIP recommends **vaccination for hepatitis B** in diabetic patients aged 19–59 years. The hepatitis B vaccine should also be considered in diabetic persons age 60 and older.

**Human papillomavirus (HPV) virus-like particle (VLP) vaccines** have demonstrated effectiveness in preventing persistent HPV infections and thus may impact the rate of cervical intraepithelial neoplasia (CIN) II–III. The ACIP recommends routine HPV vaccination for children and adults aged 9–26 years. Shared decision-making is recommended for some individuals between 27 and 45 years of age (vaccine is not licensed for adults older than 45 years).

Persons traveling to countries where infections are endemic should take the precautions described in Chapter 30 and at <https://wwwnc.cdc.gov/travel/destinations/list>. Immunization registries—confidential, population-based, computerized information systems that collect vaccination data about all residents of a geographic area—can be used to increase and sustain high vaccination coverage.

Globally, **coronavirus disease 2019 (COVID-19)** has resulted in over 1.2 million deaths in 2020. COVID-19 is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The impact on frontline workers, including health care workers, has been substantial, and the pandemic has revealed profound inequities in health and health care. In the United States, the COVID-19 mortality rates are higher in Blacks, Latinx, and Native Americans compared to Whites. Several vaccines for SARS-CoV-2 are now available and mass vaccination programs began in early 2021.

The US Preventive Services Task Force (USPSTF) recommends behavioral counseling for adolescents and adults who are sexually active and at increased risk for **sexually**

**transmitted infections.** Sexually active women aged 24 years or younger and older women who are at increased risk for infection should be screened for chlamydia and gonorrhea. Screening HIV-positive men or men who have sex with men for syphilis every 3 months is associated with improved syphilis detection.

**HIV infection** remains a major infectious disease problem in the world. The CDC recommends universal HIV screening of all patients aged 13–64, and the USPSTF recommends that clinicians screen adolescents and adults aged 15–65 years. Clinicians should integrate biomedical and behavioral approaches for HIV prevention. In addition to reducing sexual transmission of HIV, initiation of antiretroviral therapy reduces the risk for AIDS-defining events and death among patients with less immunologically advanced disease.

Daily **preexposure prophylaxis (PrEP)** with the fixed-dose combination of tenofovir disoproxil 300 mg and emtricitabine 200 mg (Truvada) should be considered for people who are HIV-negative but at substantial risk for HIV infection. Studies of men who have sex with men suggest that PrEP is very effective in reducing the risk of contracting HIV. Patients taking PrEP should be encouraged to use other prevention strategies, such as consistent condom use and choosing less risky sexual behaviors (eg, oral sex), to maximally reduce their risk. **Postexposure prophylaxis (PEP)** with combinations of antiretroviral drugs is widely used after occupational and nonoccupational contact, and may reduce the risk of transmission by approximately 80%. PEP should be initiated within 72 hours of exposure.

In immunocompromised patients, live vaccines are contraindicated, but many killed or component vaccines are safe and recommended. *Asymptomatic* HIV-infected patients have not shown adverse consequences when given live MMR and influenza vaccinations as well as tetanus, hepatitis B, *Haemophilus influenzae* type b, and pneumococcal vaccinations—all should be given. However, if poliomyelitis immunization is required, the inactivated poliomyelitis vaccine is indicated. In *symptomatic* HIV-infected patients, live-virus vaccines, such as MMR, should generally be avoided, but annual influenza vaccination is safe.

**Herpes zoster**, caused by reactivation from previous varicella zoster virus infection, affects many older adults and people with immune system dysfunction. It can cause postherpetic neuralgia, a potentially debilitating chronic pain syndrome. The ACIP recommends the herpes zoster subunit vaccine (HZ/su; Shingrix) be used for the prevention of herpes zoster and related complications in immunocompetent adults age 50 and older and in individuals who previously received Zostavax.

Chou R et al. Epidemiology of and risk factors for coronavirus infection in health care workers: a living rapid review. Ann Intern Med. 2020;173:120. [PMID: 32369541]

## PREVENTION OF CARDIOVASCULAR DISEASE

Cardiovascular diseases (CVDs), including coronary heart disease (CHD) and stroke, represent two of the most important causes of morbidity and mortality in developed countries. Several risk factors increase the risk for coronary disease and stroke. These risk factors can be divided into those that are modifiable (eg, lipid disorders, hypertension, cigarette smoking) and those that are not (eg, age, sex, family history of early coronary disease). Impressive declines in age-specific mortality rates from heart disease and stroke have been achieved in all age groups in North America during the past two decades, in large part through improvement of modifiable risk factors: reductions in cigarette smoking, improvements in lipid levels, and more aggressive detection and treatment of hypertension. This section considers the role of screening for cardiovascular risk and the use of effective therapies to reduce such risk. Key recommendations for cardiovascular prevention are shown in Table 1–3. Guidelines encourage regular assessment of global cardiovascular risk in adults 40–79 years of age without known CVD, using standard cardiovascular risk factors. The role of nontraditional risk factors for improving risk estimation remains unclear.

Cho L et al. Summary of updated recommendations for primary prevention of cardiovascular disease in women: JACC State-of-the-Art Review. J Am Coll Cardiol. 2020;75:2602. [PMID: 32439010]

Lin JS et al. Nontraditional risk factors in cardiovascular disease risk assessment: a systematic evidence report for the US Preventive Services Task Force [Internet]. Rockville, MD: Agency for Healthcare Research and Quality (US); 2018 Jul. <https://www.ncbi.nlm.nih.gov/books/NBK525925/> [PMID: 30234933]

Wall HK et al. Vital signs: prevalence of key cardiovascular disease risk factors for Million Hearts 2022—United States, 2011–2016. MMWR Morb Mortal Wkly Rep. 2018;67:983. [PMID: 3018885]

## ► Abdominal Aortic Aneurysm

One-time screening for abdominal aortic aneurysm (AAA) by ultrasonography is recommended by the USPSTF (B recommendation) in men aged 65–75 years who have ever smoked. One-time screening for AAA is associated with a relative reduction in odds of AAA-related mortality over 12–15 years (odds ratio [OR] 0.65 [95% confidence interval [CI] 0.57–0.74]) and a similar reduction in AAA-related ruptures (OR 0.62 [95% CI 0.55–0.70]). Women who have never smoked and who have no family history of AAA do not appear to benefit from such screening (D recommendation); the current evidence for women who have ever smoked or who have a family history of AAA is insufficient to assess the balance of risks versus benefits (I recommendation) (Table 1–3).

Centers for Disease Control and Prevention (CDC). Pneumococcal vaccination. <https://www.cdc.gov/vaccines/schedules/hcp/imz/adult.html>

Centers for Disease Control and Prevention (CDC). Recommended Adult Immunization Schedule for ages 19 years or older, United States, 2020. <https://www.cdc.gov/vaccines/schedules/hcp/imz/adult.html>

**Table 1–3.** Expert recommendations for cardiovascular risk prevention methods: US Preventive Services Task Force (USPSTF).<sup>1</sup>

| Prevention Method  | Recommendation/[Year Issued]   |
|--|--|
| Screening for abdominal aortic aneurysm (AAA)                            | Recommends one-time screening for AAA by ultrasonography in men aged 65–75 years who have ever smoked. (B)<br>Selectively offer screening for AAA in men aged 65–75 years who have never smoked. (C)<br>Current evidence is insufficient to assess the balance of benefits and harms of screening for AAA in women aged 65–75 years who have ever smoked or have a family history of AAA. (I)<br>Recommends against routine screening for AAA in women who have never smoked and have no family history of AAA. (D)<br>[2019]  |
| Aspirin use  | Recommends initiating low-dose aspirin use for the primary prevention of cardiovascular disease (CVD) and colorectal cancer (CRC) in adults aged 50–59 years who have a 10% or greater 10-year CVD risk, are not at increased risk for bleeding, have a life expectancy of at least 10 years, and are willing to take low-dose aspirin daily for at least 10 years. (B)<br>The decision to initiate low-dose aspirin use for the primary prevention of CVD and CRC in adults aged 60–69 years who have a 10% or greater 10-year CVD risk should be an individual one. Persons who are not at increased risk for bleeding, have a life expectancy of at least 10 years, and are willing to take low-dose aspirin daily for at least 10 years are more likely to benefit. Persons who place a higher value on the potential benefits than the potential harms may choose to initiate low-dose aspirin. (C)<br>The current evidence is insufficient to assess the balance of benefits and harms of initiating aspirin use for the primary prevention of CVD and CRC in adults younger than 50 years or older than age 70. (I)<br>[2016] |
| Blood pressure screening   | The USPSTF recommends screening for high blood pressure in adults aged 18 years or older. The USPSTF recommends obtaining measurements outside of the clinical setting for diagnostic confirmation before starting treatment. (A)<br>[2015]  |
| Serum lipid screening and use of statins for prevention                  | The USPSTF recommends that adults without a history of CVD use a low- to moderate-dose statin for the prevention of CVD events and mortality when all of the following criteria are met: (1) they are aged 40–75 years; (2) they have one or more CVD risk factors (ie, dyslipidemia, diabetes mellitus, hypertension, or smoking); and (3) they have a calculated 10-year risk of a cardiovascular event of 10% or greater.<br>Identification of dyslipidemia and calculation of 10-year CVD event risk requires universal lipids screening in adults aged 40–75 years. See the “Clinical Considerations” section of the USPSTF recommendations <sup>1</sup> for more information on lipids screening and the assessment of cardiovascular risk. (B)<br>The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of initiating statin use for the primary prevention of CVD events and mortality in adults aged 76 years and older without a history of heart attack or stroke. (I)<br>[2016]   |
| Counseling about healthful diet and physical activity for CVD prevention | Recommends offering or referring adults who are overweight or obese and have additional CVD risk factors to intensive behavioral counseling interventions to promote a healthful diet and physical activity for CVD prevention. (B)<br>[2014]<br>Recommends that primary care professionals individualize the decision to offer or refer adults without obesity who do not have hypertension, dyslipidemia, abnormal blood glucose levels, or diabetes to behavioral counseling to promote a healthful diet and physical activity. (C)<br>[2017]   |
| Screening for diabetes mellitus  | Recommends screening for abnormal blood glucose as part of cardiovascular risk assessment in adults aged 40–70 years who are overweight or obese. Clinicians should offer or refer patients with abnormal blood glucose to intensive behavioral counseling interventions to promote a healthful diet and physical activity. (B)<br>[2015]  |
| Screening for smoking and counseling to promote cessation                | Recommends that clinicians ask all adults about tobacco use, advise them to stop using tobacco, and provide behavioral interventions and US Food and Drug Administration (FDA)–approved pharmacotherapy for cessation to adults who use tobacco. (A)<br>[2015]   |

<sup>1</sup>US Preventive Services Task Force recommendations available at <http://www.uspreventiveservicestaskforce.org/BrowseRec/Index/browse-recommendations>.

**Recommendation A:** The USPSTF strongly recommends that clinicians routinely provide the service to eligible patients. (The USPSTF found good evidence that the service improves important health outcomes and concludes that benefits substantially outweigh harms.)

**Recommendation B:** The USPSTF recommends that clinicians routinely provide the service to eligible patients. (The USPSTF found at least fair evidence that the service improves important health outcomes and concludes that benefits substantially outweigh harms.)

**Recommendation C:** The USPSTF makes no recommendation for or against routine provision of the service.

**Recommendation D:** The USPSTF recommends against routinely providing the service to asymptomatic patients. (The USPSTF found at least fair evidence that the service is ineffective or that harms outweigh benefits.)

**Recommendation I:** The USPSTF concludes that the evidence is insufficient to recommend for or against routinely providing the service.

Guirguis-Blake JM et al. Primary care screening for abdominal aortic aneurysm: updated evidence report and systematic review for the US Preventive Services Task Force. JAMA. 2019;322:2219. [PMID: 31821436]

US Preventive Services Task Force, Owens DK et al. Screening for abdominal aortic aneurysm: US Preventive Services Task Force Recommendation Statement. JAMA. 2019;322:2211. [PMID: 31821437]

Ying AJ et al. Abdominal aortic aneurysm screening: a systematic review and meta-analysis of efficacy and cost. Ann Vasc Surg. 2019;54:298. [PMID: 30081169]

associated with improvement of chronic obstructive pulmonary disease symptoms. On average, women smokers who quit smoking by age 35 add about 3 years to their life expectancy, and men add more than 2 years to theirs. Smoking cessation can increase life expectancy even for those who stop after the age of 65.

Although tobacco use constitutes the most serious common medical problem, it is undertreated. Almost 40% of smokers attempt to quit each year, but only 4% are successful. Persons whose clinicians advise them to quit are 1.6 times as likely to attempt quitting. Over 70% of smokers see a physician each year, but only 20% of them receive any medical quitting advice or assistance.

Factors associated with successful cessation include having a rule against smoking in the home, being older, and having greater education. Several effective clinical interventions are available to promote smoking cessation, including counseling, pharmacotherapy, and combinations of the two.

Helpful counseling strategies are shown in Table 1–4. Additionally, a system should be implemented to identify smokers, and advice to quit should be tailored to the patient's level of readiness to change. All patients trying to quit should be offered pharmacotherapy (Table 1–5) except those with medical contraindications, women who are pregnant or breast-feeding, and adolescents. Weight gain occurs in most patients (80%) following smoking cessation. Average weight gain is 2 kg, but for some (10–15%), major weight gain—over 13 kg—may occur. Planning for the possibility of weight gain, and means of mitigating it, may help with maintenance of cessation.

Several pharmacologic therapies shown to be effective in promoting cessation are summarized in Table 1–5. Nicotine replacement therapy doubles the chance of successful quitting. The nicotine patch, gum, and lozenges are

## Cigarette Smoking

Cigarette smoking remains the most important cause of preventable morbidity and early mortality. In 2015, there were an estimated 6.4 million premature deaths in the world attributable to smoking and tobacco use; smoking is the second leading cause of disability-adjusted life-years lost. Cigarettes are responsible for one in every five deaths in the United States, or over 480,000 deaths annually. Annual cost of smoking-related health care is approximately \$130 billion in the United States, with another \$150 billion in productivity losses. Fortunately, US smoking rates have been declining; in 2015, 15.1% of US adults were smokers, and by 2018, 13.7% were smokers. Global direct health care costs from smoking in 2012 were estimated at \$422 billion, with total costs of over \$1.4 trillion.

Over 41,000 deaths per year in the United States are attributable to environmental tobacco smoke.

Smoking cessation reduces the risks of death and of myocardial infarction in people with coronary artery disease; reduces the rate of death and acute myocardial infarction in patients who have undergone percutaneous coronary revascularization; lessens the risk of stroke; and is

**Table 1–4.** Inquiries to help in support of smoking cessation.

| Component   | Helpful Clinician Statements and Inquiries   |
|---|--|
| Communicate your caring and concern   | "I am concerned about the effects of smoking on your health... <ul style="list-style-type: none"> <li>• and want you to know that I am willing to help you to quit"</li> <li>• and so how do you feel about quitting?"</li> <li>• do you have any fears or ambivalent feelings about quitting?"</li> </ul>   |
| Encourage the patient to talk about the quitting process  | "Tell me... <ul style="list-style-type: none"> <li>• why do you want to quit smoking?"</li> <li>• when you tried quitting smoking in the past, what sort of difficulties did you encounter?"</li> <li>• were you able to succeed at all, even for a while?"</li> <li>• what concerns or worries do you have about quitting now?"</li> </ul>  |
| Provide basic information about smoking (eg, its addictive nature) and successful quitting (eg, nature and time course of withdrawal) | "Did you know that... <ul style="list-style-type: none"> <li>• the nicotine in cigarette smoke is highly addictive?"</li> <li>• within a day of stopping, you will notice nicotine withdrawal symptoms, such as irritability and craving?"</li> <li>• after you quit, any smoking (even a single puff) makes it likely that you will fully relapse into smoking again?"</li> </ul> |
| Encourage the patient to make a quit attempt  | "I want you to reassure you that... <ul style="list-style-type: none"> <li>• as your clinician, I believe you are going to be able to quit."</li> <li>• there are now available many effective smoking cessation treatments"</li> <li>• more than half the people who have ever smoked have now successfully quit"</li> </ul>  |

**Table 1–5.** Medications for tobacco dependence and smoking cessation.

| Drug   | Some Formulations                         | Usual Adult Dosage <sup>1,2</sup>   | Cost 30 days                   |
|--|---|---|--------------------------------|
| <b>Nicotine Replacement Therapies (NRTs)</b>                             |   |   |                                |
| Nicotine transdermal patch <sup>3</sup> – generic (Nicoderm CQ)          | 7, 14, 21 mg/24-h patches                 | 1 patch/day <sup>4</sup>  | \$57.40                        |
| Nicotine polacrilex gum <sup>3</sup> – generic (Nicorette gum)           | 2, 4 mg/pieces                            | 8–24 pieces/day <sup>4,5,6</sup>  | \$63.12                        |
| Nicotine polacrilex lozenge <sup>3,7</sup> – generic (Nicorette lozenge) | 2, 4 mg/lozenges                          | 8–20 lozenges/day <sup>4,5,8</sup>  | \$66.24                        |
| Nicotine oral inhaler – Nicotrol   | 10 mg cartridges <sup>9</sup>             | 4–16 cartridges/day <sup>4</sup>  | \$551.11                       |
| Nicotine nasal spray – Nicotrol NS                                       | 200 sprays/10 mL bottles (0.5 mg/spray)   | 2 sprays 8–40×/day (max 10 sprays/h) <sup>3</sup>   | \$578.66<br>(4-bottle package) |
| <b>Dopaminergic-Noradrenergic Reuptake Inhibitor</b>                     |   |   |                                |
| Bupropion SR – generic   | 100, 150, 200 mg SR tablets <sup>10</sup> | 150 mg orally once daily × 3 days, then 150 mg orally twice daily                             | \$108.60                       |
| <b>Nicotinic Receptor Partial Agonist</b>                                |   |   |                                |
| Varenicline tartrate – Chantix   | 0.5, 1 mg tablets                         | 0.5 mg orally once daily × 3 days, then 0.5 mg twice daily on days 4–7, then 1 mg twice daily | \$585.60                       |

SR, sustained-release.

<sup>1</sup>Dosage reductions may be needed for liver or kidney impairment.

<sup>2</sup>Patients should receive a minimum of 3–6 months of effective therapy. In general, the dosage of NRTs can be tapered at the end of treatment; bupropion SR and varenicline can usually be stopped without a gradual dosage reduction, but some clinicians recommend a taper.

<sup>3</sup>Available over the counter for persons ≥ 18 years old.

<sup>4</sup>See expanded table for dosage titration instructions, available at: [medicalletter.org/TML-article-1576c](http://medicalletter.org/TML-article-1576c).

<sup>5</sup>Avoid eating or drinking within 15 minutes of using a gum or lozenge.

<sup>6</sup>A second piece of gum can be used within 1 hour. Continuously chewing one piece after another is not recommended.

<sup>7</sup>Also available in a mini-lozenge.

<sup>8</sup>Maximum of 5 lozenges in 6 hours or 20 lozenges/day. Use of more than 1 lozenge at a time or continuously using one after another is not recommended.

<sup>9</sup>Each cartridge delivers 4 mg of nicotine.

<sup>10</sup>Only the generic 150-mg SR tablets are FDA-approved as a smoking cessation aid.

Modified, with permission, from Drugs for smoking cessation. *Med Lett Drugs Ther.* 2019 Jul 15;61(1576):105–10. <http://www.medicalletter.org>. Average wholesale price (AWP, for AB-rated generic when available) for quantity listed. Source: IBM Micromedex Red Book (electronic version) IBM Watson Health, Greenwood Village, CO. Available at <https://micromedexsolutions.com>, accessed March 27, 2021. AWP may not accurately represent the actual pharmacy cost because wide contractual variations exist among institutions.

available over the counter and nicotine nasal spray and inhalers by prescription. The sustained-release antidepressant drug bupropion (150–300 mg/day orally) is an effective smoking cessation agent and is associated with minimal weight gain, although seizures are a contraindication. It acts by boosting brain levels of dopamine and norepinephrine, mimicking the effect of nicotine. Varenicline, a partial nicotinic acetylcholine-receptor agonist, has been shown to improve cessation rates; however, its adverse effects, particularly its effects on mood, are not completely understood and warrant careful consideration. No single pharmacotherapy is clearly more effective than others, so patient preferences and data on adverse effects should be taken into account in selecting a treatment. Combination therapy is more effective than a single pharmacologic modality. The efficacy of e-cigarettes in smoking cessation has not been well evaluated, and some users may find them addictive. Recent reports of “vaping-related” lung disease

should prompt additional caution in the use of unregulated nicotine delivery devices for smoking cessation (see Chapter 9).

Clinicians should not show disapproval of patients who fail to stop smoking or who are not ready to make a quit attempt. Thoughtful advice that emphasizes the benefits of cessation and recognizes common barriers to success can increase motivation to quit and quit rates. An upcoming medical procedure or intercurrent illness or hospitalization may motivate even the most addicted smoker to quit.

Individualized or group counseling is very cost effective, even more so than treating hypertension. Smoking cessation counseling by telephone (“quitlines”) and text messaging-based interventions have both proved effective. An additional strategy is to recommend that any smoking take place outdoors to limit the effects of passive smoke on housemates and coworkers. This can lead to smoking reduction and quitting.

Public policies, including higher cigarette taxes and more restrictive public smoking laws, have also been shown to encourage cessation, as have financial incentives directed to patients.

Anonymous. Drugs for smoking cessation. *Med Lett Drugs Ther.* 2019;61:105. [PMID: 31381546]

Black N et al. Behaviour change techniques associated with smoking cessation in intervention and comparator groups of randomized controlled trials: a systematic review and meta-regression. *Addiction.* 2020;115:2008. [PMID: 32196796]

Centers for Disease Control and Prevention (CDC). Current cigarette smoking among adults in the United States. 2020 December 10. [https://www.cdc.gov/tobacco/data\\_statistics/fact\\_sheets/adult\\_data/cig\\_smoking/index.htm](https://www.cdc.gov/tobacco/data_statistics/fact_sheets/adult_data/cig_smoking/index.htm)

Hollands GJ et al. Interventions to increase adherence to medications for tobacco dependence. *Cochrane Database Syst Rev.* 2019;8:CD009164. [PMID: 31425618]

Tibuakuu M et al. National trends in cessation counseling, prescription medication use, and associated costs among US adult cigarette smokers. *JAMA Netw Open.* 2019;2:e194585. [PMID: 31125108]

Villanti AC et al. Smoking-cessation interventions for U.S. young adults: updated systematic review. *Am J Prev Med.* 2020;59:123. [PMID: 32418800]

type 9 (PCSK9), which decreases the degradation of LDL receptors. PCSK9 inhibitors also decrease Lp(a) levels. These newer agents are very expensive so are often used mainly in high-risk patients when statin therapy does not reduce the LDL cholesterol sufficiently at maximally tolerated doses or when patients are intolerant of statins. So far, few side effects have been reported with PCSK9 inhibitor use.

Guidelines for statin and PCSK9 therapy are discussed in Chapter 28.

Mortensen MB et al. Elevated LDL cholesterol and increased risk of myocardial infarction and atherosclerotic cardiovascular disease in individuals aged 70–100 years: a contemporary primary prevention cohort. *Lancet.* 2020;396:1644. [PMID: 33186534]

Navarrete EP et al. Association between baseline LDL-C level and total and cardiovascular mortality after LDL-C lowering: a systematic review and meta-analysis. *JAMA.* 2018;319:1566. [PMID: 29677301]

US Preventive Services Task Force. Statin use for the primary prevention of cardiovascular disease in adults: US Preventive Services Task Force Recommendation Statement. *JAMA.* 2016;316:1997. [PMID: 27838723]

## ► Hypertension

According to the American Heart Association, over 133 million US adults have hypertension, of which approximately 83 million are eligible for pharmacologic treatment. Of these 83 million, hypertension is treated in only about 66% and well controlled in only about 30% (see Chapter 11). In every adult age group, higher values of systolic and diastolic blood pressure carry greater risks of stroke and heart failure. Systolic blood pressure is a better predictor of morbid events than diastolic blood pressure. Home monitoring is better correlated with target organ damage than clinic-based values. Clinicians can apply specific blood pressure criteria, such as those of the Joint National Committee or American Heart Association guidelines, along with consideration of the patient's cardiovascular risk and personal values, to decide at what levels treatment should be considered in individual cases.

Primary prevention of hypertension can be accomplished by strategies aimed at both the general population and special high-risk populations. The latter include persons with high-normal blood pressure or a family history of hypertension, Blacks, and individuals with various behavioral risk factors, such as physical inactivity; excessive consumption of salt, alcohol, or calories; and deficient intake of potassium. Effective interventions for primary prevention of hypertension include reduced sodium and alcohol consumption, weight loss, and regular exercise. Potassium supplementation lowers blood pressure modestly, and a diet high in fresh fruits and vegetables and low in fat, red meats, and sugar-containing beverages also reduces blood pressure. Interventions of unproven efficacy include pill supplementation of potassium, calcium, magnesium, fish oil, or fiber; macronutrient alteration; and stress management.

Improved identification and treatment of hypertension is a major cause of the recent decline in stroke deaths as well as the reduction in incidence of heart failure-related hospitalizations. Because hypertension is usually asymptomatic,

## ► Lipid Disorders

Higher low-density lipoprotein (LDL) cholesterol concentrations and lower high-density lipoprotein (HDL) levels are associated with an increased risk of CHD (see Chapter 28). Measurement of total and high-density lipoprotein cholesterol levels can help assess the degree of CHD risk. The best age to start screening is controversial, as is its frequency. Cholesterol-lowering therapy reduces the relative risk of CHD events, with the degree of reduction proportional to the reduction in LDL cholesterol achieved, at least at LDL levels greater than 100 mg/dL. The absolute benefits of screening for—and treating—abnormal lipid levels depend on the presence and level of other cardiovascular risk factors, including hypertension, diabetes mellitus, smoking, age, and sex. If other risk factors are present, atherosclerotic CVD risk is higher and the potential benefits of therapy are greater. Patients with known CVD are at higher risk and have larger benefits from reduction in LDL cholesterol. The optimal risk threshold for initiating statins for primary prevention remains somewhat controversial, although most guidelines now suggest statin therapy when the 10-year atherosclerotic cardiovascular risk is greater than 10%.

Evidence for the effectiveness of statin-type drugs is better than for the other classes of lipid-lowering agents or dietary changes specifically for improving lipid levels. Multiple large, randomized, placebo-controlled trials have demonstrated important reductions in total mortality, major coronary events, and strokes with lowering levels of LDL cholesterol by statin therapy for patients with known CVD. Statins also reduce cardiovascular events for patients with diabetes mellitus. For patients with no previous history of cardiovascular events or diabetes, meta-analyses have shown important reductions of cardiovascular events.

Newer antilipidemic monoclonal antibody agents (eg, evolocumab and alirocumab) lower LDL cholesterol by 50–60% by binding proprotein convertase subtilisin kexin

screening is strongly recommended to identify patients for treatment. Elevated office readings should be confirmed with repeated measurements, ideally from ambulatory monitoring or home measurements. Despite strong recommendations in favor of screening and treatment, hypertension control remains suboptimal. An intervention that included both patient and provider education was more effective than provider education alone in achieving control of hypertension, suggesting the benefits of patient participation; another trial found that home monitoring combined with telephone-based nurse support was more effective than home monitoring alone for blood pressure control. Pharmacologic management of hypertension is discussed in Chapter 11.

- Bundy JD et al. Comparison of the 2017 ACC/AHA Hypertension Guideline with earlier guidelines on estimated reductions in cardiovascular disease. *Curr Hypertens Rep.* 2019;21:76. [PMID: 31473837]
- Fryar CD et al. Hypertension prevalence and control among adults: United States, 2015–2016. *NCHS Data Brief.* 2017; (289):1–8. [PMID: 29155682]
- Ritche MD et al. Potential need for expanded pharmacologic treatment and lifestyle modification services under the 2017 ACC/AHA Hypertension Guideline. *J Clin Hypertens (Greenwich).* 2018;20:1377. [PMID: 30194806]
- Whelton PK et al. ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Hypertension.* 2018;71:1269. [PMID: 29133354]

## ► Chemoprevention

Regular use of low-dose aspirin (81–325 mg) can reduce cardiovascular events but increases gastrointestinal bleeding. Aspirin may also reduce the risk of death from several common types of cancer (colorectal, esophageal, gastric, breast, prostate, and possibly lung). The potential benefits of aspirin may exceed the possible adverse effects among middle-aged adults who are at increased cardiovascular risk, which can be defined as a 10-year risk of greater than 10%, and who do not have an increased risk of bleeding. A newer trial in older healthy adults did not find clear benefit from aspirin for reduction of cardiovascular events and saw an increase in all-cause mortality with aspirin. Therefore, aspirin should not be routinely initiated in healthy adults over age 70.

Nonsteroidal anti-inflammatory drugs may reduce the incidence of colorectal adenomas and polyps but may also increase heart disease and gastrointestinal bleeding, and thus are not recommended for colon cancer prevention in average-risk patients.

Antioxidant vitamin (vitamin E, vitamin C, and beta-carotene) supplementation produced no significant reductions in the 5-year incidence of—or mortality from—vascular disease, cancer, or other major outcomes in high-risk individuals with coronary artery disease, other occlusive arterial disease, or diabetes mellitus.

- Gaziano JM. Aspirin for primary prevention: clinical considerations in 2019. *JAMA.* 2019;321:253. [PMID: 30667488]

Huang WY et al. Frequency of intracranial hemorrhage with low-dose aspirin in individuals without symptomatic cardiovascular disease: a systematic review and meta-analysis. *JAMA Neurol.* 2019;76:906. [PMID: 31081871]

Marquis-Gravel G et al. Revisiting the role of aspirin for the primary prevention of cardiovascular disease. *Circulation.* 2019;140:1115. [PMID: 31545683]

Patrono C et al. Role of aspirin in primary prevention of cardiovascular disease. *Nat Rev Cardiol.* 2019;16:675. [PMID: 31243390]

Zheng SL et al. Association of aspirin use for primary prevention with cardiovascular events and bleeding events: a systematic review and meta-analysis. *JAMA.* 2019;321:277. [PMID: 30667501]

## PREVENTION OF OSTEOPOROSIS

See Chapter 26.

Osteoporosis, characterized by low bone mineral density, is common and associated with an increased risk of fracture. The lifetime risk of an osteoporotic fracture is approximately 50% for women and 30% for men. Osteoporotic fractures can cause significant pain and disability. As such, research has focused on means of preventing osteoporosis and related fractures. Primary prevention strategies include calcium supplementation, vitamin D supplementation, and exercise programs. The effectiveness of calcium and vitamin D for fracture prevention remain controversial, particularly in noninstitutionalized individuals.

Screening for osteoporosis on the basis of low bone mineral density is recommended for women over age 65, based on indirect evidence that screening can identify women with low bone mineral density and that treatment of women with low bone density with bisphosphonates is effective in reducing fractures. However, real-world adherence to pharmacologic therapy for osteoporosis is low: one-third to one-half of patients do not take their medication as directed. Screening for osteoporosis is also recommended in younger women who are at increased risk. The effectiveness of screening in men has not been established. Concern has been raised that bisphosphonates may increase the risk of certain uncommon atypical types of femoral fractures and rare osteonecrosis of the jaw, making consideration of the benefits and risks of therapy important when considering osteoporosis screening.

US Preventive Services Task Force. Screening for osteoporosis to prevent fractures: US Preventive Services Task Force recommendation statement. *JAMA.* 2018;319:2521. [PMID: 29946735]

US Preventive Services Task Force. Vitamin D, calcium, or combined supplementation for the primary prevention of fractures in community-dwelling adults: US Preventive Services Task Force recommendation statement. *JAMA.* 2018;319:1592. [PMID: 29677309]

Yedavally-Yellayi S et al. Update on osteoporosis. *Prim Care.* 2019;46:175. [PMID: 30704657]

## PREVENTION OF PHYSICAL INACTIVITY

Lack of sufficient physical activity is the second most important contributor to preventable deaths, trailing only tobacco use. The US Department of Health and Human Services and the CDC recommend that adults (including

older adults) engage in 150 minutes of moderate-intensity (such as brisk walking) or 75 minutes of vigorous-intensity (such as jogging or running) aerobic activity or an equivalent mix of moderate- and vigorous-intensity aerobic activity each week. In addition to activity recommendations, the CDC recommends activities to strengthen all major muscle groups (abdomen, arms, back, chest, hips, legs, and shoulders) at least twice a week.

Patients who engage in regular moderate to vigorous exercise have a lower risk of myocardial infarction, stroke, hypertension, hyperlipidemia, type 2 diabetes mellitus, diverticular disease, and osteoporosis. Regular exercise may also have a positive effect on executive function in older adults.

In longitudinal cohort studies, individuals who report higher levels of leisure-time physical activity are less likely to gain weight. Conversely, individuals who are overweight are less likely to stay active. However, at least 60 minutes of daily moderate-intensity physical activity may be necessary to maximize weight loss and prevent significant weight regain. Moreover, adequate levels of physical activity appear to be important for the prevention of weight gain and the development of obesity.

Physical activity can be incorporated into any person's daily routine. For example, the clinician can advise a patient to take the stairs instead of the elevator, to walk or bike instead of driving, to do housework or yard work, to get off the bus one or two stops earlier and walk the rest of the way, to park at the far end of the parking lot, or to walk during the lunch hour. The basic message should be the more the better, and anything is better than nothing.

When counseling patients, clinicians should advise patients about both the benefits and risks of exercise, prescribe an exercise program appropriate for each patient, and provide advice to help prevent injuries and cardiovascular complications.

Although primary care providers regularly ask patients about physical activity and advise them with verbal counseling, few providers provide written prescriptions or perform fitness assessments. Tailored interventions may potentially help increase physical activity in individuals. Exercise counseling with a prescription, eg, for walking at either a hard intensity or a moderate intensity with a high frequency, can produce significant long-term improvements in cardiorespiratory fitness. To be effective, exercise prescriptions must include recommendations on type, frequency, intensity, time, and progression of exercise and must follow disease-specific guidelines. Several factors influence physical activity behavior, including personal, social (eg, family and work), and environmental (eg, access to exercise facilities and well-lit parks) factors. Walkable neighborhoods around workplaces support physical activity such as walking and bicycling. A community-based volunteer intervention resulted in increased walking activity among older women, who were at elevated risk for both inactivity and adverse health outcomes.

Broad-based interventions targeting various factors are often the most successful, and interventions to promote physical activity are more effective when health agencies work with community partners, such as schools, businesses, and health care organizations. Enhanced community

awareness through mass media campaigns, school-based strategies, and policy approaches are proven strategies to increase physical activity.

Chen FT et al. Effects of exercise training interventions on executive function in older adults: a systematic review and meta-analysis. *Sports Med*. 2020;50:1451. [PMID: 32447717]

Jeong SW et al. Mortality reduction with physical activity in patients with and without cardiovascular disease. *Eur Heart J*. 2019;40:3547. [PMID: 31504416]

## PREVENTION OF OVERWEIGHT & OBESITY

Obesity is now a true epidemic and public health crisis that both clinicians and patients must face. Normal body weight is defined as a body mass index (BMI), calculated as the weight in kilograms divided by the height in meters squared, of less than 25; overweight is defined as a BMI = 25.0–29.9, and obesity as a BMI greater than 30.

Risk assessment of the overweight and obese patient begins with determination of BMI, waist circumference for those with a BMI of 35 or less, presence of comorbid conditions, and a fasting blood glucose and lipid panel. Obesity is clearly associated with type 2 diabetes mellitus, hypertension, hyperlipidemia, cancer, osteoarthritis, cardiovascular disease, obstructive sleep apnea, and asthma.

Obesity is associated with a higher all-cause mortality rate. Data suggest an increase among those with grades 2 and 3 obesity (BMI more than 35); however, the impact on all-cause mortality among overweight (BMI 25–30) and grade 1 obesity (BMI 30–35) is questionable. Persons with a BMI of 40 or higher have death rates from cancers that are 52% higher for men and 62% higher for women than the rates in men and women of normal weight.

Prevention of overweight and obesity involves both increasing physical activity and dietary modification to reduce caloric intake. Adequate levels of physical activity appear to be important for the prevention of weight gain and the development of obesity. Physical activity programs consistent with public health recommendations may promote modest weight loss (~2 kg); however, the amount of weight loss for any one individual is highly variable.

Clinicians can help guide patients to develop personalized eating plans to reduce energy intake, particularly by recognizing the contributions of fat, concentrated carbohydrates, and large portion sizes (see Chapter 29). Patients typically underestimate caloric content, especially when consuming food away from home. Providing patients with caloric and nutritional information may help address the current obesity epidemic.

Commercial weight loss programs are effective in promoting weight loss and weight loss management. A randomized controlled trial of over 400 overweight or obese women demonstrated the effectiveness of a free prepared meal and incentivized structured weight loss program compared with usual care.

Weight loss strategies using dietary, physical activity, or behavioral interventions can produce significant improvements in weight among persons with prediabetes and a significant decrease in diabetes incidence. Lifestyle

interventions including diet combined with physical activity are effective in achieving weight loss and reducing cardiometabolic risk factors among patients with severe obesity.

Bariatric surgical procedures, eg, adjustable gastric band, sleeve gastrectomy, and Roux-en-Y gastric bypass, are reserved for patients with morbid obesity whose BMI exceeds 40, or for less severely obese patients (with BMIs between 35 and 40) with high-risk comorbid conditions such as life-threatening cardiopulmonary problems (eg, severe sleep apnea, Pickwickian syndrome, and obesity-related cardiomyopathy) or severe diabetes mellitus. In selected patients, surgery can produce substantial weight loss (10–159 kg) over 1–5 years, with rare but sometimes severe complications. Nutritional deficiencies are one complication of bariatric surgical procedures and close monitoring of a patient's metabolic and nutritional status is essential.

Finally, clinicians seem to share a general perception that almost no one succeeds in long-term maintenance of weight loss. However, research demonstrates that approximately 20% of overweight individuals are successful at long-term weight loss (defined as losing 10% or more of initial body weight and maintaining the loss for 1 year or longer).

Ryan DH et al. Guideline recommendations for obesity management. *Med Clin North Am.* 2018;102:49. [PMID: 29156187]  
Walsh K et al. Health advice and education given to overweight patients by primary care doctors and nurses: a scoping literature review. *Prev Med Rep.* 2019;14:100812. [PMID: 30805277]

## CANCER PREVENTION

### Primary Prevention

Primary prevention of skin cancer consists of restricting exposure to ultraviolet light by wearing appropriate clothing, and use of sunscreens. Persons who engage in regular physical exercise and avoid obesity have lower rates of breast and colon cancer. Prevention of occupationally induced cancers involves minimizing exposure to carcinogenic substances, such as asbestos, ionizing radiation, and benzene compounds. Chemoprevention has been widely studied for primary cancer prevention (see earlier Chemo-prevention section and Chapter 39). Use of tamoxifen, raloxifene, and aromatase inhibitors for breast cancer prevention is discussed in Chapters 17 and 39. Hepatitis B vaccination can prevent hepatocellular carcinoma (HCC). Screening and treatment of hepatitis C is another strategy to prevent HCC (see Chapter 16); new recommendations have extended the population eligible for screening. The use of HPV vaccine to prevent cervical and possibly anal cancer is discussed earlier in this chapter. HPV vaccines may also have a role in the prevention of HPV-related head and neck cancers. The USPSTF recommends genetic counseling and, if indicated after counseling, genetic testing for women whose family or personal history is associated with an increased risk of harmful mutations in the *BRCA 1/2* gene. Guidelines for optimal cancer screening in adults over the age of 75 are unsettled; thus, an individualized

approach that considers differences in disease risk rather than chronological age alone is recommended.

Athanasiou A et al. HPV vaccination and cancer prevention. *Best Pract Res Clin Obstet Gynaecol.* 2020;65:109. [PMID: 32284298]  
US Preventive Services Task Force; Owens DK et al. Risk assessment, genetic counseling, and genetic testing for *BRCA*-related cancer: US Preventive Services Task Force Recommendation Statement. *JAMA.* 2019;322:652. [PMID: 31429903]

### Screening & Early Detection

Screening prevents death from cancers of the breast, colon, and cervix. Current cancer screening recommendations from the USPSTF are available online at <https://www.uspreventiveservicestaskforce.org/BrowseRec/Index/browse-recommendations>. Despite an increase in rates of screening for breast, cervical, and colon cancer over the last decade, overall screening for these cancers is suboptimal.

Though breast cancer mortality is reduced with mammography screening, screening mammography has both benefits and downsides. Clinicians should discuss the risks and benefits with each patient and consider individual patient preferences when deciding when to begin screening (see Chapters 17 and e6).

Digital breast tomosynthesis (three-dimensional mammography) integrated with digital mammography increases cancer detection rates compared to digital mammography alone; however, the extent of improved detection and impact on assessment outcomes need further exploration. MRI is not currently recommended for general screening, and its impact on breast cancer mortality is uncertain; nevertheless, the American Cancer Society recommends it for women at high risk (20–25% or more), including those with a strong family history of breast or ovarian cancer. Screening with both MRI and mammography might be superior to mammography alone in ruling out cancerous lesions in women with an inherited predisposition to breast cancer.

Screening for testicular cancers among asymptomatic adolescent or adult males is not recommended by the USPSTF. Prostate cancer screening remains controversial, since no completed trials have answered the question of whether early detection and treatment after screen detection produce sufficient benefits to outweigh harms of treatment. For men between the ages of 55 and 69, the decision to screen should be individualized and include a discussion of its risks and benefits with a clinician. The USPSTF recommends against PSA-based prostate cancer screening for men older than age 70 years (grade D recommendation).

Annual or biennial fecal occult blood testing reduces mortality from colorectal cancer. Fecal immunochemical tests (FIT) are superior to guaiac-based fecal occult blood tests (gFOBT) in detecting advanced adenomatous polyps and colorectal cancer, and patients are more likely to favor FIT over gFOBT. Randomized trials using sigmoidoscopy as the screening method found 20–30% reductions in mortality from colorectal cancer. Colonoscopy has also been advocated as a screening examination. CT colonography (virtual colonoscopy) is a noninvasive option in screening for colorectal cancer. It has been shown to have a high safety profile and performance similar to colonoscopy. Current

guidelines consistently recommend screening for adults 50–75 years of age; some guidelines suggest starting at age 45 due to the increasing incidence of early-onset colorectal cancer.

The USPSTF recommends screening for cervical cancer in women aged 21–65 years with a Papanicolaou smear (cytology) every 3 years or, for women aged 30–65 years who desire longer intervals, screening with cytology and HPV testing every 5 years. The American Cancer Society recommends screening for people aged 25–65 years with primary HPV testing every 5 years. The USPSTF recommends against screening in women younger than 21 years of age and average-risk women over 65 with adequate negative prior screenings. Receipt of HPV vaccination has no impact on screening intervals.

Women whose cervical specimen HPV tests are positive but cytology results are otherwise negative should repeat co-testing in 12 months (option 1) or undergo HPV-genotype-specific testing for types 16 or 16/18 (option 2). Colposcopy is recommended in women who test positive for types 16 or 16/18. Women with atypical squamous cells of undetermined significance (ASCUS) on cytology and a negative HPV test result should continue routine screening as per age-specific guidelines.

In a randomized, controlled trial, transvaginal ultrasound combined with serum cancer antigen 125 (CA-125) as screening tools to detect ovarian cancer did not reduce mortality. Furthermore, complications were associated with diagnostic evaluations to follow up false-positive screening test results. Thus, screening for ovarian cancer with transvaginal ultrasound and CA-125 is not recommended.

The USPSTF recommends offering annual lung cancer screening with low-dose CT to current smokers aged 50 to 80 years and 20-pack-year smoking history or to smokers who quit within the past 15 years. Screening should stop once a person has not smoked for 15 years or a health problem that significantly limits life expectancy has developed. Screening should not be viewed as an alternative to smoking cessation but rather as a complementary approach.

US Preventive Services Task Force; Krist AH. Screening for lung cancer: US Preventive Services Task Force Recommendation Statement. JAMA. 2021;325:962. [PMID: 33687470]

## PREVENTION OF INJURIES & VIOLENCE

Injuries remain the most important cause of loss of potential years of life before age 65. Homicide and motor vehicle accidents are a major cause of injury-related deaths among young adults, and accidental falls are the most common cause of injury-related death in older adults. Approximately one-third of all injury deaths include a diagnosis of traumatic brain injury, which has been associated with an increased risk of suicide.

Although motor vehicle accident deaths per miles driven have declined in the United States, there has been an increase in motor vehicle accidents related to distracted driving (using a cell phone, texting, eating). For 16- and 17-year-old drivers, the risk of fatal crashes increases with the number of passengers.

Men ages 16–35 are at especially high risk for serious injury and death from accidents and violence, with Blacks and Latinos at greatest risk. Deaths from firearms have reached epidemic levels in the United States. Having a gun in the home increases the likelihood of homicide nearly threefold and of suicide fivefold. Educating clinicians to recognize and treat depression as well as restricting access to lethal methods have been found to reduce suicide rates.

In addition, clinicians should try to educate their patients about always wearing seat belts and safety helmets, about the risks of using cellular telephones or texting while driving and of drinking and driving—or of using other intoxicants (including marijuana) or long-acting benzodiazepines and then driving—and about the risks of having guns in the home.

Clinicians have a critical role in the detection, prevention, and management of intimate partner violence (see Chapter e6). The USPSTF recommends screening women of childbearing age for intimate partner violence and providing or referring women to intervention services when needed. Inclusion of a single question in the medical history—“At any time, has a partner ever hit you, kicked you, or otherwise physically hurt you?”—can increase identification of this common problem. Assessment for abuse and offering of referrals to community resources create the potential to interrupt and prevent recurrence of domestic violence and associated trauma. Clinicians should take an active role in following up with patients whenever possible, since intimate partner violence screening with passive referrals to services may not be adequate.

Physical and psychological abuse, exploitation, and neglect of older adults are serious, underrecognized problems; they may occur in up to 10% of elders. Risk factors for elder abuse include a culture of violence in the family; a demented, debilitated, or depressed and socially isolated victim; and a perpetrator profile of mental illness, alcohol or drug abuse, or emotional and/or financial dependence on the victim. Clues to elder mistreatment include the patient's ill-kempt appearance, recurrent urgent-care visits, missed appointments, suspicious physical findings, and implausible explanations for injuries.

Fontham ETH et al. Cervical cancer screening for individuals at average risk: 2020 guideline update from the American Cancer Society. CA Cancer J Clin. 2020;70:321. [PMID: 32729638]

Qaseem A et al. Screening for breast cancer in average-risk women: a guidance statement from the American College of Physicians. Ann Intern Med. 2019;170:547. [PMID: 30959525]

Qaseem A et al. Screening for colorectal cancer in asymptomatic average-risk adults: a guidance statement from the American College of Physicians. Ann Intern Med. 2019;171:643. [PMID: 31683290]

US Preventive Services Task Force; Curry SJ et al. Screening for cervical cancer: US Preventive Services Task Force recommendation statement. JAMA. 2018;320:674. [PMID: 30140884]

US Preventive Services Task Force; Grossman DC et al. Screening for ovarian cancer: US Preventive Services Task Force recommendation statement. JAMA. 2018;319:588. [PMID: 29450531]

US Preventive Services Task Force; Grossman DC et al. Screening for prostate cancer: US Preventive Services Task Force recommendation statement. JAMA. 2018;319:1901. [PMID: 29801017]

- Feltner C et al. Screening for intimate partner violence, elder abuse, and abuse of vulnerable adults: evidence report and systematic review for the US Preventive Services Task Force. *JAMA*. 2018;320:1688. [PMID: 30357304]
- Jin J. JAMA Patient Page. Screening for intimate partner violence, elder abuse, and abuse of vulnerable adults. *JAMA*. 2018;320:1718. [PMID: 30357300]
- Lutgendorf MA. Intimate partner violence and women's health. *Obstet Gynecol*. 2019;134:470. [PMID: 31403968]
- Mercier É et al. Elder abuse in the out-of-hospital and emergency department settings: a scoping review. *Ann Emerg Med*. 2020;75:181. [PMID: 31959308]

intoxication, alcohol withdrawal, and several alcohol-induced mental disorders. The ICD-11 includes a new category: hazardous alcohol use. Categorized as a risk factor, hazardous alcohol use is a pattern of alcohol use that appreciably increases the risk of physical or mental health harmful consequence to the user.

Underdiagnosis and undertreatment of alcohol misuse is substantial, both because of patient denial and lack of detection of clinical clues.

As with cigarette use, clinician identification and counseling about unhealthy alcohol use are essential. The USPSTF recommends screening adults aged 18 years and older for unhealthy alcohol use. The National Institute on Alcohol Abuse and Alcoholism recommends the following single-question screening test (validated in primary care settings): "How many times in the past year have you had X or more drinks in a day?" (X is 5 for men and 4 for women, and a response of more than 1 time is considered positive.)

Those who screen positive on the single-item questionnaire should complete the Alcohol Use Disorder Identification Test (AUDIT), which consists of questions on the quantity and frequency of alcohol consumption, on alcohol dependence symptoms, and on alcohol-related problems (Table 1–6).

## PREVENTION OF SUBSTANCE USE DISORDER: ALCOHOL & ILLICIT DRUGS

Unhealthy alcohol use is a major public health problem in the United States, where approximately 51% of adults 18 years and older are current regular drinkers (at least 12 drinks in the past year). The 2015–2020 US Dietary Guidelines for Americans recommends that if alcohol is consumed, it should be consumed in moderation—up to one drink per day for women and two drinks per day for men—and only by adults of legal drinking age. The spectrum of alcohol use disorders includes alcohol dependence, harmful pattern use of alcohol, and entities such as alcohol

**Table 1–6.** Screening for alcohol abuse using the Alcohol Use Disorder Identification Test (AUDIT).

| (Scores for response categories are given in parentheses. Scores range from 0 to 40, with a cutoff score of 5 or more indicating hazardous drinking, harmful drinking, or alcohol dependence.) |                       |                                   |                               |                               |
|--|-----------------------|-----------------------------------|-------------------------------|-------------------------------|
| <b>1. How often do you have a drink containing alcohol?</b>  |                       |                                   |                               |                               |
| (0) Never  | (1) Monthly or less   | (2) Two to four times a month     | (3) Two or three times a week | (4) Four or more times a week |
| <b>2. How many drinks containing alcohol do you have on a typical day when you are drinking?</b>   |                       |                                   |                               |                               |
| (0) 1 or 2   | (1) 3 or 4            | (2) 5 or 6                        | (3) 7 to 9                    | (4) 10 or more                |
| <b>3. How often do you have six or more drinks on one occasion?</b>  |                       |                                   |                               |                               |
| (0) Never  | (1) Less than monthly | (2) Monthly                       | (3) Weekly                    | (4) Daily or almost daily     |
| <b>4. How often during the past year have you found that you were not able to stop drinking once you had started?</b>  |                       |                                   |                               |                               |
| (0) Never  | (1) Less than monthly | (2) Monthly                       | (3) Weekly                    | (4) Daily or almost daily     |
| <b>5. How often during the past year have you failed to do what was normally expected of you because of drinking?</b>  |                       |                                   |                               |                               |
| (0) Never  | (1) Less than monthly | (2) Monthly                       | (3) Weekly                    | (4) Daily or almost daily     |
| <b>6. How often during the past year have you needed a first drink in the morning to get yourself going after a heavy drinking session?</b>  |                       |                                   |                               |                               |
| (0) Never  | (1) Less than monthly | (2) Monthly                       | (3) Weekly                    | (4) Daily or almost daily     |
| <b>7. How often during the past year have you had a feeling of guilt or remorse after drinking?</b>  |                       |                                   |                               |                               |
| (0) Never  | (1) Less than monthly | (2) Monthly                       | (3) Weekly                    | (4) Daily or almost daily     |
| <b>8. How often during the past year have you been unable to remember what happened the night before because you had been drinking?</b>  |                       |                                   |                               |                               |
| (0) Never  | (1) Less than monthly | (2) Monthly                       | (3) Weekly                    | (4) Daily or almost daily     |
| <b>9. Have you or has someone else been injured as a result of your drinking?</b>  |                       |                                   |                               |                               |
| (0) No   |                       | (2) Yes, but not in the past year |                               | (4) Yes, during the past year |
| <b>10. Has a relative or friend or a doctor or other health worker been concerned about your drinking or suggested you cut down?</b>   |                       |                                   |                               |                               |
| (0) No   |                       | (2) Yes, but not in the past year |                               | (4) Yes, during the past year |

Adapted, with permission, from Babor TF, Higgins-Biddle JC, Saunders JB, Montiero MG. AUDIT. *The Alcohol Use Disorders Identification Test. Guidelines for Use in Primary Health Care*, 2nd ed. Geneva, Switzerland: World Health Organization; 2001.

Clinicians should provide those who screen positive for hazardous or risky drinking with brief behavioral counseling interventions to reduce alcohol misuse. Use of screening procedures and brief intervention methods (see Chapter 25) can produce a 10–30% reduction in long-term alcohol use and alcohol-related problems. Those whose AUDIT scores suggest alcohol use disorder (AUDIT > 12) should undergo more extensive evaluation and potential referral for treatment.

Several pharmacologic agents are effective in reducing alcohol consumption.

Prescription and nonprescription opioid-based drug abuse, misuse, and overdose has reached epidemic proportions in the United States. Deaths due to opioid overdose have dramatically increased. Opioid risk mitigation strategies include use of risk assessment tools, treatment agreements (contracts), and urine drug testing. Additional strategies include establishing and strengthening prescription drug monitoring programs, regulating pain management facilities, and establishing dosage thresholds requiring consultation with pain specialists. Medication-assisted treatment, the use of medications with counseling and behavioral therapy, is effective in the prevention of opioid overdose and substance abuse disorders. Methadone, buprenorphine, and naltrexone are FDA approved for use in medication-assisted treatment. Buprenorphine has potential as a medication to ameliorate the symptoms and signs of withdrawal from opioids and is effective in reducing concomitant cocaine and opioid abuse. The risk of overdose is lower with buprenorphine than methadone, and it is preferred for patients at high risk for methadone toxicity (see Chapter 5). The FDA supports greater access to naloxone and is currently exploring options to make naloxone more available to treat opioid overdose. (See Chapter 5.)

Use of illegal drugs—including cocaine, methamphetamine, and so-called designer drugs—either sporadically

or episodically remains an important problem. Lifetime prevalence of drug abuse is approximately 8% and is generally greater among men, young and unmarried individuals, Native Americans, and those of lower socioeconomic status. As with alcohol, drug abuse disorders often coexist with personality disorders, anxiety disorders, and other substance abuse disorders. Abuse of anabolic-androgenic steroids has been associated with use of other illicit drugs, alcohol, and cigarettes and with violence and criminal behavior.

Clinical aspects of substance abuse are discussed in Chapter 25.

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# Common Symptoms

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2

## COUGH



### ESSENTIAL INQUIRIES

- ▶ Age, occupational history, environmental exposures, risk of coronavirus disease 2019 (COVID-19) (see Chapter 32), and duration of cough.
- ▶ Use of tobacco, cannabis, e-cigarettes (vaping).
- ▶ Dyspnea (at rest or with exertion).
- ▶ Vital signs (heart rate, respiratory rate, body temperature); pulse oximetry.
- ▶ Chest examination.
- ▶ Chest radiography, especially when unexplained cough lasts longer than 3–6 weeks.

### ► General Considerations

Cough is the most common symptom for which patients seek medical attention. Cough adversely affects personal and work-related interactions, disrupts sleep, and often causes discomfort of the throat and chest wall. Most people seeking medical attention for acute cough desire symptom relief; few are worried about serious illness. Cough results from stimulation of mechanical or chemical afferent nerve receptors in the bronchial tree. Effective cough depends on an intact afferent-efferent reflex arc, adequate expiratory and chest wall muscle strength, and normal mucociliary production and clearance.

### ► Clinical Findings

#### A. Symptoms

Distinguishing **acute** (less than 3 weeks), **persistent** (3–8 weeks), and **chronic** (more than 8 weeks) cough illness syndromes is a useful first step in evaluation. Postinfectious cough lasting 3–8 weeks has also been referred to as **subacute** cough to distinguish this common, distinct clinical entity from acute and chronic cough.

**1. Acute cough**—In healthy adults, most acute cough syndromes are due to viral respiratory tract infections.

Additional features of infection such as fever, nasal congestion, and sore throat help confirm this diagnosis. Dyspnea (at rest or with exertion) may reflect a more serious condition, and further evaluation should include assessment of oxygenation (pulse oximetry or arterial blood gas measurement), airflow (peak flow or spirometry), and pulmonary parenchymal disease (chest radiography). The timing and character of the cough are not very useful in establishing the cause of acute cough syndromes, although cough-variant asthma should be considered in adults with prominent nocturnal cough, and persistent cough with phlegm increases the likelihood of chronic obstructive pulmonary disease (COPD). The presence of posttussive emesis or inspiratory whoop in adults modestly increases the likelihood of pertussis, and the absence of paroxysmal cough and the presence of fever decrease its likelihood. Uncommon causes of acute cough should be suspected in those with heart disease (heart failure [HF]) or hay fever (allergic rhinitis) and those with occupational risk factors (such as farmworkers).

**2. Persistent and chronic cough**—Cough due to acute respiratory tract infection resolves within 3 weeks in the vast majority (more than 90%) of patients. Pertussis should be considered in adolescents and adults who have persistent or severe cough lasting more than 3 weeks, who have not recently been boosted with Tdap, and who have been exposed to a person with confirmed pertussis. It should also be considered in selected geographic areas where its prevalence approaches 20% (although its exact prevalence is difficult to ascertain due to the limited sensitivity of diagnostic tests).

When angiotensin-converting enzyme (ACE) inhibitor therapy, acute respiratory tract infection, and chest radiograph abnormalities are absent, most cases of persistent and chronic cough are due to (or exacerbated by) postnasal drip (upper airway cough syndrome), asthma, or gastroesophageal reflux disease (GERD), or some combination of these three entities. Approximately 10% of cases are caused by nonasthmatic eosinophilic bronchitis. A history of nasal or sinus congestion, wheezing, or heartburn should direct subsequent evaluation and treatment, though these conditions frequently cause persistent cough in the absence of typical symptoms. Dyspnea at rest or with exertion is not commonly reported among patients with persistent cough;

dyspnea requires assessment for chronic lung disease, HF, anemia, pulmonary embolism, or pulmonary hypertension.

Bronchogenic carcinoma is suspected when cough is accompanied by unexplained weight loss, hemoptysis, and fevers with night sweats, particularly in persons with significant tobacco or occupational exposures (asbestos, radon, diesel exhaust, and metals). Persistent and chronic cough accompanied by excessive mucus secretions increases the likelihood of COPD, particularly among smokers, or of bronchiectasis if accompanied by a history of recurrent or complicated pneumonia; chest radiographs are helpful in diagnosis. Chronic cough with dry eyes may represent Sjögren syndrome. A chronic dry cough may be the first symptom of idiopathic pulmonary fibrosis.

## B. Physical Examination

Examination can direct subsequent diagnostic testing for acute cough. Pneumonia is suspected when acute cough is accompanied by vital sign abnormalities (tachycardia, tachypnea, fever). Findings suggestive of airspace consolidation (crackles, decreased breath sounds, fremitus, egophony) are significant predictors of community-acquired pneumonia but are present in a minority of cases. Purulent sputum is associated with bacterial infections in patients with structural lung disease (eg, COPD, cystic fibrosis), but it is a poor predictor of pneumonia in the otherwise healthy adult. Wheezing and rhonchi are frequent findings in adults with acute bronchitis and do not indicate consolidation or adult-onset asthma in most cases.

Examination of patients with persistent cough should look for evidence of chronic sinusitis, contributing to postnasal drip syndrome or asthma. Physical examination may help distinguish COPD from HF. In patients with cough and dyspnea, a normal match test (ability to blow out a match from 25 cm away) and maximum laryngeal height greater than 4 cm (measured from the sternal notch to the cricoid cartilage at end expiration) substantially decrease the likelihood of COPD. Similarly, normal jugular venous pressure and no hepatojugular reflux decrease the likelihood of biventricular HF.

## C. Diagnostic Studies

**1. Acute cough**—Chest radiography should be considered for any adult with acute cough whose vital signs are abnormal or whose chest examination suggests pneumonia. The relationship between specific clinical findings and the probability of pneumonia is shown in Table 2–1. A large, multicenter randomized clinical trial found that elevated serum C-reactive protein (levels greater than 30 mg/dL) improves diagnostic accuracy of clinical prediction rules for pneumonia in adults with acute cough; serum procalcitonin had only marginal utility. A meta-analysis found that lung ultrasonography had better accuracy than chest radiography for the diagnosis of adult community-acquired pneumonia. Lung ultrasonography had a pooled sensitivity of 0.95 (95% confidence interval [CI], 0.93–0.97) and a specificity of 0.90 (95% CI, 0.86–0.94). Chest radiography had a pooled sensitivity of 0.77 (95% CI, 0.73–0.80) and a specificity of 0.91 (95% CI, 0.87–0.94).

**Table 2–1.** Positive and negative likelihood ratios for history, physical examination, and laboratory findings in the diagnosis of pneumonia.

| Finding   | Positive Likelihood Ratio | Negative Likelihood Ratio |
|---|---------------------------|---------------------------|
| <b>Medical history</b>  |                           |                           |
| Fever   | 1.7–2.1                   | 0.6–0.7                   |
| Chills  | 1.3–1.7                   | 0.7–0.9                   |
| <b>Physical examination</b>   |                           |                           |
| Tachypnea (RR > 25 breaths/min)   | 1.5–3.4                   | 0.8                       |
| Tachycardia (> 100 beats/min in two studies or > 120 beats/min in one study)  | 1.6–2.3                   | 0.5–0.7                   |
| Hyperthermia (> 37.8°C)   | 1.4–4.4                   | 0.6–0.8                   |
| <b>Chest examination</b>  |                           |                           |
| Dullness to percussion  | 2.2–4.3                   | 0.8–0.9                   |
| Decreased breath sounds   | 2.3–2.5                   | 0.6–0.8                   |
| Crackles  | 1.6–2.7                   | 0.6–0.9                   |
| Rhonchi   | 1.4–1.5                   | 0.8–0.9                   |
| Egophony  | 2.0–8.6                   | 0.8–1.0                   |
| <b>Laboratory findings</b>  |                           |                           |
| Leukocytosis (> 11,000/mcL [ $11 \times 10^9/L$ ] in one study or $\geq 10,400/\text{mCL}$ [ $10.4 \times 10^9/L$ ] in another study) | 1.9–3.7                   | 0.3–0.6                   |

RR, respiratory rate.

In patients with dyspnea, pulse oximetry and peak flow help exclude hypoxemia or obstructive airway disease. However, a normal pulse oximetry value (eg, greater than 93%) does not rule out a significant alveolar-arterial (A-a) gradient when patients have effective respiratory compensation. During documented outbreaks, clinical diagnosis of influenza has a positive predictive value of ~70%; this usually obviates the need for rapid diagnostic tests. The initial evaluation of cough in immunocompromised patients is generally similar to that in immunocompetent patients with notable exceptions. For example, tuberculosis must be considered in HIV-infected patients with unexplained cough in areas with a high prevalence of tuberculosis regardless of radiographic findings.

**2. Persistent and chronic cough**—Chest radiography is indicated when ACE inhibitor therapy-related and postinfectious cough are excluded. If pertussis is suspected, polymerase chain reaction testing should be performed on a nasopharyngeal swab or nasal wash specimen—although the ability to detect pertussis decreases as the duration of cough increases. When the chest film is normal, postnasal drip, asthma, or GERD are the most likely causes. The presence of typical symptoms of these conditions directs further evaluation or empiric therapy, though typical symptoms are

**Table 2–2.** Empiric therapy or definitive testing for persistent cough.

| Suspected Condition | Step 1 (Empiric Therapy)  | Step 2 (Definitive Testing)                           |
|---------------------|---|---|
| Postnasal drip      | Therapy for allergy or chronic sinusitis                                | Sinus CT scan; ENT referral                           |
| Asthma              | Beta-2-agonist  | Spirometry; consider methacholine challenge if normal |
| GERD                | Lifestyle and diet modifications with or without proton pump inhibitors | Esophageal pH monitoring                              |

ENT, ear, nose, and throat; GERD, gastroesophageal reflux disease.

often absent. Definitive tests for determining the presence of each are available (Table 2–2). However, empiric treatment with a maximum-strength regimen for postnasal drip, asthma, or GERD for 2–4 weeks is one recommended approach since documenting the presence of postnasal drip, asthma, or GERD does not mean they are the cause of the cough. Alternative approaches to identifying patients who have asthma with its corticosteroid-responsive cough include examining induced sputum for increased eosinophil counts (greater than 3%) or providing an empiric trial of prednisone, 30 mg daily orally for 2 weeks.

Nonasthmatic eosinophilic bronchitis can be diagnosed with induced sputum analysis after the exclusion of other causes for chronic cough by clinical, radiologic, and lung function assessment. The cough usually responds well to inhaled corticosteroids.

Spirometry may help measure large airway obstruction in patients who have persistent cough and wheezing and who are not responding to asthma treatment. When empiric treatment trials are not successful, additional evaluation with pH manometry, endoscopy, barium swallow, sinus CT, or high-resolution chest CT may identify the cause.

## Differential Diagnosis

### A. Acute Cough

Acute cough may be a symptom of acute respiratory tract infection, COVID-19, asthma, allergic rhinitis, HF, and ACE inhibitor therapy, as well as many less common causes.

### B. Persistent and Chronic Cough

Causes of persistent cough include environmental exposures (cigarette smoke, air pollution), occupational exposures, pertussis, postnasal drip, asthma (including cough-variant asthma), GERD, COPD, chronic aspiration, bronchiectasis, eosinophilic bronchitis, tuberculosis or other chronic infection, interstitial lung disease, and bronchogenic carcinoma. COPD is a common cause of persistent cough among patients older than 50 years. Persistent cough may also be due to somatic cough syndrome (previously called “psychogenic cough”) or tic cough (previously called “habit cough”), or vocal fold dysfunction.

## Treatment

### A. Acute Cough

Treatment of acute cough should target the underlying etiology of the illness, the cough reflex itself, and any additional factors that exacerbate the cough. Cough duration is typically 1–3 weeks, yet patients frequently expect cough to last fewer than 10 days. Limited studies on the use of dextromethorphan suggest a minor or modest benefit.

When influenza is diagnosed (including H1N1 influenza), oral oseltamivir or zanamivir or intravenous peramivir are equally effective (1 less day of illness) when initiated within 30–48 hours of illness onset; treatment is recommended regardless of illness duration when patients have severe, complicated, or progressive influenza and in patients requiring hospitalization. In *Chlamydophila-* or *Mycoplasma*-documented infection or outbreaks, first-line antibiotics include erythromycin or doxycycline. Antibiotics do not improve cough severity or duration in patients with uncomplicated acute bronchitis. In patients with bronchitis and wheezing, inhaled beta-2-agonist therapy reduces severity and duration of cough. In patients with acute cough, treating the accompanying postnasal drip (with antihistamines, decongestants, saline nasal irrigation, or nasal corticosteroids) can be helpful. A Cochrane review ( $n = 163$ ) found codeine to be no more effective than placebo in reducing cough symptoms.

### B. Persistent and Chronic Cough

Evaluation and management of persistent cough often require multiple visits and therapeutic trials, which frequently lead to frustration, anger, and anxiety. When pertussis infection is suspected early in its course, treatment with a macrolide antibiotic (see Chapter 33) is appropriate to reduce organism shedding and transmission. When pertussis has lasted more than 7–10 days, antibiotic treatment does not affect the duration of cough, which can last up to 6 months. Early identification, revaccination with Tdap, and treatment are encouraged for adult patients who work or live with persons at high risk for complications from pertussis (pregnant women, infants [particularly younger than 1 year], and immunosuppressed individuals).

Table 2–2 outlines empiric treatments for persistent cough. There is no evidence to guide how long to continue treatment for persistent cough due to postnasal drip, asthma, or GERD. Studies have not found a consistent benefit of inhaled corticosteroid therapy in adults with persistent cough. Azithromycin three times a week for 8 weeks did not improve cough in patients without asthma.

When empiric treatment trials fail, consider other causes of chronic cough such as obstructive sleep apnea, tonsillar or uvular enlargement, and environmental fungi. The small percentage of patients with idiopathic chronic cough should be managed in consultation with an otolaryngologist or a pulmonologist; consider a high-resolution CT scan of the lungs. Treatment options include nebulized lidocaine therapy and morphine sulfate, 5–10 mg orally twice daily. Sensory dysfunction of the laryngeal branches of the vagus nerve may contribute to persistent cough syndromes and may help explain the effectiveness of

gabapentin in patients with chronic cough. Baclofen may have similar neuromodulatory action and benefit as gabapentin.

Speech pathology therapy combined with pregabalin has some benefit in chronic refractory cough. In patients with reflex cough syndrome, therapy aimed at shifting the patient's attentional focus from internal stimuli to external focal points can be helpful. Proton pump inhibitors are not effective on their own; most benefit appears to come from lifestyle modifications and weight reduction.

### ► When to Refer

- Failure to control persistent or chronic cough following empiric treatment trials.
- Patients with recurrent symptoms should be referred to an otolaryngologist, pulmonologist, or gastroenterologist.

### ► When to Admit

- Patient at high risk for tuberculosis for whom compliance with respiratory precautions is uncertain.
- Need for urgent bronchoscopy, such as suspected foreign body.
- Smoke or toxic fume inhalational injury.
- Gas exchanged is impaired by cough.
- Patients at high risk for barotrauma (eg, recent pneumothorax).

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## DYSPNEA



### ESSENTIAL INQUIRIES

- Fever, cough, risk of COVID-19 (see Chapter 32), and chest pain.
- Vital sign measurements; pulse oximetry.
- Cardiac and chest examination.
- Chest radiography and arterial blood gas measurement in selected patients.

### ► General Considerations

Dyspnea is a subjective experience or perception of uncomfortable breathing. There is a lack of empiric evidence on

the prevalence, etiology, and prognosis of dyspnea in general practice. The relationship between level of dyspnea and the severity of underlying disease varies widely among individuals. Dyspnea can result from conditions that increase the mechanical effort of breathing (eg, asthma, COPD, restrictive lung disease, respiratory muscle weakness), conditions that produce compensatory tachypnea (eg, hypoxemia, acidosis), primary pulmonary vasculopathy (pulmonary hypertension), or psychogenic conditions. The following factors play a role in how and when dyspnea presents in patients: rate of onset, previous dyspnea, medications, comorbidities, psychological profile, and severity of underlying disorder.

### ► Clinical Findings

#### A. Symptoms

The duration, severity, and periodicity of dyspnea influence the tempo of the clinical evaluation. Rapid onset or severe dyspnea in the absence of other clinical features should raise concern for pneumothorax, pulmonary embolism, or increased left ventricular end-diastolic pressure (LVEDP). Spontaneous pneumothorax is usually accompanied by chest pain and occurs most often in thin, young males and in those with underlying lung disease. Pulmonary embolism should always be suspected when a patient with new dyspnea reports a recent history (previous 4 weeks) of prolonged immobilization or surgery, estrogen therapy, or other risk factors for deep venous thrombosis (DVT) (eg, previous history of thromboembolism, cancer, obesity, lower extremity trauma) and when the cause of dyspnea is not apparent. Silent myocardial infarction, which occurs more frequently in diabetic persons and women, can result in increased LVEDP, acute HF, and dyspnea.

Accompanying symptoms provide important clues to causes of dyspnea. When cough and fever are present, pulmonary disease (particularly infection) is the primary concern; myocarditis, pericarditis, and septic emboli can present in this manner. Chest pain should be further characterized as acute or chronic, pleuritic or exertional. Although acute pleuritic chest pain is the rule in acute pericarditis and pneumothorax, most patients with pleuritic chest pain in the outpatient clinic have pleurisy due to acute viral respiratory tract infection. Periodic chest pain that precedes the onset of dyspnea suggests myocardial ischemia or pulmonary embolism. When associated with wheezing, most cases of dyspnea are due to acute bronchitis; however, other causes include new-onset asthma, foreign body, and vocal fold dysfunction. Interstitial lung disease and pulmonary hypertension should be considered in patients with symptoms (or history) of connective tissue disease. Pulmonary lymphangitic carcinomatosis should be considered if a patient has a malignancy, especially breast, lung, or gastric cancer.

When a patient reports prominent dyspnea with mild or no accompanying features, consider noncardiopulmonary causes of impaired oxygen delivery (anemia, methemoglobinemia, cyanide ingestion, carbon monoxide poisoning), metabolic acidosis, panic disorder, neuromuscular disorders, and chronic pulmonary embolism.

Platypnea-orthodeoxia syndrome is characterized by dyspnea and hypoxemia on sitting or standing that improves in the recumbent position. It may be caused by an intracardiac shunt, pulmonary vascular shunt (including hepatopulmonary syndrome), or ventilation-perfusion mismatch. Hyperthyroidism can cause dyspnea from increased ventilatory drive, respiratory muscle weakness, or pulmonary hypertension. Patients in whom moderate to severe SARS-CoV-2 disease develops, there is typically 4–10 days of upper respiratory infection symptoms followed by a precipitous increase in dyspnea.

### B. Physical Examination

A focused physical examination should include evaluation of the head and neck, chest, heart, and lower extremities. Visual inspection of the patient can suggest obstructive airway disease (pursed-lip breathing, use of accessory respiratory muscles, barrel-shaped chest), pneumothorax (asymmetric excursion), or metabolic acidosis (Kussmaul respirations). Patients with impending upper airway obstruction (eg, epiglottitis, foreign body) or severe asthma exacerbation sometimes assume a tripod position. Focal wheezing raises the suspicion for a foreign body or other bronchial obstruction. Maximum laryngeal height (the distance between the top of the thyroid cartilage and the suprasternal notch at end expiration) is a measure of hyperinflation. Obstructive airway disease is virtually nonexistent when a nonsmoking patient younger than age 45 years has a maximum laryngeal height greater than 4 cm.

Factors increasing the likelihood of obstructive airway disease include patient history of more than 40 pack-years smoking (adjusted likelihood ratio [LR]+ 11.6; LR- 0.9), patient age 45 years or older (LR+ 1.4; LR- 0.5), and maximum laryngeal height greater than or equal to 4 cm (LR+ 3.6; LR- 0.7). With all three of these factors present, the LR+ rises to 58.5 and the LR- falls to 0.3.

Absent breath sounds suggest a pneumothorax. An accentuated pulmonic component of the second heart sound (loud P<sub>2</sub>) is a sign of pulmonary hypertension and pulmonary embolism.

Clinical predictors of increased LVEDP in dyspneic patients with no prior history of HF include tachycardia, systolic hypotension, jugular venous distention, hepatojugular reflux, bibasilar crackles, third heart sound, lower extremity edema, and chest film findings of pulmonary vascular redistribution or cardiomegaly. When none is present, there is a very low probability (less than 10%) of increased LVEDP, but when two or more are present, there is a very high probability (greater than 90%) of increased LVEDP.

### C. Diagnostic Studies

Causes of dyspnea that can be managed without chest radiography are few: anemia, carbon monoxide poisoning, and ingestions causing lactic acidosis and methemoglobinemia. The diagnosis of pneumonia should be confirmed by chest radiography in most patients, and elevated blood levels of procalcitonin or C-reactive protein can support the diagnosis of pneumonia in equivocal cases or in the presence of interstitial lung disease. Conversely, a low procalcitonin

can help exclude pneumonia in dyspneic patients presenting with HF.

Chest radiography is fairly sensitive and specific for new-onset HF (represented by redistribution of pulmonary venous circulation) and can help guide treatment of patients with other cardiac diseases. NT-proBNP can assist in the diagnosis of HF.

Lung ultrasonography is superior to chest radiography in detecting pulmonary edema due to acute decompensated HF among adult patients presenting with dyspnea and in the diagnosis of pneumonia in patients admitted to an acute geriatric ward. End-expiratory chest radiography enhances detection of small pneumothoraces.

A normal chest radiograph has substantial diagnostic value. When there is no physical examination evidence of COPD or HF and the chest radiograph is normal, the major remaining causes of dyspnea include pulmonary embolism, *Pneumocystis jirovecii* infection (the initial radiograph may be normal in up to 25%), upper airway obstruction, foreign body, anemia, and metabolic acidosis. If a patient has tachycardia and hypoxemia but a normal chest radiograph and electrocardiogram (ECG), then tests to exclude pulmonary emboli, anemia, or metabolic acidosis are warranted. High-resolution chest CT is particularly useful in the evaluation of interstitial and alveolar lung disease. Helical ("spiral") CT is useful to diagnose pulmonary embolism since the images are high resolution and require only one breathhold by the patient, but to minimize unnecessary testing and radiation exposure, the clinician should first consider a clinical decision rule (with or without D-dimer testing) to estimate the pretest probability of a pulmonary embolism. It is appropriate to forego CT scanning in patients with very low probability of pulmonary embolus when other causes of dyspnea are more likely (see Chapter 9).

Laboratory findings suggesting increased LVEDP include elevated serum B-type natriuretic peptide (BNP or NT-proBNP) levels. BNP has been shown to reliably diagnose severe dyspnea caused by HF and to differentiate it from dyspnea due to other conditions.

Arterial blood gas measurement may be considered if clinical examination and routine diagnostic testing are equivocal. With two notable exceptions (carbon monoxide poisoning and cyanide toxicity), arterial blood gas measurement distinguishes increased mechanical effort causes of dyspnea (respiratory acidosis with or without hypoxemia) from compensatory tachypnea (respiratory alkalosis with or without hypoxemia or metabolic acidosis) and from psychogenic dyspnea (respiratory alkalosis). Carbon monoxide and cyanide impair oxygen delivery with minimal alterations in Po<sub>2</sub>; percent carboxyhemoglobin identifies carbon monoxide toxicity. Cyanide poisoning should be considered in a patient with profound lactic acidosis following exposure to burning vinyl (such as a theater fire or industrial accident). Suspected carbon monoxide poisoning or methemoglobinemia can also be confirmed with venous carboxyhemoglobin or methemoglobin levels. Venous blood gas testing is also an option for assessing acid-base and respiratory status by measuring venous pH and PCO<sub>2</sub> but is unable to provide information on oxygenation status. To correlate with arterial blood gas values,

venous pH is typically 0.03–0.05 units lower, and venous  $\text{PCO}_2$  is typically 4–5 mm Hg higher than arterial samples.

Because arterial blood gas testing is impractical in most outpatient settings, **pulse oximetry** has assumed a central role in the office evaluation of dyspnea. Oxygen saturation values above 96% almost always correspond with a  $\text{Po}_2$  greater than 70 mm Hg, whereas values less than 94% may represent clinically significant hypoxemia. Important exceptions to this rule include carbon monoxide toxicity, which leads to a normal oxygen saturation (due to the similar wavelengths of oxyhemoglobin and carboxyhemoglobin), and methemoglobinemia, which results in an oxygen saturation of about 85% that fails to increase with supplemental oxygen. A delirious or obtunded patient with obstructive lung disease warrants immediate measurement of arterial blood gases to exclude hypercapnia and the need for intubation, regardless of the oxygen saturation. If a patient reports dyspnea with exertion, but resting oximetry is normal, assessment of desaturation with ambulation (eg, a brisk walk around the clinic) can be useful for confirming impaired gas exchange. Persons with COVID-19 may have low oxygen saturation with minimal dyspnea and profound desaturation with minimal exertion.

A study found that for adults without known cardiac or pulmonary disease reporting dyspnea on exertion, spirometry, NT-proBNP, and CT imaging were the most informative tests.

Episodic dyspnea can be challenging if an evaluation cannot be performed during symptoms. Life-threatening causes include recurrent pulmonary embolism, myocardial ischemia, and reactive airway disease. When associated with audible wheezing, vocal fold dysfunction should be considered, particularly in a young woman who does not respond to asthma therapy. Spirometry is very helpful in further classifying patients with obstructive airway disease but is rarely needed in the initial or emergent evaluation of patients with acute dyspnea.

## Differential Diagnosis

Urgent and emergent conditions causing acute dyspnea include pneumonia, COPD, asthma, pneumothorax, pulmonary embolism, cardiac disease (eg, HF, acute myocardial infarction, valvular dysfunction, arrhythmia, intracardiac shunt), pleural effusion, COVID-19, diffuse alveolar hemorrhage, metabolic acidosis, cyanide toxicity, methemoglobinemia, and carbon monoxide poisoning. Chronic dyspnea may be caused by interstitial lung disease, pulmonary hypertension, or pulmonary alveolar proteinosis.

## Treatment

The treatment of urgent or emergent causes of dyspnea should aim to relieve the underlying cause. Pending diagnosis, patients with hypoxemia should be immediately provided supplemental oxygen unless significant hypercapnia is present or strongly suspected pending arterial blood gas measurement. Dyspnea frequently occurs in patients nearing the end of life. Opioid therapy, anxiolytics, and corticosteroids can provide substantial relief independent of the severity of hypoxemia. However, inhaled opioids are not effective.

Oxygen therapy is most beneficial to patients with significant hypoxemia ( $\text{PaO}_2$  less than 55 mm Hg) (see Chapter 5). In patients with severe COPD and hypoxemia, oxygen therapy improves exercise performance and mortality. Pulmonary rehabilitation programs are another therapeutic option for patients with moderate to severe COPD or interstitial pulmonary fibrosis. In patients with respiratory muscle weakness post stroke, high-intensity home-based training of respiratory muscles may improve their strength and endurance and reduce dyspnea. Noninvasive ventilation may be considered for patients with dyspnea caused by an acute COPD exacerbation.

## When to Refer

- Following acute stabilization, patients with advanced COPD should be referred to a pulmonologist, and patients with HF or valvular heart disease should be referred to a cardiologist.
- Cyanide toxicity or carbon monoxide poisoning should be managed in conjunction with a toxicologist.
- Lung transplantation can be considered for patients with advanced interstitial lung disease.

## When to Admit

- Impaired gas exchange from any cause or high risk of pulmonary embolism pending definitive diagnosis.
- Suspected cyanide toxicity or carbon monoxide poisoning.

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## HEMOPTYSIS



### ESSENTIAL INQUIRIES

- Fever, cough, and other symptoms of lower respiratory tract infection.
- Smoking history.
- Nasopharyngeal or gastrointestinal bleeding.
- Chest radiography and complete blood count (and, in some cases, international normalized ratio [INR]).

## ► General Considerations

Hemoptysis is the expectoration of blood that originates below the vocal folds. It is commonly classified as trivial, mild, or massive—the latter defined as more than 200–600 mL (about 1–2 cups) in 24 hours. Massive hemoptysis can be usefully defined as any amount that is hemodynamically significant or threatens ventilation. Its in-hospital mortality was 6.5% in one study. The initial goal of management of massive hemoptysis is therapeutic, not diagnostic.

The causes of hemoptysis can be classified anatomically. Blood may arise from the trachea due to malignant invasion; from the airways in COPD, bronchiectasis, bronchial Dieulafoy disease, and bronchogenic carcinoma; from the pulmonary vasculature in left ventricular failure, mitral stenosis, pulmonary embolism, pulmonary arterial hypertension, telangiectasias, arteriovenous malformations, and multiple pulmonary artery aneurysms; from the systemic circulation in intralobar pulmonary sequestration, aortobronchial fistula; or from the pulmonary parenchyma in pneumonia, fungal infections, inhalation of crack cocaine, granulomatosis with polyangiitis, or Takayasu arteritis with pulmonary arteritis. Diffuse alveolar hemorrhage—manifested by alveolar infiltrates on chest radiography—is due to small vessel bleeding usually caused by autoimmune or hematologic disorders, or rarely precipitated by hypertensive emergency or warfarin therapy. Most cases of hemoptysis presenting in the outpatient setting are due to infection (eg, acute or chronic bronchitis, pneumonia, tuberculosis, aspergillosis). Hemoptysis due to lung cancer increases with age, causing up to 20% of cases among older adults. Pulmonary venous hypertension (eg, mitral stenosis, pulmonary embolism) causes hemoptysis in less than 10% of cases. Most cases of hemoptysis that have no visible cause on CT scan or bronchoscopy will resolve within 6 months without treatment, with the notable exception of patients at high risk for lung cancer (smokers older than 40 years). Iatrogenic hemorrhage may follow transbronchial lung biopsies, anticoagulation, or pulmonary artery rupture due to distal placement of a balloon-tipped catheter. Obstructive sleep apnea may be a risk factor for hemoptysis. Amyloidosis of the lung can cause hemoptysis, as can endometriosis. No cause is identified in up to 15–30% of cases.

## ► Clinical Findings

### A. Symptoms

Blood-tinged sputum in the setting of an upper respiratory tract infection in an otherwise healthy, young (age under 40 years) nonsmoker does not warrant an extensive diagnostic evaluation if the hemoptysis subsides with resolution of the infection. However, hemoptysis is frequently a sign of serious disease, especially in patients with a high prior probability of underlying pulmonary pathology. Hemoptysis is the only symptom found to be a specific predictor of lung cancer. There is no value in distinguishing blood-streaked sputum and cough productive of blood during evaluation; the goal of the history is to identify patients at risk for one of the disorders listed earlier. Pertinent features include duration of symptoms, presence of respiratory infection, and past or current tobacco use.

Nonpulmonary sources of hemorrhage—from the sinuses or the gastrointestinal tract—must be excluded.

### B. Physical Examination

Elevated pulse, hypotension, and decreased oxygen saturation suggest large-volume hemorrhage that warrants emergent evaluation and stabilization. The nares and oropharynx should be carefully inspected to identify a potential upper airway source of bleeding. Chest and cardiac examination may reveal evidence of HF or mitral stenosis.

### C. Diagnostic Studies

Diagnostic evaluation should include a chest radiograph and complete blood count. Kidney function tests, urinalysis, and coagulation studies are appropriate in specific circumstances. Hematuria that accompanies hemoptysis may be a clue to Goodpasture syndrome or vasculitis. Flexible bronchoscopy reveals endobronchial cancer in 3–6% of patients with hemoptysis who have a normal (non-lateralizing) chest radiograph. Nearly all these patients are smokers over the age of 40, and most will have had symptoms for more than 1 week. High-resolution chest CT scan complements bronchoscopy; it can visualize unsuspected bronchiectasis and arteriovenous malformations and will show central endobronchial cancers in many cases. It is the test of choice for suspected small peripheral malignancies. Helical pulmonary CT angiography (CTA) is the initial test of choice for evaluating patients with suspected pulmonary embolism, although caution should be taken to avoid large contrast loads in patients with even mild chronic kidney disease (serum creatinine greater than 2.0 g/dL or rapidly rising creatinine in normal range). Helical CT scanning can be avoided in patients who are at “unlikely” risk for pulmonary embolism using the Wells score or PERC rule for pulmonary embolism and the sensitive D-dimer test (see Chapter 9). Echocardiography may reveal evidence of HF or mitral stenosis.

### ► Treatment

Management of mild hemoptysis consists of identifying and treating the specific cause. Massive hemoptysis is life-threatening. The airway should be protected with endotracheal intubation, ventilation ensured, and effective circulation maintained. If the location of the bleeding site is known, the patient should be placed in the decubitus position with the involved lung dependent. Uncontrollable hemorrhage warrants rigid bronchoscopy and surgical consultation. In stable patients, flexible bronchoscopy may localize the site of bleeding, and angiography can embolize the involved bronchial arteries. Embolization is effective initially in 85% of cases, although rebleeding may occur in up to 20% of patients during the following year. The anterior spinal artery arises from the bronchial artery in up to 5% of people, and paraplegia may result if it is inadvertently cannulated and embolized.

One double-blind, randomized controlled trial compared treatment with inhalations of tranexamic acid (an antifibrinolytic drug) versus placebo (normal saline) in patients hospitalized with mild hemoptysis (less than 200 mL of expectorated blood per 24 hours). Compared to

patients receiving placebo (normal saline), more patients treated with tranexamic acid experienced resolution of hemoptysis within 5 days of admission (96% versus 50%;  $P < 0.0005$ ). In addition, mean hospital length of stay was shorter for the tranexamic acid group, and fewer patients required invasive procedures (interventional bronchoscopy, angiographic embolization) to control the hemorrhage. Another randomized study found that compared to the control group, patients given tranexamic acid on admission had significantly lower in-hospital mortality (11.5% versus 9.0%).

### ► When to Refer

- Patients should be referred to a pulmonologist when bronchoscopy of the lower respiratory tract is needed.
- Patients should be referred to an otolaryngologist when an upper respiratory tract bleeding source is identified.
- Patients with severe coagulopathy complicating management should be referred to a hematologist.

### ► When to Admit

- To stabilize bleeding process in patients at risk for or experiencing massive hemoptysis.
- To correct disordered coagulation (using clotting factors or platelets, or both) or to reverse anticoagulation.
- To stabilize gas exchange.

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## CHEST PAIN



### ESSENTIAL INQUIRIES

- Pain onset, character, location/size, duration, periodicity, and exacerbators; shortness of breath.
- Vital signs; chest and cardiac examinations.
- Electrocardiography and biomarkers of myocardial necrosis in selected patients.

### ► General Considerations

Chest pain (or chest discomfort) can occur as a result of cardiovascular, pulmonary, pleural, or musculoskeletal disease; esophageal or other gastrointestinal disorders; herpes zoster; cocaine use; or anxiety states. The frequency

and distribution of life-threatening causes of chest pain, such as acute coronary syndrome (ACS), pericarditis, aortic dissection, vasospastic angina, pulmonary embolism, pneumonia, and esophageal perforation, vary substantially between clinical settings.

Systemic lupus erythematosus, rheumatoid arthritis, reduced estimated glomerular filtration rate, and HIV infection are conditions that confer a strong risk of coronary artery disease. Precocious ACS may represent acute thrombosis independent of underlying atherosclerotic disease. In patients aged 35 years or younger, risk factors for ACS are obesity, hyperlipidemia, and smoking.

Chest pain characteristics that can lead to early diagnosis of acute myocardial infarction do not differ in frequency or strength of association between men and women. Because pulmonary embolism can present with a wide variety of symptoms, consideration of the diagnosis and rigorous risk factor assessment for venous thromboembolism (VTE) is critical. Classic VTE risk factors include cancer, trauma, recent surgery, prolonged immobilization, pregnancy, oral contraceptives, and family history and prior history of VTE. Other conditions associated with increased risk of pulmonary embolism include HF and COPD. Sickle cell anemia can cause acute chest syndrome. Patients with this syndrome often have chest pain, fever, and cough.

### ► Clinical Findings

#### A. Symptoms

Myocardial ischemia is usually described as a dull, aching sensation of “pressure,” “tightness,” “squeezing,” or “gas,” rather than as sharp or spasmodic. Pain reaching maximum intensity in seconds is uncommon. Ischemic symptoms usually subside within 5–20 minutes but may last longer. Progressive symptoms or symptoms at rest may represent unstable angina. Prolonged chest pain episodes might represent myocardial infarction, although up to one-third of patients with acute myocardial infarction do not report chest pain. When present, pain due to myocardial ischemia is commonly accompanied by a sense of anxiety or uneasiness. The location is usually retrosternal or left precordial. Because the heart lacks somatic innervation, precise localization of pain due to cardiac ischemia is difficult; the pain is commonly referred to the throat, lower jaw, shoulders, inner arms, upper abdomen, or back. Ischemic pain may be precipitated or exacerbated by exertion, cold temperature, meals, stress, or combinations of these factors and is usually relieved by rest. However, many episodes do not conform to these patterns, and atypical presentations of ACS are more common in older adults, women, and persons with diabetes mellitus. Other symptoms that are associated with ACS include shortness of breath; dizziness; a feeling of impending doom; and vagal symptoms, such as nausea and diaphoresis. In older persons, fatigue is a common presenting complaint of ACS.

There are gender differences in the perception and presenting symptoms of young patients with acute myocardial infarction. Women were more likely than men to present with three or more associated symptoms (eg, epigastric symptoms, palpitations, and pain or discomfort in the jaw,

neck, arms, or between the shoulder blades; 61.9% for women versus 54.8% for men,  $P < 0.001$ ). In adjusted analyses, women with an ST-segment-elevation acute myocardial infarction were more likely than men to present without chest pain (odds ratio, 1.51; 95% CI, 1.03–2.22). In comparison with men, women were more likely to perceive symptoms as stress/anxiety (20.9% versus 11.8%,  $P < 0.001$ ) but less likely to attribute symptoms to muscle pain (15.4% versus 21.2%,  $P = 0.03$ ).

One analysis found the following clinical features to be associated with acute myocardial infarction: (1) from the history: chest pain that radiates to the left, right, or both arms (LR+ 2.3, 2.9, 7.1); diaphoresis (LR+ 2.0); and nausea and vomiting (LR+ 1.9); (2) from the physical examination: third heart sound (LR+ 3.2), systolic blood pressure less than or equal to 80 mm Hg (LR + 3.1), pulmonary crackles (LR+ 2.1); and (3) from the electrocardiogram: any ST-segment elevation greater than or equal to 1 mm (LR+ 11.2), any ST depression (LR+ 3.2), any Q wave (LR+ 3.9), any conduction defect (LR+ 2.7), and new conduction defect (LR+ 6.3).

A meta-analysis found the clinical findings and risk factors most suggestive of ACS were prior abnormal stress test (specificity, 96%; LR, 3.1 [95% CI, 2.0–4.7]), peripheral arterial disease (specificity, 97%; LR, 2.7 [95% CI, 1.5–4.8]), and pain radiation to both arms (specificity, 96%; LR, 2.6 [95% CI, 1.8–3.7]). The ECG findings associated with ACS were ST-segment depression (specificity, 95%; LR, 5.3 [95% CI, 2.1–8.6]) and any evidence of ischemia (specificity, 91%; LR, 3.6 [95% CI, 1.6–5.7]). Risk scores derived from both the History, Electrocardiogram, Age, Risk Factors, Troponin (HEART) trial and Thrombolysis in Myocardial Infarction (TIMI) trial performed well in detecting ACS (LR, 13 [95% CI, 7.0–24] for HEART score of 7–10, and LR, 6.8 [95% CI, 5.2–8.9] for TIMI score of 5–7).

Hypertrophy of either ventricle or aortic stenosis may also give rise to chest pain with less typical features. Pericarditis produces pain that may be greater when supine than upright and increases with breathing, coughing, or swallowing. Pleuritic chest pain is usually not ischemic, and pain on palpation may indicate a musculoskeletal cause. Aortic dissection classically produces an abrupt onset of tearing pain of great intensity that often radiates to the back; however, this classic presentation occurs in a small proportion of cases. Anterior aortic dissection can also lead to myocardial or cerebrovascular ischemia.

In pulmonary embolism, chest pain is present in about 75% of cases. The chief objective in evaluating patients with suspected pulmonary embolism is to assess the patient's clinical risk for VTE based on medical history and associated symptoms and signs (see above and Chapter 9). Rupture of the thoracic esophagus iatrogenically or secondary to vomiting is another cause of chest pain.

## B. Physical Examination

Findings on physical examination can occasionally yield important clues to the underlying cause of chest pain; however, a normal physical examination should never be used as the sole basis for ruling out most diagnoses, particularly ACS and aortic dissection. Vital signs (including pulse oximetry) and cardiopulmonary examination are always the first

steps for assessing the urgency and tempo of the subsequent examination and diagnostic workup. Although chest pain that is reproducible or worsened with palpation strongly suggests a musculoskeletal cause, up to 15% of patients with ACS will have reproducible chest wall tenderness. Pointing to the location of the pain with one finger has been shown to be highly correlated with nonischemic chest pain.

Aortic dissection can result in differential blood pressures (greater than 20 mm Hg), pulse amplitude deficits, and new diastolic murmurs. Although hypertension is considered the rule in patients with aortic dissection, systolic blood pressure less than 100 mm Hg is present in up to 25% of patients.

A cardiac friction rub represents pericarditis until proven otherwise. It can best be heard with the patient sitting forward at end-expiration. Tamponade should be excluded in all patients with a clinical diagnosis of pericarditis by assessing pulsus paradoxus (a decrease in systolic blood pressure greater than 10 mm Hg during inspiration) and inspection of jugular venous pulsations. Subcutaneous emphysema is common following cervical esophageal perforation but present in only about one-third of thoracic perforations (ie, those most commonly presenting with chest pain).

The absence of abnormal physical examination findings in patients with suspected pulmonary embolism usually serves to *increase* its likelihood, although a normal physical examination is also compatible with the much more common conditions of panic/anxiety disorder and musculoskeletal disease.

## C. Diagnostic Studies

Unless a competing diagnosis can be confirmed, an ECG is warranted in the initial evaluation of most patients with acute chest pain to help exclude ACS. In a study of 11 emergency departments in Italy, 67% of patients with confirmed ACS had new-onset alterations of the ECG (compared with only 6.2% among non-ACS patients). ST-segment elevation is the ECG finding that is the strongest predictor of acute myocardial infarction; however, up to 20% of patients with ACS can have a normal ECG.

In the emergency department, patients with suspected ACS can be safely removed from cardiac monitoring if they are pain-free at initial physician assessment and have a normal or nonspecific ECG. This decision rule had 100% sensitivity for serious arrhythmia (95% CI, 80–100%). Clinically stable patients with cardiovascular disease risk factors, normal ECG, normal cardiac biomarkers, and no alternative diagnoses (such as typical GERD or costochondritis) should be followed up with a timely exercise stress test that includes perfusion imaging. However, more than 25% of patients with stable chest pain referred for noninvasive testing will have normal coronary arteries and no long-term clinical events. The ECG can also provide evidence for alternative diagnoses, such as pericarditis and pulmonary embolism. Chest radiography is often useful in the evaluation of chest pain and is always indicated when cough or shortness of breath accompanies chest pain. Findings of pneumomediastinum or new pleural effusion are consistent with esophageal perforation. Stress echocardiography is useful in risk stratifying patients with chest pain, even among those with significant obesity.

Diagnostic protocols using a single high-sensitivity troponin assay combined with a standardized clinical assessment are an efficient strategy to rapidly determine whether patients with chest pain are at low risk and may be discharged from the emergency department. Six established risk scores are (1) the modified Goldman Risk Score, (2) TIMI Risk Score, (3) Global Registry of Acute Cardiac Events (GRACE) Risk Score, (4) HEART Risk Score, (5) Vancouver Chest Pain Rule, and (6) the European Society of Cardiology (ESC) 0/1-h algorithm. A study comparing these risk scores (not including the ESC algorithm) for predicting acute myocardial infarction within 30 days reported a sensitivity of 98% (which correlates with a negative predictive value of greater than or equal to 99.5%). Patients eligible for discharge (about 30%) were those with a TIMI score of less than or equal to 1, modified Goldman score of less than or equal to 1 with normal high-sensitivity troponin T, TIMI score of 0, or HEART score of less than or equal to 3 with normal high-sensitivity troponin I. In Black patients with average cardiovascular risk, HEART score is a better predictive tool for 6-week major adverse cardiac events (MACE) when compared to TIMI score. Six-week MACE among patients with low-to-moderate risk based on HEART score was 3.11 (95% CI, 1.43–6.76;  $P = 0.004$ ).

While some studies of high-sensitivity cardiac troponin suggest that it may be the best cardiac biomarker, it may not outperform conventional troponin assays if an appropriate cutoff is used.

Patients who arrive at the emergency department with chest pain of intermediate or high probability for ACS without electrocardiographic or biomarker evidence of a myocardial infarction can be safely discharged from an observation unit after stress cardiac MRI. Sixty-four-slice coronary CTA is an alternative to stress testing in the emergency department for detecting ACS among patients with normal or nonspecific ECG and normal biomarkers. A meta-analysis of nine studies found ACS in 10% of patients, and an estimated sensitivity of CTA for ACS of 95% and specificity of 87%, yielding a negative LR of 0.06 and a positive LR of 7.4.

Computed tomography-derived fractional flow reserve (FFR<sub>CT</sub>) in acute chest pain has higher specificity for anatomic and physiologic assessment of coronary artery stenosis compared with coronary CTA.

Coronary CTA applied early in the evaluation of suspected ACS does not identify more patients with significant coronary artery disease requiring coronary revascularization, shorten hospital stay, or allow for more direct discharge from the emergency department compared to high-sensitivity troponins. Thus, functional testing appears to be the best initial noninvasive test in symptomatic patients with suspected coronary artery disease. CTA is an option for patients who do not have access to functional testing.

For patients at low risk for ACS, an initial diagnostic strategy of stress echocardiography or cardiovascular magnetic resonance is associated with similar cardiac event rates, but a substantially lower invasive testing rate.

A minimal-risk model developed by the PROMISE investigators includes 10 clinical variables that correlate

with normal coronary CTA results and no clinical events: (1) younger age; (2) female sex; (3) racial or ethnic minority; (4–6) no history of hypertension, diabetes, or dyslipidemia; (7) no family history of premature coronary artery disease; (8) never smoking; (9) symptoms unrelated to physical or mental stress; and (10) higher high-density lipoprotein cholesterol level. In the PROMISE trial, women had higher rates of normal noninvasive testing compared with men, but women with abnormalities on such testing were less likely to be referred for catheterization or to receive statin therapy.

In the evaluation of pulmonary embolism, diagnostic test decisions and results must be interpreted in the context of the clinical likelihood of VTE. A negative D-dimer test is helpful for excluding pulmonary embolism in patients with low clinical probability of VTE (3-month incidence = 0.5%); however, the 3-month risk of VTE among patients with intermediate and high risk of VTE is sufficiently high in the setting of a negative D-dimer test (3.5% and 21.4%, respectively) to warrant further imaging given the life-threatening nature of this condition if left untreated. CTA (with helical or multidetector CT imaging) has replaced ventilation-perfusion scanning as the preferred initial diagnostic test, having approximately 90–95% sensitivity and 95% specificity for detecting pulmonary embolism (compared with pulmonary angiography). However, for patients with high clinical probability of VTE, lower extremity ultrasound or pulmonary angiogram may be indicated even with a normal helical CT.

Panic disorder is a common cause of chest pain, accounting for up to 25% of cases that present to emergency departments and a higher proportion of cases presenting in primary care office practices. Features that correlate with an increased likelihood of panic disorder include absence of coronary artery disease, atypical quality of chest pain, female sex, younger age, and a high level of self-reported anxiety. Depression is associated with recurrent chest pain with or without coronary artery disease (odds ratio, 2.11; 95% CI, 1.18–3.79).

## ► Treatment

Treatment of chest pain should be guided by the underlying etiology. The term “noncardiac chest pain” is used when a diagnosis remains elusive after patients have undergone an extensive workup. Almost half reported symptom improvement with high-dose proton pump inhibitor therapy. Relief of constipation may be therapeutic in proton pump inhibitor refractory noncardiac chest pain. A meta-analysis of 15 trials suggested modest to moderate benefit for psychological (especially cognitive-behavioral) interventions. It is unclear whether tricyclic or selective serotonin reuptake inhibitor antidepressants have benefit in noncardiac chest pain. Hypnotherapy may offer some benefit.

## ► When to Refer

- Refer patients with poorly controlled, noncardiac chest pain to a pain specialist.
- Refer patients with sickle cell anemia to a hematologist.

## ► When to Admit

- Failure to adequately exclude life-threatening causes of chest pain, particularly myocardial infarction, dissecting aortic aneurysm, pulmonary embolism, and esophageal rupture.
- High risk of pulmonary embolism and a positive sensitive D-dimer test.
- TIMI score of 1 or more, HEART score greater than 3, abnormal ECG, and abnormal 0- and 2-hour troponin tests.
- Pain control for rib fracture that impairs gas exchange.

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## PALPITATIONS



### ESSENTIAL INQUIRIES

- ▶ Forceful, rapid, or irregular beating of the heart.
- ▶ Rate, duration, and degree of regularity of heartbeat; age at first episode.
- ▶ Factors that precipitate or terminate episodes.
- ▶ Light-headedness or syncope; neck pounding.
- ▶ Chest pain; history of myocardial infarction or structural heart disease.

## ► General Considerations

Palpitations are defined as an unpleasant awareness of the forceful, rapid, or irregular beating of the heart. They are the primary symptom for approximately 16% of patients presenting to an outpatient clinic with a cardiac complaint. In an observational cohort study of palpitations at an outpatient cardiac unit, cardiac arrhythmias were the cause of palpitations in 81% of cases. Palpitations represent 5.8 of every 1000 emergency department visits, with an admission rate of 24.6%. While palpitations are usually benign, they are occasionally the symptom of a life-threatening arrhythmia. To avoid missing a dangerous cause of the patient's symptom, clinicians sometimes pursue expensive and invasive testing when a conservative diagnostic evaluation is often sufficient. The converse is also true. Table 2–3 lists history, physical examination, and ECG findings suggesting a cardiovascular cause for the palpitations.

**Table 2–3.** Palpitations: Patients at high risk for a cardiovascular cause.

#### Historical risk factors

- Family history of significant arrhythmias
- Personal or family history of syncope or resuscitated sudden death
- History of myocardial infarction (and likely scarred myocardium)
- Palpitations that occur during sleep

#### Anatomic abnormalities

- Structural heart disease such as dilated or hypertrophic cardiomyopathies
- Valvular disease (stenotic or regurgitant)

#### ECG findings

- Long QT syndrome
- Bradycardia
- Second- or third-degree heart block
- Sustained ventricular arrhythmias

## ► Clinical Findings

### A. Symptoms

Guiding the patient through a careful description of their palpitations may indicate a mechanism and narrow the differential diagnosis. Pertinent questions include the age at first episode; precipitants; and rate, duration, and degree of regularity of the heartbeat during the subjective palpitations. Palpitations lasting less than 5 minutes and a family history of panic disorder reduce the likelihood of an arrhythmic cause ( $LR+ = 0.38$  and  $LR+ = 0.26$ , respectively). To better understand the symptom, the examiner can ask the patient to “tap out” the rhythm with his or her fingers. The circumstances associated with onset and termination can also be helpful in determining the cause. Palpitations that start and stop abruptly suggest supraventricular or ventricular tachycardias. Termination of palpitations using vagal maneuvers (eg, Val-salva maneuver) suggests supraventricular tachycardia.

Three common descriptions of palpitations are (1) “flip-flopping” (or “stop and start”), often caused by premature contraction of the atrium or ventricle, with the perceived “stop” from the pause following the contraction, and the “start” from the subsequent forceful contraction; (2) rapid “fluttering in the chest,” with regular “fluttering” suggesting supraventricular or ventricular arrhythmias (including sinus tachycardia) and irregular “fluttering” suggesting atrial fibrillation, atrial flutter, or tachycardia with variable block; and (3) “pounding in the neck” or neck pulsations, often due to “cannon” A waves in the jugular venous pulsations that occur when the right atrium contracts against a closed tricuspid valve.

Palpitations associated with chest pain suggest ischemic heart disease, or if the chest pain is relieved by leaning forward, pericardial disease. Palpitations associated with light-headedness, presyncope, or syncope suggest hypotension and may signify a life-threatening cardiac arrhythmia. Palpitations that occur regularly with exertion suggest a rate-dependent bypass tract or hypertrophic cardiomyopathy. If a benign etiology cannot be ascertained at the initial visit, then ambulatory monitoring or prolonged cardiac monitoring in the hospital might be warranted.

Noncardiac symptoms should also be elicited since the palpitations may be caused by a normal heart responding to a metabolic or inflammatory condition. Weight loss suggests hyperthyroidism. Palpitations can be precipitated by vomiting or diarrhea that leads to electrolyte disorders and hypovolemia. Hyperventilation, hand tingling, and nervousness are common when anxiety or panic disorder is the cause of the palpitations. Palpitations associated with flushing, episodic hypertension, headaches, anxiety, and diaphoresis may be caused by a pheochromocytoma or paraganglioma.

A family history of palpitations or sudden death suggests an inherited etiology such as long QT syndrome or Brugada syndrome. Chagas disease may cause palpitations and acute myocarditis. Younger patients should be asked about consumption of “energy drinks.” Finally, dual use of cigarettes and e-cigarettes may cause palpitations.

### B. Physical Examination

Careful cardiovascular examination can find abnormalities that can increase the likelihood of specific cardiac arrhythmias. The midsystolic click of mitral valve prolapse can suggest the diagnosis of a supraventricular arrhythmia. The harsh holosystolic murmur of hypertrophic cardiomyopathy, which occurs along the left sternal border and increases with the Valsalva maneuver, suggests atrial fibrillation or ventricular tachycardia. A crescendo mid-diastolic murmur may be caused by an atrial myxoma. The presence of dilated cardiomyopathy, suggested on examination by a displaced and enlarged cardiac point-of-maximal impulse, increases the likelihood of ventricular tachycardia and atrial fibrillation. In patients with chronic atrial fibrillation, in-office exercise (eg, a brisk walk in the hallway) may reveal an intermittent accelerated ventricular response. The clinician should also look for signs of hyperthyroidism (eg, tremulousness, brisk deep tendon reflexes, or fine hand tremor), or signs of stimulant drug use (eg, dilated pupils or skin or nasal septal perforations). Visible neck pulsations (LR+, 2.68; 95% CI, 1.25–5.78) in association with palpitations increase the likelihood of atrioventricular nodal reentry tachycardia.

### C. Diagnostic Studies

**1. ECG**—A 12-lead ECG should be performed on all patients reporting palpitations. Although in most instances a specific arrhythmia will not be detected on the tracing, a careful evaluation of the ECG can help the clinician deduce a likely etiology in certain circumstances.

For instance, bradyarrhythmias and heart block can be associated with ventricular ectopy or escape beats that may be experienced as palpitations. Evidence of prior myocardial infarction on ECG (eg, Q waves) increases the patient's risk of nonsustained or sustained ventricular tachycardia. Ventricular preexcitation (Wolff-Parkinson-White syndrome) is suggested by a short PR interval (less than 0.20 ms) and delta waves (upsloping PR segments). Left ventricular hypertrophy with deep septal Q waves in I, AVL, and V4 through V6 is seen in patients with hypertrophic obstructive cardiomyopathy. The presence of left atrial enlargement

as suggested by a terminal P-wave force in V1 more negative than 0.04 msec and notching in lead II reflects an increased risk of atrial fibrillation. A prolonged QT interval and abnormal T-wave morphology suggest the long QT syndrome, and an increased risk of ventricular tachycardia. Persistent ST-segment elevations in ECG leads V1–V3 (particularly with a coved or saddle-back pattern) suggest Brugada syndrome.

**2. Monitoring devices**—For high-risk patients (Table 2–3), further diagnostic studies are warranted. A stepwise approach has been suggested—starting with ambulatory monitoring devices (ambulatory ECG monitoring if the palpitations are expected to occur within the subsequent 72-hour period, event monitoring if less frequent). An implantable loop recorder can be used for extended monitoring if clinical suspicion is high, especially if there is syncope. A single-lead, lightweight, continuously recording ambulatory adhesive patch monitor (Zio Patch) worn for 14–21 days increases diagnostic yield while reducing cost of diagnosis in patients with recurrent unexplained palpitations. Inpatient continuous monitoring is indicated if serious arrhythmias are strongly suspected despite normal findings on the ambulatory monitoring; invasive electrophysiologic testing should be done if the ambulatory or inpatient monitor records a worrisome arrhythmia.

In patients with a prior myocardial infarction, ambulatory cardiac monitoring or signal-averaged ECG is an appropriate next step to help exclude ventricular tachycardia. ECG exercise testing is appropriate in patients with suspected coronary artery disease and in patients who have palpitations with physical exertion. Echocardiography is useful when physical examination or ECG suggests structural abnormalities or decreased ventricular function.

### ► Differential Diagnosis

When assessing a patient with palpitations in an urgent care setting, the clinician must ascertain whether the symptoms represent (1) a significant cardiovascular disease, (2) a cardiac manifestation of a systemic disease such as thyrotoxicosis, (3) an arrhythmia that is minor and transient, or (4) a benign somatic symptom that is amplified by the patient's underlying psychological state.

Patients with palpitations who seek medical attention in an emergency department instead of a medical clinic are more likely to have a cardiac cause (47% versus 21%), whereas psychiatric causes are more common among those who seek attention in office practices (45% versus 27%). In a study of patients who went to a university medical clinic with the chief complaint of palpitations, causes were cardiac in 43%, psychiatric in 31%, and miscellaneous in 10%.

Cardiac arrhythmias that can result in symptoms of palpitations include sinus bradycardia; sinus, supraventricular, and ventricular tachycardia; premature ventricular and atrial contractions; sick sinus syndrome; and advanced atrioventricular block.

Cardiac nonarrhythmic causes of palpitations include valvular heart diseases, such as aortic regurgitation or stenosis, atrial or ventricular septal defect, cardiomyopathy, congenital heart disease, pericarditis, arrhythmogenic right

ventricular cardiomyopathy, and atrial myxoma. Mitral valve prolapse is not associated with arrhythmic events, but ventricular arrhythmias are frequent in mitral annulus disjunction.

The most common psychiatric causes of palpitations are anxiety and panic disorder. The release of catecholamines during a significant stress or panic attack can trigger an arrhythmia. Asking a single question, “Have you experienced brief periods, for seconds or minutes, of an overwhelming panic or terror that was accompanied by racing heartbeats, shortness of breath, or dizziness?” can help identify patients with panic disorder.

Miscellaneous causes of palpitations include fever, dehydration, hypoglycemia, anemia, thyrotoxicosis, mastocytosis, and pheochromocytoma. Drugs such as cocaine, alcohol, caffeine, pseudoephedrine, and illicit ephedra can precipitate palpitations, as can prescription medications, including digoxin, amitriptyline, erythromycin and other drugs that prolong the QT interval, class 1 antiarrhythmics, dihydropyridine calcium channel blockers, phenothiazines, theophylline, and beta-agonists.

## Treatment

After ambulatory monitoring, most patients with palpitations are found to have benign atrial or ventricular ectopy or nonsustained ventricular tachycardia. In patients with structurally normal hearts, these arrhythmias are not associated with adverse outcomes. Abstention from caffeine and tobacco may help. Often, reassurance suffices. If not, or in very symptomatic patients, a trial of a beta-blocker may be prescribed. A three-session course of cognitive-behavioral therapy that includes some physical activity has proven effective for patients with benign palpitations with or without chest pain. For treatment of specific atrial or ventricular arrhythmias, see Chapter 10.

## When to Refer

- For electrophysiologic studies.
- For advice regarding treatment of atrial or ventricular arrhythmias.

## When to Admit

- Palpitations associated with syncope or near-syncope, particularly when the patient is aged 75 years or older and has an abnormal ECG, hematocrit less than 30%, shortness of breath, respiratory rate higher than 24/min, or a history of HF.
- Patients with risk factors for a serious arrhythmia.

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## LOWER EXTREMITY EDEMA



### ESSENTIAL INQUIRIES

- History of venous thromboembolism.
- Symmetry of swelling.
- Pain.
- Change with dependence.
- Skin findings: hyperpigmentation, stasis dermatitis, lipodermatosclerosis, atrophie blanche, ulceration.

## General Considerations

Acute and chronic lower extremity edema present important diagnostic and treatment challenges. Lower extremities can swell in response to increased venous or lymphatic pressures, decreased intravascular oncotic pressure, increased capillary leak, and local injury or infection. **Chronic venous insufficiency** is by far the most common cause, affecting up to 2% of the population, and the incidence of venous insufficiency has not changed over the past 25 years. Venous insufficiency is a common complication of DVT; however, only a small number of patients with chronic venous insufficiency report a history of this disorder. Venous ulceration commonly affects patients with chronic venous insufficiency, and its management is labor-intensive and expensive. Normal lower extremity venous pressure (in the erect position: 80 mm Hg in deep veins, 20–30 mm Hg in superficial veins) and cephalad venous blood flow require competent bicuspid venous valves, effective muscle contractions, normal ankle range of motion, and normal respirations. When one or more of these components fail, venous hypertension may result. Chronic exposure to elevated venous pressure by the postcapillary venules in the legs leads to leakage of fibrinogen and growth factors into the interstitial space, leukocyte aggregation and activation, and obliteration of the cutaneous lymphatic network.

## Clinical Findings

### A. Symptoms and Signs

**1. Unilateral lower extremity edema**—Among common causes of unilateral lower extremity swelling, DVT is the most life-threatening. Clues suggesting DVT include a history of cancer, recent limb immobilization, or confinement to bed for at least 3 days following major surgery within the past month (Table 2–4). Adults with varicose veins have a significantly increased risk of DVT. Lower extremity swelling and inflammation in a limb recently affected by DVT could represent anticoagulation failure and thrombus recurrence but more often are caused by **postphlebitic syndrome** with valvular incompetence. Other causes of a painful, swollen calf include cellulitis, musculoskeletal disorders (Baker cyst rupture [“pseudothrombophlebitis”]), gastrocnemius tear or rupture, calf strain or trauma, and left common iliac vein compression (May-Thurner

**Table 2–4.** Risk stratification of adults referred for ultrasound to rule out DVT.

| Step 1:  |                               |                         |
|--|-------------------------------|-------------------------|
| <b>Score 1 point for each</b>  |                               |                         |
| Untreated malignancy   |                               |                         |
| Paralysis, paresis, or recent plaster immobilization                                       |                               |                         |
| Recently bedridden for > 3 days due to major surgery within 4 weeks                        |                               |                         |
| Localized tenderness along distribution of deep venous system                              |                               |                         |
| Entire leg swelling  |                               |                         |
| Swelling of one calf > 3 cm more than the other (measured 10 cm below tibial tuberosity)   |                               |                         |
| Ipsilateral pitting edema  |                               |                         |
| Collateral superficial (nonvaricose) veins   |                               |                         |
| Previously documented DVT  |                               |                         |
| Step 2:  |                               |                         |
| <b>Subtract 2 points if alternative diagnosis has equal or greater likelihood than DVT</b> |                               |                         |
| Step 3:  |                               |                         |
| <b>Obtain sensitive D-dimer for score <math>\geq 0</math></b>                              |                               |                         |
| Score  | D-Dimer Positive <sup>1</sup> | D-Dimer Negative        |
| 0–1  | Obtain ultrasound             | Ultrasound not required |
| $\geq 2$   | Obtain ultrasound             |                         |

DVT, deep venous thrombosis.

<sup>1</sup>"Positive" is above local laboratory threshold based on specific test and patient age.

syndrome), as well as other sites of nonthrombotic venous outflow obstruction, such as the inguinal ligament, iliac bifurcation, and popliteal fossa.

**2. Bilateral lower extremity edema**—Bilateral involvement and significant improvement upon awakening favor systemic causes (eg, venous insufficiency) and can be presenting symptoms of volume overload (HF, cirrhosis, kidney disease [eg, nephrotic syndrome]). The most frequent symptom of chronic venous insufficiency is the sensation of "heavy legs," followed by itching. Chronic exposure to elevated venous pressure accounts for the brawny, fibrotic skin changes observed in patients with chronic venous insufficiency as well as the predisposition toward skin ulceration, particularly in the medial malleolar area. Pain, particularly if severe, is uncommon in uncomplicated venous insufficiency.

Lower extremity swelling is a familiar complication of therapy with calcium channel blockers (particularly felodipine and amlodipine), pioglitazone, gabapentin, and minoxidil. Prolonged airline flights (longer than 10 hours) are associated with edema even in the absence of DVT.

## B. Physical Examination

Physical examination should include assessment of the heart, lungs, and abdomen for evidence of pulmonary

hypertension (primary or secondary to chronic lung disease), HF, or cirrhosis. The skin findings related to chronic venous insufficiency depend on the severity and chronicity of the disease, ranging from hyperpigmentation and stasis dermatitis to abnormalities highly specific for chronic venous insufficiency: lipodermatosclerosis (thick, brawny skin; in advanced cases, the lower leg resembles an inverted champagne bottle) and atrophie blanche (small, depigmented macules within areas of heavy pigmentation). The size of both calves should be measured 10 cm below the tibial tuberosity and pitting and tenderness elicited. Swelling of the entire leg or of one leg 3 cm more than the other suggests deep venous obstruction. The left calf is normally slightly larger than the right as a result of the left common iliac vein coursing under the aorta.

A shallow, large, modestly painful ulcer located over the medial malleolus is a hallmark of chronic venous insufficiency, whereas small, deep, and more painful ulcers are more apt to be due to arterial insufficiency, vasculitis, or infection. Diabetic vascular ulcers, however, may be painless. When an ulcer is on the foot or above the mid-calf, causes other than venous insufficiency should be considered.

The physical examination is usually inadequate to distinguish lymphedema from venous insufficiency. Only the Kaposi-Stemmer sign (the inability to pinch or pick up a fold of skin at the base of the second toe because of its thickness) was a significant predictor of lymphedema (odds ratio, 7.9;  $P = 0.02$ ).

## C. Diagnostic Studies

Patients without an obvious cause of acute lower extremity swelling (eg, calf strain) should have an ultrasound performed, since DVT is difficult to exclude on clinical grounds. A prediction rule allows a clinician to exclude a lower extremity DVT in patients without an ultrasound if the patient has low pretest probability for DVT and a negative sensitive D-dimer test (the "Wells prediction rule") (Chapter 9).

The diagnostic study of choice to detect chronic venous insufficiency due to venous incompetence is duplex ultrasonography. Assessment of the ankle-brachial pressure index (ABPI) is important in the management of chronic venous insufficiency, since peripheral arterial disease may be exacerbated by compression therapy. Caution is required in interpreting the results of ABPI in older patients and diabetic patients due to the decreased compressibility of their arteries. A urine dipstick test that is strongly positive for protein can suggest nephrotic syndrome, and a serum creatinine can help estimate kidney function. Lymphoscintigraphy can be used to confirm a clinical suspicion of lymphedema.

## Treatment

Treatment of lower extremity edema should be guided by the underlying cause. See relevant chapters for treatment of edema in patients with HF (Chapter 10), nephrosis (Chapter 22), cirrhosis (Chapter 16), and lymphedema and venous stasis ulcers (Chapter 12). Edema resulting from calcium channel blocker therapy responds to concomitant therapy with ACE inhibitors or angiotensin receptor blockers.

In patients with chronic venous insufficiency without a comorbid volume overload state (eg, HF), it is best to avoid diuretic therapy. These patients have relatively decreased intravascular volume, and administration of diuretics may first enhance sodium retention through increased secretion of renin and angiotensin and then result in acute kidney injury and oliguria. Instead, the most effective treatment involves (1) leg elevation, above the level of the heart, for 30 minutes three to four times daily, and during sleep; (2) compression therapy; and (3) ambulatory exercise to increase venous return through calf muscle contractions.

A wide variety of stockings and devices are effective in decreasing swelling and preventing ulcer formation. They should be put on with awakening, before hydrostatic forces result in edema. To control mild edema, 20–30 mm Hg compression is usually sufficient, whereas 30–40 mm Hg compression is usually required to control moderate to severe edema associated with ulcer formation. To maintain improvement, consider switching from an elastic stocking to one made of inelastic grosgrain material. Patients with decreased ABPI should be managed in concert with a vascular surgeon. Compression stockings (12–18 mm Hg at the ankle) are effective in preventing edema and asymptomatic thrombosis associated with long airline flights in low- to medium-risk persons, and compression therapy decreases recurrence of cellulitis among patients with chronic venous insufficiency. Support stockings are recommended for pregnant women during air travel. For lymphedema, bandaging systems applied twice weekly can be effective. Multi-component compression bandaging may offer additional benefit. Short-term manual lymphatic drainage treatment may improve chronic venous insufficiency severity, symptoms, and quality of life. For patients with reduced mobility and leg edema, intermittent pneumatic compression treatment can reduce edema and improve ankle range of motion.

Liposuction, suction-assisted lipectomy, and subcutaneous drainage may have treatment benefit if conservative measures fail in treatment of lymphedema.

## ► When to Refer

- Refer patients with chronic lower extremity ulcerations requiring specialist wound care.
- Refer patients with nephrotic syndrome to a nephrologist.
- Refer patients with coexisting severe arterial insufficiency (claudication) that would complicate treatment with compression stockings to a vascular surgeon.

## ► When to Admit

- Pending definitive diagnosis in patients at high risk for DVT despite normal lower extremity ultrasound.
- Severe, acute swelling raising concern for an impending compartment syndrome.
- Severe edema that impairs ability to ambulate or perform activities of daily living.

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## FEVER & HYPERHERMIA



### ESSENTIAL INQUIRIES

- ▶ Age; injection substance use.
- ▶ Localizing symptoms; weight loss; joint pain.
- ▶ Immunosuppression or neutropenia; history of cancer, risk of COVID-19 (see Chapter 32).
- ▶ Medications.
- ▶ Travel.

## ► General Considerations

The average normal oral body temperature taken in mid-morning is 36.7°C (range 36–37.4°C). This range includes a mean and 2 standard deviations, thus encompassing 95% of a normal population (normal diurnal temperature variation is 0.5–1°C).

The normal rectal or vaginal temperature is 0.5°C higher than the oral temperature, and the axillary temperature is 0.5°C lower. However, a normal body temperature based on a peripheral thermometer (tympanic membrane, temporal artery, axillary, oral) does not always exclude the presence of a fever. To exclude a fever, a rectal temperature is more reliable than an oral temperature (particularly in patients who breathe through their mouth, who are tachypneic, or who are in an intensive care unit setting where a rectal temperature probe can be placed to detect fever).

Fever is a regulated rise to a new “set point” of body temperature in the hypothalamus induced by pyrogenic cytokines. These cytokines include interleukin-1 (IL-1), tumor necrosis factor (TNF), interferon-gamma, and interleukin-6 (IL-6). The elevation in temperature results from either increased heat production (eg, shivering) or decreased heat loss (eg, peripheral vasoconstriction). Body temperature in cytokine-induced fever seldom exceeds 41.1°C unless there is structural damage to hypothalamic regulatory centers.

## ► Clinical Findings

### A. Fever

Fever as a symptom provides important information about the presence of illness—particularly infections—and about changes in the clinical status of the patient. Fever may be

more predictive of bacteremia in elderly patients. The fever pattern, however, is of marginal value for most specific diagnoses except for the relapsing fever of malaria, borreliosis, and occasional cases of lymphoma, especially Hodgkin disease. Furthermore, the degree of temperature elevation does not necessarily correspond to the severity of the illness. Fever, with rash and eosinophilia, defines the drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome.

In general, the febrile response tends to be greater in children than in adults. In older persons, neonates, and persons receiving certain medications (eg, nonsteroidal anti-inflammatory drugs [NSAIDs], corticosteroids), a normal temperature or even hypothermia may be observed. Markedly elevated body temperature may result in profound metabolic disturbances. High temperature during the first trimester of pregnancy may cause birth defects, such as anencephaly. Fever increases insulin requirements and alters the metabolism and disposition of drugs used for the treatment of the diverse diseases associated with fever.

The source of fever varies by population and setting. In a study involving patients who underwent shoulder arthroplasty, fever was documented in 92 patients. Among these 92 patients, an infectious cause was found in only 6 patients. In the neurointensive care unit, fever can occur directly from brain injury (called “central fever”). One model predicted “central fever” with 90% probability if a patient met all of the following criteria: (1) less than 72 hours of neurologic intensive care unit admission; (2) presence of subarachnoid hemorrhage, intraventricular hemorrhage, or brain tumor; (3) absence of infiltrate on chest radiograph; and (4) negative cultures. Procalcitonin and C-reactive protein may have some utility in differentiating infectious and central fever in the ICU.

Fever may also be more common in patients with other forms of trauma. In a study enrolling 268 patients, including patients with multiple injuries ( $n = 59$ ), isolated head injuries ( $n = 97$ ), isolated body injuries ( $n = 100$ ), and minor trauma ( $n = 12$ ), the incidence of fever was similar in all groups irrespective of injury (11–24%). In all groups, there was a significant association between the presence of early fever and death in the hospital (6–18% versus 0–3%), as well as longer median intensive care unit stays (3–7 days versus 2–3 days). Spinal cord injury may cause fever by the loss of supraspinal control of the sympathetic nervous system and defective thermoregulation due to loss of sensation.

Among pregnant women, the prevalence of intrapartum fever of  $38^{\circ}\text{C}$  or greater in pregnancies of 36 weeks’ gestation or more is 6.8% (or 1 in 15 women in labor), but the neonatal sepsis rate among affected mothers is 0.24% (or less than 1 in 400 babies). This finding calls into question the need for universal laboratory work, cultures, and antibiotic treatment pending culture results for this newborn population.

There is increasing evidence that postoperative atelectasis does not cause fever. However, febrile nonhemolytic transfusion reaction is common, occurring in about 1% of transfusion episodes, and is mediated by proinflammatory cytokines elaborated by donor leukocytes during storage.

## B. Hyperthermia

Hyperthermia—not mediated by cytokines—occurs when body metabolic heat production (as in thyroid storm) or environmental heat load exceeds normal heat loss capacity or when there is impaired heat loss (eg, heat stroke). Body temperature may rise to levels (more than  $41.1^{\circ}\text{C}$ ) capable of producing irreversible protein denaturation and resultant brain damage; no diurnal variation is observed.

**Malignant catatonia** is a disorder consisting of cataleptic symptoms, hyperthermia, autonomic instability, and altered mental status.

**Neuroleptic malignant syndrome**, a variant of malignant catatonia, is a rare and potentially lethal idiosyncratic reaction to neuroleptic medications, particularly haloperidol and fluphenazine; however, it has also been reported with the atypical neuroleptics (such as olanzapine or risperidone) (see Chapter 25). **Serotonin syndrome** resembles neuroleptic malignant syndrome but occurs within hours of ingestion of agents that increase levels of serotonin in the central nervous system, including serotonin reuptake inhibitors, monoamine oxidase inhibitors, tricyclic antidepressants, meperidine, dextromethorphan, bromocriptine, tramadol, lithium, and psychostimulants (such as cocaine, methamphetamine, and MDMA) (see Chapter 38). Clonus and hyperreflexia are more common in serotonin syndrome, whereas “lead pipe” rigidity is more common in neuroleptic malignant syndrome. Neuroleptic malignant and serotonin syndromes share common clinical and pathophysiologic features with **malignant hyperthermia of anesthesia** (see Chapter 38).

## C. Fever of Undetermined Origin

See Fever of Unknown Origin, Chapter 30.

## ► Treatment

Most fever is well tolerated. When the temperature is less than  $40^{\circ}\text{C}$ , symptomatic treatment only is required. The treatment of fever with antipyretics does not appear to affect mortality of critically ill patients or affect the number of intensive care unit-free days. A temperature greater than  $41^{\circ}\text{C}$  is likely to be hyperthermia rather than cytokine-mediated fever, and *emergent management is indicated*. (See Heat Stroke, Chapter 37.)

## A. General Measures for Removal of Heat

Regardless of the cause of the fever, alcohol sponges, cold sponges, ice bags, ice-water enemas, and ice baths will lower body temperature (see Chapter 37). They are more useful in hyperthermia, since patients with cytokine-related fever will attempt to override these therapies.

## B. Pharmacologic Treatment of Fever

**1. Antipyretic drugs**—Antipyretic therapy is not needed except for patients with marginal hemodynamic status. Early administration of acetaminophen to treat fever due to probable infection did not affect the number of intensive care unit-free days. Aspirin or acetaminophen, 325–650 mg

every 4 hours, is effective in reducing fever. These drugs are best administered around the clock, rather than as needed, since “as needed” dosing results in periodic chills and sweats due to fluctuations in temperature caused by varying levels of drug.

**2. Antimicrobial therapy**—Antibacterial and antifungal prophylactic regimens are recommended only for patients expected to have less than 100 neutrophils/mcL for more than 7 days, unless other factors increase risks for complications or mortality. However, empiric antibiotic therapy is sometimes warranted. Even before infection can be documented, prompt broad-spectrum antimicrobials are indicated for febrile patients who have hemodynamic instability, severe neutropenia (neutrophils less than 500/mcL), asplenia (surgical or from sickle cell disease), or immunosuppression (from HIV infection [see Chapter 31] or from medications such as systemic corticosteroids, azathioprine, cyclosporine) (Tables 30–4 and 30–5).

Febrile neutropenic patients should receive initial doses of empiric antibacterial therapy within an hour of triage and should either be monitored for at least 4 hours to determine suitability for outpatient management or be admitted to the hospital (see Infections in the Immunocompromised Patient, Chapter 30). Inpatient treatment is standard to manage febrile neutropenic episodes, although carefully selected patients may be managed as outpatients after systematic assessment beginning with a validated risk index (eg, Multinational Association for Supportive Care in Cancer [MASCC] score or Talcott rules). In the MASCC index calculation, low-risk factors include the following: age under 60 years (2 points), burden of illness (5 points for no or mild symptoms and 3 points for moderate symptoms), outpatient status (3 points), solid tumor or hematologic malignancy with no previous fungal infection (4 points), no COPD (4 points), no dehydration requiring parenteral fluids (3 points), and systolic blood pressure greater than 90 mm Hg (5 points). Patients with MASCC scores 21 or higher or in Talcott group 4 (presentation as an outpatient without significant comorbidity or uncontrolled cancer), and without other risk factors, can be managed safely as outpatients.

The carefully selected outpatients determined to be at low risk by MASCC score (particularly in combination with a normal serum C-reactive protein level) or by Talcott rules can be managed with an oral fluoroquinolone plus amoxicillin/clavulanate (or clindamycin, if penicillin allergic), unless fluoroquinolone prophylaxis was used before fever developed. For treatment of fever during neutropenia following chemotherapy, outpatient parenteral antimicrobial therapy can be provided effectively and safely in low-risk patients with a single agent such as cefepime, piperacillin/tazobactam, imipenem, meropenem, or doripenem. High-risk patients should be referred for inpatient management with combination parenteral antimicrobial therapy based on specific risk factors such as pneumonia-causing pathogens or central line-associated bloodstream infections (see Infections in the Immunocompromised Patient and Table 30–5 in Chapter 30 and see Infections in Chapter 39).

If a fungal infection is suspected in patients with prolonged fever and neutropenia, fluconazole is an equally effective but less toxic alternative to amphotericin B.

### C. Treatment of Hyperthermia

Discontinuation of the offending agent is mandatory. Treatment of neuroleptic malignant syndrome includes dantrolene in combination with bromocriptine or levodopa (see Chapter 25). Treatment of serotonin syndrome includes administration of a central serotonin receptor antagonist—cyproheptadine or chlorpromazine—alone or in combination with a benzodiazepine (see Chapter 38). In patients for whom it is difficult to distinguish which syndrome is present, treatment with a benzodiazepine may be the safest therapeutic option.

### ► When to Admit

- Presence of additional vital sign abnormalities or evidence of end-organ dysfunction in clinical cases when early sepsis is suspected.
- For measures to control a temperature higher than 41°C or when fever is associated with seizure or other mental status changes.
- Heat stroke (see Chapter 37).
- Malignant catatonia; neuroleptic malignant syndrome; serotonin syndrome; malignant hyperthermia of anesthesia.

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## INVOLUNTARY WEIGHT LOSS

### ESSENTIAL INQUIRIES

- Age; caloric intake; secondary confirmation (eg, changes in clothing size).
- Fever; change in bowel habits.
- Substance abuse.
- Age-appropriate cancer screening history.

### ► General Considerations

Body weight is determined by a person's caloric intake, absorptive capacity, metabolic rate, and energy losses.

Body weight normally peaks by the fifth or sixth decade and then gradually declines at a rate of 1–2 kg per decade. In NHANES II, a national survey of community-dwelling elders (aged 50–80 years), recent involuntary weight loss (more than 5% usual body weight) was reported by 7% of respondents, and this was associated with a 24% higher mortality. In postmenopausal women, unintentional weight loss was associated with increased rates of hip and vertebral fractures.

### ► Etiology

Involuntary weight loss is regarded as clinically significant when it exceeds 5% or more of usual body weight over a 6- to 12-month period. It often indicates serious physical or psychological illness. Physical causes are usually evident during the initial evaluation. The most common causes are cancer (about 30%), gastrointestinal disorders (about 15%), and dementia or depression (about 15%). Nearly half of patients with Parkinson disease have weight loss associated with disease progression. When an adequately nourished-appearing patient complains of weight loss, inquiry should be made about exact weight changes (with approximate dates) and about changes in clothing size. Family members can provide confirmation of weight loss, as can old documents such as driver's licenses. A mild, gradual weight loss occurs in some older individuals because of decreased energy requirements. However, rapid involuntary weight loss is predictive of morbidity and mortality. In addition to various disease states, causes in older individuals include loss of teeth and consequent difficulty with chewing, medications interfering with taste or causing nausea, alcoholism, and social isolation. Among Blacks at an adult day health center, 65% had a significant nutritional disorder: 48.5% reported involuntary weight loss or gain, 21% ate fewer than two meals daily, and 41.2% had tooth loss or mouth pain.

### ► Clinical Findings

Once the weight loss is established, the history, medication profile, physical examination, and conventional laboratory and radiologic investigations (eg, complete blood count, liver biochemical tests, kidney panel, serologic tests including HIV, thyroid-stimulating hormone [TSH] level, urinalysis, fecal occult blood test, and chest radiography) usually reveal the cause. Age-appropriate cancer screening should be completed as recommended by guidelines (eg, Papanicolaou smear, mammography, fecal occult blood test [FOBT]/screening colonoscopy/flexible sigmoidoscopy, possibly prostate-specific antigen [PSA]) (Chapter 1). Whole-body CT imaging is increasingly used for diagnosis; one study found its diagnostic yield to be 33.5%. When these tests are normal, the second phase of evaluation should focus on more definitive gastrointestinal investigation (eg, tests for malabsorption, endoscopy). However, one prospective case study in patients with unintentional weight loss showed that colonoscopy did not find colorectal cancer if weight loss was the sole indication for the test.

If the initial evaluation is unrevealing, follow-up is preferable to further diagnostic testing. Death at 2-year follow-up was not nearly as common in patients with unexplained

involuntary weight loss (8%) as in those with weight loss due to malignant (79%) and established nonmalignant diseases (19%). Psychiatric consultation should be considered when there is evidence of depression, dementia, anorexia nervosa, or other emotional problems. Ultimately, in approximately 15–25% of cases, no cause for the weight loss can be found.

### ► Differential Diagnosis

Malignancy, gastrointestinal disorders (poorly fitting dentures, cavities, swallowing or malabsorption disorders, pancreatic insufficiency), HF, psychological problems (dementia, depression, paranoia), endocrine disorders (hyperthyroidism, hypothyroidism, hyperparathyroidism, hypoadrenalinism), eating problems (dietary restrictions, lack of money for food), social problems (alcohol use disorder, social isolation), and medication side effects are all established causes.

### ► Treatment

Weight stabilization occurs in most surviving patients with both established and unknown causes of weight loss through treatment of the underlying disorder and caloric supplementation. Nutrient intake goals are established in relation to the severity of weight loss, in general ranging from 30 to 40 kcal/kg/day. In order of preference, route of administration options include oral, temporary nasojejunal tube, or percutaneous gastric or jejunal tube. Parenteral nutrition is reserved for patients with serious associated problems. A variety of pharmacologic agents have been proposed for the treatment of weight loss. These can be categorized into appetite stimulants (corticosteroids, progestational agents, cannabinoids, and serotonin antagonists); anabolic agents (growth hormone, ghrelin, and testosterone derivatives); and anticatabolic agents (omega-3 fatty acids, pentoxifylline, hydrazine sulfate, and thalidomide). There is no evidence that appetite stimulants decrease mortality, and they may have severe adverse side effects. Exercise training may prevent or even reverse the process of muscle wasting in HF ("cardiac cachexia"). Protein supplementation combined with resistance exercise training and aerobic activity may prevent aging-related muscle mass attenuation and functional performance. Some patients with cancer-associated weight loss may benefit from nutritional assessment and intervention as decreased food intake may be playing a role.

### ► When to Refer

- Weight loss caused by malabsorption.
- Persistent nutritional deficiencies despite adequate supplementation.
- Weight loss as a result of anorexia or bulimia.

### ► When to Admit

- Severe protein-energy malnutrition, including the syndromes of kwashiorkor and marasmus.
- Vitamin deficiency syndromes.

- Cachexia with anticipated progressive weight loss secondary to unmanageable psychiatric disease.
- Careful electrolyte and fluid replacement in protein-energy malnutrition and avoidance of “re-feeding syndrome.”

Dunne RF et al. Cachexia and sarcopenia in older adults with cancer: a comprehensive review. *Cancers (Basel)*. 2019;11:1861. [PMID: 31769421]

Goh Y et al. Diagnostic utility of whole body CT scanning in patients with unexplained weight loss. *PLoS One*. 2018;13:e0200686. [PMID: 30052642]

Peixoto da Silva S et al. Cancer cachexia and its pathophysiology: links with sarcopenia, anorexia and asthenia. *J Cachexia Sarcopenia Muscle*. 2020;11:619. [PMID: 32142217]

Torné Cachot J et al. Isolated involuntary weight loss: epidemiology and predictive factors of malignancy. *Med Clin (Barc)*. 2019;152:384. [PMID: 30297253]

Valentova M et al. Cardiac cachexia revisited: the role of wasting in heart failure. *Heart Fail Clin*. 2020;16:61. [PMID: 31735316]

Alcohol use disorder, vitamin C deficiency (scurvy), side effects from medications (eg, sedatives and beta-blockers), and psychological conditions (eg, insomnia; depression; anxiety; panic attacks; dysthymia; and somatic symptom disorder, formerly called somatization disorder) may be the cause. Common outpatient infectious causes include mononucleosis and sinusitis. These conditions are usually associated with other characteristic signs, but patients may emphasize fatigue and not reveal their other symptoms unless directly asked. The lifetime prevalence of significant fatigue (present for at least 2 weeks) is about 25%. Fatigue of unknown cause or related to psychiatric illness exceeds that due to physical illness, injury, alcohol, or medications.

Although frequently associated with Lyme disease, severe fatigue as a long-term sequela is rare.

## ► Treatment

Management of fatigue involves identification and treatment of conditions that contribute to fatigue, such as cancer, pain, depression, disordered sleep, weight loss, and anemia. Resistance training and aerobic exercise lessens fatigue and improves performance for a number of chronic conditions associated with a high prevalence of fatigue, including HF, COPD, arthritis, and cancer. Continuous positive airway pressure is an effective treatment for obstructive sleep apnea. Psychostimulants such as methylphenidate have shown inconsistent results in randomized trials of treatment of cancer-related fatigue. Modafinil and armodafinil appear to be effective, well-tolerated agents in HIV-positive patients with fatigue and as adjunctive agents in patients with depression or bipolar disorder with fatigue. Testosterone replacement in hypoandrogenic men over age 65 had no significant benefits for walking distance or vitality, as assessed by the Functional Assessment of Chronic Illness Therapy-Fatigue scale. But men receiving the testosterone reported slightly better mood and lower severity of depressive symptoms than those receiving placebo. Methylphenidate, as well as cognitive-behavioral therapy, may improve mental fatigue and cognitive function in patients with traumatic brain injury. Vitamin D treatment significantly improved fatigue in kidney transplantation patients as well as in otherwise healthy persons with vitamin D deficiency. Internet-based cognitive-behavioral therapy is effective in reducing severe fatigue in breast cancer survivors. Therapeutic Care (a complementary medicine modality that uses acupressure) reduces fatigue in some patients with breast cancer receiving chemotherapy. Six weeks of Swedish massage therapy reduced fatigue in female breast cancer survivors who had surgery plus radiation and/or chemotherapy/chemoprevention. There is limited and preliminary evidence that rasagiline, modafinil, and doxepin are associated with improvement of fatigue in Parkinson disease.

The treatment of subclinical hypothyroidism is unlikely to benefit symptoms of fatigue. The TRUST study found that treatment of subclinical hypothyroidism with levothyroxine did not improve symptoms of fatigue as measured by the Tiredness score ( $3.2 \pm 17.7$  in placebo group and  $3.8 \pm 18.4$ , respectively; between-group difference,  $0.4$ ; 95% CI,  $-2.1$  to  $+2.9$ ). Oral melatonin does

## FATIGUE



### ESSENTIAL INQUIRIES

- Weight loss; fever.
- Sleep-disordered breathing.
- Medications; substance use.

## ► General Considerations

Fatigue, as an isolated symptom, accounts for 1–3% of visits to generalists. The symptom of fatigue is often poorly described and less well defined by patients than symptoms associated with specific dysfunction of organ systems. Fatigue or lassitude and the closely related complaints of weakness, tiredness, and lethargy are often attributed to overexertion, poor physical conditioning, sleep disturbance, obesity, undernutrition, and emotional problems. A history of the patient’s daily living and working habits may obviate the need for extensive and unproductive diagnostic studies.

## ► Clinical Findings

Clinically relevant fatigue is composed of three major components: generalized weakness (difficulty in initiating activities); easy fatigability (difficulty in completing activities); and mental fatigue (difficulty with concentration and memory). Important diseases that can cause fatigue include hyperthyroidism and hypothyroidism, HF, infections (endocarditis, hepatitis), COPD, interstitial lung disease, end-stage renal disease, sleep apnea, anemia, autoimmune disorders, multiple sclerosis, irritable bowel syndrome, Parkinson disease, cerebral vascular accident, and cancer. Solution-focused therapy has a significant initial beneficial effect on the severity of fatigue and quality of life in patients with quiescent inflammatory bowel disease.

not improve fatigue in patients with advanced cancer. Exceeding the RDA for protein intake does not increase muscle or physical function, nor augment anabolic response to testosterone in older men.

### ► When to Refer

- Infections not responsive to standard treatment.
- Difficult-to-control hyperthyroidism or hypothyroidism.
- Severe psychological illness.
- Malignancy.

### ► When to Admit

- Failure to thrive.
- Fatigue severe enough to impair activities of daily living.

Kinkead B et al. Massage therapy decreases cancer-related fatigue: results from a randomized early phase trial. *Cancer*. 2018;124:546. [PMID: 29044466]

Twisk FNM. Myalgic encephalomyelitis, chronic fatigue syndrome, and chronic fatigue: three distinct entities requiring complete different approaches. *Curr Rheumatol Rep*. 2019; 21:27. [PMID: 31073713]

## ACUTE HEADACHE



### ESSENTIAL INQUIRIES

- ▶ Age > 40 years.
- ▶ Rapid onset and severe intensity (ie, “thunderclap” headache), trauma, onset during exertion.
- ▶ Fever, vision changes, neck stiffness.
- ▶ HIV infection.
- ▶ Current or past history of hypertension.
- ▶ Neurologic findings (mental status changes, motor or sensory deficits, loss of consciousness).

### ► General Considerations

Headache is a common reason that adults seek medical care. In the United States, it accounts for approximately 13 million visits each year to physicians' offices, urgent care clinics, and emergency departments. It is the fifth most common reason for emergency department visits, and second most common reason for neurologic consultation in the emergency department. A broad range of disorders can cause headache (see Chapter 24). This section deals only with acute nontraumatic headache in adults and adolescents. The challenge in the initial evaluation of acute headache is to identify which patients are presenting with an uncommon but life-threatening condition; approximately 1% of patients seeking care in emergency department settings and considerably less in office practice settings fall into this category.

Diminution of headache in response to typical migraine therapies (such as serotonin receptor antagonists or

ketorolac) does not rule out critical conditions such as subarachnoid hemorrhage or meningitis as the underlying cause. A “sentinel headache” before a subarachnoid hemorrhage is a sudden, intense, persistent headache different from previous headaches; it precedes subarachnoid hemorrhage by days or weeks and occurs in 15–60% of patients with spontaneous subarachnoid hemorrhage.

### ► Clinical Findings

#### A. Symptoms

A careful history and physical examination should aim to identify causes of acute headache that require immediate treatment. These causes can be broadly classified as imminent or completed **vascular events** (intracranial hemorrhage, thrombosis, cavernous sinus thrombosis, vasculitis, malignant hypertension, arterial dissection, cerebral venous thrombosis, transient ischemic attack, or aneurysm), **infections** (abscess, encephalitis, or meningitis), **intracranial masses** causing intracranial hypertension, **preeclampsia**, and **carbon monoxide poisoning**. Having the patient carefully describe the onset of headache can be helpful in diagnosing a serious cause.

Report of a sudden-onset headache that reaches maximal and severe intensity within seconds or a few minutes is the classic description of a “thunderclap” headache; it should precipitate workup for subarachnoid hemorrhage, since the estimated prevalence of subarachnoid hemorrhage in patients with thunderclap headache is 43%.

Thunderclap headache during the postpartum period precipitated by the Valsalva maneuver or recumbent positioning may indicate reversible cerebral vasoconstriction syndrome or irreversible cerebral venous sinus thrombosis. Venous-specific imaging sequences may be needed for diagnosis. Other historical features that raise the need for diagnostic testing include headache brought on by cough, exertion, or sexual activity.

The medical history can also guide the need for additional workup. Under most circumstances (including a normal neurologic examination), new headache in a patient older than 50 years or with HIV infection warrants immediate neuroimaging (Table 2–5). When the patient has a history of hypertension—particularly uncontrolled hypertension—a complete search for other features of “malignant hypertension” is appropriate to determine the urgency of control of hypertension (see Chapter 11). Headache and hypertension associated with pregnancy may be due to preeclampsia. Episodic headache associated with the triad of hypertension, palpitations, and sweats is suggestive of pheochromocytoma. In the absence of thunderclap headache, advanced age, and HIV infection, a careful physical examination and detailed neurologic examination will usually determine acuity of the workup and need for further diagnostic testing. A history consistent with hypercoagulability is associated with an increased risk of cerebral venous thrombosis.

Symptoms can also be useful for diagnosing migraine headache in the absence of the “classic” migraine pattern of scintillating scotoma followed by unilateral headache, photophobia, and nausea and vomiting (Table 2–6).

**Table 2–5.** Clinical features associated with acute headache that warrant urgent or emergent neuroimaging.

|   |
|---|
| <b>Prior to lumbar puncture</b>   |
| Abnormal neurologic examination   |
| Abnormal mental status  |
| Abnormal funduscopic examination (papilledema; loss of venous pulsations) |
| Meningeal signs   |
| <b>Emergent (conduct prior to leaving office or emergency department)</b> |
| Abnormal neurologic examination   |
| Abnormal mental status  |
| “Thunderclap” headache  |
| <b>Urgent (scheduled prior to leaving office or emergency department)</b> |
| HIV-positive patient <sup>1</sup>   |
| Age > 50 years (normal neurologic examination)                            |

<sup>1</sup>Use CT with or without contrast or MRI if HIV positive.

Data from American College of Emergency Physicians. Clinical policy: critical issues in the evaluation and management of patients presenting to the emergency department with acute headache. Ann Emerg Med. 2002;39:108–22.

The presence of three or more of these symptoms (nausea, photophobia, phonophobia, and exacerbation by physical activity) can establish the diagnosis of migraine (in the absence of other clinical features that warrant neuroimaging studies), and the presence of only one or two symptoms (provided one is not nausea) can help rule out migraine. A systematic list called the SNNOOP10 has been developed as a screening method for secondary causes of headache (Table 2–7).

## B. Physical Examination

Critical components of the physical examination of the patient with acute headache include vital signs, neurologic examination, and vision testing with funduscopic examination. The finding of fever with acute headache warrants additional maneuvers to elicit evidence of meningeal inflammation, such as Kernig and Brudzinski signs. The absence of jolt accentuation of headache cannot accurately rule out meningitis. Patients older than 60 years should be examined for scalp or temporal artery tenderness.

**Table 2–6.** Summary likelihood ratios (LRs) for individual clinical features associated with migraine diagnosis.

| Clinical Feature                  | LR+ (95% CI)  | LR- (95% CI)     |
|-----------------------------------|---------------|------------------|
| Nausea                            | 19 (15–25)    | 0.19 (0.18–0.20) |
| Photophobia                       | 5.8 (5.1–6.6) | 0.24 (0.23–0.26) |
| Phonophobia                       | 5.2 (4.5–5.9) | 0.38 (0.36–0.40) |
| Exacerbation by physical activity | 3.7 (3.4–4.0) | 0.24 (0.23–0.26) |

CI, confidence interval.

Careful assessment of visual acuity, ocular gaze, visual fields, pupillary defects, optic disks, and retinal vein pulsations is crucial. Diminished visual acuity is suggestive of glaucoma, temporal arteritis, or optic neuritis. Ophthalmoplegia or visual field defects may be signs of venous sinus thrombosis, tumor, or aneurysm. Afferent pupillary defects can be due to intracranial masses or optic neuritis. In the setting of headache and hypertension, retinal cotton wool spots, flame hemorrhages, and disk swelling indicate acute severe hypertensive retinopathy. Ipsilateral ptosis and miosis suggest Horner syndrome and in conjunction with acute headache may signify carotid artery dissection. Finally, papilledema or absent retinal venous pulsations are signs of elevated intracranial pressure—findings that should be followed by neuroimaging prior to performing lumbar puncture (Table 2–5). On nonmydriatic fundoscopy, up to 8.5% of patients who arrive at the emergency department complaining of headache had abnormalities; although few had other significant physical examination findings, 59% of them had abnormal neuroimaging studies.

Complete neurologic evaluations are also critical and should include assessment of mental status, motor and sensory systems, reflexes, gait, cerebellar function, and pronator drift. Any abnormality on neurologic evaluation (especially mental status) warrants emergent neuroimaging (Table 2–5).

## C. Diagnostic Studies

Neuroimaging is summarized in Table 2–5. Under most circumstances, a noncontrast head CT is sufficient to exclude intracranial hypertension with impending herniation, intracranial hemorrhage, and many types of intracranial masses (notable exceptions include lymphoma and toxoplasmosis in HIV-positive patients, herpes simplex encephalitis, and brain abscess). When needed, a contrast study can be ordered to follow a normal noncontrast study. A normal neuroimaging study does not exclude subarachnoid hemorrhage and should be followed by lumbar puncture. One study supported a change of practice wherein a lumbar puncture can be withheld when a head CT scan was performed less than 6 hours after headache onset and showed no evidence of subarachnoid hemorrhage (negative predictive value 99.9% [95% CI, 99.3–100.0%]).

In patients for whom there is a high level of suspicion for subarachnoid hemorrhage or aneurysm, a normal CT and lumbar puncture should be followed by angiography within the next few days (provided the patient is medically stable).

Lumbar puncture is also indicated to exclude infectious causes of acute headache, particularly in patients with fever or meningeal signs. Cerebrospinal fluid tests should routinely include Gram stain, white blood cell count with differential, red blood cell count, glucose, total protein, and bacterial culture. In appropriate patients, also consider testing cerebrospinal fluid for VDRL (syphilis), cryptococcal antigen (HIV-positive patients), acid-fast bacillus stain and culture, and complement fixation and culture for coccidioidomycosis. Storage of an extra tube with 5 mL of cerebrospinal fluid is also prudent for conducting unanticipated tests in the immediate future. Polymerase chain

**Table 2–7.** SNNOOP10 list of “red” flags for secondary causes of headache.

| Sign or Symptom                                     | Related Secondary Headaches  |
|---|--|
| Systemic symptoms <sup>1</sup>                      | Headache attributed to infection, nonvascular intracranial disorders, carcinoid, or pheochromocytoma   |
| Neoplasm in history                                 | Neoplasms of the brain; metastasis   |
| Neurologic deficit/dysfunction                      | Headaches attributed to vascular, nonvascular intracranial disorders; brain abscess and other infections   |
| Onset of headache is sudden or abrupt               | Subarachnoid hemorrhage and other headache attributed to cranial or cervical vascular disorders  |
| Older age (> 50 years)                              | Giant cell arteritis and other headache attributed to cranial or cervical vascular disorders; neoplasms and other nonvascular intracranial disorders   |
| Pattern change or recent onset of headache          | Neoplasms, headaches attributed to vascular, nonvascular intracranial disorders  |
| Positional headache                                 | Intracranial hypertension or hypotension   |
| Precipitated by sneezing, coughing, or exercise     | Posterior fossa malformations; Chiari malformation   |
| Papilledema   | Neoplasms and other nonvascular intracranial disorders; intracranial hypertension  |
| Progressive headache and atypical presentations     | Neoplasms and other nonvascular intracranial disorders   |
| Pregnancy or puerperium                             | Headaches attributed to cranial or cervical vascular disorders; postdural puncture headache; hypertension-related disorders (eg, preeclampsia); cerebral sinus thrombosis; hypothyroidism; anemia; diabetes mellitus |
| Painful eye with autonomic features                 | Pathology in posterior fossa, pituitary region, or cavernous sinus; Tolosa-Hunt syndrome (severe, unilateral headaches with orbital pain and ophthalmoplegia due to extraocular palsies); other ophthalmic causes    |
| Posttraumatic onset of headache                     | Acute and chronic posttraumatic headache; subdural hematoma and other headache attributed to vascular disorders  |
| Immune system pathology, eg, HIV                    | Opportunistic infections   |
| Painkiller overuse or new drug at onset of headache | Medication overuse headache; drug incompatibility  |

<sup>1</sup>“Orange” flag for isolated fever alone.

Reproduced, with permission, from Do TP et al. Red and orange flags for secondary headaches in clinical practice: SNNOOP10 list. Neurology. 2019;92:134.

reaction tests for specific infectious pathogens (eg, herpes simplex 2) should also be considered in patients with evidence of central nervous system infection but no identifiable pathogen.

The Ottawa subarachnoid hemorrhage clinical decision rule had 100% sensitivity (and 13–15% specificity in different studies) in predicting subarachnoid hemorrhage. According to it, patients who seek medical attention in an emergency department complaining of an acute nontraumatic headache should be evaluated for subarachnoid hemorrhage if they have one or more of the following factors: age 40 years or older, neck pain or stiffness, witnessed loss of consciousness, onset during exertion, thunderclap headache (instantly peaking pain), or limited neck flexion on examination.

In addition to neuroimaging and lumbar puncture, additional diagnostic tests for exclusion of life-threatening causes of acute headache include erythrocyte sedimentation rate (temporal arteritis; endocarditis), urinalysis (malignant hypertension; preeclampsia), and sinus CT (bacterial sinusitis, independently or as a cause of venous sinus thrombosis).

## Treatment

Treatment should be directed at the cause of acute headache. In patients in whom migraine or migraine-like headache has been diagnosed, early treatment with ketorolac (oral, nasal, or intramuscular), dihydroergotamine, lasmiditan, ubrogepant, or triptans (oral, nasal, subcutaneous) can often abort or provide significant relief of symptoms (see Chapter 24). Intravenous prochlorperazine plus diphenhydramine was more effective for migraine pain relief than intravenous hydromorphone in the emergency department. There appears to be no benefit of adding intravenous diphenhydramine to intravenous metoclopramide. Prochlorperazine appears to be superior to ketamine for the treatment of benign headaches in the emergency department. Sumatriptan may be less effective as immediate therapy for migraine attacks with aura compared to attacks without aura. There may be a role for oral corticosteroids to prevent rebound headache after emergency department discharge, but in one study, long-acting intramuscular methylprednisolone acetate did not decrease the frequency of post-emergency department discharge

headache days compared with oral dexamethasone. Parenteral morphine and hydromorphone are best avoided as first-line therapy.

Subanesthetic ketamine infusions may be beneficial in individuals with chronic migraine and new daily persistent headache that has not responded to other aggressive treatments. Peripheral nerve blocks may be a safe and effective way to treat headaches in older adults. Surgical decompression of peripheral cranial and spinal nerves at trigger sites have been used to treat migraine. Noninvasive vagus nerve stimulation has shown promise in the management of migraine and acute cluster headaches.

High-flow oxygen therapy may also provide effective treatment for all headache types in the emergency department setting (eg, benefitting older patients with cluster headaches). Peripheral nerve blocks for treatment-refractory migraine may be an effective therapeutic option in pregnancy. The oral 5-HT<sub>1F</sub> receptor agonist, lasmiditan, has been approved for the acute treatment of migraine with or without aura in adults. The CGRP monoclonal antibodies (erenumab, fremanezumab, galcanezumab) have been approved for prevention of migraine. Galcanezumab has activity against cluster headache.

Regular exercise may have a prophylactic effect on migraine frequency; however, new, intense exercise can trigger migraine.

## ► When to Refer

- Frequent migraines not responsive to standard therapy.
- Migraines with atypical features.
- Chronic daily headaches due to medication overuse.

## ► When to Admit

- Need for repeated doses of parenteral pain medication.
- To facilitate an expedited workup requiring a sequence of neuroimaging and procedures.
- To monitor for progression of symptoms and to obtain neurologic consultation when the initial emergency department workup is inconclusive.
- Pain severe enough to impair activities of daily living or impede follow-up appointments or consultations.
- Patients with subarachnoid hemorrhage, intracranial mass, or meningitis.

Burch R. Migraine and tension-type headache: diagnosis and treatment. *Med Clin North Am.* 2019;103:215. [PMID: 30704678]

Diamanti S et al. Leading symptoms in cerebrovascular diseases: what about headache? *Neurol Sci.* 2019;40:147. [PMID: 30891639]

Do TP et al. Red and orange flags for secondary headaches in clinical practice: SNNOOP10 list. *Neurology.* 2019;92:134. [PMID: 30587518]

Guryildirim M et al. Acute headache in the emergency setting. *Radiographics.* 2019;39:1739. [PMID: 31589569]

Sjulstad AS et al. What is currently the best investigational approach to the patient with sudden-onset severe headache? *Headache.* 2019;59:1834. [PMID: 31710108]

Wu WT et al. The Ottawa subarachnoid hemorrhage clinical decision rule for classifying emergency department headache patients. *Am J Emerg Med.* 2020;38:198. [PMID: 30765279]

## DYSURIA



### ESSENTIAL INQUIRIES

- ▶ Fever; new back or flank pain; nausea or vomiting.
- ▶ Vaginal discharge.
- ▶ Pregnancy risk.
- ▶ Structural abnormalities.
- ▶ Instrumentation of urethra or bladder.

## ► General Considerations

Dysuria (painful urination) is a common reason for adults and adolescents to seek urgent medical attention.

An inflammatory process (eg, urinary tract infection [UTI], autoimmune disorder) underlies most causes of dysuria. In women, cystitis will be diagnosed in up to 50–60% of cases. Cystitis has an incidence of 0.5–0.7% per year in sexually active young women. The key objective in evaluating women with dysuria is to exclude serious upper urinary tract disease, such as acute pyelonephritis, and sexually transmitted diseases. In elderly men, dysuria may be a symptom of prostatitis. In contrast, in younger men, urethritis accounts for the vast majority of cases of dysuria. Male cyclists had no worse sexual or urinary functions than swimmers or runners, but cyclists were more prone to urethral stricture.

## ► Clinical Findings

### A. Symptoms

Well-designed cohort studies have shown that some women can be reliably diagnosed with uncomplicated cystitis without a physical examination or urinalysis, and randomized controlled trials show that telephone management of uncomplicated cystitis is safe and effective. An increased likelihood of cystitis is present when women report multiple irritative voiding symptoms (dysuria, urgency, frequency), fever, or back pain (positive LRs = 1.6–2.0). A cohort study found that the symptom of dysuria most reliably predicted a culture-positive UTI. Inquiring about symptoms of vulvovaginitis is imperative. When women report dysuria and urinary frequency, and deny vaginal discharge and irritation, the LR for culture-confirmed cystitis is 24.5. In contrast, when vaginal discharge or irritation is present, as well as dysuria or urinary frequency, the LR is 0.7. Gross hematuria in women with voiding symptoms usually represents hemorrhagic cystitis but can also be a sign of bladder cancer (particularly in older patients) or upper tract disease. Failure of hematuria to resolve with antibiotic treatment should prompt further evaluation of the bladder and kidneys. Chlamydial

infection should be strongly considered among women aged 25 years or younger who are sexually active and seeking medical attention for a suspected UTI for the first time or who have a new partner.

Because fever and back pain, as well as nausea and vomiting, are considered harbingers of (or clinical criteria for) acute pyelonephritis, women with these symptoms should usually be examined by a clinician prior to treatment in order to exclude coexistent urosepsis, hydronephrosis, or nephrolithiasis that would affect management decisions. Risk factors for acute pyelonephritis among women 18–49 years of age relate to sexual behaviors (frequent sexual intercourse [3 times per week or more], new sexual partner in previous year, recent spermicide use), as well as diabetes mellitus and recent UTI or incontinence.

Finally, pregnancy, underlying structural factors (polycystic kidney disease, nephrolithiasis, neurogenic bladder), immunosuppression, diabetes mellitus, and a history of recent bladder or urethral instrumentation usually alter the treatment regimen (antibiotic choice or duration of treatment, or both) for cystitis. Presence of UTI during pregnancy is strongly associated with preeclampsia (particularly UTI during the third trimester).

## B. Physical Examination

Fever, tachycardia, or hypotension suggests the possibility of urosepsis and potential need for hospitalization. A focused examination in women, in uncomplicated circumstances, could be limited to ascertainment of costovertebral angle tenderness and to a lower abdominal and pelvic examination if the history suggests vulvovaginitis or cervicitis.

## C. Diagnostic Studies

**1. Urinalysis**—Urinalysis is probably overutilized in the evaluation of dysuria. The probability of culture-confirmed UTI among women with a history and physical examination compatible with uncomplicated cystitis is about 70–90%. Urinalysis is most helpful in atypical presentations of cystitis. Dipstick detection (greater than trace) of leukocytes, nitrites, or blood supports a diagnosis of cystitis. When both leukocyte and nitrite tests are positive, the LR is 4.2, and when both are negative, the LR is 0.3. The negative predictive value of urinalysis is not sufficient to exclude culture-confirmed UTI in women with multiple and typical symptoms, and randomized trial evidence shows that antibiotic treatment is beneficial to women with typical symptoms and negative urinalysis dipstick tests. Microscopy of unspun urine may also be helpful in diagnosis and reduces unnecessary use of antibiotics. The combination of urgency, dysuria, and pyuria assessed with the high-power objective (40 $\times$ ) for pus cells (more than 1 pus cell/7 high-power fields) had a positive predictive value of 71 and LR of 2.97.

**2. Urine culture**—Urine culture should be considered for all women with upper tract symptoms (prior to initiating antibiotic therapy), as well as those with dysuria and a negative urine dipstick test. In symptomatic women, a clean-catch urine culture is considered positive when  $10^2$ – $10^3$

colony-forming units/mL of a uropathogenic organism are detected. The benefit of DNA next-generation sequencing and expanded quantitative urine culture is being studied, and in a recent study, multiplex polymerase chain reaction analysis was found to be as beneficial as a urine culture.

**3. Renal imaging**—When severe flank or back pain is present, the possibility of complicated kidney infection (peri-nephric abscess, nephrolithiasis) or of hydronephrosis should be considered. Renal ultrasound or CT scanning should be done to rule out abscess and hydronephrosis. To exclude nephrolithiasis, noncontrast helical CT scanning is more accurate than intravenous urography and is the diagnostic test of choice. In a meta-analysis, the positive and negative LRs of helical CT scanning for diagnosis of nephrolithiasis were 23.2 and 0.05, respectively.

## Differential Diagnosis

The differential diagnosis of dysuria in women includes acute cystitis, acute pyelonephritis, vaginitis (*Candida*, bacterial vaginosis, *Trichomonas*, herpes simplex), urethritis/cervicitis (*Chlamydia*, gonorrhea), and interstitial cystitis/painful bladder syndrome. Pelvic congestion syndrome (dilated and refluxing pelvic veins) may also cause dysuria and pelvic pain.

Nucleic acid amplification tests from first-void urine or vaginal swab specimens are highly sensitive for detecting chlamydial infection. Other infectious pathogens associated with dysuria and urethritis in men include *Mycoplasma genitalium* and Enterobacteriaceae.

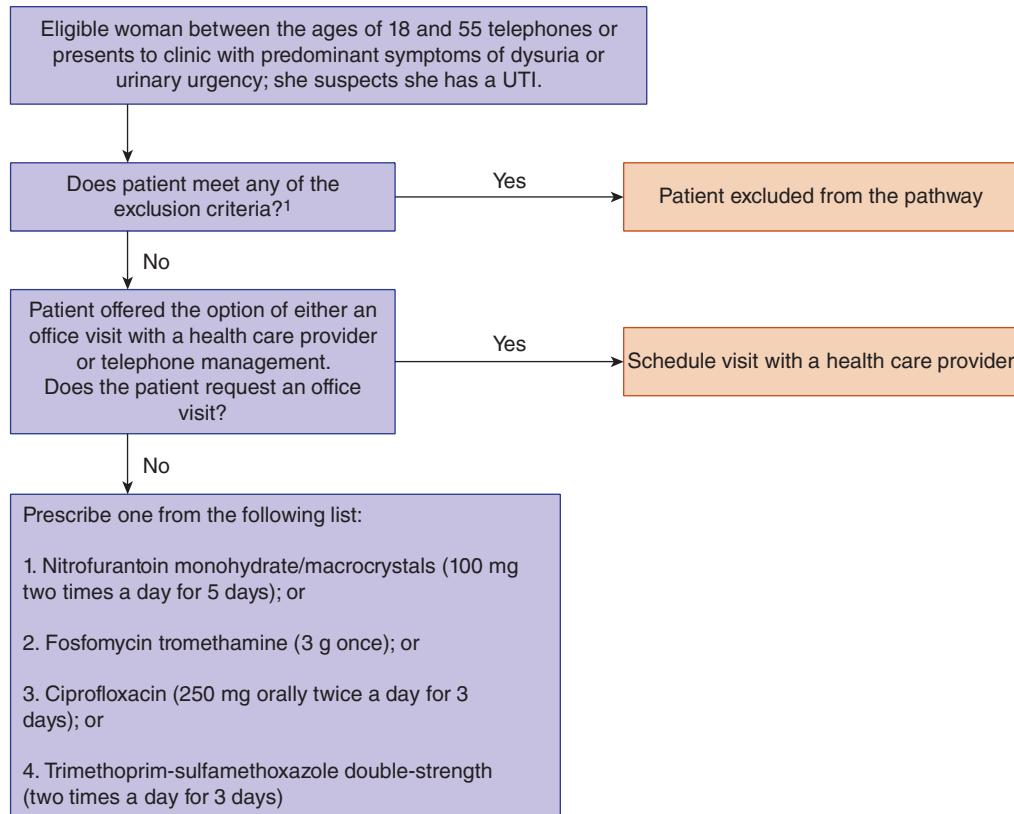
## Treatment

Definitive treatment is directed to the underlying cause of the dysuria. An evidence-informed algorithm for managing suspected UTI in women is shown in Figure 2–1. This algorithm supports antibiotic treatment of most women with multiple and typical symptoms of UTI without performing urinalysis or urine culture. Antibiotic selection should be guided by local resistance patterns and expert-panel clinical practice guidelines; major options for uncomplicated cystitis include nitrofurantoin, cephalosporins, ciprofloxacin, fosfomycin, and trimethoprim-sulfamethoxazole. Five days of nitrofurantoin resulted in a significantly greater likelihood of clinical and microbiologic resolution than single-dose fosfomycin.

In a study of 47 patients with UTIs due to multidrug-resistant bacteria, treatment with fosfomycin resulted in clinical cure rates of 87% and 94% at 48 hours and 14 days, respectively.

According to the American Academy of Pediatrics' Committee on Drugs, antibiotics that are usually acceptable when treating women who are breastfeeding include trimethoprim-sulfamethoxazole (unless G6PD deficiency is present), amoxicillin, nitrofurantoin, ciprofloxacin, and ofloxacin. Plazomicin, a novel neoglycoside, is FDA approved for the treatment of adults with complicated urinary tract infections who have limited or no alternative treatment options.

In men, prolonged treatment of UTIs (more than 7 days) out of concern for delayed clearance of infection



**▲ Figure 2–1.** Proposed algorithm for evaluating women with symptoms of acute urinary tract infection (UTI). (Data from Gupta K et al; Infectious Diseases Society of America; European Society for Microbiology and Infectious Diseases. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: A 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. Clin Infect Dis. 2011;52:e103.)

within the prostate does not appear to reduce early or late recurrences. A 5-day course of fluoroquinolones in outpatient men with UTI is as effective as a 10-day course.

Symptomatic relief can be provided with phenazopyridine, a urinary analgesic that is available over the counter; it is used in combination with antibiotic therapy (when a UTI has been confirmed) but for no more than 2 days. Patients should be informed that phenazopyridine will cause orange/red discoloration of their urine and other body fluids (eg, some contact lens wearers have reported discoloration of their lenses). Rare cases of methemoglobinemia and hemolytic anemia have been reported, usually with overdoses or underlying kidney dysfunction. NSAIDs have also been shown to be of symptomatic benefit, but less effective than antibiotic therapy. Although some women recover from uncomplicated UTI when treated with NSAIDs alone (53% in a Norwegian study), the rate of

progression to pyelonephritis was substantial. Delayed antibiotic therapy in elderly patients with UTI leads to a substantially higher rate of bloodstream infections and all-cause mortality. If a broad-spectrum antibiotic was initially prescribed empirically for UTI and urine culture results return establishing efficacy of a narrow-spectrum antibiotic, treatment should be “de-escalated” to the narrow-spectrum antimicrobial. Among premenopausal women with recurrent UTIs, increased daily water consumption decreased the mean number of cystitis episodes over a 12-month period (1.7 [95% CI, 1.5–1.8] in the increased water consumption group compared with 3.2 [95% CI, 3.0–3.4] in the control group) and reduced the number of antibiotic prescriptions received (1.9 [95% CI, 1.7–2.2] and 3.6 [95% CI, 3.3–4.0], respectively). In patients with asymptomatic renal calculi and recurrent UTIs, stone extraction eliminated infections in 50% of women.

In cases of interstitial cystitis/painful bladder syndrome (see Chapter 23), patients will often respond to a multimodal approach that may include urethral/vesicular dilation, biofeedback, cognitive-behavioral therapy, antidepressants, dietary changes, vaginal emollients, and other supportive measures. Vaginal estrogen effectively relieves urinary urgency and frequency as well as recurrent UTIs related to vulvovaginal atrophy of menopause (also known as genitourinary syndrome of menopause).

A meta-analysis found that antibiotic treatment for most people with asymptomatic bacteriuria is not beneficial and may be harmful. Antibiotic treatment benefits both pregnant women with asymptomatic bacteriuria as well as persons about to undergo urologic surgery. The USPSTF recommends screening pregnant women for asymptomatic bacteriuria by obtaining a urine culture (B recommendation). The USPSTF recommends against screening for asymptomatic bacteriuria in nonpregnant adults (D recommendation).

There were no differences in the prevalence of postoperative UTI in women who had mixed-flora on preoperative urine cultures compared to those with no growth on preoperative urine cultures.

### ► When to Refer

- Anatomic abnormalities leading to repeated urinary infections.
- Infections associated with nephrolithiasis.
- Persistent interstitial cystitis/painful bladder syndrome.

### ► When to Admit

- Severe pain requiring parenteral medication or impairing ambulation or urination (such as severe primary herpes simplex genitalis).
- Dysuria associated with urinary retention or obstruction.
- Pyelonephritis with ureteral obstruction.
- Symptoms and signs suggesting urosepsis.

Alidjanov JF et al. Reliability of symptom-based diagnosis of uncomplicated cystitis. *Urol Int.* 2019;102:83. [PMID: 30419565]

Aslam S et al. Recurrent urinary tract infections in adult women. *JAMA.* 2020;323:658. [PMID: 31995139]

Chu CM et al. Diagnosis and treatment of urinary tract infections across age groups. *Am J Obstet Gynecol.* 2018;219:40. [PMID: 29305250]

Kolman KB. Cystitis and pyelonephritis: diagnosis, treatment, and prevention. *Prim Care.* 2019;46:191. [PMID: 31030820]

Maki DG. USPSTF recommends screening for asymptomatic bacteriuria in pregnant women but not nonpregnant adults. *Ann Intern Med.* 2020;172:JC14. [PMID: 32066147]

Tornic J et al. The challenge of asymptomatic bacteriuria and symptomatic urinary tract infections in patients with neurogenic lower urinary tract dysfunction. *J Urol.* 2020;203:579. [PMID: 31526261]

# Preoperative Evaluation & Perioperative Management

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3

## EVALUATION OF THE ASYMPTOMATIC PATIENT

Patients without significant medical problems—especially those under age 50—are at very low risk for perioperative complications. Their preoperative evaluation should include a history and physical examination; emphasis should be on a pharmacologic history and assessment of functional status, exercise tolerance, and cardiopulmonary status to look for unrecognized disease that may require further evaluation prior to surgery. In addition, a directed bleeding history (Table 3–1) should be taken to uncover coagulopathy that could contribute to excessive surgical blood loss. Routine preoperative laboratory tests in asymptomatic healthy patients under age 50 have *not* been found to help predict or prevent complications. Even elderly patients undergoing minor or minimally invasive procedures (such as cataract surgery) are unlikely to benefit from preoperative screening tests.

Martin SK et al. Routine preoperative laboratory tests for elective surgery. JAMA. 2017;318:567. [PMID: 28787493]

## CARDIAC RISK ASSESSMENT & REDUCTION IN NONCARDIAC SURGERY

The most important perioperative cardiac complications are myocardial infarction (MI) and cardiac death; postoperative myocardial injury is a major predictor of mortality. Other complications include heart failure (HF), arrhythmias, and unstable angina. The principal patient-specific

risk factor for cardiac complications is the presence of end-organ cardiovascular disease. This includes not only coronary artery disease and HF but also cerebrovascular disease and chronic kidney disease. Diabetes mellitus, especially if treated with insulin, is considered a cardiovascular disease equivalent that increases the risk of cardiac complications. Major abdominal, thoracic, and vascular surgical procedures (especially abdominal aortic aneurysm repair) carry a higher risk of postoperative cardiac complications, likely due to their associated major fluid shifts, hemorrhage, and hypoxemia. These risk factors were identified in a validated, multifactorial risk prediction tool: the Revised Cardiac Risk Index (RCRI) (Table 3–2). The American College of Surgeons' National Surgical Quality Improvement Program (NSQIP) risk prediction tool uses patient age, the location or type of operation, serum creatinine greater than 1.5 mg/dL (132.6 μmol/L), dependency in activities of daily living, and the patient's American Society of Anesthesiologists physical status classification as predictors for postoperative MI or cardiac arrest. An online risk calculator using the NSQIP tool can be found at <http://www.qxmd.com/calculate-online/cardiology/gupta-perioperative-cardiac-risk>. The American College of Cardiology and American Heart Association endorse both prediction tools. Patients with two or more RCRI predictors or a risk of perioperative MI or cardiac arrest in excess of 1% as calculated by the NSQIP prediction tool are deemed to be at elevated risk for cardiac complications.

Limited exercise capacity (eg, the inability to walk for two blocks at a normal pace or climb a flight of stairs without resting) also predicts higher cardiac risk. Emergency operations are also associated with greater cardiac risk but should not be delayed for extensive cardiac evaluation. Instead, patients facing emergency surgery should be medically optimized for surgery as quickly as possible and closely monitored for cardiac complications during the perioperative period.

**Table 3–1.** Directed bleeding history: Findings suggestive of a bleeding disorder.

|   |
|---|
| Unprovoked bruising on the trunk of > 5 cm in diameter  |
| Frequent unprovoked epistaxis or gingival bleeding  |
| Menorrhagia with iron deficiency  |
| Hemarthrosis with mild trauma   |
| Prior excessive surgical blood loss or reoperation for bleeding                                   |
| Family history of abnormal bleeding   |
| Presence of severe kidney or liver disease  |
| Use of medications that impair coagulation, including nutritional supplements and herbal remedies |

## ► Role of Preoperative Noninvasive Ischemia Testing

Most patients can be accurately risk-stratified by history and physical examination. A resting electrocardiogram

**Table 3–2.** Revised Cardiac Risk Index (RCRI).

| Independent Predictors of Postoperative Cardiac Complications     |  |
|---|--|
| Intrathoracic, intraperitoneal, or suprainguinal vascular surgery |  |
| History of ischemic heart disease                                 |  |
| History of heart failure  |  |
| Insulin treatment for diabetes mellitus                           |  |
| Serum creatinine level > 2 mg/dL (> 176.8 μmol/L)                 |  |
| History of cerebrovascular disease                                |  |
| Scoring (Number of Predictors Present)                            | Risk of Major Cardiac Complications <sup>1</sup> |
| None  | 0.4%   |
| One   | 1%   |
| Two   | 2.4%   |
| More than two   | 5.4%   |

<sup>1</sup>Cardiac death, myocardial infarction, or nonfatal cardiac arrest. Data from Devereaux PJ et al. Perioperative cardiac events in patients undergoing noncardiac surgery: a review of the magnitude of the problem, the pathophysiology of the events and methods to estimate and communicate risk. CMAJ. 2005; 173:627.

(ECG) should be obtained in patients with at least one RCRI predictor prior to major surgery but generally omitted in asymptomatic patients undergoing minor operations. Additional noninvasive stress testing rarely improves risk stratification or management, especially in patients without cardiovascular disease undergoing minor operations, or who have at least fair functional capacity. Stress testing has more utility in patients with elevated risk scores on clinical prediction tools, especially if they have poor functional status. In these patients, the absence of ischemia on dipyridamole scintigraphy or dobutamine stress echocardiography is reassuring; in contrast, extensive inducible ischemia predicts a high risk of cardiac complications, particularly with vascular surgery, which may not be modifiable by either medical management or coronary revascularization. The predictive value of an abnormal stress test result for nonvascular surgery patients is less well established. An approach to perioperative cardiac risk assessment and management in patients with known or suspected stable coronary artery disease is shown in Figure 3–1.

## ► Role of Cardiac Biomarkers

Preoperative B-type natriuretic peptide (BNP) or N-terminal fragment of proBNP (NT-proBNP) levels directly correlate with the risk for perioperative cardiac complications, and their measurement may improve risk assessment. A meta-analysis of 2179 patients found that BNP greater than or equal to 92 ng/L or NT-proBNP greater than or equal to 300 ng/L before noncardiac surgery were associated with a fourfold increase in 30-day mortality and MI. American and European cardiology society guidelines are equivocal

about the use of biomarkers to enhance risk prediction; the Canadian Cardiovascular Society, however, strongly recommends measuring BNP or NT-proBNP levels prior to major noncardiac surgery in patients older than 65 years and younger patients with cardiovascular disease or a RCRI score greater than or equal to 1.

## ► Perioperative Management of Patients with Coronary Artery Disease

Patients with acute coronary syndromes require immediate management of their cardiac disease prior to any preoperative evaluation (see Chapter 10).

### A. Medications

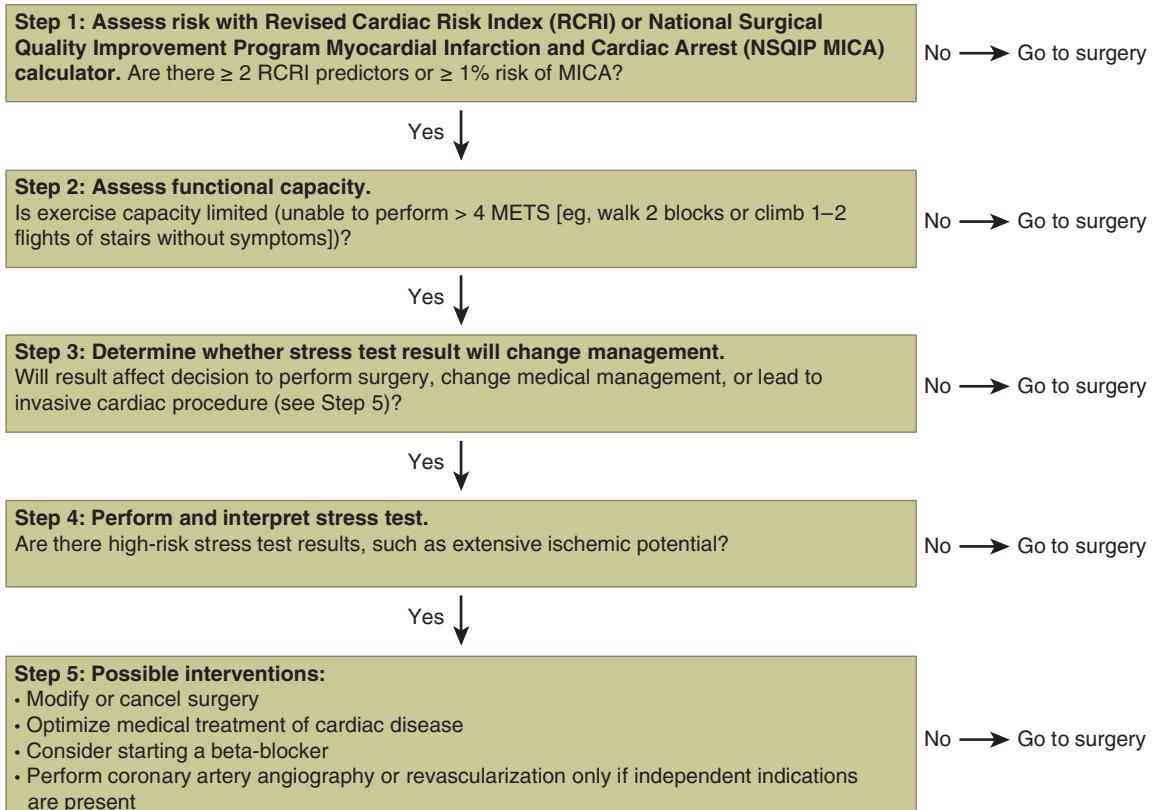
**1. Antianginal medications**—Preoperative antianginal medications, including beta-blockers, calcium channel blockers, and nitrates, should be continued throughout the perioperative period. Several trials have shown that initiation of beta-blockers before major noncardiac surgery reduces the risk of nonfatal MI. However, in the largest trial, a high, fixed dose of metoprolol succinate increased total mortality and the risk of stroke. Because of the uncertain benefit-to-risk ratio, initiation of perioperative beta-blockade should be considered only in patients with a high risk of cardiac complications. If used, beta-blockers should be started well in advance of surgery, to allow time to gradually titrate up the dose without causing excessive bradycardia or hypotension. They should not be started on the day of surgery. Possible indications and starting doses for prophylactic beta-blockade are presented in Table 3–3. See Hypertension section, below, regarding perioperatively holding antihypertensive medications for patients with hypertension who do not have coronary artery disease.

**2. Statins**—Several randomized trials found that HMG-CoA reductase inhibitors (statins) prevent MI in patients undergoing noncardiac surgery. Safety concerns, such as liver failure or rhabdomyolysis, have not materialized in these studies. It is unclear how far in advance of surgery statins must be started and what doses are needed to see benefits. However, based on treatment protocols used in clinical trials, at least a moderate statin dose (eg, atorvastatin 20 mg or fluvastatin 80 mg orally daily) should be considered in all patients undergoing vascular surgery and other patients deemed to be at high risk for cardiac complications, regardless of lipid levels, and initiated at least 30 days before surgery if possible. Patients already taking statins should continue these agents during the perioperative period.

**3. Aspirin**—In patients without coronary stents, initiation of aspirin therapy before noncardiac surgery is not recommended because it did not reduce cardiac risk and caused increased bleeding in a large, randomized trial. Holding long-term prophylactic aspirin therapy in such patients does not increase cardiac risk.

### B. Coronary Revascularization

Patients who have previously had coronary artery bypass grafting (CABG) surgery or percutaneous coronary

**Notes:**

Step 2: Reasonable to avoid stress test in patients with excellent functional capacity ( $> 10$  METs) and not unreasonable to avoid stress test in patients with moderate or good functional capacity (4–10 METs); patients with unknown functional capacity should be considered unable to perform 4 METs.

Step 3: Regardless of decision to perform stress test, patients should receive optimal guideline-concordant medical therapy.

Step 4: Pharmacologic stress test preferred due to assumption of poor exercise capacity.

Step 5: Possible indications for beta-blockers include  $\geq 3$  RCRI predictors, ischemia on stress test, or indications independent of surgery.

▲ **Figure 3–1.** Approach to cardiac evaluation in stable patients undergoing major elective surgery. METs, metabolic equivalents.

**Table 3–3.** Indications for prophylactic perioperative beta-blockade.<sup>1</sup>

|                      |  |
|----------------------|--|
| Strong indications   | Patient already taking beta-blocker to treat ischemia, arrhythmia, or hypertension   |
| Possible indications | Patient with myocardial ischemia detected on preoperative stress testing<br>Patient has $\geq 3$ Revised Cardiac Risk Index predictors (see Table 3–2) |

<sup>1</sup>Initial dose recommendations: atenolol 25 mg orally daily, bisoprolol 2.5 mg orally daily, or metoprolol tartrate 25 mg orally twice daily. The dose of beta-blocker should be carefully titrated to keep heart rate  $< 70$  beats per minute and systolic blood pressure  $> 100$  mm Hg. Avoid initiating beta-blockade on the day of surgery.

interventions (PCI) have a relatively low risk of cardiac complications when undergoing subsequent noncardiac surgery. However, a trial that randomized over 500 patients with angiographically proven coronary artery disease to either coronary revascularization (with either CABG or PCI) or medical management alone before vascular surgery found no difference in postoperative MI, 30-day mortality, and long-term mortality. Thus, **preoperative CABG or PCI should be performed only when patients have guideline-concordant indications independent of the planned noncardiac operation**. In addition, surgical patients who have undergone recent coronary stenting are at high risk for stent thrombosis, especially if antiplatelet therapy is stopped prematurely. Therefore, elective surgery should be deferred for at least 30 days after placement of a bare-metal stent and ideally for 6 months after placement of

a drug-eluting stent. If this delay poses significant risks, such as in patients undergoing an operation for cancer, surgery could be considered 3 months after drug-eluting stent implantation. Antiplatelet agents should be continued perioperatively if possible or resumed as soon as possible after surgery. The patient, surgeon, anesthesiologist, and cardiologist should discuss risks and benefits of delaying surgery and management options for dual antiplatelet therapy.

### ► Heart Failure & Left Ventricular Dysfunction

**Elective surgery should be postponed until decompensated HF (manifested by an elevated jugular venous pressure, an audible third heart sound, or evidence of pulmonary edema) has been brought under control.** In patients with compensated HF, the risk of perioperative cardiac complications is similar in patients with ischemic or nonischemic cardiomyopathy. HF with reduced ejection fraction likely confers more risk than HF with preserved ejection fraction. Guidelines recommend preoperative echocardiography in patients without known HF who have unexplained dyspnea and in patients with known HF with clinical deterioration. A small observational study found that routine echocardiography in patients with suspected heart disease or those aged 65 years or older prior to emergency noncardiac surgery frequently led to a change in diagnosis or management plan. While this is not an established practice, **preoperative echocardiography should be considered when there is uncertainty about the patient's cardiac status.**

Patients receiving diuretics and digoxin should have serum electrolyte and digoxin levels measured prior to surgery because abnormalities in these levels may increase the risk of perioperative arrhythmias. Clinicians must be cautious not to give too much diuretic, since the volume-depleted patient will be much more susceptible to intraoperative hypotension. The surgeon and anesthesiologist should be made aware of the presence and severity of left ventricular dysfunction so that appropriate decisions can be made regarding perioperative fluid management and intraoperative monitoring.

### ► Postoperative Myocardial Infarction

In a large cohort study, postoperative MI (defined by a combination of ECG abnormality and cardiac enzyme elevation) typically occurred within 3 days of surgery and was asymptomatic in the majority of cases. Clinical findings that should prompt its consideration include unexplained hypotension, hypoxemia, and delirium. Postoperative MI is associated with increased mortality, even when asymptomatic. Elevated postoperative troponin levels correlate directly with mortality risk, even in patients without ECG abnormalities or other findings of myocardial ischemia. The Canadian Cardiovascular Society advocates routine screening of high-risk patients, while American and European guidelines remain equivocal. It remains unclear how asymptomatic postoperative MI or troponin elevation should be managed, but optimizing secondary cardiac risk reduction strategies is reasonable.

### ► Valvular Heart Disease

If the nature or severity of valvular lesions is unknown, or if there has been a recent change in clinical status, echocardiography should be performed prior to noncardiac surgery. In addition, patients with known or suspected stenotic or regurgitant valvular disease that is moderately severe or worse should undergo echocardiography within 1 year before surgery. Candidates for valvular intervention independent of the planned noncardiac surgery should have the valve correction procedure performed first. Patients with uncorrected critical or symptomatic aortic stenosis are at particular risk for cardiac complications. They should undergo surgery only after consultation with a cardiologist and anesthesiologist. Patients with mitral stenosis require heart rate control to prolong diastolic filling time. Regurgitant valvular lesions are generally less problematic during surgery because the vasodilatory effect of anesthetics promotes forward flow. Patients with aortic or mitral regurgitation likely benefit from afterload reduction and careful attention to volume status, but negative chronotropes should be avoided to reduce the regurgitant volume.

### ► Arrhythmias

The finding of a rhythm disturbance on preoperative evaluation should prompt consideration of further cardiac evaluation, particularly when the finding of structural heart disease would alter perioperative management. **Patients with a rhythm disturbance without evidence of underlying heart disease are at low risk for perioperative cardiac complications.** While long-term antiarrhythmic medications should be continued perioperatively, there is no evidence that the use of medications to suppress an asymptomatic arrhythmia alters perioperative risk.

Patients with symptomatic arrhythmias should not undergo elective surgery until their cardiac condition has been addressed. Adequate rate control of atrial fibrillation or other supraventricular arrhythmias should be established prior to surgery. Symptomatic ventricular tachycardia must be thoroughly evaluated and controlled prior to surgery. Patients who have independent indications for a permanent pacemaker or implanted defibrillator should have it placed prior to noncardiac surgery. The anesthesiologist must be notified that a patient has an implanted pacemaker or defibrillator to prevent device malfunction from intraoperative electrocautery.

### ► Hypertension

No evidence supports delaying surgery in order to better control mild to moderate hypertension (systolic blood pressure below 180 mm Hg and diastolic blood pressure below 110 mm Hg). Severe hypertension (systolic pressure greater than 180 mm Hg or a diastolic pressure greater than 110 mm Hg) appears to be an independent predictor of perioperative cardiac complications, including MI and HF. It is reasonable to consider delaying surgery in patients with such severe hypertension until blood pressure can be controlled, although it is not known whether the risk of cardiac complications is reduced with this approach.

Most medications for chronic hypertension should generally be continued up to and including the day of surgery. Cardiology societies' guidelines differ in their recommendation on whether to continue or hold angiotensin-converting enzyme inhibitors and angiotensin receptor blockers on the day of surgery. Continuation increases the risk of intraoperative and postoperative hypotension, whereas holding these agents increases postoperative hypertension. Diuretic agents are frequently held on the day of surgery to prevent hypovolemia and electrolyte disorders if they are not needed to control HF; however, the benefit of this practice is uncertain.

Patients without chronic hypertension may manifest hypertension after surgery, and patients being treated for hypertension often experience decreased control of their blood pressure. Potential causes include elevated sympathetic tone due to injury or pain, volume overload from intravenous fluids, hypercarbia, urine retention, and withholding long-term antihypertensive medications. Before initiating postoperative medical management of hypertension, reversible contributors should be addressed.

Duceppe E et al. Canadian Cardiovascular Society guidelines on perioperative cardiac risk assessment and management for patients who undergo noncardiac surgery. *Can J Cardiol.* 2017;33:17. [PMID: 27865641]

Tateosian VS et al. Preoperative cardiac evaluation for noncardiac surgery. *Anesthesiol Clin.* 2018;36:509. [PMID: 30390775]

## PULMONARY EVALUATION IN NON-LUNG RESECTION SURGERY

Pneumonia and respiratory failure requiring prolonged mechanical ventilation are the most important postoperative pulmonary complications. The occurrence of these complications has been associated with a significant increase in mortality and hospital length of stay. Pulmonary thromboembolism is another serious complication; prophylaxis against venous thromboembolic disease is detailed in Table 14–14.

### Risk Factors for the Development of Postoperative Pulmonary Complications

Procedure-related risk factors for postoperative pulmonary complications include location of surgery (highest rates occur in cardiac, thoracic, and upper abdominal cases), prolonged anesthesia, and emergency cases. Operations not requiring general anesthesia tend to have lower rates of postoperative pulmonary complications; laparoscopic procedures tend to have lower risk than comparable open procedures.

A summary of patient-specific risk factors for pulmonary complications is presented in Table 3–4. Advanced age appears to confer increased risk. The presence and severity of systemic disease of any type is associated with pulmonary complications. In particular, patients with chronic obstructive pulmonary disease (COPD) or HF have at least twice the risk of postoperative pulmonary complications compared with patients without these conditions. As with preoperative cardiac risk assessment, physical debility and poor functional capacity predict

**Table 3–4.** Clinical risk factors for postoperative pulmonary complications.

|   |
|---|
| Upper abdominal or cardiothoracic surgery |
| Prolonged anesthesia time (> 4 hours)     |
| Emergency surgery                         |
| Age > 60 years                            |
| Chronic obstructive pulmonary disease     |
| Heart failure                             |
| Severe systemic disease                   |
| Tobacco use (> 20 pack-years)             |
| Impaired cognition or sensorium           |
| Functional dependency or prior stroke     |
| Preoperative sepsis                       |
| Low serum albumin level                   |
| Obstructive sleep apnea                   |

higher risk of postoperative pulmonary complications. A risk calculator for predicting postoperative respiratory failure based on the NSQIP patient database is available (<http://www.qxmd.com/calculate-online/respirology/postoperative-respiratory-failure-risk-calculator>).

### Pulmonary Function Testing & Laboratory Studies

The main role for preoperative pulmonary function testing (PFT) is to identify pulmonary disease in patients with unexplained symptoms prior to major abdominal or cardiothoracic surgery. In patients with diagnosed lung disease, PFT often add little information above clinical assessment. Chest radiographs in unselected patients also rarely add clinically useful information. The benefit of polysomnography to diagnose obstructive sleep apnea prior to bariatric surgery is unproven. Arterial blood gas measurement is not routinely recommended except in patients with known lung disease and suspected hypoxemia or hypercapnia.

### Preoperative Risk Reduction

Retrospective studies have shown that smoking cessation reduced the incidence of pulmonary complications, but only if it was initiated at least 1–2 months before surgery. A meta-analysis of randomized trials found that preoperative smoking cessation programs reduced both pulmonary and surgical wound complications, especially if smoking cessation was initiated at least 4 weeks prior to surgery. **The preoperative period may be an optimal time to initiate smoking cessation efforts.** A systematic review found that smoking cessation programs started in a preoperative evaluation clinic increased the odds of abstinence at 3–6 months by nearly 60%.

### Postoperative Risk Reduction

Postoperative risk reduction strategies have centered on promoting lung expansion through the use of incentive spirometry, continuous positive airway pressure (CPAP), intermittent positive-pressure breathing (IPPB), and deep breathing exercises. Although trial results have been mixed, all these techniques have been shown to reduce the

incidence of postoperative atelectasis and, in a few studies, to reduce the incidence of other postoperative pulmonary complications. In most comparative trials, these methods were equally effective. Given the higher cost of CPAP and IPPB, **incentive spirometry and deep breathing exercises are the preferred methods for most patients.** Multi-component respiratory care programs may be particularly beneficial. One program termed “I COUGH”—an acronym for *Incentive spirometry, Coughing and deep breathing, Oral care, Understanding (patient education), Get out of bed (early ambulation), and Head of bed elevation*—reduced the rates of pneumonia and unplanned intubation after general and vascular surgery.

Lumb AB. Pre-operative respiratory optimisation: an expert review. *Anaesthesia*. 2019;74:43. [PMID: 30604419]  
 Selzer A et al. Preoperative pulmonary evaluation. *Med Clin North Am*. 2019;103:585. [PMID: 30955524]

## EVALUATION OF THE PATIENT WITH LIVER DISEASE

Patients with serious liver disease are at increased risk for perioperative morbidity, and decompensated liver disease is associated with an extremely high perioperative mortality. Appropriate preoperative evaluation requires consideration of the effects of anesthesia and surgery on postoperative liver function and of the complications associated with anesthesia and surgery in patients with preexisting liver disease.

### Risk Assessment in Surgical Patients with Liver Disease

Screening unselected patients with liver biochemical tests has a low yield and is not recommended. Patients with suspected or known liver disease based on history or physical examination, however, should have measurement of liver enzyme levels as well as tests of hepatic synthetic function performed prior to surgery.

Elective surgery in patients with acute viral or alcoholic hepatitis should be delayed until the acute episode has resolved. In three small series of patients with acute viral hepatitis who underwent abdominal surgery, the mortality rate was roughly 10%. Similarly, patients with undiagnosed alcoholic hepatitis had high mortality rates when undergoing abdominal surgery. In the absence of cirrhosis or synthetic dysfunction, chronic viral hepatitis is unlikely to increase risk significantly. Similarly, nonalcoholic fatty liver disease without cirrhosis probably does not pose a serious risk in surgical patients.

In patients with cirrhosis, postoperative complication rates correlate with the severity of liver dysfunction. Traditionally, severity of dysfunction has been assessed with the Child-Pugh score (see Chapter 16). A conservative approach would be to avoid elective surgery in patients with Child-Pugh class C cirrhosis and pursue it with great caution in class B patients. The Model for End-stage Liver Disease (MELD) score, based on serum bilirubin and creatinine levels, and the prothrombin time expressed as the international normalized ratio (INR), also predicted

surgical mortality and outperformed the Child-Pugh classification in some studies. A web-based risk assessment calculator incorporating age and MELD score can predict both perioperative and long-term mortality (<https://www.mayoclinic.org/medical-professionals/model-end-stage-liver-disease/post-operative-mortality-risk-patients-cirrhosis>). Generally, a MELD score less than 10 predicts low risk, whereas a score greater than 16 portends high mortality after elective surgery.

When surgery is elective, controlling ascites, encephalopathy, and coagulopathy preoperatively is prudent. Ascites is a particular problem in abdominal operations, where it can lead to wound dehiscence and hernias. Great care should be taken when using analgesics and sedatives, since these can worsen hepatic encephalopathy; in general, short-acting agents and lower doses should be used. Postoperative constipation should be aggressively treated because it can precipitate encephalopathy. Kidney function and volume status need to be closely monitored to prevent acute kidney injury and volume overload, which are common complications in these patients. Patients with coagulopathy should receive vitamin K and may need fresh frozen plasma transfusion at the time of surgery; however, transfusing to a specific INR target for cirrhosis is discouraged.

Northup PG et al. AGA Clinical Practice Update: surgical risk assessment and perioperative management in cirrhosis. *Clin Gastroenterol Hepatol*. 2019;17:595. [PMID: 30273751]

## PREOPERATIVE HEMATOLOGIC EVALUATION

Three of the more common clinical situations faced by the medical consultant are the patient with anemia, the assessment of bleeding risk, and the perioperative management of long-term anticoagulation.

The main goals of the preoperative evaluation of the anemic patient are to determine the need for preoperative diagnostic evaluation and the need for transfusion. **When feasible, the diagnostic evaluation of the patient with previously unrecognized anemia should be done prior to surgery because certain types of anemia (particularly those due to sickle cell disease, hemolysis, and acute blood loss) have implications for perioperative management.** These types of anemia are typically associated with an elevated reticulocyte count. Preoperative anemia is associated with higher perioperative morbidity and mortality. It is not known whether raising preoperative hemoglobin level to specific targets will improve postoperative outcomes. The clinician determining the need for preoperative transfusion in an individual patient must consider factors other than the absolute hemoglobin level, including the presence of cardiopulmonary disease, the type of surgery, and the likely severity of surgical blood loss. The few studies that have compared different postoperative transfusion thresholds failed to demonstrate improved outcomes with a more aggressive transfusion strategy. Based on available evidence, the AABB (formerly American Association of Blood Banks) recommends transfusion for a hemoglobin level less than 8 g/dL (80 g/L) or for symptomatic anemia in patients undergoing orthopedic or cardiac surgery.

**Table 3–5.** Recommendations for perioperative management of direct-acting oral anticoagulants.

| Drug and Kidney Function   | Last Dose Before Procedure  | Resume Medication   |
|--|---|---|
| Dabigatran with normal creatinine clearance (> 50 mL/min/1.73 m <sup>2</sup> [0.83 mL/s/m <sup>2</sup> ]); rivaroxaban, apixaban, edoxaban | 2 days before procedure with low risk of bleeding or 3 days before procedure with high risk of bleeding | If hemostasis adequate, resume 24 hours after procedure with low risk of bleeding or 48–72 hours after procedure with high risk of bleeding |
| Dabigatran with reduced creatinine clearance (30–50 mL/min/1.73 m <sup>2</sup> [0.5–0.83 mL/s/m <sup>2</sup> ])                            | 3 days before procedure with low risk of bleeding or 5 days before procedure with high risk of bleeding |   |

The most important component of the bleeding risk assessment is a directed bleeding history (see Table 3–1). Patients who provide a reliable history of no abnormal bleeding on directed bleeding history and have no suggestion of abnormal bleeding on physical examination are at very low risk for having an occult bleeding disorder. Laboratory tests of hemostatic parameters in these patients are generally not needed. When the directed bleeding history is unreliable or incomplete, or when abnormal bleeding is suggested, a formal evaluation of hemostasis should be done prior to surgery and should include measurement of the prothrombin time, activated partial thromboplastin time, and platelet count (see Chapter 13).

Patients receiving long-term oral anticoagulation are at risk for thromboembolic complications when an operation requires interruption of this therapy. However, “bridging anticoagulation,” where unfractionated or low-molecular-weight heparin is administered parenterally while oral anticoagulants are held, has not been shown to be beneficial and can increase bleeding. A cohort study found that direct-acting oral anticoagulants (DOACs) could be safely managed without bridging by using a protocol based on the patient’s kidney function where the

DOACs are withheld several days prior to surgery and restarted 24–48 hours after surgery if hemostasis appears adequate (Table 3–5). A randomized trial of bridging anticoagulation in surgical patients taking warfarin for atrial fibrillation demonstrated no difference in thromboembolism. Bleeding complications were twice as common in patients who received bridging anticoagulation. **Most experts recommend bridging therapy only in patients at high risk for thromboembolism.** An approach to perioperative anticoagulation management with warfarin is shown in Table 3–6, but the recommendations must be considered in the context of patient preference and hemorrhagic risk.

Doherty JU et al. 2017 ACC Expert consensus decision pathway for periprocedural management of anticoagulation in patients with nonvalvular atrial fibrillation. A report of the American College of Cardiology Clinical Expert Consensus Document Task Force. *J Am Coll Cardiol.* 2017;69:871. [PMID: 28081965]  
 Douketis JD et al. Perioperative management of patients with atrial fibrillation receiving a direct oral anticoagulant. *JAMA Intern Med.* 2019;179:1469. [PMID: 31380891]  
 Shander A et al. How I treat anemia in the perisurgical setting. *Blood.* 2020;136:814. [PMID: 32556314]

**Table 3–6.** Recommendations for management of perioperative anticoagulation with warfarin.

| Thromboembolic Risk without Anticoagulation   | Recommendation   |
|---|--|
| <b>Low</b> (eg, atrial fibrillation with CHADS <sub>2</sub> score 0–4, <sup>1</sup> mechanical bileaflet aortic valve prosthesis, or single venous thromboembolism > 3 months ago without hypercoagulability condition <sup>2</sup> )   | Stop warfarin 5 days before surgery<br>Measure INR the day before surgery to confirm that it is acceptable (< 1.6 for most operations)<br>Resume warfarin when hemostasis permits<br>No bridging with parenteral anticoagulants before or after surgery  |
| <b>High</b> (eg, either atrial fibrillation or mechanical heart valve with stroke < 3 months prior, atrial fibrillation with CHADS <sub>2</sub> score 5 or 6, mechanical mitral valve prosthesis, caged-ball or tilting disk valve prosthesis, or venous thrombosis < 3 months ago or associated with hypercoagulability condition <sup>2</sup> ) | Stop warfarin 5 days before surgery<br>Begin bridging with therapeutic dose UFH infusion or LMWH 2 days after stopping oral anticoagulation<br>Administer last dose of LMWH 24 hours before surgery; discontinue UFH 4–6 hours before surgery<br>Measure INR the day before surgery to confirm that it is acceptable (< 1.6 for most operations)<br>Resume warfarin when hemostasis permits<br>If hemostasis permits, resume bridging with therapeutic dose UFH infusion or LMWH beginning 48–72 hours after surgery and continuing until the INR is therapeutic |

<sup>1</sup>1 point each for heart failure, hypertension, diabetes mellitus, and age > 75 years, and 2 points for stroke or transient ischemic attack.

<sup>2</sup>Patients should receive venous thromboembolism prophylaxis after surgery (see Chapter 14).

INR, international normalized ratio; LMWH, low-molecular-weight heparin; UFH, unfractionated heparin.

## NEUROLOGIC EVALUATION

Delirium can occur after any major operation but is particularly common after hip fracture repair and cardiovascular surgery, where the incidence is 30–60%. **Postoperative delirium has been associated with higher rates of major postoperative cardiac and pulmonary complications, poor functional recovery, increased length of hospital stay, increased risk of subsequent dementia and functional decline, and increased mortality.** The American Geriatrics Society recommends screening preoperative patients for these delirium risk factors: age greater than 65 years, chronic cognitive impairment or dementia, severe illness, poor vision or hearing, and the presence of infection. Patients with any of these risk factors should be enrolled in a multi-component, nonpharmacologic delirium prevention program after surgery, which includes interventions such as reorientation, sleep hygiene, bowel and bladder care, mobilization and physical therapy, and the elimination of unnecessary medications. Moderate-quality evidence supports the use of these nonpharmacologic interventions.

Only a minority of patients with postoperative delirium will have a single, reversible etiology for their condition (see Delirium, Chapter 4). Evaluation of delirious patients should exclude electrolyte derangements, occult urinary tract infection, and adverse effects from psychotropic medications such as opioids, sedatives, anticholinergic agents, and antispasmodics. Conservative management includes reassuring and reorienting the patient; eliminating unneeded medications, intravenous lines, and urinary catheters; and keeping the patient active during the day while allowing uninterrupted sleep at night. Use of multimodal postoperative analgesic strategies can reduce or avoid the need for opioids. When agitation jeopardizes patient or provider safety, neuroleptic agents given at the lowest effective dose for the shortest duration needed are preferred over the use of benzodiazepines or physical restraints.

Stroke complicates less than 1% of all surgical procedures but may occur in 1–6% of patients undergoing cardiac or carotid artery surgery. Most of the strokes in cardiac surgery patients are embolic in origin, and about half occur within the first postoperative day. A retrospective analysis found that patients who had previously suffered a stroke had an 18% risk of MI, recurrent stroke, or cardiac death if they underwent noncardiac surgery within 3 months of the stroke. This risk declined over time and reached its nadir 9 months after the stroke, suggesting a benefit to delaying elective surgery.

Symptomatic carotid artery stenosis is associated with a high risk of stroke in patients undergoing cardiac surgery. In general, patients with independent indications for correction of carotid stenosis should have the procedure done prior to elective surgery. In contrast, most studies suggest that asymptomatic carotid bruits and asymptomatic carotid stenosis are associated with little or no increased risk of stroke in surgical patients.

Hood R et al. Peri-operative neurological complications. *Anesthesia*. 2018;73:67. [PMID: 29313909]

## MANAGEMENT OF ENDOCRINE DISEASES

### ► Diabetes Mellitus

Poor preoperative glycemic control, as indicated by an elevated hemoglobin A<sub>1c</sub> level, is associated with a greater risk of surgical complications, particularly infections. However, a strategy of delaying surgery until glycemic control improves has not been rigorously studied. The ideal postoperative blood glucose target is also unknown. Based on trials that showed increased mortality in hospitalized patients randomized to tight control, the American College of Physicians recommends maintaining serum glucose between 140 mg/dL and 200 mg/dL (7.8–11.1 mmol/L), whereas the British National Health Service guidelines recommend a range of 108–180 mg/dL (6–10 mmol/L).

The goal of management for all diabetic patients is the prevention of severe hyperglycemia or hypoglycemia in the perioperative period. In addition, patients with type 1 diabetes are at risk for developing ketoacidosis. Increased secretion of cortisol, epinephrine, glucagon, and growth hormone during and after surgery causes insulin resistance and hyperglycemia in diabetic patients. Conversely, reduced caloric intake after surgery and frequent, unpredictable periods of fasting increase the risk for hypoglycemia. Thus, all surgical diabetic patients require frequent blood glucose monitoring. Ideally, patients with diabetes should undergo surgery early in the morning. The specific pharmacologic management of diabetes during the perioperative period depends on the type of diabetes (insulin-dependent or not), the level of glycemic control, and the type and length of surgery.

#### A. Diabetes Controlled by Diet

For people with diabetes controlled with diet alone, no special precautions must be taken unless diabetic control is markedly disturbed by the procedure. If this occurs, small doses of short-acting insulin as needed will correct the hyperglycemia.

#### B. Diabetes Treated With Oral Hypoglycemic Agents

Oral hypoglycemic agents should be held on the day of surgery. They should not be restarted after surgery until oral intake is adequate and unlikely to be interrupted. If there is significant hyperglycemia, small doses of short-acting insulin are given as needed. If this approach does not provide adequate control, an insulin infusion should be started in the manner indicated below. Postoperative kidney function should be checked with a serum creatinine level prior to restarting metformin.

#### C. Diabetes Treated With Insulin

The protocol used to control glucose depends on (1) the kind of diabetes (type 1 or type 2); (2) whether it is minor surgery (lasting less than 2 hours and patient able to eat

afterward) or major surgery (lasting more than 2 hours, with invasion of a body cavity, and patient not able to eat afterward); and (3) the preoperative insulin regimen (basal bolus or premixed insulin twice a day or premeal bolus only or regular insulin before meals and NPH at bedtime).

**1. Preoperative insulin regimen**—For patients with either type 1 or type 2 diabetes who are receiving insulin, a common practice is to reduce the last preoperative dose of long-acting, basal insulin by 30–50% and hold short-acting nutritional insulin.

**2. Perioperative insulin regimen**—Patients with type 1 diabetes must receive some insulin to prevent the development of diabetic ketoacidosis. **Consultation with an endocrinologist or hospitalist should be strongly considered when a patient with type 1 diabetes mellitus undergoes major surgery.** Major surgical procedures in patients with type 1 diabetes lasting more than 2 hours usually require an insulin infusion. Many patients with type 2 diabetes who are taking insulin do well perioperatively without insulin for a few hours, but some will also need insulin infusion to maintain adequate glycemic control. An insulin infusion is a complex procedure for a high-risk medication and involves extensive monitoring, dose titrations, and contingency plans. There are a number of algorithms available for insulin infusions (<http://ucsfinpatientdiabetes.pbworks.com>).

**3. Postoperative insulin regimen**—After surgery, when a patient with either type 1 or type 2 diabetes has resumed adequate oral intake, subcutaneous administration of insulin can be restarted and intravenous administration of insulin and dextrose can be stopped 30 minutes after the first subcutaneous dose. Insulin needs may vary in the first several days after surgery because of continuing postoperative stresses and because of variable caloric intake. In this situation, multiple doses of short-acting insulin plus some long-acting basal insulin, guided by blood glucose determinations, can keep the patient in acceptable metabolic control. Use of correctional insulin only (without basal or nutritional insulin) after surgery is discouraged. A trial comparing correctional insulin with basal-bolus dosing found that the latter strategy led to fewer postoperative complications.

## ► Glucocorticoid Replacement

Hypotension or shock resulting from primary or secondary adrenocortical insufficiency is rare, and the practice of administering supraphysiologic “stress-dose” glucocorticoid perioperatively has not been well studied. A guideline from rheumatology and orthopedic surgery societies recommends that patients taking glucocorticoids continue their regimen when undergoing arthroplasty and not receive “stress-dose” glucocorticoids. Another approach is to administer stress-dose glucocorticoids to any patient who has received the equivalent of at least 7.5 mg of prednisone daily for 3 weeks within the past year when they undergo major surgery. A commonly used stress-dose regimen is hydrocortisone 100 mg intravenously daily, divided every 8 hours, beginning before induction of anesthesia and stopped after 24 hours without tapering. Patients who have

been taking less than 5 mg of prednisone daily and those receiving alternate-day glucocorticoid dosing are unlikely to require supplemental coverage.

## ► Thyroid Disease

Severe symptomatic hypothyroidism has been associated with perioperative complications, including intraoperative hypotension, HF, cardiac arrest, and death. Elective surgery should be delayed in patients with severe hypothyroidism until adequate thyroid hormone replacement can be achieved. Patients with symptomatic hyperthyroidism are at risk for perioperative thyroid storm and should not undergo elective surgery until their thyrotoxicosis is controlled; an endocrinologist should be consulted if emergency surgery is needed. Patients with mild hypothyroidism (median thyroid-stimulating hormone level 8.6 milli-international units/L) tolerate surgery well, with only a slight increase in the incidence of intraoperative hypotension; surgery need not be delayed for the month or more required to ensure adequate thyroid hormone replacement.

Duggan EW et al. Perioperative hyperglycemia management: an update. *Anesthesiology*. 2017;126:547. [PMID: 28121636]  
Freudzon L. Perioperative steroid therapy: where's the evidence? *Curr Opin Anaesthesiol*. 2018;31:39. [PMID: 29227289]

## KIDNEY DISEASE

The development of acute kidney injury in patients undergoing general surgery is an independent predictor of mortality, even if mild or if kidney dysfunction resolves. The mortality associated with the development of perioperative acute kidney injury that requires dialysis exceeds 50%. Risk factors associated with postoperative deterioration in kidney function are shown in Table 3–7. Several medications, including “renal-dose” dopamine, mannitol, *N*-acetylcysteine, and clonidine, have not been proved effective in clinical trials to preserve kidney function during the perioperative period and should not be

**Table 3–7.** Risk factors for the development of acute kidney injury after general surgery.<sup>1</sup>

- Age > 55 years
- Male sex
- Chronic kidney disease
- Heart failure
- Diabetes mellitus
- Hypertension
- Ascites
- Intraperitoneal surgery
- Emergency surgery

<sup>1</sup>Presence of 5 or more risk factors is associated with > 3% risk of creatinine elevation > 2 mg/dL (176.8 μmol/L) above baseline or requirement for dialysis.

Reproduced, with permission, from Kheterpal S et al. Development and validation of an acute kidney injury risk index for patients undergoing general surgery: results from a national data set. *Anesthesiology*. 2009;110:505.

used for this indication. **Maintenance of adequate intravascular volume is likely to be the most effective method to reduce the risk of perioperative deterioration in kidney function.** Exposure to renal-toxic agents, such as nonsteroidal anti-inflammatory drugs and intravenous contrast, should be minimized or avoided. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers reduce renal perfusion and may increase the risk of perioperative acute kidney injury. Although firm evidence is lacking, it may be useful to temporarily discontinue these medications in patients at risk for perioperative acute kidney injury.

Although the mortality rate for elective major surgery is low (1–4%) in patients with dialysis-dependent chronic kidney disease, the risk for perioperative complications, including postoperative hyperkalemia, pneumonia, fluid overload, and bleeding, is substantially increased. Postoperative hyperkalemia requiring emergent hemodialysis has been reported to occur in 20–30% of these patients. Patients should undergo dialysis preoperatively within 24 hours before surgery, and their serum electrolyte levels should be measured just prior to surgery and monitored closely during the postoperative period.

Zarbock A et al. Update on perioperative acute kidney injury. Anesth Analg. 2018;127:1236. [PMID: 30138176]

## ANTIBIOTIC PROPHYLAXIS OF SURGICAL SITE INFECTIONS

Surgical site infection is estimated to occur in roughly 4% of general or vascular operations. Although the type of procedure is the main factor determining the risk of

developing a surgical site infection, certain patient factors have been associated with increased risk, including diabetes mellitus, older age, obesity, smoking, heavy alcohol consumption, admission from a long-term care facility, and multiple medical comorbidities. **For most major procedures, the use of prophylactic antibiotics has been demonstrated to reduce the incidence of surgical site infections.** Several general conclusions can be drawn from studies of different antibiotic regimens for surgical procedures. First, substantial evidence suggests that a single dose of an appropriate intravenous antibiotic—or combination of antibiotics—is as effective as multiple-dose regimens that extend into the postoperative period. Second, for most procedures, a first-generation cephalosporin (eg, cefazolin 2 g intravenously) is as effective as later-generation agents. Third, prophylactic antibiotics should be given intravenously at induction of anesthesia or roughly 30–60 minutes prior to the skin incision.

Guidelines for antibiotic prophylaxis against infective endocarditis in patients undergoing invasive procedures are presented in Chapter 33. Given the lack of evidence for antibiotic prophylaxis against prosthetic joint infection before dental procedures, guidelines from the American Academy of Orthopedic Surgeons and the American Dental Association recommend against this practice.

Berríos-Torres SI et al; Healthcare Infection Control Practices Advisory Committee. Centers for Disease Control and Prevention guideline for the prevention of surgical site infection, 2017. JAMA Surg. 2017;152:784. [PMID: 28467526]

Liu Z et al. Intraoperative interventions for preventing surgical site infection: an overview of Cochrane Reviews. Cochrane Database Syst Rev. 2018;2:CD012653. [PMID: 29406579]

# Geriatric Disorders

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4

## GENERAL PRINCIPLES OF GERIATRIC CARE

The following principles help in caring for older adults:

1. Many disorders are multifactorial in origin and are best managed by multifactorial interventions.
2. Diseases often present atypically or with nonspecific symptoms (eg, confusion, functional decline).
3. Not all abnormalities require evaluation and treatment.
4. Complex medication regimens, adherence problems, and polypharmacy are common challenges.
5. Multiple chronic conditions often coexist and should be managed in concert with one another.

## COMPREHENSIVE ASSESSMENT OF THE OLDER ADULT

In addition to conventional assessment of symptoms, diseases, and medications, comprehensive assessment addresses three topics: **prognosis, values and preferences, and ability to function independently**. Comprehensive assessment is warranted before major clinical decisions are made.

### ► Assessment of Prognosis

When an older person's life expectancy is longer than 10 years (ie, 50% of similar persons live longer than 10 years), it is reasonable to consider effective tests and treatments much as they are considered in younger persons. When life expectancy is less than 10 years (and especially when it is much less), choices of tests and treatments should be made based on their ability to affect a clinical outcome that is valued by the patient in the context of their estimated life expectancy. The relative benefits and harms of tests and treatments often change as prognosis worsens, and net benefit (benefits minus harms) often worsens.

When an older patient's clinical situation is dominated by a single disease process (eg, lung cancer metastatic to brain), prognosis can be estimated well with a disease-specific instrument. Even in this situation, however, prognosis generally worsens with age (especially over age 90 years) and with the presence of serious age-related conditions, such as dementia, malnutrition, or functional impairment.

When an older patient's clinical situation is not dominated by a single disease process, prognosis can be estimated initially by considering basic demographic and health elements (Figure 4–1). For example, less than 25% of men aged 95 will live 5 years, whereas nearly 75% of women aged 70 will live 10 years. The prognosis for older persons living at home can be estimated by considering age, sex, comorbid conditions, and function. The prognosis is worse for older persons discharged from the hospital than for those living at home and can be estimated by considering sex, comorbid conditions, and function at discharge. A compilation of indices with online calculators that allow for estimating prognosis in multiple clinical settings can be found at ePrognosis (<https://epronosis.ucsf.edu>).

### ► Assessment of Values & Preferences

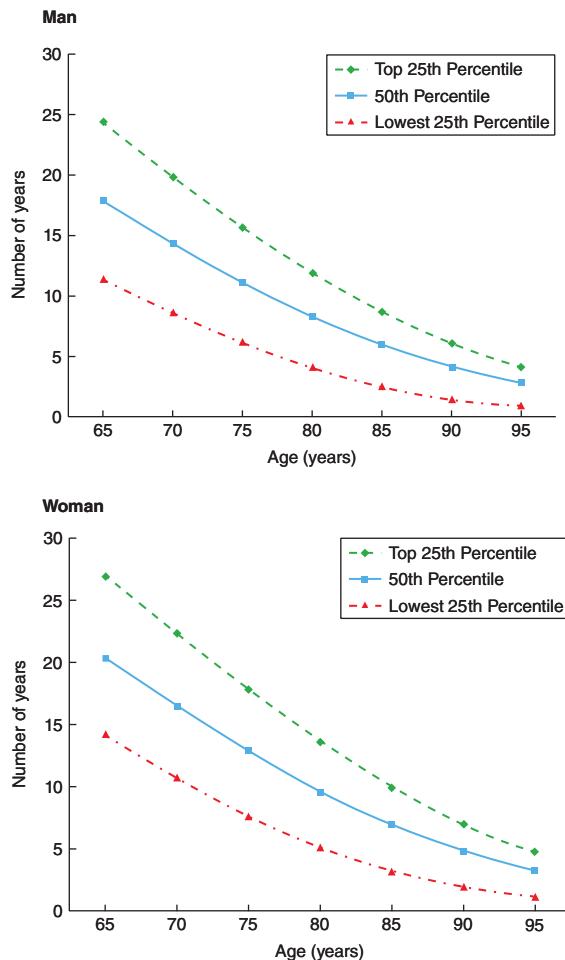
Although patients vary in their values and preferences, many frail older patients prioritize maintaining their independence over prolonging survival. Values and preferences are determined by speaking directly with a patient or, when the patient cannot express preferences reliably, with the patient's surrogate.

In assessing values and preferences (ie, what matters most to patients), it is important to keep in mind the following:

1. Patients are experts about their preferences for outcomes and experiences; however, they often do not have adequate information to make and express informed preferences for specific tests or treatments.
2. Patients' preferences often change over time. For example, some patients find living with a disability more acceptable than they thought before experiencing it.

### ► Assessment of Function

People often lose function in multiple domains as they age, with the result that they may not be able to do some activities as quickly or capably and may need assistance. Assessment of function improves prognostic estimates. **Assessment of function is essential to determine an individual's needs in the context of his or her values and preferences and the possible effects of recommended treatment.**



**Figure 4-1.** Median life expectancy of older men and women. (Data derived from Arias E. United States Life Tables, 2011. *Natl Vital Stat Rep*. 2015;64(11):1–63.)

About one-fourth of patients over age 65 and half of persons older than 85 need help performing their **basic activities of daily living (ADLs:** bathing, dressing, eating, transferring from bed to chair, continence, toileting) or **instrumental activities of daily living (IADLs:** transportation, shopping, cooking, using the telephone, managing money, taking medications, housecleaning, laundry).

**Functional screening** should include assessment of ADLs and IADLs and questions to detect weight loss, falls, incontinence, depressed mood, self-neglect, fear for personal safety, and common serious impairments (eg, hearing, vision, cognition, and mobility). Standard functional screening measures may not be useful in capturing subtle impairments in highly functional independent older adults. One technique for these patients is to identify and ask about a target activity, such as bowling or gardening, regularly. Difficulty with or discontinuation of the particular activity may indicate new or worsening impairment (such as cognitive impairment, urinary incontinence, or hearing loss). Additional gentle questioning or assessment may help uncover such changes.

## ► Frailty

Frailty is a syndrome characterized by loss of physiologic reserve and dysregulation across multiple systems, ultimately resulting in greater risk of poor health outcomes. Estimates of its prevalence in community-dwelling older adults range from 5% to 17%. Elements of frailty include **weakness (grip strength), slow gait speed, decreased physical activity, weight loss, and exhaustion or low energy.** While there is not one universally agreed upon definition or assessment tool for frailty, generally an individual is defined as frail when three or more of the above features are present. Persons with frailty are at increased risk for falls, hospitalization, functional decline, poorer outcomes associated with medical interventions (eg, surgery, dialysis, chemotherapy), and death. **Exercise, particularly strength and resistance training, can increase walking speed and improve function.** There is evidence that optimal nutrition, particularly higher levels of protein intake, may be associated with reduced incidence of frailty. However, once frailty is established, the treatment is largely supportive, multifactorial, and individualized based on patient goals, life expectancy, and chronic conditions. Sometimes, transitioning a patient to a comfort-focused or hospice approach is the most appropriate clinical intervention when irreversible complications from frailty develop.

Garrard JW et al. Comprehensive geriatric assessment in primary care: a systematic review. *Aging Clin Exp Res*. 2020; 32:197. [PMID: 30968287]

Pilotto A et al. A multidimensional approach to frailty in older people. *Ageing Res Rev*. 2020;60:101047. [PMID: 32171786]

## MANAGEMENT OF COMMON GERIATRIC PROBLEMS

### 1. Dementia



#### ESSENTIALS OF DIAGNOSIS

- Progressive decline of intellectual function.
- Acquired deficits in one or more cognitive domains severe enough to cause impairment of function.
- Not due to delirium or another mental disorder.

## ► General Considerations

Dementia is an acquired, persistent, and progressive impairment in intellectual function, with compromise of one or more cognitive domains. *The Diagnostic and Statistical Manual of Mental Disorders*, 5th edition, identifies these domains (with example deficits) as: (1) **complex attention** (easily distracted, difficulty performing calculations), (2) **executive function** (poor abstraction, mental flexibility, planning, and judgment), (3) **learning and memory** (difficulty recalling items from a list, forgetting

recent events), (4) **language** (word finding and object naming difficulty), (5) **perceptual-motor function** (difficulty navigating in known environments, copying a drawing), and (6) **social cognition** (change in personality, trouble reading social cues). The diagnosis of dementia requires a significant decline in function that is *severe enough to result in the loss of independence in IADLs*.

While dementia prevalence doubles every 5 years in the older population, reaching 30–50% at age 85, the prevalence among US adults 65 years or older has been declining. This improvement has been attributed to higher education levels and better control of cardiovascular risk factors. Alzheimer disease accounts for roughly two-thirds of dementia cases in the United States, with vascular dementia (either alone or combined with Alzheimer disease) and Lewy body dementia accounting for much of the rest.

Depression and delirium are also common in older adults, may coexist with dementia, and may also present with cognitive impairment. Major depressive disorder may occur in up to 20–50% of patients with dementia, and because they share common features, distinguishing the two can prove difficult. Delirium, characterized by acute confusion, occurs much more commonly in patients with underlying dementia.

## ► Clinical Findings

### A. Screening

**1. Cognitive impairment**—According to the US Preventive Services Task Force (USPSTF), there is insufficient evidence to recommend for or against screening all older adults for cognitive impairment. While there is logic in the argument that early detection may improve future planning and patient outcomes, empiric evidence that demonstrates a clear benefit for either patients or caregivers is lacking. It is important to note, however, that the Medicare Annual Wellness Visit mandates that clinicians assess patients for cognitive impairment based on the clinician's observations and reports from others.

At-home genetic testing for a susceptibility gene that is associated with late-onset Alzheimer disease (APOE-e4) has US Food and Drug Administration approval. While the presence of the APOE-e4 allele increases the risk of developing Alzheimer disease, quantifying such risk for an individual is difficult. Because it is possible to have one or two copies of the APOE-e4 allele and not develop Alzheimer disease or to have no copies and yet still become stricken, genetic testing is not widely recommended and, if considered, should not proceed without genetic counseling.

When there is suspicion of cognitive impairment, several cognitive tests have been validated for clinical use. The **mini-cog** is a combination of a three-item word recall with a clock drawing task, and it can be completed in 3 minutes. When a patient fails this simple test, further cognitive evaluation with a standardized instrument is warranted. The **Montreal Cognitive Assessment (MoCA®)** is a 30-point test that takes about 10 minutes to administer and examines several areas of cognitive function. A score below 26 has a sensitivity of 0.94 or more and a specificity of 0.60 or less. Free downloadable versions in multiple languages

are available at <http://www.mocatest.org>. As of 2021, completion of a training and certification program is required to gain access to the test.

**2. Decision-making capacity**—Older adults with cognitive impairment commonly face serious medical decisions, and the clinicians involved in their care must ascertain whether the capacity exists to make medical decisions. While no single test of capacity exists, the following five elements should be considered in a thorough assessment: (1) ability to express a choice; (2) understanding relevant information about the risks and benefits of planned therapy and the alternatives (including no treatment), in the context of one's values; (3) comprehension of the problem and its consequences; (4) ability to reason; and (5) consistency of choice. A patient's choice should follow from an understanding of the consequences.

Sensitivity must be used in applying these five components to people of various cultural backgrounds. Decision-making capacity varies over time. Furthermore, the capacity to make a decision is a **function of the decision in question**. A woman with mild dementia may lack the capacity to consent to coronary artery bypass grafting yet retain the capacity to designate a surrogate decision maker.

### B. Symptoms and Signs

Most patients with dementia can be identified in a primary care setting after completion of a history (often requiring collateral information), a physical examination, and cognitive testing. The clinician can gather additional information about the type of dementia by asking about (1) the rate of progression of the deficits as well as their nature (including any personality or behavioral change); (2) the presence of other neurologic and psychiatric symptoms, particularly motor problems and psychotic symptoms; (3) risk factors for HIV; (4) family history of dementia; and (5) medications, with particular attention to recent changes.

Workup is directed at identifying any potentially *reversible* causes of dementia. However, such cases are rare. For a detailed description of the symptoms and signs of different forms of dementia, see Chapter 24.

### C. Physical Examination

The neurologic examination emphasizes assessment of mental status but should also include evaluation for sensory deficits, previous strokes, parkinsonism, and peripheral neuropathy. The examination should focus on identifying comorbid conditions that may aggravate the individual's disability. For a detailed description of the neuropsychological assessment, see Chapter 24.

### D. Laboratory Findings

Laboratory studies should include a complete blood count and serum electrolytes, calcium, creatinine, glucose, thyroid-stimulating hormone (TSH), and vitamin B<sub>12</sub> levels. While hypothyroidism or vitamin B<sub>12</sub> deficiency may contribute to the cognitive impairment, treating these conditions typically does *not* reverse the dementia. HIV and rapid plasma reagins (RPR) tests, a heavy metal screen,

and liver biochemical tests may be informative in selected patients but are not part of routine testing. For a detailed description of laboratory findings, see Chapter 24.

## E. Imaging

Most patients should receive neuroimaging as part of the workup to rule out subdural hematoma, tumor, previous stroke, and hydrocephalus (usually normal pressure). Those who are younger; those who have focal neurologic symptoms or signs, seizures, or gait abnormalities; and those with an acute or subacute onset are most likely to have positive findings and most likely to benefit from MRI scanning. In older patients with a more classic picture of Alzheimer disease for whom neuroimaging is desired, a noncontrast CT scan is sufficient. For a detailed description of imaging, see Chapter 24.

## Differential Diagnosis

Older individuals experience occasional difficulty retrieving items from memory (usually word-finding difficulty) and experience a slowing in their rate of information processing. In the amnestic type of **mild cognitive impairment**, a patient complains of memory problems, demonstrates mild deficits (most commonly in short-term memory) on formal testing, but the impairment does not significantly impact function. Annual dementia conversion rates vary from less than 5% to 20%. No medications have been demonstrated to delay the progression of mild cognitive impairment to Alzheimer disease. An elderly patient with intact cognition but with severe impairments in vision or hearing commonly becomes confused in an unfamiliar medical setting and consequently may be falsely labeled as demented.

Delirium can be distinguished from dementia by its acute onset, fluctuating course, and deficits in attention rather than memory. Many medications have been associated with delirium and other types of cognitive impairment in older patients. Anticholinergic agents, hypnotics, neuroleptics, opioids, nonsteroidal anti-inflammatory drugs (NSAIDs), antihistamines (both H<sub>1</sub>- and H<sub>2</sub>-antagonists), and corticosteroids are just some of the medications that have been associated with cognitive impairment in elders.

## Treatment

Patients and families should be made aware of the Alzheimer's Association (<http://www.alz.org>) as well as the wealth of helpful community and online resources and publications available. Caregiver support, education, and counseling may prevent or delay nursing home placement. Education should include the manifestations and natural history of dementia as well as the availability of local support services, such as respite care. Exercise should be a component of treatment as evidence suggests physical activity may have beneficial effects on cognition and physical function.

## A. Cognitive Impairment

**1. Acetylcholinesterase inhibitors**—Donepezil, galantamine, and rivastigmine are acetylcholinesterase inhibitors approved for the treatment of Alzheimer disease.

These medications produce a modest improvement in cognitive function that is *not* likely to be detected in routine clinical encounters, and they have *not* convincingly been shown to delay functional decline or institutionalization. There is insufficient evidence to recommend their use in mild cognitive impairment to slow the progression toward dementia.

Starting (and maximum) doses are donepezil, 5 mg orally once daily (maximum 10 mg once daily); galantamine, 4 mg orally twice daily (maximum 12 mg twice daily); extended-release galantamine, 8 mg orally once daily (maximum 24 mg once daily); rivastigmine, 1.5 mg orally twice daily (maximum 6 mg twice daily); and rivastigmine transdermal patch, 4.6 mg/24 h (maximum 13.3 mg/24 h for severe disease). Dosages are increased as tolerated at no less than 4-week intervals. Donepezil is also available in a 23-mg tablet, but this higher dose is associated with greater frequency of side effects without appreciable increase in benefit. The most bothersome side effects of acetylcholinesterase inhibitors include diarrhea, nausea, anorexia, weight loss, and syncope. As dementia progresses, some patients with moderate to severe cognitive impairment may continue to experience subjective benefits from acetylcholinesterase inhibitors, but the medication should be discontinued in those patients who have had no apparent benefit, who experience side effects, or for whom the financial outlay is a burden. While there are no published guidelines that describe what constitutes an adequate treatment trial, evaluation after 2 months at the highest tolerated dose is reasonable.

**2. Memantine**—In clinical trials, patients with moderate to severe Alzheimer disease have been shown to have statistical benefit from the use of memantine (5 mg orally daily to 10 mg twice daily), an N-methyl-D-aspartate (NMDA) antagonist. Long-term and meaningful functional outcomes have yet to be demonstrated, and evidence suggests there is no clinically meaningful benefit to giving memantine in combination with an acetylcholinesterase inhibitor. Evidence does not support the use of memantine in other forms of dementia.

## B. Behavioral Problems

**1. Nonpharmacologic approaches**—Behavioral problems in patients with dementia are often best managed nonpharmacologically. Initially, it should be established that the problem is not unrecognized delirium, pain, urinary obstruction, or fecal impaction. Determining whether the caregiver or institutional staff can tolerate the behavior is also helpful, since it is often easier to find ways to accommodate to the behavior than to modify it. If not, the caregiver should keep a brief log in which the behavior is described along with antecedent events and consequences. This may uncover patterns that delineate precipitants of the behavior or perhaps that the behavior is somehow being rewarded. Caregivers are taught to use simple language when communicating with the patient, to break down activities into simple component tasks, and to use a “distract, not confront” approach when the patient seems disturbed by a troublesome issue. Additional steps to address behavioral problems include providing structure

and routine, discontinuing all medications except those considered absolutely necessary, and correcting, if possible, sensory deficits.

**2. Pharmacologic approaches**—There is no clear consensus about pharmacologic approaches to the treatment of behavioral problems in patients who have not benefited from nonpharmacologic therapies. Pharmacologic treatment should be reserved for those patients who pose an imminent danger to others or themselves or when symptoms are substantially distressing to the patient.

Despite evidence of harm and recommendations against their use, antipsychotic medications have remained a mainstay for the treatment of behavioral disturbances, particularly agitation and aggression, largely because of the lack of alternatives. The atypical antipsychotic agents (eg, risperidone, olanzapine, quetiapine, aripiprazole) are increasingly becoming the first choice because of an overall better side-effect profile compared to typical agents (eg, haloperidol) but should be used with caution in patients with vascular risk factors due to an increased risk of stroke; they can also cause weight gain and are also associated with hyperglycemia in diabetic patients and are considerably more expensive. Both typical and atypical antipsychotics increase mortality compared with placebo when used to treat elderly patients with dementia and behavioral disturbances. Starting and target dosages should be much lower than those used in schizophrenia (eg, haloperidol, 0.5–2 mg orally; risperidone, 0.25–2 mg orally).

Citalopram at a dose of 30 mg daily may improve symptoms of agitation; however, according to the US Food and Drug Administration, the maximum recommended dose is 20 mg daily for patients older than 60 years because of the risk of QT prolongation and associated dysrhythmia. Thus, while citalopram may be used to treat agitation, safe and effective dosing for patients older than age 60 has not been established. In the specific instance of patients with Lewy body dementia, treatment with acetylcholinesterase inhibitors has been shown to improve behavioral symptoms. Valproate medications have been used in the treatment of agitated and physically aggressive behavior, but evidence demonstrates no identifiable benefit.

### C. Driving

Although drivers with dementia are at an increased risk for motor vehicle accidents, many patients continue to drive safely well beyond the time of initial diagnosis, making the timing of when to recommend that a patient stop driving particularly challenging.

There is no clear-cut evidence to suggest a single best approach to determining an individual patient's capability, and there is no accepted "gold-standard" test. The result is that clinicians must consider several factors upon which to base their judgment. For example, determining the severity of dementia can be useful. Patients with very mild or mild dementia according to the Clinical Dementia Rating Scale were able to pass formal road tests at rates of 88% and 69%, respectively. **Experts agree that patients with moderately severe or more advanced dementia should be counseled to stop driving.** Although not well studied, clinicians

should also consider the effects of comorbid conditions and medications and the role each may play in contributing to the risk of driving by a patient with dementia. Assessment of the ability to carry out IADLs may also assist in the determination of risk. Finally, in some cases of mild dementia, referral may be needed to a driver rehabilitation specialist for evaluation. Although not standardized, this evaluation often consists of both off- and on-road testing. Experts recommend such an evaluation for patients with mild dementia, for those with dementia for whom new impairment in driving skills is observed, and for those with significant deficits in cognitive domains, such as attention, executive function, and visuospatial skills.

Clinicians must also be aware of the reporting requirements in their individual jurisdictions. When a clinician has made the decision to report an unsafe driver to the Department of Motor Vehicles, he or she must consider the impact of a potential breach in confidentiality and must weigh and address, in advance when possible, the consequences of the loss of driving independence.

### D. Advance Financial Planning

Difficulty in managing financial affairs often develops early in the course of dementia. Although expertise is not expected, clinicians should have some proficiency to address financial concerns. Just as clinicians counsel patients and families about advance care planning, the same should be done to educate about the need for advance financial planning and to recommend that patients complete a **durable power of attorney for finance matters (DPOAF)** while the capacity to do so still exists.

No gold-standard test is available to identify when a patient with dementia no longer has financial capacity. However, the clinician should be on the lookout for signs that a patient is either at risk for or actually experiencing financial incapacity. Because financial impairment can occur when dementia is mild, making that diagnosis should alone be enough to warrant further investigation. Questioning patients and caregivers about late, missed, or repeated bill payments, unusual or uncharacteristic purchases or gifts, overdrawn bank accounts, or reports of missing funds can provide evidence of suspected financial impairment. Patients with dementia are also at increased risk for becoming victims of financial abuse, and some answers to these same questions might also be signs of potential exploitation. When financial abuse is suspected, clinicians should be aware of the reporting requirements in their local jurisdictions.

### ► Prognosis

Life expectancy after a diagnosis of Alzheimer disease is typically 3–15 years; it may be shorter than previously reported. Other neurodegenerative dementias, such as Lewy body dementia, show more rapid decline. Hospice care is often appropriate for patients with end-stage dementia.

### ► When to Refer

Referral for neuropsychological testing may be helpful to distinguish dementia from depression, to diagnose dementia in persons of very poor education or very high

premorbid intellect, and to aid diagnosis when impairment is mild.

- McCollum L et al. Cognitive impairment evaluation and management. *Med Clin North Am.* 2020;104:807. [PMID: 32773047]
- Phillips NA et al. Special issues on using the Montreal Cognitive Assessment for telemedicine assessment during COVID-19. *J Am Geriatr Soc.* 2020;68:942. [PMID: 32253754]
- Smith EE et al. Canadian Consensus Conference on Diagnosis and Treatment of Dementia (CCCDTD)5: guidelines for management of vascular cognitive impairment. *Alzheimers Dement (N Y).* 2020;6:e12056. [PMID: 33209971]
- Tung EE et al. Approach to the older adult with new cognitive symptoms. *Mayo Clin Proc.* 2020;95:1281. [PMID: 32498781]

## 2. Depression

### ESSENTIALS OF DIAGNOSIS

- ▶ May manifest in older adults as physical complaints (eg, fatigue, anhedonia) rather than complaints of depressed mood.
- ▶ Often undertreated in older adults. Approximately one-third of those treated with an antidepressant will achieve remission, and two-thirds will need additional treatment.

### ► General Considerations

Major depressive disorder has prevalence rates of approximately 2% among community-dwelling adults aged 55 years and older. Prevalence rises with increasing age as well as conditions such as chronic illness, multimorbidity, cognitive impairment, and functional impairment. Major depressive disorder is less common in older adults than younger adults, but *depressive symptoms* (not meeting criteria for major depressive disorder) are common and present in up to 15% of older adults. Depression is more common among hospitalized and institutionalized elders. Older single men have the highest rate of completed suicides of any demographic group.

New incidence of depressive symptoms may be an early sign of cognitive impairment in older adults; therefore, evaluation of depression should include cognitive assessment. Older patients with depression and depressive symptoms who have comorbid conditions (eg, heart failure) are at higher risk for hospitalization, tend to have longer hospital stays, and have worse outcomes than patients without depression.

### ► Clinical Findings

The Patient Health Questionnaire-2 (PHQ-2) is highly sensitive for detecting major depression in persons over age 65. Positive responses should be followed up with more comprehensive, structured interviews, such as the PHQ-9.

Evaluation of depression should include a careful review of substances that can contribute to depressive

symptoms, such as medications (eg, benzodiazepines) and alcohol/illicit drugs. A thorough review of the medical history is critical, since many medical problems can cause fatigue, lethargy, or hypoactive delirium, all of which may be mistaken for depression.

### ► Treatment

First-line treatment is the same for older adults as it is for younger adults; psychotherapy and selective serotonin reuptake inhibitor (SSRI) medications are the mainstays of treatment. Adjunctive treatment may include psychosocial interventions, increased physical activity, reduction of substance use (eg, alcohol), reduction of potentially contributing medications, or electroconvulsive therapy. Depressed older adults may do better with a collaborative or multidisciplinary care model that includes socialization and other support elements. In older patients with depressive symptoms who do not meet criteria for major depressive disorder, nonpharmacologic treatments are indicated.

Choice of antidepressant agent is usually based on side-effect profile, cost, and patient-specific factors, such as presenting symptoms and comorbidities. SSRIs are used as first-line agents because they are relatively well-tolerated and have good evidence to support efficacy (see Table 25–7). Older adults are more susceptible to SSRI-induced hyponatremia, falls, and osteoporosis. Serotonin-norepinephrine reuptake inhibitors (eg, duloxetine and venlafaxine) lead to more adverse events versus placebo than do SSRIs. Non-SSRI agents, such as mirtazapine and duloxetine, may be chosen for patients with additional indications. Mirtazapine may be useful for patients with weight loss, anorexia, or insomnia. Duloxetine is useful in patients who also have neuropathic pain. Regardless of the medication chosen, many experts recommend starting elders at a relatively low dose, titrating to full dose slowly, and continuing for a longer trial (at least 8 weeks) before trying a different medication. Titration to full dose is critical to achieve efficacy of treatment. Of note, the maximum citalopram dose for older adults is 20 mg orally daily, due to dose-dependent QT prolongation.

One-third of older adults achieve remission after adequate treatment with first-line SSRI treatment. For the remainder, referral to a mental health specialist is indicated. For those who do not achieve remission, augmentation therapy (eg, with lithium, methylphenidate, or aripiprazole) can enhance clinical response. Esketamine, the S-enantiomer of ketamine, is approved for treatment-resistant depression, but studies of its safety and efficacy did not include adults older than age 65. For patients with severe or catatonic depression, electroconvulsive therapy has high rates of efficacy (60–80%) and should be considered.

Pharmacologic treatment for the first episode of depression should continue for 1 year after remission. Clinicians and patients should share in decision-making regarding maintenance therapy for depression, since risk of major depressive disorder recurrence is high. This decision should weigh how long-term pharmacotherapy may contribute to polypharmacy and adverse effects in the landscape of their patient's comorbidities and medication regimen.

## ► When to Refer

- Any patient who might be considered for electroconvulsive therapy should be referred for psychiatric evaluation.
- Consider referral for patients who have mania, psychosis, catatonia, or treatment-resistant depression.

## ► When to Admit

Consider psychiatric evaluation and admission for patients who have psychosis, suicidality, homicidity, catatonia, grave disability, or self-neglect.

Haigh EAP et al. Depression among older adults: a 20-year update on five common myths and misconceptions. *Am J Geriatr Psychiatry*. 2018;26:107. [PMID: 28735658]

Krishnamoorthy Y et al. Diagnostic accuracy of various forms of geriatric depression scale for screening of depression among older adults: systematic review and meta-analysis. *Arch Gerontol Geriatr*. 2020;87:104002. [PMID: 31881393]

Meyer JP et al. Electroconvulsive therapy in geriatric psychiatry: a selective review. *Clin Geriatr Med*. 2020;36:265. [PMID: 32222301]

Sobieraj DM et al. Adverse effects of pharmacologic treatments of major depression in older adults. *J Am Geriatr Soc*. 2019;67:1571. [PMID: 31140587]

Zhang H et al. Comparison of the Geriatric Depression Scale-15 and the Patient Health Questionnaire-9 for screening depression in older adults. *Geriatr Gerontol Int*. 2020;20:138. [PMID: 31820572]

## 3. Delirium



### ESSENTIALS OF DIAGNOSIS

- Rapid onset and fluctuating course.
- Primary deficit in attention rather than memory.
- May be hypoactive or hyperactive.
- Dementia frequently coexists.

## ► General Considerations

Delirium is an acute, fluctuating disturbance of consciousness, associated with a change in cognition or development of perceptual disturbances (see also Chapter 25). It is the pathophysiologic consequence of an underlying general medical condition, such as infection, coronary ischemia, hypoxemia, or metabolic derangement. Delirium occurs in 29–64% of hospitalized older adults, persists in 25% or more, and is associated with worse clinical outcomes (higher in-hospital and postdischarge mortality, longer lengths of stay, delayed and limited recovery of physical function, greater probability of placement in a nursing facility).

Although the acutely agitated elderly patient often comes to mind when considering delirium (**hyperactive delirium**), many episodes are subtler. Such **hypoactive delirium** may be suspected only if one notices new cognitive slowing or inattention.

Cognitive impairment is an important risk factor for delirium. Other risk factors include severe illness, polypharmacy, use of psychoactive medications, sensory impairment, depression, and alcoholism.

## ► Clinical Findings

Several bedside instruments are available for the assessment of delirium (<http://www.hospitalelderlifeprogram.org/delirium-instruments/>). The **confusion assessment method (CAM)** requires (1) acute onset and fluctuating course and (2) inattention and either (3) disorganized thinking or (4) altered level of consciousness. The 3D CAM (3-minute diagnostic CAM) is particularly useful for clinical assessment of delirium.

A key component of a delirium workup is review of medications because polypharmacy, the addition of a new medication, an increase in dose of a medication, or the discontinuation of a medication known to cause withdrawal symptoms are all associated with the development of delirium. Medications that are particularly likely to increase the risk of delirium include sedative/hypnotics, anticholinergics, opioids, benzodiazepines, and H<sub>1</sub>- and H<sub>2</sub>-antihistamines.

Evaluation of most patients should include a complete blood count; blood urea nitrogen (BUN); serum electrolytes, creatinine, glucose, calcium, albumin, and liver biochemical tests; urinalysis; and ECG. In selected cases, serum magnesium, medication levels, arterial blood gas measurements, blood cultures, chest radiography, urinary toxin screen, and lumbar puncture may be helpful. When delirium develops during a hospitalization in the absence of trauma or new localizing neurologic signs, a head CT is rarely revealing.

## ► Prevention

The best evidence for prevention comes from nonpharmacologic multicomponent interventions. These components include improving cognition (frequent reorientation, activities, socialization with family and friends when possible), sleep (massage, noise reduction, minimizing interruptions at night), mobility (early initiation of rehabilitation services as appropriate), vision (visual aids and adaptive equipment), hearing (portable amplifiers, cerumen disimpaction), and hydration status (volume repletion). No medications, including antipsychotics, have been consistently shown to prevent delirium or improve outcomes such as length of stay or mortality should delirium develop.

## ► Treatment

Management of established episodes of delirium combines the elements of preventive interventions with reassurance and reorientation, treatment of underlying causes, eliminating unnecessary medications, and avoidance of indwelling catheters and restraints. Antipsychotics have long been a mainstay of delirium treatment in hospitalized adults, but evidence is accumulating that they offer little to no benefit and can cause harm. Data from a 2019 systematic review of haloperidol and second-generation antipsychotics found

no difference in delirium severity or duration, hospital length of stay, or mortality when compared to placebo. QT interval prolongation was more common in the antipsychotic group, but there was no difference in extrapyramidal effects. Evidence for other potential outcomes was insufficient to assess. Benzodiazepines should be avoided except in the circumstance of alcohol or benzodiazepine withdrawal. In ventilated patients in the intensive care unit setting, dexmedetomidine or propofol (or both) may also be useful alternatives or adjuncts to antipsychotic therapy in patients with delirium.

Most episodes of delirium clear in a matter of days after correction of the precipitant, but some patients suffer episodes of much longer duration, and a significant percentage never return to their former baseline level of functioning.

### ► When to Refer

If an initial evaluation does not reveal the cause of delirium or if entities other than delirium are in the differential diagnosis, referral to a neuropsychologist, neurologist, or geropsychiatrist should be considered.

### ► When to Admit

Patients with delirium of unknown cause should be admitted for an expedited workup if consistent with the patient's goals of care.

Hsieh TT et al. Delirium in the elderly. *Clin Geriatr Med.* 2020;36:183. [PMID: 3222295]

Kotfis K et al. COVID-19: ICU delirium management during SARS-CoV-2 pandemic. *Crit Care.* 2020;24:176. [PMID: 32345343]

Mart MF et al. Prevention and management of delirium in the intensive care unit. *Semin Respir Crit Care Med.* 2021;42:112. [PMID: 32746469]

Rieck KM et al. Delirium in hospitalized older adults. *Hosp Pract (1995).* 2020;48:3. [PMID: 31874064]

Salvi F et al. Non-pharmacological approaches in the prevention of delirium. *Eur Geriatr Med.* 2020;11:71. [PMID: 32297241]

## 4. Immobility

Mobility limitations are common in older adults and are associated with increased rates of morbidity, hospitalization, disability, and mortality. Hospital-associated bed rest is a common precipitant of immobility and functional decline. Among hospitalized medical patients over age 70, about 10% experience a decline in function, and those who experience critical illness are particularly at high risk.

The hazards of bed rest in older adults are multiple, serious, quick to develop, and slow to reverse. Within days of being confined to bed, deconditioning of the cardiovascular system occurs. This involves fluid shifts, decreased cardiac output, decreased peak oxygen uptake, increased resting heart rate, and postural hypotension. More striking changes occur in skeletal muscle, resulting in loss of strength and function. Pressure injuries, venous thromboembolism, and falls are additional serious outcomes of immobility and deconditioning.

### ► Prevention & Treatment

Physical activity should be encouraged for all elders, particularly sedentary elders. Physical activity is associated with a myriad of health benefits in older adults. Structured physical activity programs may help reduce mobility-related disability among community-dwelling elders.

When immobilization cannot be avoided, several measures can be used to minimize its consequences. To reduce the risks of contracture and weakness, range-of-motion and strengthening exercises should be started immediately and continued as long as the patient is in bed. Avoiding restraints and discontinuing intravenous lines and urinary catheters will increase opportunities for early mobility. Graduated ambulation should begin as soon as it is feasible. Among hospitalized elders, exercise protocols can improve functional outcomes. Prior to discharge, physical therapists can recommend appropriate exercises and assistive devices; after discharge, they can recommend safety modifications and maintenance exercises. Severe functional disability impeding the ability to care for oneself independently often leads to discharge to an acute or subacute rehabilitation facility. Recovery from these illness-related deconditioning takes weeks to months, and in many cases full recovery to the pre-illness physical condition does not occur.

Flint LA et al. Rehabbed to death. *N Engl J Med.* 2019;380:408. [PMID: 30699322]

Martínez-Velilla N et al. Effect of exercise intervention on functional decline in very elderly patients during acute hospitalization: a randomized clinical trial. *JAMA Intern Med.* 2019;179:28. [PMID: 30419096]

Pahor M et al. Impact and lessons from the Lifestyle Interventions and Independence for Elders (LIFE) clinical trials of physical activity to prevent mobility disability. *J Am Geriatr Soc.* 2020;68:872. [PMID: 32105353]

## 5. Falls & Gait Disorders

Annually, about one-third of people over age 65 fall, and the frequency of falls increases markedly with advancing age. About 10% of falls result in serious injuries. Complications from falls (eg, hip fracture, subdural hematoma) are the leading cause of death from injury in persons over age 65, and fall-associated mortality is increasing.

Every older person should be asked about falls. Assessment of patients who fall should include postural blood pressure and pulse; cardiac examination; evaluations of strength, range of motion, cognition, and proprioception; and examination of feet and footwear. A thorough gait assessment should be performed in all older people. Gait and balance can be readily assessed by the “Up and Go Test,” in which the patient is asked to stand up from a sitting position without use of hands, walk 10 feet, turn around, walk back, and sit down. Patients who take less than 10 seconds are usually normal, while patients who take longer than 13.5 seconds are considered at increased risk for falling. The ability to recognize common patterns of gait disorders is an extremely useful clinical skill to develop. Examples of gait abnormalities and their causes are listed in Table 4-1.

**Table 4–1.** Evaluation of gait abnormalities.

| Gait Abnormality                        | Possible Causes   |
|---|---|
| Inability to stand without use of hands | Deconditioning<br>Myopathy (hyperthyroidism, alcohol, statin-induced)<br>Hip or knee pain   |
| Unsteadiness upon standing              | Orthostatic hypotension<br>Balance problem (peripheral neuropathy, vision problem, vestibular, other central nervous system causes)<br>Generalized weakness |
| Stagger with eyes closed                | Often indicates that vision is compensating for another deficit   |
| Short steps                             | Weakness<br>Parkinson disease or related condition  |
| Asymmetry                               | Cerebrovascular accident<br>Focal pain or arthritis   |
| Wide-based gait                         | Fear, balance problems  |
| Flexed knees                            | Contractures, quadriceps weakness   |
| Slow gait                               | Fear of falling, weakness, deconditioning, peripheral vascular disease, chronic obstructive pulmonary disease, heart failure, angina pectoris               |

## ► Causes of Falls

Balance and ambulation require a complex interplay of cognitive, neuromuscular, and cardiovascular function. With age, balance mechanisms can become compromised, reaction time slows, and postural sway increases. These changes predispose the older person to a fall when challenged by an additional insult to any of these systems.

Falls in older people are rarely due to a single cause, and effective intervention entails a comprehensive assessment of the patient's intrinsic deficits (eg, diseases and medications), the activity engaged in at the time of the fall, and environmental obstacles (Table 4–2).

Intrinsic deficits are those that impair sensory input, judgment, blood pressure regulation, reaction time, and balance and gait. Dizziness may be closely related to the

**Table 4–2.** Fall risk factors, targeted interventions, and best evidence for fall prevention.

| To Consider for All Patients   |   |
|--|---|
| Exercise or physical therapy   | Tai Chi, gait training, balance training, strength training   |
| Multifactorial intervention  | Home safety assessment, medication review, review of specific conditions (below), advice on appropriate footwear, vision check, adaptive aids as appropriate, physical therapy or exercise as appropriate |
| Condition  | Targeted Intervention   |
| Postural hypotension (> 20 mm Hg drop in systolic blood pressure, or systolic blood pressure < 90 mm Hg) | Behavioral recommendations, such as hand clenching, elevation of head of bed; discontinuation or substitution of high-risk medications  |
| Use of benzodiazepine or sedative/hypnotic agent   | Education about sleep hygiene; discontinuation or substitution of medications   |
| Use of multiple prescription medications   | Review of medications with a focus on discontinuation (deprescribing)   |
| Environmental hazards  | Removal or mitigation of hazards; installation of safety equipment (eg, grab bars)  |
| Gait impairment  | Gait training, assistive devices, balance or strengthening exercises  |
| Impairment in transfer or balance  | Balance exercises, training in transfers, environmental alterations (eg, grab bars)   |
| Impairment in leg or arm muscle strength or limb range of motion   | Exercise with resistance bands or putty, with graduated increases in resistance   |
| Vision impairment  | Cataract surgery or other interventions as appropriate (eg, corrective lenses)  |
| Inability to get up after a fall   | Medic-alert system, physical therapy training for strategies  |
| High-risk footwear   | Education on appropriate footwear (eg, avoid slippers, high heels)  |

deficits associated with falls and gait abnormalities. While it may be impossible to isolate a sole “cause” or a “cure” for falls, gait abnormalities, or dizziness, it is often possible to identify and ameliorate some of the underlying contributory conditions and improve the patient’s overall function.

Medication use is one of the most common, significant, and reversible causes of falling. A meta-analysis found that sedative/hypnotics, antidepressants, and benzodiazepines were the classes of medications most likely to be associated with falling. The use of multiple medications simultaneously has also been associated with an increased fall risk. Other often overlooked but treatable contributors include postural hypotension (including postprandial, which peaks 30–60 minutes after a meal), insomnia, use of multifocal lenses, and urinary urgency.

Since most falls occur in or around the home, a visit by a visiting nurse, physical therapist, or health care provider for a **home safety evaluation** may be beneficial in identifying environmental obstacles and is generally reimbursed by third-party payers, including Medicare.

## ► Complications of Falls

The most common fractures resulting from falls are of the wrist, hip, and vertebrae. There is a high mortality rate (approximately 20% in 1 year) in elderly women with hip fractures, particularly if they were debilitated prior to the time of the fracture. Fear of falling again is a common, serious, but treatable factor in the older person’s loss of confidence and independence. Referral to a physical therapist for gait training with special devices is often all that is required.

Chronic subdural hematoma is an easily overlooked complication of falls that must be considered in any elderly patient presenting with new neurologic symptoms or signs, including evidence of new cognitive impairment. Headache and known history of trauma may both be absent.

Patients who are unable to get up from a fall are at risk for dehydration, electrolyte imbalance, pressure injuries, rhabdomyolysis, and hypothermia.

## ► Prevention & Management

**Exercise** is the intervention that is most consistently reported to reduce the risk of falls. Balance focused exercises (eg, Tai Chi), gait, and strength training appear to be more effective for fall prevention than general exercise programs (Table 4-2).

Multifactorial interventions appear to have a small benefit in preventing falls. These interventions include an assessment of potentially modifiable risk factors and tailored interventions to reduce risk. Emphasis is placed on treating all contributory medical conditions, minimizing environmental hazards, and eliminating medications where the harms may outweigh the benefits (eg, sedative-hypnotics).

The USPSTF recommends *against* vitamin D supplementation to prevent falls in community-dwelling adults. Vitamin D supplementation might be considered for high-risk individuals (eg, institutionalized elders) on a case-by-case

basis. High-dose vitamin D (60,000 international units per month) has been shown to *increase* the incidence of falls.

Assistive devices, such as canes and walkers, are useful for many older adults but are often used incorrectly. Canes should be used on the “good” side. The height of walkers and canes should generally be about the level of the wrist. Physical therapists are invaluable in assessing the need for an assistive device, selecting the best device, and training a patient in its correct use.

Eyeglasses, particularly bifocal or graduated lenses, may increase the risk of falls, particularly in the early weeks of use. Patients should be counseled about the need to take extra care when new eyeglasses are being used.

Patients with repeated falls are often reassured by the availability of telephones at floor level, a mobile telephone on their person, or a lightweight radio call system. Their therapy should also include training in techniques for arising after a fall.

## ► When to Refer

Patients with a recent history of falls should be referred for physical therapy, eye examination, and home safety evaluation.

## ► When to Admit

If the patient has new falls that are unexplained, particularly in combination with a change in the physical examination or an injury requiring surgery, hospitalization should be considered.

Ganz DA et al. Prevention of falls in community-dwelling older adults. N Engl J Med. 2020;382:734. [PMID: 32074420]

Liu-Ambrose T et al. Effect of a home-based exercise program on subsequent falls among community-dwelling high-risk older adults after a fall: a randomized clinical trial. JAMA. 2019;321:2092. [PMID: 31162569]

Pahor M. Falls in older adults: prevention, mortality, and costs. JAMA. 2019;321:2080. [PMID: 31162553]

Senderovich H et al. Do exercises prevent falls among older adults: where are we now? A systematic review. J Am Med Dir Assoc. 2020;21:1197. [PMID: 32646820]

US Preventive Services Task Force; Grossman DC et al. Interventions to prevent falls in community-dwelling older adults: US Preventive Services Task Force recommendation statement. JAMA. 2018;319:1696. [PMID: 29710141]

## 6. Urinary Incontinence

### ESSENTIALS OF DIAGNOSIS

- Involuntary loss of urine.
- Stress incontinence: leakage of urine upon coughing, sneezing, or standing.
- Urge incontinence: urgency and inability to delay urination.
- Overflow incontinence: variable presentation.

## ► General Considerations

Urinary incontinence in older adults is common, and interventions can improve most patients. Many patients do not voluntarily disclose their experience with urinary incontinence to their health care providers, making it all the more important for providers to inquire. A simple question about involuntary leakage of urine is a reasonable annual screen: “Do you have a problem with urine leaks or accidents?”

## ► Classification

### A. Transient Causes

Use of the mnemonic “DIAPPERS” may be helpful in remembering the categories of “transient” urinary incontinence.

**1. Delirium**—A clouded sensorium impedes recognition of both the need to void and the location of the nearest toilet. Delirium is the most common cause of incontinence in hospitalized patients.

**2. Infection**—Symptomatic urinary tract infection can cause or contribute to urgency and incontinence. Asymptomatic bacteriuria does not.

**3. Atrophic urethritis and vaginitis**—Atrophic urethritis and vaginitis can usually be diagnosed presumptively by the presence of vaginal mucosal telangiectasia, petechiae, erosions, erythema, or friability. Urethral inflammation, if symptomatic, may contribute to incontinence in some women.

**4. Pharmaceuticals**—Medications are one of the most common causes of transient incontinence. Typical offending agents include potent diuretics, anticholinergics, psychotropics, opioid analgesics, alpha-blockers (in women), alpha-agonists (in men), and calcium channel blockers.

**5. Psychological factors**—Severe depression with psychomotor retardation may impede the ability or motivation to reach a toilet.

**6. Excess urinary output**—Excess urinary output may overwhelm the ability of an older person to reach a toilet in time. In addition to diuretics, common causes include excess fluid intake; metabolic abnormalities (eg, hyperglycemia, hypercalcemia, diabetes insipidus); and peripheral edema (when previously dependent legs assume a horizontal position in bed).

**7. Restricted mobility**—(See Immobility, above.) If mobility cannot be improved, access to a urinal or commode (eg, at the bedside) may improve continence.

**8. Stool impaction**—This is a common cause of urinary incontinence in hospitalized or immobile patients. Although the mechanism is still unknown, a clinical clue to its presence is the onset of both urinary and fecal incontinence.

### B. Established Causes

Causes of “established” incontinence should be addressed after any “transient” causes have been managed appropriately.

**1. Detrusor overactivity (urge incontinence)**—Detrusor overactivity refers to uninhibited bladder contractions that cause leakage. It is the most common cause of established incontinence in older adults, accounting for two-thirds of cases. Women will complain of urinary leakage after the onset of an intense urge to urinate that cannot be fore stalled. In men, the symptoms are similar, but detrusor overactivity commonly coexists with urethral obstruction from benign prostatic hyperplasia. Because detrusor overactivity also may be due to bladder stones or tumor, the abrupt onset of otherwise unexplained urge incontinence—especially if accompanied by perineal or suprapubic discomfort or sterile hematuria—should be investigated by urine cytology and cystoscopy.

**2. Urethral incompetence (stress incontinence)**—Urethral incompetence is the second most common cause of established urinary incontinence in older women. In men, it most commonly occurs after radical prostatectomy. Stress incontinence is characterized by instantaneous leakage of urine in response to an increase in intra-abdominal pressure. It commonly coexists with detrusor overactivity causing “mixed” incontinence. Typically, urinary loss occurs with laughing, coughing, or lifting heavy objects. To test for stress incontinence, have the patient relax her perineum and cough vigorously (a single cough) while standing with a full bladder. Instantaneous leakage indicates stress incontinence. A delay of several seconds or persistent leakage suggests that the problem is instead caused by an uninhibited bladder contraction induced by coughing.

**3. Overflow incontinence**—Urethral obstruction (due to prostatic enlargement, urethral stricture, bladder neck contracture, or prostatic cancer) is a common cause of established incontinence in older men but is rare in older women. It can present as dribbling incontinence after voiding, urge incontinence due to detrusor overactivity, or overflow incontinence due to urinary retention. Detrusor underactivity is less common but can also cause overflow incontinence. It may be idiopathic or have an identifiable cause including medications and sacral lower motor nerve dysfunction. When it causes incontinence, detrusor underactivity is associated with urinary frequency, nocturia, and frequent leakage of small volumes. Although the measurement of postvoid residual (PVR) volume is not considered standard in the evaluation of urinary incontinence, it should be measured when overflow is suspected. No standardized cutoff has been established for PVR, but it is generally above 200 mL in overflow incontinence and can be measured using portable ultrasound.

## ► Treatment

### A. Transient Causes

Each identified transient cause should be treated regardless of whether an established cause coexists. For patients with urinary retention induced by an anticholinergic agent, discontinuation of the medication should first be considered. If this is not feasible, substituting a less anticholinergic agent may be useful.

## B. Established Causes

**1. Detrusor overactivity**—The cornerstone of treatment is **bladder training**. Patients start by voiding on a schedule based on the shortest interval recorded on a bladder record. They then gradually lengthen the interval between voids by 30 minutes each week using relaxation techniques to postpone the urge to void. Lifestyle modifications, including weight loss and caffeine reduction, may also improve incontinence symptoms. For cognitively impaired patients and nursing home residents who are unable to manage on their own, **timed and prompted voiding** initiated by caregivers is effective. **Pelvic floor muscle (“Kegel”) exercises** can reduce the frequency of incontinence episodes when performed correctly and sustained.

If behavioral approaches prove insufficient, several FDA-approved **antimuscarinic agents** may provide additional benefit. Available regimens of these agents include short-acting tolterodine, 1–2 mg orally twice a day; long-acting tolterodine, 2–4 mg orally daily; short-acting oxybutynin, 2.5–5 mg orally twice or three times a day; long-acting oxybutynin, 5–15 mg orally daily; oxybutynin transdermal patch, 3.9 mg/day applied twice weekly; oxybutynin 10% transdermal gel, 100 mg applied daily; fesoterodine, 4–8 mg orally once daily; trospium chloride, 20 mg orally once or twice daily; long-acting trospium chloride, 60 mg orally daily; darifenacin, 7.5–15 mg orally daily; and solifenacin, 5–10 mg orally daily. All of these agents appear to have similar efficacy and side-effect profiles (eg, delirium/cognitive impairment, dry mouth, constipation, urinary retention). Long-acting and topical preparations are generally better tolerated.

The beta-3-agonists **mirabegron**, 25–50 mg orally daily, and **vibegron**, 75 mg orally once daily, are FDA approved for overactive bladder symptoms, which include urge urinary incontinence. In trials comparing mirabegron with antimuscarinic agents, the efficacy and safety profiles have been comparable, with less dry mouth reported in persons who received mirabegron. The experience accruing among adults over the age of 70 shows that adherence rates may be superior to the antimuscarinic medications.

An alternative to oral agents is an injection of **onabotulinum toxin A** into the detrusor muscle. While effective, it can lead to urinary retention and the need for self-catheterization.

The combination of behavioral therapy and antimuscarinics appears to be more effective than either alone, although one study in a group of younger women showed that adding behavioral therapy to individually titrated doses of extended-release oxybutynin was no better than with medication treatment alone.

In men with both benign prostatic hyperplasia and detrusor overactivity and with PVR of 150 mL or less, an antimuscarinic agent added to an alpha-blocker may provide additional relief of lower urinary tract symptoms.

**2. Urethral incompetence (stress incontinence)**—**Lifestyle modifications**, including limiting caffeine and fluid intake, may be helpful for some women, particularly women with mixed stress/urge incontinence; strong evidence supports weight loss in obese women. **Pelvic floor**

**muscle exercises** are effective for women with mild to moderate stress incontinence. Instruct the patient to pull in the pelvic floor muscles and hold for 6–10 seconds and to perform three sets of 8–12 contractions daily. Benefits may not be seen for 6 weeks. **Pessaries** or **vaginal cones** may be helpful in some women but should be prescribed only by providers who are experienced with using these modalities.

No medications are approved for the treatment of stress incontinence, and a clinical practice guideline from the American College of Physicians recommends against pharmacologic treatment. Although a last resort, **surgery** is the most effective treatment for stress incontinence; cure rates as high as 96% can result, even in older women.

**3. Overflow incontinence**—Most men with overflow incontinence from obstructive uropathy will first undergo bladder decompression with intermittent or indwelling catheterization followed by initiation of alpha-blocking agents (eg, terazosin, 1–10 mg orally daily; prazosin, 1–5 mg orally twice daily; or tamsulosin, 0.4–0.8 mg orally daily taken 30 minutes after a meal). Finasteride, 5 mg orally daily, can provide additional benefit in men with an enlarged prostate. If medical therapy fails to allow for adequate bladder emptying, surgical decompression can be an option. A variety of nonsurgical techniques make decompression feasible even for frail men. For the nonoperative candidate with urinary retention, intermittent or indwelling catheterization is used. For the patient with a poorly contractile bladder, augmented voiding techniques (eg, double voiding, suprapubic pressure) can prove effective. If further emptying is needed, intermittent or indwelling catheterization is the only option. Antibiotics should be used only for symptomatic urinary tract infection or as prophylaxis against recurrent symptomatic infections in a patient using intermittent catheterization; they should not be used as prophylaxis in a patient with an indwelling catheter.

### ► When to Refer

- Men with urinary obstruction who do not respond to medical therapy should be referred to a urologist.
- Women who do not respond to medical and behavioral therapy should be referred to a urogynecologist or urologist.

Sung VW et al. Effect of behavioral and pelvic floor muscle therapy combined with surgery vs surgery alone on incontinence symptoms among women with mixed urinary incontinence: the ESTEEM randomized clinical trial. JAMA. 2019;322:1066. [PMID: 31529007]

Vaughan CP et al. Urinary incontinence in women. Ann Intern Med. 2020;172:ITC17. [PMID: 32016335]

## 7. Involuntary Weight Loss

### ► General Considerations

Aging, even in the absence of disease, is associated with reduced appetite. Involuntary weight loss affects substantial numbers of older adults. Most studies of involuntary weight loss in community-dwelling older adults define it as loss of 5% of body weight in 6 months or 10% of body weight in 1 year.

## ► Clinical Findings

The many potential causes of involuntary weight loss include **medical conditions** (60–70%; eg, cancer cachexia, chronic heart failure) and **psychiatric conditions** (10–20%; eg, depression), but in up to 25% of cases the cause of weight loss cannot be identified. **Social factors**, such as access to food and dental health, should be investigated. The clinical evaluation should search for symptoms and signs that could point to a potential cause (eg, abdominal pain to peptic ulcer disease; tachycardia to hyperthyroidism). When the history, physical examination, and basic laboratory studies do not suggest a possible diagnosis, additional evaluation (eg, total body CT scan) is usually low yield. When no other cause is identified, the frailty syndrome should be considered in the differential diagnosis.

## ► Treatment

Initial treatment should focus on identifying medical causes of involuntary weight loss while also addressing and improving social barriers, such as social isolation and access to food. Social meals can improve intake and nutrition. Oral nutritional supplements of 200–1000 kcal/day can increase weight and improve outcomes in malnourished hospitalized older adults but have *not* been shown to have benefits in community-dwelling older adults. Sodium-containing flavor enhancers (eg, iodized salt) can improve food intake without adverse health effects when there is no contraindication to their use. Megestrol acetate as an appetite stimulant has *not* been shown to increase lean body mass or lengthen life among elders and has significant side effects. For those patients with advanced dementia, percutaneous liquid artificial nutrition (“tube feeding”) is *not* recommended, but rather assiduous hand feeding may allow maintenance of weight and provide more comfort.

Clegg ME et al. Optimizing nutrition in older people. *Maturitas*. 2018;112:34. [PMID: 29704915]

## 8. Pressure Injury



### ESSENTIALS OF DIAGNOSIS

- Examine at-risk patients on admission to the hospital and daily thereafter.
- Pressure injury is classified into one of six categories:
  - Stage 1: Non-blanchable erythema of intact skin
  - Stage 2: Partial-thickness skin loss with exposed dermis
  - Stage 3: Full-thickness skin loss
  - Stage 4: Full-thickness skin and tissue loss
  - Unstageable: Obscured full-thickness skin and tissue loss
  - Deep tissue: Persistent non-blanchable, deep red, maroon, or purple discolored

## ► General Considerations

The National Pressure Injury Advisory Panel changed the term “pressure ulcer” to “pressure injury” to more accurately reflect the fact that stage 1 and deep tissue injury describe damage to intact skin, compared to the ulcers described in the other four stages. Most pressure injuries develop during a hospital stay for an acute illness. The primary risk factor for pressure injuries is immobility. Other contributing risk factors include reduced sensory perception, moisture (urinary and fecal incontinence), poor nutritional status, and friction and shear forces.

Deep tissue and unstageable pressure injury are included in the six pressure injury stages. An area of purple or maroon discolored intact skin or blood-filled blister is characteristic of deep tissue injury. The area may be preceded by tissue that is painful, firm, mushy, boggy, warmer, or cooler compared with adjacent tissue. Ulcers in which the base is covered by slough (yellow, tan, gray, green, or brown) or eschar (tan, brown, or black) are considered unstageable.

Older adults admitted to hospitals and nursing homes should be assessed for their risk of developing pressure injuries, and several risk assessment instruments can be used, including the Braden Scale and the Norton score.

## ► Prevention

Using specialized support surfaces (including mattresses, beds, and cushions), patient repositioning, optimizing nutritional status, reducing shear and friction forces, and moisturizing sacral skin are strategies that have been shown to reduce pressure injury. For moderate- to high-risk patients, mattresses or overlays that reduce tissue pressure below that of a standard mattress appear to be superior to standard mattresses.

## ► Evaluation

Evaluation of pressure injuries should include patient’s risk factors and goals of care; injury stage, size, and depth; absence or presence (and type) of exudate; appearance of the wound bed and possible surrounding infection; and sinus tracking, or cellulitis.

## ► Treatment

High-quality evidence that rigorously examines the effectiveness of various treatments remains limited. Clinicians should therefore focus on the principles of wound care, including pressure reduction, removing necrotic debris, and maintaining a moist wound bed that will promote healing and formation of granulation tissue. The type of dressing that is recommended depends on the location and depth of the wound, whether necrotic tissue or dead space is present, and the amount of exudate (Table 4–3). Pressure-reducing devices (eg, air-fluid beds and low-air-loss beds) are associated with improved healing rates. Although poor nutritional status is a risk factor for the development of pressure injury, the evidence that nutritional supplementation helps correct pressure injury is limited.

Providers can become easily overwhelmed by the array of products available for the treatment of established

**Table 4–3.** Pressure injury dressings and other measures.

| Injury Type        | Dressing Type and Considerations   |
|--------------------|--|
| Stage 1            | Polyurethane film<br>Hydrocolloid wafer<br>Semipermeable foam dressing   |
| Stage 2            | Hydrocolloid wafers<br>Semipermeable foam dressing<br>Polyurethane film  |
| Stages 3 and 4     | For highly exudative wounds, use highly absorptive dressing or packing, such as calcium alginate<br>Wounds with necrotic debris must be debrided<br>Debridement can be autolytic, enzymatic, or surgical<br>Shallow, clean wounds can be dressed with hydrocolloid wafers, semipermeable foam, or polyurethane film<br>Deep wounds can be packed with gauze; if the wound is deep and highly exudative, an absorptive packing should be used |
| Heel injury        | Do not remove eschar on heel pressure injury because it can help promote healing (eschar in other locations should be debrided)  |
| Unstageable        | Debride if appropriate before deciding on further therapy  |
| Deep tissue injury | Offload pressure to the affected area  |

pressure injuries. Most institutions should designate a wound care expert or team to select a streamlined wound care product line that has simple guidelines. In a patient with end-stage disease who is receiving end-of-life care, appropriate treatment might be directed toward palliation only (including minimizing dressing changes and odors) rather than efforts directed at healing.

## ► Complications

Bacteria contaminate all chronic pressure injuries with skin loss, but it can be difficult to identify those wounds that are infected. Suspicion for infection should rise if there is pain, increased or foul-smelling wound drainage, erythema of the skin around the wound, or if the wound will not heal. Fever and leukocytosis are other indicators of systemic infection but are not always present. Culture from a superficial swab adds little valuable diagnostic information. For nonhealing infected wounds without evidence of systemic involvement, topical antiseptics (eg, silver sulfadiazine) are recommended and may need to be accompanied by debridement of necrotic tissue. When systemic infections such as cellulitis and osteomyelitis are present, oral or parenteral antibiotics are warranted and medication choice should be guided by tissue culture, but obtaining this can be painful and it is not always readily available.

## ► When to Refer

- Pressure injuries that are large or nonhealing should be referred to a plastic or general surgeon or dermatologist for biopsy, debridement, and possible skin grafting.
- For hospitalized patients or residents of skilled nursing facilities in whom pressure injuries develop, early involvement of a wound care specialist is crucial.

## ► When to Admit

Patients with pressure injury should be admitted if the primary residence is unable to provide adequate wound care or pressure reduction, or if the wound is infected or requires complex or surgical care.

Gillespie BM et al. Repositioning for pressure injury prevention in adults. Cochrane Database Syst Rev. 2020;6:CD009958. [PMID: 32484259]

Moore Z et al. Prevention of pressure ulcers among individuals cared for in the prone position: lessons for the COVID-19 emergency. J Wound Care. 2020;29:312. [PMID: 32530776]

## 9. Pharmacotherapy & Polypharmacy



- Older adults experience more adverse drug events than younger patients. Evaluate for dose reduction or drug avoidance based on kidney function, comorbidities, and other medication use.
- The AGS Beers Criteria list is useful for identifying high-risk medications for older adults. Particular caution/avoidance should be used in prescribing benzodiazepines and other sedative-hypnotic medications.

## ► General Considerations

More adverse drug events occur in older adults compared to younger patients for many reasons, including changing drug metabolism in the kidney or liver or both, drug interaction with comorbid conditions, and interactions between multiple medications. Polypharmacy itself is associated with adverse health outcomes, including falls, impaired cognition, hospitalizations, and death.

Medication metabolism is often impaired in older adults due to decreased glomerular filtration rate, reduced hepatic clearance, and changes in body composition (eg, lean body mass). Most emergency hospitalizations for adverse medication events among older adults result from commonly prescribed medications used alone or in combination.

## ► Precautions in Prescribing Medications

Most medications prescribed for chronic disease management should be initiated at the low end of the usual adult dosage range, with slow increases in dosage until a

therapeutic level is reached or intolerable side effects develop. At the same time, it is imperative that a medication's therapeutic dose be achieved, since older adults are at risk for undertreatment of conditions such as depression, if the starting dose is not increased with careful monitoring.

Optimal medication adherence is less likely with increasing numbers of pills and doses, high cost, poor communication about medication changes as well as expected benefits and side effects; other factors affecting adherence include cognitive impairment, insurance issues, and psychosocial barriers. When possible, the clinician should simplify both dosing schedules with the fewest number of pills and doses (combination formulations can be useful in this regard, though perhaps complicating future dose adjustments) as well as modes of administration (eg, oral, ocular, transdermal, subcutaneous, inhalational). Other helpful medication management techniques include use of a single pharmacy, use of pillboxes or pharmacy-packaged medication sets, clarity about the prescriber of each medication (and ideally use of fewer prescribers), infrequent medication changes, and clear instructions about all medication changes using the "teach-back" method of patient communication. Clinicians should ask patients about their ability to afford their medications, and counsel patients about strategies for cost containment (eg, switching to a more affordable Medicare Part D plan during open enrollment and interrogating drug formularies for low-cost alternatives).

The patient or caregiver should bring in all medications at each visit in order to achieve an accurate **medication reconciliation** and reinforce reasons for medication use, dosage, frequency of administration, and possible adverse effects. Patients should also bring all supplements and over-the-counter medications used, including analgesics and sleep aids. Medication reconciliation is particularly important if the patient sees multiple clinicians. Clinicians should be aware of the "prescribing cascade" in which a medication is prescribed to counter the side effect of another medication.

The risk of toxicity goes up with the number of medications prescribed. Certain combinations of medications (eg, warfarin and many antibiotics, angiotensin-converting enzyme inhibitors and NSAIDs, opioids and sedative-hypnotics) are particularly likely to cause drug-drug interactions and should be monitored carefully.

Trials of medication discontinuation (deprescribing) should be considered when the original indication is unclear or the patient is having side effects. Medication discontinuation is particularly important in patients with limited life expectancy who may be experiencing increasing burdens from polypharmacy and modest, if any, benefits from the medication (eg, bisphosphonates, antilipemics). Clinical tools such as "STOPP/START" and the AGS Beers Criteria can inform safe medication prescribing for older adults.

## ► When to Refer

- Refer patients with polypharmacy or poor medication adherence to a clinical pharmacist, when available.

- Refer homebound patients with poor medication adherence and suboptimal chronic disease management to a home health nurse for medication reconciliation and teaching.

Fick DM et al. American Geriatrics Society 2019 Updated AGS Beers Criteria® for potentially inappropriate medication use in older adults. *J Am Geriatr Soc.* 2019;67:674. [PMID: 30693946]

Nicosia FM et al. What is a medication-related problem? A qualitative study of older adults and primary care clinicians. *J Gen Intern Med.* 2020;35:724. [PMID: 31677102]

Thevelin S et al. Potentially inappropriate prescribing and related hospital admissions in geriatric patients: a comparative analysis between the STOPP and START criteria versions 1 and 2. *Drugs Aging.* 2019;36:453. [PMID: 30694444]

## 10. Vision Impairment

Visual impairment due to age-related refractive error ("presbyopia"), macular degeneration, cataracts, glaucoma, or diabetic retinopathy is associated with several negative physical and mental health outcomes. These include falls, impaired mobility, and reduced quality of life. While the 2016 USPSTF guideline and 2018 Cochrane Review conclude that there is insufficient evidence for routine visual impairment screening, the American Academy of Ophthalmology recommends a complete eye examination every 1–2 years after age 65. Serious and correctable vision disorders are prevalent and morbid enough that it is reasonable for most elders to undergo a comprehensive eye examination by an ophthalmologist or optometrist every 1–2 years. Eye examinations should certainly be prioritized for patients with new or recurring falls, changes in vision, and conditions with risk of eye complications (eg, diabetes mellitus, thyroid disease). Patients with significant visual loss should be referred to low-vision community programs for support and assessment for assistive devices.

Clarke EL et al. Community screening for visual impairment in older people. *Cochrane Database Syst Rev.* 2018;2:CD001054. [PMID: 29460275]

Ehrlich JR et al. Prevalence of falls and fall-related outcomes in older adults with self-reported vision impairment. *J Am Geriatr Soc.* 2019;67:239. [PMID: 30421796]

## 11. Hearing Impairment

Hearing loss in older adults is very common yet often undertreated. Over one-third of persons older than age 65 and half of those older than age 85 have some degree of hearing loss. Hearing loss is associated with social isolation, depression, disability, cognitive impairment and accelerated cognitive decline, hospitalization, and nursing home placement. Hearing loss is undertreated because it is underrecognized by clinicians and hearing assistive devices are expensive and not typically covered by insurance.

Although the USPSTF found insufficient evidence for routine hearing screening, clinicians should periodically ask patients about hearing loss and refer them to audiology if hearing loss is suspected. A reasonable clinical screen is to ask patients if they have noticed any hearing impairment. Those who answer "yes" should be referred

for audiometry. For those who answer “no” but in whom hearing loss is still suspected, further in-office screening can be performed using the **whispered voice test**. To determine the degree to which hearing impairment interferes with functioning, the provider may ask patients if they become frustrated when conversing with family members, have challenges understanding conversations, are embarrassed when meeting new people, or have difficulty watching television. Caregivers or family members can provide important collateral information regarding potential hearing loss and the impact of hearing loss on social interactions.

Hearing loss assistive devices and technology include hearing aids, cochlear implants, sound amplification for telephones and televisions, speech to text software, smart phone applications, hearing loops, and alerting devices to inform hearing-impaired people of an event such as a fire alarm. Hearing amplification and cochlear implantation improve hearing-related quality of life and reduce depressive symptoms. Compliance with hearing amplification can be a challenge because of the high device cost, dissatisfaction with performance, and stigma associated with hearing aid use. Newer digital devices may perform better but are considerably more expensive. US federal law allows for the sale of over-the-counter devices that can be purchased directly without a prescription from a clinician. These devices are most appropriate for patients with mild to moderate hearing loss. Cochlear implantation is an under-utilized treatment that is recommended for older adults with profound sensory hearing loss. It improves understanding of speech and quality of life. Portable hearing amplifiers (eg, “pocket talkers”) are low-cost hand-held devices with a headset for the patient and microphone to amplify sound for the speaker. These devices are particularly useful to communicate with hearing-impaired patients in clinic and inpatient settings. In order to facilitate successful communication with hearing-impaired patients, providers should face toward patients when speaking, speak at a moderate pace and in a low tone, and practice the “teachback” method in order to assess that information was adequately transmitted.

Alattar AA et al. Hearing impairment and cognitive decline in older, community-dwelling adults. *J Gerontol: Series A*. 2020;75:567. [PMID: 30753308]

Carlson ML. Cochlear implantation in adults. *N Engl J Med*. 2020;382:1531. [PMID: 32294347]

## 12. Elder Mistreatment & Self-Neglect

**Elder abuse** is defined as “acts whereby a trusted person causes or creates risk of harm to an older adult.” **Self-neglect** is the most common form of elder abuse and occurs among all demographic strata. In the United States, about 10% of adults over age 60 have experienced some sort of abuse or neglect in the previous year. Financial abuse is on the rise, and older adults with cognitive impairment are particularly vulnerable. Each year, at least 5% of elders are victims of financial abuse or scams.

Elder abuse risk factors include limited social support and poor physical health. Clues to the presence of elder

**Table 4–4.** Phrases and actions that may be helpful in situations of suspected abuse or neglect.

### Questions for the Elder

1. Has anyone hurt you?
2. Are you afraid of anybody?
3. Is anyone taking or using your money without your permission?

### Questions for the Caregiver

1. Are your relative's needs more than you can handle?
2. Are you worried that you might hit your relative?
3. Have you hit your relative?

### If abuse is suspected

Tell the patient that you are concerned, want to help, and will call

Adult Protective Services for further assistance

Document any injuries

Document the patient's words

Document whether the patient has decision-making capacity  
using a tool such as “Aid to Capacity Evaluation”

mistreatment or self-neglect include observing that the patient's behavior changes in the presence of the caregiver, delays between injury occurrence and treatment seeking, inconsistencies between an observed injury and its associated explanation, lack of appropriate clothing or hygiene, and unfilled prescriptions. Elder abuse and self-neglect can cause many health consequences, such as long-term care placement, anxiety, depression, and death.

While the USPSTF has not endorsed any screening tools to identify elder abuse, clinicians caring for older adults should maintain a high index of suspicion and meet with patients without the presence of caregivers on occasion. In these encounters, clinicians can ask questions about the caregiver relationship, and directly question about possible mistreatment and neglect, if suspected (Table 4–4).

When self-neglect is suspected, it is critical to establish whether a patient has decision-making capacity regarding the suspected neglectful behavior. A patient who has full decision-making capacity should be provided help and support but can choose to live in conditions of self-neglect, providing that the public is not endangered by their actions. In contrast, a patient who lacks decision-making capacity and lives in conditions of self-neglect requires more aggressive intervention, such as in-home help, conservatorship, or placement in a supervised setting. Cognitive assessment may provide some insight into whether cognitive impairment is contributing to self-neglect, but these tools are not designed to assess decision-making capacity. A standardized tool, such as the “Aid to Capacity Evaluation,” is easy to administer, has good performance characteristics for determining decision-making capacity, and is available free online at <http://www.jcb.utoronto.ca/tools/documents/ace.pdf>.

### ► When to Refer

- Refer older adults suffering from suspected elder abuse or self-neglect to **Adult Protective Services**, as required

by law in most states (consult the National Center on Elder Abuse at <https://ncea.acl.gov/>)

- Refer to a mental health professional for evaluation in cases in which decision-making capacity is unclear or if untreated mental illness is suspected to play a role in self-neglect.

surrogate decision-makers need to be identified and conservatorship may need to be pursued for safe discharge planning.

Curry SJ et al. Screening for intimate partner violence, elder abuse, and abuse of vulnerable adults: US Preventive Services Task Force final recommendation statement. *JAMA*. 2018;320:1678. [PMID: 3035730]

DeLiema M et al. Financial fraud among older Americans: evidence and implications. *J Gerontol B Psychol Sci Soc Sci*. 2020;75:861. [PMID: 30561718]

Van Den Bruele AB et al. Elder abuse. *Clin Geriatr Med*. 2019;35:103. [PMID: 30390976]

## ► When to Admit

- Admit older adults who would be unsafe in the community when an alternative plan cannot be put into place in a timely manner. In cases of self-neglect,

# 5

# Palliative Care & Pain Management

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## PALLIATIVE CARE

### DEFINITION & SCOPE

Palliative care is medical care focused on improving quality of life for people living with serious illness. Serious illness is defined as “a condition that carries a high risk of mortality, negatively impacts quality of life and daily function, and/or is burdensome in symptoms, treatments or caregiver stress.” Palliative care addresses and treats symptoms, supports patients’ families and loved ones, and through clear communication helps ensure that care aligns with patients’ preferences, values, and goals. Near the end of life, palliative care may become the sole focus of care, but palliative care *alongside* cure-focused treatment or disease management is beneficial throughout the course of a serious illness, regardless of its prognosis.

Palliative care includes management of physical symptoms, such as pain, dyspnea, nausea and vomiting, constipation, delirium, and agitation; emotional distress, such as depression, anxiety, and interpersonal strain; and existential distress, such as spiritual crisis. While palliative care is a medical subspecialty recognized by the American Board of Medical Specialties (“specialty palliative care”) and is typically provided by an interdisciplinary team of experts, *all* clinicians should have the skills to provide “generalist” or “primary palliative care” including managing pain; treating dyspnea; identifying mood disorders; communicating about prognosis and patient preferences for care; and helping address spiritual distress. The fourth edition of the National Consensus Project’s Clinical Practice Guidelines for Quality Palliative Care emphasizes that palliative care is the responsibility of all clinicians and disciplines caring for people with serious illness, in all health care settings (including hospitals, primary care and specialty clinics, nursing homes, and the community).

The scope of primary palliative care and the ideal timing to begin specialty palliative care for patients with different illnesses is an evolving area of practice.

During any stage of illness, patients should be screened routinely for symptoms. Any symptoms that cause significant suffering are a medical emergency that should be

managed aggressively with frequent elicitation and reassessment as well as individualized treatment. While patients at the end of life may experience a host of distressing symptoms, pain, dyspnea, and delirium are among the most feared and burdensome. Management of these common symptoms is described later in this chapter.

The ethical principle of “**double effect**” argues that the potential to hasten imminent death is acceptable if it comes as the known but unintended consequence of a primary intention to provide comfort and relieve suffering. Randomized studies have shown that palliative care provided alongside disease-focused treatment can improve quality of life, promote symptom management, and even prolong life in some situations.

As is true for clinicians of all medical specialties, palliative care clinicians and the systems of care for people with serious illness in the United States are influenced by systemic racial bias. Practitioners must work to identify and rectify injustice in how patient symptoms are assessed and treated as well as in how palliative care services are offered.

- Gärtner J et al. Early palliative care: pro, but please be precise! *Oncol Res Treat*. 2019;42:11. [PMID: 30685764]
- Huang YL et al. Review article: End-of-life care for older people in the emergency department: a scoping review. *Emerg Med Australas*. 2020;32:7. [PMID: 31820582]
- Kluger BM et al. Comparison of integrated outpatient palliative care with standard care in patients with Parkinson disease and related disorders: a randomized clinical trial. *JAMA Neurol*. 2020;77:551. [PMID: 32040141]
- Mechler K et al. Palliative care approach to chronic diseases: end stages of heart failure, chronic obstructive pulmonary disease, liver failure, and renal failure. *Prim Care*. 2019;46:415. [PMID: 31375190]
- Ornstein KA et al. Evaluation of racial disparities in hospice use and end-of-life treatment intensity in the REGARDS cohort. *JAMA Netw Open*. 2020;3:e2014639. [PMID: 32833020]
- Ruiz M et al. Role of early palliative care interventions in hematological malignancies and bone marrow transplant patients: barriers and potential solutions. *Am J Hosp Palliat Care*. 2018;35:1456. [PMID: 29699418]
- Zhou K et al. Palliative care in heart failure: a meta-analysis of randomized controlled trials. *Herz*. 2019;44:440. [PMID: 29468259]

## PALLIATION OF COMMON NONPAIN SYMPTOMS

### DYSPNEA

Dyspnea is the subjective experience of difficulty breathing and may be characterized by patients as tightness in the chest, shortness of breath, breathlessness, or a feeling of suffocation. Up to half of people at the end of life may experience severe dyspnea.

Treatment of dyspnea is first directed at the cause (see Chapter 9) if a workup is consistent with the patient's goals. Dyspnea responds to opioids, which have been proven effective in multiple randomized trials. Starting doses are typically lower than would be necessary for the relief of moderate pain. Immediate-release morphine given orally (2–4 mg every 4 hours) or intravenously (1–2 mg every 4 hours) treats dyspnea effectively. Sustained-release morphine given orally at 10 mg daily is safe and effective for most patients with ongoing dyspnea. Many patients who become seriously ill with COVID-19 experience dyspnea and may require opioids as well as supplemental oxygen. Supplemental oxygen may be useful for the dyspeptic patient *who is hypoxic* with any illness. Fresh air from a window or fan may provide relief for dyspeptic patients who are not necessarily hypoxic. Judicious use of noninvasive ventilation, including high-flow oxygen via nasal cannula, as well as nonpharmacologic relaxation techniques, such as meditation and guided imagery, may be beneficial for some patients. Benzodiazepines may be useful adjuncts for treatment of dyspnea-related anxiety.

### NAUSEA & VOMITING

Nausea and vomiting are common and distressing symptoms. As with pain, the management of nausea may be optimized by regular dosing and often requires multiple medications targeting one or more of the four major inputs to the vomiting center (see Chapter 15).

**Vomiting associated with opioids** is discussed below. Nasogastric suction may provide rapid, short-term relief for **vomiting associated with constipation** (in addition to laxatives), **gastroparesis, or gastric outlet or bowel obstruction**. Prokinetic agents, such as metoclopramide (5–20 mg orally or intravenously four times a day), can be helpful in the setting of partial gastric outlet obstruction. Transdermal scopolamine (1.5-mg patch every 3 days) can reduce peristalsis and cramping pain, and H<sub>2</sub>-blocking medications can reduce gastric secretions. High-dose corticosteroids (eg, dexamethasone, 20 mg orally or intravenously daily in divided doses) can be used in refractory cases of nausea or vomiting or when it is due to bowel obstruction or **increased intracranial pressure**. Malignant bowel obstruction in people with advanced cancer is a poor prognostic sign and surgery is rarely helpful.

**Vomiting due to disturbance of the vestibular apparatus** may be treated with anticholinergic and antihistaminic agents (including diphenhydramine, 25 mg orally or intravenously every 8 hours, or scopolamine, 1.5-mg patch every 3 days).

Benzodiazepines (eg, lorazepam, 0.5–1.0 mg given orally every 6–8 hours) can be effective in preventing the *anticipatory* nausea and anxiety associated with chemotherapy. For emetogenic chemotherapy, therapy includes combinations of 5-HT<sub>3</sub>-antagonists (eg, ondansetron, granisetron, dolasetron, or palonosetron), neurokinin-1 receptor antagonists (eg, aprepitant, fosaprepitant, or rolapitant), the N-receptor antagonist netupitant combined with palonosetron (NEPA), olanzapine, dexamethasone, and prochlorperazine. In addition to its effect on mood, mirtazapine, 15–45 mg orally nightly, may help with nausea and improve appetite. Finally, dronabinol (2.5–20 mg orally every 4–6 hours) can be helpful in the management of nausea and vomiting. Patients report relief from medical cannabis, although the tetrahydrocannabinol (THC) or cannabidiol (CBD) strains that are most effective remain unclear.

### CONSTIPATION

Given the frequent use of opioids, poor dietary intake, physical inactivity, and lack of privacy, constipation is a common problem in seriously ill and dying patients. Clinicians must inquire about any difficulty with hard or infrequent stools. Constipation is an easily preventable and treatable cause of discomfort, distress, and nausea and vomiting (see Chapter 15).

Constipation may be prevented or relieved if patients can increase their activity and their intake of fluids. Simple considerations, such as privacy, undisturbed toilet time, and a bedside commode rather than a bedpan, may be important for some patients.

A prophylactic bowel regimen with a stimulant laxative (senna or bisacodyl) should be started when opioid treatment is begun. Table 15–4 lists other agents (including osmotic laxatives such as polyethylene glycol and lactulose) that can be added as needed. Docusate, a stool softener, is not recommended because it does not add benefit beyond stimulant laxatives. Peripherally acting mu-receptor antagonists (including the oral agents naloxegol and naldemedine, and the subcutaneous methylnaltrexone) are recommended to treat opioid-induced constipation in laxative-refractory opioid-induced constipation. Evidence is insufficient to recommend lubiprostone or prucalopride for opioid-induced constipation. Patients who report being constipated and then have diarrhea typically are passing liquid stool around impacted stool.

### FATIGUE

Fatigue is the most common complaint among people with cancer. Anemia, hypothyroidism, hypogonadism, cognitive and functional impairment, and malnutrition can contribute to fatigue and should be corrected if possible (and desired by the patient). Because pain, depression, and fatigue often coexist, pain and depression should be managed appropriately in patients with fatigue. Fatigue from medication adverse effects and polypharmacy is common and should be addressed. For nonspecific fatigue, physical activity, exercise, and physical rehabilitation are safest and may be most effective. Although psychostimulants, such as

methylphenidate (5–10 mg orally in the morning and afternoon) or modafinil (100–200 mg orally in the morning), are commonly used to manage cancer-related fatigue, strong evidence for effectiveness is lacking. American ginseng (*Panax quinquefolius*) has been shown to be effective for cancer-related fatigue but may have an estrogenic effect. Corticosteroids may have a short-term benefit. Caffeinated beverages can help.

## DELIRIUM & AGITATION

Many patients die in a state of delirium—a waxing and waning in level of consciousness and a change in cognition that develops over a short time and is manifested by misinterpretations, illusions, hallucinations, sleep-wake cycle disruptions, psychomotor disturbances (eg, lethargy, restlessness), and mood disturbances (eg, fear, anxiety). Delirium may be hyperactive, hypoactive, or mixed. Agitated delirium at the end of life has been called **terminal restlessness**.

Some patients with delirium may appear “pleasantly confused,” although it is difficult to know what patients experience. In the absence of obvious distress in the patient, a decision by the patient’s family and clinicians not to treat delirium may be prudent. Agitated delirium at the end of life, however, is often distressing to patients and family and requires treatment. Delirium may interfere with the family’s ability to interact with the patient and may prevent a patient from being able to recognize and report important symptoms. Common reversible causes of delirium include urinary retention, constipation, anticholinergic medications, and pain; these should be addressed whenever possible. There is no evidence that dehydration causes or that hydration relieves delirium. Careful attention to patient safety and nonpharmacologic strategies to help the patient remain oriented (clock, calendar, familiar environment, reassurance and redirection from caregivers) may be sufficient to prevent or manage mild delirium. A randomized trial of placebo compared to risperidone or haloperidol in delirious patients demonstrated *increased* mortality with neuroleptics. Thus, **neuroleptic agents generally should be avoided**. When agitated delirium is refractory to other treatments and remains intolerable, however, especially at the end of life, neuroleptic agents (eg, haloperidol, 1–10 mg orally, subcutaneously, intramuscularly, or intravenously twice or three times a day, or risperidone, 1–3 mg orally twice a day) or frank sedation may be required.

- Keeley P et al. Symptom burden and clinical profile of COVID-19 deaths: a rapid systematic review and evidence summary. *BMJ Support Palliat Care*. 2020;10:381. [PMID: 32467101]
- Navari RM et al. Olanzapine for the treatment of advanced cancer-related chronic nausea and/or vomiting: a randomized pilot trial. *JAMA Oncol*. 2020;6:895. [PMID: 32379269]
- Nikooie R et al. Antipsychotics for treating delirium in hospitalized adults: a systematic review. *Ann Intern Med*. 2019; 171:485. [PMID: 31476770]
- Rao VL et al. Medical management of opioid-induced constipation. *JAMA*. 2019;322:2241. [PMID: 31682706]
- Verberkt CA et al. Effect of sustained-release morphine for refractory breathlessness in chronic obstructive pulmonary disease on health status: a randomized clinical trial. *JAMA Intern Med*. 2020;180:1306. [PMID: 32804188]

## CARE OF PATIENTS AT THE END OF LIFE

In the United States, more than 2.8 million people die each year. Caring for patients at the end of life is an important responsibility and a rewarding opportunity for clinicians. From the medical perspective, the end of life may be defined as that time when death—whether due to terminal illness or acute or chronic illness—is expected within hours to months and can no longer be reasonably forestalled by medical intervention. Palliative care at the end of life focuses on relieving distressing symptoms and promoting quality of life, as it does in all other stages of illness. For patients at the end of life, palliative care may become the sole focus of care.

Emanuel EJ. The status of end-of-life care in the United States: the glass is half full. *JAMA*. 2018;320:239. [PMID: 30027232]

### ► Prognosis at the End of Life

Clinicians must help patients understand when they are approaching the end of life. Most patients, and their family caregivers, want accurate prognostic information. This information influences patients’ treatment decisions, may change how they spend their remaining time, and does *not* negatively impact patient survival. One-half or more of cancer patients do not understand that many treatments they might be offered are palliative and not curative.

While certain diseases, such as cancer, are more amenable to prognostic estimates, the other common causes of death—including heart disease, stroke, chronic lung disease, dementia, and, most recently, COVID-19—have more variable trajectories and difficult-to-predict prognoses. Even for patients with cancer, clinician estimates of prognosis are often inaccurate and generally overly optimistic. The advent of new anticancer treatments including immunotherapy and targeted therapies has made prognosis more challenging in some cancers. Nonetheless, clinical experience, epidemiologic data, guidelines from professional organizations, and computer modeling and prediction tools (eg, the Palliative Performance Scale or <http://eprognosis.ucsf.edu>) may be used to help offer patients more realistic estimates of prognosis. Clinicians can also ask themselves “Would I be surprised if this patient died in the next year?” to determine whether a discussion of prognosis would be appropriate. If the answer is “no,” then the clinician should initiate a discussion. Recognizing that patients may have different levels of comfort with prognostic information, clinicians can introduce the topic by simply saying, “I have information about the likely time course of your illness. Would you like to talk about it?”

Chu C et al. Prognostication in palliative care. *Clin Med (Lond)*. 2019;19:306. [PMID: 31308109]

Hui D et al. Prognostication in advanced cancer: update and directions for future research. *Support Care Cancer*. 2019;27:1973. [PMID: 30863893]

### ► Expectations About the End of Life

Death is often regarded by clinicians, patients, and families as a failure of medical science. This attitude can create or heighten a sense of guilt about the failure to prevent dying.

Both the general public and clinicians often view death as an enemy to be battled furiously in hospitals rather than as an inevitable outcome to be experienced as a part of life at home. As a result, most people in the United States die in hospitals or long-term care facilities even though they may have wished otherwise. There is a trend of fewer deaths in hospitals and more deaths at home or in other community settings.

Relieving suffering, providing support, and helping the patient make the most of their life should be foremost considerations, even when the clinician and patient continue to pursue cure of potentially reversible disease. Patients at the end of life and their families identify a number of elements as important to quality end-of-life care: managing pain and other symptoms adequately, avoiding inappropriate prolongation of dying, communicating clearly, preserving dignity, preparing for death, achieving a sense of control, relieving the burden on others, and strengthening relationships with loved ones.

## ► Communication & Care of the Patient

Caring for patients at the end of life requires the same skills clinicians use in other tasks of medical care: diagnosing treatable conditions, providing patient education, facilitating decision making, and expressing understanding and caring. Communication skills are vitally important and can be improved through training. Higher-quality communication is associated with greater satisfaction and awareness of patient wishes. Clinicians must become proficient at delivering serious news and then dealing with its consequences (Table 5–1). Smartphone and Internet communication resources are available to support clinicians ([www.vitaltalk.org](http://www.vitaltalk.org)), and evidence suggests that communication checklists and guides can be effective. When the clinician and patient do not share a common language, the use of a professional interpreter is needed to facilitate clear communication and help broker cultural issues.

Three further obligations are central to the clinician's role at this time. First, he or she must work to identify, understand, and relieve physical, psychological, social, and spiritual distress or suffering. Second, clinicians can serve as facilitators or catalysts for hope. While hope for a particular outcome such as cure may fade, it can be refocused on what is *still* possible. Although a patient may hope for a "miracle," other more likely hopes can be encouraged and

**Table 5–1.** Suggestions for the delivery of serious news.

- Prepare an appropriate place and time.
- Address basic information needs.
- Be brief and direct; avoid jargon and euphemisms.
- Allow for silence and expression of emotions.
- Assess and validate patient reactions.
- Respond to immediate discomforts and risks.
- Listen actively and express empathy.
- Achieve a common perception of the problem.
- Reassure that care will continue.
- Ensure follow-up and make specific plans for the future.

supported, including hope for relief of pain, for reconciliation with loved ones, for discovery of meaning, and for spiritual growth. With such questions as "What is still possible now for you?" and "When you look to the future, what do you hope for?" clinicians can help patients uncover hope, explore meaningful and realistic goals, and develop strategies to achieve them.

Finally, dying patients' feelings of isolation and fear demand that clinicians assert that they will care for the patient throughout the final stage of life. The *promise of nonabandonment* is the central principle of end-of-life care and is a clinician's pledge to serve as a caring partner, a resource for creative problem solving and relief of suffering, a guide during uncertain times, and a witness to the patient's experiences—no matter what happens. Clinicians can say to a patient, "I will care for you whatever happens."

Paladino J et al. Evaluating an intervention to improve communication between oncology clinicians and patients with life-limiting cancer: a cluster randomized clinical trial of the Serious Illness Care Program. *JAMA Oncol*. 2019;5:801. [PMID: 30870556]

## ► Caring for the Family

Clinicians must be attuned to the potential impact of illness on the patient's family, including greater physical caregiving responsibilities and financial burdens as well as higher rates of anxiety, depression, chronic illness, and even mortality. The threatened loss of a loved one may create or reveal dysfunctional or painful family dynamics. Family caregivers, most often women, commonly provide the bulk of care for patients at the end of life, yet their work is often not adequately acknowledged, supported, or compensated. Clinicians should recognize that in many cases patients and their families are the unit of care. Simply acknowledging and praising the caregiver can provide much needed and appreciated support.

Clinicians can help families confront the imminent loss of a loved one but often must negotiate amid complex and changing family needs. Identifying a spokesperson for the family, conducting family meetings, allowing all to be heard, and providing time for consensus may help the clinician work effectively with the family. Telemedicine allows family members to participate in medical visits even if they are far away. Providing good palliative care to the patient can reduce the risk of depression and complicated grief in loved ones after the patient's death. Palliative care support directly for caregivers improves caregiver depression.

Durepos P et al. What does death preparedness mean for family caregivers of persons with dementia? *Am J Hosp Palliat Care*. 2019;36:436. [PMID: 30518228]

## ► Clinician Self-Care

Many clinicians find caring for patients at the end of life to be one of the most rewarding aspects of practice. However, working with the dying is also sad and can invoke feelings of grief and loss in clinicians. Clinicians must be able to

tolerate its uncertainty, ambiguity, and existential challenges. Clinicians also need to recognize and respect their own limitations, attend to their own needs, and work in sustainable health care systems in order to avoid being overburdened, overly distressed, or emotionally depleted.

Horn DJ et al. Burnout and self care for palliative care practitioners. *Med Clin North Am.* 2020;104:561. [PMID: 32312415]  
Medisauskaitė A et al. Reducing burnout and anxiety among doctors: randomized controlled trial. *Psychiatry Res.* 2019;274:383. [PMID: 30852432]

Zanatta F et al. Resilience in palliative healthcare professionals: a systematic review. *Support Care Cancer.* 2020;28:971. [PMID: 31811483]

such as <https://prepareforyourcare.org>. Most patients with a serious illness have already thought about end-of-life issues, want to discuss them with their clinician, want the clinician to bring up the subject, and feel better for having had the discussion. Patients who have such discussions with their clinicians are more satisfied with their clinician, are perceived by their family as having a better quality of life at the end of life, are less likely to die in the hospital, and are more likely to utilize hospice care. The loved ones of patients who engage in advance care planning discussions are less likely to suffer from depression during bereavement. In the United States, Medicare provides payment to clinicians for having advance care planning discussions with patients.

One type of advance directive is the **Durable Power of Attorney for Health Care (DPOA-HC)** that allows the patient to designate a surrogate decision maker. The DPOA-HC is particularly useful because it is often difficult to anticipate what specific decisions will need to be made. The responsibility of the surrogate is to provide “substituted judgment”—to decide as the *patient* would, not as the *surrogate* wants. Clinicians should encourage patients to talk with their surrogates about their preferences generally and about scenarios that are likely to arise, such as the need for mechanical ventilation in a patient with end-stage emphysema or in any patient with possible SARS-CoV-2 infection. In the absence of a designated surrogate, clinicians usually turn to family members or next of kin. Regulations require health care institutions to inform patients of their rights to formulate an advance directive. **Physician (or Medical) Orders for Life-Sustaining Treatment (POLST or MOLST) or Physician (or Medical) Orders for Scope of Treatment (POST or MOST)** forms are clinician orders that document patient preferences and accompany patients wherever they are cared for—home, hospital, or nursing home. They are available in most states and used to complement advance directives for patients approaching the end of life.

Cauley CE et al. DNR, DNI, and DNO? *J Palliat Med.* 2020;23:829. [PMID: 31718398]

Kim JW et al. Completion rate of physician orders for life-sustaining treatment for patients with metastatic or recurrent cancer: a preliminary, cross-sectional study. *BMC Palliat Care.* 2019;18:84. [PMID: 31640677]

Lee RY et al. Association of Physician Orders for Life-Sustaining Treatment with ICU admission among patients hospitalized near the end of life. *JAMA.* 2020;323:950. [PMID: 32062674]

Pearse W et al. Advance care planning in the context of clinical deterioration: a systematic review of the literature. *Palliat Care.* 2019;12:1178224218823509. [PMID: 30718959]

### ► Do Not Attempt Resuscitation Orders

Because the “default” in US hospitals is that patients will undergo CPR in the event of cardiopulmonary arrest, as part of advance care planning, clinicians should elicit patient preferences about CPR. Most patients and many clinicians overestimate the chances of success of CPR. Only about 17% of all patients who undergo CPR in the hospital survive to hospital discharge and, among people with multisystem organ failure, metastatic cancer, and sepsis, the

**Advance directives** are oral or written statements made by patients when they are competent that project their autonomy into the future and are intended to guide care should they lose the ability to make and communicate their own decisions. Advance directives are an important part of **advance care planning**—defined by an international Delphi panel as “a process that supports adults at any age or stage of health in understanding and sharing their personal values, life goals, and preferences regarding future medical care. The goal of advance care planning is to help ensure that people receive medical care that is consistent with their values, goals and preferences during serious and chronic illness.” Advance directives take effect when the patient can no longer communicate his or her preferences directly. While oral statements about these matters are ethically binding, they are not legally binding in all states. State-specific advance directive forms are available from a number of sources, including the National Hospice Palliative Care Organization ([nhpco.org/advanceddirective](http://nhpco.org/advanceddirective)).

Clinicians should facilitate the process for all patients—ideally, well before the end of life—to consider their preferences, to appoint a surrogate, to talk to that person about their preferences, and to complete a formal advance directive. There are numerous resources that can be helpful,

likelihood of survival to hospital discharge following CPR is virtually nil. Patients may ask their hospital clinician to write an order that CPR not be attempted should they experience cardiac arrest. Although this order initially was referred to as a “DNR” (**do not resuscitate**) order, many clinicians prefer the term “DNAR” (**do not attempt resuscitation**) to emphasize the low likelihood of success. Some clinicians and institutions use an order to “Allow Natural Death” for situations in which death is imminent and the patient wishes to receive only those interventions that will promote comfort.

For most patients at the end of life, decisions about CPR may not be about *whether* they will live but about *how* they will die. Clinicians should correct the misconception that withholding CPR in appropriate circumstances is tantamount to “not doing everything” or “just letting someone die.” While respecting the patient’s right to make the decision—and keeping in mind their own biases and prejudices—clinicians should offer explicit recommendations about DNAR orders and protect dying patients and their families from feelings of guilt and from the sorrow associated with vain hopes. Clinicians should discuss what interventions will be continued and started to promote quality of life rather than focusing only on what interventions will be stopped or not begun. For patients with implanted cardioverter defibrillators (ICDs), clinicians must also address the issue of turning off these devices, while leaving the pacemaker function on, as death approaches to prevent the uncommon but distressing situation of the ICD discharging during the dying process.

## ► Hospice & Other Palliative Care Services

In the United States, hospice is a specific type of palliative care service that comprehensively addresses the needs of the dying, focusing on their comfort while not attempting to prolong their life or hasten their death. In the United States, 48.2% of people with Medicare who die use hospice, most at home or in a nursing home where they can be cared for by their family, other caregivers, and visiting hospice staff. Hospice care can also be provided in institutional residences and hospitals. As is true of all types of palliative care, hospice emphasizes individualized attention and human contact (though limited by COVID-19 safety concerns) and uses an interdisciplinary team approach. Hospice care can include arranging for respite for family caregivers and assisting with referrals for legal, financial, and other services. Patients in hospice require a physician, preferably their primary care clinician or specialist, to oversee their care.

In the United States, hospice care was used by 1.55 million Medicare beneficiaries in 2018 (the most recent year for which there are published data), about 30% of whom had cancer. Hospice is rated highly by families and has been shown to increase patient satisfaction and to decrease family caregiver mortality. In 2018, 51% of hospice patients died at home; 30% died in a skilled nursing facility. Despite evidence that suggests that hospice care does not shorten length of life, hospice care tends to be engaged very late, often near the very end of life. In 2018, the mean average length of stay

in hospice care in the United States was 90 days, but the median length of stay was 18 days. Overall, 54% of patients died within 30 days of enrolling in a hospice, and 28% of patients died within 7 days of starting hospice.

In the United States, most hospice organizations require clinicians to estimate the patient’s prognosis to be less than 6 months, since this is a criterion for eligibility under the Medicare hospice benefit and is typically the same for other insurance coverage. Many patients wait to enroll in hospice until they have decided with certainty that they no longer wish to pursue curative intent treatment. This approach contributes to late referrals and to many patients missing out on valuable hospice services. Patients can be encouraged to enroll in hospice while they are still deciding about further curative intent treatment and can disenroll if they decide to pursue it.

## ► Cultural Issues

The individual patient’s experience of dying occurs in the context of a complex interaction of personal, philosophic, and cultural values. Various religious, ethnic, gender, class, and cultural traditions influence a patient’s style of communication, comfort in discussing particular topics, expectations about dying and medical interventions, and attitudes about the appropriate disposition of dead bodies. While there are differences in beliefs regarding advance directives, autopsy, organ donation, hospice care, and withdrawal of life-sustaining interventions among patients of different ethnic groups, clinicians should be careful not to make assumptions about individual patients. Clinicians must appreciate that palliative care is susceptible to the same explicit and implicit biases documented in other medical disciplines. Being sensitive to a person’s cultural beliefs and respecting traditions are important responsibilities of the clinician caring for a patient at the end of life. A clinician may ask a patient, “What do I need to know about you and your beliefs that will help me take care of you?” and “How do you deal with these issues in your family?”

Abdullah R et al. Preferences and experiences of Muslim patients and their families in Muslim-majority countries for end-of-life care: a systematic review and thematic analysis. *J Pain Symptom Manage.* 2020;60:1223. [PMID: 32659320]

Acquaviva KD. *LGBT-Inclusive Hospice and Palliative Care: A Practical Guide to Transforming Professional Practice*. Harrington Park Press, LLC. New York, NY, 2017.

De Souza J et al. Perspectives of elders and their adult children of Black and minority ethnic heritage on end-of-life conversations: a meta-ethnography. *Palliat Med.* 2020;34:195. [PMID: 31965907]

Mathew-Geevarughese SE et al. Cultural, religious, and spiritual issues in palliative care. *Prim Care.* 2019;46:399. [PMID: 31375189]

Wang SY et al. Racial differences in health care transitions and hospice use at the end of life. *J Palliat Med.* 2019;22:619. [PMID: 30615546]

## ► Nutrition & Hydration

People approaching the end of life often lose their appetite and most stop eating and drinking in their last days. Clinicians should explain to families that the dying patient is not

suffering from hunger or thirst; rather, the discontinuation of eating and drinking is part of dying. The anorexia-cachexia syndrome frequently occurs in patients with advanced cancer, and cachexia is common and a poor prognostic sign in patients with heart failure. Seriously ill people often have no hunger despite not eating at all and the associated ketonemia can produce a sense of well-being, analgesia, and mild euphoria. Although it is unclear to what extent withholding hydration at the end of life creates an uncomfortable sensation of thirst, any such sensation is usually relieved by simply moistening the dry mouth with ice chips, hard candy, swabs, or popsicles. Although this normal process of diminishing oral intake and accompanying weight loss is very common, it can be distressing to patients and families who may associate the offering of food with compassion and love and lack of eating with distressing images of starvation. In response, patients and families often ask about supplemental enteral or parenteral nutrition.

Supplemental artificial nutrition and hydration offer no benefit to those at the end of life and rarely achieve patient and family goals. The American Geriatrics Society recommends against liquid artificial nutrition (“tube feeding”) in people with advanced dementia because it does not provide any benefit. Furthermore, enteral feeding may cause nausea and vomiting in ill patients and can lead to diarrhea in the setting of malabsorption. Artificial nutrition and hydration may increase oral and airway secretions as well as increase the risk of choking, aspiration, and dyspnea; ascites, edema, and effusions may be worsened. In addition, liquid artificial nutrition by nasogastric and gastrostomy tubes and parenteral nutrition impose risks of infection, epistaxis, pneumothorax, electrolyte imbalance, and aspiration—as well as the need to physically restrain the delirious patient to prevent dislodgment of tubes and catheters.

Individuals at the end of life have a right to voluntarily refuse all nutrition and hydration. Because they may have deep social and cultural significance for patients, families, and clinicians themselves, decisions about artificial nutrition and hydration are not simply medical. Eliciting perceived goals of artificial nutrition and hydration and correcting misperceptions can help patients and families make clear decisions.

Hoffman MR. Tracheostomies and PEGs: when are they really indicated? *Surg Clin North Am.* 2019;99:955. [PMID: 31446920]

Mayers T et al. International review of national-level guidelines on end-of-life care with focus on the withholding and withdrawing of artificial nutrition and hydration. *Geriatr Gerontol Int.* 2019;19:847. [PMID: 31389113]

patient and family about the expected course of events and the difficulty of determining the precise timing of death after withdrawal of interventions. Sedative and analgesic agents should be administered to ensure patient comfort even at the risk of respiratory depression or hypotension. While “death rattle,” the sound of air flowing over airway secretions, is common in actively dying patients and can be distressing to families, it is doubtful that it causes discomfort to the patient. Turning the patient can decrease the sound of death rattle. There is no evidence that any medications reduce death rattle, and suctioning should be avoided since it can cause patient discomfort.

McPherson K et al. Limitation of life-sustaining care in the critically ill: a systematic review of the literature. *J Hosp Med.* 2019;14:303. [PMID: 30794145]

Reignier J et al. Withholding and withdrawing life-support in adults in emergency care: joint position paper from the French Intensive Care Society and French Society of Emergency Medicine. *Ann Intensive Care.* 2019;9:105. [PMID: 31549266]

## ► Physician-Assisted Death

Physician-assisted death is the legally sanctioned process by which patients who have a terminal illness may request and receive a prescription from a physician for a lethal dose of medication that they themselves would self-administer for the purpose of ending their own life. Terminology for this practice varies. “Physician-assisted death” is used here to clarify that a willing physician provides assistance in accordance with the law (by writing a prescription for a lethal medication) to a patient who makes a request for it and who meets specific criteria. Patients, family members, nonmedical and medical organizations, clinicians, lawmakers, and the public frequently use other terms, such as “physician or medical aid in dying,” “aid in dying,” “death with dignity,” or “physician-assisted suicide.” Use of the latter term is discouraged because when this action is taken according to the law, it is not considered suicide and people who are actively suicidal are not eligible for this process.

Although public and state support for physician-assisted death has grown in the United States, physician-assisted death remains an area of debate. As of 2019, physician-assisted death has been legalized with careful restriction and specific procedures for residents in eight US states (Oregon, Washington, Vermont, Colorado, Hawaii, Maine, New Jersey, and California) and in the District of Columbia, making it available to 22% of the US population. The Supreme Court in Montana ruled that the state constitution does not bar physician-assisted death. Internationally, physician-assisted death (and/or euthanasia, the administration a lethal dose of medication by a clinician) is legal in nine countries (the Netherlands, Belgium, Luxembourg, Switzerland, Colombia, Canada, Germany, Japan, and the Australian state of Victoria). The current US state laws permitting it generally require physician certification of a terminal disease with a prognosis of 6 months or less and require the individual to be an adult resident of the state, to be physically capable of self-administering the medication, and capable of making and communicating

## ► Withdrawal of Curative Efforts

Requests from appropriately informed and competent patients or their surrogates for withdrawal of life-sustaining interventions must be respected. Limitation of life-sustaining interventions prior to death is common practice in ICUs in the United States. The withdrawal of life-sustaining interventions, such as mechanical ventilation, must be approached carefully to avoid patient suffering and distress for those in attendance. Clinicians should educate the

their own health care decisions. Any clinician that participates in physician-assisted death should be familiar with the laws governing its use in their jurisdiction and seek recommendations and help with writing the appropriate prescription.

Requests for physician-assisted death are relatively rare and ultimately use of the prescribed medication leads to less than 0.5% of all deaths in the United States. Patient motivations for physician-assisted death generally revolve around preserving dignity, self-respect, and autonomy (control), and maintaining personal connections at the end of life rather than experiencing intolerable pain or suffering. Some patients who have requested medication to self-administer for a physician-assisted death later withdraw their request when provided palliative care interventions.

Each clinician must decide his or her personal approach in caring for patients who ask about physician-assisted death. Regardless of the clinician's personal feelings about the process, the clinician can respond initially by exploring the patient's reasons and concerns that prompted the request. During the dialog, the clinician should inform the patient about palliative options, including hospice care; access to expert symptom management; and psychological, social, and spiritual support, as needed, and provide reassurance and commitment to address future problems that may arise. For clinicians who object to physician-assisted death on moral or ethical grounds, referral to another clinician may be necessary and may help the patient avoid feeling abandoned. That clinician must be willing to provide the prescription for lethal medication, to care for the patient until death, to sign the death certificate listing the underlying terminal condition as the cause of death, and in some jurisdictions to complete a mandatory follow-up form.

Downar J et al. Early experience with medical assistance in dying in Ontario, Canada: a cohort study. *CMAJ*. 2020;192:E173. [PMID: 32051130]

Gerson SM et al. Medical aid in dying, hastened death and suicide: a qualitative study of hospice professionals' experiences from Washington State. *J Pain Symptom Manage*. 2020;59:679. [PMID: 31678464]

Gruenewald DA et al. Options of last resort: palliative sedation, physician aid in dying, and voluntary cessation of eating and drinking. *Med Clin North Am*. 2020;104:539. [PMID: 32312414]

Patel T. Clinician responses to legal requests for hastened death: a systematic review and meta-synthesis of qualitative research. *BMJ Support Palliat Care*. 2021;11:59. [PMID: 32601150]

Russell JA. Physician-hastened-death in patients with progressive neurodegenerative or neuromuscular disorders. *Semin Neurol*. 2018;38:522. [PMID: 30321890]

promote beneficence and autonomy, such as surgery or bone marrow transplantation, may violate the clinician's obligation for nonmaleficence; thus, balancing the benefits and risks of treatments is a fundamental ethical responsibility. While in the vast majority of cases clinicians and patients and families will agree on the appropriateness of and decisions to withdraw life-sustaining interventions, in rare cases, such as CPR in multisystem organ failure, clinicians may determine *unilaterally* that a particular intervention offers no possibility of benefit and thus need not be done. In such cases, the clinician's intention to withhold CPR should be communicated to the patient and family and documented, and the clinician must consult with another clinician not involved in the care of the patient. If differences of opinion persist about the appropriateness of particular care decisions, consultation with an institutional ethics committee should be sought. Because such unilateral actions violate the autonomy of the patient, clinicians should *rarely* resort to them. Studies confirm that most disagreements between patients and families and clinicians can be resolved with good communication. Although clinicians and family members often feel differently about withholding versus withdrawing life-sustaining interventions, there is consensus among ethicists, supported by legal precedent, of their ethical equivalence.

Chessa F et al. Ethical and legal considerations in end-of-life care. *Prim Care*. 2019;46:387. [PMID: 31375188]

Rodrigues P et al. Palliative sedation for existential suffering: a systematic review of argument-based ethics literature. *J Pain Symptom Manage*. 2018;55:1577. [PMID: 29382541]

## ► Psychological, Social, & Spiritual Issues

Dying is not exclusively or even primarily a biomedical event. It is an intimate personal experience with profound psychological, interpersonal, and existential meanings. For many people at the end of life, the prospect of impending death stimulates a deep and urgent assessment of their identity, the quality of their relationships, the meaning and purpose of their life, and their legacy.

### A. Psychological Challenges

In 1969, Dr. Elisabeth Kübler-Ross identified five psychological reactions or patterns of emotions that patients at the end of life may experience: denial and isolation, anger, bargaining, depression, and acceptance. Most patients will experience these reactions throughout the course of illness but not in an orderly progression. In addition to these five reactions are the perpetual challenges of anxiety and fear of the unknown. Simple information, listening, assurance, and support may help patients with these psychological challenges. Patients and families rank emotional support as one of the most important aspects of good end-of-life care. Psychotherapy and group support may be beneficial as well.

Despite the significant emotional stress of facing death, clinical depression is *not* normal at the end of life and should be treated. Cognitive and affective signs of depression, such as feelings of worthlessness, hopelessness, or helplessness, may help distinguish depression from the low

## ► Ethical & Legal Issues

Clinicians' care of patients at the end of life is guided by the same ethical and legal principles that inform other types of medical care. Foremost among these are (1) truth-telling, (2) nonmaleficence, (3) beneficence, (4) autonomy, (5) confidentiality, and (6) procedural and distributive justice. Important ethical principles may come into conflict when caring for patients. For example, many treatments that

energy and other vegetative signs common with advanced illness. Although traditional antidepressant treatments such as selective serotonin reuptake inhibitors are effective, more rapidly acting medications, such as dextroamphetamine (2.5–7.5 mg orally at 8 AM and noon) or methylphenidate (2.5–10 mg orally at 8 AM and noon), may be particularly useful when the end of life is near or while waiting for another antidepressant medication to take effect. Ketamine is now approved, with restrictions, as a treatment for depression and psychedelics are being explored as rapid-onset treatment for anxiety and depression at the end of life. Some research suggests a mortality benefit from treating depression in the setting of serious illness.

## B. Social Challenges

At the end of life, patients should be encouraged to take care of personal, professional, and business obligations. These tasks include completing important work or personal projects, distributing possessions, writing a will, and making funeral and burial arrangements. The prospect of death often prompts patients to examine the quality of their interpersonal relationships and to begin the process of saying goodbye (Table 5–2). Concern about estranged relationships or “unfinished business” with significant others and interest in reconciliation may become paramount at this time.

## C. Spiritual Challenges

Spirituality includes the attempt to understand or accept the underlying meaning of life, one's relationships to oneself and other people, one's place in the universe, one's legacy, and the possibility of a “higher power” in the universe. People may experience spirituality as part of or distinct from particular religious practices or beliefs.

Unlike physical ailments, such as infections and fractures, which usually require a clinician's intervention to be treated, the patient's spiritual concerns often require only a clinician's attention, listening, and witness. Clinicians can inquire about the patient's spiritual concerns and ask whether the patient wishes to discuss them. For example, asking, “How are you within yourself?” or “Are you at peace?” communicates that the clinician is interested in the patient's whole experience and provides an opportunity for the patient to share perceptions about his or her inner life. Questions that might constitute an existential “review of systems” are presented in Table 5–3. Formal legacy work and dignity therapy have been shown to be effective in improving quality of life and spiritual well-being.

**Table 5–2.** Five statements often necessary for the completion of important interpersonal relationships.

|                     |                               |
|---------------------|-------------------------------|
| 1. “Forgive me.”    | (An expression of regret)     |
| 2. “I forgive you.” | (An expression of acceptance) |
| 3. “Thank you.”     | (An expression of gratitude)  |
| 4. “I love you.”    | (An expression of affection)  |
| 5. “Goodbye.”       | (Leave-taking)                |

Source: Byock I. *Dying Well: Peace and Possibilities at the End of Life*. New York: Riverhead Books, an imprint of Penguin Group (USA) LLC, 1997.

**Table 5–3.** An existential review of systems.

### Intrapersonal

- “What does your illness/dying mean to you?”
- “What do you think caused your illness?”
- “How have you been healed in the past?”
- “What do you think is needed for you to be healed now?”
- “What is right with you now?”
- “What do you hope for?”
- “Are you at peace?”

### Interpersonal

- “Who is important to you?”
- “To whom does your illness/dying matter?”
- “Do you have any unfinished business with significant others?”

### Transpersonal

- “What is your source of strength, help, or hope?”
- “Do you have spiritual concerns or a spiritual practice?”
- “If so, how does your spirituality relate to your illness/dying, and how can I help integrate your spirituality into your health care?”
- “What do you think happens after we die?”
- “What do you think is trying to happen here?”

Attending to the spiritual concerns of patients calls for listening to their stories. Storytelling gives patients the opportunity to verbalize what is meaningful to them and to leave something of themselves behind—a legacy, the promise of being remembered. Storytelling may be facilitated by suggesting that the patient share his or her life story with family members, make an audio or video recording, assemble a photo album, organize a scrapbook, or write or dictate an autobiography.

The end of life offers an opportunity for psychological, interpersonal, and spiritual development and a chance to experience and achieve important goals. Individuals may grow—even experience a heightened sense of well-being or transcendence—in the process of dying. Through listening, support, and presence, clinicians may help foster this learning and be a catalyst for this transformation. Rather than thinking of dying simply as the termination of life, clinicians and patients may be guided by a developmental model of life that recognizes a series of lifelong developmental tasks and landmarks and allows for growth at the end of life.

Puchalski CM et al. Spiritual considerations. Hematol Oncol Clin North Am. 2018;32:505. [PMID: 29729785]  
Wholihan D. Psychological issues of patient transition from intensive care to palliative care. Crit Care Nurs Clin North Am. 2019;31:547. [PMID: 31685121]

## TASKS AFTER DEATH

After the death of a patient, the clinician is called upon to perform a number of tasks, both required and recommended. The clinician must plainly and directly inform the family of the death, complete a death certificate, contact an organ procurement organization, and request an autopsy. Providing words of sympathy and reassurance, time for questions and initial grief and, for people who die in the hospital or other health care facility, a quiet private room for the family to grieve is appropriate and much appreciated.

## ► The Pronouncement & Death Certificate

In the United States, state policies direct clinicians to confirm the death of a patient in a formal process called “pronouncement.” The diagnosis of death is typically easy to make, and the clinician need only verify the absence of spontaneous respirations and cardiac activity by auscultating for each for 1 minute. A note describing these findings, the time of death, and that the family has been notified is entered in the patient’s medical record. In many states, when a patient whose death is expected dies outside of the hospital (at home or in prison, for example), nurses may be authorized to report the death over the telephone to a physician who assumes responsibility for signing the death certificate within 24 hours. For traumatic deaths, some states allow emergency medical technicians to pronounce a patient dead at the scene based on clearly defined criteria and with physician telephonic or radio supervision.

While the pronouncement may often seem like an awkward and unnecessary formality, clinicians may use this time to reassure the patient’s loved ones at the bedside that the patient died peacefully and that all appropriate care had been given. Both clinicians and families may use the ritual of the pronouncement as an opportunity to begin to process emotionally the death of the patient.

Physicians are legally required to report certain deaths to the coroner and to accurately report the underlying cause of death on the death certificate. This reporting is important both for patients’ families (for insurance purposes and the need for an accurate family medical history) and for the epidemiologic study of disease and public health. For example, it is important to understand the number of deaths due to COVID-19 and for clinicians to accurately report this cause of death. The physician should be specific about the major cause of death being the condition without which the patient would not have died (eg, “decompensated cirrhosis”) and its contributory cause (eg, “hepatitis B and hepatitis C infections, chronic alcoholic hepatitis, and alcoholism”) as well as any associated conditions (eg, “acute kidney injury”)—and not simply put down “cardiac arrest” as the cause of death. In relevant cases, it is prohibited (in some jurisdictions) to list either “physician-assisted death” (or any synonymous term) or the medication used to accomplish it (eg, secobarbital) on the death certificate; instead, the clinician prescribing the lethal dose of medication for this purpose and following the patient until death must (in most jurisdictions) complete and submit a follow-up form and list the cause of death as the underlying condition that led to death.

Hatano Y et al. Physician behavior toward death pronouncement in palliative care units. *J Palliat Med.* 2018;21:368. [PMID: 28945507]

## ► Autopsy & Organ Donation

Discussing the options and obtaining consent for autopsy and organ donation with patients prior to death is a good practice as it advances the principle of patient autonomy and lessens the responsibilities of distressed family

members during the period immediately following the death. In the United States, federal regulations require that a designated representative of an organ procurement organization approach the family about organ donation because designated organ transplant personnel are more experienced and successful than treating clinicians at obtaining consent for organ donation from surviving family members. While most people in the United States support the donation of organs for transplants, organ transplantation is severely limited by the availability of donor organs. The families of donors experience a sense of reward in contributing, even through death, to the lives of others.

The results of an autopsy may help surviving family members and clinicians understand the exact cause of a patient’s death and foster a sense of closure. Despite the use of more sophisticated diagnostic tests, the rate of unexpected findings at autopsy has remained stable, and thus, an autopsy can provide important health information to families. Pathologists can perform autopsies without interfering with funeral plans or the appearance of the deceased. A clinician–family conference to review the results of the autopsy provides a good opportunity for clinicians to assess how well families are grieving and to answer questions.

Buja LM et al. The importance of the autopsy in medicine: perspectives of pathology colleagues. *Acad Pathol.* 2019;6:2374289519834041. [PMID: 30886893]

## ► Follow-Up & Grieving

Proper care of patients at the end of life includes following up with surviving family members after the patient has died. Contacting loved ones by telephone or video telemedicine technology enables the clinician to assuage any guilt about decisions the family may have made, assess how families are grieving, reassure them about the nature of normal grieving, and identify complicated grief or depression. Clinicians can recommend support groups and counseling as needed. A card or telephone call from the clinician to the family days to weeks after the patient’s death (and perhaps on the anniversary of the death) allows the clinician to express concern for the family and the deceased. For patients dying during the COVID-19 pandemic, physical closeness, leave-taking, and bereavement rituals have been constrained by the need for social distancing.

After a patient dies, clinicians also grieve. Although clinicians may be relatively unaffected by the deaths of some patients, other deaths may cause feelings of sadness, loss, and guilt. These emotions should be recognized as the first step toward processing and healing them. Each clinician may find personal or communal resources that help with the process of grieving. Shedding tears, sharing with colleagues, taking time for reflection, and engaging in traditional or personal mourning rituals all may be effective. Attending the funeral of a patient who has died can be a satisfying personal experience that is almost universally appreciated by families and that may be the final element in caring well for people at the end of life.

- Johannsen M et al. Psychological interventions for grief in adults: a systematic review and meta-analysis of randomized controlled trials. *J Affect Disord.* 2019;253:69. [PMID: 31029856]
- Wallace CL et al. Grief during the COVID-19 pandemic: considerations for palliative care providers. *J Pain Symptom Manage.* 2020;60:e70. [PMID: 32298748]

## PAIN MANAGEMENT

### TAXONOMY OF PAIN

The International Association for the Study of Pain (IASP) defines **pain** as an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage. **Acute pain** resolves within the expected period of healing and is self-limited. **Chronic pain** persists beyond the expected period of healing and is itself a disease state. In general, chronic pain is defined as extending beyond 3–6 months, although definitions vary in terms of the time period from initial onset of nociception. **Cancer pain** is in its own special category because of the unique ways neoplasia and its therapies (such as surgery, chemotherapy, or radiation therapy) can lead to burdensome pain. Finally, related to cancer pain, there is **pain at the end of life**, for which measures to alleviate suffering may take priority over promoting restoration of function.

Pain is a worldwide burden; across the globe; one in five adults suffers from pain. In 2010, members from 130 countries signed the Declaration of Montreal stating that access to pain management is a fundamental human right. The first CDC guidelines on opioid prescribing for chronic pain, including chronic noncancer pain, cancer pain, and pain at the end of life, were published in March of 2016, and continue to be updated.

Centers for Disease Control and Prevention (CDC). CDC guideline for prescribing opioids for chronic pain. 2019 Aug 28. <https://www.cdc.gov/drugoverdose/prescribing/guideline.html>

Dowell D et al. No shortcuts to safer opioid prescribing. *N Engl J Med.* 2019;380:2285. [PMID: 31018066]

National Institutes of Health (NIH). National Institute on Drug Abuse. Opioid Crisis and Pain Management. 2020 Jul 1. <https://www.drugabuse.gov/nidamed-medical-health-professionals/opioid-crisis-pain-management>

### ACUTE PAIN

Acute pain resolves within the expected period of healing and is self-limited. Common examples include pain from dental caries, kidney stones, surgery, or trauma. Management of acute pain depends on comprehending the type of pain (somatic, visceral, or neuropathic) and on understanding the risks and benefits of potential therapies. At times, treating the underlying cause of the pain (eg, dental caries) may be all that is needed, and pharmacologic therapies may not be required for additional analgesia. On the other hand, not relieving acute pain can have consequences beyond the immediate suffering. Inadequately treated acute pain can develop into chronic pain in some patients. This transition from acute to chronic pain (so-called

“chronification” of pain) depends on the pain’s cause, type, and severity and on the patient’s age, psychological status, and genetics, among other factors. This transition is an area of increasing study because chronic pain leads to significant societal costs beyond the individual’s experiences of suffering, helplessness, and depression. Emerging studies have shown that increased intensity and duration of acute pain may be correlated with a higher incidence of chronic pain, and regional anesthesia, ketamine, gabapentinoids, and cyclooxygenase (COX) inhibitors may be helpful for prevention of chronic postsurgical pain. These approaches are particularly important given concerns that exposure to opioids in the perioperative period can lead to chronic opioid dependence beyond the immediate postoperative period.

The Oxford League Table of Analgesics is a useful guide; for example, it lists the number-needed-to-treat for specific doses of various medications to relieve acute pain. Nonsteroidal anti-inflammatory drugs (NSAIDs) or COX inhibitors are at the top of the list, with the lowest number-needed-to-treat. These medications can be delivered via oral, intramuscular, intravenous, intranasal, rectal, and other routes of administration. They generally work by inhibiting COX-1 and -2 and therefore reduce the levels of prostaglandins involved in inflammatory nociception (eg, PG<sub>I2</sub> and PG<sub>E2</sub>). These oxygenase enzymes also determine levels of other breakdown products such as other prostaglandins, thromboxane, and prostacyclins that play a role in renal, gastrointestinal, and cardiovascular homeostasis. For this reason, the primary limitation of the COX inhibitors is their side effects of gastritis; kidney dysfunction; bleeding; hypertension; and cardiovascular adverse events, such as myocardial infarction or stroke. Ketorolac is primarily a COX-1 inhibitor that has an analgesic effect as potent as morphine at the appropriate dosage. Like most pharmacologic therapies, the limitation of COX inhibitors is that they have a “ceiling” effect, meaning that beyond a certain dose, there is no additional benefit.

Acetaminophen (paracetamol) is effective as a sole agent, or in combination with a COX inhibitor or an opioid in acute pain. Its mechanism of action remains undetermined but is thought to act centrally through mechanisms such as the prostaglandin, serotonergic, and opioid pathways. It is one of the most widely used and best tolerated analgesics; its primary limitation is hepatotoxicity when given in high doses or to patients with underlying impaired liver function.

Postoperatively, **patient-controlled analgesia (PCA)** with intravenous morphine, hydromorphone, or another opioid can achieve analgesia faster and with less daily medication requirement than with standard “as needed” or even scheduled intermittent dosing. PCA has been adapted for use with oral analgesic opioid medications and for neuraxial delivery of both opioids and local anesthetics in the epidural and intrathecal spaces. The goal of PCA is to maintain a patient’s plasma concentration of opioid in the “therapeutic window,” between the minimum effective analgesic concentration and a toxic dose.

In order to prevent opioid use disorder and prolonged inappropriate opioid use, multimodal analgesia (including regional anesthesia) has been employed to decrease the need for postoperative opioids. Patients may undergo either neuraxial anesthesia with an epidural catheter, for

example, or regional anesthesia with a nerve block with or without a catheter. These techniques are effective for both intraoperative pain and postoperative pain management and can diminish the need for both intraoperative and postoperative opioids.

- Helander EM et al. Multimodal analgesia, current concepts, and acute pain considerations. *Curr Pain Headache Rep.* 2017;21:3. [PMID: 28132136]
- Small C et al. Acute postoperative pain management. *Br J Surg.* 2020;107:e70. [PMID: 31903595]
- Tubog TD. Overview of multimodal analgesia initiated in the perioperative setting. *J Perioper Pract.* 2020;1750458920928843. [PMID: 32508237]

## CHRONIC NONCANCER PAIN

Chronic noncancer pain may begin as acute pain that then fails to resolve and extends beyond the expected period of healing or it may be a primary disease state, rather than the symptom residual from another condition. Common examples of chronic noncancer pain include chronic low-back pain and arthralgias (often somatic in origin), chronic abdominal pain and pelvic pain (often visceral in origin), and chronic headaches, peripheral neuropathy, and posttherapeutic neuralgia (neuropathic origin). Chronic noncancer pain is common, with the World Health Organization estimating a worldwide prevalence of 20%. In the United States, 11% of adults suffer from chronic noncancer pain, and the Institute of Medicine estimates that it costs \$635 billion annually in treatment and lost productivity costs.

Chronic noncancer pain requires interdisciplinary management. Generally, no one therapy by itself is sufficient to manage such chronic pain. Physical or functional therapy and cognitive behavioral therapy have been shown to be the most effective for treating chronic noncancer pain, but other modalities including pharmacologic therapy, interventional modalities, and complementary/integrative approaches are useful in caring for affected patients.

**Chronic low-back pain** is one example of a common chronic noncancer pain. It causes more disability globally than any other condition. Chronic low-back pain includes spondylosis, spondylolisthesis, and spinal canal stenosis (Chapter 24), and the “failed back surgery syndrome,” a term used to refer to patients in whom chronic pain develops and/or persists after lumbar spine surgery. Also referred to as the post-laminectomy pain syndrome, it can affect 10–40% of patients after lumbar spine surgery.

The importance of clinicians knowing the many causes of chronic low-back pain and, in particular, understanding how anatomic structures relate to one another and how they can cause the different types of low-back pain, has been highlighted by the epidemic of opioid abuse in the United States since the year 2000. In fact, evidence-based practice does *not* support the use of prolonged opioid therapy for chronic low-back pain.

- Krebs EE et al. Effect of opioid vs nonopioid medications on pain-related function in patients with chronic back pain or hip or knee osteoarthritis pain: the SPACE randomized clinical trial. *JAMA.* 2018;319:872. [PMID: 29509867]

Qaseem A et al. Nonpharmacologic and pharmacologic management of acute pain from non-low back, musculoskeletal injuries in adults: a clinical guideline from the American College of Physicians and American Academy of Family Physicians. *Ann Intern Med.* 2020;173:739. [PMID: 32805126]

Zhao L et al. Treatment of discogenic low back pain: current treatment strategies and future options—a literature review. *Curr Pain Headache Rep.* 2019;23:86. [PMID: 31707499]

## CANCER PAIN

Cancer pain deserves its own category because it is unique in cause and in therapies. Cancer pain consists of both acute pain and chronic pain from the neoplasm itself and from the therapies associated with it, such as surgery, chemotherapy, radiation, and immunotherapy. In addition, patients with cancer pain may also have acute or chronic non–cancer-related pain, and this possibility should not be overlooked when taking care of cancer patients.

Cancer pain includes somatic pain (eg, neoplastic invasion of tissue such as painful fungating chest wall masses in breast cancer), visceral pain (eg, painful hepatomegaly from liver metastases, stretching the liver capsule), neuropathic pain (eg, neoplastic invasion of sacral nerve roots), or pain from a paraneoplastic syndrome (eg, peripheral neuropathy related to anti-Hu antibody production). Chemotherapy can cause peripheral neuropathies, radiation can cause neuritis or skin allodynia, and surgery can cause persistent postsurgical pain syndromes such as post-mastectomy or post-thoracotomy pain syndromes.

Generally, patients with cancer pain do not exhibit a single type of pain—they may have multiple reasons for pain and thus benefit from a comprehensive and multimodal strategy. The WHO Analgesic Ladder, first published in 1986, suggests starting medication treatment with nonopioid analgesics, then weak opioid agonists, followed by strong opioid agonists. While opioid therapy can be helpful for a majority of patients living with cancer pain, therapy must be individualized depending on the individual patient, their family, and the clinician. For example, if one of the goals of care is to have a lucid and coherent patient, opioids may not be the optimal choice; interventional therapies such as implantable devices may be an option, weighing their risks and costs against their potential benefits. Alternatively, in dying patients, provided there is careful documentation of continued, renewed, or accelerating pain, use of opioid doses exceeding those recommended as standard for acute (postoperative) pain is acceptable.

One of the unique challenges in treating cancer pain is that it is often a “moving target,” with disease progression and improvements in disease progression or worsening pain directly stemming from chemotherapy, radiation, or immunotherapy. Therefore, frequent adjustments may be required to any pharmacologic regimen. Interventional approaches such as celiac plexus neurolysis and intrathecal therapy are well-studied and may be appropriate both for analgesia as well as reduction of side effects from systemic medications. Radiation therapy (including single-fraction external beam treatments) or radionuclide therapy (eg, strontium-89), which aims to decrease the size of both

primary and metastatic disease, is one of the unique options for patients with pain from cancer.

- Boland EG et al. Cannabinoids for adult cancer-related pain: systematic review and meta-analysis. *BMJ Support Palliat Care*. 2020;10:14. [PMID: 31959586]
- Careskey H et al. Interventional anesthetic methods for pain in hematology/oncology patients. *Hematol Oncol Clin North Am*. 2018;32:433. [PMID: 29729779]
- Lau J et al. Interventional anesthesia and palliative care collaboration to manage cancer pain: a narrative review. *Can J Anaesth*. 2020;67:235. [PMID: 31571119]
- Magee D et al. Cancer pain: where are we now? *Pain Manag*. 2019;9:63. [PMID: 30516438]
- Mercadante S et al. The use of alternative therapies in conjunction with opioids for cancer pain. *Expert Rev Anticancer Ther*. 2019;19:697. [PMID: 31298971]
- Swarm RA et al. Adult Cancer Pain, Version 3.2019, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw*. 2019;17:977. [PMID: 31390582]

## PAIN AT THE END OF LIFE

Pain is what many people say they fear most about dying, and pain at the end of life is consistently undertreated. Up to 75% of patients dying of cancer, heart failure, chronic obstructive pulmonary disease, AIDS, or other diseases experience pain. In the United States, the Joint Commission includes pain management standards in its reviews of health care

organizations and, in 2018, it began mandating that each hospital have a designated leader in pain management.

The ratio of risk versus benefit changes in end-of-life pain management. Harms from the use of opioid analgesics, including death, eg, from respiratory depression (rare), are perhaps less of a concern in patients approaching the end of life. In all cases, clinicians must be prepared to use appropriate doses of opioids in order to relieve this distressing symptom for these patients. Typically, for ongoing cancer pain, a long-acting opioid analgesic can be given around the clock with a short-acting opioid medication as needed for “breakthrough” pain.

## PRINCIPLES OF PAIN MANAGEMENT

The experience of pain is unique to each person and influenced by many factors, including the patient's prior experiences with pain, meaning given to the pain, emotional stresses, and family and cultural influences. Pain is a subjective and multi-faceted phenomenon, and clinicians cannot reliably detect its existence or quantify its severity without asking the patient directly. A brief means of assessing pain and evaluating the effectiveness of analgesia is to ask the patient to rate the degree of pain along a numeric or visual pain scale (Table 5–4), assessing trends over time. Clinicians should ask about the nature, severity, timing,

**Table 5–4.** Pain assessment scales.

| A. Numeric Rating Scale  |                       |                              |                      |                      |                  |
|--|-----------------------|------------------------------|----------------------|----------------------|------------------|
| No pain  |                       | Worst pain                   |                      |                      |                  |
| 0    1    2    3    4    5    6    7    8    9    10             |                       |                              |                      |                      |                  |
|  |                       |                              |                      |                      |                  |
| B. Numeric Rating Scale Translated into Word and Behavior Scales |                       |                              |                      |                      |                  |
| Pain Intensity   | Word Scale            | Nonverbal Behaviors          |                      |                      |                  |
| 0  | No pain               | Relaxed, calm expression     |                      |                      |                  |
| 1–2  | Least pain            | Stressed, tense expression   |                      |                      |                  |
| 3–4  | Mild pain             | Guarded movement, grimacing  |                      |                      |                  |
| 5–6  | Moderate pain         | Moaning, restlessness        |                      |                      |                  |
| 7–8  | Severe pain           | Crying out                   |                      |                      |                  |
| 9–10   | Excruciating pain     | Increased intensity of above |                      |                      |                  |
| C. Wong-Baker FACES Pain Rating Scale <sup>1</sup>               |                       |                              |                      |                      |                  |
|  |                       |                              |                      |                      |                  |
| 0<br>No hurt   | 1<br>Hurts Little Bit | 2<br>Hurts Little More       | 3<br>Hurts Even More | 4<br>Hurts Whole Lot | 5<br>Hurts Worst |

<sup>1</sup>Especially useful for patients who cannot read English (and for pediatric patients).

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location, quality, and aggravating and relieving factors of the pain.

General guidelines for diagnosis and management of pain are recommended for the treatment of all patients with pain but clinicians must comprehend that such guidelines may not be suited for every individual. Because of pain's complexity, it is important to understand benefits and risks of treatment with growing evidence for each patient. Distinguishing between nociceptive (somatic or visceral) and neuropathic pain is essential to proper management.

In addition, while clinicians should seek to diagnose the underlying cause of pain and then treat it, they must balance the burden of diagnostic tests or therapeutic interventions with the patient's suffering. For example, single-fraction radiation therapy for painful bone metastases or nerve blocks for neuropathic pain may obviate the need for ongoing treatment with analgesics and their side effects. Regardless of decisions about seeking and treating the underlying cause of pain, every patient should be offered prompt pain relief.

The aim of effective pain management is to meet specific goals, such as preservation or restoration of function or quality of life, and this aim must be discussed between clinician and patient, as well as their family. For example, some patients may wish to be completely free of pain even at the cost of significant sedation, while others will wish to control pain to a level that still allows maximal cognitive functioning.

Whenever possible, the oral route of analgesic administration is preferred because it is easier to manage at home, is not itself painful, and imposes no risk from needle exposure. In unique situations, or near the end of life, transdermal, subcutaneous, rectal, and intravenous routes of administration are used; intrathecal administration is used when necessary.

Finally, pain management should not automatically indicate opioid therapy. While some individuals fare better with opioid therapy in specific situations, this does not mean that opioids are the answer for every patient. There are situations where opioids actually make the quality of life worse for individuals, due to a lack of adequate analgesic effect or due to their side effects.

## ► Barriers to Good Care

One barrier to good pain control is that many clinicians have limited training and clinical experience with pain management and thus are reluctant to attempt to manage severe pain. Lack of knowledge about the proper selection and dosing of analgesic medications carries with it attendant and typically exaggerated fears about the side effects of pain medications. Consultation with a palliative care or a pain management specialist may provide additional expertise.

## PHARMACOLOGIC PAIN MANAGEMENT STRATEGIES

Pain generally can be well controlled with nonopioid and opioid analgesic medications, complemented by nonpharmacologic adjunctive and interventional treatments. For

mild to moderate pain, acetaminophen, aspirin, and NSAIDs (also known as COX inhibitors) may be sufficient. For moderate to severe pain, especially for those with acute pain, short courses of opioids are sometimes necessary; for those with cancer pain or pain from advanced, progressive serious illness, opioids are generally required and interventional modalities should be considered. In all cases, the choice of an analgesic medication must be guided by careful attention to the physiology of the pain and the benefits and risks of the particular analgesic being considered.

### ► Acetaminophen, Aspirin, Celecoxib, & NSAIDs (COX Inhibitors)

Table 5–5 provides comparison information for acetaminophen, aspirin, the COX-2 inhibitor celecoxib and the NSAIDs. An appropriate dose of acetaminophen may be just as effective an analgesic and antipyretic as an NSAID but without the risk of gastrointestinal bleeding or ulceration. Acetaminophen can be given at a dosage of 500–1000 mg orally every 6 hours, not to exceed 4000 mg/day maximum for short-term use. Total acetaminophen doses should not exceed 3000 mg/day for long-term use or 2000 mg/day for older patients and for those with liver disease. Hepatotoxicity is of particular concern because of how commonly acetaminophen is also an ingredient in various over-the-counter medications and because of failure to account for the acetaminophen dose in combination acetaminophen-opioid medications such as Vicodin or Norco. The FDA has limited the amount of acetaminophen available in some combination analgesics (eg, in acetaminophen plus codeine preparations).

Aspirin (325–650 mg orally every 4 hours) is an effective analgesic, antipyretic, and anti-inflammatory medication. Gastrointestinal irritation and bleeding are side effects that are lessened with enteric-coated formulations and by concomitant use of proton pump inhibitor medication. Bleeding, allergy, and an association with Reye syndrome in children and adolescents further limit its use.

NSAIDs are antipyretic, analgesic, and anti-inflammatory. Treatment with NSAIDs increases the risk of gastrointestinal bleeding 1.5 times; the risks of bleeding and nephrotoxicity are both increased in elderly patients. Gastrointestinal bleeding and ulceration may be prevented with either the concurrent use of proton pump inhibitors (eg, omeprazole, 20–40 mg orally daily) or the use of celecoxib (100 mg orally daily to 200 mg orally twice daily), the only COX-2 inhibitor available. Celecoxib and the NSAIDs can lead to fluid retention, kidney injury, and exacerbations of heart failure and should be used with caution in patients with that condition. Topical formulations of NSAIDs (such as diclofenac 1.3% patch or 1% gel), placed over the painful body part for treatment of musculoskeletal pain, are associated with less systemic absorption and fewer side effects than oral administration and are likely underutilized in patients at risk for gastrointestinal bleeding.

Noori SA et al. Nonopiod versus opioid agents for chronic neuropathic pain, rheumatoid arthritis pain, cancer pain and low back pain. Pain Manag. 2019;9:205. [PMID: 30681031]

**Table 5–5.** Acetaminophen, aspirin, and useful nonsteroidal anti-inflammatory drugs and COX inhibitors.

| Medication<br>(alphabetic order)                                     | Usual Dose for<br>Adults $\geq$ 50 kg   | Usual Dose<br>for Adults<br>$<$ 50 kg <sup>1</sup>   | Cost per Unit  | Cost for<br>30 Days <sup>2</sup> | Comments <sup>3</sup>  |
|--|---|--|--|----------------------------------|--|
| Acetaminophen<br>(Ofirmev)   | 1000 mg intrave-nously every 6–8 hours  |  | \$48.00 per vial of 1000 mg                          | \$5760.00                        |  |
| Acetaminophen or paracetamol <sup>4</sup><br>(Tylenol, Datirol, etc) | 325–500 mg orally every 4 hours or 500–1000 mg orally every 6 hours, up to 2000–4000 mg/day | 10–15 mg/kg every 4 hours orally; 15–20 mg/kg every 4 hours rectally, up to 2000–3000 mg/day | \$0.02/500 mg (oral) OTC; \$0.43/650 mg (rectal) OTC | \$3.60 (oral); \$77.40 (rectal)  | Not an NSAID because it lacks peripheral anti-inflammatory effects. Equivalent to aspirin as analgesic and antipyretic agent.<br>Limit dose to 4000 mg/day in acute pain, and to 3000 mg/day in chronic pain. Limit doses to 2000 mg/day in older patients and those with liver disease.<br>Be mindful of multiple sources of acetaminophen as in combination analgesics, cold remedies, and sleep aids. |
| Aspirin <sup>5</sup>   | 325–650 mg orally every 4 hours   | 10–15 mg/kg every 4 hours orally; 15–20 mg/kg every 4 hours rectally                         | \$0.01/325 mg OTC; \$1.51/600 mg (rectal) OTC        | \$3.60 (oral); \$271.80 (rectal) | Available also in enteric-coated oral form that is more slowly absorbed but better tolerated.  |
| Celecoxib <sup>4</sup> (Celebrex)                                    | 200 mg orally once daily (osteoarthritis); 100–200 mg orally twice daily (RA)               | 100 mg orally once or twice daily  | \$4.37/100 mg; \$7.57/200 mg                         | \$227.10 OA; \$454.20 RA         | Cyclooxygenase-2 inhibitor. No antiplatelet effects. Lower doses for elderly who weigh $<$ 50 kg. Lower incidence of endoscopic gastrointestinal ulceration than NSAIDs. Not known if true lower incidence of gastrointestinal bleeding. Celecoxib is contraindicated in sulfonamide allergy.  |
| Diclofenac (Flector)   | 1.3% topical patch applied twice daily  |  | \$14.92/patch  | \$895.20                         | Apply patch to most painful area. Diclofenac 1% gel is available over the counter.   |
| Diclofenac (Voltaren, Cataflam, others)                              | 50–75 mg orally two or three times daily; 1% gel 2–4 g four times daily                     |  | \$0.95/50 mg; \$1.14/75 mg; \$0.52/g gel             | \$85.50; \$102.60; \$249.60 gel  | May impose higher risk of hepatotoxicity. Enteric-coated product; slow onset. Topical formulations may result in fewer side effects than oral formulations.  |
| Diclofenac sustained release (Voltaren-XR, others)                   | 100–200 mg orally once daily  |  | \$2.70/100 mg  | \$162.00                         |  |
| Etodolac (Lodine, others)  | 200–400 mg orally every 6–8 hours   |  | \$1.32/400 mg  | \$158.40                         |  |
| Ibuprofen (Caldolor)   | 400–800 mg intrave-nously every 6 hours   |  | \$22.99/800 mg vial                                  | \$2758.80                        |  |
| Ibuprofen (Motrin, Advil, Rufen, others)                             | 400–800 mg orally every 6 hours   | 10 mg/kg orally every 6–8 hours  | \$0.27/600 mg Rx; \$0.02/200 mg OTC                  | \$37.40; \$3.60                  | Relatively well tolerated and inexpensive.   |

(continued)

**Table 5–5.** Acetaminophen, aspirin, and useful nonsteroidal anti-inflammatory drugs and COX inhibitors. (continued)

| Medication<br>(alphabetic order)                        | Usual Dose for<br>Adults $\geq$ 50 kg   | Usual Dose<br>for Adults<br>$<$ 50 kg <sup>1</sup> | Cost per Unit                          | Cost for<br>30 Days <sup>2</sup> | Comments <sup>3</sup>   |
|---|---|--|--|----------------------------------|---|
| Indomethacin<br>(Indocin, Indometh,<br>others)          | 25–50 mg orally two<br>to four times daily  |  | \$0.38/25 mg;<br>\$0.64/50 mg          | \$45.60; \$76.80                 | Higher incidence of dose-related<br>toxic effects, especially gastrointesti-nal and bone marrow<br>effects.                       |
| Ketorolac<br>tromethamine                               | 10 mg orally every<br>4–6 hours to a<br>maximum of<br>40 mg/day orally  |  | \$2.16/10 mg                           | Not recom-mended                 | Short-term use (< 5 days) only;<br>otherwise, increased risk of<br>gastrointestinal side effects.                                 |
| Ketorolac<br>tromethamine <sup>6</sup>                  | 60 mg intramuscularly<br>or 30 mg intrave-nously initially,<br>then 30 mg every<br>6 hours intramus-cularly or<br>intravenously |  | \$1.45/30 mg                           | Not recom-mended                 | Intramuscular or intravenous<br>NSAID as alternative to opioid.<br>Lower doses for elderly.<br>Short-term use (< 5 days)<br>only. |
| Magnesium salicylate<br>(various)                       | 325–650 mg orally<br>every 6 hours  |  | \$0.25/325 mg OTC                      | \$60.00                          |   |
| Meloxicam (Mobic)                                       | 7.5 mg orally every<br>12 hours   |  | \$2.78/7.5 mg                          | \$166.80                         | Intermediate COX-2/COX-1 ratio<br>similar to diclofenac.  |
| Nabumetone<br>(Relafen)                                 | 500–1000 mg orally<br>once daily (max<br>dose 2000 mg/day)  |  | \$1.30/500 mg;<br>\$1.45/750 mg        | \$78.00; \$87.00                 | May be less ulcerogenic than<br>ibuprofen, but overall side<br>effects may not be less.   |
| Naproxen (Naprosyn,<br>Anaprox, Aleve<br>[OTC], others) | 250–500 mg orally<br>every 6–8 hours  | 5 mg/kg every<br>8 hours                           | \$1.19/500 mg Rx;<br>\$0.04/220 mg OTC | \$142.80; \$3.60<br>OTC          | Generally well tolerated. Lower<br>doses for elderly.   |

<sup>1</sup>Acetaminophen and NSAID dosages for adults weighing  $<$  50 kg should be adjusted for weight.

<sup>2</sup>Average wholesale price (AWP, for AB-rated generic when available) for quantity listed. Source: IBM Micromedex Red Book (electronic version) IBM Watson Health. Greenwood Village, CO, USA. Available at <https://www.micromedexsolutions.com>, accessed March 27, 2021. AWP may not accurately represent the actual pharmacy cost because wide contractual variations exist among institutions.

<sup>3</sup>The adverse effects of headache, tinnitus, dizziness, confusion, rashes, anorexia, nausea, vomiting, gastrointestinal bleeding, diarrhea, nephrotoxicity, visual disturbances, etc, can occur with any of these drugs. Tolerance and efficacy are subject to great individual variations among patients. Note: All NSAIDs can increase serum lithium levels.

<sup>4</sup>Acetaminophen and celecoxib lack antiplatelet effects.

<sup>5</sup>May inhibit platelet aggregation for 1 week or more and may cause bleeding.

<sup>6</sup>Has the same gastrointestinal toxicities as oral NSAIDs.

COX, cyclooxygenase; OA, osteoarthritis; OTC, over the counter; RA, rheumatoid arthritis; Rx, prescription.

## ► Opioids

### A. A Shared Decision-Making Approach to Clinical Opioid Use

For many patients at the end of life, opioids are the main-stay of pain management (Tables 5–6 and 5–7). Opioids are appropriate for managing severe pain at the end of life due to any cause, including neuropathic pain, cancer pain, and pain from other serious illnesses. Using opioids long-term in other settings requires careful consideration.

In an effort to treat chronic pain more aggressively, clinicians in the United States dramatically increased the prescription of opioids beginning in the mid-1990s and

peaking in 2012. More attention to treating chronic non-cancer pain undoubtedly improved the lives of many patients, but the increase in prescribed opioids had a deleterious effect on the health of the population as a whole. The increased population exposure to prescription opioids appears to have expanded the market for illicit opioids (heroin, fentanyl and its derivatives), with concomitant increase in opioid use disorder and in opioid overdoses, which caused more than 50,000 deaths in 2019. The CDC named both misuse of prescription medications and opioid overdoses as epidemics in the United States and released guidelines in 2016 to limit the risks of prescribed opioids (<https://www.cdc.gov/drugoverdose/prescribing/resources.html>).

**Table 5–6.** Opioids.

| Medication  | Approximate Equianalgesic Dose (compared to morphine 30 mg orally or 10 mg intravenously/subcutaneously) <sup>1</sup> |  | Usual Starting Dose  |   |                            |  |
|---|---|--|--|---|----------------------------|--|
|   | Oral  | PARENTERAL   | Adults ≥ 50 kg Body Weight   |   | Adults < 50 kg Body Weight |  |
| Opioid Agonists <sup>2,3</sup>                          | Oral  | PARENTERAL   | Oral   | PARENTERAL  | Oral                       | PARENTERAL   |
| Buprenorphine parenteral <sup>4</sup><br>(Buprenex)     |   | 300 mcg intravenously slowly once, may be repeated after 30–60 minutes once; or 600 mcg intramuscularly once |  | 300 mcg intravenously slowly once, may be repeated after 30–60 minutes once; or 600 mcg intramuscularly once; \$14.34/300 mcg |                            |  |
| Buprenorphine transdermal <sup>4</sup> (BuTrans)        | Not available   | Not available  | Not available orally.<br>Transdermal doses available: 5, 10, and 20 mcg/h. Initiate 5 mcg/h patch for opioid-naïve patients (may currently be using nonopioid analgesics); \$114.77/10 mcg/h.  | Not available   | Not available              | Not available  |
| Buprenorphine sublingual <sup>4</sup><br>(Belbuca)      | Sublingual strip approved for pain  |  | In opioid-naïve or opioid-intolerant patients, individualize dose every 12 hours. Start: 75 mcg buccally every 12–24 hours for at least 4 days, then increase to 150 mcg buccally every 12 hours, then may increase by no more than 150 mcg buccally every 12 hours no more frequently than every 4 days.<br>Maximum: 900 mcg/12 hours; \$7.33/75 mcg. |   |                            |  |
| Fentanyl  | Not available   | 100 mcg every hour   | Not available  | 50–100 mcg intravenously/intramuscularly every hour or 0.5–1.5 mcg/kg/h intravenous infusion; \$0.80/100 mcg                  | Not available              | 0.5–1 mcg/kg intravenously every 1–4 hours or 1–2 mcg/kg intravenously × 1, then 0.5–1 mcg/kg/h infusion |
| Fentanyl oral transmucosal<br>(Actiq); buccal (Fentora) | Not available   | Not available  | 200 mcg transmucosal; 100 mcg buccal; \$18.80/200 mcg transmucosal; \$94.98/200 mcg buccal   | Not available   | Not available              | Not available  |

|  |  |                         |  |   |                                    |                             |
|--|--|-------------------------|--|---|------------------------------------|-----------------------------|
| Fentanyl transdermal   | Conversion to fentanyl patch is based on total daily dose of oral morphine <sup>2</sup> : morphine 60–134 mg/day orally = fentanyl 25 mcg/h patch; morphine 135–224 mg/day orally = fentanyl 50 mcg/h patch; morphine 225–314 mg/day orally = fentanyl 75 mcg/h patch; and morphine 315–404 mg/day orally = fentanyl 100 mcg/h patch | Not available           | Not available orally<br>12.5–25 mcg/h patch every 72 hours; \$8.56/25 mcg/h  | Not available                               | 12.5–25 mcg/h patch every 72 hours | Not available               |
| Hydrocodone, extended release (Zohydro ER)   | 20 mg <sup>1</sup>   | Not available           | 10 mg every 12 hours;<br>\$12.00/10 mg   | Not available                               | Not available                      | Not available               |
| Hydromorphone <sup>5</sup> (Dilaudid)  | 7.5 mg every 3–4 hours   | 1.5 mg every 3–4 hours  | 1–2 mg every 3–4 hours;<br>\$0.42/2 mg   | 1.5 mg every 3–4 hours;<br>\$1.02/2 mg      | 0.06 mg every 3–4 hours            | 0.015 mg/kg every 3–4 hours |
| Hydromorphone extended release (Exalgo)  | 45–60 mg every 24 hours  | Not available           | 8 mg every 24 hours; \$9.24/8 mg   | Not available                               | Not available                      | Not available               |
| Levorphanol  | 4 mg every 6–8 hours   | Not available           | 4 mg every 6–8 hours; \$53.40/2 mg   | Not available                               | 0.04 mg/kg every 6–8 hours         | Not available               |
| Meperidine <sup>6</sup> (Demerol)  | 300 mg every 2–3 hours; usual dose 50–150 mg every 3–4 hours   | 100 mg every 3 hours    | Not recommended  | 100 mg every 3 hours;<br>\$7.60/100 mg      | Not recommended                    | 0.75 mg/kg every 2–3 hours  |
| Methadone (Dolophine, others)  | 10–20 mg every 6–8 hours (when converting from < 100 mg long-term daily oral morphine <sup>7</sup> )   | 5–10 mg every 6–8 hours | 5–20 mg every 6–8 hours;<br>\$0.31/10 mg   | 2.5–10 mg every 6–8 hours;<br>\$21.00/10 mg | 0.2 mg/kg every 6–8 hours          | 0.1 mg/kg every 6–8 hours   |
| Morphine <sup>5</sup> immediate release (morphine sulfate tablets, Roxanol liquid) | 30 mg every 3–4 hours (around-the-clock dosing); 60 mg every 3–4 hours (single or intermittent dosing)   | 10 mg every 3–4 hours   | 4–8 mg every 3–4 hours; used for breakthrough pain in patients already taking controlled-release preparations; \$0.49/15 mg tab; \$0.67/20 mg liquid | 10 mg every 3–4 hours;<br>\$4.66/10 mg      | 0.3 mg/kg every 3–4 hours          | 0.1 mg/kg every 3–4 hours   |
| Morphine controlled release (MS Contin)  | 90–120 mg every 12 hours   | Not available           | 15–60 mg every 12 hours;<br>\$1.50/30 mg   | Not available                               | Not available                      | Not available               |
| Morphine extended release (Kadian)   | 180–240 mg every 24 hours  | Not available           | 20–30 mg every 24 hours; \$5.69/30 mg  | Not available                               | Not available                      | Not available               |

(continued)

**Table 5–6.** Opioids. (continued)

| Medication   | Approximate Equianalgesic Dose (compared to morphine 30 mg orally or 10 mg intravenously/subcutaneously) <sup>1</sup>      |                        | Usual Starting Dose   |  |                             |                 |
|--|--|------------------------|---|--|-----------------------------|-----------------|
|  |  |                        | Adults ≥ 50 kg Body Weight  |  | Adults < 50 kg Body Weight  |                 |
|  | Oral   | Parenteral             | Oral  | Parenteral   | Oral                        | Parenteral      |
| Oxycodone (Roxicodone, OxyIR)  | 20–30 mg every 3–4 hours   | Not available          | 5–10 mg every 3–4 hours; \$0.15/5 mg  | Not available  | 0.2 mg/kg every 3–4 hours   | Not available   |
| Oxycodone controlled release (Oxycontin)   | 40 mg every 12 hours   | Not available          | 20–40 mg every 12 hours; \$9.93/20 mg   |  |                             |                 |
| Oxymorphone <sup>5,8</sup> oral, immediate release (Opana)                       | 10 mg every 6 hours  | Not available          | 5–10 mg every 6 hours; \$1.26/5 mg  | Not available  |                             |                 |
| <b>Combination Opioid Agonist–Nonopiod Preparations</b>                          |  |                        |   |  |                             |                 |
| Codeine <sup>9,10</sup> (with aspirin or acetaminophen) <sup>11</sup>            | 180–200 mg every 3–4 hours; commonly available dose in combination with acetaminophen, 15–60 mg of codeine every 4–6 hours | 130 mg every 3–4 hours | 60 mg every 4–6 hours; \$0.35/60 mg   | 60 mg every 2 hours intramuscularly/subcutaneously; not available in the United States | 0.5–1 mg/kg every 3–4 hours | Not recommended |
| Hydrocodone <sup>8</sup> (in Lortab, others) <sup>11</sup>                       | 30 mg every 3–4 hours  | Not available          | 10 mg every 3–4 hours; \$0.41/5 mg  | Not available  | 0.2 mg/kg every 3–4 hours   | Not available   |
| Oxycodone <sup>10</sup> (in Percodan, others) <sup>11</sup>                      | 30 mg every 3–4 hours  | Not available          | 10 mg every 3–4 hours; \$0.08/5 mg  | Not available  | 0.2 mg/kg every 3–4 hours   | Not available   |
| <b>Combination Opioid Agonist–Norepinephrine Reuptake Inhibitor Preparations</b> |  |                        |   |  |                             |                 |
| Tapentadol (Nucynta)   | Not known  | Not known              | Start 50–100 mg once, may repeat dose in 1 hour. Can increase to 50–100 mg every 4 hours. Maximum daily dose 600 mg; \$14.36/100 mg.            | Not available  |                             | Not available   |
| Tapentadol, extended release (Nucynta ER)  | Not known  | Not known              | Start 50 mg orally every 12 hours. Can increase by 50-mg increments twice daily every 3 days to dose of 100–250 mg twice daily; \$18.36/100 mg. | Not available  |                             | Not available   |

|                   |           |           |  |               |  |               |
|-------------------|-----------|-----------|--|---------------|--|---------------|
| Tramadol (Ultram) | Not known | Not known | Start 25 mg orally daily. Can increase by 25 mg every 3 days to 25 mg orally 4 times daily, then may increase by 50 mg/day every 3 days to 100 mg orally 4 times daily. Limit of 300 mg/day in patients > 75 years old;<br>\$0.83/50 mg. | Not available |  | Not available |
|-------------------|-----------|-----------|--|---------------|--|---------------|

<sup>1</sup>Published tables vary in the suggested doses that are equianalgesic to morphine. Clinical response is the criterion that must be applied for each patient; titration to clinical efficacy is necessary. Because there is not complete cross-tolerance among these drugs, it is usually necessary to use a lower than equianalgesic dose initially when changing drugs and to retitrate to response.

<sup>2</sup>Conversion is conservative; therefore, do not use these equianalgesic doses for converting back from fentanyl patch to other opioids because they may lead to inadvertent overdose. Patients may require breakthrough doses of short-acting opioids during conversion to transdermal fentanyl.

<sup>3</sup>Several significantly more potent formulations of buprenorphine are available but generally reserved for the treatment of opioid use disorder with or without comorbid constant pain, most often by pain management specialists: a sublingual tablet (Subutex and others) or a sublingual film (Suboxone and others) in which the buprenorphine is combined with naloxone; a subdermal implant of buprenorphine alone (Probuphine); and a subcutaneous depot injection (Sublocade). Each of these is used in maintenance treatment to reduce problematic use of other opioids. See text.

<sup>4</sup>In opioid-experienced patients, taper current opioids to 30 mg/day oral morphine equivalent prior to starting buprenorphine. Thereafter, buprenorphine dosing schedule depends on prior current oral morphine equivalent:

- < 30 mg/day, 75 mcg buccally every 12 hours;
- 30–89 mg/day, 150 mcg buccally every 12 hours;
- 90–160 mg/day, 300 mcg buccally every 12 hours;

In all patients, use same dose escalation and maximum dose as shown for opioid-naïve patients.

<sup>5</sup>*Caution:* For morphine, hydromorphone, and oxymorphone, rectal administration is an alternative route for patients unable to take oral medications. Equianalgesic doses may differ from oral and parenteral doses. A short-acting opioid should normally be used for initial therapy.

<sup>6</sup>Not recommended for chronic pain. Doses listed are for brief therapy of acute pain only. Switch to another opioid for long-term therapy.

<sup>7</sup>Methadone conversion varies depending on the equivalent total daily dose of morphine. Consult with a pain management or palliative care expert for conversion.

<sup>8</sup>*Caution:* Recommended doses do not apply to adult patients with kidney or liver impairment or other conditions affecting drug metabolism.

<sup>9</sup>*Caution:* Individual doses of codeine above 60 mg often are not appropriate because of diminishing incremental analgesia with increasing doses but continually increasing nausea, constipation, and other side effects.

<sup>10</sup>*Caution:* Doses of aspirin and acetaminophen in combination products must also be adjusted to the patient's body weight.

<sup>11</sup>*Caution:* Monitor total acetaminophen dose carefully, including any OTC use. Total acetaminophen dose maximum 3 g/day. If liver impairment or heavy alcohol use, maximum is 2 g/day. Available dosing formulations of these combination medications are being adjusted to reflect increased caution about acetaminophen toxicity. Acetaminophen doses in a single combination tablet or capsule will be limited to no more than 325 mg.

Note: Average wholesale price (AWP, generic when available) for quantity listed. Source: IBM Micromedex Red Book (electronic version) IBM Watson Health. Greenwood Village, CO, USA. Available at <https://www.micromedexsolutions.com>, accessed March 27, 2021. AWP may not accurately represent the actual pharmacy cost because wide contractual variations exist among institutions.

**Table 5–7.** Opioids advantages and disadvantages.

| Medication  | Potential Advantages   | Potential Disadvantages   |
|---|--|---|
| <b>Opioid Agonists</b>  |  |   |
| Buprenorphine transdermal (BuTrans)                                   | 7-day analgesia; may be initiated in opioid-naïve patients with 5 mcg/h.<br>Can titrate up dose by 5 mcg/h after 72 hours, to a maximum dose of 20 mcg/h.              |   |
| Buprenorphine sublingual (Belbuca)                                    |  | Used by pain management specialists.<br>Do no cut, chew, swallow strip. Taper slowly to discontinue.<br>Use lowest effective dose, shortest effective treatment duration. Titrate slowly in patients age > 65 years.                                  |
| Fentanyl  | Possibly less neuroexcitatory effects, including in kidney failure.  |   |
| Fentanyl oral transmucosal (Actiq); buccal (Fentora)                  | For pain breaking through long-acting opioid medication.   | Transmucosal and buccal formulations are not bioequivalent; there is higher bioavailability in buccal formulation.  |
| Fentanyl transdermal  | Stable medication blood levels.  | Not for use in opioid-naïve patients. Minimum starting dose is 25 mcg/h patch in patients who have been taking stable dose of opioids for at least 1 week at the equivalent of at least 60 mg/day of oral morphine.                                   |
| Hydrocodone, extended release (Zohydro ER)                            | Available as an extended-release formulation without acetaminophen.  |   |
| Hydromorphone (Dilaudid)  | Similar to morphine. Available in injectable high-potency preparation, rectal suppository.   | Short duration.   |
| Hydromorphone extended release (Exalgo)                               | Similar to morphine.   | Taper dose 25–50% every 2–3 days to 8 mg/day to discontinue.  |
| Levorphanol   | Longer acting than morphine sulfate.   |   |
| Meperidine (Demerol)  | Use only when single-dose, short-duration analgesia is needed, as for outpatient procedures like colonoscopy. Not recommended for chronic pain or for repeated dosing. | Short duration. Normeperidine metabolite accumulates in kidney failure and other situations, and in high concentrations may cause irritability and seizures.  |
| Methadone (Dolophine, others)   | Somewhat longer acting than morphine. Useful in cases of intolerance to morphine. May be particularly useful for neuropathic pain. Available in liquid formulation.    | Analgesic duration shorter than plasma duration. May accumulate, requiring close monitoring during first weeks of treatment. Equianalgesic ratios vary with opioid dose. Risk of QT prolongation at doses > 100–150 mg/day. Baseline ECG recommended. |
| Morphine immediate release (morphine sulfate tablets, Roxanol liquid) | Standard of comparison; multiple dosage forms available.   | No unique problems when compared with other opioids.<br>Active metabolite accumulates in kidney dysfunction.  |
| Morphine extended release (Kadian)                                    | Once-daily dosing possible.  |   |
| Oxycodone (Roxicodone, OxyIR)   | Similar to morphine.   |   |
| Oxycodone controlled release (Oxycontin)                              |  | Physical and chemical pill formulation to deter misuse (injection or intranasal administration).  |
| Oxymorphone oral, immediate release (Opana)                           |  | Taking with food can increase serum levels by 50%. Equianalgesic dosing conversion range is wide.   |
| <b>Combination Opioid Agonist–Nonopioid Preparations</b>              |  |   |
| Codeine (with aspirin or acetaminophen)                               | Similar to morphine.   | Closely monitor for efficacy as patients vary in their ability to convert the prodrug codeine to morphine.  |

(continued)

**Table 5–7.** Opioids advantages and disadvantages. (continued)

| Medication   | Potential Advantages | Potential Disadvantages   |
|--|----------------------|---|
| Hydrocodone (in Lortab, others)  |                      | Combination with acetaminophen limits dosage titration.                                 |
| Oxycodone (in Percodan, Percocet, and others)                                    | Similar to morphine. | Combination with aspirin and acetaminophen limits dosage titration.                     |
| <b>Combination Opioid Agonist–Norepinephrine Reuptake Inhibitor Preparations</b> |                      |   |
| Tapentadol (Nucynta)   |                      | Avoid in severe kidney or liver impairment.   |
| Tapentadol, extended release (Nucynta ER)  |                      | Avoid in severe kidney or liver impairment.   |
| Tramadol (Ultram)  |                      | If creatinine clearance < 30, limit to 200 mg/day; with cirrhosis, limit to 100 mg/day. |

Also in 2016, the US Surgeon General directly appealed to prescribing physicians to focus on combating the opioid epidemic and issued a report titled “Facing Addiction in America” (<https://addiction.surgeongeneral.gov/sites/default/files/surgeon-generals-report.pdf>). The CDC later issued a follow up clarification to their guidelines to encourage clinicians and insurers to avoid the unintended consequence of denying opioids to patients with cancer, sickle cell disease, and other conditions not targeted in the guidelines for chronic, noncancer pain. As of late 2020, experts recommend prescribing a limited supply of opioids to patients with severe, acute pain (fracture, postoperative), avoiding initiation of opioids for chronic noncancer pain, careful monitoring of patients already on opioid therapy for chronic noncancer pain, and evidence-based treatment of opioid use disorder if it is diagnosed.

Taking the approach of carefully evaluating benefits and risks in individual cases allows the opportunity for shared decision making between patient and clinician. Clinical trials do suggest more harms than benefits for the population of people prescribed opioids for chronic noncancer pain. Observational data indicate that when patients taking high doses of opioids long-term reduce their doses, their pain does not get worse and may actually improve. It is incumbent upon the clinician to provide frank advice to patients prescribed long-term opioids for chronic noncancer pain and to offer safer alternatives when the benefit is insufficient or the risks are too high.

## B. Assessing Benefits of Opioids

Opioids have long been known to be effective in managing acute pain. The potential benefits of daily opioid therapy for patients with chronic noncancer pain are less impressive. For example, research demonstrates that the beneficial effect of opioids for chronic noncancer pain is modest in magnitude and limited in duration. No measures have been identified to predict a good response. For patients already receiving daily, long-term opioid therapy, clinicians should discuss these modest benefits to help set realistic goals of therapy (eg, moving from an average pain level of a “7” to a “4”) (see Table 5–4). Many experts

recommend developing a specific goal of improved function (eg, return to work or to an exercise regimen) and tracking the patient’s progress toward achieving this goal.

For the many patients who do not have specific measurable goals, monitoring response to treatment over time can be difficult. A useful tracking measure derived from the Brief Pain Inventory and validated for use in primary care is the “PEG,” which directs patients to quantify on a scale of 0–10 the following three outcomes over the last week: average pain intensity, how much the pain has affected their enjoyment of life, and how much their pain has impacted their general activity. Patients who do not progress toward their goal or whose PEG scores remain high over time are not responding to opioids, and clinicians should reconsider the original diagnosis and use other modalities (both pharmacologic and nonpharmacologic) to provide analgesia. Without a clear analgesic benefit from opioids for chronic noncancer pain, the risks predominate, and the ineffective therapy should be discontinued in a patient-centered manner.

## C. Formulations and Regimens

Full opioid agonists such as morphine, hydromorphone, oxycodone, methadone, fentanyl, hydrocodone, tramadol, and codeine are used most commonly (Table 5–6). Hydrocodone and codeine are typically combined with acetaminophen or an NSAID, although acetaminophen in these combinations is restricted to 300–325 mg per unit dose due to the risk of hepatotoxicity. Extended-release hydrocodone without acetaminophen is also available. Short-acting formulations of oral morphine sulfate (starting dosage 4–8 mg orally every 3–4 hours), hydromorphone (1–2 mg orally every 3–4 hours), or oxycodone (5 mg orally every 3–4 hours) are useful for severe acute pain not controlled with other analgesics. The transmucosal intermediate-release fentanyl products, such as oral transmucosal fentanyl (200 mcg orale dissolved in the mouth) or buccal fentanyl (100 mcg dissolved in the mouth), can be used for treating patients with **cancer pain** that breaks through long-acting medications, or it can be administered before activity known to cause more pain (such as burn wound dressing changes).

Clinicians prescribing opioids must understand the concept of **equianalgesic dosing**. The dosages of any full opioid agonists used to control pain can be converted into an equivalent dose of any other opioid. This approach is helpful in estimating the appropriate dose of a long-acting opioid based on the amount of short-acting opioid required over the preceding days. For example, 24-hour opioid requirements established using short-acting opioid medications can be converted into equivalent dosages of long-acting medications or formulations. Cross-tolerance is often incomplete, however, so generally only two-thirds to three-quarters of the full, calculated equianalgesic dosage is administered initially when switching between opioid formulations.

For chronic stable *cancer* pain, **long-acting medications** are preferred, such as oral sustained-release formulations of morphine (one to three times a day), hydromorphone (once daily), oxymorphone (two times a day), oxycodone (two or three times a day), hydrocodone (two times a day), or methadone (three or four times a day), all of which have long half-lives. However, in chronic *noncancer* pain, long-acting full opioid agonists increase risks of complication (see section Common Side Effects of Opioids, below) without demonstrable improvement in pain control.

The partial agonist **buprenorphine** is effective in the treatment of moderate to severe chronic pain and is available in parenteral, transdermal, and buccal formulations. Attractive benefits of buprenorphine compared to other opioids include its long half-life, lower risk of sedation and respiratory depression during treatment, and lower likelihood of withdrawal upon discontinuation. When using formulations indicated for pain, the risk of the partial agonist precipitating withdrawal is low, and other opioids may still be used in conjunction as needed.

The **parenteral** formulation of buprenorphine (Buprenex) can be used for more acute pain in settings where more rapid onset or higher peak is required. The usual dosages are 300 mcg intravenously once (may be repeated once after 30–60 minutes) or as 600 mcg intramuscularly once. The **transdermal patch** of buprenorphine (BuTrans) is available in dosages of 5, 10, and 20 mcg/h. The **buccal buprenorphine** strip formulation (Belbuca) is sometimes used by pain management specialists for moderate to severe constant pain. It can be more frequently uptitrated since it is given twice daily. Depending on the patient's current opioid usage, it can be started at 75–300 mcg once or twice daily, then escalated by 150- to 450-mcg doses twice daily to a maximum of 900 mcg twice daily.

In addition, buprenorphine comes in significantly more potent formulations generally reserved for the treatment of opioid use disorder with or without comorbid constant pain: a **sublingual tablet** (Subutex and others), a **sublingual film** (Suboxone and others) in which the buprenorphine is combined with naloxone, a **subdermal implant** of buprenorphine alone (Probuphine), and **subcutaneous depot injections** (Sublocade, Brixadi). These are used in maintenance treatment to reduce problematic use of other opioids but should be considered for off-label analgesic use in patients who have been maintained on high doses of

other opioids, although observational evidence indicates that most patients experience improvement in their pain control after transition.

**Methadone** deserves special consideration among the long-acting opioids because it is inexpensive, available in a liquid formulation, and may have added efficacy for neuropathic pain. However, equianalgesic dosing is complex because it varies with the patient's dose, and caution must be used at higher methadone doses (generally more than 100–150 mg/day) because of the risk of QT prolongation. These additional risks have led many guidelines to recommend against the prescription of methadone by nonexperts, except at the end of life where comfort is the only goal.

**Transdermal fentanyl** is only appropriate to use with patients already tolerant to other opioids for at least 1 week at a dose equivalent to at least 60 mg/day of oral morphine (equivalent to a transdermal fentanyl 25 mcg/h patch applied topically every 72 hours). Therefore, it should not be used in the postoperative setting. It should not be the first opioid used with any patient. Since transdermal fentanyl can require 24–48 hours to achieve a pharmacologic "steady state," patients should be weaned off their current opioid and given short-acting opioids while awaiting the full analgesic effect of a newly prescribed transdermal fentanyl patch. Changes in dose of transdermal fentanyl should be made no more frequently than every 6 days.

While some clinicians inexperienced with the management of severe pain at the end of life may be more comfortable prescribing combined nonopioid-opioid agents, full agonist opioids are typically a better choice in patients with such severe pain because the dose of opioid is not limited by the toxicities of the acetaminophen, aspirin, or NSAID component of combination preparations. In end-of-life care, there may be no maximal allowable or effective dose for full opioid agonists, but for patients with longer life expectancy or for patients suffering from chronic noncancer pain, expert guidelines recommend avoiding long-term opioids when possible, and limiting total daily dose to less than the equivalent of 90 mg of morphine. When titrating, clinicians should confirm that increasing doses of opioid provide additional pain relief and remember that not all pain is opioid sensitive and that certain types of pain, such as neuropathic pain, may respond better to agents other than opioids, or to combinations of opioids with coanalgesic medications for neuropathic pain (see below).

In cancer pain, failure of a previously effective opioid dose to adequately relieve the pain is usually due to worsening of the underlying condition, such as cancer growth or new metastasis. In this case, for moderate unrelieved pain, the dose of opioid can be increased by 25–50%. For severe unrelieved pain, increasing by 50–100% may be appropriate. The frequency of dosing should be adjusted so that pain control is continuous. Long-term dosing may then be adjusted by adding the average daily amount of short-acting opioid necessary for breakthrough pain over the preceding 72–96 hours to the long-acting medication dose. In establishing or reestablishing adequate dosing, frequent reassessments of the patient's pain and medication side effects are necessary.

In noncancer pain, inadequate pain relief is not necessarily associated with worsening disease. Clinicians should evaluate with careful physical examination and judicious use of advanced imaging tests; they should reconsider the success of the opioid in managing the pain condition. For such patients taking long-term opioid therapy, the dose increases described above would be inappropriate.

#### D. Common Side Effects of Opioids

At higher doses or with long-term use of opioids, patients may experience increasing difficulty with the side effects. Opioid-related **constipation** should be anticipated and prevented in all patients. Constipation is common at any dose of opioid, and tolerance to this side effect does not develop over time. Prescribing a bowel regimen (see Chapter 15) to a patient taking opioids long term is a quality of care measure supported by the National Quality Forum.

**Sedation** can be expected with opioids, although tolerance to this effect and to side effects other than constipation typically develops within 24–72 hours at a stable dose. Sedation typically appears well before significant respiratory depression. If treatment for sedation is desired, dextroamphetamine (2.5–7.5 mg orally at 8 AM and noon) or methylphenidate (2.5–10 mg orally at 8 AM and noon) may be helpful. Caffeinated beverages can also ameliorate minor opioid sedation. For patients with noncancer pain who experience sedation, decreasing the available dose is recommended.

Opioid-induced **neurotoxicity**, including myoclonus, hyperalgesia, delirium with hallucinosis, and seizures, may develop in patients who take high doses of opioids for a prolonged period. Opioid-induced hyperalgesia appears to be a result of changes in both the peripheral and central nervous systems such that typically benign or even soothing stimuli (eg, light massage) may be perceived as painful (allodynia); increasing the opioid dose may exacerbate the problem. Opioid-induced neurotoxicity symptoms typically resolve after lowering the dose or switching opioids (“opioid rotation”). While waiting for the level of the offending opioid to fall in patients receiving end-of-life care, low doses of clonazepam, baclofen, or gabapentin may be helpful for treating myoclonus; haloperidol may be useful for treating delirium. Avoiding or correcting dehydration may be helpful for avoiding opioid-induced neurotoxicity.

**Nausea** may occur with initiation of opioid therapy and resolve after a few days. Notably, unrelieved constipation may be a more likely cause of nausea in the setting of opioid use than opioid-induced nausea. Severe or persistent nausea despite treatment of constipation can be managed by switching opioids or by giving haloperidol, 0.5–4 mg orally, subcutaneously, or intravenously every 6 hours or prochlorperazine, 10 mg orally or intravenously or 25 mg rectally every 6 hours. Ondansetron, 4–8 mg orally or intravenously every 6 hours, also relieves nausea but can contribute to constipation. Mirtazapine and medical cannabis may each have a role in treating opioid-induced nausea. Most antiemetic treatments can contribute to sedation.

The risk of **respiratory depression** with opioids may be decreased by initiating the opioid drug at a low dose and titrating it upward slowly, taking advantage of physiologic **tolerance**. Patients at particular risk for respiratory depression include those with obstructive or central sleep apnea, chronic obstructive pulmonary disease, and baseline CO<sub>2</sub> retention; those with liver or kidney or combined liver-kidney failure; and those with adrenal insufficiency or frank myxedema. Yet, even patients with severe pulmonary disease and obstructive sleep apnea can tolerate low-dose opioids, although these patients should be monitored carefully. Hospitalized patients with these conditions who require increased doses of opioids should be monitored with continuous pulse oximetry.

While physiologic **tolerance** (requiring increasing dosage to achieve the same analgesic effect) and **dependence** (requiring continued dosing to prevent symptoms of medication withdrawal) are expected with regular opioid use, the use of opioids at the end of life for relief of pain and dyspnea is not generally associated with a risk of psychological **addiction** (use of a substance despite negative health or social consequences, cravings to use a substance, compulsive use or loss of control over level or duration of use). If opioid use disorder is diagnosed in a patient, then the appropriate treatment is opioid agonist therapy with either methadone or buprenorphine, often accompanied by psychosocial interventions. Patients with opioid use disorder or other substance use disorders may need pain relief and may benefit from additional opioids, but their pain control will be inadequate without proper treatment of the substance use disorder. Increasingly, clinicians are recognizing a form of “refractory” or “complicated” physical dependence—without behaviors typical of addiction—as another complication associated with longer duration of opioid and higher dose.

Additional adverse side effects of long-term opioid use include **hypogonadism**, **falls**, **fractures**, and **difficult interactions with the health care system**. Finally, **diversion** of medication from patients to whom they are prescribed into other hands is an additional risk that must be considered when prescribing long-term opioids. Diversion can represent opportunism, eg, when a patient sells medication in order to make money. In addition, family members (including children), acquaintances, or strangers may steal or extort medication for their own use or monetary gain.

#### E. Limiting Risks of Opioids

A number of interventions have been used in an effort to limit the risks of opioids for patients with chronic noncancer pain, but data demonstrating the effectiveness of such measures are limited. At the population level, reductions in mortality from prescription drug overdose have been associated with reductions in the number of prescriptions for opioids. Nevertheless, nearly all medical society consensus panels and expert guidelines recommend using risk assessment tools, patient-provider agreements, urine drug testing, dose limitations, limits on the use of some medications, and medication treatments of opioid use disorder.

**1. Risk assessment tool**—No highly predictive models adequately predict harms or benefits from long-term opioids for chronic noncancer pain. Nevertheless, most published guidelines recommend using an instrument like the Opioid Risk Tool (available at <https://www.drugabuse.gov/sites/default/files/files/OpioidRiskTool.pdf>) to determine how closely to monitor patients who are receiving opioids long term, or whether to offer long-term opioids at all.

**2. Patient-provider agreements**—These documents of informed consent have a modest effect, with a 7–23% reduction in aberrant behaviors reported. They do represent an opportunity for the clinician to discuss explicitly the risks and benefits of opioids for chronic noncancer pain, protocols and procedural requirements for refills and monitoring, and consequences of worrisome behaviors.

**3. Urine drug testing**—Urine drug testing is a toxicology tool borrowed from addiction treatment programs with goals of limiting diversion and identifying risky secondary drug use. Guidelines recommend more frequent urine drug testing with any increased risk as determined by dose, risk assessment tool, or recent behavior. It is imperative that clinicians choose the tests appropriately and understand the limitations of toxicology testing when using this tool. Universal testing is recommended, given provider inability to judge misuse of medication and documented racial biases in monitoring.

**4. Dose limitations**—Risk of overdose increases approximately linearly with dose in observational studies. The CDC considers doses above the equivalent of 50 mg of morphine per day to be risky, and specifically recommends against prescribing more than 120 mg of morphine per day. To avoid withdrawal, clinicians must be cautious when tapering a patient's long-term dose. No data support one tapering regimen over another, but for patients taking opioids for years, the CDC recommends no more than a monthly decrease of 10% of the original daily dose.

**5. Special medication limitations**—Many guidelines recommend that the prescription of methadone and fentanyl be limited to pain management, addiction, or palliative care specialists. Because of the increasing incidence of opioid overdoses, recent professional guidelines recommend against concurrent prescription of opioids with benzodiazepines.

**6. Antidote to overdose**—Distributing naloxone, a quick-onset opioid-receptor antagonist, has long been known to reduce overdose deaths in people who use heroin. More recently, prescribing naloxone to patients taking opioids for chronic noncancer pain has been demonstrated to reduce rates of opioid overdose deaths. Educating both patients and their caregivers on the use of “rescue” naloxone is important, since those experiencing sedation and respiratory suppression from opioid overdose will not be able to self-administer the naloxone. In addition to pre-loaded needle-tipped syringes, intranasal and intramuscular autoinjector naloxone preparations are approved for sale in the United States, where an increasing number of states authorize pharmacies to dispense naloxone in the absence of a prescription. CDC guidelines recommend,

and some state laws require, prescribing naloxone for any patient with history of overdose, substance use disorder, concomitant benzodiazepine use, or daily doses above 50 mg morphine equivalent.

**7. Medication treatment of opioid use disorder**—Some patients who have been treated with long-term opioids will develop an opioid use disorder, and when this diagnosis is made, their opioid management should transition to appropriate treatment with methadone or buprenorphine maintenance. Both of these options have demonstrated a mortality benefit for patients with opioid addiction. Depending on jurisdiction, restrictions on how these—or other opioid agonist—treatments are delivered will apply.

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- Tucker HR et al. Harms and benefits of opioids for management of non-surgical acute and chronic low back pain: a systematic review. *Br J Sports Med*. 2020;54:664. [PMID: 30902816]
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## ► Medications for Neuropathic Pain

When taking a patient's history, listening for pain descriptions such as “burning,” “shooting,” “pins and needles,” or “electricity,” and for pain associated with numbness is essential because such a history suggests neuropathic pain. Studies are mixed with regard to efficacy of opioids for neuropathic pain. However, a number of nonopioid medications have also been found to be effective in randomized trials (Table 5–8). Successful management of neuropathic pain often requires the use of more than one effective medication. Since these medications bind to receptors on a large variety of neurons, they often have central nervous system side effects. These side effects often limit reaching therapeutic doses and may be the reason for higher numbers needed to treat (NNT 4–7) as compared to NSAIDs (NNT 2–4) (Table 5–9).

The calcium channel alpha2-delta ligands, gabapentin and pregabalin, are first-line therapies for neuropathic pain. Both medications have no significant medication interactions. However, they can cause sedation, dizziness, ataxia, and gastrointestinal side effects. Both gabapentin and pregabalin require dose adjustments in patients with kidney dysfunction. Gabapentin should be started at low dosages of 100–300 mg orally once daily and titrated upward by 300 mg/day every 4–7 days by adding additional doses throughout the day with a typical effective dose of 1800–3600 mg/day in three divided doses. Pregabalin

**Table 5–8.** Pharmacologic management of neuropathic pain.

| Medication <sup>1</sup>                                       | Starting Dose   | Typical Dose  |
|---|---|---|
| <b>Antidepressants<sup>2</sup></b>                            |   |   |
| Nortriptyline   | 10 mg orally at bedtime                                     | 10–150 mg orally at bedtime                                   |
| Amitriptyline   | 10 mg orally at bedtime                                     | 10–150 mg orally at bedtime                                   |
| Desipramine   | 12.5 mg orally at bedtime                                   | 12.5–250 mg orally at bedtime (can be divided into two doses) |
| <b>Calcium Channel Alpha2-Delta Ligands</b>                   |   |   |
| Gabapentin <sup>3</sup>                                       | 100–300 mg orally once to three times daily                 | 300–1200 mg orally three times daily                          |
| Pregabalin <sup>4</sup>                                       | 50 mg orally three times daily                              | 50–150 mg orally three times daily                            |
| <b>Selective Serotonin Norepinephrine Reuptake Inhibitors</b> |   |   |
| Duloxetine  | 30–60 mg orally daily or 20 mg orally twice daily in elders | 60–120 mg orally daily  |
| Venlafaxine <sup>5</sup>                                      | 75 mg orally daily divided into two or three doses          | 150–225 mg orally daily divided into two or three doses       |
| <b>Opioids</b>  | (see Table 5–6)   | (see Table 5–6)   |
| <b>Topical and Other Medications</b>                          |   |   |
| Lidocaine transdermal   | 4% or 5% patch applied daily, for a maximum of 12 hours     | 1–3 patches applied daily for a maximum of 12 hours           |
| Diclofenac transdermal  | 1.3% patch or 1% gel  | Patch applied twice daily or gel applied three times daily    |
| Tramadol hydrochloride <sup>6</sup>                           | 50 mg orally four times daily                               | 100 mg orally two to four times daily                         |

<sup>1</sup>Begin at the starting dose and titrate up every 4 or 5 days. Within each category, drugs listed in order of prescribing preference.

<sup>2</sup>Begin with a low dose. Use the lowest effective dose. Pain relief may be achieved at doses below antidepressant doses, thereby minimizing adverse side effects. Do not combine with serotonin or norepinephrine reuptake inhibitors.

<sup>3</sup>Common side effects include nausea, somnolence, and dizziness. Must adjust dose for kidney impairment.

<sup>4</sup>Common side effects include dizziness, somnolence, peripheral edema, and weight gain. Must adjust dose for kidney impairment.

<sup>5</sup>Caution: Can cause hypertension and ECG changes. Consider obtaining baseline ECG and monitor.

<sup>6</sup>Tramadol is classified by the DEA as a Schedule IV controlled substance.

**Table 5–9.** Medications used for treatment of peripheral neuropathic pain.

| Type of Medication        | Numbers Needed to Treat (NNT) for Peripheral Neuropathies Compared to NSAIDs |
|---------------------------|--|
| Tricyclic antidepressants | 2.1  |
| Opioids                   | 2.6  |
| Cannabinoids              | 3.4  |
| Pregabalin                | 4.5  |
| Tramadol                  | 4.9  |
| Duloxetine                | 5.1  |
| Capsaicin 0.04%           | 6.2  |
| Gabapentin                | 6.5  |
| SSRIs                     | 6.8  |

NSAIDs, nonsteroidal anti-inflammatory drugs; SSRIs, selective serotonin reuptake inhibitors.

Data from Moulin D et al; Canadian Pain Society. Pharmacological management of chronic neuropathic pain: revised consensus statement from the Canadian Pain Society. Pain Res Manag. 2014;19:328.

should be started at 40–150 mg/day in two or three divided doses. If necessary, the dose of pregabalin can be titrated upward to 300–600 mg/day in two or three divided doses. Both medications are relatively safe in accidental overdose and may be preferred over tricyclic antidepressants (TCAs) for a patient with a history of heart failure or arrhythmia or if there is a risk of suicide. Prescribing both gabapentin and an opioid for neuropathic pain may provide better analgesia at lower doses than if each is used as a single agent.

The serotonin norepinephrine reuptake inhibitors (SNRIs) duloxetine and venlafaxine are also first-line treatments for neuropathic pain. Patients should be advised to take duloxetine on a full stomach because nausea is a common side effect. Duloxetine may provide increased benefit for neuropathic pain up to a total daily dose of 120 mg, beyond the 60-mg limit used for depression. Duloxetine generally should not be combined with other serotonin or norepinephrine uptake inhibitors, but it can be combined with gabapentin or pregabalin. Lower doses of venlafaxine have more serotonin than norepinephrine activity; therefore, higher doses may be required to treat neuropathic pain. Because venlafaxine can cause hypertension and induce ECG changes, patients with cardiovascular risk

factors should be carefully monitored when starting this medication. Desvenlafaxine, the active metabolite of venlafaxine, is also available and may be tolerated better than venlafaxine.

TCAs are another class of medications for neuropathic pain that work through the norepinephrine and serotonin pathways. Among the TCAs that are effective for neuropathic pain, nortriptyline and desipramine are preferred over amitriptyline because they cause less orthostatic hypotension and have fewer anticholinergic effects. Start with a low dosage (10–25 mg orally daily) and titrate upward in 10-mg increments every 4 or 5 days aiming to use the lowest effective dose and to titrate up to a maximum of no greater than 100 mg daily. It may take several weeks for a TCA to have its full analgesic effect for neuropathic pain. Because TCAs and SNRIs both work through the serotonin and norepinephrine pathways, they generally should not be co-prescribed, particularly due to concerns for the serotonin syndrome.

Topical medications, such as lidocaine 5% patch and capsaicin 8% patches, are considered second-line therapies. The lidocaine 5% patch is particularly effective in postherpetic neuralgia and may be effective in other types of localized neuropathic pain. Due to its relatively minimal adverse effects, it is commonly used despite being considered second line. Topical lidocaine 4% patches and cream are available over the counter. Other medications effective for neuropathic pain include tramadol and tapentadol, both of which are opioids with norepinephrine activity. Medical cannabis strains high in cannabidiol have proven efficacy for some types of neuropathic pain.

Alles SRA et al. Etiology and pharmacology of neuropathic pain. *Pharmacol Rev.* 2018;70:315. [PMID: 29500312]

Szok D et al. Therapeutic approaches for peripheral and central neuropathic pain. *Behav Neurol.* 2019;2019:8685954. [PMID: 31871494]

has been used successfully for neuropathic and other pain syndromes refractory to opioids, although research data are limited.

Michelet D et al. Ketamine for chronic non-cancer pain: a meta-analysis and trial sequential analysis of randomized controlled trials. *Eur J Pain.* 2018;22:632. [PMID: 29178663]

## INTEGRATIVE THERAPIES & OTHER PAIN MANAGEMENT

Nonpharmacologic and noninterventional therapies are valuable in treating pain. In fact, physical or functional therapy and cognitive behavioral therapy have been shown to be the most effective for management of chronic pain. In particular, cognitive behavioral therapy has been proven effective in multiple randomized controlled studies as a primary evidence-based treatment for chronic pain. Hot or cold packs, massage, and physical therapy can be helpful for musculoskeletal pain. Similarly, integrative medicine therapies of acupuncture, chiropractic care, biofeedback, meditation, music therapy, guided imagery, cognitive distraction, and framing may be of help in treating pain. Because mood and psychological issues play an important role in the patient's perception of and response to pain, psychotherapy, support groups, prayer, and pastoral counseling can also help in pain management. Depression and anxiety, which may be instigated by chronic pain or may alter the response to pain, should be treated aggressively with antidepressants and anxiolytics.

Urits I et al. An update on cognitive therapy for the management of chronic pain: a comprehensive review. *Curr Pain Headache Rep.* 2019;23:57. [PMID: 31292747]

Zhao M et al. Acupressure therapy for acute ankle sprains: a randomized clinical trial. *PM R Phys Med Rehab.* 2018;10:36. [PMID: 28634002]

## SELECTED INTERVENTIONAL MODALITIES FOR PAIN RELIEF

Pain management specialists are physicians who have completed a residency in anesthesiology, physical medicine and rehabilitation, neurology, internal medicine, emergency medicine, or psychiatry and usually also a fellowship in pain management to learn medication management and interventional techniques for acute, chronic, and cancer pain. Interventional pain management modalities performed by pain management specialists involve neuro-modulation of specific targets to alleviate pain. The procedures they perform include percutaneous needle injection of local anesthetics and/or corticosteroids, radio-frequency (thermal) lesioning, cryotherapy, chemical neurolysis, or surgical implantation of intrathecal medication delivery pump systems or neurostimulation devices. While invasive procedures carry their own inherent risks such as bleeding or infection, they can drastically reduce or even obviate the need for conventional pharmacological therapies that may have side effects or be burdensome to the individual.

## ► Adjuvant Pain Medications & Treatments

If pain cannot be controlled without intolerable medication side effects, clinicians should consider using lower doses of multiple medications, which is done commonly for neuropathic pain, rather than larger doses of one or two medications.

For metastatic bone pain, the anti-inflammatory effect of NSAIDs can be helpful. Furthermore, bisphosphonates (such as pamidronate and zoledronic acid) and receptor activator of NF- $\kappa$ B ligand (RANKL) inhibitors (such as denosumab) may relieve such bone pain, although they are generally more useful for prevention of bone metastases than for analgesia.

Corticosteroids, such as dexamethasone, prednisone, and methylprednisolone, can be helpful for patients with headache due to increased intracranial pressure, pain from spinal cord compression, metastatic bone pain, and neuropathic pain due to invasion or infiltration of nerves by tumor. Because of the side effects of long-term corticosteroid administration, they are most appropriate for short-term use and in patients with end-stage disease. Low-dose intravenous, oral, buccal, and nasal ketamine

For some patients, a nerve block, such as a celiac plexus block for pain from pancreatic cancer, can provide substantial relief. Intrathecal pumps may be most useful for patients with severe pain responsive to opioids but who require such large doses that systemic side effects (eg, sedation, urinary retention, and constipation) become limiting. In the palliative care setting, these pumps are appropriate when life expectancy is long enough to justify the discomfort and cost of surgical implantation.

Clinicians do not need to know all the details of interventional pain procedures but should consider referring their patients to pain management specialists if such procedures may be beneficial. For example, a common question is whether prolonged opioid therapy with its inherent risks is better than an injection or an implanted device. Beyond knowing the benefits and risks, fiscal considerations may be key.

Tables 5–10 and 5–11 list the procedures and the agents typically used in interventional pain modalities.

## INTRATHECAL DRUG DELIVERY SYSTEM

### A. Indications

Intrathecal drug delivery therapy is indicated for patients with both malignant and nonmalignant pain and has been shown to be effective, cost-effective, and safe. It is generally accepted that intrathecal opioids have a 100- to 300-fold

**Table 5–11.** Agents used<sup>1</sup> in neuromodulatory therapies.

|  |
|--|
| <b>Voltage-gated sodium channel blockade—local anesthetics</b> |
| Lidocaine  |
| Mepivacaine  |
| Bupivacaine  |
| Ropivacaine  |
| <b>Corticosteroids</b>   |
| Triamcinolone  |
| Methylprednisolone   |
| Dexamethasone  |
| <b>Opioids</b>   |
| Morphine   |
| Hydromorphone  |
| Fentanyl   |
| <b>Adjuvants</b>   |
| Clonidine  |
| Dexmedetomidine  |
| Others   |
| <b>Chemical neurolysis</b>                                     |
| Alcohol  |
| Phenol   |
| Glycerol   |
| <b>Thermal neurolysis</b>                                      |
| Radiofrequency ablation  |
| Cryoanalgesia  |
| <b>Neurostimulation</b>  |
| Various patterns, frequency, amplitude, pulse width            |

<sup>1</sup>Injected or applied.

List is not comprehensive but includes most commonly used agents.

**Table 5–10.** Interventional techniques for chronic pain by anatomic location.

|   |
|---|
| <b>Neuraxial</b>  |
| Intrathecal   |
| Epidural (caudal, lumbar, thoracic, cervical; interlaminar vs transforaminal) |
| <b>Paraneuraxial (planar blockade)</b>  |
| Paravertebral (intercostal)   |
| Transversus abdominis plane/quadratus lumborum                                |
| Pectoralis and serratus anterior  |
| <b>Peripheral nerve (perineural blockade)</b>                                 |
| Brachial plexus and branches  |
| Lumbar plexus and branches  |
| <b>Joints</b>   |
| Intra-articular injections  |
| Joint denervation procedures  |
| <b>Sympathetic ganglion</b>   |
| Gasserian ganglion  |
| Sphenopalatine ganglion   |
| Cervical sympathetic blockade (stellate ganglion)                             |
| Lumbar sympathetic blockade   |
| Celiac plexus   |
| Superior hypogastric plexus   |
| Ganglion impar  |
| <b>Continuous neuraxial drug delivery</b>                                     |
| Epidural (tunneled catheter, port)  |
| Intrathecal (implanted intrathecal pump)                                      |
| <b>Neurostimulation</b>   |
| Dorsal column stimulation (spinal cord stimulation)                           |
| Dorsal root ganglion stimulation  |
| Peripheral nerve or field stimulation   |

efficacy compared with oral opioids; therefore, the best candidates may be patients with good analgesic benefit from opioids but burdensome side effects. Common indications include cancer pain, chronic low-back pain (in particular, post-laminectomy syndrome), complex regional pain syndrome, and other causes of neuropathic pain. In a randomized controlled trial comparing intrathecal therapy with comprehensive medication management in cancer pain, intrathecal therapy was shown to be superior in both analgesia as well as to have fewer side effects. Due to the cost of implanting the device as well as the recovery time needed from surgical implantation, it is recommended that patients have a life expectancy of at least 2–3 months.

### B. Procedure

Intrathecal drug delivery systems consist of a pump with a drug reservoir, typically implanted in the abdominal wall, connected to a catheter that delivers medications into the intrathecal space. Initial percutaneous trialing is indicated for patients with noncancer or cancer pain; such percutaneous trialing may consist of either epidural or intrathecal delivery of bolus or continuous medication to determine efficacy and side effect profiles of planned therapeutic agent(s). Some cancer patients may not undergo a trial to avoid delaying final implantation. Subsequent implantation

of an intrathecal drug delivery system involves two incisions: one in the spine to accommodate the catheter and anchor, and another in the lower abdominal region to create a pocket to hold the pump. The catheter is tunneled through the lower abdominal and flank subcutaneous tissues to connect to the pump. Both trial and implantation are typically performed under sedation with local anesthetic infiltration; spinal anesthesia delivered from the pump itself can also be utilized for pump implantation. Some patients may require general anesthesia to tolerate the implantation procedure.

### C. Medications Used

According to the Polyanalgesic Conference Consensus (PACC) guidelines for both malignant and nonmalignant pain, first-line intrathecal delivery medications include monotherapy with either morphine or ziconotide, a calcium channel inhibitor. However, the PACC guidelines also state that de facto practice includes combination therapy with opioids (eg, fentanyl, hydromorphone) and local anesthetic (eg, bupivacaine) and may include other medications (eg, baclofen or clonidine). Respiratory depression and sedation are two of the most concerning side effects of many intrathecal medications. Ziconotide may cause myositis and polyarthralgias as well as psychiatric and neurologic adverse effects (it is contraindicated in patients with preexisting psychosis). Side effects of morphine and fentanyl include nausea, edema, constipation, urinary retention, and pruritus.

### D. Advantages and Disadvantages

The main advantage of intrathecal delivery therapy is targeted delivery of medication to the spinal cord with increased efficacy and diminished side effects compared with systemic analgesic medications. Intrathecal therapy has been found to be effective with decreased side effects and improved analgesia in 80% of cancer patients. The increased efficacy is due to the 100- to 300-fold increased concentration of intrathecal drug compared with systemic medication. However, intrathecal therapy requires regular pump refills and may be complicated by infections, catheter or pump malfunctions requiring surgical revision, or development of catheter tip granulomas, potentially leading to inadequate analgesia or neurologic deficits. Pump batteries may last from 5 years to 10 years depending on usage. Fatalities surrounding intrathecal therapy have been linked to respiratory depression; patients must be monitored for respiratory depression or sedation when initiating or increasing intrathecal therapeutic agents. Some intrathecal pumps need to be emptied prior to MRI; due to the magnetic forces of the MRI, the entirety of the drug reservoir could inadvertently open. Therefore, it is critical that the type of pump is known prior to placing the patient and pump in an MRI machine. Additionally, anticoagulants and NSAIDs need to be stopped prior to pump implantation and need to be held briefly after the implantation as well; this temporary cessation imposes the risk of potentially causing blood clots.

### E. Alternatives

For patients with limited life expectancy, continuous epidural drug delivery via an external pump or subcutaneous port may be more appropriate. Systemic medication delivered orally, intravenously, topically, or even by a subcutaneous infusion (as in palliative care settings) are alternatives to intrathecal therapy.

- Abd-Elsayed A et al. Intrathecal drug delivery for chronic pain syndromes: a review of considerations in practice management. *Pain Physician*. 2020;23:E591. [PMID: 33185379]
- Sindt JE et al. Initiation of intrathecal drug delivery dramatically reduces systemic opioid use in patients with advanced cancer. *Neuromodulation*. 2020;23:978. [PMID: 32459393]
- Sindt JE et al. The rate of infectious complications after intrathecal drug delivery system implant for cancer-related pain is low despite frequent concurrent anticancer treatment or leukopenia. *Anesth Analg*. 2020;131:280. [PMID: 31990731]
- Sommer B et al. Long-term outcome and adverse events of intrathecal opioid therapy for nonmalignant pain syndrome. *Pain Pract*. 2020;20:8. [PMID: 31291509]
- Spiegel MA et al. Evaluation of an intrathecal drug delivery protocol leads to rapid reduction of systemic opioids in the oncological population. *J Palliat Med*. 2021;24:418. [PMID: 32640912]

## SPINAL STIMULATION

### A. Indications

Spinal stimulation targets neuropathic pain in the trunk and limbs, such as failed back surgery syndrome, complex regional pain syndrome, and radiculopathy. There is also growing literature around its use for neuropathic pain associated with cancer.

### B. Procedure

Neurostimulation devices consist of an implantable pulse generator typically placed in the flank or abdomen just under the skin and an array of electrical contacts on small cylindrical or paddle leads placed in the epidural space. **Neurostimulation** devices transmit electrical pulses to the spinal cord or dorsal root ganglion to block pain transmission. Paddle leads require neurosurgical implantation with laminotomy (and general anesthesia), while percutaneous wire leads may be implanted under sedation. Patients undergo a 3- to 7-day trial during which the leads are attached to an external battery source and undergo programming with different pulse waveforms to assess therapeutic efficacy prior to surgical implantation of permanent leads and implantable pulse generator.

### C. Frequencies Used

Traditional neurostimulation resulted in paresthesias that were used to mask pain. It was presumed that these paresthesias were the result of stimulation of the dorsal column axons. Recent studies have revealed that analgesia can be obtained independent of paresthesias by altering a variety of spinal cord stimulation parameters, including constant high-frequency stimulation and burst high-frequency stimulation. More recent double-blind, randomized, controlled

trials have revealed that both functional status and pain scores could be significantly improved in spinal cord stimulation systems that were capable of adapting the output to the patient's individual neural response in a closed loop fashion. For more focal neuropathic pain conditions such as postoperative inguinal nerve injuries or thoracic post herpetic neuralgias, stimulation of the dorsal root ganglion is able to provide focal analgesia. These newer, more versatile systems deliver paresthesia-free analgesia with analgesic response rates that have steadily increased from about 50% with the traditional devices to about 80%. The newer devices also have greater longevity and most are MRI compatible.

### D. Advantages and Disadvantages

Spinal cord stimulation is a reversible technology that may provide superior analgesic efficacy while eliminating the need for systemic medications. Current literature suggests spinal cord stimulation is efficacious in 80–90% of well-selected patients, such as those with neuropathic low-back pain due to post-laminectomy syndrome. In fact, spinal cord stimulation has now advanced to a higher position in the treatment continuum; it can be considered before using long-term moderate doses of systemic opioids. On the other hand, because it is a surgical procedure, it may be associated with complications, such as infection, lead migration, device malfunction, or neurologic deficits. While MRIs were contraindicated with some older systems, most newer systems allow for limited MRI imaging. Batteries may require daily charging but typically do not require replacement for 5–10 years. Similar to intrathecal pumps, anticoagulants and NSAIDs need to be stopped prior to implantation of spinal cord stimulation devices because of the potential risks (eg, bleeding). The implanting surgeon, prescribing physician, and patient need to discuss the benefits and risks before proceeding.

### E. Alternatives

In addition to medication management for pain, two neuromodulatory techniques may serve as alternatives to dorsal horn and dorsal root ganglion stimulation. Peripheral nerve stimulation is an emerging technology; it targets peripheral nerves using a similar system of a lead connected to a pulse generator. It may be most appropriate when there is a very specific neurologic target. Transcutaneous electrical nerve stimulators (TENS) and systemic pharmacologic therapies are alternatives.

Deer TR et al. A systematic literature review of spine neurostimulation therapies for the treatment of pain. *Pain Med*. 2020;21:1421. [PMID: 32034422]

Hofmeister M et al. Effectiveness of neurostimulation technologies for the management of chronic pain: a systematic review. *Neuromodulation*. 2020;23:150. [PMID: 31310417]

Lefaucheur JP et al. Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS): an update (2014–2018). *Clin Neurophysiol*. 2020;131:474. [PMID: 31901449]

Leung et al. Left dorsolateral prefrontal cortex rTMS in alleviating MTBI related headaches and depressive symptoms. *Neuromodulation*. 2018;21:390. [PMID: 28557049]

Mekhail N et al. Long-term safety and efficacy of closed-loop spinal cord stimulation to treat chronic back and leg pain (Evoke): a double-blind, randomised, controlled trial. *Lancet Neurol*. 2020;19:123. [PMID: 31870766]

Mekhail N et al. Choice of spinal cord stimulation versus targeted drug delivery in the management of chronic pain: a predictive formula for outcomes. *Reg Anesth Pain Med*. 2020. [Epub ahead of print] [PMID: 31932490]

Moisset X et al. Neurostimulation methods in the treatment of chronic pain. *J Neural Transm (Vienna)*. 2020;127:673. [PMID: 31637517]

## CELIAK PLEXUS BLOCK & NEUROLYSIS

### A. Indications

A celiac plexus block refers to injection of a long-acting anesthetic (eg, bupivacaine) with or without a corticosteroid (eg, methylprednisolone); with steroids, the block can provide relief for a few weeks to months. Celiac plexus neurolysis involves injection of a neurolytic agent (eg, alcohol or phenol); it may provide pain relief more consistently for 2–6 months. The most common indication is pancreatic cancer pain, but it can be used for pain from other malignancies (eg, stomach, liver, spleen, kidney, and gastrointestinal tract) or from chronic pancreatitis. Multiple randomized controlled trials and meta-analyses have shown superiority of celiac plexus neurolysis to medication management for pancreatic cancer, but evidence of its efficacy for chronic pancreatitis is more mixed.

### B. Procedure

The most common approach is a percutaneous posterior approach under fluoroscopy guidance, with bilateral needles targeted to the celiac plexus at the level of T12–L1. Alternatively, ultrasound, CT, or endoscopic guidance can be used. Minimal sedation is required for the percutaneous approaches, while heavy sedation or general anesthesia may be required for endoscopic guidance.

### C. Medications Used

Chemical neurolysis with alcohol or phenol is used to extend the duration of the analgesia to 2 or more months compared to a block with local anesthetic (eg, bupivacaine) and corticosteroid (eg, methylprednisolone), which produces an analgesic duration of weeks to months. For chemical neurolysis, alcohol is used most often because it does not require compounding, and importantly has a lower chance of permanent neurologic damage compared with phenol; however, it is more painful on injection.

### D. Advantages and Disadvantages

The primary advantage is improved analgesia without need for systemic medications and their untoward effects. Neurolytic celiac plexus blockade is effective in 70–80% of patients. Common side effects of celiac plexus interventions include transient hypotension and transient diarrhea. Transient or permanent spinal cord damage is rare, although there is an increased risk of its occurrence with plexus (chemical) neurolysis compared with plexus (anesthetic) block.

## E. Alternatives

Standard pain management is with oral or transdermal systemic analgesic (eg, opioid) medication. Intrathecal therapy is also an alternative, especially for cancer pain.

Ashlock K. Celiac plexus block: management of abdominal pain in patients with late-stage cancer. *Clin J Oncol Nurs.* 2018;22:663. [PMID: 30451994]

Careskey H et al. Interventional anesthetic methods for pain in hematology/oncology patients. *Hematol Oncol Clin North Am.* 2018;32:433. [PMID: 29729779]

Filippiadis DK et al. Percutaneous neurolysis for pain management in oncological patients. *Cardiovasc Intervent Radiol.* 2019;42:791. [PMID: 30783779]

Lau J et al. Interventional anesthesia and palliative care collaboration to manage cancer pain: a narrative review. *Can J Anaesth.* 2020;67:235. [PMID: 31571119]

Sachdev AH et al. Celiac plexus block and neurolysis: a review. *Gastrointest Endosc Clin N Am.* 2018;28:579. [PMID: 30241645]

improvement of radiculopathy in both the lumbar and cervical regions. In a Cochrane analysis, side effects were noted in 10–24% of surgical cases but no side effects were reported for any conservative treatments. Disadvantages include possible postdural puncture headache, transient weakness, and, rarely, permanent neurologic deficits. Patients who are receiving systemic anticoagulation may need to hold their anticoagulants before receiving corticosteroid injections, which could increase their risk of cardiovascular events; these cases should be discussed with the clinician managing the anticoagulation prior to performing any epidural corticosteroid injections.

## E. Alternatives

Alternatives include conservative therapy, such as oral analgesic medication management, physical therapy, pain psychology, acupuncture, and surgery.

House LM et al. Cervical epidural steroid injection: techniques and evidence. *Phys Med Rehabil Clin N Am.* 2018;29:1. [PMID: 29173656]

Rivera CE. Lumbar epidural steroid injections. *Phys Med Rehabil Clin N Am.* 2018;29:73. [PMID: 29173666]

Yang S et al. Epidural steroid injection versus conservative treatment for patients with lumbosacral radicular pain. *Medicine (Baltimore).* 2020;99:e21283. [PMID: 32791709]

Zaina F et al. Surgical versus non-surgical treatment for lumbar spinal stenosis. *Cochrane Database Syst Rev.* 2016;2016:CD010264. [PMID: 26824399]

## EPIDURAL CORTICOSTEROID INJECTION

### A. Indications

Epidural corticosteroid injections are indicated for patients with chronic neck pain, low-back pain, and radicular pain resulting from central or neuroforaminal stenosis in the cervical, thoracic, or lumbosacral region. Both central and neuroforaminal stenosis may be caused by degenerative disk disease, disk herniation, or facet arthropathy. Epidural corticosteroid injections are relatively safe and are appropriate after conservative measures, such as physical therapy and analgesic medications, have been tried and found unsuccessful.

### B. Procedure

Fluoroscopy is typically used to assist with visualizing the bony landmarks; either an interlaminar or a transforaminal approach can be used. Interlaminar access is obtained by placing a needle between the lamina of adjacent vertebral levels, whereas transforaminal access is obtained by inserting a needle through the neuroforamen to access the epidural space. These needle insertion procedures can be performed with topical local anesthetic or with minimal sedation.

### C. Medications Used

Typically, a particulate corticosteroid such as methylprednisolone is used alone or in combination with a local anesthetic. For the transforaminal approach, where vascular access is more of a concern, a nonparticulate corticosteroid such as dexamethasone may be preferred.

### D. Advantages and Disadvantages

Epidural corticosteroid injections are advantageous for patients who have not responded to conservative therapy, are not surgical candidates, or do not wish to be surgical candidates. The best evidence of the effectiveness of epidural corticosteroid injections is the short-term

### When to Refer

Patients should be referred to pain management specialists if they have:

- Pain that does not respond to opioids at typical doses or causes major adverse effects at typical doses.
- Pain that cannot be controlled expeditiously or safely by other clinicians.
- Neuropathic pain that does not respond to first-line treatments.
- Complex medication management that uses buprenorphine or methadone.
- Severe pain from malignancy, including primary disease (eg, pancreatic cancer) or metastatic disease (eg, bony metastases).

### When to Admit

- Severe exacerbation of pain not responsive to previous stable oral opioids given around-the-clock plus breakthrough doses.
- Pain that is so severe that it cannot be controlled at home.
- Uncontrollable side effects from opioids, including nausea, vomiting, myoclonus, and altered mental status.
- Need for a surgical procedure, such as implantation of an intrathecal drug delivery pump or neurostimulation device.

# Dermatologic Disorders

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## INTRODUCTION

Dermatologic diseases are diagnosed by the types of lesions they cause. To make a diagnosis: (1) identify the type of lesion(s) the patient exhibits by morphology establishing a differential diagnosis (Table 6–1); and (2) obtain the elements of the history, physical examination, and appropriate laboratory tests to confirm the diagnosis. Specific clinical situations, such as an immunocompromised or critically ill patient, lead to different diagnostic considerations.

## PRINCIPLES OF DERMATOLOGIC THERAPY

### ► Frequently Used Treatment Measures

#### A. Bathing

Soap should be used only in the axillae and groin and on the feet by persons with dry or inflamed skin. Soaking in water for 10–15 minutes before applying topical corticosteroids or emollient enhances their efficacy (Soak and Smear).

#### B. Topical Therapy

Nondermatologists should become familiar with a representative agent in each category for each indication (eg, topical corticosteroid, topical retinoid, etc).

**1. Corticosteroids**—Topical corticosteroid creams, lotions, ointments, gels, foams, and sprays are presented in Table 6–2. Topical corticosteroids are divided into classes based on potency. Agents within the same class are equivalent therapies; however, prices of topical corticosteroids vary dramatically. For a given agent, higher lipophilicity (greasiness) corresponds with increased potency; ie, triamcinolone 0.1% ointment is more potent than triamcinolone 0.1% cream which in turn is more potent than triamcinolone 0.1% lotion. The potency of a topical corticosteroid may be dramatically increased by occlusion (covering with a water-impermeable barrier) for at least 4 hours. Depending on the location of the skin condition, gloves, plastic wrap, moist pajamas covered by dry pajamas (wet wraps), or plastic occlusive suits for patients can be used. Caution should be used in applying topical corticosteroids to areas of thin skin (face, genitals, skin folds). Topical corticosteroid use on the

eyelids may result in glaucoma or cataracts. One may estimate the amount of topical corticosteroid needed by using the “rule of nines” (as in burn evaluation; see Figure 37–2). Approximately 20–30 g is needed to cover the entire body surface of an adult. Systemic absorption does occur with topical corticosteroids, but complications of systemic corticosteroids are rare.

**2. Emollients for dry skin (“moisturizers”)**—Dry skin is a result of abnormal function of the epidermis. Emollients restore the epidermis by promoting keratinocyte differentiation and by producing innate antimicrobials; some restore skin barrier lipids, including ceramides. Ointments and creams, rather than lotion, are the best moisturizers. **Emollients are most effective when applied to wet skin.** If the skin is too greasy after application, pat dry with a damp towel. Plain petrolatum is allergen-free and can be used if allergic contact dermatitis to topical products is suspected.

The scaly appearance of dry skin may be improved by emollients with concomitant use of keratolytics including urea, lactic acid, or glycolic acid-containing products provided no inflammation (erythema or pruritus) is present.

**3. Drying agents for weepy dermatoses**—If the skin is weepy from infection or inflammation, drying agents may be beneficial. The best drying agent is water, applied as repeated compresses for 15–30 minutes, alone or with aluminum salts (Burrow solution, Domeboro tablets).

**4. Topical antipruritics**—Lotions that contain 0.5% each of camphor and menthol (Sarna) or pramoxine hydrochloride 1% (with or without 0.5% menthol, eg, Prax, PrameGel, Aveeno Anti-Itch lotion) are effective antipruritic agents. Hydrocortisone, 1% or 2.5%, may be incorporated for its anti-inflammatory effect (Pramosone cream, lotion, or ointment). Doxepin cream 5% reduces pruritus but may cause drowsiness. Pramoxine and doxepin are most effective when applied with topical corticosteroids. Topical capsaicin and lidocaine can be effective in some forms of neuropathic itch.

#### C. Systemic Antipruritic Drugs

**1. Antihistamines and antidepressants**—H<sub>1</sub>-blockers are the agents of choice for pruritus due to histamine, such as urticaria. Otherwise, they appear to benefit itchy patients

**Table 6–1.** Morphologic categorization of skin lesions and diseases.

|                              |   |
|------------------------------|---|
| Pigmented                    | Freckle, lentigo, seborrheic keratosis, nevus, blue nevus, halo nevus, atypical nevus, melanoma   |
| Scaly                        | Psoriasis, dermatitis (atopic, stasis, seborrheic, chronic allergic contact or irritant contact), xerosis (dry skin), lichen simplex chronicus, tinea pedis/cruris/corporis, tinea versicolor, secondary syphilis, pityriasis rosea, discoid lupus erythematosus, exfoliative dermatitis, actinic keratoses, Bowen disease, Paget disease, drug eruption                                    |
| Vesicular                    | Herpes simplex, varicella, herpes zoster, pompholyx (vesicular dermatitis of palms and soles), vesicular tinea, autoeczematization, dermatitis herpetiformis, miliaria crystallina, scabies, photosensitivity, acute contact allergic dermatitis, drug eruption   |
| Weepy or encrusted           | Impetigo, acute contact allergic dermatitis, any vesicular dermatitis   |
| Pustular                     | Acne vulgaris, acne rosacea, folliculitis, candidiasis, miliaria pustulosa, pustular psoriasis, any vesicular dermatitis, drug eruption   |
| Figurate ("shaped") erythema | Urticaria, erythema multiforme, erythema migrans, cellulitis, erysipelas, erysipeloid, arthropod bites  |
| Bullous                      | Impetigo, blistering dactylitis, pemphigus, pemphigoid, porphyria cutanea tarda, drug eruptions, erythema multiforme, toxic epidermal necrolysis  |
| Papular                      | <b>Hyperkeratotic:</b> warts, corns, seborrheic keratoses<br><b>Purple-violet:</b> lichen planus, drug eruptions, Kaposi sarcoma, lymphoma cutis, Sweet syndrome<br><b>Flesh-colored, umbilicated:</b> molluscum contagiosum<br><b>Pearly:</b> basal cell carcinoma, intradermal nevi<br><b>Small, red, inflammatory:</b> acne, rosacea, miliaria rubra, candidiasis, scabies, folliculitis |
| Pruritus <sup>1</sup>        | Xerosis, scabies, pediculosis, lichen planus, lichen simplex chronicus, bites, systemic causes, anogenital pruritus   |
| Nodular, cystic              | Erythema nodosum, furuncle, cystic acne, follicular (epidermal) inclusion cyst, metastatic tumor to skin  |
| Photodermatitis              | Drug eruption, polymorphic light eruption, lupus erythematosus  |
| Morbilliform                 | Drug eruption, viral infection, secondary syphilis  |
| Erosive                      | Any vesicular dermatitis, impetigo, aphthae, lichen planus, erythema multiforme, intertrigo   |
| Ulcerated                    | Decubiti, herpes simplex, skin cancers, parasitic infections, syphilis (chancre), chancroid, vasculitis, stasis, arterial disease, pyoderma gangrenosum   |

<sup>1</sup>Not a morphologic class but included because it is one of the most common dermatologic presentations.

**Table 6–2.** Useful topical dermatologic therapeutic agents.<sup>1</sup>

| Agent  | Formulations, Strengths, and Prices <sup>2</sup>  | Frequency of Application | Potency Class | Common Indications   | Comments  |
|--|---|--------------------------|---------------|--|---|
| <b>Corticosteroids (Listed in Order of Increasing Potency)</b> |   |                          |               |  |   |
| Hydrocortisone acetate   | Cream 1%: \$5.59/28.4 g<br>Ointment 1%: \$3.91/40 g<br>Solution 1%: \$7.34/44 mL          | Twice daily              | Low           | Seborrheic dermatitis<br>Pruritus ani<br>Intertrigo                                    | Not the same as valerate or hydrocortisone butyrate<br>Not for poison oak OTC lotion (Aquanil HC), OTC solution (Scalpicin) |
|  | Cream 2.5%: \$11.01/30 g  |                          |               | As for 1% hydrocortisone   | Perhaps better for pruritus ani<br>Not clearly better than 1%<br>More expensive<br>Not OTC                                  |
| Alclometasone dipropionate (Aclovate)                          | Cream 0.05%: \$48.08/15 g<br>Ointment 0.05%: \$20.00/15 g                                 | Twice daily              | Low           | As for hydrocortisone  | More efficacious than hydrocortisone<br>Perhaps causes less atrophy   |
| Desonide   | Cream 0.05%: \$21.60/15 g<br>Ointment 0.05%: \$23.25/15 g<br>Lotion 0.05%: \$222.92/60 mL | Twice daily              | Low           | As for hydrocortisone<br>For lesions on face or body folds resistant to hydrocortisone | More efficacious than hydrocortisone<br>Can cause rosacea or atrophy<br>Not fluorinated                                     |

(continued)

**Table 6–2.** Useful topical dermatologic therapeutic agents.<sup>1</sup> (continued)

| Agent                                  | Formulations, Strengths, and Prices <sup>2</sup>  | Frequency of Application   | Potency Class    | Common Indications  | Comments   |
|--|---|----------------------------|------------------|---|--|
| Clocortolone (Cloderm)                 | Cream 0.1%: \$322.47/45 g   | Three times daily          | Medium           | Contact dermatitis<br>Atopic dermatitis   | Does not cross-react with other corticosteroids chemically and can be used in patients allergic to other corticosteroids   |
| Prednicarbate (Dermatop)               | Emollient cream 0.1%: \$137.10/60 g<br>Ointment 0.1%: \$30.00/15 g  | Twice daily                | Medium           | As for triamcinolone  | May cause less atrophy<br>No generic formulations<br>Preservative-free   |
| Triamcinolone acetonide                | Cream 0.1%: \$3.89/15 g<br>Ointment 0.1%: \$5.57/15 g<br>Lotion 0.1%: \$42.42/60 mL                                   | Twice daily                | Medium           | Eczema on extensor areas<br>Used for psoriasis with tar<br>Seborrheic dermatitis and psoriasis on scalp | Caution in body folds, face<br>Economical in 0.5-lb and 1-lb sizes for treatment of large body surfaces<br>Economical as solution for scalp  |
|  | Cream 0.025%: \$15 g<br>Ointment 0.025%: \$10.40/80 g   | Twice daily                | Medium           | As for 0.1% strength  | Possibly less efficacy and few advantages over 0.1% formulation  |
| Fluocinolone acetonide                 | Cream 0.025%: \$33.77/15 g<br>Ointment 0.025%: \$33.77/15 g<br>Solution 0.01%: \$180.00/60 mL                         | Twice daily<br>Twice daily | Medium<br>Medium | As for triamcinolone<br>As for triamcinolone  |  |
| Mometasone furoate (Elocon)            | Cream 0.1%: \$26.85/15 g<br>Ointment 0.1%: \$23.85/15 g<br>Lotion 0.1%: \$55.45/60 mL                                 | Once daily                 | Medium           | As for triamcinolone  | Often used inappropriately on the face or on children<br>Not fluorinated   |
| Desoximetasone                         | Cream 0.05%: \$62.43/15 g<br>Cream 0.25%: \$49.80/15 g<br>Gel 0.05%: \$298.38/60 g<br>Ointment 0.25%: \$18.00/15 g    | Twice daily                | High             | As for triamcinolone  | Comparable potency to fluocinonide<br>Suggested for use when allergic contact dermatitis to topical corticosteroid is suspected; ointment useful when allergic contact dermatitis to propylene glycol is suspected |
| Diflorasone diacetate                  | Cream 0.05%: \$209.68/15 g<br>Ointment 0.05%: \$209.68/15 g   | Twice daily                | High             | Nummular dermatitis<br>Allergic contact dermatitis<br>Lichen simplex chronicus                          |  |
| Fluocinonide (Lidex)                   | Cream 0.05%: \$45.55/15 g<br>Gel 0.05%: \$59.56/15 g<br>Ointment 0.05%: \$28.50/15 g<br>Solution 0.05%: \$97.19/60 mL | Twice daily                | High             | As for betamethasone<br>Gel useful for poison oak   | Economical generics<br>Lidex cream can cause stinging on eczema<br>Lidex emollient cream preferred   |
| Betamethasone dipropionate (Diprolene) | Cream 0.05%: \$41.60/15 g<br>Ointment 0.05%: \$50.45/15 g<br>Lotion 0.05%: \$45.00/60 mL                              | Twice daily                | Ultra-high       | For lesions resistant to high-potency corticosteroids<br>Lichen planus<br>Insect bites                  | Economical generics available  |

(continued)

**Table 6–2.** Useful topical dermatologic therapeutic agents.<sup>1</sup> (continued)

| Agent  | Formulations, Strengths, and Prices <sup>2</sup>   | Frequency of Application | Potency Class | Common Indications                                  | Comments  |
|--|--|--------------------------|---------------|---|---|
| Clobetasol propionate (Temovate)                                     | Cream 0.05%: \$114.75/15 g<br>Ointment 0.05%: \$155.45/15 g<br>Lotion 0.05%: \$289.28/60 mL                | Twice daily              | Ultra-high    | As for betamethasone dipropionate                   | Somewhat more potent than diflorasone<br>Limited to 2 continuous weeks of use<br>Limited to 50 g or less per week<br>Cream may cause stinging; use “emollient cream” formulation<br>Generic available |
| Halobetasol propionate (Ultravate)                                   | Cream 0.05%: \$45.84/15 g<br>Ointment 0.05%: \$15 g  | Twice daily              | Ultra-high    | As for clobetasol                                   | Same restrictions as clobetasol<br>Cream does not cause stinging<br>Compatible with calcipotriene (Dovonex)   |
| Flurandrenolide (Cordran)  | Tape: \$857.28/24" × 3" roll<br>Lotion 0.05%: \$360.00/120 mL  | Every 12 hours           | Ultra-high    | Lichen simplex chronicus                            | Tape version protects the skin and prevents scratching  |
| <b>Nonsteroidal Anti-inflammatory Agents (Listed Alphabetically)</b> |  |                          |               |   |   |
| Crisaborole (Eucrisa)  | Ointment 2%: \$806.17/60 g   | Twice daily              | N/A           | Atopic dermatitis                                   | Steroid substitute not causing atrophy or striae<br>May sting or burn on initial application  |
| Pimecrolimus <sup>3</sup> (Elidel)                                   | Cream 1%: \$608.71/60 g  | Twice daily              | N/A           | Atopic dermatitis                                   | Steroid substitute not causing atrophy or striae  |
| Tacrolimus <sup>3</sup> (Protopic)                                   | Ointment 0.1%: \$325.20/60 g<br>Ointment 0.03%: \$325.20/60 g  | Twice daily              | N/A           | Atopic dermatitis                                   | Steroid substitute not causing atrophy or striae<br>Burns in ≥ 40% of patients with eczema  |
| <b>Antibiotics (for Acne) (Listed Alphabetically)</b>                |  |                          |               |   |   |
| Clindamycin phosphate  | Solution 1%: \$28.94/30 mL<br>Gel 1%: \$54.00/30 mL<br>Lotion 1%: \$115.38/60 mL<br>Pledget 1%: \$50.58/60 | Twice daily              | N/A           | Mild papular acne                                   | Lotion is less drying than solution, gel, or pledgets for patients with sensitive skin<br>Recommend use with benzoyl peroxide to avoid antibiotic resistance from monotherapy                         |
| Clindamycin/Benzoyl peroxide (BenzaClin)                             | Gel: \$90.00/25 g<br>Gel: \$156.00/50 g  | Twice daily              | N/A           | As for clindamycin                                  | No generic<br>More effective than either agent alone  |
| Dapsone  | Gel 5%: \$585.60/60 g  | Once daily               | N/A           | Mild papulopustular acne                            | More expensive, well tolerated<br>Recommend use with benzoyl peroxide to avoid antibiotic resistance from monotherapy   |
| Erythromycin   | Solution 2%: \$47.63/60 mL<br>Gel 2%: \$60.48/30 g<br>Pledget 2%: \$92.65/60                               | Twice daily              | N/A           | As for clindamycin                                  | Many different manufacturers<br>Economical<br>Recommend use with benzoyl peroxide to avoid antibiotic resistance from monotherapy   |
| Erythromycin/Benzoyl peroxide (Benzamycin)                           | Gel: \$199.08/23.3 g<br>Gel: \$75.00/46.6 g  | Twice daily              | N/A           | As for clindamycin<br>Can help treat comedonal acne | No generic<br>More expensive<br>More effective than other topical antibiotics<br>Main jar requires refrigeration  |

(continued)

**Table 6–2.** Useful topical dermatologic therapeutic agents.<sup>1</sup> (continued)

| Agent  | Formulations, Strengths, and Prices <sup>2</sup>                                       | Frequency of Application | Potency Class | Common Indications                            | Comments   |
|--|--|--------------------------|---------------|---|--|
| <b>Antibiotics (for Impetigo)</b>                      |  |                          |               |   |  |
| Mupirocin (Bactroban)                                  | Ointment 2%: \$25.00/22 g<br>Cream 2%: \$245.16/15 g                                   | Three times daily        | N/A           | Impetigo, folliculitis                        | Because of cost, use limited to tiny areas of impetigo<br>Used in the nose twice daily for 5 days to reduce staphylococcal carriage  |
| Retapamulin (Altabax)                                  | Ointment 1%: \$389.38/15 g   | Twice daily              | N/A           | Impetigo                                      | For <i>Staphylococcus aureus</i> or <i>Streptococcus pyogenes</i> infection<br>Typically reserved for mupirocin-resistant infections |
| <b>Antifungals: Imidazoles (Listed Alphabetically)</b> |  |                          |               |   |  |
| Clotrimazole   | Cream 1%: \$5.70/15 g OTC<br>Solution 1%: \$45.10/10 mL                                | Twice daily              | N/A           | Dermatophyte and <i>Candida</i> infections    | Available OTC<br>Inexpensive generic cream available   |
| Econazole (Spectazole)                                 | Cream 1%: \$30.04/15 g   | Once daily               | N/A           | As for clotrimazole                           | Somewhat more effective than clotrimazole and miconazole   |
| Ketoconazole (Nizoral)                                 | Cream 2%: \$30.90/15 g   | Once daily               | N/A           | As for clotrimazole                           | Somewhat more effective than clotrimazole and miconazole   |
| Miconazole   | Cream 2%: \$7.20/30 g OTC  | Twice daily              | N/A           | As for clotrimazole                           | As for clotrimazole  |
| Oxiconazole (Oxistat)                                  | Cream 1%: \$614.73/30 g<br>Lotion 1%: \$771.91/30 mL                                   | Twice daily              | N/A           | As for clotrimazole                           |  |
| Sertaconazole (Ertaczo)                                | Cream 2%: \$1079.41/60 g   | Twice daily              | N/A           | Refractory tinea pedis                        | By prescription<br>More expensive  |
| Sulconazole (Exelderm)                                 | Cream 1%: \$72.38/15 g<br>Solution 1%: \$416.66/30 mL                                  | Twice daily              | N/A           | As for clotrimazole                           | No generic<br>Somewhat more effective than clotrimazole and miconazole   |
| <b>Other Antifungals (Listed Alphabetically)</b>       |  |                          |               |   |  |
| Butenafine (Mentax)                                    | Cream 1%: \$8.01/12 g OTC  | Once daily               | N/A           | Dermatophytes                                 | Fast response; high cure rate;<br>expensive<br>Available OTC   |
| Ciclopirox (Loprox) (Penlac)                           | Cream 0.77%: \$51.10/30 g<br>Lotion 0.77%: \$48.80/30 g<br>Solution 8%: \$52.95/6.6 mL | Twice daily              | N/A           | As for clotrimazole                           | No generic<br>Somewhat more effective than clotrimazole and miconazole   |
| Efinaconazole (Jublia)                                 | Solution 10%: \$772.34/4 mL  | Once daily for 48 weeks  | N/A           | Onychomycosis                                 | No generic; more effective than ciclopirox for nail disease  |
| Naftifine (Naftin)                                     | Cream 1%: \$375.38/60 g<br>Gel 1%: \$472.63/60 mL                                      | Once daily               | N/A           | Dermatophytes                                 | No generic<br>Somewhat more effective than clotrimazole and miconazole   |
| Tavaborole (Kerydin)                                   | Solution 5%: \$616.42/4 mL   | Once daily for 48 weeks  | N/A           | Onychomycosis                                 | No generic available   |
| Terbinafine (Lamisil)                                  | Cream 1%: \$8.72/12 g OTC  | Once daily               | N/A           | Dermatophytes                                 | Fast clinical response OTC   |
| <b>Antipruritics (Listed Alphabetically)</b>           |  |                          |               |   |  |
| Camphor/menthol (Sarna)                                | Lotion 0.5%/0.5%: \$8.28/222 mL  | Two to three times daily | N/A           | Mild eczema, xerosis, mild contact dermatitis |  |

(continued)

**Table 6–2.** Useful topical dermatologic therapeutic agents.<sup>1</sup> (continued)

| Agent                          | Formulations, Strengths, and Prices <sup>2</sup>                            | Frequency of Application  | Potency Class | Common Indications   | Comments  |
|--------------------------------|---|---------------------------|---------------|--|---|
| Capsaicin (various)            | Cream 0.025–0.1%<br>Cream 0.025%: \$9.95/60 g<br>Cream 0.075%: \$10.39/56 g | Three to four times daily | N/A           | Topical antipruritic, best used for neuropathic itching  | Burning/stinging with initial application that subsides with consistent ongoing use   |
| Doxepin (Zonalon)              | Cream 5%: \$722.32/45 g   | Four times daily          | N/A           | Topical antipruritic, best used in combination with appropriate topical corticosteroid to enhance efficacy | Can cause sedation  |
| Pramoxine hydrochloride (Prax) | Lotion 1%: \$19.64/120 mL OTC   | Four times daily          | N/A           | Dry skin, varicella, mild eczema, pruritus ani   | OTC formulations (Prax, Aveeno Anti-Itch Cream or Lotion; Itch-X Gel)<br>By prescription mixed with 1% or 2% hydrocortisone |

<sup>1</sup>For a given agent, higher lipophilicity (greasiness) corresponds with increased potency; for example, triamcinolone 0.1% ointment is more potent than triamcinolone 0.1% cream, which in turn is more potent than triamcinolone 0.1% lotion.

<sup>2</sup>Average wholesale price (AWP, for AB-rated generic when available) for quantity listed. AWP may not accurately represent the actual pharmacy cost because wide contractual variations exist among institutions. Source: IBM Micromedex. Red Book (electronic version). Watson Health, Greenwood Village, CO, USA. Available at <https://www.micromedexsolutions.com/> (cited March 27, 2021).

<sup>3</sup>Topical tacrolimus and pimecrolimus should be used only when other topical treatments are ineffective. Treatment should be limited to an area and duration to be as brief as possible. Treatment with these agents should be avoided in persons with known immunosuppression, HIV infection, bone marrow and organ transplantation, or lymphoma; those at high risk for lymphoma; and those with a prior history of lymphoma.

N/A, not applicable; OTC, over-the-counter.

only by their sedating effects. Hydroxyzine 25–50 mg orally at night is a typical dose. Sedating and nonsedating antihistamines are of limited value for the treatment of pruritus associated with inflammatory skin disease. Preferable agents include antidepressants (such as doxepin, mirtazapine, and paroxetine) and agents that act either directly on the neurons that perceive or modulate pruritus (such as gabapentin, pregabalin, and duloxetine).

## 2. Systemic corticosteroids—(See Chapter 26.)

Andrade A et al. Interventions for chronic pruritus of unknown origin. Cochrane Database Syst Rev. 2020;1:CD013128. [PMID: 31981369]

McEwen MW et al. Drugs on the horizon for chronic pruritus. Dermatol Clin. 2018;36:335. [PMID: 29929605]

van Zuuren EJ et al. Emollients and moisturisers for eczema. Cochrane Database Syst Rev. 2017;2:CD012119. [PMID: 28166390]

Fair-complexioned persons should use a sunscreen daily with a sun protective factor (SPF) of at least 30. Clinicians should reinforce regular sunscreen use and reapplication every few hours or more depending on exercise level and exposure to water. Sunscreens with protection against UVA as well as UVB are helpful in managing photosensitivity disorders. Aggressive sunscreen use should be accompanied by vitamin D supplementation in persons at risk for osteopenia. Health implications of systemic absorption of chemical sunscreens are unknown.

Henrikson NB et al. Behavioral counseling for skin cancer prevention: evidence report and systematic review for the US Preventive Services Task Force. JAMA. 2018;319:1143. [PMID: 29558557]

Matta MK et al. Effect of sunscreen application on plasma concentration of sunscreen active ingredients: a randomized clinical trial. JAMA. 2020;323:256. [PMID: 31961417]

Yeager DG et al. What's new in photoprotection: a review of new concepts and controversies. Dermatol Clin. 2019;37:149. [PMID: 30850037]

## ► Sunscreens

**Protection from ultraviolet light reduce the incidence of sunburn, actinic keratoses, melanoma, and some non-melanoma skin cancers when initiated at any age and in any skin type.** The best protection is shade, but protective clothing, avoidance of direct sun exposure during the peak hours of the day, and daily use of sunscreens are important.

## ► Complications of Topical Dermatologic Therapy

Complications of topical therapy include allergy, irritation, and other side effects. Reactions may result from the active or inactive ingredients, including fragrances and preservatives.

### A. Allergy

Of the topical antibiotics, neomycin and bacitracin have the greatest potential for sensitization. Diphenhydramine, benzocaine, vitamin E, aromatic oils, preservatives, fragrances, tea tree oil, and even the topical corticosteroids themselves can cause allergic contact dermatitis.

### B. Irritation

Preparations of tretinoin, benzoyl peroxide, and other acne medications should be applied sparingly to the skin.

### C. Other Side Effects

Topical corticosteroids may induce acne-like lesions on the face (steroid rosacea) and atrophic striae in body folds.

## COMMON DERMATOSES

### PIGMENTED LESIONS

#### MELANOCYTIC NEVI (Normal Moles)

In general, a benign mole is a small (less than 6 mm) macule or papule with a well-defined border and homogeneous beige or pink to dark brown pigment. They represent benign melanocytic growths.

Moles have a typical natural history. Early in life, moles often appear as flat, small, brown lesions and are termed “junctional nevi” because the nevus cells are at the junction of the epidermis and dermis. Over time, these moles enlarge and often become raised, reflecting the appearance of a dermal component, giving rise to “compound nevi” (Figure 6–1). Moles may darken and grow during pregnancy. As White patients enter their eighth decade, most moles have lost their junctional component and dark pigmentation. At every stage of life, normal moles should be well demarcated, symmetric, and uniform in contour and color. Regular mole screening is



**▲ Figure 6–1.** Benign, compound nevus on the back. (Used, with permission, from Richard P. Usatine, MD, in Usatine RP, Smith MA, Mayeaux EJ Jr, Chumley HS. *The Color Atlas and Synopsis of Family Medicine*, 3rd ed. McGraw-Hill, 2019.)

not an evidence-based recommendation for all adults, although rates of screening continue to rise.

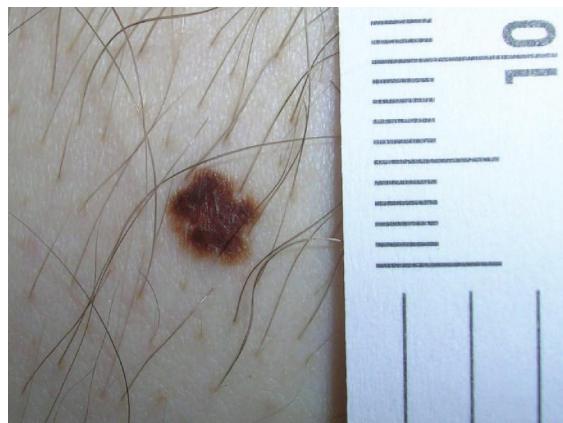
Stefanaki C et al. Clinical and dermoscopic characteristics of congenital melanocytic naevi. *J Eur Acad Dermatol Venereol*. 2018;32:1674. [PMID: 29633355]

#### ATYPICAL NEVI

The term “atypical nevus” or “atypical mole” has supplanted “dysplastic nevus.” The diagnosis of atypical moles is made clinically and not histologically. Moles should be removed only if they are suspected to be melanomas. Dermoscopy by a trained clinician may be a useful tool in the evaluation of atypical nevi. Clinically, these moles are large (6 mm or more in diameter), with an ill-defined, irregular border and irregularly distributed pigmentation (Figure 6–2). It is estimated that 5–10% of the White population in the United States has one or more atypical nevi, for which recreational sun exposure is a primary risk in nonfamilial settings. There is an increased risk of melanoma in patients with 50 or more nevi with one or more atypical moles and one mole at least 8 mm or larger and patients with any number of definitely atypical moles. These patients should be educated in how to recognize changes in moles and be monitored every 6–12 months by a clinician. Kindreds with familial melanoma (numerous atypical nevi and a family history of two first-degree relatives with melanoma) require closer attention, since their risk of developing single or multiple melanomas approaches 50% by age 50.

Kim CC et al; Pigmented Lesion Subcommittee, Melanoma Prevention Working Group. Risk of subsequent cutaneous melanoma in moderately dysplastic nevi excisionally biopsied but with positive histologic margins. *JAMA Dermatol*. 2018;154:1401. [PMID: 30304348]

Rishpon A et al. Melanoma risk stratification of individuals with a high-risk naevus phenotype—a pilot study. *Australas J Dermatol*. 2019;60:e292. [PMID: 30941757]



**▲ Figure 6–2.** Atypical (dysplastic) nevus on the chest. Note irregular border and variegation in color. (Used, with permission, from Richard P. Usatine, MD, in Usatine RP, Smith MA, Mayeaux EJ Jr, Chumley H. *The Color Atlas of Family Medicine*, 2nd ed. McGraw-Hill, 2013.)



**▲ Figure 6–3.** Blue nevus on the left cheek, a darkly pigmented blue-black macule with some resemblance to a melanoma due to its dark pigmentation. (Used, with permission, from Richard P. Usatine, MD, in Usatine RP, Smith MA, Mayeaux EJ Jr, Chumley HS. *The Color Atlas and Synopsis of Family Medicine*, 3rd ed. McGraw-Hill, 2019.)

## BLUE NEVI

Blue nevi are small, slightly elevated, blue-black lesions (Figure 6–3) that favor the dorsal hands. They are common in persons of Asian descent and may be single or multiple. If the lesion has remained unchanged for years, it may be considered benign, since malignant blue nevi are rare. However, blue-black papules and nodules that are new or growing must be evaluated to rule out nodular melanoma.

Baykal C et al. The spectrum of benign dermal dendritic melanocytic proliferations. *J Eur Acad Dermatol Venereol*. 2019;33:1029. [PMID: 30767282]

## FRECKLES & LENTIGINES

Freckles (ephelides) and lentigines are flat brown macules, typically between 3 mm and 5 mm in diameter. Freckles first appear in young children, darken with ultraviolet exposure, and fade with cessation of sun exposure. They are determined by genetic factors. In adults, lentigines

gradually appear in sun-exposed areas, particularly the face, dorsal hands, upper back, and upper chest, starting in the fourth to fifth decade of life, and are associated with photoaging as well as estrogen and progesterone use. They may have a very irregular border (inkspot lentigines). They do not fade with cessation of sun exposure. They should be evaluated like all pigmented lesions: if the pigmentation is homogeneous and they are symmetric and flat, they are most likely benign. They can be treated with topical retinoids such as 0.1% tretinoin or 0.1% adapalene, hydroquinone, laser/light therapy, or cryotherapy.

Bagatin E et al. Comparable efficacy of adapalene 0.3% gel and tretinoin 0.05% cream as treatment for cutaneous photoaging. *Eur J Dermatol*. 2018;28:343. [PMID: 30105991]

## SEBORRHEIC KERATOSES

Seborrheic keratoses are benign papules and plaques, beige to brown or even black, 3–20 mm in diameter, with a velvety or warty surface (Figure 6–4). They appear to be stuck or pasted onto the skin. They are extremely common—especially in older adults—and may be mistaken for melanomas or other types of cutaneous neoplasms. No treatment is needed. They may be frozen with liquid nitrogen or curetted if itchy or inflamed but usually recur after treatment.

Wollina U. Recent advances in managing and understanding seborrheic keratosis. *F1000Res*. 2019;8:F1000 Faculty Rev-1520. [PMID: 31508199]



**▲ Figure 6–4.** Seborrheic keratosis with light pigmentation, with waxy, dry, “stuck-on,” appearance. (Used, with permission, from Richard P. Usatine, MD, in Usatine RP, Smith MA, Mayeaux EJ Jr, Chumley HS. *The Color Atlas and Synopsis of Family Medicine*, 3rd ed. McGraw-Hill, 2019.)

## MALIGNANT MELANOMA



### ESSENTIALS OF DIAGNOSIS

- ▶ May be flat or raised with irregular borders.
- ▶ Examination may show varying colors, including red, white, black, and blue.
- ▶ Should be suspected in any pigmented skin lesion with recent change in appearance.
- ▶ Less than 30% develop from existing moles.



**▲ Figure 6–5.** Malignant melanoma. Note the classic “ABCDE” features: asymmetry, irregular border, multiple colors, diameter greater than 6 mm, and evolution or change. (Used, with permission, from Richard P. Usatine, MD, in Usatine RP, Smith MA, Mayeaux EJ Jr, Chumley HS. *The Color Atlas and Synopsis of Family Medicine*, 3rd ed. McGraw-Hill, 2019.)

### ► General Considerations

Malignant melanoma, the fifth most common of all cancers in the United States, is the leading cause of death due to skin disease and has doubled in incidence over the past 30 years. In 2019, approximately 100,350 new melanomas were diagnosed in the United States, with approximately 60% in men. In 2019, melanoma caused an estimated 6850 deaths (two-thirds in men). The lifetime risk of melanoma is 2% in Whites and 0.1–0.5% in non-Whites. One in four cases occurs before age 40. Increased detection of early melanomas has led to increased survival, but fatalities continue to increase, especially in men older than 70 years.

Tumor thickness is the single most important prognostic factor. Ten-year survival rates related to melanoma thickness are less than 1 mm, 95%; 1–2 mm, 80%; 2–4 mm, 55%. With lymph node involvement, the 5-year survival rate is 62%; with distant metastases, it is 16%.

### ► Clinical Findings

Primary malignant melanomas may be classified into various clinicohistopathologic types, including lentigo maligna melanoma (arising on chronically sun-exposed skin of older individuals); superficial spreading malignant melanoma (two-thirds of all melanomas arising on intermittently sun-exposed skin); nodular malignant melanoma; acral-lentiginous melanomas (arising on palms, soles, and nail beds); ocular melanoma; and malignant melanomas on mucous membranes. These different types of melanoma appear to have different oncogenic mutations, which may be important in the treatment of patients with advanced disease. Less than 30% of melanomas develop from existing moles. Clinical features of pigmented lesions suspicious for melanoma are an irregular, notched border where the pigment appears to be spreading into the normal surrounding skin and irregular surface topography (ie, partly raised and partly flat) (Figure 6–5). Color variegation is present and is an important indication for referral. A useful mnemonic is the ABCDE rule: Asymmetry, Border irregularity, Color variegation, Diameter greater than 6 mm, and Evolution. **The history of a changing mole (evolution, including bleeding and ulceration) is the single most important historical reason for close evaluation and possible referral.** A mole that appears distinct from the patient’s other moles deserves special scrutiny—the “ugly duckling sign.” A patient with a large number of moles is

statistically at increased risk for melanoma and deserves annual total body skin examination by a primary care clinician or dermatologist, particularly if the lesions are atypical in appearance.

While superficial spreading melanoma is largely a disease of Whites, persons of other races are at risk for this and other types of melanoma, particularly acral lentiginous melanomas. These occur as dark, irregularly shaped lesions on the palms and soles and as new, often broad and solitary, darkly pigmented, longitudinal streaks in the nails, typically with involvement of the proximal nail fold. Acral lentiginous melanoma may be a difficult or delayed diagnosis because benign pigmented lesions of the hands, feet, and nails occur commonly in more darkly pigmented persons, and clinicians may hesitate to biopsy these sites. Clinicians should give special attention to new or changing lesions in these areas.

### ► Treatment

Treatment starts with complete excision of the melanoma with a normal margin. After histologic diagnosis, reexcision is recommended with margins dictated by the thickness of the tumor. Recommended surgical margins are 0.5–1 cm for melanoma in situ, 1 cm for lesions less than 1 mm in thickness, and 1–2 cm for lesions more than 1 mm in thickness.

Referral of intermediate-risk and high-risk patients to centers with expertise in melanoma is strongly recommended. Sentinel lymph node biopsy (selective lymphadenectomy) using preoperative lymphoscintigraphy and intraoperative lymphatic mapping is effective for staging melanoma patients with intermediate risk without clinical adenopathy and is recommended for all patients with

lesions over 1 mm in thickness or with high-risk histologic features (ulceration). This procedure may not confer a survival advantage. Identifying the oncogenic mutations in patients with advanced melanoma may dictate targeted therapy, most commonly to specific BRAF mutations. Additionally, immunotherapy treatments directed toward immune costimulatory molecules such as PD-1 can activate systemic immune-directed destruction of metastatic melanoma.

Amaria RN et al. Neoadjuvant systemic therapy in melanoma: recommendations of the International Neoadjuvant Melanoma Consortium. *Lancet Oncol.* 2019;20:e378. [PMID: 31267972]

Coit DG et al. Cutaneous Melanoma, Version 2.2019, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw.* 2019;17:367. [PMID: 30959471]

Michelin O et al. Cutaneous melanoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol.* 2019;30:1884. [PMID: 31566661]

Swetter SM et al. Guidelines of care for the management of primary cutaneous melanoma. *J Am Acad Dermatol.* 2019; 80:208. [PMID: 30392755]

and upper trunk. The flexural surfaces of elbows and knees are often involved. In chronic cases, the skin is dry and lichenified. In dark-skinned patients with severe disease, pigmentation may be lost in lichenified areas. During acute flares, widespread redness with weeping, either diffusely or in discrete plaques, is common. Since virtually all patients with atopic dermatitis have skin disease before age 5, a new diagnosis of atopic dermatitis in an adult over age 30 should be made only after consultation with a dermatologist.

## B. Laboratory Findings

Food allergy is an uncommon cause of flares of atopic dermatitis in adults. Eosinophilia and increased serum IgE levels may be present.

## Differential Diagnosis

Atopic dermatitis must be distinguished from irritant or allergic contact dermatitis triggered by an external agent. Seborrheic dermatitis is less pruritic, with frequent scalp and central face involvement, greasy and scaly lesions, and responds quickly to therapy. Psoriasis is marked by sharply demarcated thickly scaled plaques on elbows, knees, scalp, and intergluteal cleft. Secondary staphylococcal or herpetic infections may exacerbate atopic dermatitis and should be considered during hyperacute, weeping flares of atopic dermatitis. An infra-auricular fissure is a cardinal sign of secondary infection.

## Treatment

Patient education regarding gentle skin care and exactly how to use medications is critical to successful management of atopic dermatitis.

### A. General Measures

Atopic patients have hyperirritable skin. Anything that dries or irritates the skin may trigger dermatitis. Atopic individuals are sensitive to low humidity and often flare in the winter. Adults with atopic disorders should not bathe more than once daily. Soap should be confined to the armpits, groin, scalp, and feet. Washcloths and brushes should not be used. After rinsing, the skin should be patted dry (not rubbed) and then immediately—within minutes—covered with a thin film of an emollient or a corticosteroid as needed. Plain petrolatum can be used if contact dermatitis resulting from additives in medication is suspected. Skin may be irritated by rough fabrics, including wools and acrylics. Cottons are preferable, but synthetic blends also are tolerated. Other triggers may include sweating, ointments, and heat.

### B. Local Treatment

Corticosteroids should be applied sparingly to the dermatitis once or twice daily and rubbed in well. Their potency should be appropriate to the severity of the dermatitis. In general, for treatment of lesions on the body (excluding genitalia, axillary or crural folds), one should begin with triamcinolone 0.1% or a stronger corticosteroid, then taper

## SCALING DISORDERS

### ATOPIC DERMATITIS



#### ESSENTIALS OF DIAGNOSIS

- ▶ Pruritic, xerotic, exudative, or lichenified eruption on face, neck, upper trunk, wrists, and hands and in the antecubital and popliteal folds.
- ▶ Personal or family history of atopy (eg, asthma, allergic rhinitis, atopic dermatitis).
- ▶ Tendency to recur.
- ▶ Onset in childhood most common; onset after age 30 is uncommon.

### General Considerations

Atopic dermatitis (also known as eczema) has distinct presentations in people of different ages and races. Diagnostic criteria for atopic dermatitis must include pruritus, typical morphology and distribution (flexural lichenification, hand eczema, nipple eczema, and eyelid eczema in adults), onset in childhood, and chronicity. Also helpful are (1) a personal or family history of atopy (asthma, allergic rhinitis, atopic dermatitis), (2) xerosis-ichthyosis, (3) facial pallor with infraorbital darkening, (4) elevated serum IgE, and (5) repeated skin infections.

### Clinical Findings

#### A. Symptoms and Signs

Itching is a key clinical feature and may be severe and prolonged. Ill-defined, scaly, red plaques affect the face, neck,

to hydrocortisone or another slightly stronger mild corticosteroid (alclometasone, desonide). **It is vital that patients taper off corticosteroids and substitute emollients as the dermatitis clears to avoid side effects of corticosteroids.** Tapering is also important to avoid dermatitis flares that may follow abrupt cessation. Tacrolimus ointment (Protopic 0.03% or 0.1%), pimecrolimus cream (Elidel 1%), and crisaborole (Eucrisa 2%) can be effective in managing atopic dermatitis when applied twice daily. Burning with application occurs in about 50% of patients using Protopic and 10–25% using Elidel but may resolve with continued treatment. These noncorticosteroid medications prevent complications of long-term corticosteroid use, including atrophy or striae. They are safe for application on the face and eyelids but are more expensive than generic topical corticosteroids.

*There is a Food and Drug Administration (FDA) black box warning for both topical tacrolimus and pimecrolimus due to concerns about the development of T-cell lymphoma. The agents should be used sparingly and only in locations where less expensive corticosteroids cannot be used. They should be avoided in patients at high risk for lymphoma (ie, those with HIV, iatrogenic immunosuppression, or prior lymphoma).*

The treatment of atopic dermatitis is dictated by the pattern of the dermatitis—acute/weepy, subacute/scaly, or chronic/lichenified.

**1. Acute weeping lesions**—Staphylococcal or herpetic superinfection should be excluded by bacterial or viral culture, or both. Use water or aluminum subacetate solution (Domeboro or burow solution), or colloidal oatmeal as a bath or as wet dressings for 10–30 minutes two to four times daily. Lesions on extremities may be bandaged for protection at night. Use high-potency corticosteroids after soaking but spare the face and body folds. Tacrolimus is usually not tolerated at this stage. Systemic corticosteroids may be required. An allergic or irritating contactant should also be considered when acute weeping lesions are present, since contact dermatitis is more likely to develop in atopic patients.

**2. Subacute or scaly lesions**—The lesions are dry but still red and pruritic. Mid- to high-potency corticosteroids in ointment form should be continued until skin lesions are cleared and itching is decreased substantially. At that point, patients should begin a 2- to 4-week taper from twice-daily to daily dosing with topical corticosteroids to reliance on emollients, with occasional use of corticosteroids only to inflamed areas. It is preferable to switch to daily use of a low-potency corticosteroid instead of further tapering the frequency of usage of a more potent corticosteroid. Tacrolimus and pimecrolimus may be substituted if corticosteroids cannot be stopped completely.

**3. Chronic, dry, lichenified lesions**—Thickened and usually well demarcated, they are best treated with high-potency to ultra-high-potency corticosteroid ointments. Nightly occlusion for 2–6 weeks may enhance the initial response. Adding tar preparations, such as liquor carbonis detergens 10% in Aquaphor or 2% crude coal tar may be beneficial.

**4. Maintenance treatment**—Once symptoms have improved, constant application of effective moisturizers is recommended to prevent flares. In patients with moderate disease, use of topical anti-inflammatories only on weekends or three times weekly can prevent flares.

### C. Systemic and Adjuvant Therapy

Systemic corticosteroids are indicated only for severe acute exacerbations. Oral prednisone dosages should be high enough to suppress the dermatitis quickly, usually starting with 1 mg/kg daily. The dosage is then tapered off over a period of 2–4 weeks. Owing to the chronic nature of atopic dermatitis and the side effects of long-term systemic corticosteroids, **ongoing use of these agents is not recommended for maintenance therapy.** Bedtime doses of hydroxyzine, diphenhydramine, or doxepin may be helpful via their sedative properties to mitigate perceived pruritus. Phototherapy can be an important adjunct for severely affected patients. Dupilumab is a targeted immunomodulator with minimal systemic adverse effects and requires minimal laboratory monitoring. Oral cyclosporine, mycophenolate mofetil, methotrexate, tofacitinib, or azathioprine may also be used for the most severe and recalcitrant cases.

### ► Complications of Treatment

The clinician should monitor for skin atrophy. Fissures, crusts, erosions, or pustules may indicate staphylococcal or herpetic infection clinically. Eczema herpeticum (herpes simplex superinfection) is manifested by monomorphic vesicles, crusts, or scalloped erosions superimposed on atopic dermatitis or other extensive eczematous processes and is treated with oral or intravenous acyclovir. Systemic antistaphylococcal antibiotics—such as a first-generation cephalosporin or doxycycline if methicillin-resistant *Staphylococcus aureus* is suspected—should be given only if indicated and guided by bacterial culture. Cultures to exclude methicillin-resistant *S aureus* are recommended. In this setting, continuing and augmenting the topical anti-inflammatory treatment often improves the dermatitis despite the presence of infection.

### ► Prognosis

Atopic dermatitis runs a chronic or intermittent course. Affected adults may have only hand dermatitis. Prognostic factors for persistence into adulthood include generalized disease or onset early in childhood and asthma. Only 40–60% of these patients have lasting remissions.

Faiz S et al. Effectiveness and safety of dupilumab for the treatment of atopic dermatitis in a real-life French multicenter adult cohort. J Am Acad Dermatol. 2019;81:143. [PMID: 30825533]

Thyssen JP et al. Clinical management of atopic dermatitis in adults: mapping of expert opinion in 4 Nordic countries using a modified Delphi process. Acta Derm Venereol. 2020;100:adv00015. [PMID: 31709450]

Wollenberg A et al. Consensus-based European guidelines for treatment of atopic eczema (atopic dermatitis) in adults and children: part II. J Eur Acad Dermatol Venereol. 2018;32:850. [PMID: 29878606]

## LICHEN SIMPLEX CHRONICUS (Circumscribed Neurodermatitis)



### ESSENTIALS OF DIAGNOSIS

- ▶ Chronic itching and scratching.
- ▶ Lichenified lesions with exaggerated skin lines overlying a thickened, well-circumscribed, scaly plaque.
- ▶ Predilection for nape of neck, wrists, external surfaces of forearms, lower legs, and genitals.

### ► General Considerations

Lichen simplex chronicus represents a self-perpetuating scratch-itch cycle that is hard to disrupt.

### ► Clinical Findings

Intermittent itching incites the patient to scratch the lesions and may interfere with sleep. Dry, hypertrophic, lichenified plaques appear on the neck, wrists, ankles, or perineum (Figure 6–6). The patches are rectangular, thickened, and hyperpigmented. The skin lines are exaggerated.

### ► Differential Diagnosis

This disorder can be differentiated from plaque-like lesions such as psoriasis (redder lesions having whiter scales on the elbows, knees, and scalp and nail findings), lichen planus (violaceous, usually smaller polygonal papules), and nummular (coin-shaped) dermatitis. Lichen simplex chronicus may complicate chronic atopic dermatitis or scabetic infestation.

### ► Treatment

For lesions in extragenital regions, ultra-high potency topical corticosteroids are effective, with or without occlusion,



▲ **Figure 6–6.** Lichen simplex chronicus on the hand.  
(Used, with permission, from Lindy Fox, MD.)

when used twice daily for several weeks (Table 6–2). In some patients, flurandrenolide (Cordran) tape may be effective, since it prevents scratching and rubbing of the lesion. The injection of triamcinolone acetonide suspension (5–10 mg/mL) into the lesions may occasionally be curative. Continuous occlusion with a flexible hydrocolloid dressing for 7 days at a time for 1–2 months may also be helpful. Dupilumab is a new treatment option for generalized disease or prurigo nodularis, its related condition. For genital lesions, see the section Pruritus Ani.

### ► Prognosis

The disease tends to remit during treatment but may recur or develop at another site.

Calugareanu A et al; French Group of Research and Study in Atopic Dermatitis (Groupe de Recherche sur l'Eczéma Atopique, GREAT) from the French Society of Dermatology (SFD). Effectiveness and safety of dupilumab for the treatment of prurigo nodularis in a French multicenter adult cohort of 16 patients. *J Eur Acad Dermatol Venereol.* 2020;34:e74. [PMID: 31529718]

Qureshi AA et al. A systematic review of evidence-based treatments for prurigo nodularis. *J Am Acad Dermatol.* 2019; 80:756. [PMID: 30261199]

## PSORIASIS



### ESSENTIALS OF DIAGNOSIS

- ▶ Silvery scales on bright red, well-demarcated plaques, usually on the knees, elbows, and scalp.
- ▶ Nails: pitting and onycholysis (separation of the nail plate from the bed).
- ▶ Mild itching is common.
- ▶ May be associated with psoriatic arthritis.
- ▶ Histopathology helpful.

### ► General Considerations

Psoriasis is a common benign, chronic inflammatory skin disease with both a genetic basis and known environmental triggers. Injury or irritation of normal skin tends to induce lesions of psoriasis at the site (Koebner phenomenon). Obesity worsens psoriasis, and significant weight loss may lead to substantial improvement. Psoriasis has several variants—the most common is the plaque type and hand involvement is also common. Eruptive (guttate) psoriasis consisting of numerous, smaller lesions 3–10 mm in diameter occurs occasionally after streptococcal pharyngitis. Rarely, life-threatening forms (generalized pustular and erythrodermic psoriasis) may occur.

### ► Clinical Findings

There are often no symptoms, but itching may occur and be severe. Favored sites include the scalp, elbows, knees,



▲ **Figure 6-7.** Extensive plaque psoriasis involving trunk of person with dark skin type. (Used, with permission, from Kanade Shinkai, MD.)

palms and soles, and nails. The lesions are red, sharply defined plaques covered with silvery scale (Figure 6-7). The glans penis and vulva may be affected. Occasionally, only the flexures (axillae, inguinal areas) are involved (termed inverse psoriasis). Fine stippling (“pitting”) in the nails is highly suggestive of psoriasis (Figure 6-8) as is onycholysis. The combination of red plaques with silvery scales on elbows and knees, with scaliness in the scalp or nail findings, is diagnostic. Patients with psoriasis often have a pink or red intergluteal fold. Not all patients have findings in all locations. Some patients have mainly hand or foot dermatitis with minimal findings elsewhere. There may be associated arthritis that is most commonly distal and oligoarticular, although the rheumatoid variety with a negative rheumatoid factor may occur. The psychosocial impact of psoriasis is a major factor in determining the treatment of the patient.



▲ **Figure 6-8.** Nail pitting due to psoriasis in a patient with dark skin. (Used, with permission, from Richard P. Usatine, MD, in Usatine RP, Smith MA, Mayeaux EJ Jr, Chumley HS. *The Color Atlas and Synopsis of Family Medicine*, 3rd ed. McGraw-Hill, 2019.)

## ► Differential Diagnosis

Psoriasis lesions are well demarcated and affect extensor surfaces—in contrast to atopic dermatitis, with poorly demarcated plaques in flexural distribution. In body folds, scraping and culture for *Candida* and examination of scalp and nails will distinguish inverse psoriasis from intertrigo and candidiasis. Dystrophic changes in nails may mimic onychomycosis, and a potassium hydroxide (KOH) preparation or fungal culture is valuable in diagnosis. The cutaneous features of reactive arthritis, pityriasis rosea, systemic lupus erythematosus, and syphilis mimic psoriasis.

## ► Treatment

There are many therapeutic options in psoriasis to be chosen according to the extent (body surface area [BSA] affected) and the presence of other findings (for example, arthritis). Certain medications, such as beta-blockers, anti-malarials, statins, lithium, and prednisone taper may flare or worsen psoriasis. Patients with moderate to severe psoriasis should be managed by or in conjunction with a dermatologist.

### A. Limited Disease

For patients with large plaques and less than 10% of the BSA involved, the easiest regimen is to use a high-potency to ultra-high-potency topical corticosteroid cream or ointment. It is best to restrict the ultra-high-potency corticosteroids to 2–3 weeks of twice-daily use and then use them in a pulse fashion three or four times on weekends or switch to a mid-potency corticosteroid. Topical corticosteroids rarely induce a lasting remission. Initially, patients may be treated with twice-daily topical corticosteroids plus a vitamin D analog (calcipotriene ointment 0.005% or calcitriol ointment 0.003%) twice daily. This rapidly clears the lesions; eventually, the topical corticosteroids are stopped, and once- or twice-daily application of the vitamin D analog is continued long-term. Calcipotriene usually cannot be applied to the groin or face because of irritation. Treatment of extensive psoriasis with vitamin D analogs may result in hypercalcemia, so that the maximum dose for calcipotriene is 100 g/week and for calcitriol it is 200 g/week. Calcipotriene is incompatible with many topical corticosteroids (but not halobetasol), so if used concurrently, it must be applied at a different time. For patients with numerous small papules and plaques, such as guttate psoriasis, phototherapy is the best therapy.

For thick plaques on the scalp, start with a tar shampoo, used daily if possible. Additional treatments include 6% salicylic acid gel (eg, Keralyt), P & S solution (phenol, mineral oil, and glycerin), or fluocinolone acetonide 0.01% in oil (Derma-Smoothe/FS) under a shower cap at night, and shampoo in the morning. In order of increasing potency, triamcinolone 0.1%, fluocinolone, betamethasone dipropionate, amcinonide, and clobetasol are available in solution form for use on the scalp twice daily. Tacrolimus ointment 0.1% or 0.03% or pimecrolimus cream 1% may be effective in intertriginous, genital, and facial psoriasis, where potent corticosteroids are not recommended due to skin atrophy.

## B. Moderate Disease

Psoriasis affecting 10–30% of the patient's BSA is frequently treated with UV phototherapy, either in a medical office or via a home light unit. Systemic agents listed below may also be used.

## C. Moderate to Severe Disease

If psoriasis in a given location is severe or involves more than 30% of the body surface, it is difficult to treat with topical agents. These patients may be best managed in partnership with a dermatologist, especially when considering systemic therapy. The treatment of choice is outpatient narrowband UVB (NB-UVB) three times weekly. Clearing occurs in an average of 7 weeks, and maintenance may be required.

Psoralen plus UVA (PUVA) photochemotherapy may be effective even in patients who have not responded to standard NB-UVB treatment. Long-term use of PUVA (greater than 250 doses) is associated with an increased risk of skin cancer (especially squamous cell carcinoma and perhaps melanoma) in persons with fair complexions. Thus, periodic examination (every 3–6 months) of the skin is imperative.

Methotrexate is effective for severe psoriasis in doses up to 25 mg once weekly according to published protocols. Long-term methotrexate use may be associated with cirrhosis. After receiving a 3.5–4-g cumulative dose, the patient should be referred to a hepatologist for evaluation. Administration of folic acid, 1–2 mg daily, can eliminate nausea caused by methotrexate without compromising efficacy.

Acitretin, a synthetic retinoid, is most effective for pustular psoriasis in oral dosages of 0.5–0.75 mg/kg/day. Liver enzymes and serum lipids must be checked periodically. Because acitretin is a teratogen and persists for 2–3 years in fat, women of childbearing age must wait at least 3 years after completing acitretin treatment before considering pregnancy. When used as single agents, retinoids will flatten psoriatic plaques, but will rarely result in complete clearing. Retinoids find their greatest use when combined with phototherapy—either UVB or PUVA, with which they are synergistic.

Cyclosporine dramatically improves psoriasis and may be used to control severe cases. Rapid relapse (rebound) frequently occurs after cessation of therapy, so another agent must be added if cyclosporine is stopped. The tumor necrosis factor (TNF) inhibitors etanercept (Enbrel), infliximab (Remicade), and adalimumab (Humira) are effective in pustular and chronic plaque psoriasis and are also effective for the associated arthritis. Infliximab provides the most rapid response and can be used for severe pustular or erythrodermic flares. Etanercept is used more frequently for long-term treatment at a dose of 50 mg subcutaneously twice weekly for 3 months, then 50 mg once weekly. All three TNF inhibitors can also induce or worsen psoriasis. IL-12/23 monoclonal antibodies (ustekinumab [Stelara], guselkumab), Janus kinase inhibitors (tofacitinib, approved for use in rheumatoid arthritis but with strong data supporting its use in psoriasis), and

IL-17 monoclonal antibodies (secukinumab, brodalumab, and ixekizumab) may be the most effective treatments among biologics. The oral phosphodiesterase 4 inhibitor apremilast is an approved option for plaque-type psoriasis with minimal immunosuppressive effects and requires no laboratory monitoring.

## ► Prognosis

The course of psoriasis may be chronic and unpredictable, and it may be refractory to treatment. Patients (especially those older than 40 years) should be monitored for metabolic syndrome, which correlates with the severity of their skin disease. Complications of systemic therapy occur and active monitoring for infection is needed.

Armstrong AW et al. Comparison of biologics and oral treatments for plaque psoriasis: a meta-analysis. *JAMA Dermatol*. 2020;156:256. [PMID: 32022825]

Armstrong AW et al. Pathophysiology, clinical presentation, and treatment of psoriasis: a review. *JAMA*. 2020;323:1945. [PMID: 32427307]

Menter A et al. Joint AAD-NPF guidelines of care for the management and treatment of psoriasis with biologics. *J Am Acad Dermatol*. 2019;80:1029. [PMID: 30772098]

Elmets CA et al. Joint AAD-NPF guidelines of care for the management and treatment of psoriasis with awareness and attention to comorbidities. *J Am Acad Dermatol*. 2019;80:1073. [PMID: 30772097]

## PITYRIASIS ROSEA



### ESSENTIALS OF DIAGNOSIS

- Oval, fawn-colored, scaly eruption following cleavage lines of trunk.
- Herald patch precedes eruption by 1–2 weeks.
- Occasional pruritus.

## ► General Considerations

Pityriasis rosea is a common mild, acute inflammatory disease that is 50% more common in females. Young adults are principally affected, mostly in the spring or fall. Concurrent household cases have been reported.

## ► Clinical Findings

Itching is common but usually mild. The diagnosis is made by finding one or more classic lesions, such as oval, fawn-colored plaques up to 2 cm in diameter. The centers of a few lesions may have a characteristic crinkled or “cigarette paper” appearance and a collarette scale, ie, a thin bit of scale that is bound at the periphery and free in the center. Lesions follow cleavage lines on the trunk (so-called Christmas tree pattern, Figure 6–9), and the proximal portions of the extremities are often involved. A variant that affects the flexures (axillae and groin), so-called inverse pityriasis rosea, and a papular variant, especially in Black



**▲ Figure 6-9.** Pityriasis rosea with scaling lesions following skin lines and resembling a Christmas tree.

(Used, with permission, from EJ Mayeaux, MD, in Usatine RP, Smith MA, Mayeaux EJ Jr, Chumley HS. *The Color Atlas and Synopsis of Family Medicine*, 3rd ed. McGraw-Hill, 2019.)

patients, also occur. An initial lesion (“herald patch”) that is often larger than the later lesions often precedes the general eruption by 1–2 weeks. The eruption usually lasts 6–8 weeks and heals without scarring.

### ► Differential Diagnosis

Serologic testing for syphilis should be performed unless perfectly typical pityriasis rosea lesions are present. Palmar and plantar or mucous membrane lesions or adenopathy are features suggestive of secondary syphilis. Tinea corporis may present with a few red, slightly scaly plaques. Rarely, there are more than a few plaques, but the number of plaques do not compare to the number seen in pityriasis rosea. A potassium hydroxide examination should be performed to exclude a fungal cause. Seborrheic dermatitis on occasion presents on the body with poorly demarcated patches over the sternum, in the pubic area, and in the axillae. Tinea versicolor lacks the typical collarette rimmed lesions. Guttate or plaque psoriasis is an important diagnostic consideration and biopsy can help differentiate these from pityriasis rosea. Certain medications and immunizations rarely may induce a skin eruption mimicking pityriasis rosea.

### ► Treatment

Pityriasis rosea often requires no treatment unless patients are symptomatic. In darker-skinned individuals, more aggressive management may be indicated because dyspigmentation of lesions may result. Oral acyclovir may improve the rash appearance. While well-designed clinical

trials have not demonstrated highly effective treatments, most dermatologists recommend UVB treatments or a short course of prednisone for severe or severely symptomatic cases. For mild to moderate cases, topical corticosteroids of medium strength (triamcinolone 0.1%) and oral antihistamines may be used if pruritus is bothersome. The role of macrolide antibiotics is not evidence based.

### ► Prognosis

Pityriasis rosea is usually an acute self-limiting illness that typically disappears in about 6 weeks, although prolonged variants have been reported.

Contreras-Ruiz J et al. Interventions for pityriasis rosea. Cochrane Database Syst Rev. 2019;2019:CD005068. [ PMID: 31684696 ]

## SEBORRHEIC DERMATITIS



### ESSENTIALS OF DIAGNOSIS

- Dry scales and underlying erythema.
- Scalp, central face, presternal, interscapular areas, umbilicus, and body folds.

### ► General Considerations

Seborrheic dermatitis is an acute or chronic papulosquamous dermatitis that often coexists with psoriasis and is associated with inflammation due to *Malassezia* species.

### ► Clinical Findings

The scalp, face, chest, back, umbilicus, eyelid margins, genitalia, and body folds have dry scales (dandruff) or oily yellowish scurf (Figure 6-10). Pruritus is a variable finding. Patients with Parkinson disease, HIV-infected patients, and patients who become acutely ill often have seborrheic dermatitis.

### ► Differential Diagnosis

There is a spectrum from seborrheic dermatitis to scalp psoriasis. Extensive seborrheic dermatitis may simulate intertrigo in flexural areas, but scalp, face, and sternal involvement suggests seborrheic dermatitis.

### ► Treatment

#### A. Seborrhea of the Scalp

Shampoos that contain zinc pyrithione or selenium are used daily if possible. These may be alternated with ketoconazole shampoo (1% or 2%) used twice weekly. A combination of shampoos is used in refractory cases. Tar shampoos are also effective for milder cases and for scalp psoriasis. Topical corticosteroid solutions or lotions are then added if necessary and are used twice daily. (See treatment for scalp psoriasis, above.)



**▲ Figure 6–10.** Close-up of seborrheic dermatitis showing flaking skin and erythema around the beard region. (Reproduced with permission from Richard P. Usatine, MD in Usatine RP, Mayeaux EJ Jr, Chumley HS. *The Color Atlas and Synopsis of Family Medicine*, 3rd ed. McGraw-Hill, 2019.)

### B. Facial Seborrheic Dermatitis

The mainstay of therapy is a mild corticosteroid (hydrocortisone 1%, alclometasone, desonide) used intermittently and not near the eyes. If the disorder cannot be controlled with intermittent use of a mild topical corticosteroid alone, ketoconazole 2% cream is added twice daily. Topical tacrolimus and pimecrolimus are steroid-sparing alternatives.

### C. Seborrheic Dermatitis of Nonhairy Areas

Low-potency corticosteroid creams—ie, 1% or 2.5% hydrocortisone, desonide, or alclometasone dipropionate—are highly effective.

### D. Seborrhea of Intertriginous Areas

Apply low-potency corticosteroid lotions or creams twice daily for 5–7 days and then once or twice weekly for maintenance as necessary. Selenium lotion, ketoconazole, or clotrimazole gel or cream may be a useful adjunct. Tacrolimus or pimecrolimus topically may avoid corticosteroid atrophy in chronic cases.

### E. Involvement of Eyelid Margins

“Marginal blepharitis” usually responds to gentle cleaning of the lid margins nightly as needed, with undiluted baby shampoo or eyelid cleanser using a cotton swab.

### ► Prognosis

The tendency is for lifelong recurrences. Individual outbreaks may last weeks, months, or years.

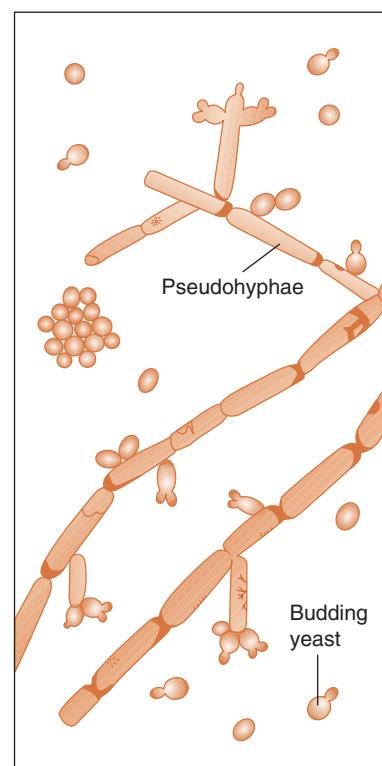
Borda LJ et al. Treatment of seborrheic dermatitis: a comprehensive review. *J Dermatolog Treat*. 2019;30:158. [PMID: 29737895]  
Elgash M et al. Seborrheic dermatitis in skin of color: clinical considerations. *J Drugs Dermatol*. 2019;18:24. [PMID: 30681789]

## FUNGAL INFECTIONS OF THE SKIN

The diagnosis of fungal infections of the skin is based on the location and characteristics of the lesions and on the following laboratory examinations: (1) Direct demonstration of fungi in 10% KOH evaluation of suspected lesions. “**If it’s scaly, scrape it**” is a time-honored maxim (Figure 6–11). (2) Cultures of organisms from skin scrapings. (3) Histologic sections of biopsies stained with periodic acid-Schiff technique may be diagnostic if scrapings and cultures are falsely negative.

### ► Principles of Treatment

A diagnosis should always be confirmed by KOH preparation, culture, or biopsy. Many other diseases cause scaling, and use of an antifungal agent without a firm diagnosis makes subsequent diagnosis more difficult. In general, fungal infections are treated topically except for those with extensive involvement or involving the nails or hair follicles. In these situations, oral agents may be useful, with special attention to their side effects and complications, including hepatic toxicity.



**▲ Figure 6–11.** KOH preparation of fungus demonstrating pseudohyphae and budding yeast forms. (Reproduced, with permission, from Nicoll D et al. *Guide to Diagnostic Tests*, 7th ed. McGraw-Hill, 2017.)

## ► General Measures & Prevention

Since moist skin favors the growth of fungi, dry the skin carefully after perspiring heavily or after bathing. The use of a hair dryer on a low setting may be helpful. Antifungal or drying powders may be useful with the exception of powders containing corn starch, which may exacerbate fungal infections. The use of topical corticosteroids for other diseases may be complicated by intercurrent tinea or candidal infection, and topical antifungals are often used in intertriginous areas with corticosteroids to prevent this.

### 1. Tinea Corporis or Tinea Circinata



#### ESSENTIALS OF DIAGNOSIS

- ▶ Ring-shaped lesions with an advancing scaly border and central clearing or scaly patches with a distinct border.
- ▶ Microscopic examination of scrapings or culture confirms the diagnosis.

## ► General Considerations

The lesions are often on exposed areas of the body such as the face and arms. A history of exposure to an infected pet (who may have scaly rash or patches of alopecia) may occasionally be obtained, usually indicating *Microsporum* infection. *Trichophyton rubrum* is the most common pathogen, usually representing extension onto the trunk or extremities of tinea cruris, pedis, or manuum.

## ► Clinical Findings

### A. Symptoms and Signs

Itching may be present. In classic lesions, rings of erythema have an advancing scaly border and central clearing.

### B. Laboratory Findings

The diagnosis should be confirmed by KOH preparation or culture.

## ► Differential Diagnosis

Positive fungal studies distinguish tinea corporis from other skin lesions with annular configuration, such as the annular lesions of psoriasis, lupus erythematosus, syphilis, granuloma annulare, and pityriasis rosea. Psoriasis has typical lesions on elbows, knees, scalp, and nails. Secondary syphilis is often manifested by characteristic palmar, plantar, and mucous membrane lesions. Tinea corporis rarely has the large number of symmetric lesions seen in pityriasis rosea. Granuloma annulare lacks scale.

## ► Complications

Complications include extension of the disease down the hair follicles (which presents as papules and pustules and requires systemic antifungals to cure) and pyoderma.

## ► Prevention

Treat infected household pets (*Microsporum* infections). To prevent recurrences, the use of foot powder and keeping feet dry by wearing sandals, or changing socks can be useful.

## ► Treatment

### A. Local Measures

Tinea corporis responds to most topical antifungals, including terbinafine, butenafine, econazole, miconazole, and clotrimazole, most of which are available over the counter in the United States (see Table 6–2). Terbinafine and butenafine require shorter courses and lead to the most rapid response. **Treatment should be continued for 1–2 weeks after clinical clearing.** Betamethasone dipropionate with clotrimazole (Lotrisone) is not recommended. Long-term improper use may result in side effects from the high-potency corticosteroid component, especially in body folds.

### B. Systemic Measures

Itraconazole as a single weeklong pulse of 200 mg orally daily is effective in tinea corporis. Terbinafine, 250 mg orally daily for 1 month, is an alternative.

## ► Prognosis

Tinea corporis usually responds promptly to conservative topical therapy or to an oral agent within 4 weeks.

May PJ et al. Treatment, prevention and public health management of impetigo, scabies, crusted scabies and fungal skin infections in endemic populations: a systematic review. *Trop Med Int Health.* 2019;24:280. [PMID: 30582783]

### 2. Tinea Cruris (Jock Itch)



#### ESSENTIALS OF DIAGNOSIS

- ▶ Marked itching in intertriginous areas, usually sparing the scrotum.
- ▶ Peripherally spreading, sharply demarcated, centrally clearing erythematous lesions.
- ▶ May have associated tinea infection of feet or toenails.
- ▶ Laboratory examination with microscope or culture confirms diagnosis.

## ► General Considerations

Tinea cruris lesions are confined to the groin and gluteal cleft. Intractable pruritus ani may occasionally be caused by a tinea infection.

## ► Clinical Findings

### A. Symptoms and Signs

Itching may be severe, or the rash may be asymptomatic. The lesions have sharp margins, cleared centers, and active, spreading scaly peripheries. Follicular pustules are sometimes encountered. The area may be hyperpigmented on resolution.

### B. Laboratory Findings

Hyphae can be demonstrated microscopically in KOH preparations or skin biopsy. The organism may be cultured.

## ► Differential Diagnosis

Tinea cruris must be distinguished from other lesions involving the intertriginous areas, such as candidiasis, seborrheic dermatitis, intertrigo, psoriasis of body folds (“inverse psoriasis”), and erythrasma (corynebacterial infection of intertriginous areas). Candidiasis is generally bright red and marked by satellite papules and pustules outside of the main border of the lesion. *Candida* typically involves the scrotum. Seborrheic dermatitis also often involves the face, sternum, axillae, and genitalia (but not the crural folds). Intertrigo tends to be less red, less scaly, and present in obese individuals in moist body folds with less extension onto the thigh. “Inverse psoriasis” is characterized by distinct plaques. Other areas of typical psoriatic involvement should be checked, and the KOH examination will be negative. Erythrasma is best diagnosed with Wood (ultraviolet) light—a brilliant coral-red fluorescence is seen.

## ► Treatment

### A. General Measures

Drying powder (eg, miconazole nitrate [Zeasorb-AF]) can be dusted into the involved area in patients with excessive perspiration or occlusion of skin due to obesity as a preventive measure but is less helpful for treatment.

### B. Local Measures

Any of the topical antifungal preparations listed in Table 6–2 may be used. Terbinafine cream is curative in over 80% of cases after once-daily use for 7 days.

### C. Systemic Measures

One week of either itraconazole, 200 mg orally daily, or terbinafine, 250 mg orally daily, can be effective.

## ► Prognosis

Tinea cruris usually responds promptly to topical or systemic treatment but often recurs.

### 3. Tinea Manuum & Tinea Pedis (Tinea of Palms & Soles)



## ESSENTIALS OF DIAGNOSIS

- ▶ Most often presents with asymptomatic scaling.
- ▶ May progress to fissuring or maceration in toe web spaces.
- ▶ May be a portal of entry for bacteria causing lower extremity cellulitis.
- ▶ Itching, burning, and stinging of interdigital web; scaling palms and soles; vesicles on soles in inflammatory cases.
- ▶ KOH preparation or fungal culture of skin scrapings is usually positive.

## ► General Considerations

Tinea of the feet (athlete’s foot) is an extremely common acute or chronic dermatosis. Most infections are caused by *Trichophyton* species.

## ► Clinical Findings

### A. Symptoms and Signs

The presenting symptom may be itching, burning, or stinging. Pain may indicate secondary infection with complicating cellulitis. Interdigital tinea pedis is the most common predisposing cause of lower extremity cellulitis in healthy individuals. Regular examination of the feet of diabetic patients for evidence of scaling and fissuring and treatment of any identified tinea pedis may prevent complications. Tinea pedis has several presentations that vary with the location. On the sole and heel, tinea may appear as chronic noninflammatory scaling, occasionally with thickening and fissuring. This may extend over the sides of the feet in a “moccasin” distribution (Figure 6–12). The KOH preparation is usually positive. Tinea pedis often appears as



**▲ Figure 6–12.** Tinea pedis in the moccasin distribution. (Used, with permission, from Richard P. Usatine, MD, in Usatine RP, Smith MA, Mayeaux EJ Jr, Chumley HS. *The Color Atlas and Synopsis of Family Medicine*, 3rd ed. McGraw-Hill, 2019.)



**▲ Figure 6–13.** Tinea pedis in the interdigital space between fourth and fifth digits. The differential diagnosis includes a bacterial primary or secondary infection with gram-negative organisms. (Used, with permission, from Richard P. Usatine, MD, in Usatine RP, Smith MA, Mayeaux EJ Jr, Chumley HS. *The Color Atlas and Synopsis of Family Medicine*, 3rd ed. McGraw-Hill, 2019.)

a scaling or fissuring of the toe webs, often with maceration (Figure 6–13). As the web spaces become more macerated, the KOH preparation and fungal culture are less often positive because bacterial species begin to dominate. Finally, there may also be vesicles, bullae, or generalized exfoliation of the skin of the soles, or nail involvement in the form of discoloration, friability, and thickening of the nail plate.

### B. Laboratory Findings

KOH and culture do not always demonstrate pathogenic fungi from macerated areas.

### ► Differential Diagnosis

Another skin condition involving the same areas is interdigital erythema (use Wood light). Psoriasis may be a cause of chronic scaling on the palms or soles and may cause nail changes. Repeated fungal cultures should be negative, and the condition will not respond to antifungal therapy. Contact dermatitis will often involve the dorsal surfaces and will respond to topical or systemic corticosteroids. Vesicular lesions should be differentiated from pompholyx (dyshidrosis) and scabies by proper scraping of the roofs of individual vesicles. Rarely, gram-negative organisms may cause toe web infections, manifested as an acute erosive flare of interdigital disease. This entity is treated with aluminum salts and imidazole antifungal agents or ciclopirox. *Candida* may also cause erosive interdigital disease.

### ► Prevention

The essential factor in prevention is personal hygiene. Wear open-toed sandals if possible. Use of sandals in community showers and bathing places is often recommended, though the effectiveness of this practice has not been studied. Careful drying between the toes after showering is essential. A hair dryer used on low setting may be helpful.

Socks should be changed frequently, and absorbent non-synthetic socks are preferred. Apply dusting and drying powders as necessary. The use of powders containing anti-fungal agents (eg, Zeasorb-AF) or long-term use of anti-fungal creams may prevent recurrences of tinea pedis.

## ► Treatment

### A. Local Measures

**1. Macerated stage**—Treat with aluminum subacetate solution soaks for 20 minutes twice daily. Broad-spectrum antifungal creams and solutions (containing imidazoles or ciclopirox) (Table 6–2) will help combat diphtheroids and other gram-positive organisms present at this stage and alone may be adequate therapy. If topical imidazoles fail, 1 week of once-daily topical allylamine treatment (terbinafine or butenafine) will often result in clearing.

**2. Dry and scaly stage**—Use any of the antifungal agents listed in Table 6–2. The addition of urea 10–20% lotion or cream may increase the efficacy of topical treatments in thick (“moccasin”) tinea of the soles.

### B. Systemic Measures

Itraconazole, 200 mg orally daily for 2 weeks or 400 mg daily for 1 week, or terbinafine, 250 mg orally daily for 2–4 weeks, may be used in refractory cases. If the infection is cleared by systemic therapy, the patient should be encouraged to begin maintenance with topical therapy, since recurrence is common.

## ► Prognosis

For many individuals, tinea pedis is a chronic affliction, temporarily cleared by therapy only to recur. Treatment of tinea pedis or manuum without systemic treatment of affected nails may result in recurrent skin disease.

Goiset A et al. Characteristics, associated diseases, and management of gram-negative toe-web infection: a French experience. Acta Derm Venereol. 2019;99:1121. [PMID: 31502652]

### 4. Tinea Versicolor (Pityriasis Versicolor)

#### ESSENTIALS OF DIAGNOSIS

- Velvety, tan, pink, or white macules or white macules that do not tan with sun exposure.
- Fine scales that are not visible but are seen by scraping the lesion.
- Central upper trunk the most frequent site.
- Yeast and short hyphae observed on microscopic examination of scales.

## ► General Considerations

Tinea versicolor is a mild, superficial *Malassezia* infection of the skin (usually of the upper trunk). This yeast is

a colonizer of all humans, which accounts for the high recurrence rate after treatment. The eruption is often called to patients' attention by the fact that the involved areas will not tan, and the resulting hypopigmentation may be mistaken for vitiligo. A hyperpigmented form is not uncommon.

## ► Clinical Findings

### A. Symptoms and Signs

Lesions are asymptomatic, but a few patients note itching. The lesions are velvety, tan, pink, or white macules or thin papules that vary from 4 mm to 5 mm in diameter to large confluent areas. The lesions initially do not look scaly, but scales may be readily obtained by scraping the area. Lesions may appear on the trunk, upper arms, neck, and groin.

### B. Laboratory Findings

Large, blunt hyphae and thick-walled budding spores ("spaghetti and meatballs") are seen on KOH. Fungal culture is not useful.

## ► Differential Diagnosis

Vitiligo usually presents with larger periorificial and acral lesions and is also characterized by total (not partial) depigmentation. Vitiligo does not scale. Pink and red-brown lesions on the chest are differentiated from seborrheic dermatitis of the same areas by the KOH preparation.

## ► Treatment & Prognosis

### A. Initial Treatment

Topical treatments include selenium sulfide lotion, which may be applied from neck to waist daily and left on for 5–15 minutes for 7 days; this treatment is repeated weekly for a month. Ketoconazole shampoo, 1% or 2%, lathered on the chest and back and left on for 5 minutes may also be used weekly for treatment. Clinicians must stress to the patient that the raised and scaly aspects of the rash are being treated; the alterations in pigmentation may take months to fade or fill in.

A regimen of two doses of oral fluconazole, 300 mg, 14 days apart, is first-line treatment; the risk of hepatitis is minimal. Additional doses may be required in severe cases or humid climates. Ketoconazole is no longer recommended as first-line treatment because of the risk of drug-induced hepatitis.

### B. Maintenance Therapy

Topical treatments as described above can be used for maintenance therapy. Selenium sulfide lotion should be used monthly, and ketoconazole shampoo, 1% or 2%, may be used to prevent recurrence. Imidazole creams, solutions, and lotions (eg, clotrimazole or miconazole) are quite effective for localized areas but are too expensive for use over large areas, such as the chest and back. Without maintenance therapy, recurrences will occur in over 80% of "cured" cases over the subsequent 2 years.

Hudson A et al. JAMA patient page. Tinea versicolor. JAMA. 2018;320:1396. [PMID: 30285180]  
Saleem MD et al. Acquired disorders with hypopigmentation: a clinical approach to diagnosis and treatment. J Am Acad Dermatol. 2019;80:1233. [PMID: 30236514]

## CUTANEOUS LUPUS ERYTHEMATOSUS



### ESSENTIALS OF DIAGNOSIS

- ▶ Localized violaceous red plaques, usually on the head (discoid lupus erythematosus) or the trunk (chronic cutaneous lupus erythematosus).
- ▶ Scaling, follicular plugging, atrophy, dyspigmentation, and telangiectasia of involved areas.
- ▶ Photosensitivity.
- ▶ Distinctive histology.

## ► General Considerations

Common forms of cutaneous lupus include chronic cutaneous lupus erythematosus (CCLE), typically chronic scarring (discoid) lupus erythematosus (DLE), and erythematous non-scarring red plaques of subacute cutaneous lupus erythematosus (SCLE). All occur most frequently in photoexposed areas. Permanent hair loss and loss of pigmentation are common sequelae of discoid lesions. Systemic lupus erythematosus (SLE) is discussed in Chapter 20. Patients with SLE may have DLE or SCLE lesions.

## ► Clinical Findings

### A. Symptoms and Signs

Symptoms are usually mild. In DLE, the lesions consist of violaceous red, well-localized, single or multiple plaques, 5–20 mm in diameter, usually on the face, scalp, and external ears (conchal bowl). In discoid lesions, there is atrophy, telangiectasia, central depigmentation or scarring, a hyperpigmented rim, and follicular plugging. On the scalp, significant permanent hair loss may occur. In SCLE, the lesions are erythematous annular or psoriasiform plaques up to several centimeters in diameter and favor the upper chest and back.

### B. Laboratory Findings

In patients with DLE, SLE should be considered if the following findings are present: positive antinuclear antibody (ANA), other positive serologic studies (eg, anti-double-stranded DNA or anti-Smith antibody), high erythrocyte sedimentation rate, proteinuria, hypocomplementemia, widespread lesions (not localized to the head), nail fold changes (dilated or thrombosed nail fold capillary loops), or arthralgias with or without arthritis. Patients with marked photosensitivity and symptoms otherwise suggestive of lupus may have negative ANA tests but are positive for antibodies against Ro/SSA or La/SSB (SCLE).

## ► Differential Diagnosis

The diagnosis is based on the clinical appearance confirmed by skin biopsy in all cases. In DLE, the scales are dry and “thumbtack-like” and can thus be distinguished from those of seborrheic dermatitis and psoriasis. Older lesions have hyperpigmented borders, depigmented central scarring, or areas of hair loss that will also differentiate lupus from these diseases. Ten percent of patients with SLE have discoid skin lesions, and 5% of patients with discoid lesions have SLE. A number of medications may induce SCLE with a positive Ro/SSA.

## ► Treatment

### A. General Measures

Use photoprotective clothing and broad-spectrum sunblock of SPF of 30 or more daily. UVA coverage is essential in photosensitive patients. Avoid using radiation therapy or medications that are potentially photosensitizing when possible.

### B. Local Treatment

For limited lesions, the following should be tried before systemic therapy: high-potency corticosteroid creams applied each night and covered with airtight, thin, pliable plastic film (eg, Saran Wrap); Cordran tape; or ultra-high-potency corticosteroid cream or ointment applied twice daily without occlusion.

### C. Local Infiltration

Triamcinolone acetonide suspension, 2.5–10 mg/mL, may be injected into the lesions of DLE once a month.

### D. Systemic Treatment

**1. Antimalarials**—These medications should be used only when the diagnosis is secure because they have been associated with flares of psoriasis, which may be in the differential diagnosis.

**A. HYDROXYCHLOROQUINE SULFATE**—Daily dose of no more than 5 mg/kg orally (real-weight) for several months may be effective and is often used prior to chloroquine. A minimum 3-month trial is recommended. Screening for ocular toxicity is needed.

**B. CHLOROQUINE SULFATE**—250 mg orally daily may be effective in some cases when hydroxychloroquine is not.

**2. Isotretinoin**—Isotretinoin, 1 mg/kg/day orally, is effective in hypertrophic DLE lesions.

**3. Thalidomide**—Thalidomide is effective in refractory cases in doses of 50–300 mg orally daily. Monitor for neuropathy. Lenalidomide (5–10 mg orally daily) may also be effective with less risk for neuropathy.

Isotretinoin, thalidomide, and lenalidomide are teratogens and should be used with appropriate contraception and monitoring in women of childbearing age.

## ► Prognosis

The disease is persistent but not life-endangering unless systemic lupus is present. Treatment with one or more antimalarials is effective in more than half of cases. Patients with cutaneous lupus erythematosus should be examined and tested annually (complete blood count and urinalysis) to screen for early signs of systemic involvement. Although the only morbidity may be cosmetic, this can have significant quality of life impact in more darkly pigmented patients with widespread disease. Scarring alopecia can be prevented or lessened with close attention and aggressive therapy. Over years, DLE tends to become inactive. Drug-induced SCLE usually resolves over months when the inciting medication is stopped.

Chasset F et al. Current concepts and future approaches in the treatment of cutaneous lupus erythematosus: a comprehensive review. *Drugs*. 2019;79:1199. [PMID: 31228033]

Fairley JL et al. Management of cutaneous manifestations of lupus erythematosus: a systematic review. *Semin Arthritis Rheum*. 2020;50:95. [PMID: 31526594]

## CUTANEOUS T-CELL LYMPHOMA (Mycosis Fungoides)



- Localized or generalized erythematous scaling patches that progress to plaques and nodules.
- Sometimes associated with pruritus, lymphadenopathy.
- Distinctive histology.

## ► General Considerations

Mycosis fungoides is a cutaneous T-cell lymphoma that begins on the skin and may remain there for years or decades. It may progress to systemic disease, including Sézary syndrome (erythroderma with circulating malignant T cells).

## ► Clinical Findings

### A. Symptoms and Signs

Localized or generalized erythematous scaly patches or plaques are present usually on the trunk. Plaques are almost always over 5 cm in diameter. Pruritus is a frequent complaint and can be severe. The lesions often begin as nondescript or nondiagnostic patches, and it is not unusual for the patient to have skin lesions for more than a decade before the diagnosis can be confirmed. Follicular involvement with hair loss is characteristic of mycosis fungoides, and its presence should raise the suspicion of mycosis fungoides for any pruritic eruption. In more advanced cases, tumors appear. Local or diffuse lymph node enlargement may be due to benign expansion of the node (dermatopathic lymphadenopathy) or involvement with mycosis fungoides.

## B. Laboratory Findings

Diagnosis is based on skin biopsy though numerous biopsies may be required before the diagnosis can be confirmed. In more advanced disease, circulating malignant T cells (Sézary cells) can be detected in the blood (T-cell gene rearrangement test). Eosinophilia may be present.

## ► Differential Diagnosis

Mycosis fungoides may be confused with psoriasis, drug eruption, photoallergy, eczematous dermatitis, syphilis, or tinea corporis. Histologic examination can distinguish these conditions.

## ► Treatment

The treatment of mycosis fungoides is complex. Early and aggressive treatment has not been proven to cure or prevent disease progression. Skin-directed therapies, including topical corticosteroids, topical mechlorethamine, bexarotene gel, and UV phototherapy, are used initially. If the disease progresses, PUVA plus retinoids, PUVA plus interferon, extracorporeal photopheresis, bexarotene, histone deacetylase inhibitors (romidepsin or vorinostat), targeted immunomodulators (brentuximab, mogamulizumab), and total skin electron beam treatment are used.

## ► Prognosis

Mycosis fungoides is usually slowly progressive (over decades). Prognosis is better in patients with patch or plaque stage disease and worse in patients with erythroderma, tumors, and lymphadenopathy. Survival is not reduced in patients with limited patch disease. Elderly patients with limited disease commonly die of other causes. Overly aggressive treatment may lead to complications and premature demise.

Larocca C et al. Mycosis fungoides and Sézary syndrome: an update. Hematol Oncol Clin North Am. 2019;33:103. [PMID: 30497668]

Peterson E et al. Cutaneous T cell lymphoma: a difficult diagnosis demystified. Dermatol Clin. 2019;37:455. [PMID: 31466586]

## EXFOLIATIVE DERMATITIS (Exfoliative Erythroderma)



### ESSENTIALS OF DIAGNOSIS

- ▶ Scaling and erythema over most of the body.
- ▶ Itching, malaise, fever, chills, weight loss.

## ► General Considerations

Erythroderma describes generalized redness and scaling of the skin of more than 30% BSA. A preexisting dermatosis is the cause of exfoliative dermatitis in two-thirds of cases, including psoriasis, atopic dermatitis, contact dermatitis, pityriasis rubra pilaris, and seborrheic dermatitis.

Reactions to topical or systemic medications account for about 15% of cases, cancer (paraneoplastic symptom of lymphoma, solid tumors, and most commonly, cutaneous T-cell lymphoma) for about 10%, and 10% are idiopathic. Widespread scabies is an important diagnostic consideration since patients with erythrodermic presentation are highly contagious. At the time of acute presentation, without a clear-cut prior history of skin disease or medication exposure, it may be impossible to make a specific diagnosis of the underlying condition, and diagnosis may require continued observation.

## ► Clinical Findings

### A. Symptoms and Signs

Symptoms may include itching, weakness, malaise, fever, and weight loss. Chills are prominent. Erythema and scaling are widespread. Loss of hair and nails can occur. Generalized lymphadenopathy may be due to lymphoma or leukemia or may be reactive. The mucosae are typically spared.

### B. Laboratory Findings

A skin biopsy is required and may show changes of a specific inflammatory dermatitis or cutaneous T-cell lymphoma. Peripheral leukocytes may show clonal rearrangements of the T-cell receptor in Sézary syndrome.

## ► Complications

Protein and electrolyte loss as well as dehydration may develop in patients with generalized inflammatory exfoliative erythroderma; sepsis may occur.

## ► Treatment

### A. Topical Therapy

Home treatment is with cool to tepid baths and application of mid-potency corticosteroids under wet dressings or with the use of an occlusive plastic suit. If the condition becomes chronic and unmanageable in an outpatient setting, the patient should be hospitalized.

### B. Specific Measures

Stop all medications, if possible. Systemic corticosteroids may provide marked improvement in severe or fulminant exfoliative dermatitis, but long-term therapy should be avoided (see Chapter 26). For cases of psoriatic erythroderma and pityriasis rubra pilaris, acitretin, methotrexate, cyclosporine, or a TNF inhibitor may be indicated. Erythroderma secondary to lymphoma or leukemia requires specific topical or systemic chemotherapy. Suitable antibiotic medications with coverage for *Staphylococcus* should be given when there is evidence of bacterial infection.

## ► Prognosis

Careful follow-up is necessary because identifying the cause of exfoliative erythroderma early in the course of the disease may be impossible. Most patients improve or recover completely but some may require long-term

therapy. Deaths are rare in the absence of cutaneous T-cell lymphoma. A minority of patients will suffer from undiminished erythroderma for indefinite periods.

Inamadar AC et al. The rash that becomes an erythroderma. Clin Dermatol. 2019;37:88. [PMID: 30981298]

## MISCELLANEOUS SCALING DERMATOSES

Isolated scaly patches may represent actinic (solar) keratoses, nonpigmented seborrheic keratoses, or Bowen or Paget disease.

### 1. Actinic Keratoses

Actinic keratoses are small (0.2–0.6 cm) macules or papules—flesh-colored, pink, or slightly hyperpigmented—that feel like sandpaper and are tender to palpation. They occur on sun-exposed parts of the body in persons of fair complexion. Actinic keratoses are considered premalignant, but 1:1000 lesions per year progress to squamous cell carcinoma.

Application of liquid nitrogen provides rapid eradication of lesions, which crust and disappear in 10–14 days. “Field treatment” with a topical agent to an anatomic area where the actinic keratoses are most prevalent (eg, forehead, dorsal hands, etc) can be considered in patients with multiple lesions in one region. Fluorouracil cream is the most effective topical agent used for field treatment; imiquimod and ingenol mebutate are also effective, as is photodynamic therapy. Combination therapy may be clinically beneficial. Any lesions that persist should be evaluated for possible biopsy.

Jansen MHE et al. Randomized trial of four treatment approaches for actinic keratosis. N Engl J Med. 2019;380:935. [PMID: 30855743]

Hept MV et al. Cryosurgery combined with topical interventions for actinic keratosis: a systematic review and meta-analysis. Br J Dermatol. 2019;180:740. [PMID: 30447074]

Hept MV et al. Efficacy of photodynamic therapy combined with topical interventions for the treatment of actinic keratosis: a meta-analysis. J Eur Acad Dermatol Venereol. 2019;33:863. [PMID: 30710390]

### 2. Bowen Disease & Paget Disease

Bowen disease (intraepidermal squamous cell carcinoma) can develop on sun-exposed and non-sun-exposed skin. The lesion is usually a small (0.5–3 cm), well-demarcated, slightly raised, pink to red, scaly plaque and may resemble psoriasis or a large actinic keratosis. Lesions may progress to invasive squamous cell carcinoma. Excision or other definitive treatment such as topical treatment (fluorouracil or imiquimod) or photodynamic therapy is indicated.

Extramammary Paget disease, a manifestation of intraepidermal carcinoma or underlying genitourinary or gastrointestinal cancer, resembles chronic eczema and usually involves apocrine areas such as the genitalia. Mammary Paget disease of the nipple, a unilateral or rarely bilateral red scaling plaque that may ooze, is associated with an underlying intraductal mammary carcinoma (see Figure 17–3). While these lesions appear as red patches and

plaques in fair-skinned persons, in darker-skinned individuals, hyperpigmentation may be prominent.

Edey KA et al. Interventions for the treatment of Paget's disease of the vulva. Cochrane Database Syst Rev. 2019;6:CD009245. [PMID: 31167037]

Merritt BG et al. Extramammary Paget disease. Dermatol Clin. 2019;37:261. [PMID: 31084720]

## INTERTRIGO

Intertrigo is caused by the macerating effect of heat, moisture, and friction. It is especially likely to occur in obese persons and in humid climates. The symptoms are itching, stinging, and burning. The body folds develop fissures, erythema, maceration, and superficial denudation. Candidiasis may complicate intertrigo. “Inverse psoriasis,” seborrheic dermatitis, tinea cruris, erythrasma, and candidiasis must be ruled out.

Maintain hygiene in the area, and keep it dry. Compresses may be useful acutely. Hydrocortisone 1% cream plus an imidazole or clotrimazole 1% cream is effective. Recurrences are common.

Kottner J et al. Prevalence of intertrigo and associated factors: a secondary data analysis of four annual multicentre prevalence studies in the Netherlands. Int J Nurs Stud. 2020;104:103437. [PMID: 32105975]

## VESICULAR DERMATOSES

### HERPES SIMPLEX (Cold or Fever Sore; Genital Herpes)



#### ESSENTIALS OF DIAGNOSIS

- Recurrent small grouped vesicles (especially orolabial and genital) on an erythematous base.
- May follow minor infections, trauma, stress, or sun exposure.
- Regional tender lymphadenopathy may occur.
- Direct fluorescent antibody tests are positive.

### ► General Considerations

Over 85% of adults have serologic evidence of herpes simplex type 1 (HSV-1) infections, most often acquired asymptotically in childhood. Occasionally, primary infections may be manifested as severe gingivostomatitis. Thereafter, the patient may have recurrent self-limited attacks, provoked by sun exposure, orofacial surgery, fever, or a viral infection.

About 25% of the US population has serologic evidence of infection with herpes simplex type 2 (HSV-2). HSV-2 causes lesions whose morphology and natural history are similar to those caused by HSV-1 but are typically located on the genitalia or buttocks of both sexes. The infection is

acquired by sexual contact. In monogamous heterosexual couples where one partner has HSV-2 infection, seroconversion of the noninfected partner occurs in 10% over a 1-year period. Up to 70% of such infections appeared to be transmitted during periods of asymptomatic shedding. Genital herpes may also be due to HSV-1.

## ► Clinical Findings

### A. Symptoms and Signs

The principal symptoms are burning and stinging. Neuralgia may precede or accompany attacks. The lesions consist of small, grouped vesicles on an erythematous base that can occur anywhere but that most often occur on the vermillion border of the lips (Figure 6–14), the penile shaft, the labia, the perianal skin, and the buttocks. Any erosion or fissure in the anogenital region can be due to herpes simplex. Regional lymph nodes may be swollen and tender. The lesions usually crust and heal in 1 week. Immunosuppressed patients may have unusual variants, including verrucous or nodular herpes lesions at typical sites of involvement. Lesions of herpes simplex must be distinguished from chancroid, syphilis, pyoderma, or trauma.

### B. Laboratory Findings

Direct fluorescent antibody slide tests offer rapid, sensitive diagnosis. Viral culture or polymerase chain reaction (PCR) may also be helpful. Herpes serology is not used in the diagnosis of an acute genital ulcer. Specific HSV-2 serology by Western blot assay or enzyme-linked immunosorbent assay (ELISA) can determine who is HSV-infected and potentially infectious, but routine HSV-2 screening is not recommended by the United States Preventive Services Task Force.

## ► Complications

Complications include pyoderma, eczema herpeticum, herpetic whitlow, herpes gladiatorum (epidemic herpes



**▲ Figure 6–14.** Orolabial herpes simplex showing derroofed blisters (ulcer). (Used, with permission, from Richard P. Usatine, MD, in Usatine RP, Smith MA, Mayeaux EJ Jr, Chumley HS. *The Color Atlas and Synopsis of Family Medicine*, 3rd ed. McGraw-Hill, 2019.)

transmitted by contact), proctitis, esophagitis, neonatal infection, keratitis, and encephalitis.

## ► Treatment

### A. Systemic Therapy

Three systemic agents are available for the treatment of acute herpes infections: acyclovir, valacyclovir, and famciclovir. All three agents are very effective, and when used properly, virtually nontoxic. Only acyclovir is available for intravenous administration. In the immunocompetent, with the exception of severe orolabial herpes, only genital disease is treated.

**1. For first clinical episode**—Recommended treatment for the first clinical episodes of herpes simplex includes acyclovir, 400 mg orally five times daily (or 800 mg three times daily); valacyclovir, 1000 mg orally twice daily; or famciclovir, 250 mg orally three times daily; treatment is for 7–10 days, depending on the severity of the outbreak.

**2. For mild recurrences**—Most cases do not require therapy. Pharmacotherapy of recurrent HSV is of limited benefit, reducing the average outbreak by only 12–24 hours. **To be effective, the treatment must be initiated by the patient at the first sign of recurrence.** If treatment is desired, recurrent genital herpes outbreaks may be treated with 3 days of valacyclovir, 500 mg orally twice daily; 5 days of acyclovir, 200 mg orally five times a day, or 5 days of famciclovir, 125 mg orally twice daily. Valacyclovir, 2 g twice daily for 1 day, and famciclovir, 1 g once or twice in 1 day, are equally effective short-course alternatives and can abort impending recurrences of both orolabial and genital herpes. The addition of a potent topical corticosteroid three times daily reduces the duration, size, and pain of orolabial herpes treated with an oral antiviral agent.

**3. For frequent or severe recurrences**—Suppressive treatment reduces recurrences by 85%, viral shedding by more than 90%, and the risk of transmission by 50%. The recommended suppressive doses, taken continuously, are acyclovir, 400 mg orally twice daily; valacyclovir, 500 mg orally once daily; or famciclovir, 125–250 mg orally twice daily. Pritelivir, 100 mg orally once daily, may have superior reduction of viral shedding in HSV-2 compared to valacyclovir, 500 mg orally once daily. Long-term suppression appears safe, and after 5–7 years a substantial proportion of patients can discontinue treatment.

Sunscreens are useful adjuncts in preventing sun-induced HSV-1 recurrences. A preventive antiviral medication should be started beginning 24 hours prior to ultraviolet light exposure, dental surgery, or orolabial cosmetic surgery. The use of latex condoms and patient education have proved effective in reducing genital herpes transmission in some but not all studies. No single or combination intervention absolutely prevents transmission.

### B. Local Measures

In general, topical therapy has only limited efficacy and is generally not recommended because evidence shows that it only minimally reduces skin healing time.

## ► Prognosis

Aside from the complications described above, recurrent attacks last several days, and patients recover without sequelae.

Crimi S et al. Herpes virus, oral clinical signs and QoL: systematic review of recent data. *Viruses*. 2019;11:463. [PMID: 31117264]

## HERPES ZOSTER (Shingles)

See Chapter 32.

## POMPHOLYX

### ESSENTIALS OF DIAGNOSIS

- ▶ Pruritic “tapioca” vesicles of 1–2 mm on the palms, soles, and sides of fingers.
- ▶ Vesicles may coalesce to form multiloculated blisters.
- ▶ Scaling and fissuring may follow drying of the blisters.
- ▶ Appearance in the third decade, with lifelong recurrences.

## ► General Considerations

Pompholyx, or vesiculobullous dermatitis of the palms and soles, is formerly known as dyshidrosis or dyshidrotic eczema. About half of patients have an atopic background, and many patients report flares with stress. Patients with widespread dermatitis due to any cause may develop pompholyx-like eruptions as a part of an autoeczematization response.

## ► Clinical Findings

Small clear vesicles resembling grains of tapioca stud the skin at the sides of the fingers and on the palms (Figure 6–15) and may also affect the soles, albeit less frequently. They may be associated with intense itching. Later, the vesicles dry and the area becomes scaly and fissured.

## ► Differential Diagnosis

Unroofing the vesicles and examining the blister roof with a KOH preparation will reveal hyphae in cases of bullous tinea. Patients with inflammatory tinea pedis may have a vesicular autoeczematization of the palms. Nonsteroidal anti-inflammatory drugs (NSAIDs) may produce an eruption very similar to that of vesiculobullous dermatitis on the hands.

## ► Prevention

There is no known way to prevent attacks if the condition is idiopathic. About one-third to one-half of patients with vesiculobullous hand dermatitis have a relevant contact allergen, especially nickel. Patch testing and avoidance of identified allergens can lead to improvement.



▲ **Figure 6–15.** Severe pompholyx. (Used, with permission, from Richard P. Usatine, MD, in Usatine RP, Smith MA, Mayeaux EJ Jr, Chumley HS. *The Color Atlas and Synopsis of Family Medicine*, 3rd ed. McGraw-Hill, 2019.)

## ► Treatment

Topical and systemic corticosteroids help some patients dramatically; however systemic corticosteroids are generally not appropriate therapy. A high-potency topical corticosteroid used early may help abort the flare and ameliorate pruritus. Topical corticosteroids are also important in treating the scaling and fissuring that are seen after the vesicular phase. Oral altretinoin may be effective. It is essential that patients avoid anything that irritates the skin; they should wear cotton gloves inside vinyl gloves when doing dishes or other wet chores and use a hand cream after washing the hands. Patients respond to PUVA therapy and injection of botulinum toxin into the palms as for hyperhidrosis.

## ► Prognosis

For most patients, the disease is an inconvenience. For some, vesiculobullous hand eczema can be incapacitating.

Agner T et al. Hand eczema: epidemiology, prognosis and prevention. *J Eur Acad Dermatol Venereol*. 2020;34:4. [PMID: 31860734]

Elsner P et al. Hand eczema: treatment. *J Eur Acad Dermatol Venereol*. 2020;34:13. [PMID: 31860736]

Lee GR et al. Current and emerging therapies for hand eczema. *Dermatol Ther*. 2019;32:e12840. [PMID: 30693618]

## PORPHYRIA CUTANEA TARDA

### ESSENTIALS OF DIAGNOSIS

- ▶ Noninflammatory blisters on sun-exposed sites, especially the dorsal surfaces of the hands.
- ▶ Hypertrichosis, skin fragility.
- ▶ Associated liver disease.
- ▶ Elevated urine porphyrins.



**▲ Figure 6-16.** Porphyria cutanea tarda of hands in patient with darker skin. (Used, with permission, from Kanade Shinkai, MD.)

## ► General Considerations

Porphyria cutanea tarda is the most common type of porphyria. Cases are sporadic or hereditary. The disease is associated with ingestion of certain medications (eg, estrogens) and alcoholic liver disease, hemochromatosis, or hepatitis C.

## ► Clinical Findings

### A. Symptoms and Signs

Patients complain of painless blistering and fragility of the skin of the dorsal surfaces of the hands (Figure 6-16). Facial hypertrichosis and hyperpigmentation are common.

### B. Laboratory Findings

Urinary uroporphyrins are elevated twofold to fivefold above coproporphyrins. Patients may also have abnormal liver biochemical tests, evidence of hepatitis C infection, increased liver iron stores, and hemochromatosis gene mutations.

## ► Differential Diagnosis

Skin lesions identical to those of porphyria cutanea tarda may be seen in patients who undergo dialysis and in those who take certain medications (tetracyclines, voriconazole, and NSAIDs, especially naproxen). In this so-called pseudoporphyria, the biopsy results are the same as those associated with porphyria cutanea tarda, but urine porphyrins are normal.

## ► Prevention

Barrier sun protection with clothing is required. Although the lesions are triggered by sun exposure, the wavelength of light triggering the lesions is beyond that absorbed by sunscreens.

## ► Treatment

Stopping all triggering medications and substantially reducing or stopping alcohol consumption alone may lead to improvement in most cases. Phlebotomy at a rate of 1 unit every 2–4 weeks will gradually lead to improvement. Very low-dose antimalarial medication (as low as 200 mg of hydroxychloroquine orally twice weekly), alone or in combination with phlebotomy, increases porphyrin excretion and improves the skin disease. Deferasirox, an iron chelator, can also be beneficial. Treatment is continued until the patient is asymptomatic. Urine porphyrins may be monitored.

## ► Prognosis

Most patients improve with treatment. Sclerodermoid skin lesions may develop on the trunk, scalp, and face.

Singal AK. Porphyria cutanea tarda: recent update. *Mol Genet Metab.* 2019;128:271. [PMID: 30683557]

## DERMATITIS HERPETIFORMIS

Dermatitis herpetiformis is an uncommon disease manifested by pruritic papules, vesicles, and papulovesicles mainly on the elbows, knees, buttocks, posterior neck, and scalp. It appears to have its highest prevalence in Northern Europe and is associated with HLA antigens -B8, -DR3, and -DQ2. The histopathology is distinctive. Circulating antibodies to tissue transglutaminase are present in 90% of cases. NSAIDs may cause flares. Patients have gluten-sensitive enteropathy, but nondermatologic disease is subclinical in the great majority. However, ingestion of gluten is the cause of dermatitis herpetiformis, and strict long-term avoidance of dietary gluten may eliminate the need for treatment or decrease the dose of dapsone (initial treatment dose is 100–200 mg orally daily) required to control the disease. Patients with dermatitis herpetiformis are at increased risk for development of gastrointestinal lymphoma, and this risk is reduced by a gluten-free diet.

Salmi TT. Dermatitis herpetiformis. *Clin Exp Dermatol.* 2019;44:728. [PMID: 31093998]

## WEEPING OR CRUSTED LESIONS

### IMPETIGO



### ESSENTIALS OF DIAGNOSIS

- Superficial blisters filled with purulent material that rupture easily.
- Crusted superficial erosions.
- Positive Gram stain and bacterial culture.



**▲ Figure 6-17.** Typical honey-crusted plaque on the lip of an adult with impetigo. (Used, with permission, from Richard P. Usatine, MD, in Usatine RP, Smith MA, Mayeaux EJ Jr, Chumley HS. *The Color Atlas and Synopsis of Family Medicine*, 3rd ed. McGraw-Hill, 2019.)

## ► General Considerations

Impetigo is a contagious and autoinoculable infection of the skin (epidermis) caused by staphylococci or streptococci.

## ► Clinical Findings

### A. Symptoms and Signs

The lesions consist of macules, vesicles, bullae, pustules, and honey-colored crusts that when removed leave denuded red areas (Figure 6-17). The face and other exposed parts are most often involved. Ecthyma is a deeper form of impetigo caused by staphylococci or streptococci, with ulceration and scarring that occurs frequently on the extremities.

### B. Laboratory Findings

Gram stain and culture confirm the diagnosis. In temperate climates, most cases are associated with *S aureus* infection. *Streptococcus* species are more common in tropical infections.

## ► Differential Diagnosis

The main differential diagnoses, especially of honey-colored crusting, are acute allergic contact dermatitis and herpes simplex. Contact dermatitis may be suggested by the history or by linear distribution of the lesions, and culture should be negative for staphylococci and streptococci. Herpes simplex infection usually presents with grouped vesicles or discrete erosions and may be associated with a history of recurrences. Viral cultures are positive.

## ► Treatment

Soaks and scrubbing can be beneficial, especially in unroofing lakes of pus under thick crusts. Topical agents, such as mupirocin, ozenoxacin, and retapamulin, are first-line treatment options for infections limited to small areas. In

widespread cases, or in immunosuppressed individuals, systemic antibiotics are indicated. Cephalexin, 250 mg orally four times daily, is usually effective. Doxycycline, 100 mg orally twice daily, is a reasonable alternative. Community-associated methicillin-resistant *S aureus* (CA-MRSA) may cause impetigo, for which initial treatment may include doxycycline (100 mg orally twice daily) or trimethoprim-sulfamethoxazole (TMP-SMZ, double-strength tablet orally twice daily). Recurrent impetigo is associated with nasal carriage of *S aureus* and is treated with rifampin, 300 mg orally twice daily for 5 days. Intranasal mupirocin ointment twice daily for 14 days eliminates most MRSA strains. Bleach baths ( $\frac{1}{4}$  to  $\frac{1}{2}$  cup per 20 liters of bathwater for 15 minutes three to five times weekly) for all family members and the use of dilute household bleach to clean showers and other bath surfaces may help reduce the spread. Infected individuals should not share towels with household members. Among hospitalized patients colonized with MRSA, decolonization with chlorhexidine washes combined with nasal mupirocin for 5 days twice per month for 6 months resulted in 30% lower risk of MRSA infection than education alone.

Galli L et al; Italian Pediatric Infectious Diseases Society; Italian Pediatric Dermatology Society. Common community-acquired bacterial skin and soft-tissue infections in children: an intersociety consensus on impetigo, abscess, and cellulitis treatment. Clin Ther. 2019;41:532. [PMID: 30777258]

Huang SS et al; Project CLEAR Trial. Decolonization to reduce postdischarge infection risk among MRSA carriers. N Engl J Med. 2019;380:638. [PMID: 30763195]

## CONTACT DERMATITIS

### ESSENTIALS OF DIAGNOSIS

- Erythema and edema, with pruritus, vesicles, bullae, weeping, or crusting.
- **Irritant contact dermatitis:** occurs only in area of direct contact with irritant.
- **Allergic contact dermatitis:** extends beyond area of direct contact with allergen; positive patch test.

## ► General Considerations

Contact dermatitis (irritant or allergic) is an acute or chronic dermatitis that results from direct skin contact with chemicals or allergens. Eighty percent of cases are due to excessive exposure to or additive effects of universal irritants (eg, soaps, detergents, organic solvents) and are called **irritant contact dermatitis**. The most common causes of **allergic contact dermatitis** are poison ivy or poison oak, topically applied antimicrobials (especially bacitracin and neomycin), anesthetics (benzocaine), preservatives, jewelry (nickel), rubber, essential oils, propolis (from bees), vitamin E, and adhesive tape. Occupational exposure is an important cause of allergic contact dermatitis.

## ► Clinical Findings

### A. Symptoms and Signs

**1. Allergic contact dermatitis**—The acute phase is characterized by intense pruritus, tiny vesicles, and weepy and crusted lesions. The lesions, distributed on exposed parts or in unusual asymmetric patterns, consist of erythematous macules, papules, and vesicles and may occur beyond the contact area, distinguishing it from irritant dermatitis. The affected area may also be edematous and warm, simulating—and at times complicated by—bacterial or viral infection. The pattern of the eruption may be diagnostic (eg, typical linear streaked vesicles on the extremities in poison oak or ivy dermatitis [Figure 6–18]). The location will often suggest the cause: scalp involvement suggests hair dyes or shampoos; face involvement suggests creams, cosmetics, soaps, shaving materials, nail polish; and neck involvement suggests jewelry, hair dyes. Reactions may not develop for 48–72 hours after exposure.

**2. Irritant contact dermatitis**—The rash is erythematous and scaly (but less likely vesicular) and occurs only in the direct sites of contact with the irritant. Resolving or chronic contact dermatitis presents with scaling, erythema, and possibly thickened skin. Itching, burning, and stinging may be severe in both allergic and irritant contact

dermatitis. Reactions may develop within 24 hours of contact exposure.

### B. Laboratory Findings

Gram stain and culture will rule out impetigo or secondary infection (impetiginization). After the episode of allergic contact dermatitis has cleared, patch testing may be useful if the triggering allergen is not known.

## ► Differential Diagnosis

Asymmetric distribution, blotchy erythema around the face, linear lesions, and a history of exposure help distinguish acute contact dermatitis from other skin lesions. The most commonly mistaken diagnosis is impetigo, herpetic infection, or cellulitis. Chronic allergic contact dermatitis must be differentiated from scabies, particularly if itching is generalized; atopic dermatitis; and pompholyx.

## ► Prevention

Prompt removal of the causative oil by washing with liquid soap may be effective if done within 30 minutes after exposure to poison oak or ivy. Goop (oil remover) and Tecnu (chemical inactivator) are also effective but much more expensive without increased efficacy. Over-the-counter barrier creams may be effective when applied prior to exposure and prevent/reduce the severity of the dermatitis.

The mainstay of prevention is identification of the agent causing the dermatitis and strict avoidance of exposure or use of protective clothing and gloves. Some allergens will transmit through latex gloves. In industry-related cases, prevention may require moving or retraining the worker.

## ► Treatment

### A. Overview

Localized involvement (except on the face) can often be managed solely with topical agents. While local measures are important, severe or widespread involvement is difficult to manage without systemic corticosteroids because even the highest-potency topical corticosteroids seem not to work well on vesicular and weepy lesions. **Irritant contact dermatitis** is treated by protection from the irritant and use of topical corticosteroids as for atopic dermatitis (described above). The treatment of **allergic contact dermatitis** is detailed below.

### B. Local Measures

**1. Acute weeping dermatitis**—Gentle cleansing and drying compresses (such as Domeboro) are recommended. Calamine lotion or zinc oxide paste may be used between wet dressings, especially for involvement of intertriginous areas or when oozing is not marked. Lesions on the extremities may be bandaged with wet dressings for 30–60 minutes several times a day. High-potency topical corticosteroids in gel or cream form (eg, fluocinonide, clobetasol, or halobetasol) may help suppress acute contact dermatitis and relieve itching. This treatment should be followed by tapering of the number of applications per day.



**▲ Figure 6–18.** Allergic contact dermatitis to an adhesive dressing in patient with darker skin. Key features are erythematous papules with impetigo-like honey-colored crusting. (Used, with permission, from Kanade Shinkai, MD.)

or use of a mid-potency corticosteroid, such as triamcinolone 0.1% cream to prevent rebound of the dermatitis. A soothing formulation is 2 oz of 0.1% triamcinolone acetonide cream in 7.5 oz Sarna lotion (0.5% camphor, 0.5% menthol, 0.5% phenol) mixed by the patient.

**2. Subacute dermatitis (subsiding)**—Mid-potency (triamcinolone 0.1%) to high-potency corticosteroids (clobetasol, fluocinonide, desoximetasone) are the mainstays of therapy.

**3. Chronic dermatitis (dry and lichenified)**—High-potency to superpotency corticosteroids are used in ointment form. Occlusion may be helpful on the hands.

### C. Systemic Therapy

For acute severe cases, prednisone may be given orally for 12–21 days. Prednisone, 60 mg for 4–7 days, 40 mg for 4–7 days, and 20 mg for 4–7 days, without a further taper is one useful regimen. The key is to use enough corticosteroid (and as early as possible) to achieve a clinical effect and to taper slowly over 2–3 weeks to avoid rebound.

### ► Prognosis

Allergic contact dermatitis is self-limited if reexposure is prevented but often takes 2–3 weeks for full resolution. Removal of the causative agent is paramount to avoid recurrences.

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 Bains SN et al. Irritant contact dermatitis. *Clin Rev Allergy Immunol*. 2019;56:99. [PMID: 30293200]  
 Nassau S et al. Allergic contact dermatitis. *Med Clin North Am*. 2020;104:61. [PMID: 31757238]

## PUSTULAR DISORDERS

### ACNE VULGARIS



#### ESSENTIALS OF DIAGNOSIS

- ▶ Almost universal in puberty; may begin in premenarchal girls and present or persist into the fourth or fifth decade.
- ▶ Comedones are the hallmark. Severity varies from comedonal to papular or pustular inflammatory acne to cysts or nodules.
- ▶ Face, neck, and upper trunk may be affected.
- ▶ Scarring may be a sequela of the disease or picking by the patient.

### ► General Considerations

Acne vulgaris is polymorphic. Open and closed comedones, papules, pustules, and cysts are found.

In younger persons, acne vulgaris is more common and more severe in males. It does not always clear spontaneously when maturity is reached. Twelve percent of women and 3% of men over age 25 have acne vulgaris. This rate does not decrease until the fourth or fifth decade of life. The skin lesions parallel sebaceous activity. Pathogenic events include plugging of the infundibulum of the follicles, retention of sebum, overgrowth of the acne bacillus (*Cutibacterium acnes*) with resultant release of and irritation by accumulated fatty acids, and foreign-body reaction to extrafollicular sebum. Antibiotics may help control acne because of their antibacterial or anti-inflammatory properties.

Hyperandrogenism may be a cause of acne in women and may or may not be accompanied by hirsutism or irregular menses. Polycystic ovary syndrome (PCOS) is the most common identifiable cause. Acne may develop in patients who use systemic corticosteroids or topical fluorinated corticosteroids on the face. Acne may be exacerbated or caused by cosmetic creams or oils.

### ► Clinical Findings

There may be mild tenderness, pain, or itching. The lesions occur mainly over the face, neck, upper chest, back, and shoulders. Comedones (tiny, flesh-colored, white or black noninflamed superficial papules that give the skin a rough texture or appearance) are the hallmark of acne vulgaris. Inflammatory papules, pustules, ectatic pores, acne cysts, and scarring are also seen (Figure 6–19).

Acne may have different presentations at different ages. Preteens often present with comedones as their first lesions. Inflammatory lesions in young teenagers are often found in the middle of the face, extending outward as the patient becomes older. Women in their third and fourth decades (often with no prior history of acne) commonly present with papular lesions on the chin and jawline.

### ► Differential Diagnosis

In adults, rosacea presents with papules and pustules in the middle third of the face, but absence of truncal



**▲ Figure 6–19.** Acne vulgaris. Extensive comedones and hyperpigmented macules are present in patient with dark skin. (Used, with permission, from Kanade Shinkai, MD.)

involvement, telangiectasia, flushing, and the absence of comedones distinguish rosacea from acne vulgaris. A pustular eruption on the face in patients receiving antibiotics or with otitis externa should be investigated with culture to rule out a gram-negative folliculitis. Pustules on the face can also be caused by tinea infections. Lesions on the back are more problematic. When they occur alone, staphylococcal folliculitis, miliaria ("heat rash") or, uncommonly, *Malassezia* (*Pityrosporum*) folliculitis should be suspected. Bacterial culture, trial of an antistaphylococcal antibiotic, and observing the response to therapy will help in the differential diagnosis. In patients with HIV infection, folliculitis is common and may be either staphylococcal folliculitis or eosinophilic folliculitis (typically pruritic tumid papules on the face and neck).

## ► Complications

Cyst formation, pigmentary changes, scarring, and poor quality of life may result.

## ► Treatment

### A. General Measures

**1. Education of the patient**—Education on proper use of medications and cosmetics is paramount. Because lesions take 4–6 weeks to improve, clinical improvement should be measured by the number of new lesions forming after 6–8 weeks of therapy. Additional time (3–4 months) will be required to see improvement on the back and chest, as these areas are slowest to respond. Avoid topical exposure to oils, cocoa butter (theobroma oil), and greases in cosmetics, including hair products. Scarring may occur with or without the patient manipulating the lesions. It is essential that the patient be educated in a supportive way about this complication. Anxiety and depression are common in patients with excoriated acne.

**2. Diet**—A low glycemic diet has been associated with improvement and lower incidence of acne. This improvement was associated with a reduction in insulin resistance. Hyperinsulinemia has also been associated with acne in both eumenorrheic women and individuals with PCOS.

### B. Comedonal Acne

Treatment of acne is based on the type and severity of lesions. Comedones require treatment different from that of pustules and cystic lesions. In assessing severity, take the sequelae of the lesions into account. An individual who gets only a few new lesions per month that scar or leave postinflammatory hyperpigmentation must be treated much more aggressively than a comparable patient whose lesions clear without sequelae. Hygiene plays little role in acne treatment, and a mild soap is almost always recommended. The agents effective in comedonal acne are listed below in the order in which they should be tried.

**1. Topical retinoids**—Tretinoin is very effective for comedonal acne or for treatment of the comedonal component of more severe acne, but its usefulness is limited by

irritation. Start with 0.025% cream (not gel) and have the patient use it at first twice weekly at night, increasing frequency to nightly as tolerated. A few patients cannot tolerate this low-strength preparation more than three times weekly, which may still promote improvement. A lentil-sized amount is sufficient to cover the entire face. To avoid irritation, have the patient wait 20 minutes after washing to apply. For patients irritated by standard tretinoin preparations, other options are adapalene gel 0.1% and reformulated tretinoin (Renova, Retin A Micro, Avita). Although the absorption of tretinoin is minimal, its use during pregnancy is contraindicated. Patients should be warned that their acne may flare in the first 4 weeks of treatment.

**2. Benzoyl peroxide**—Benzoyl peroxide products are available in concentrations of 2.5%, 4%, 5%, 8%, and 10%, but 2.5% is as effective as 10% and less irritating. In general, water-based and not alcohol-based gels should be used to decrease irritation. Single formulations of benzoyl peroxide in combination with several other topical agents, including adapalene and topical antibiotics (erythromycin, clindamycin phosphate), are available.

### C. Papular or Cystic Inflammatory Acne

Brief treatment (3 weeks to 3 months) with topical or oral antibiotics is the mainstay for treatment of inflammatory acne that does not respond to topical therapy with retinoids or benzoyl peroxide. Topical clindamycin phosphate and erythromycin are used only for mild papular acne or for patients who refuse or cannot tolerate oral antibiotics. To decrease resistance, benzoyl peroxide should be used in combination with the topical antibiotic.

**1. Mild acne**—The first choice of topical antibiotics in terms of efficacy and relative lack of induction of resistant *C acnes* is the combination of erythromycin or clindamycin with benzoyl peroxide topical gel or wash (Table 6–2). These may be used once or twice daily. The addition of tretinoin cream or gel at night may increase improvement, since it works via a different mechanism. Topical retinoids ideally are used as a long-term maintenance therapy.

**2. Moderate acne**—Common oral antibiotics used for acne include doxycycline (100 mg twice daily), minocycline (50–100 mg once or twice daily), TMP-SMZ (one double-strength tablet twice daily), or a cephalosporin (cefadroxil or cephalexin 500 mg twice daily), which should be used in combination with benzoyl peroxide to minimize development of antibiotic resistance. It may take 3 months or more for truncal acne to resolve with oral antibiotic treatment. In general, discontinuing antibiotics immediately without adjunctive topical therapy results in prompt recurrence. Topical retinoids are excellent for long-term maintenance following antibiotics. Subantimicrobial dosing of doxycycline (40–50 mg orally daily) can be used in patients who require long-term systemic therapy. Combination oral contraceptives or spironolactone (50–200 mg orally daily) are highly effective alternatives in women with treatment-resistant acne. Tetracycline, minocycline, and

doxycycline are contraindicated in pregnancy, but certain oral erythromycins or cephalosporins may be used.

### 3. Severe acne—

**A. ISOTRETINOIN**—A vitamin A analog, isotretinoin is used for the treatment of severe acne that has not responded to conventional therapy. An oral dosage of 0.5–1 mg/kg/day for 20 weeks for a cumulative dose of at least 120 mg/kg is usually adequate for severe cystic acne. If the severe acne is not adequately controlled by antibiotics, patients should be offered isotretinoin therapy before they experience significant scarring. *Isotretinoin is absolutely contraindicated during pregnancy because of its teratogenicity.* Two forms of effective contraception must be used; abstinence is an acceptable alternative. Informed consent must be obtained before its use, and patients must be enrolled in a monitoring program (iPledge). In addition to its teratogenicity, isotretinoin has numerous serious side effects and should only be prescribed by clinicians (usually dermatologists) well aware of these issues. Cheilitis, dry skin, and photosensitivity are almost universal side effects. Consider ordering laboratory tests, including total cholesterol levels, triglyceride levels, and liver enzyme tests (particularly alanine aminotransferase, which is the most liver-specific enzyme), in patients before treatment and after achieving therapeutic dosing; monitoring through the entire treatment may not be high value.

Abnormal laboratory tests, especially elevated liver enzymes and triglyceride levels, return to normal quickly upon conclusion of therapy. The medication may induce long-term remissions in 40–60%, or acne may recur that is more easily controlled with conventional therapy. Occasionally, a second course is needed if acne does not respond or recurs.

**B. INTRALESIONAL INJECTION**—Intralesional injection of dilute suspensions of triamcinolone acetonide (2.5 mg/mL, 0.05 mL per lesion) will often hasten the resolution of deeper papules and occasional cysts.

**C. SCAR REVISION**—Cosmetic improvement may be achieved by excision and punch-grafting of deep scars and by physical or chemical abrasion of inactive acne lesions, particularly flat, superficial scars.

### ► Prognosis

Acne vulgaris eventually remits spontaneously, but when this will occur cannot be predicted. The condition may persist throughout adulthood and may lead to severe scarring if left untreated. Patients treated with antibiotics continue to improve for the first 3–6 months of therapy. Relapse during treatment may suggest the emergence of resistant *C acnes*. The disease is chronic and tends to flare intermittently in spite of treatment. Remissions following systemic treatment with isotretinoin may be lasting in up to 60% of cases. Relapses after isotretinoin usually occur within 3 years and require a second course in up to 20% of patients. Immediate relapse after isotretinoin discontinuation may suggest hyperandrogenism or other underlying hormonal disorders in a female patient.

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Kollai SS et al. Topical retinoids in acne vulgaris: a systematic review. Am J Clin Dermatol. 2019;20:345. [PMID: 30674002]  
Zaenglein AL. Acne vulgaris. N Engl J Med. 2018;379:1343. [PMID: 30281982]

## ROSACEA



### ESSENTIALS OF DIAGNOSIS

- ▶ A chronic disorder affecting the face.
- ▶ Neurovascular component: erythema and telangiectasis and a tendency to flush easily.
- ▶ Acneiform component: papules and pustules may be present.
- ▶ Glandular component: sebaceous hyperplasia and fibrosis of affected areas (eg, rhinophyma).

### ► General Considerations

Rosacea is a common condition that presents in adulthood. The pathogenesis of this chronic disorder is not known. Topical corticosteroids applied to the face can induce rosacea-like conditions.

### ► Clinical Findings

Patients frequently report flushing or exacerbation of their rosacea due to heat, hot drinks, spicy food, sunlight, exercise, alcohol, emotions, or menopausal flushing. The cheeks, nose, chin, and ears—at times the entire face—may be affected. No comedones are seen. In its mildest form, erythema and telangiectasias are seen on the cheeks. Inflammatory papules may be superimposed on this background and may evolve to pustules (Figure 6–20). Associated seborrhea may be found. The patient often complains of burning or stinging with episodes of flushing and extremely cosmetic-intolerant skin. Patients may have associated ophthalmic disease, including blepharitis, keratitis, and chalazion, which often requires topical or systemic antibiotic or immunosuppressive therapy.

### ► Differential Diagnosis

Rosacea is distinguished from acne by the presence of the neurovascular component and the absence of comedones. Lupus is often misdiagnosed, but the presence of pustules excludes that diagnosis.

### ► Treatment

Educating patients to avoid the factors they know to produce exacerbations is important. Patients should wear a broad-spectrum mineral-based sunscreen; zinc- or titanium-based sunscreens are tolerated best. Medical management is most effective for the inflammatory papules



**▲ Figure 6-20.** Rosacea in a 34-year-old woman showing erythema, papules, and pustules covering much of the face. (Used, with permission, from Richard P. Usatine, MD, in Usatine RP, Smith MA, Mayeaux EJ Jr, Chumley HS. *The Color Atlas and Synopsis of Family Medicine*, 3rd ed. McGraw-Hill, 2019.)

and pustules and the erythema that surrounds them. Rosacea is usually a lifelong condition, so maintenance therapy is required. Most treatments target the papulopustular and cystic components. Only certain topical agents (brimonidine and oxymetazoline) and laser benefit erythema. Telangiectasias are benefited by laser therapy, and phymatosus overgrowth of the nose can be treated by surgical reduction. Rhinophyma must be managed using surgical reduction.

### A. Local Therapy

Avoidance of triggers (especially alcohol and spicy or hot foods) and drinking ice water may be effective in reducing facial erythema and flushing. Metronidazole (cream, gel, or lotion), 0.75% applied twice daily or 1% applied once daily, and ivermectin 1% cream applied once daily are effective topical treatments. Another effective treatment includes topical clindamycin (solution, gel, or lotion) 1% applied twice daily. Response is noted in 4–8 weeks. Sulfur-sodium sulfacetamide-containing topicals are helpful in patients only partially responsive to topical antibiotics. Topical retinoids can be carefully added for maintenance. Topical brimonidine tartrate gel 0.33% or oxymetazoline 1% cream can temporarily reduce the erythema, and laser treatment has longer-term benefit for erythema.

### B. Systemic Therapy

Oral tetracyclines should be used when topical therapy is inadequate. Minocycline or doxycycline, 50–100 mg orally once or twice daily, is effective. Metronidazole or amoxicillin, 250–500 mg orally twice daily, or rifaximin, 400 mg orally three times daily (for 10 days), may be used in refractory cases. Side effects are few, although metronidazole may cause a disulfiram-like effect when the patient ingests alcohol and neuropathy with long-term use. Long-term maintenance with subantimicrobial dosing of minocycline or doxycycline is recommended once the initial flare of rosacea has resolved. Isotretinoin may succeed where other measures fail. A dosage of 0.5 mg/kg/day orally for 12–28 weeks is recommended, although very low-dose isotretinoin may also be effective. See precautions above.

### ► Prognosis

Rosacea tends to be a persistent process. With the regimens described above, it can usually be controlled adequately.

Alexis AF et al. Global epidemiology and clinical spectrum of rosacea, highlighting skin of color: review and clinical practice experience. *J Am Acad Dermatol*. 2019;80:1722. [PMID: 30240779]

van Zuuren EJ et al. Interventions for rosacea based on the phenotype approach: an updated systematic review including GRADE assessments. *Br J Dermatol*. 2019;181:65. [PMID: 30585305]

## FOLLICULITIS (Including Sycosis)



- Itching and burning in hairy areas.
- Pustule surrounding and including the hair follicle.

### ► General Considerations

**Folliculitis** has multiple causes. It is frequently caused by staphylococcal infection and may be more common in the diabetic patient. When the lesion is deep-seated, chronic, and recalcitrant on the head and neck, it is called **sycosis**.

Gram-negative folliculitis, which may develop during antibiotic treatment of acne, may present as a flare of acne pustules or nodules. *Klebsiella*, *Enterobacter*, *Escherichia coli*, and *Proteus* have been isolated from these lesions.

Hot tub folliculitis (*Pseudomonas* folliculitis), caused by *Pseudomonas aeruginosa*, is characterized by pruritic or tender follicular, pustular lesions occurring within 1–4 days after bathing in a contaminated hot tub, whirlpool, or swimming pool. Flu-like symptoms may be present. Rarely, systemic infections may result. Neutropenic patients should avoid these exposures.

Nonbacterial folliculitis may also be caused by friction and oils. Occlusion, perspiration, and chronic rubbing (eg, from tight jeans or other heavy fabrics on the buttocks and thighs) can worsen this type of folliculitis.

Steroid acne may be seen during topical or systemic corticosteroid therapy and presents as eruptive monomorphic papules and papulopustules on the face and trunk. It responds to topical benzoyl peroxide.

Eosinophilic folliculitis is a sterile folliculitis that presents with urticarial papules with prominent eosinophilic infiltration. It is most common in immunosuppressed patients, especially those with AIDS. It may appear first with institution of highly active antiretroviral therapy (ART) and be mistaken for a drug eruption.

Pseudofolliculitis is caused by ingrowing of tightly curled hairs in the beard area. In this entity, the papules and pustules are located at the side of and not in follicles. It may be treated by growing a beard, by using chemical depilatories, or by shaving with a foil-guard razor. Medically indicated laser hair removal is dramatically beneficial in patients with pseudofolliculitis and can be done on patients of any skin color.

*Malassezia (Pityrosporum) folliculitis* presents as 1- to 2-mm pruritic pink papulopustules on the upper trunk, hairline, and arms. It is often pruritic and tends to develop during periods of excessive sweating. It can also occur in immunosuppressed patients.

Demodex folliculitis is caused by the mite *Demodex folliculorum*. It presents as 1–2 mm papules and pustules on an erythematous base, often on the background of rosacea-like changes, in patients who have not responded to conventional treatment for rosacea. It is more common in immunosuppressed patients. KOH from the pustules will demonstrate *Demodex folliculorum* mites.

## ► Clinical Findings

The symptoms range from slight burning and tenderness to intense itching. The lesions consist of pustules of hair follicles (Figure 6-21).



▲ **Figure 6-21.** Bacterial folliculitis. Hair emanating from the center of the pustule is the clinical hallmark of folliculitis. (Used, with permission, from Richard P. Usatine, MD, in Usatine RP, Smith MA, Mayeaux EJ Jr, Chumley HS. *The Color Atlas and Synopsis of Family Medicine*, 3rd ed. McGraw-Hill, 2019.)

## ► Differential Diagnosis

It is important to differentiate bacterial from nonbacterial folliculitis. The history is important for pinpointing the causes of nonbacterial folliculitis, and a Gram stain and culture are indispensable. One must differentiate folliculitis from acne vulgaris or pustular miliaria (heat rash) and from infections of the skin, such as impetigo or fungal infections, especially *Malassezia (Pityrosporum)* folliculitis. *Pseudomonas* folliculitis is often suggested by the history of hot tub use. Eosinophilic folliculitis in AIDS often requires biopsy for diagnosis.

## ► Complications

Abscess formation is the major complication of bacterial folliculitis.

## ► Prevention

Correct any predisposing local causes, such as oils or friction. Be sure that the water in hot tubs and spas is treated properly. If staphylococcal folliculitis is persistent, treatment of nasal or perineal carriage with rifampin, 600 mg daily for 5 days, or with topical mupirocin ointment 2% twice daily for 5 days, may help. Prolonged oral clindamycin, 150–300 mg/day for 4–6 weeks, or oral TMP-SMZ given 1 week per month for 6 months can be effective in preventing recurrent staphylococcal folliculitis and furunculosis. Bleach baths ( $\frac{1}{4}$  to  $\frac{1}{2}$  cup per 20 liters of bathwater for 15 minutes three to five times weekly) may reduce cutaneous staphylococcal carriage and not contribute to antibiotic resistance. Control of blood glucose in diabetes may reduce infections.

## ► Treatment

### A. Local Measures

Anhydrous ethyl alcohol containing 6.25% aluminum chloride, applied three to seven times weekly to lesions, may be helpful, especially for chronic frictional folliculitis of the buttocks. Topical antibiotics are generally ineffective if bacteria have invaded the hair follicle but may be prophylactic if used as an aftershave in patients with recurrent folliculitis after shaving.

### B. Specific Measures

*Pseudomonas* folliculitis clears spontaneously in non-neutropenic patients if the lesions are superficial. It may be treated with ciprofloxacin, 500 mg orally twice daily for 5 days.

Systemic antibiotics are recommended for bacterial folliculitis due to other organisms. Extended periods of treatment (4–8 weeks or more) with antistaphylococcal antibiotics are required if infection has involved the scalp or densely hairy areas, such as the axilla, beard, or groin (see Table 30-4).

Gram-negative folliculitis in acne patients may be treated with isotretinoin in compliance with all precautions discussed above (see Acne Vulgaris).

Eosinophilic folliculitis may be treated initially by the combination of potent topical corticosteroids and oral anti-histamines. In more severe cases, treatment is with one of the following: topical permethrin (application for 12 hours every other night for 6 weeks); itraconazole, 200–400 mg orally daily; UVB or PUVA phototherapy; or isotretinoin, 0.5 mg/kg/day orally for up to 5 months. A remission may be induced by some of these therapies, but long-term treatment may be required.

*Malassezia (Pityrosporum)* folliculitis is treated with topical sulfacetamide lotion twice a day, alone or in combination with itraconazole or fluconazole.

Demodex folliculitis can be treated until cleared with topical 5% permethrin applied every other night; oral ivermectin, 200 mcg/kg once weekly; oral metronidazole, 500 mg once daily or 250 mg three times daily; or oral ivermectin and metronidazole.

## ► Prognosis

Bacterial folliculitis is occasionally stubborn and persistent, requiring prolonged or intermittent courses of antibiotics.

Chaitidis N et al. Oral treatment with/without topical treatment vs topical treatment alone in *Malassezia Folliculitis* patients: a systematic review and meta-analysis. *Dermatol Ther.* 2020;33:e13460. [PMID: 32319163]

Jacob S et al. Treatment of *Demodex*-associated inflammatory skin conditions: a systematic review. *Dermatol Ther.* 2019;32:e13103. [PMID: 31583801]

Nussbaum D et al. Pseudofolliculitis barbae: a review of current treatment options. *J Drugs Dermatol.* 2019;18:246. [PMID: 30909328]

## MILIARIA (Heat Rash)



### ESSENTIALS OF DIAGNOSIS

- ▶ Burning, itching, superficial aggregated small vesicles, papules, or pustules on covered areas of the skin, usually the trunk.
- ▶ More common in hot, moist climates.
- ▶ Rare forms associated with fever and even heat prostration.

## ► General Considerations

Miliaria occurs most commonly on the trunk and intertriginous areas. A hot, moist environment is the most frequent cause. Occlusive clothing, fever while bedridden, and medications that enhance sweat gland function (eg, clonidine, beta-blockers, opioids) may increase the risk. Plugging of the ostia of sweat ducts occurs, with ultimate rupture of the sweat duct, producing an irritating, stinging reaction.

## ► Clinical Findings

The usual symptoms are burning and itching. The histologic depth of sweat gland obstruction determines the

clinical presentation: miliaria crystallina in the superficial (subcorneal) epidermis, miliaria rubra in the deep epidermis, and miliaria profunda in the dermis. The lesions consist of small (1–3 mm) nonfollicular lesions. Subcorneal thin-walled, discrete clear fluid-filled vesicles are termed “miliaria crystallina.” When fluid is turbid and lesions present as vesicopustules or pustules, they are called miliaria pustulosa. Miliaria rubra (prickly heat) presents as pink papules. Miliaria profunda presents as nonfollicular skin-colored papules that develop after multiple bouts of miliaria rubra. In a hospitalized patient, the reaction virtually always affects the back.

## ► Differential Diagnosis

Miliaria is to be distinguished from a drug eruption and folliculitis.

## ► Prevention

Use of a topical antibacterial preparation, such as chlorhexidine, prior to exposure to heat and humidity may help prevent the condition. Frequent turning or sitting of the hospitalized patient may reduce miliaria on the back.

## ► Treatment

The patient should keep cool and wear light clothing. A mid-potency corticosteroid (triamcinolone acetonide, 0.1%) in a lotion or cream may be applied two to four times daily. Secondary infections (superficial pyoderma) are treated with appropriate antistaphylococcal antibiotics. Anticholinergic medications (eg, glycopyrrolate 1 mg orally twice a day or topically applied) may be helpful in severe cases.

## ► Prognosis

Miliaria is usually a mild disorder, but severe forms (tropical anhidrosis and asthenia) result from interference with the heat-regulating mechanism.

Wat M et al. Clear vesicular eruption in the intensive care unit. *JAAD Case Rep.* 2019;5:754. [PMID: 31516988]

## MUCOCUTANEOUS CANDIDIASIS



### ESSENTIALS OF DIAGNOSIS

- ▶ Severe pruritus of vulva, anus, or body folds.
- ▶ Superficial denuded, beefy-red areas with or without satellite vesicopustules.
- ▶ Whitish curd-like concretions on the oral and vaginal mucous membranes.
- ▶ Yeast and pseudohyphae on microscopic examination of scales or curd.

## ► General Considerations

Mucocutaneous candidiasis is a superficial fungal infection that may involve almost any cutaneous or mucous surface. It is particularly likely to occur in diabetic patients, during pregnancy, in obese persons, and in the setting of immunosuppression. Systemic antibiotics, oral corticosteroids, hormone replacement therapy, and oral contraceptive agents may be contributory. Oral and interdigital candidiasis may be the first sign of HIV infection (see Chapter 31). Denture use predisposes the elderly to infection.

## ► Clinical Findings

### A. Symptoms and Signs

Itching may be intense. Burning is reported, particularly around the vulva and anus. The lesions consist of superficially denuded, beefy-red areas in the depths of the body folds, such as in the groin and the intergluteal cleft, beneath the breasts, at the angles of the mouth, in the webspaces of digits, and in the umbilicus. The peripheries of these denuded lesions are superficially undermined, and there may be satellite vesicopustules. Whitish, curd-like concretions may be present on mucosal lesions (Figure 6–22). Paronychia may occur.

### B. Laboratory Findings

Clusters of budding yeast and pseudohyphae can be seen under high power (400 $\times$ ) when skin scales or curd-like lesions are mounted in 10% KOH. Culture can confirm the diagnosis.

## ► Differential Diagnosis

Intertrigo, seborrheic dermatitis, tinea cruris, “inverse psoriasis,” and erythrasma involving the same areas may mimic mucocutaneous candidiasis.



**▲ Figure 6–22.** Oral mucosal candidiasis. (Used with permission from Sol Silverman, Jr, DDS, Public Health Image Library, CDC.)

## ► Complications

Systemic invasive candidiasis with candidemia may occur in patients who are immunosuppressed or receiving broad-spectrum antibiotic or intravenous hypertonic glucose solutions (eg, hyperalimentation). There may or may not be clinically evident mucocutaneous candidiasis.

## ► Treatment

### A. General Measures

Affected parts should be kept dry and exposed to air as much as possible. Water immersion should be minimized and gloves should be worn for those with infected nails or digital skin. If possible, discontinue systemic antibiotics. For treatment of systemic invasive candidiasis, see Chapter 36.

### B. Local Measures

**1. Nails and paronychia**—Apply clotrimazole solution 1% twice daily. Thymol 4% in ethanol applied once daily is an alternative.

**2. Skin**—Apply either nystatin ointment or clotrimazole cream 1%, with hydrocortisone cream 1–2.5%, twice daily. Gentian violet 0.5% solution is economical and highly effective in treating mucocutaneous candidiasis, but the purple discoloration may represent a cosmetic issue. Severe or widespread cutaneous disease responds to fluconazole, 100–200 mg orally daily, for 1 week.

**3. Vulvar and anal mucous membranes**—For vaginal candidiasis, single-dose fluconazole (150 mg orally) is effective. Intravaginal clotrimazole, miconazole, terconazole, or nystatin may also be used. Long-term suppressive therapy may be required for recurrent or “intractable” cases. Non-albicans candidal species may be identified by culture in some refractory cases and may respond to oral itraconazole, 200 mg twice daily for 2–4 weeks.

**4. Balanitis**—This is most frequent in uncircumcised men, usually caused by *Candida*. Topical nystatin ointment is the initial treatment if the lesions are mildly erythematous or superficially erosive. Soaking with dilute 5% aluminum acetate for 15 minutes twice daily may quickly relieve burning or itching. Chronicity and relapses, especially after sexual contact, suggest reinfection from a sexual partner who should be treated. Severe purulent balanitis is usually due to bacteria. If it is so severe that phimosis occurs, oral antibiotics—some with activity against anaerobes—are required; if rapid improvement does not occur, urologic consultation is indicated.

**5. Mastitis**—Lancinating breast pain and nipple dermatitis in breast-feeding women may be a manifestation of *Candida* colonization/infection of the breast ducts. Topical nystatin cream and clotrimazole 0.1% cream are safe during lactation. Topical gentian violet 0.5% daily for 7 days is also useful. Oral fluconazole, 200 mg daily for 2 weeks, is effective and also safe during lactation.

## ► Prognosis

Cases of cutaneous candidiasis range from the easily cured to the intractable and prolonged.

Taudorf EH et al. Cutaneous candidiasis—an evidence-based review of topical and systemic treatments to inform clinical practice. *J Eur Acad Dermatol Venereol.* 2019;33:1863. [PMID: 31287594]

Watchorn RE et al. Genital diseases in the mature man. *Clin Dermatol.* 2018;36:197. [PMID: 29566924]

Yano J et al. Current patient perspectives of vulvovaginal candidiasis: incidence, symptoms, management and post-treatment outcomes. *BMC Womens Health.* 2019;19:48. [PMID: 30925872]

## ERYTHEMAS

### REACTIVE ERYTHEMAS

#### 1. Urticaria & Angioedema



#### ESSENTIALS OF DIAGNOSIS

- ▶ Evanescent wheals or hives with or without angioedema.
- ▶ Intense itching; very rarely, pruritus may be absent.
- ▶ Urticaria is divided into acute and chronic forms.
- ▶ Most episodes are acute and self-limited (1–2 weeks).
- ▶ Chronic urticaria (lasting > 6 weeks) may have an autoimmune basis.

#### ► General Considerations

Urticaria involves hives, angioedema or both. It may be acute (less than 6 weeks' duration) or chronic (more than 6 weeks' duration). Chronic urticaria is further divided into chronic spontaneous urticaria and chronic inducible urticaria. Chronic inducible urticaria is reproducibly triggered by specific exposures. Examples include cholinergic urticaria, solar urticaria, cold urticaria, dermatographism, and delayed pressure urticaria. True urticaria should be differentiated from diseases that present with similar lesions that are not true urticaria (eg, adult-onset Still disease, urticarial vasculitis, and cryopyrin-associated periodic syndromes). Some patients with chronic spontaneous urticaria demonstrate autoantibodies directed against mast cell IgE receptors. In general, a careful history and physical examination are helpful but extensive costly workups are not indicated.

#### ► Clinical Findings

##### A. Symptoms and Signs

Lesions are itchy, red swellings of a few millimeters to many centimeters (Figure 6–23). The morphology of the lesions may vary over a period of minutes to hours, resulting



▲ **Figure 6–23.** Urticaria. (Used, with permission, from TG Berger, MD, Dept Dermatology, UCSF)

in geographic or bizarre patterns. Individual lesions in true urticaria last less than 24 hours and often only 2–4 hours. Angioedema is involvement of deeper subcutaneous tissue with swelling of the lips, eyelids, palms, soles, and genitalia. **Angioedema is no more likely than urticaria to be associated with systemic complications, such as laryngeal edema or hypotension.** Dermatographism is induced by scratching and can be elicited during the clinic visit by scratching the patient's skin. The wheals of cholinergic urticaria are 2–3 mm in diameter with a large surrounding red flare.

##### B. Laboratory Findings

The most common causes of acute urticaria are foods, upper respiratory infections, and medications. The cause of chronic spontaneous urticaria is often not found. Although laboratory studies are not generally helpful in the evaluation of acute or chronic urticaria, a complete blood count with differential, erythrocyte sedimentation rate, C-reactive protein, thyroid-stimulating hormone, and liver biochemical tests may be appropriate for some patients with chronic urticaria. Elevated inflammatory markers suggest an alternate diagnosis. In patients with individual lesions that persist past 24 hours, skin biopsy may confirm neutrophilic urticaria or urticarial vasculitis. A functional ELISA test looking for antibodies against the high-affinity receptor for IgE (Fc-Epsilon RI) can detect patients with an autoimmune basis for their chronic urticaria.

##### ► Differential Diagnosis

Papular urticaria resulting from insect bites persists for days. A central punctum can usually be seen. Streaked

urticular lesions may be seen in the 24–48 hours before blisters appear in acute allergic plant dermatitis, eg, poison ivy, oak, or sumac. Urticular responses to heat, sun, water, and pressure are quite rare. Urticular vasculitis is defined as cutaneous vasculitis where the skin lesions clinically mimic urticaria. Lesions last longer than 24 hours and often sting or burn rather than itch. Patients do not respond to antihistamines. Urticular vasculitis may be caused by viral hepatitis and may be seen as part of serum sickness. In hereditary angioedema, there is generally a positive family history and gastrointestinal or respiratory symptoms. Wheals are not part of the syndrome, and lesions are not pruritic.

## Treatment

### A. General Measures

A detailed search by history for a cause of urticaria should be undertaken, so that treatment can be tailored to include the provocative condition. The etiology of acute urticaria is found in less than half of cases. The etiology of chronic urticaria is found in even fewer cases. Patients with chronic autoimmune urticaria may have other autoimmune diseases and be more difficult to treat. In cases of chronic inducible urticaria, exposure to physical factors, such as heat, cold, sunlight, pressure, heat induced by exercise, excitement, and hot showers, should be modulated.

### B. Systemic Treatment

The mainstay of treatment initially includes H<sub>1</sub>-antihistamines. Initial therapy is hydroxyzine, 10–25 mg orally two or three times daily, or as a single nightly dose of 50–75 mg to reduce daytime sedation. Cyproheptadine, 4 mg orally four times daily, may be especially useful for cold urticaria. Second-generation H<sub>1</sub>-antihistamines are added if the generic sedating antihistamines are not effective. Options include fexofenadine, 180 mg orally once daily; or cetirizine or loratadine, 10 mg orally daily. Higher doses of second-generation antihistamines may be required (up to four times the standard recommended dose) and increase the likelihood of response to therapy to 60%. Combining antihistamines (eg, fexofenadine plus cetirizine) at these higher doses can be done safely to achieve remission in refractory cases, since less than 40% of cases of chronic urticaria respond to standard to H<sub>1</sub> blockade.

Doxepin (a tricyclic antidepressant with potent antihistaminic properties), 10–75 mg orally at bedtime, can be very effective in chronic urticaria. It has anticholinergic side effects.

If a skin biopsy of a lesion of chronic urticaria identifies neutrophils as a significant component of the inflammatory infiltrate, dapsone or colchicine (or both) may be useful.

Asymptomatic foci of infection—sinusitis, vaginal candidiasis, cholecystitis, and intestinal parasites—may rarely cause chronic urticaria. Although systemic corticosteroids in a dose of about 40 mg daily will usually suppress acute and chronic urticaria, the use of corticosteroids is rarely indicated and, once withdrawn, the urticaria virtually always returns. Instead of instituting systemic corticosteroids,

consultation should be sought from a dermatologist or an allergist with experience in managing severe urticaria. Omalizumab is approved for the treatment of refractory chronic urticaria and should be considered when severe chronic urticaria fails to respond to high-dose antihistamines.

### C. Local Treatment

Local treatment is rarely rewarding.

### Prognosis

Acute urticaria usually lasts only a few days to weeks. Half of patients whose urticaria persists for longer than 6 weeks will have it for years.

Antia C et al. Urticaria: a comprehensive review: epidemiology, diagnosis, and work-up. *J Am Acad Dermatol*. 2018;79:599. [PMID: 30241623]

Kaplan AP. Diagnosis, pathogenesis, and treatment of chronic spontaneous urticaria. *Allergy Asthma Proc*. 2018;39:184. [PMID: 29669665]

Kolkhir P et al. New treatments for chronic urticaria. *Ann Allergy Asthma Immunol*. 2020;124:2. [PMID: 31446134]

Maurer M et al. Ligelizumab for chronic spontaneous urticaria. *N Engl J Med*. 2019;381:1321. [PMID: 31577874]

Zuberbier T et al. The EAACI/GA<sup>2</sup>LEN/EDF/WAO guideline for the definition, classification, diagnosis and management of urticaria. *Allergy*. 2018;73:1393. [PMID: 29336054]

## 2. Erythema Multiforme/Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis

### ESSENTIALS OF DIAGNOSIS

#### Erythema multiforme

- Herpes simplex is most common cause.
- Cutaneous lesions are true three ring targets.
- Presents on the extensor surfaces, palms, soles, or mucous membranes.
- Disease remains localized.

#### Stevens-Johnson syndrome and toxic epidermal necrolysis

- Stevens-Johnson syndrome: Less than 10% BSA detachment.
- Stevens-Johnson syndrome/toxic epidermal necrolysis overlap: 10–30% BSA detachment.
- Toxic epidermal necrolysis: Greater than 30% BSA detachment.
- Medications are most common cause.
- Cutaneous lesions are targetoid but often not true three ring targets.
- Favors the trunk.
- Involves two or more mucous membranes.
- May progress to significant BSA involvement and may be life-threatening.

## ► General Considerations

Erythema multiforme is an acute inflammatory skin disease that was traditionally divided clinically into minor and major types based on the clinical findings. Approximately 90% of cases of erythema multiforme minor follow outbreaks of herpes simplex, and so it is preferably termed “herpes-associated erythema multiforme.” The term “erythema multiforme major” has largely been abandoned.

Stevens-Johnson syndrome (SJS) is defined as atypical target lesions with less than 10% BSA detachment; toxic epidermal necrolysis (TEN) is defined as lesions with greater than 30% BSA detachment; and patients with SJS/TEN overlap have between 10% and 30% BSA detachment. The abbreviation SJS/TEN is often used to refer to these three variants of what is considered one syndrome. SJS/TEN is characterized by toxicity and involvement of two or more mucosal surfaces (often oral and conjunctival but can involve any mucosal surface, including respiratory epithelium). SJS/TEN is most often caused by oral or, less commonly, topical medications, especially sulfonamides, NSAIDs, allopurinol, and anticonvulsants. In certain races, polymorphisms of antigen-presenting major histocompatibility (MHC) loci increase the risk for the development of SJS/TEN. *Mycoplasma pneumoniae* may trigger a mucocutaneous reaction with skin and oral lesions closely resembling SJS in children/young adults, which tends not to progress to TEN-like disease and carries an overall good prognosis.

## ► Clinical Findings

### A. Symptoms and Signs

A classic target lesion, as in herpes-associated erythema multiforme, consists of three concentric zones of color change, most often found acrally on the hands, feet, elbows, and knees (Figure 6-24). SJS/TEN presents with raised



**▲ Figure 6-24.** Erythema multiforme with classic target lesions. Note the three zones of color change. (Used, with permission, from Richard P. Usatine, MD, in Usatine RP, Smith MA, Mayeaux EJ Jr, Chumley HS. *The Color Atlas and Synopsis of Family Medicine*, 3rd ed. McGraw-Hill, 2019.)



**▲ Figure 6-25.** Stevens-Johnson syndrome. (Used, with permission, from TG Berger, MD, Dept Dermatology, UCSF.)

purpuric target-like lesions, with only two zones of color change and a central blister, or nondescript reddish or purpuric macules favoring the trunk and proximal upper extremities (Figure 6-25). Pain on eating, swallowing, and urination can occur if relevant mucosae are involved.

### B. Laboratory Findings

Skin biopsy is diagnostic. Direct immunofluorescence studies are negative. Blood tests are not useful for diagnosis.

## ► Differential Diagnosis

Urticaria and drug eruptions are the chief entities that must be differentiated from erythema multiforme. In true urticaria, lesions are not purpuric or bullous, last less than 24 hours, and respond to antihistamines. Urticaria multiforme is a distinct eruption in infants and young children and presents with fever and targetoid urticarial plaques. The differential diagnosis of SJS/TEN includes autoimmune bullous diseases (eg, pemphigus vulgaris, bullous pemphigoid, and linear IgA bullous dermatosis), acute systemic lupus erythematosus, vasculitis, and Sweet syndrome. The presence of a blistering eruption requires biopsy and dermatologic consultation for appropriate diagnosis and treatment.

## ► Complications

The tracheobronchial mucosa, conjunctiva, and genital and urethral mucosa may be involved and may result in scarring in severe cases. *Ophthalmologic consultation is required if ocular involvement is present because vision loss is the major consequence of SJS/TEN.*

## ► Treatment

### A. General Measures

Toxic epidermal necrolysis is best treated in an acute care environment, which may include an ICU or a burn unit. Patients should be admitted if mucosal involvement interferes with hydration and nutrition or extensive blistering

develops. Open lesions should be managed like second-degree burns. Immediate discontinuation of the inciting medication (before blistering occurs) is a significant predictor of outcome. Delay in establishing the diagnosis and inadvertently continuing the offending medication results in higher morbidity and mortality.

### B. Specific Measures

Oral and topical corticosteroids are useful in the oral variant of erythema multiforme. Oral acyclovir prophylaxis of herpes simplex infections may be effective in preventing recurrent herpes-associated erythema multiforme minor.

The most important aspect of treatment for SJS/TEN is to stop the offending medication and to move patients with greater than 25–30% BSA involvement to an appropriate acute care environment. Nutritional and fluid support and high vigilance for infection are the most important aspects of care. Reviews of systemic treatments for SJS and TEN have been conflicting. Some data support the use of high-dose corticosteroids. If corticosteroids are to be tried, they should be used early, before blistering occurs, and in high doses (prednisone, 1–2 mg/kg/day). Intravenous immunoglobulin (IVIG) (1 g/kg/day for 4 days) used early in the course has resulted in decreased mortality in some studies. Cyclosporine (3–5 mg/kg/day for 7 days) may also be effective. Etanercept is the treatment of choice in some centers.

### C. Local Measures

Topical corticosteroids are not very effective in this disease (except the oral variant).

## ► Prognosis

Erythema multiforme minor usually lasts 2–6 weeks and may recur. SJS/TEN may be serious with a mortality of 30% in cases with greater than 30% BSA involvement.

Micheletti RG et al. Stevens-Johnson syndrome/toxic epidermal necrolysis: a multicenter retrospective study of 377 adult patients from the United States. *J Invest Dermatol.* 2018; 138:2315. [PMID: 2975282]

Noe MH et al. Development and validation of a risk prediction model for in-hospital mortality among patients with Stevens-Johnson syndrome/toxic epidermal necrolysis-ABCD-10. *JAMA Dermatol.* 2019;155:448. [PMID: 30840032]

Seminario-Vidal L et al. Society of Dermatology Hospitalists supportive care guidelines for the management of Stevens-Johnson syndrome/toxic epidermal necrolysis in adults. *J Am Acad Dermatol.* 2020;82:1553. [PMID: 32151629]

Trayes KP et al. Erythema multiforme: recognition and management. *Am Fam Physician.* 2019;100:82. [PMID: 31305041]

Zhang S et al. Biologic TNF-alpha inhibitors in the treatment of Stevens-Johnson syndrome and toxic epidermal necrolysis: a systemic review. *J Dermatolog Treat.* 2020;31:66. [PMID: 30702955]

## 3. Erythema Migrans

Erythema migrans is a unique cutaneous eruption that characterizes the localized or generalized early stage of



▲ **Figure 6–26.** Erythema migrans due to *Borrelia burgdorferi* (Lyme disease). (Used, with permission, from Thomas Corson, MD, in Usatine RP, Smith MA, Mayeaux EJ Jr, Chumley HS. *The Color Atlas and Synopsis of Family Medicine*, 3rd ed. McGraw-Hill, 2019.)

Lyme disease (caused by *Borrelia burgdorferi*) (Figure 6–26) (See also Chapter 34).

## INFECTIOUS ERYTHEMAS

### 1. Erysipelas



#### ESSENTIALS OF DIAGNOSIS

- Edematous, circumscribed, hot, erythematous area, with raised advancing border.
- Central face or lower extremity frequently involved.
- Pain and systemic toxicity may be striking.

## ► General Considerations

Erysipelas is a superficial form of cellulitis that is caused by beta-hemolytic streptococci.

## ► Clinical Findings

### A. Symptoms and Signs

The symptoms are pain, malaise, chills, and moderate fever. A bright red spot appears and then spreads to form a tense, sharply demarcated, glistening, smooth, hot plaque. The sharp margin characteristically makes noticeable advances in days or even hours (Figure 6–27). The lesion is edematous with a raised edge and may pit slightly with the finger. Vesicles or bullae occasionally develop on the surface. The lesion does not usually become pustular or gangrenous and heals without scar formation. The disease may complicate any break in the skin that provides a



▲ **Figure 6–27.** Cellulitis. (Used, with permission, from Lindy Fox, MD.)

portal of entry for the organism. On the face, erysipelas begins near a fissure at the angle of the nose. On the lower extremity, tinea pedis with interdigital fissuring is a common portal of entry.

### B. Laboratory Findings

Leukocytosis is almost invariably present; blood cultures may be positive.

### ► Differential Diagnosis

Erysipeloid is a benign bacillary infection by *Erysipelothrix rhusiopathiae* that produces cellulitis of the skin of the fingers or the backs of the hands in fishermen and meat handlers.

### ► Complications

Unless erysipelas is promptly treated, death may result from bacterial dissemination, particularly in older adults.

### ► Treatment

Intravenous antibiotics effective against group A beta-hemolytic streptococci and staphylococci should be considered, but outpatient treatment with oral antibiotics has demonstrated equal efficacy. Oral regimens include a 7-day course with penicillin VK (250 mg), dicloxacillin (250 mg), or a first-generation cephalosporin (250 mg) four times a day. Alternatives in penicillin-allergic patients are clindamycin (250 mg twice daily orally for 7–14 days) or erythromycin (250 mg four times daily orally for 7–14 days), the latter only if the infection is known to be due to streptococci.

### ► Prognosis

With appropriate treatment, rapid improvement is expected. The presence of lymphedema carries the greatest risk of recurrence.

## 2. Cellulitis



### ESSENTIALS OF DIAGNOSIS

- ▶ Edematous, expanding, erythematous, warm plaque with or without vesicles or bullae.
- ▶ Lower leg is frequently involved.
- ▶ Pain, chills, and fever are commonly present.
- ▶ Septicemia may develop.

### ► General Considerations

Cellulitis, a diffuse spreading infection of the dermis and subcutaneous tissue, is usually on the lower leg (Figure 6–27) and most commonly due to gram-positive cocci, especially group A beta-hemolytic streptococci and *S aureus*. Rarely, gram-negative rods or even fungi can produce a similar picture. In otherwise healthy persons, the most common portal of entry for lower leg cellulitis is toe web intertrigo with fissuring, usually a complication of interdigital tinea pedis. Other diseases that predispose to cellulitis are prior episodes of cellulitis, chronic edema, venous insufficiency with secondary edema, lymphatic obstruction, saphenectomy, and other perturbations of the skin barrier. Bacterial cellulitis is almost never bilateral.

### ► Clinical Findings

#### A. Symptoms and Signs

Cellulitis begins as a tender small patch. Swelling, erythema, and pain are often present. The lesion expands over hours, so that from onset to presentation is usually 6 to 36 hours. As the lesion grows, the patient becomes more ill with progressive chills, fever, and malaise. Lymphangitis and lymphadenopathy are often present. If septicemia develops, hypotension may develop, followed by shock.

#### B. Laboratory Findings

Leukocytosis or at least a neutrophilia (left shift) may be present from early in the course. Blood cultures are positive in only 4% of patients. If a central ulceration, pustule, or abscess is present, culture may be of value. Aspiration of the advancing edge has a low yield (less than 20%) and is usually not performed. In immunosuppressed patients, or if an unusual organism is suspected and there is no localized site to culture, a full-thickness skin biopsy should be sent for routine histologic evaluation and for culture (bacterial, fungal, and mycobacterial). If a primary source for the infection is identified (wound, leg ulcer, toe web intertrigo), cultures from these sites isolate the causative pathogen in half of cases and can be used to guide antibiotic therapy.

### ► Differential Diagnosis

Two potentially life-threatening entities that can mimic cellulitis (ie, present with a painful, red, swollen lower

extremity) include deep venous thrombosis and necrotizing fasciitis. The diagnosis of necrotizing fasciitis should be suspected in a patient who has a toxic appearance, bullae, crepitus or anesthesia of the involved skin, overlying skin necrosis, and laboratory evidence of rhabdomyolysis (elevated creatine kinase) or disseminated intravascular coagulation. While these findings may be present with severe cellulitis and bacteremia, it is essential to rule out necrotizing fasciitis because rapid surgical debridement is essential. Other noninfectious skin lesions that may resemble cellulitis are termed “pseudocellulitis.” Diseases in this differential include sclerosing panniculitis, an acute, exquisitely tender red plaque on the medial lower legs above the malleolus in patients with venous stasis or varicosities, and acute severe contact dermatitis on a limb, which produces erythema, vesication, and edema, as seen in cellulitis, but with itching instead of pain. Bilateral lower leg bacterial cellulitis is exceedingly rare, and other diagnoses, especially severe stasis dermatitis (see Figure 12–2), should be considered in this setting. Severe lower extremity stasis dermatitis usually develops over days to weeks rather than hours as with cellulitis. It is also not as tender to palpation as cellulitis. Cryptococcal cellulitis in the organ transplant recipient is often bilateral. The ALT-70 is a predictive model to diagnose cellulitis or a cellulitis mimic and to provide guidance about when a dermatology consultation is needed. The ALT-70 variables are asymmetry (3 points), leukocytosis of 10,000/mcL ( $10 \times 10^9/L$ ) or more at presentation (2 points), tachycardia above 90 beats per minute (1 point), and age 70 years or older (1 point). An ALT-70 score above 5 points carries more than an 82% chance of a true cellulitis while a score below 2 points suggests a greater than 83% chance of a cellulitis mimicker.

## Treatment

Intravenous or parenteral antibiotics may be required for the first 2–5 days, with adequate coverage for *Streptococcus* and *Staphylococcus*. Methicillin-susceptible *S aureus* (MSSA) can be treated with nafcillin, cefazolin, clindamycin, dicloxacillin, cephalexin, doxycycline, or TMP-SMZ. If MRSA is suspected or proven, treatment options include vancomycin, linezolid, clindamycin, daptomycin, doxycycline, or TMP-SMZ. In mild cases or following the initial parenteral therapy, oral dicloxacillin or cephalexin, 250–500 mg four times daily for 5–10 days, is usually adequate. In patients in whom intravenous treatment is not instituted, the first dose of oral antibiotic can be doubled to achieve high blood levels rapidly. In patients with recurrent lower leg cellulitis (three to four episodes per year), oral penicillin 250 mg twice daily or oral erythromycin 250–500 mg twice daily can decrease the risk of recurrence. Prior episodes of cellulitis, lymphedema, chronic venous insufficiency, peripheral vascular disease, and deep venous thrombosis are associated with an increased risk of recurrent cellulitis. Additional measures to prevent recurrences include compression, treating toe web intertrigo and tinea pedis, and controlling venous insufficiency.

## When to Admit

- Severe local symptoms and signs.
- Signs of sepsis.
- Elevated white blood cell count of 10,000/mcL ( $10 \times 10^9/L$ ) or more with marked left shift. Failure to respond to oral antibiotics.

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Klotz C et al. Adherence to antibiotic guidelines for erysipelas or cellulitis is associated with a favorable outcome. *Eur J Clin Microbiol Infect Dis*. 2019;38:703. [PMID: 30685804]

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Patel M et al. The red leg dilemma: a scoping review of the challenges of diagnosing lower limb cellulitis. *Br J Dermatol*. 2019;180:993. [PMID: 30422315]

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## BLISTERING DISEASES

Some autoimmune skin disorders are characterized by formation of bullae or blisters. The most common of these diseases are pemphigus and its variants and bullous pemphigoid and its variants. Other less common disorders include dermatitis herpetiformis and linear IgA bullous dermatosis.

## PEMPHIGUS

### ESSENTIALS OF DIAGNOSIS

- ▶ Relapsing crops of bullae, often fragile and leading to erosions.
- ▶ Often preceded by mucous membrane bullae, erosions, and ulcerations.
- ▶ Superficial detachment of the skin after pressure or trauma variably present (Nikolsky sign).
- ▶ Acantholysis on biopsy.
- ▶ Immunofluorescence studies and serum ELISA for pathogenic antibodies are confirmatory.

## General Considerations

Pemphigus is an uncommon intraepidermal blistering disease occurring on skin and mucous membranes. It is caused by autoantibodies to adhesion molecules expressed in the skin and mucous membranes. The bullae appear spontaneously and are tender and painful when they rupture. Drug-induced pemphigus has been reported. There are several forms of pemphigus: pemphigus vulgaris and its variant, pemphigus vegetans; and the more superficially blistering pemphigus foliaceus and its variant, pemphigus

erythematosus. All forms may present at any age but most commonly in middle age. The vulgaris form begins in the mouth in over 50% of cases. The foliaceus form may be associated with other autoimmune diseases or may be drug-induced. Paraneoplastic pemphigus, a unique form of the disorder, is associated with numerous types of benign and malignant neoplasms, most frequently chronic lymphocytic leukemia, Castleman disease, B cell lymphoma, plasmacytoma, and thymoma.

## ► Clinical Findings

### A. Symptoms and Signs

Pemphigus is characterized by an insidious onset of flaccid bullae, crusts, and erosions in crops or waves (Figure 6–28). In pemphigus vulgaris, lesions often appear first on the oral mucous membranes. These rapidly become erosive. The scalp is another site of early involvement. Rubbing a cotton swab or finger laterally on the surface of uninvolved skin may cause easy separation of the epidermis (Nikolsky sign). Downward pressure on a fresh bulla may cause lateral spread (Asboe-Hansen sign). Pemphigus vegetans presents as erosive vegetating plaques, most often in intertriginous areas. Pemphigus foliaceus is a superficial form of pemphigus where cutaneous lesions present as flaccid bullae that quickly evolve into superficial erosions and thin pink plaques with overlying scale. Mucosal lesions are rare in pemphigus foliaceus. Pemphigus erythematosus has overlapping features of pemphigus foliaceus and lupus erythematosus. It presents with flaccid bullae that develop overlying scale and crust in a photodistributed area. Again, mucosal lesions are rare. Paraneoplastic pemphigus is histologically and immunologically distinct from other forms of the disease. Oral lesions predominate and cutaneous erythematosus plaques resembling erythema multiforme

are characteristic. Survival rates are low because of the underlying malignancy.

### B. Laboratory Findings

The diagnosis is made by light microscopy, direct and indirect immunofluorescence (IIF) microscopy, and ELISA assays to detect autoantibodies to intercellular adhesion molecules (desmogliens 3 and 1).

## ► Differential Diagnosis

Blistering diseases include erythema multiforme (Figure 6–24), SJS/TEN, drug eruptions, bullous impetigo, contact dermatitis, dermatitis herpetiformis, and bullous pemphigoid, but flaccid blisters are not typical of these diseases, and acantholysis is not seen on biopsy. All these diseases have clinical characteristics and immunofluorescence test results that distinguish them from pemphigus. Pemphigus foliaceus must be distinguished from subacute cutaneous lupus erythematosus.

## ► Complications

Secondary infection commonly occurs; this is a major cause of morbidity and mortality. Disturbances of fluid, electrolyte, and nutritional intake can occur as a result of painful oral ulcers.

## ► Treatment

### A. General Measures

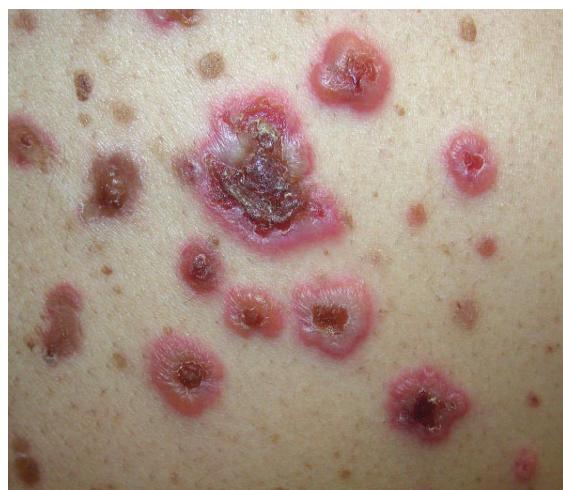
Patients with severe disease should be hospitalized at bed rest and provided intravenous antibiotics and feedings as indicated. Anesthetic troches used before eating ease painful oral lesions.

### B. Systemic Measures

Pemphigus requires systemic therapy as early in its course as possible. Initial therapy is with prednisone, 60–80 mg orally daily. In all but the mildest cases, a steroid-sparing agent is added from the beginning, since the disease course is long and the steroid-sparing agents take several weeks to exert their activity. Rituximab (1 g intravenously on days 1 and 15 as induction therapy followed by 500 mg intravenously every 6 months as maintenance therapy) is FDA approved for the treatment of pemphigus vulgaris, associated with induction of a complete remission, and considered by many experts to be first-line therapy. Repeated courses are efficacious and well tolerated in patients who do not achieve complete remission or relapse. Azathioprine (2–4 mg/kg orally daily) or mycophenolate mofetil (1–1.5 g orally twice daily) are other therapeutic options. In refractory cases, monthly IVIG (2 g/kg intravenously over 3–4 days), pulse intravenous corticosteroids, cyclophosphamide, or plasmapheresis can be used.

### C. Local Measures

In patients with limited disease, skin and mucous membrane lesions should be treated with topical corticosteroids.



▲ **Figure 6–28.** Pemphigus vulgaris on the back with crusted and intact bullae. (Used, with permission, from Eric Kraus, MD, in Usatine RP, Smith MA, Mayeaux EJ Jr, Chumley HS. *The Color Atlas and Synopsis of Family Medicine*, 3rd ed. McGraw-Hill, 2019.)

Complicating infection requires appropriate systemic and local antibiotic therapy.

## ► Prognosis

Without antibiotic or corticosteroid treatment, the disease is fatal within 5 years. The course now tends to be chronic in most patients; however, up to one-third experience remission. Infection is the most frequent cause of death, usually from *S aureus* septicemia.

- Bilgic A et al. What is novel in the clinical management of pemphigus. *Expert Rev Clin Pharmacol*. 2019;12:973. [PMID: 31550941]  
 Pollmann R et al. Pemphigus: a comprehensive review on pathogenesis, clinical presentation and novel therapeutic approaches. *Clin Rev Allergy Immunol*. 2018;54:1. [PMID: 29313220]  
 Schmidt E et al. Pemphigus. *Lancet*. 2019;394:882. [PMID: 31498102]

## BULLOUS PEMPHIGOID

Bullous pemphigoid is a relatively benign pruritic disease characterized by tense blisters in flexural areas, usually remitting in 5 or 6 years, with a course characterized by exacerbations and remissions. Most affected persons are over the age of 60 and men are affected twice as frequently as women. The appearance of blisters may be preceded by pruritic urticarial or edematous lesions for months. Oral lesions are present in one-third. The disease may occur in various forms, including localized, vesicular, vegetating, erythematous, erythrodermic, and nodular. Drugs may induce bullous pemphigoid.

The diagnosis is made by biopsy with direct immunofluorescence examination and serum antibody testing. Light microscopy shows a subepidermal blister. With direct immunofluorescence, IgG and C3 are found at the dermal-epidermal junction. ELISA tests for bullous pemphigoid antibodies (BP 180 or BP 230) are 87% sensitive and 95% specific. If the patient has mild disease, ultrapotent topical corticosteroids may be adequate. Prednisone (0.75 mg/kg orally daily) is often used to achieve rapid control of more widespread disease. Tetracycline (500 mg orally three times daily) or doxycycline (100 mg orally twice a day), alone or combined with nicotinamide—not nicotinic acid or niacin—(up to 1.5 g orally daily), may control the disease in patients who cannot use corticosteroids or may allow for decreasing or eliminating corticosteroids after control is achieved. Dapsone (50–200 mg orally daily) is particularly effective in mucous membrane pemphigoid. If these medications are not effective, methotrexate (5–25 mg orally weekly), azathioprine (2–4 mg/kg orally daily), or mycophenolate mofetil (1–1.5 g orally twice daily) may be used as steroid-sparing agents. Intravenous immunoglobulin, rituximab, and omalizumab have been used with success in refractory cases.

- Kremer N et al. Rituximab and omalizumab for the treatment of bullous pemphigoid: a systematic review of the literature. *Am J Clin Dermatol*. 2019;20:209. [PMID: 30421306]  
 Lamberts A et al. Nonbulous pemphigoid: a systematic review. *J Am Acad Dermatol*. 2018;78:989. [PMID: 29102490]

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## PAPULES

### WARTS



#### ESSENTIALS OF DIAGNOSIS

- Verrucous papules anywhere on the skin or mucous membranes, usually no > 1 cm in diameter.
- Prolonged incubation period (average 2–18 months).
- Spontaneous “cures” of common warts in 50% at 2 years.
- “Recurrences” (new lesions) are frequent.

## ► General Considerations

Warts (common, plantar, and genital [condylomata acuminata]) are caused by human papillomaviruses (HPVs). Typing of HPV lesions is not a part of standard medical evaluation except in the case of anogenital dysplasia.

## ► Clinical Findings

There are usually no symptoms. Tenderness on pressure occurs with plantar warts; itching occurs with anogenital warts (Figure 6–29). Flat warts are most evident under oblique illumination. Periungual warts may be dry, fissured, and hyperkeratotic and may resemble hangnails. Plantar warts resemble plantar corns or calluses.

## ► Differential Diagnosis

Some warty-looking lesions are actually seborrheic keratoses, hypertrophic actinic keratoses or squamous cell carcinomas. Some genital warty lesions are condylomata lata of secondary syphilis. Molluscum contagiosum lesions are pearly with a central dell. In AIDS, wart-like lesions may be caused by varicella zoster virus.

## ► Prevention

Administration of a vaccine against certain anogenital HPV types (including 6, 11, 16, 18, 31, 33, 45, 52, and 58) can prevent infection with these wart types and reduce anogenital, oropharyngeal, and cervical cancer. It is recommended for teenagers and young adults, men who have sex with men, and immunocompromised patients (see Chapters 1 and 18). There may be a role for adjuvant vaccination in HPV-infected patients.

## ► Treatment

Treatment is aimed at inducing “wart-free” intervals for as long as possible without scarring, since no treatment can



**▲ Figure 6–29.** Condylomata acuminata around the clitoris, labia minor, and opening of the vagina. (Used, with permission, from Richard P. Usatine, MD, in Usatine RP, Smith MA, Mayeaux EJ Jr, Chumley HS. *The Color Atlas and Synopsis of Family Medicine*, 3rd ed. McGraw-Hill, 2019.)

guarantee a remission or prevent recurrences. In immunocompromised patients, the goal is to control the size and number of lesions present. Certain types (HPV 1) are more responsive to treatment than others (eg, HPV 2, HPV 27).

#### A. Treatment of Nongenital Warts

For common warts of the hands, patients are usually offered liquid nitrogen or keratolytic agents. The former may work in fewer treatments but requires office visits and is painful.

**1. Liquid nitrogen**—Liquid nitrogen cryotherapy is applied to achieve a thaw time of 30–45 seconds. Two freeze-thaw cycles are given every 2–4 weeks for several visits. Scarring will occur if it is used incorrectly. Liquid nitrogen may cause permanent depigmentation in darkly pigmented individuals.

**2. Keratolytic agents and occlusion**—Salicylic acid products may be used against common warts or plantar warts. They are applied, then occluded. Plantar warts may be treated by applying a 40% salicylic acid plaster after paring. The plaster may be left on for 5–6 days, then removed, the lesion pared down, and another plaster applied. Although it may take weeks or months to eradicate the wart, the method is safe and effective with almost no side effects.

Chronic occlusion alone with water-impermeable tape (duct tape, adhesive tape) is less effective than cryotherapy.

**3. Operative removal**—Plantar warts may be removed by blunt dissection.

**4. Laser therapy**—The CO<sub>2</sub> laser can be effective for treating recurrent warts, periungual warts, plantar warts, and genital warts. It leaves open wounds that must fill in with granulation tissue over 4–6 weeks and is best reserved for warts resistant to all other modalities. Lasers may also be used every 3–4 weeks to ablate common, plantar, facial, and anogenital warts but are not more effective than cryotherapy in controlled trials. Photodynamic therapy can be considered in refractory widespread flat warts.

**5. Immunotherapy**—Squaric acid dibutylester may be applied 1–5 times weekly in a concentration of 0.2–2% directly to the warts to induce a mild contact dermatitis. Between 60% and 80% of warts clear over 10–20 weeks. Injection of *Candida* antigen starting at 1:50 dilution and repeated every 3–4 weeks may be similarly effective in stimulating immunologic regression of common and planter warts.

**6. Other agents**—Bleomycin (1 unit/mL), injected into common and plantar warts has been shown to have a high cure rate. It should be used with caution on digital warts because of the potential complications of Raynaud phenomenon, nail loss, and terminal digital necrosis. 5-Fluorouracil 5% cream applied once or twice daily, usually with occlusion, has similar efficacy to other treatment methods.

**7. Physical modalities**—Soaking warts in hot (42.2°C) water for 10–30 minutes daily for 6 weeks has resulted in involution in some cases.

#### B. Treatment of Genital Warts

**1. Liquid nitrogen**—Cryotherapy is first-line clinician-applied surgical treatment for genital warts. Liquid nitrogen cryotherapy is applied to achieve a thaw time of 30–45 seconds. Two freeze-thaw cycles are given every 2–4 weeks for several visits. Scarring will occur if it is used incorrectly. Liquid nitrogen may cause permanent depigmentation in pigmented individuals.

**2. Podophyllum resin**—For genital warts, the purified active component of the podophyllum resin, podofilox, is applied by the patient twice daily 3 consecutive days a week for cycles of 4–6 weeks. It is less irritating and more effective than “clinician-applied” podophyllum resin. After a single 4-week cycle, 45% of patients were wart-free but 60% relapsed at 6 weeks. Thus, multiple cycles of treatment are often necessary. Patients unable to obtain the take-home podofilox may be treated in the clinician’s office by painting each wart carefully (protecting normal skin) every 2–3 weeks with 25% podophyllum resin (podophyllin) in compound tincture of benzoin.

**3. Imiquimod**—A 5% cream of this local interferon inducer has moderate activity in clearing external genital warts.

Treatment is once daily on 3 alternate days per week. Response may be slow. Complete clearing of lesions occurs in 77% of women and 40% of men with 13% recurrences in the short term.

Although imiquimod is considerably more expensive than podophyllotoxin, it is the “patient-administered” treatment of choice for external genital warts in women due to its high response rate and safety. In men, podophyllin resin remains the preferred initial treatment due to its more rapid response, lower cost, and similar efficacy; imiquimod is used for recurrences or refractory cases. Imiquimod has no demonstrated efficacy for—and should not be used to treat—plantar or common warts.

**4. Sinecatechins**—Derived from green tea extract, sinecatechins (10% or 15%) is FDA approved for the treatment of anogenital warts. Application three times daily for 16 weeks achieves clearance rates from 40% to 81%, with the 15% formulation resulting in higher efficacy.

**5. Operative removal**—For pedunculated or large genital warts, snip biopsy (scissors) removal followed by light electrocautery is more effective than cryotherapy.

**6. Laser therapy**—See Treatment of Nongenital Warts, above. For genital warts, it has not been shown that laser therapy is more effective than electrosurgical removal. Photodynamic therapy can be considered in refractory genital warts.

## ► Prognosis

There is a striking tendency to develop new lesions. Warts may disappear spontaneously or may be unresponsive to treatment. Combining therapies (eg, liquid nitrogen plus immunotherapy) may improve therapeutic response.

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Salman S et al. Intraleisonal immunotherapy for the treatment of warts: a network meta-analysis. *J Am Acad Dermatol*. 2019; 80:922. [PMID: 30003983]



▲ **Figure 6–30.** Umbilicated—molluscum. (Used, with permission, from Richard P. Usatine, MD, in Usatine RP, Smith MA, Mayeaux EJ Jr, Chumley HS. *The Color Atlas and Synopsis of Family Medicine*, 3rd ed. McGraw-Hill, 2019.)

confined to the penis, pubis, and inner thighs and are considered a sexually transmitted infection.

Molluscum contagiosum is common in patients with AIDS, usually with a helper T-cell count less than 100/mcL (0.1 × 10<sup>9</sup>/L). Extensive lesions tend to develop over the face and neck as well as in the genital area.

The diagnosis is easily established in most instances because of the distinctive central umbilication of the dome-shaped lesion. Estimated time to remission is 13 months. The best treatment is by curettage or applications of liquid nitrogen as for warts—but more briefly. When lesions are frozen, the central umbilication often becomes more apparent. Light electrosurgery with a fine needle is also effective. Cantharadin (applied in the office and then washed off by the patient 4 hours later) is a safe and effective option. Another treatment option is 10% or 15% potassium hydroxide solution applied twice daily until lesions clear. Salicylic acid, podophyllotoxin, tretinoin, and imiquimod are additional treatment options. Physical destruction with pulsed dye laser or via extraction of molluscum bodies with a comedone extractor or curette is also effective. Lesions are difficult to eradicate in patients with AIDS unless immunity improves; however, with highly effective antiretroviral treatment, molluscum will usually spontaneously clear.

Meza-Romero R et al. Molluscum contagiosum: an update and review of new perspectives in etiology, diagnosis, and treatment. *Clin Cosmet Investig Dermatol*. 2019;12:373. [PMID: 31239742]

Teixidó C et al. Efficacy and safety of topical application of 15% and 10% potassium hydroxide for the treatment of Molluscum contagiosum. *Pediatr Dermatol*. 2018;35:336. [PMID: 29479727]

Vakharia PP et al. Efficacy and safety of topical cantharidin treatment for molluscum contagiosum and warts: a systematic review. *Am J Clin Dermatol*. 2018;19:791. [PMID: 30097988]

## MOLLUSCUM CONTAGIOSUM

Molluscum contagiosum, caused by a poxvirus, presents as single or multiple dome-shaped, waxy papules 2–5 mm in diameter that are umbilicated (Figure 6–30). Lesions at first are firm, solid, and flesh-colored but upon reaching maturity become soft, whitish, or pearly gray and may suppurate. The principal sites of involvement are the face, lower abdomen, and genitals.

The lesions are autoinoculable and spread by wet skin-to-skin contact. In sexually active individuals, they may be

**BASAL CELL CARCINOMA****ESSENTIALS OF DIAGNOSIS**

- ▶ Pearly papule, erythematous patch > 6 mm, or nonhealing ulcer in sun-exposed areas (face, trunk, lower legs).
- ▶ History of bleeding.
- ▶ Fair-skinned person with a history of sun exposure (often intense, intermittent).

**► General Considerations**

Basal cell carcinomas are the most common form of cancer. They occur on sun-exposed skin in otherwise normal, fair-skinned individuals; ultraviolet light is the cause. Basal cell carcinomas can be divided into clinical and histologic subtypes, which determine both clinical behavior and treatment. The clinical subtypes include superficial, nodular, pigmented, and morpheaform. The histologic subtypes include superficial, nodular, micronodular, and infiltrative. Morpheaform, micronodular, and infiltrative basal cell carcinomas are not amenable to topical therapy or electrodesiccation and curettage and typically require surgical excision or Mohs micrographic surgery. Because a second basal cell carcinoma develops in up to half of patients, skin examination is required at least yearly to detect new or recurrent lesions. Nicotinamide, 500 mg orally twice daily, can decrease the rate of development of basal cell carcinomas by 20% in high-risk groups.

**► Clinical Findings**

The most common presentation is a papule or nodule that may have a central scab or erosion (Figure 6-31).



**▲ Figure 6-31.** Pearly nodular basal cell carcinoma on the face of a 52-year-old woman present for 5 years. (Used, with permission, from Richard P. Usatine, MD, in Usatine RP, Smith MA, Mayeaux EJ Jr, Chumley HS. *The Color Atlas and Synopsis of Family Medicine*, 3rd ed. McGraw-Hill, 2019.)

Occasionally the nodules have stippled pigment (pigmented basal cell carcinoma). Intradermal nevi without pigment on the face of older White individuals may resemble basal cell carcinomas. Basal cell carcinomas grow slowly, attaining a size of 1–2 cm or more in diameter, usually only after years of growth. There is a waxy, “pearly” appearance, with telangiectatic vessels easily visible. It is the pearly or translucent quality of these lesions that is most diagnostic, a feature best appreciated if the skin is stretched. On the back and chest, basal cell carcinomas appear as reddish, somewhat shiny, scaly thin papules or plaques. Morpheaform basal cell carcinomas are scar-like in appearance. Basal cell carcinomas are more common and more likely to recur in immunosuppressed patients, including those with non-Hodgkin lymphoma and those who have undergone solid organ or allogeneic hematopoietic stem cell transplantation.

**► Treatment**

Lesions suspected to be basal cell carcinomas should be biopsied by shave or punch biopsy. Therapy is then aimed at eradication with minimal cosmetic deformity. The histopathologic classification of basal cell carcinomas determines therapy. Imiquimod (applied topically 5 nights per week for 6–10 weeks depending on patient reaction) and 5-fluorouracil (applied topically twice daily for up to 12 weeks) may be appropriate for select patients with superficial basal cell carcinomas, but the treated area must be observed for evidence of complete cure. Superficial or nodular type lesions can be treated with curettage and electrodesiccation, excision, or Mohs micrographic surgery, while those that are classified as micronodular or infiltrative should be treated with excision or Mohs micrographic surgery depending on the size and location of the lesion.

Surgical excision has a recurrence rate of 5% or less. The technique of three cycles of curettage and electrodesiccation depends on the skill of the operator and is not recommended for head and neck lesions or basal cell carcinomas with morpheaform, infiltrative, or micronodular histopathology. After 4–6 weeks of healing, it leaves a broad, hypopigmented, at times hypertrophic scar.

Mohs micrographic surgery—removal of the tumor followed by immediate frozen section histopathologic examination of margins with subsequent reexcision of tumor-positive areas and final closure of the defect—gives the highest cure rates (98%) and results in least tissue loss. It is an appropriate therapy for tumors of the eyelids, nasolabial folds, canthi, external ear, and temple; for recurrent lesions; where tissue sparing is needed for cosmesis; and for those with morpheaform, infiltrative, or micronodular histopathology in certain locations.

Photodynamic therapy and topical application of a photosensitizing agent followed by irradiation by a light source (typically blue or red), may be appropriate for some superficial and small nodular basal cell carcinomas.

Radiotherapy is effective and sometimes appropriate for older individuals (over age 65), but recurrent tumors after radiation therapy are more difficult to treat and may be

more aggressive. Radiation therapy is the most expensive method to treat basal cell carcinoma and should be used only if other treatment options are not appropriate.

Hedgehog pathway inhibitors (vismodegib, sonidegib) are reserved for the treatment of advanced or metastatic basal cell carcinoma or in patients with extensive tumor burden (eg, basal cell nevus syndrome).

Higgins S et al. Review of nonmelanoma skin cancer in African Americans, Hispanics, and Asians. *Dermatol Surg*. 2018;44:903. [PMID: 29746428]

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**Figure 6–32.** Squamous cell carcinoma: an irregular-shaped pink plaque with overlying hemorrhagic crust in a chronically sun-exposed area. (Used, with permission, from Richard P. Usatine, MD, in Usatine RP, Smith MA, Mayeaux EJ Jr, Chumley H. *The Color Atlas of Family Medicine*, 2nd ed. McGraw-Hill, 2013.)

## SQUAMOUS CELL CARCINOMA

### ESSENTIALS OF DIAGNOSIS

- ▶ Nonhealing ulcer or warty nodule.
- ▶ Skin damage due to long-term sun exposure.
- ▶ Common in fair-skinned organ transplant recipients.

Squamous cell carcinoma usually occurs subsequent to prolonged sun exposure on exposed parts in fair-skinned individuals who sunburn easily and tan poorly. It may arise from an actinic keratosis. The lesions appear as small red, conical, hard nodules that occasionally ulcerate (Figure 6–32). In actinically induced squamous cell cancers, rates of metastasis are estimated from retrospective studies to be 3–7%. Squamous cell carcinomas of the ear, temple, lip, oral cavity, tongue, and genitalia have much higher rates of recurrence or metastasis and require special management. Patients with multiple squamous cell carcinomas (especially more than 10) have higher rates of local recurrence and nodal metastases. Nicotinamide, 500 mg orally twice daily, can decrease the rate of development of squamous cell carcinomas by 30% in high-risk groups.

Squamous cell carcinoma *in situ* can be treated with imiquimod or 5-fluorouracil (in similar dosing as for superficial basal cell carcinoma) or curettage and electrodesiccation. The preferred treatment for invasive squamous cell carcinoma is excision or Mohs micrographic surgery. Mohs micrographic surgery is recommended for

high-risk lesions (lips, temples, ears, nose), recurrent tumors, aggressive histologic subtypes (perineural or perivascular invasion), large lesions (greater than 1.0 cm on face, greater than 2.0 cm on trunk or extremities), immunosuppressed patients, lesions developing within a scar, and tumors arising in the setting of genetic diseases. Follow-up for squamous cell carcinoma must be more frequent and thorough than for basal cell carcinoma, starting at every 3 months, with careful examination of lymph nodes for 1 year, then twice yearly thereafter.

Transplant patients with squamous cell carcinomas represent a highly specialized patient population. Biologic behavior of skin cancer in organ transplant recipients may be aggressive, and careful management is required. Multiple squamous cell carcinomas are very common on the sun-exposed skin of organ transplant patients. The tumors begin to appear after 5 years of immunosuppression. Regular dermatologic evaluation in at-risk organ transplant recipients is recommended. Other forms of immunosuppression, such as allogeneic hematopoietic stem cell transplants, chronic lymphocytic leukemia, HIV/AIDS, and chronic iatrogenic immunosuppression, may also increase skin cancer risk and be associated with more aggressive skin cancer behavior.

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## VIOLACEOUS TO PURPLE PAPULES & NODULES

### LICHEN PLANUS



### ESSENTIALS OF DIAGNOSIS

- ▶ Pruritic, violaceous, flat-topped papules with fine white streaks and symmetric distribution.
- ▶ Lacy or erosive lesions of the buccal, vulvar, and vaginal mucosa; nail dystrophy.
- ▶ Commonly seen along linear scratch marks (Koebner phenomenon) on anterior wrists, penis, and legs.
- ▶ Diagnostic histopathology.

### ► General Considerations

Lichen planus is an inflammatory pruritic disease of the skin and mucous membranes characterized by distinctive papules with a predilection for the flexor surfaces and trunk. The three cardinal findings are typical skin lesions, mucosal lesions, and histopathologic features of band-like infiltration of lymphocytes in the upper dermis. Lichenoid drug eruptions can resemble lichen planus clinically and histologically. The most common medications include sulfonamides, tetracyclines, quinidine, NSAIDs, beta-blockers, and hydrochlorothiazide. Hepatitis C infection is found with greater frequency in lichen planus patients than in controls. Allergy to mercury and other metal-containing amalgams can trigger oral lesions identical to lichen planus.

### ► Clinical Findings

The lesions are violaceous, flat-topped, angulated papules, up to 1 cm in diameter, discrete or in clusters (Figure 6–33),



**▲ Figure 6–33.** Lichen planus. (Used, with permission, from TG Berger, MD, Dept Dermatology, UCSF.)

with very fine white streaks (Wickham striae) on the flexor surfaces of the wrists and ankles; on lower back; and on mucous membranes, including the penis, lips, tongue, buccal, vulvar, vaginal, esophageal, and anorectal mucosa. Itching is mild to severe. The papules may become bullous or eroded. The disease may be generalized. Mucous membrane lesions have a lacy white network overlying them that may be confused with leukoplakia. The presence of oral and vulvovaginal lichen planus in the same patient is common. Patients with both these mucous membranes involved are at much higher risk for esophageal lichen planus. The Koebner phenomenon (appearance of lesions in areas of trauma) may be seen.

A special form of lichen planus is the erosive or ulcerative variety, a major problem in the mouth or genitalia. Squamous cell carcinoma develops in up to 5% of patients with erosive oral or genital lichen planus and may occur in esophageal lichen planus. There is also an increased risk of squamous cell carcinoma developing in lesions of hypertrophic lichen planus on the lower extremities.

### ► Differential Diagnosis

Lichen planus must be distinguished from similar lesions produced by medications and other papular lesions, such

as psoriasis, lichen simplex chronicus, graft-versus-host disease, and syphilis. Lichen planus on the mucous membranes must be differentiated from leukoplakia. Erosive oral lesions require biopsy and often direct immunofluorescence for diagnosis since lichen planus may simulate other erosive diseases, especially autoimmune blistering diseases that involve the oral mucosa.

## Treatment

### A. Topical Therapy

Superpotent topical corticosteroids applied twice daily are most helpful for localized disease in nonflexural areas. Alternatively, high-potency corticosteroid cream or ointment may be used nightly under thin, pliable plastic film.

Topical tacrolimus appears effective in oral and vaginal erosive lichen planus, but long-term therapy is required to prevent relapse. If tacrolimus is used, lesions must be observed carefully for development of squamous cell carcinoma. Since absorption can occur through mucous membranes, serum tacrolimus levels should be checked at least once if widespread mucosal application (more than 5–10 cm<sup>2</sup>) is used. If the erosive oral lichen planus lesions are adjacent to a metal-containing amalgam, removal of the amalgam may result in clearing of the erosions.

### B. Systemic Therapy

NB-UVB, bath PUVA, oral PUVA, and the combination of an oral retinoid plus PUVA (re-PUVA) are all forms of phototherapy that can improve lichen planus. Hydroxychloroquine, 200 mg orally twice daily, acitretin 10–25 mg orally daily, cyclosporine 3–5 mg/kg orally, and mycophenolate mofetil, 1 g orally twice daily, can also be effective in mucosal and cutaneous lichen planus. Apremilast, 30 mg twice daily, has reported efficacy in case series. Corticosteroids may be required in severe cases or in circumstances where the most rapid response to treatment is desired. Unfortunately, relapse almost always occurs as the corticosteroids are tapered, making systemic corticosteroid therapy an impractical option for the management of chronic lichen planus.

## Prognosis

Lichen planus is a benign disease, but it may persist for months or years and may be recurrent. Hypertrophic lichen planus and oral lesions tend to be especially persistent, and neoplastic degeneration has been described in chronically eroded lesions.

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## KAPOSI SARCOMA

### General Considerations

Human herpes virus 8 (HHV-8), or Kaposi sarcoma-associated herpes virus, is the cause of all forms of Kaposi sarcoma. Kaposi sarcoma occurs in several forms. **Classic Kaposi sarcoma** occurs in older men, has a chronic clinical course, and is rarely fatal. **Endemic Kaposi sarcoma** occurs in an often aggressive form in young Black men of equatorial Africa. **Iatrogenic Kaposi sarcoma** occurs in patients receiving immunosuppressive therapy and improves upon decreasing immunosuppression. Although antiretroviral therapy has reduced the prevalence of HIV-related Kaposi sarcoma, Kaposi sarcoma continues to occur in both well controlled HIV infection or AIDS.

Red or purple plaques or nodules on cutaneous or mucosal surfaces are characteristic. Marked edema may occur with few or no skin lesions. Kaposi sarcoma commonly involves the gastrointestinal tract and can be screened for by fecal occult blood testing. In asymptomatic patients, these lesions are not sought or treated. Pulmonary Kaposi sarcoma can present with shortness of breath, cough, hemoptysis, or chest pain; it may be asymptomatic, appearing only on chest radiograph. Bronchoscopy may be indicated. The incidence of AIDS-associated Kaposi sarcoma is diminishing. However, chronic Kaposi sarcoma can develop in patients with HIV infection, high CD4 counts, and low viral loads. In this setting, the Kaposi sarcoma usually resembles the endemic form, being indolent and localized. At times, however, it can be clinically aggressive. The presence of Kaposi sarcoma at the time of antiretroviral initiation is associated with Kaposi sarcoma-immune reconstitution inflammatory syndrome, which has an especially aggressive course in patients with visceral disease.

## Treatment

For Kaposi sarcoma in elders, palliative local therapy with intralesional chemotherapy or radiation is usually all that is required. In the setting of iatrogenic immunosuppression, the treatment of Kaposi sarcoma is primarily reduction of doses of immunosuppressive medications. In AIDS-associated Kaposi sarcoma, the patient should first be given ART. Other therapeutic options include cryotherapy or intralesional vinblastine (0.1–0.5 mg/mL) for cosmetically objectionable lesions; radiation therapy for accessible and space-occupying lesions; and laser surgery for certain intraoral and pharyngeal lesions. Systemic therapy is indicated in patients with skin disease that is symptomatic or asymptomatic but cosmetically unacceptable or those with advanced cutaneous, oral visceral, or nodal disease. ART plus chemotherapy appears to be more effective than ART alone (see Table 39–3). First-line systemic therapies include

liposomal doxorubicin and paclitaxel. Other therapeutic options include pomalidomide, etoposide, gemcitabine, imatinib, interferon alpha-2b, thalidomide, vinorelbine, bleomycin plus vincristine, bevacizumab, and lenalidomide.

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## PRURITUS

Pruritus is the sensation that provokes a desire to scratch. Pruritus as a medical complaint is 40% as common as low back pain. Elderly Asian men are most significantly affected, with 20% of all health care visits in Asian men over the age of 65 involving the complaint of itch. The quality of life of a patient with chronic pruritus is the same as a patient undergoing hemodialysis.

**Dry skin is the first cause of itch that should be sought**, since it is common and easily treated. The next step in evaluation is deciding whether a primary skin lesion with associated pruritus is present or absent. Examples of primary cutaneous pruritic diseases include scabies, atopic dermatitis, insect bites, pediculosis, contact dermatitis, drug reactions, urticaria, psoriasis, lichen planus, and fiberglass dermatitis, all of which have recognizable morphologies. The treatment of an underlying primary skin condition usually results in control of the associated pruritus.

Persistent pruritus not explained by cutaneous disease or association with a primary skin eruption should prompt a staged workup for systemic causes. Common causes of pruritus associated with systemic diseases include endocrine disorders (eg, hypothyroidism, hyperthyroidism, or hyperparathyroidism), psychiatric disturbances, lymphoma, leukemia, and other internal malignant disorders, iron deficiency anemia, HIV, hypercalcemia, cholestasis, and some neurologic disorders. Calcium channel blockers can cause pruritus with or without eczema, even years after they have been started, and it may take up to 1 year for pruritus to resolve after the calcium channel blocker has been stopped.

## Treatment

The treatment of chronic pruritus can be frustrating. Most cases of pruritus are not mediated by histamine, hence the poor response of many patients to antihistamines. Emollients for dry skin are listed in Table 6-2. Emollient creams (preferred over lotions) should be generously applied from neck to toe immediately after towel drying and again one more time per day. Neuropathic pruritus responds to neurally acting agents, such as gabapentin (starting at 300 mg orally at around 4 PM and a second dose of 600 mg orally

at bedtime) or pregabalin (150 mg orally daily). Combinations of antihistamines, sinequan, gabapentin, pregabalin, mirtazapine, and opioid antagonists can be attempted in refractory cases. In cancer-associated and other forms of pruritus, aprepitant 80 mg orally daily for several days can be dramatically effective. Pruritus in conjunction with uremia and hemodialysis and to a lesser degree the pruritus of liver disease may be helped by phototherapy with ultraviolet B or PUVA. Gabapentin or mirtazapine may relieve the pruritus of chronic kidney disease. IL-31 blockade (nemolizumab), IL-4 blockade (dupilumab), and inhibition of the Janus kinase pathway (tofacitinib) have shown some efficacy in the treatment of chronic pruritus.

## Prognosis

Elimination of external factors and irritating agents may give complete relief. Pruritus accompanying a specific skin disease will subside when the skin disease is controlled. Pruritus accompanying serious internal disease may not respond to any type of therapy.

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## ANOGENITAL PRURITUS

### ESSENTIALS OF DIAGNOSIS

- ▶ Anogenital itching, chiefly nocturnal.
- ▶ Skin findings are highly variable, ranging from none to excoriations and inflammation of any degree, including lichenification.

## General Considerations

Anogenital pruritus may be due to a primary inflammatory skin disease (intertrigo, psoriasis, lichen simplex chronicus, seborrheic dermatitis, lichen sclerosus), contact dermatitis (soaps, wipes, colognes, douches, and topical treatments), irritating secretions (diarrhea, leukorrhea, or trichomoniasis), infections (candidiasis, dermatophytosis, erythrasma), or oxyuriasis (pinworms). Erythrasma (Figure 6-34) is diagnosed by coral-red fluorescence with Wood light and cured with erythromycin. Squamous cell carcinoma of the anus and extramammary Paget disease are rare causes of genital pruritus.



**▲ Figure 6–34.** Erythema of the axilla. (Used, with permission, from Richard P. Usatine, MD, in Usatine RP, Smith MA, Mayeaux EJ Jr, Chumley H. *The Color Atlas of Family Medicine*, 2nd ed. McGraw-Hill, 2013.)

In pruritus ani, hemorrhoids are often found, and leakage of mucus and bacteria from the distal rectum onto the perianal skin may be important in cases in which no other skin abnormality is found.

Many women experience pruritus vulvae. Pruritus vulvae does not usually involve the anal area, though anal itching may spread to the vulva. In men, pruritus of the scrotum is most commonly seen in the absence of pruritus ani.

Up to one-third of unidentified causes of anogenital pruritus may be due to nerve impingements of the lumbosacral spine, so evaluation of lumbosacral spine disease is appropriate if no skin disorder is identified and topical therapy is ineffective.

## ► Clinical Findings

### A. Symptoms and Signs

The only symptom is itching. Physical findings are usually not present, but there may be erythema, fissuring, maceration, lichenification, excoriations, or changes suggestive of candidiasis or tinea.

### B. Laboratory Findings

Microscopic examination or culture of tissue scrapings may reveal yeasts or fungi. Stool examination may show pinworms. Radiologic studies may demonstrate lumbar-sacral spinal disease.

## ► Differential Diagnosis

The etiologic differential diagnosis consists of *Candida* infection, parasitosis, local irritation from contactants or irritants, nerve impingement, and other primary skin disorders of the genital area, such as psoriasis, seborrhea, intertrigo, or lichen sclerosus.

## ► Prevention

Instruct the patient in proper anogenital hygiene after treating systemic or local conditions.

## ► Treatment

Treating constipation, preferably with high-fiber management (psyllium), may help. Instruct the patient to use very soft or moistened tissue or cotton after bowel movements and to clean the perianal area thoroughly with cool water if possible. Women should use similar precautions after urinating. Patch testing reveals clinically relevant allergy in about 20% of patients, often to methylchloroisothiazolinone or methylisothiazolinone, preservatives commonly found in “baby wipes” and other personal care products.

Pramoxine cream or lotion or hydrocortisone-pramoxine (Pramosone), 1% or 2.5% cream, lotion, or ointment, is helpful for anogenital pruritus and should be applied after a bowel movement. Topical doxepin cream 5% is similarly effective but may be sedating. Topical calcineurin inhibitors (tacrolimus 0.03%) improve pruritus ani in patients with atopic dermatitis. Underclothing should be changed daily, and in men, the seam of their “boxers” should not rub against or contact the scrotum. Balneol Perianal Cleansing Lotion or Tucks premoistened pads, ointment, or cream may be very useful for pruritus ani. About one-third of patients with scrotal or anal pruritus will respond to capsaicin cream 0.006%. In cases where underlying spinal neurologic disease is suspected, gabapentin or pregabalin may be helpful. The use of high-potency topical corticosteroids should be avoided in the genital area.

## ► Prognosis

Although benign, anogenital pruritus is often persistent and recurrent.

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## SCABIES



### ESSENTIALS OF DIAGNOSIS

- ▶ Generalized very severe itching; infestation usually spares the head and neck.
- ▶ Burrows, vesicles, and pustules, especially on finger webs and in wrist creases.
- ▶ Mites, ova, and brown dots of feces (scybala) visible microscopically.
- ▶ Red papules or nodules on the scrotum and on the penile glans and shaft are pathognomonic.

## ► General Considerations

Scabies is caused by infestation with *Sarcoptes scabiei*, affecting over 200 million people worldwide. Close physical contact for 15–20 minutes with an infected person is the typical mode of transmission. However, scabies may be acquired by contact with the bedding of an infested individual. Facility-associated scabies is common, primarily in long-term care facilities, and misdiagnosis is common. Index patients are usually elderly and immunosuppressed. When these patients are hospitalized, hospital-based epidemics can occur and are difficult to eradicate when health care workers become infected and spread the infestation to other patients.

## ► Clinical Findings

### A. Symptoms and Signs

Itching is almost always present and can be severe. The lesions consist of generalized excoriations with small pruritic vesicles, pustules, and “burrows” in the interdigital spaces of the hands and feet, on the heels of the palms, wrists (Figure 6–35), elbows, umbilicus, around the axillae, on the areolae in women, or on the penile shaft and scrotum in men. The burrow appears as a short irregular mark, 2–3 mm long and the width of a hair. Characteristic nodular lesions may occur on the scrotum or penis and along the posterior axillary line. The infestation usually spares the head and neck (though these areas may be involved in infants, older adults, and patients with AIDS).

Hyperkeratotic or crusted scabies presents as thick flaking scale. These areas contain millions of mites, and these patients are highly infectious. Pruritus is often absent. Patients with widespread hyperkeratotic scabies are at risk for superinfection with *S aureus*, which in some cases progresses to sepsis if left untreated. Crusted scabies is the cause of 83% of scabies outbreaks in institutions.

### B. Laboratory Findings

The diagnosis should be confirmed by microscopic demonstration of the organism, ova, or feces in a mounted

specimen, examined with tap water, mineral oil, or KOH. Best results are obtained when multiple lesions are scraped, choosing the best unexcoriated lesions from interdigital webs, wrists, elbows, or feet. A No. 15 blade is used to scrape each lesion until it is flat. Patients with crusted/hyperkeratotic scabies must be evaluated for immunosuppression (especially HIV and HTLV-1 infections) if no iatrogenic cause of immunosuppression is present. Patients with hyperkeratotic scabies and associated bacterial superinfection may have laboratory findings consistent with infection and, if severe, sepsis.

## ► Differential Diagnosis

Scabies must be distinguished from the various forms of pediculosis, from bedbug and flea bites, and from other causes of pruritus.

## ► Treatment & Prognosis

Treatment is aimed at killing scabies mites and controlling the dermatitis, which can persist for months after effective eradication of the mites. Bedding and clothing should be laundered or cleaned or set aside for 14 days in plastic bags. High heat (60°C) is required to kill the mites and ova. Treatment is aimed at all infected persons in a family or institutionalized group. Otherwise, reinfestations will likely occur, which is why scabies in nursing home patients, institutionalized or mentally impaired patients, and AIDS patients may be much more difficult to treat.

**1. Permethrin 5% cream**—Treatment with permethrin, a highly effective and safe agent, consists of a single application from the neck down for 8–12 hours then washed off, repeated in 1 week. Patients often continue to itch for several weeks after treatment. Use of triamcinolone 0.1% cream helps resolve the dermatitis.

Pregnant patients should be treated only if they have documented scabies themselves. Permethrin 5% cream once for 12 hours—or 5% or 6% sulfur in petrolatum applied nightly for 3 nights from the collarbones down—may be used.

Most failures in normal persons are related to incorrect use or incomplete treatment of the housing unit. In these cases, repeat treatment with permethrin once weekly for 2 weeks, with re-education regarding the method and extent of application, is suggested.

**2. Ivermectin**—In immunocompetent individuals, 200 mcg/kg orally is effective in about 75% of cases with a single dose and 95% of cases with two doses 2 weeks apart. Since the drug is not ovicidal, the second dose theoretically kills eggs that might have hatched after the first dose was given.

Ivermectin is often used in combination with permethrin. In immunosuppressed persons and those with crusted (hyperkeratotic) scabies, multiple doses of ivermectin (every 2 weeks for 2 or 3 doses) plus topical therapy with permethrin every 3 days to once weekly, depending on degree of involvement, may be effective when topical treatment and oral therapy alone fail. A topical keratolytic (urea) should be used to help remove the scale of hyperkeratotic scabies, thereby decreasing the mite load.



▲ **Figure 6–35.** Scabies. A polymorphic eruption of papulovesicles and excoriated papules scattered on the chest. (Used, with permission, from Kanade Shinkai, MD.)

Ivermectin can be beneficial in mass treatment to eradicate widespread infection. In endemic areas, mass intervention with ivermectin is effective in controlling both scabies and associated bacterial infections.

If secondary pyoderma is present, it is treated with systemic antibiotics. Staphylococcal superinfection may lead to sepsis. In areas where nephritogenic streptococcal strains are prevalent, infestation with scabies or exposure to scabies-infested dogs may be followed by acute post-streptococcal glomerulonephritis.

Persistent pruritic post-scabetic papules may be treated with mid- to high-potency corticosteroids or with intraleisional triamcinolone acetonide (2.5–5 mg/mL).

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## PEDICULOSIS



### ESSENTIALS OF DIAGNOSIS

- ▶ Pruritus with excoriation.
- ▶ Nits on hair shafts; lice on skin or clothes.
- ▶ Occasionally, sky-blue macules (maculae ceruleae) on the inner thighs or lower abdomen in pubic lice infestation.

### General Considerations

Pediculosis is a parasitic infestation of the skin of the scalp, trunk, or pubic areas. Body lice usually occur among people who live in overcrowded dwellings with inadequate hygiene facilities. Pubic lice may be sexually transmitted. Head lice may be transmitted by shared use of hats or combs. Adults in contact with children with head lice frequently acquire the infestation.

There are three different varieties (1) **pediculosis capitis**, caused by *Pediculus humanus* var *capitis* (head louse); (2) **pediculosis corporis**, caused by *Pediculus humanus* var *corporis* (body louse); and (3) **pediculosis pubis**, caused by *Phthirus pubis* (pubic louse, “crabs”).

Head and body lice are similar in appearance and are 3–4 mm long. The body louse can seldom be found on the body, because the insect comes onto the skin only to feed and must be looked for in the seams of the clothing. Trench fever, relapsing fever, and typhus are transmitted by the

body louse in countries where those diseases are endemic. In the United States, *Bartonella quintana*, the organism that causes trench fever, has been found in lice infesting the homeless population.

### Clinical Findings

In body lice infestations, itching may be very intense, and scratching may result in deep excoriations, especially over the upper shoulders, axillae, posterior flanks, and neck. In some cases, only itching is present, with few excoriations seen. Pyoderma (bacterial infection of the skin) may be the presenting sign. Diagnosis is made by examining the seams of clothing for nits and lice. Head lice presents as scalp pruritus often accompanied by erosions on the occipital scalp, posterior neck, and upper back. Diagnosis is made by finding lice on the scalp or small nits resembling pussy willow buds on the scalp hairs close to the skin. Nits are easiest to see above the ears and at the nape of the neck. Pubic lice infestations are occasionally generalized, particularly in hairy individuals; the lice may even be found on the eyelashes and in the scalp. Diagnosis is made by finding lice or nits on pubic hair, body hair, or eyelashes.

### Differential Diagnosis

Head lice infestation must be distinguished from seborrheic dermatitis, body lice infestation from scabies and bedbug bites, and pubic lice infestation from anogenital pruritus and eczema.

### Treatment

**1. Pediculosis capitis**—Permethrin 1% cream rinse (Nix) is a topical over-the-counter pediculicide and ovicide. It is applied to the scalp and hair and left on for 8 hours before being rinsed off. Although it is the treatment of choice for head lice, permethrin resistance is common. Malathion lotion 1% (Ovide) is very effective, but it is highly volatile and flammable, so application must be done in a well-ventilated room or out of doors. Topical ivermectin 0.5% lotion, benzyl alcohol 5%, Oxyphthirine® lotion, spinosad 0.9% suspension, dimethicone, and abametapir 0.74% lotion are additional agents that appear to have efficacy against pediculosis capitis; of these, topical ivermectin is the most effective. All infested persons in a household, school, or other facility should ideally be treated at the same time. Other than topical ivermectin, topical therapies should be repeated 7–9 days after the initial treatment. For involvement of eyelashes, petrolatum is applied thickly twice daily for 8 days, and remaining nits are then plucked off. Systemic treatment options, often used in combination with topical agents, are oral ivermectin (200 mcg/kg orally, repeated in 7 days) (for children older than 5 years and more than 15 kg) and oral TMP-SMZ (10 mg TMP/kg/day and 50 mg SMZ/kg/day divided twice daily for 10 days).

**2. Pediculosis corporis**—Body lice are treated by disposing of the infested clothing and addressing the patient’s social situation.

**3. Pediculosis pubis**—Application of permethrin rinse 1% for 10 minutes or permethrin cream 5% for 8 hours to the pubis is effective. Sexual contacts should be treated. Clothes and bedclothes should be washed and dried at high temperature.

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## SKIN LESIONS DUE TO OTHER ARTHROPODS



### ESSENTIALS OF DIAGNOSIS

- ▶ Localized urticarial papules with pruritus.
- ▶ Lesions in linear groups of three ("breakfast, lunch, and dinner") are characteristic of bedbugs.
- ▶ Furuncle-like lesions containing live arthropods.
- ▶ Tender erythematous patches that migrate ("larva migrans").

## ► General Considerations

Some arthropods (eg, mosquitoes and biting flies) are readily detected as they bite. Many others are not because they are too small, because there is no immediate reaction, or because they bite during sleep. Reactions are allergic and may be delayed for hours to days. Patients are most apt to consult a clinician when the lesions are multiple and pruritus is intense.

Many persons react most severely to their earliest contacts with an arthropod, thus presenting with pruritic lesions when traveling, moving into new quarters, etc. Body lice, fleas, bedbugs, and mosquitoes should be considered. Bedbug exposure typically occurs in hotels and in housing with inadequate hygiene but also occurs in stable domiciles. Spiders are often incorrectly believed to be the source of bites, but they rarely attack humans. However, the brown recluse spider (*Loxosceles laeta*, *L. reclusa*) may cause severe necrotic reactions and death due to intravascular hemolysis, and the black widow spider (*Latrodectus mactans*) may cause severe systemic symptoms and death. (See also Chapter 38.) The majority of patient-diagnosed, clinician-diagnosed, and even published cases of brown recluse spider bites (or loxoscelism) are incorrect, especially if made in areas where these spiders are not endemic. Many of these lesions are actually due to CA-MRSA.

In addition to arthropod bites, the most common lesions are venomous stings (wasps, hornets, bees, ants,

scorpions) or bites (centipedes), furuncle-like lesions due to fly maggots or sand fleas in the skin, and a linear creeping eruption due to a migrating larva.

## ► Clinical Findings

The diagnosis may be difficult when the patient has not noticed the initial attack but suffers a delayed reaction. Individual bites are often in clusters and tend to occur either on exposed parts (eg, midges and gnats) or under clothing, especially around the waist or at flexures (eg, small mites or insects in bedding or clothing). The reaction is often delayed for 1–24 hours or more. Pruritus is almost always present and may be all but intolerable once the patient starts to scratch. Secondary infection may follow scratching. Urticarial wheals are common. Papules may become vesicular. The diagnosis is aided by searching for exposure to arthropods and by considering the patient's occupation and recent activities.

The principal arthropods are as follows:

1. **Fleas:** Fleas are bloodsucking ectoparasites that feed on dogs, cats, humans, and other species. Flea saliva produces papular urticaria in sensitized individuals. To break the life cycle of the flea, one must treat the home and pets, using quick-kill insecticides, residual insecticides, and a growth regulator.
2. **Bedbugs:** In crevices of beds or furniture; bites tend to occur in lines or clusters. Papular urticaria is a characteristic lesion of bedbug (*Cimex lectularius*) bites. Bedbugs are not restricted to any socioeconomic group and are a major health problem in some major metropolitan areas, especially in commercial and residential hotels.
3. **Ticks:** Usually picked up by brushing against low vegetation.
4. **Chiggers or red bugs:** These are larvae of trombiculid mites. A few species confined to particular regions and locally recognized habitats (eg, berry patches, woodland edges, lawns, brush turkey mounds in Australia, poultry farms) attack humans, often around the waist, on the ankles, or in flexures, raising intensely itching erythematous papules after a delay of many hours. The red chiggers may sometimes be seen in the center of papules that have not yet been scratched.
5. **Bird and rodent mites:** Larger than chiggers, bird mites infest birds and their nests. Bites are multiple anywhere on the body. Room air conditioning units may suck in bird mites and infest the inhabitants of the room. Rodent mites from mice or rats may cause similar effects. If the domicile has evidence of rodent activity, then rodent mite dermatitis should be suspected, as the mites are rarely found. Pet rodents or birds may be infested with mites, maintaining the infestation.
6. **Mites in stored products:** These are white and almost invisible and infest products, such as copra, vanilla pods, sugar, straw, cottonseeds, and cereals. Persons who handle these products may be attacked, especially on the hands and forearms and sometimes on the feet.
7. **Caterpillars of moths with urticating hairs:** The hairs are blown from cocoons or carried by emergent moths,

causing severe and often seasonally recurrent outbreaks after mass emergence. The gypsy moth is a cause in the eastern United States.

8. **Tungiasis:** Tungiasis is due to the burrowing flea known as *Tunga penetrans* and is found in Africa, the West Indies, and South and Central America. The female burrows under the skin, sucks blood, swells to 0.5 cm, and then ejects her eggs onto the ground. Ulceration, lymphangitis, gangrene, and septicemia may result, in some cases with lethal effect. Simple surgical removal is usually performed.

## ► Prevention

Arthropod infestations are best prevented by avoidance of contaminated areas, personal cleanliness, and disinfection of clothing, bedclothes, and furniture as indicated. Chiggers and mites can be repelled by permethrin applied to the head and clothing. (It is not necessary to remove clothing.) Bedbugs are no longer repelled by permethrin and can survive for up to 1 year without feeding. Aggressive cleaning, usually requiring removal of the affected occupant from the domicile, may be necessary to eradicate bedbug infestation in a residence.

## ► Treatment

Living arthropods should be removed carefully with tweezers after application of alcohol and preserved in alcohol for identification. In endemic Rocky Mountain spotted fever areas, ticks should not be removed with the bare fingers.

Corticosteroid lotions or creams are helpful for the associated pruritus. Topical antibiotics may be applied if secondary infection is suspected. Localized persistent lesions may be treated with intralesional corticosteroids.

Stings produced by many arthropods may be alleviated by applying papain powder (Adolph's Meat Tenderizer) mixed with water, or aluminum chloride hexahydrate (Xerac AC).

Extracts from venom sacs of bees, wasps, yellow jackets, and hornets are available for immunotherapy of patients at risk for anaphylaxis.

Kamath S et al. Infestations, bites, and insect repellents. *Pediatr Ann*. 2020;49:e124. [PMID: 32155278]  
Parola P et al. Bedbugs. *N Engl J Med*. 2020;382:2230. [PMID: 32492304]

## INFLAMMATORY NODULES

### ERYTHEMA NODOSUM

#### ESSENTIALS OF DIAGNOSIS

- ▶ Painful nodules without ulceration on anterior aspects of legs.
- ▶ Slow regression over several weeks to resemble contusions.

- ▶ Women are predominantly affected by a ratio of 10:1 compared to men.
- ▶ Some cases associated with infection, inflammatory bowel disease, or medication exposure.
- ▶ Evaluation for underlying cause is essential.

## ► General Considerations

Erythema nodosum is a symptom complex of panniculitis characterized by tender, erythematous nodules that appear most commonly on the extensor surfaces of the lower legs. It usually lasts about 6 weeks and may recur. Most cases are idiopathic in nature. However, erythema nodosum can be considered a skin sign of systemic disease. Evaluation and management include making the diagnosis, treating the symptoms, and searching for an underlying cause. The disease may be associated with various infections—streptococcosis, primary coccidiomycosis, other deep fungal infections, tuberculosis, *Yersinia pseudotuberculosis* and *Y enterocolitica* infection, diverticulitis, or syphilis. It may accompany sarcoidosis, Behcet disease, and inflammatory bowel disease. Erythema nodosum may be associated with pregnancy or with use of oral contraceptives.

## ► Clinical Findings

### A. Symptoms and Signs

The subcutaneous swellings are exquisitely tender and may be preceded by fever, malaise, and arthralgia. They are most often located on the anterior surfaces of the legs below the knees but may occur on the arms, trunk, and face. The lesions, 1–10 cm in diameter, are at first pink to red; with regression, all the various hues seen in a contusion can be observed (Figure 6–36) but, as a rule, the lesions do not ulcerate.

### B. Laboratory Findings

Evaluation of patients presenting with acute erythema nodosum should include a careful history (including medication exposures) and physical examination. Significant findings include a history of prior upper respiratory infection, diarrheal illness, exposure to tuberculosis, or symptoms of any deep fungal infection endemic to the area. All patients should get a chest radiograph, a purified protein derivative or blood interferon gamma release assay (such as QuantiFERON) (see Pulmonary Tuberculosis in Chapter 9), and two consecutive ASO/DNAse B titers at 2- to 4-week intervals. Coccidiomycosis should be looked for in patients from endemic areas. If no underlying cause is found, only a small percentage of patients will go on to develop a significant underlying illness (usually sarcoidosis) over the next year.

## ► Differential Diagnosis

Unlike other forms of panniculitis, a defining feature of erythema nodosum is that it does not ulcerate. Erythema



**▲ Figure 6–36.** Erythema nodosum. (Used, with permission, from TG Berger, MD, Dept Dermatology, UCSF.)

induratum from tuberculosis is seen on the posterior surfaces of the legs and may ulcerate. Lupus panniculitis presents as tender nodules in fatty areas of the buttocks and posterior arms and heals with depressed scars. In polyarteritis nodosa, the subcutaneous nodules are often associated with fixed livedo reticularis. In its late stages, erythema nodosum must be distinguished from simple bruises and contusions.

## ► Treatment

The underlying cause should be identified and treated. Primary therapy is with NSAIDs in usual doses. Saturated solution of potassium iodide, 5–15 drops three times daily, results in prompt involution in many cases. Complete bed rest may be advisable if the lesions are painful. Systemic therapy directed against the lesions themselves may include corticosteroid therapy (see Chapter 26) (unless contraindicated by associated infection), dapsone, colchicine, or hydroxychloroquine.

## ► Prognosis

The lesions usually disappear after about 6 weeks but may recur.

Inamadar AC et al. The rash with painful and erythematous nodules. *Clin Dermatol*. 2019;37:129. [PMID: 30981293]  
Leung AKC et al. Erythema nodosum. *World J Pediatr*. 2018;14:548. [PMID: 30269303]

## FURUNCULOSIS (Boils) & CARBUNCLES



### ESSENTIALS OF DIAGNOSIS

- ▶ Extremely painful inflammatory abscess based on a hair follicle.
- ▶ Coagulase-positive *S aureus* is the causative organism.
- ▶ Predisposing condition (diabetes mellitus, HIV disease, injection drug use) sometimes present.

## ► General Considerations

A **furuncle (boil)** is a deep-seated infection (abscess) caused by *S aureus* that involves the hair follicle and adjacent subcutaneous tissue. The most common sites of occurrence are the hairy parts exposed to irritation and friction, pressure, or moisture. Because the lesions are autoinoculable, they are often multiple. Diabetes mellitus (especially if using insulin injections), injection drug use, allergy injections, and HIV disease all increase the risk of staphylococcal infections by increasing the rate of carriage. Certain other exposures including hospitalization, athletic teams, prisons, military service, and homelessness may also increase the risk of infection.

A **carbuncle** consists of several furuncles developing in adjoining hair follicles and coalescing to form a conglomerate, deeply situated mass with multiple drainage points.

Recurrent furunculosis (three or more episodes in 12 months) tends to occur in those with direct contact with other infected individuals, especially family members.

## ► Clinical Findings

### A. Symptoms and Signs

Pain and tenderness may be prominent. The abscess is either rounded or conical. It gradually enlarges, becomes fluctuant, and then softens and opens spontaneously after a few days to 1–2 weeks to discharge a core of necrotic tissue and pus. The inflammation occasionally subsides before necrosis occurs.

### B. Laboratory Findings

There may be slight leukocytosis. Pus can be cultured to rule out MRSA or other bacteria. Culture of the anterior

nares and anogenital area (including the rectum to test for gastrointestinal carriage) may identify chronic staphylococcal carriage in cases of recurrent cutaneous infection.

## ► Differential Diagnosis

The most common entity in the differential is an inflamed **epidermal inclusion cyst** that suddenly becomes red, tender, and expands greatly in size over one to a few days. The history of a prior cyst in the same location, the presence of a clearly visible cyst orifice, and the extrusion of malodorous cheesy material (rather than purulent material) helps in the diagnosis. Tinea profunda (deep dermatophyte infection of the hair follicle) may simulate recurrent furunculosis. Furunculosis is also to be distinguished from deep mycotic infections, such as sporotrichosis; from other bacterial infections, such as anthrax and tularemia (rare); from atypical mycobacterial infections; and from acne cysts. Hidradenitis suppurativa (acne inversa) presents with recurrent tender, sterile abscesses in the axillae and groin, on the buttocks, or below the breasts. The presence of old scars or sinus tracts plus negative cultures suggests this diagnosis.

## ► Complications

Serious and sometimes fatal complications of staphylococcal infection such as septicemia can occur.

## ► Prevention

Identifying and eliminating the source of infection is critical to prevent recurrences after treatment. The source individual may have chronic dermatitis or be an asymptomatic carrier of MRSA. Nasal carriage of MRSA and the number of children in a household are risk factors for transmission between household members. Local measures, such as meticulous handwashing; no sharing of towels, clothing, and personal hygiene products; avoiding loofas or sponges in the bath or shower; changing underwear, sleepwear, towels, and washcloths daily; aggressive scrubbing of showers, bathrooms, and surfaces with bleach; bleach baths ( $\frac{1}{4}$ – $\frac{1}{2}$  cup per 20 liters of bathwater for 15 minutes three to five times weekly), 4% chlorhexidine washes, and isolation of infected patients who reside in institutions to prevent spread are all effective measures.

## ► Treatment

### A. Specific Measures

Incision and drainage is recommended for all loculated suppurations and is the mainstay of therapy. Systemic antibiotics are usually given. Patients who receive antibiotics (specifically, TMP-SMZ [160/800 or 320/1600 mg orally twice a day for 10 days or 7 days, respectively] or clindamycin [300 mg orally three times daily for 10 days]) at the time of drainage have higher cure and lower reinfection rates. Other oral antibiotic options include dicloxacillin or

cephalexin, 1 g daily in divided doses for 10 days. For suspected MRSA, doxycycline 100 mg twice daily, TMP-SMZ double-strength one tablet twice daily, clindamycin 150–300 mg twice daily, and linezolid 400 mg twice daily for 7–10 days are effective. Recurrent furunculosis may be effectively treated with a combination of cephalaxin (250–500 mg orally four times daily) or doxycycline (100 mg orally twice daily) for 2–4 weeks plus either rifampin (300 mg orally twice daily for 5 days) or long-term clindamycin (150–300 mg orally daily for 1–2 months). Shorter courses of antibiotics (7–14 days) plus longer-term daily 4% chlorhexidine whole body washing and intranasal, axilla, and anogenital mupirocin or retapamulin may also cure recurrent furunculosis. Oral vancomycin (1 g twice daily for 5 days) can treat gastrointestinal carriage of *S aureus*. Family members, pets, and intimate contacts may need evaluation for staphylococcal carrier state and perhaps concomitant treatment. Stopping high-risk behavior, such as injection drug use, can also prevent recurrence.

### B. Local Measures

Immobilize the part and avoid overmanipulation of inflamed areas. Use moist heat to help larger lesions “localize.” Use surgical incision and drainage after the lesions are “mature.”

## ► Prognosis

Recurrent crops may occur for months or years.

Nowicka D et al. *Staphylococcus aureus* and host immunity in recurrent furunculosis. Dermatology. 2019;235:295. [PMID: 30995649]

## EPIDERMAL INCLUSION CYST



### ESSENTIALS OF DIAGNOSIS

- Firm dermal papule or nodule.
- Overlying black comedone or “punctum.”
- Expressible foul-smelling cheesy material.
- May become red and drain, mimicking an abscess.

## ► General Considerations

Epidermal inclusion cysts (EICs) are common, benign growths of the upper portion of the hair follicle. They are common in Gardner syndrome and may be the first sign of the condition.

EICs favor the face and trunk and may complicate nodulocystic acne vulgaris. Individual lesions range in size from 0.3 cm to several centimeters. An overlying pore or punctum is characteristic. Dermoscopy can aid in observing a tiny punctum when not visible to the naked eye.

Lateral pressure may lead to extrusion of a foul-smelling, cheesy material.

## ► Differential Diagnosis

EICs are distinguished from lipomas by being more superficial (in the dermis, not the subcutaneous fat) and by their overlying punctum. Many other benign and malignant tumors may superficially resemble EICs, but all lack the punctum.

## ► Complications

EICs may rupture, creating an acute inflammatory nodule very similar to an abscess. Cultures of the expressed material will be sterile.

## ► Treatment

Treatment is not required if asymptomatic. Small (1–3 cm) lesions can be treated with a punch incision and removal of cystic contents. Inflamed lesions may be treated with incision and drainage or intralesional triamcinolone acetomide 5–10 mg/mL. For large or symptomatic cysts, surgical excision is curative.

Cheeley J et al. Comparison of elliptical excision versus punch incision for the treatment of epidermal inclusion cysts: a prospective, randomized study. *J Am Acad Dermatol*. 2018; 79:360. [PMID: 29229572]

## PHOTODERMATITIS

### ESSENTIALS OF DIAGNOSIS

- Painful or pruritic erythema, edema, or vesiculation on sun-exposed surfaces (face, neck, hands, and "V" of the chest).
- Inner upper eyelids and area under the chin are spared.

## ► General Considerations

Photodermatitis is a cutaneous reaction to ultraviolet radiation. It comprises four groups: (1) primary, idiopathic immunologically mediated photodermatoses; (2) drug- or chemical-induced photodermatoses; (3) dermatoses that are worsened or aggravated by ultraviolet exposure; and (4) genetic diseases with mutations predisposing to photodermatitis.

Primary photodermatoses include polymorphic light eruption, chronic actinic dermatitis, and actinic prurigo. Drug- or chemical-induced photodermatitis may be either exogenous or endogenous in origin. Porphyria cutanea tarda and pellagra are examples of endogenous

phototoxic dermatoses. Exogenous drug- or chemical-induced photodermatitis manifests either as phototoxicity (a tendency for the individual to sunburn more easily than expected) or as photoallergy (a true immunologic reaction that presents with dermatitis). Drug-induced phototoxicity is triggered by UVA. Contact photosensitivity may occur with plants, perfumes, and sunscreens. The sunscreen oxybenzone (a benzophenone) is a common cause of photoallergic dermatitis. Dermatoses that are worsened or aggravated by ultraviolet exposure include systemic lupus erythematosus and dermatomyositis. Three percent of persons with atopic dermatitis, especially middle-aged women, are photosensitive.

## ► Clinical Findings

### A. Symptoms and Signs

The acute inflammatory phase of phototoxicity, if severe enough, is accompanied by pain, fever, gastrointestinal symptoms, malaise, and even prostration. Signs include erythema, edema, and possibly vesiculation and oozing on exposed surfaces. Peeling of the epidermis and pigmentary changes often result. The key to diagnosis is localization of the rash to photoexposed areas, though eruptions may become generalized with time to involve photoprotected areas. The lower lip may be affected.

### B. Laboratory Findings

Blood and urine tests are generally not helpful unless porphyria cutanea tarda is suggested by the presence of blistering, scarring, milia (white cysts 1–2 mm in diameter) and skin fragility of the dorsal hands, and facial hypertrichosis. Eosinophilia may be present in chronic photoallergic responses.

## ► Differential Diagnosis

The differential diagnosis is long. If a clear history of the use of a topical or systemic photosensitizer is not available and if the eruption is persistent, then a workup including biopsy and light testing may be required. Photodermatitis must be differentiated from contact dermatitis that may develop from one of the many substances in sunscreens or suntan lotions, as these may often have a similar distribution. Sensitivity to actinic rays may also be part of a more serious condition, such as porphyria cutanea tarda or lupus erythematosus. These disorders are diagnosed by appropriate blood or urine tests. The most common medications causing a phototoxic reaction are vemurafenib, NSAIDs, voriconazole, tetracyclines, quinolones, hydrochlorothiazide, amiodarone, and chlorpromazine. Other potent photosensitizers include TMP/SMZ, quinine or quinidine, griseofulvin, eculizumab, topical and systemic retinoids (tretinoin, isotretinoin, acitretin), and calcium channel blockers. Polymorphous light eruption (PMLE) is a common idiopathic photodermatitis and often has its onset in the third to fourth decades, except in Native Americans and Latinos, in whom it may present in childhood. PMLE is chronic in nature. Transitory periods of spontaneous remission do occur.

## ► Complications

Some individuals continue to chronically react to light even when they no longer exposed to photosensitizing medications.

## ► Prevention

While sunscreens are useful agents in general and should be used by persons with photosensitivity, patients may react to such low amounts of energy that sunscreens alone may not be sufficient. Sunscreens with an SPF of 30–60 and broad UVA coverage, containing dicamphor sulfonic acid (Mexoryl SX), avobenzone (Parasol 1789), titanium dioxide, and micronized zinc oxide, are especially useful in patients with photoallergic dermatitis. Photosensitivity due to porphyria is not prevented by sunscreens and requires barrier protection (clothing) to prevent outbreaks.

## ► Treatment

### A. Specific Measures

Medications should be suspected in cases of photosensitivity even if the particular medication (such as hydrochlorothiazide) has been used for months.

### B. Local Measures

When the eruption is vesicular or weepy, treatment is similar to that of any acute dermatitis, using cooling and soothing wet dressings.

Sunscreens should be used as described above. Mid-potency to high-potency topical corticosteroids are of limited benefit in phototoxic reactions but may help in PMLE and photoallergic reactions. Since the face is often involved, close monitoring for corticosteroid side effects is recommended.

### C. Systemic Measures

Aspirin may have some value for fever and pain of acute sunburn. Systemic corticosteroids in doses as described for acute contact dermatitis may be required for severe photosensitivity reactions. Otherwise, different photodermatoses are treated in specific ways.

Patients with severe photoallergy may require immunosuppressives, such as azathioprine, in the range of 50–300 mg/day, or cyclosporine, 3–5 mg/kg/day.

## ► Prognosis

The most common phototoxic sunburn reactions are usually benign and self-limited. PMLE and some cases of photoallergy can persist for years.

Blakely KM et al. Drug-induced photosensitivity—an update: culprit drugs, prevention and management. *Drug Saf*. 2019; 42:827. [PMID: 30888626]

Gutierrez D et al. Photodermatoses in skin of colour. *J Eur Acad Dermatol Venereol*. 2018;32:1879. [PMID: 29888465]

Hinton AN et al. Feeling the burn: phototoxicity and photoallergy. *Dermatol Clin*. 2020;38:165. [PMID: 31753189]

## ULCERS

### LEG ULCERS SECONDARY TO VENOUS INSUFFICIENCY



#### ESSENTIALS OF DIAGNOSIS

- ▶ History of varicosities, thrombophlebitis, or post-phlebitic syndrome.
- ▶ Irregular ulceration, often on the medial lower legs above the malleolus.
- ▶ Edema of the legs, varicosities, hyperpigmentation, red and scaly areas (stasis dermatitis), and scars from old ulcers support the diagnosis.

## ► General Considerations

Patients at risk may have a history of venous insufficiency, family history, varicosities, obesity, or genetic diseases that predispose to venous insufficiency (see Chronic Venous Insufficiency, Chapter 12). The left leg is usually more severely affected than the right.

## ► Clinical Findings

### A. Symptoms and Signs

Classically, chronic edema is followed by a dermatitis, which is often pruritic. These changes are followed by hyperpigmentation, skin breakdown, and eventually sclerosis of the skin of the lower leg (Figure 6–37). Red, pruritic patches of stasis dermatitis often precede ulceration (Figure 12–2). The ulcer base may be clean, but it often has a yellow fibrin eschar that may require surgical removal (Figure 6–38). Ulcers that appear on the feet, toes, or above the knees should be approached with other diagnoses in mind.



▲ **Figure 6–37.** Venous stasis ulcer. (Used, with permission, from Lindy Fox, MD.)



▲ **Figure 6–38.** Ulcer—venous stasis ulcer. (Used, with permission, from Richard P. Usatine, MD, in Usatine RP, Smith MA, Mayeaux EJ Jr, Chumley HS. *The Color Atlas and Synopsis of Family Medicine*, 3rd ed. McGraw-Hill, 2019.)

## B. Laboratory Findings

Because venous insufficiency plays a role in 75–90% of lower leg ulcerations, testing of venous competence is a required part of a leg ulcer evaluation even when no changes of venous insufficiency are present (see Chapter 12). Doppler examination is usually sufficient (except in the diabetic patient) to evaluate venous competence. Arterial insufficiency may coexist with venous disease. An ankle/brachial index (ABI) less than 0.7 indicates the presence of significant arterial disease and requires vascular surgery consultation.

## ► Differential Diagnosis

The differential includes vasculitis, pyoderma gangrenosum, arterial ulcerations, infection, trauma, skin cancer, arachnid bites, and sickle cell anemia. When the diagnosis is in doubt, a punch biopsy from the border (not base) of the lesion may be helpful.

## ► Prevention

Compression stockings to reduce edema are the most important means of prevention. Compression should achieve a pressure of 30 mm Hg below the knee and 40 mm Hg at the ankle. The stockings should not be used in patients with arterial insufficiency with an ABI less than 0.7. Pneumatic sequential compression devices may be of great benefit when edema is refractory to standard compression dressings.

## ► Treatment

### A. Local Measures

Clean the base of the ulcer with saline or cleansers, such as Saf-Clens®. A curette or small scissors can be used to remove the yellow fibrin eschar; local anesthesia may be used if the areas are very tender.

Overall, there is little evidence to support topical antibiotics for the treatment of venous insufficiency ulcerations.

Metronidazole gel is used to reduce bacterial growth and odor. Silver impregnated dressings may aid in healing. Red dermatitic skin is treated with a medium- to high-potency corticosteroid ointment such as triamcinolone acetonide 0.1% ointment. The ulcer is then covered with an occlusive hydroactive dressing (DuoDerm® or Cutinova®) or a polyurethane foam (Allevyn) followed by an Unna zinc paste boot. This is changed weekly. The ulcer should begin to heal within weeks, and healing should be complete within 4–6 months. If the patient has no history of skin cancer in the area, becaplermin (Regranex) may be applied to ulcers that are not becoming smaller or developing a granulating base. Some ulcerations require skin grafting.

No topical intervention has evidence to suggest that it will improve healing of arterial leg ulcers.

## B. Systemic Therapy

Pentoxifylline, 400 mg orally three times daily administered with compression dressings, is beneficial in accelerating healing of venous insufficiency leg ulcers. Zinc supplementation is occasionally beneficial in patients with low serum zinc levels.

In the absence of cellulitis, there is no role for systemic antibiotics in the treatment of venous insufficiency ulcers. The diagnosis of cellulitis in the setting of a venous insufficiency ulcer can be very difficult. Surface cultures are of limited value. Cellulitis should be considered in the following settings: (1) expanding warmth and erythema surrounding the ulceration, with or without (2) increasing pain of the ulceration. The patient may also report increased exudate from the ulceration, but this without the other cardinal findings of cellulitis does not confirm the diagnosis of cellulitis. If cellulitis accompanies the ulcer, oral antibiotics are recommended: dicloxacillin, 250 mg four times a day, or levofloxacin, 500 mg once daily for 1–2 weeks, is usually adequate. Routine use of antibiotics and treating bacteria isolated from a chronic ulcer without clinical evidence of infection is discouraged. If the ulcer fails to heal or there is a persistent draining tract in the ulcer, underlying osteomyelitis should be sought.

## ► Prognosis

The combination of limited debridement, compression dressings or stockings, and moist dressings will heal the majority of venous stasis ulcers within an average of 18 months. These modalities need to be applied at least 80% of the time to optimize ulcer healing. Topical growth factors, antibiotics, debriding agents, and xenografts and autografts can be considered in recalcitrant cases but are not required in most patients. Exercise in combination with compression therapy has an adjuvant role in promoting the healing of venous ulcerations. The failure of venous insufficiency ulcerations to heal is most often related to inconsistent use of basic treatment methods. Ongoing control of edema is essential to prevent recurrent ulceration. The use of compression stockings following ulcer healing is critical to prevent recurrence, with recurrence rates 2–20 times higher if patients do not comply with compression stocking use. Patients with an ABI below 0.5 or refractory

ulcerations (or both) should be considered for surgical procedure (artery-opening procedures or ablation of the incompetent superficial vein). Early endovenous ablation has been shown to improve healing in patients with venous insufficiency ulcers.

Gohel MS et al. A randomized trial of early endovenous ablation in venous ulceration. *N Engl J Med.* 2018;378:2105. [PMID: 29688123]

Jull A et al. Prescribed exercise with compression vs compression alone in treating patients with venous leg ulcers: a systematic review and meta-analysis. *JAMA Dermatol.* 2018;154:1304. [PMID: 30285080]

Khoobari S et al. Utility of skin biopsy and culture in the diagnosis and classification of chronic ulcers: a single-institution, retrospective study. *Am J Dermatopathol.* 2019;41:343. [PMID: 30461422]

Norman G et al. Dressings and topical agents for treating venous leg ulcers. *Cochrane Database Syst Rev.* 2018;6:CD012583. [PMID: 29906322]

Rabe E et al. Indications for medical compression stockings in venous and lymphatic disorders: an evidence-based consensus statement. *Phlebology.* 2018;33:163. [PMID: 28549402]

Raffetto JD. Pathophysiology of chronic venous disease and venous ulcers. *Surg Clin North Am.* 2018;98:337. [PMID: 29502775]

disorders include pigmented nevi, mosaic hyperpigmentation, ephelides (juvenile freckles), and lentigines (senile freckles). Hyperpigmentation due to systemic diseases may be seen in association with Addison disease, vitamin B<sub>12</sub> deficiency, hemochromatosis, and Wilson disease. Melasma (chloasma) occurs as patterned hyperpigmentation of the face, most commonly as a direct effect of estrogens. It may occur during pregnancy, exposure to oral contraceptives, or be idiopathic. Although more common in women, melasma affects both sexes and all races.

**2. Hypopigmentation and depigmentation**—Depigmenting disorders in this category are vitiligo, albinism, and piebaldism. In vitiligo, pigment cells (melanocytes) are destroyed (Figure 6–39). Vitiligo, present in approximately 1% of the population, may be associated with other autoimmune disorders, such as autoimmune thyroid disease, pernicious anemia, diabetes mellitus, and Addison disease.

## B. Secondary Pigmentary Disorders

Any damage to the skin (irritation, allergy, infection, excoriation, burns, or dermatologic therapy, such as chemical peels and freezing with liquid nitrogen) may result in hyperpigmentation or hypopigmentation. Several disorders of clinical importance are described below.

**1. Hyperpigmentation**—The most common type of secondary hyperpigmentation occurs after another inflammatory dermatologic condition, such as acne, lichen planus, or eczema, and is most commonly seen in moderately complexioned persons (Asians, Hispanics, and light-skinned Black individuals). It is called post-inflammatory hyperpigmentation. Hemosiderin deposition, as in stasis dermatitis, may lead to hyperpigmentation that is red-brown in color.

Pigmentation may be produced by certain medications, eg, chloroquine, chlorpromazine, minocycline (Figure 6–40), and amiodarone. Fixed drug eruptions to phenolphthalein (in laxatives), TMP-SMZ, NSAIDs, and tetracyclines also lead to hyperpigmentation, typically in annular patches.

## MISCELLANEOUS DERMATOLOGIC DISORDERS<sup>1</sup>

### PIGMENTARY DISORDERS

Although the color of skin may be altered by many diseases and agents, the vast majority of patients have either an increase or decrease in pigment secondary to an inflammatory disease, such as acne or atopic dermatitis.

Other pigmentary disorders include those resulting from exposure to exogenous pigments, such as carotenemia, argyria, and tattooing. Other endogenous pigmentary disorders are attributable to metabolic substances (eg, hemosiderin [iron]) in purpuric processes, to homogenetic acid in ochronosis, and bile pigments.

### Classification

Disorders of hyperpigmentation or hypopigmentation may be considered to be primary or secondary to other disorders. Depigmentation, the absence of all pigment, should be differentiated from hypopigmentation, in which the affected skin is lighter than baseline skin color, but not completely devoid of pigment.

The evaluation of pigmentary disorders is helped by Wood light, which accentuates epidermal pigmentation in hyperpigmented disorders and highlights complete loss of pigment in depigmentating disorders. Depigmentation, as seen in vitiligo, enhances with Wood light examination, whereas postinflammatory hypopigmentation does not.

### A. Primary Pigmentary Disorders

**1. Hyperpigmentation**—The disorders in this category are nevoid, congenital, or acquired. Nevoid and congenital



**▲ Figure 6–39. Depigmented—vitiligo.** (Used, with permission, from Richard P. Usatine, MD, in Usatine RP, Smith MA, Mayeaux EJ Jr, Chumley HS. *The Color Atlas and Synopsis of Family Medicine*, 3rd ed. McGraw-Hill, 2019.)

<sup>1</sup>Hirsutism is discussed in Chapter 26.



**▲ Figure 6-40.** Minocycline hyperpigmentation.  
(Used, with permission, from Lindy Fox, MD.)

**2. Hypopigmentation**—Hypopigmentation may complicate atopic dermatitis, lichen planus, psoriasis, discoid lupus, and lichen simplex chronicus. It may also be posttraumatic or iatrogenic (eg, due to the use of superpotent topical corticosteroids) or both. *Clinicians must exercise special care in using liquid nitrogen on any patient with olive or darker complexions, since doing so may result in hypopigmentation or depigmentation, at times permanent.* Intralesional or intra-articular injections of high concentrations of corticosteroids may also cause localized temporary hypopigmentation.

## ► Complications

Actinic keratoses and skin cancers are more likely to develop in persons with vitiligo. Severe emotional trauma may occur in extensive vitiligo and other types of hypopigmentation and hyperpigmentation, particularly in naturally dark-skinned persons.

## ► Treatment & Prognosis

### A. Hyperpigmentation

Therapeutic bleaching preparations generally contain hydroquinone. Hydroquinone has occasionally caused unexpected hypopigmentation, hyperpigmentation, or even secondary ochronosis and pigmented milia, particularly with prolonged use.

**The role of exposure to ultraviolet light cannot be overstressed as a factor promoting or contributing to most disorders of hyperpigmentation, and such**

**exposure should be minimized.** Melasma, ephelides, and postinflammatory hyperpigmentation may be treated with varying success with 4% hydroquinone and a sunscreen containing UVA photoprotectants (Avobenzone, Mexoryl, zinc oxide, titanium dioxide). Tretinoin cream, 0.025–0.05%, may be added. Adjuvant topical options for melasma include kojic acid, ascorbic acid, cysteamine, niacinamide, and azelaic acid. Superficial melasma responds well to topical therapy, but if there is predominantly dermal deposition of pigment (does not enhance with Wood light), the prognosis is poor. Response to therapy may take months and requires avoidance of sunlight. Hyperpigmentation often recurs after treatment if the skin is exposed to ultraviolet light. Tranexamic acid, 250 mg twice a day for 8–12 weeks, is an oral treatment for melasma. It should not be used in patients with hypercoagulability. Acne with postinflammatory hyperpigmentation responds well to azelaic acid and tretinoin, since both address acne and hyperpigmentation. Solar lentigines respond to liquid nitrogen application. Tretinoin 0.1% cream or tazarotene 0.1% used over 10 months can fade solar lentigines, facial hyperpigmentation, and postinflammatory hyperpigmentation. Lasers are available for the removal of epidermal and dermal pigment and should be considered for patients whose responses to medical treatment are inadequate.

### B. Hypopigmentation

In secondary hypopigmentation, repigmentation may occur spontaneously. Cosmetics such as Covermark and Dermablend are highly effective for concealing disfiguring patches. Therapy of vitiligo is long and tedious, and the patient must be strongly motivated. If less than 20% of the skin is involved (most cases), topical tacrolimus 0.1% twice daily is the first-line therapy. A superpotent corticosteroid may also be used, but local skin atrophy from prolonged use may ensue. With 20–25% involvement, narrowband UVB or oral PUVA is the best option. Severe phototoxic response (sunburn) may occur with PUVA. The face and upper chest respond best, and the fingertips and the genital areas do not respond as well to treatment. Years of treatment may be required. There is evidence that topical or systemic JAK inhibitors (tofacitinib, ruxolitinib) may be effective in some patients with recalcitrant vitiligo.

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## ALOPECIA

### ► Classification

Alopecias are divided into scarring and nonscarring forms. When evaluating a patient who complains of hair loss, it is most important to determine if follicular markings (the opening where hair exits the skin) are present or absent. Present follicular markings suggest a nonscarring alopecia; absent follicular markings suggest a scarring alopecia.

### ► Nonscarring Alopecia

Nonscarring alopecia may occur in association with various systemic diseases, such as SLE, secondary syphilis, hyperthyroidism or hypothyroidism, iron deficiency anemia, vitamin D deficiency, and pituitary insufficiency. Prompt and adequate control of the underlying disorder usually leads to hair regrowth. Specific types of nonscarring alopecia are described below.

**Androgenetic alopecia**, the most common form of alopecia, is of genetic predetermination. In men, the earliest changes occur at the anterior portions of the calvarium on either side of the "widow's peak" and on the crown (vertex). The extent of hair loss is variable and unpredictable. Minoxidil 5% is available over the counter and can be recommended for persons with recent onset (less than 5 years) and smaller areas of alopecia. Approximately 40% of patients treated twice daily for a year will have moderate to dense growth. Finasteride (Propecia), 1 mg orally daily, has similar efficacy and may be additive to minoxidil.

Androgenetic alopecia also occurs in women. Classically, there is retention of the anterior hairline while there is diffuse thinning of the vertex scalp hair and a widening of the part. Treatment includes topical minoxidil (5% once daily) and, in women not of childbearing potential, finasteride at doses up to 2.5 mg/day orally. A workup consisting of determination of serum testosterone, DHEAS, iron, total iron-binding capacity, thyroid function tests, vitamin D level, and a complete blood count will identify most other causes of hair thinning in premenopausal women. Women who complain of thin hair but show little evidence of alopecia need follow-up, because more than 50% of the scalp hair can be lost before the clinician can perceive it.

**Telogen effluvium** is a transitory increase in the number of hairs in the telogen (resting) phase of the hair growth cycle. This may occur spontaneously; appear at the termination of pregnancy; be precipitated by "crash dieting," high fever, stress from surgery, shock, malnutrition, or iron deficiency; or be provoked by hormonal contraceptives. Whatever the cause, telogen effluvium usually has a latent period of 4 months. The prognosis is generally good. The condition is diagnosed by the presence of large numbers of hairs with white bulbs coming out upon gentle tugging of

the hair. Counts of hairs lost by the patient on combing or shampooing often exceed 150 per day, compared to an average of 70–100. If iron deficiency is suspected, a serum ferritin should be obtained, and any value less than 40 ng/mL followed with supplementation.

**Alopecia areata** is of unknown cause but is believed to be an immunologic process. Typically, there are patches that are perfectly smooth and without scarring. Tiny hairs 2–3 mm in length, called "exclamation hairs," may be seen. Telogen hairs are easily dislodged from the periphery of active lesions. The beard, brows, and lashes may be involved. Involvement may extend to all of the scalp hair (**alopecia totalis**) or to all scalp and body hair (**alopecia universalis**). Severe forms may be treated by systemic corticosteroid therapy, although recurrences follow discontinuation of therapy. Alopecia areata is occasionally associated with autoimmune disorders, including Hashimoto thyroiditis, pernicious anemia, Addison disease, and vitiligo. Additional comorbidities may include SLE, atopy, and mental health disease.

Intralesional corticosteroids are frequently effective for alopecia areata. Triamcinolone acetonide in a concentration of 2.5–10 mg/mL is injected in aliquots of 0.1 mL at approximately 1- to 2-cm intervals, not exceeding a total dose of 30 mg per month for adults. Alopecia areata is usually self-limiting, with complete regrowth of hair in 80% of patients with focal disease. Some mild cases are resistant to treatment, as are the extensive totalis and universalis types. Support groups for patients with extensive alopecia areata are beneficial. Oral JAK inhibitors (ruxolitinib, tofacitinib) are therapeutic options for patients with highly morbid disease, although relapse is the rule once the medication has been stopped. Efficacy of topical JAK inhibitors for alopecia areata is under investigation.

In **trichotillomania** (the pulling out of one's own hair), the patches of hair loss are irregular, with short, growing hairs almost always present, since they cannot be pulled out until they are long enough. The patches are often unilateral, occurring on the same side as the patient's dominant hand. The patient may be unaware of the habit. N-acetylcysteine (1200–2400 mg orally per day for 12 weeks) may be effective.

### ► Scarring (Cicatricial) Alopecia

Cicatricial alopecia may occur following any type of trauma or inflammation that may scar hair follicles. Examples include chemical or physical trauma, bacterial or fungal infections, severe herpes zoster, chronic discoid lupus erythematosus (DLE), systemic sclerosis (scleroderma), and excessive ionizing radiation. The specific cause is often suggested by the history, the distribution of hair loss, and the appearance of the skin, as in DLE. Specific dermatologic diseases of the scalp that result in scarring alopecia include lichen planopilaris, frontal fibrosing alopecia, dissecting cellulitis of the scalp, and folliculitis decalvans. Biopsy is useful in the diagnosis of scarring alopecia, but specimens must be taken from the active border and not from the scarred central zone. Scarring alopecias are irreversible and permanent. It is important to diagnose and treat the scarring process as early in its course as possible.

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## NAIL DISORDERS

### 1. Morphologic Nail Abnormalities

#### ► Classification

Acquired nail disorders may be classified as local or associated with systemic or generalized skin diseases.

#### A. Local Nail Disorders

1. Onycholysis (distal separation of the nail plate from the nail bed, usually of the fingers) is caused by excessive exposure to water, soaps, detergents, alkalies, and industrial cleaning agents. Candidal infection of the nail folds and subungual area, nail hardeners, drug-induced photosensitivity, hyperthyroidism, hypothyroidism, and psoriasis may cause onycholysis.
2. Distortion of the nail, including nail splitting, occurs as a result of chronic inflammation or infiltration of the nail matrix underlying the eponychial fold. Such changes may be caused by impingement on the nail matrix by inflammatory diseases (eg, psoriasis, lichen planus, eczema), warts, tumors, or cysts.
3. Discoloration and crumbly thickened nails are noted in dermatophyte infection and psoriasis.
4. Allergic reactions (to resins in undercoats and polishes or to nail glues) are characterized by onycholysis or by grossly distorted, hypertrophic, and misshapen nails.
5. Paronychia is inflammation of the lateral or proximal nail folds. Acute paronychia presents as a painful erythematous papulonodule or frank abscess of the nail fold and is most commonly due to infection with *S aureus* (Figure 6-41). Chronic paronychia is most often caused by irritation from water or chemicals with resultant inflammation and possible *Candida* superinfection.

#### B. Nail Changes Associated with Systemic or Generalized Skin Diseases

1. Beau lines (transverse furrows) affect all nails and classically develop after a serious systemic illness.
2. Atrophy of the nails may be related to trauma or to vascular or neurologic disease.
3. Clubbed fingers may be due to the prolonged hypoxemia associated with cardiopulmonary disorders (Figure 6-42) (see Chapter 9).



▲ **Figure 6-41.** Acute paronychia. (Used, with permission, from E.J. Mayeaux Jr, MD, in Usatine RP, Smith MA, Mayeaux EJ Jr, Chumley HS. *The Color Atlas and Synopsis of Family Medicine*, 3rd ed. McGraw-Hill, 2019.)

4. Spoon nails may be seen in anemic patients.
5. Stippling or pitting of the nails is seen in psoriasis, alopecia areata, and hand eczema (Figure 6-8).
6. Nail hyperpigmentation may be caused by many chemotherapeutic agents, but especially the taxanes.

#### ► Differential Diagnosis

Onychomycosis may cause nail changes identical to those seen in psoriasis. Careful examination for more



▲ **Figure 6-42.** Clubbing of the finger in a 31-year-old man with congenital heart disease. Note the thickening around the proximal nail folds. (Used, with permission, from Richard P. Usatine, MD, in Usatine RP, Smith MA, Mayeaux EJ Jr, Chumley HS. *The Color Atlas and Synopsis of Family Medicine*, 3rd ed. McGraw-Hill, 2019.)

characteristic lesions elsewhere on the body is essential to the diagnosis of the nail disorders. Cancer should be suspected (eg, Bowen disease or squamous cell carcinoma) as the cause of any persistent solitary subungual or periumgual lesion.

## ► Complications

Toenail changes may lead to an ingrown nail—in turn often complicated by bacterial infection and occasionally by exuberant granulation tissue. Poor manicuring and poorly fitting shoes may contribute to this complication. Cellulitis may result.

## ► Treatment & Prognosis

Treatment consists usually of careful debridement and manicuring and, above all, reduction of exposure to irritants (soaps, detergents, alkali, bleaches, solvents, etc). Longitudinal grooving due to temporary lesions of the matrix, such as warts, synovial cysts, and other impingements, may be cured by removal of the offending lesion.

Acute paronychia is treated with topical antibiotics and drainage of the abscess, if present. To incise and drain an acute staphylococcal paronychia, insert a flat metal spatula or sharpened hardwood stick into the nail fold where it adjoins the nail. This will release pus from a mature lesion.

Treatment of chronic paronychia includes minimizing wetwork and toxic contactants, wearing gloves while performing tasks that expose the skin to water, minimizing trauma to the nail folds, and a combination of topical corticosteroids and an anticandidal twice daily to the affected area.

## 2. Tinea Unguium (Onychomycosis)

Tinea unguium is a trichophyton infection of one or more (but rarely all) fingernails or toenails. The species most commonly found is *T rubrum*. "Saprophytic" fungi may rarely cause onychomycosis (less than 5% of cases). Evidence supporting a genetic defect in the innate and adaptive immune system may explain why some people suffer from chronic tinea pedis and onychomycosis.

The nails are lusterless, brittle, and hypertrophic, and the substance of the nail is friable. Laboratory diagnosis is mandatory since only 50% of dystrophic nails are due to dermatophytosis. Portions of the nail should be clipped, digested with 10% KOH, and examined under the microscope for hyphae. Fungi may also be cultured from debris collected from underneath the nail plate. Periodic acid-Schiff stain of a histologic section of the nail plate also demonstrates the fungus readily. Each technique is positive in only 50% of cases so several different tests may need to be performed. Periodic acid-Schiff staining of nail plate coupled with fungal culture has a sensitivity of 96%.

Onychomycosis is difficult to treat because of the long duration of therapy required and the frequency of recurrences. Fingernails respond more readily than toenails. For toenails, treatment is indicated for patients with discomfort, inability to exercise, diabetes, and immune compromise.

In general, systemic therapy is required to effectively treat nail onychomycosis. Although historically topical therapy has had limited value, evidence suggests that efinaconazole 10% performs better than other topical treatment options. Tavaborole 5% solution is also approved for the treatment of onychomycosis, but its clearance rates do not appear to be as good as those of efinaconazole. Adjunctive value of surgical procedures is unproven, and the efficacy of laser treatments is lacking, especially with regard to long-term cures.

Fingernails can virtually always be cured, and toenails are cured 35–50% of the time and are clinically improved about 75% of the time. In all cases, before treatment, the diagnosis should be confirmed. The costs of the various treatment options should be known and the most cost-effective treatment chosen. Medication interactions must be avoided. Ketoconazole, due to its higher risk for hepatotoxicity, is not recommended to treat any form of onychomycosis. For fingernails, ultramicrocrystalline griseofulvin 250 mg orally three times daily for 6 months can be effective. Alternative treatments are (in order of preference) oral terbinafine, 250 mg daily for 6 weeks; oral itraconazole, 200–400 mg daily for 7 days each month for 2 months; and oral itraconazole, 200 mg daily for 2 months. Off-label use of fluconazole, 150–400 mg once weekly for 6–9 months, can also be effective, but there is limited evidence for this option. Once clear, fingernails usually remain free of disease for some years.

Onychomycosis of the toenails does not respond to griseofulvin therapy. The best treatment, which is also FDA approved, is oral terbinafine 250 mg daily for 12 weeks. Pulse terbinafine therapy with two cycles of 4 weeks on and 4 weeks off may be as efficacious as continuous oral therapy. Liver biochemical tests, complete blood count, and kidney function should be performed before oral therapy. Because the risk of idiosyncratic injury is very low (transaminitis occurs in less than 0.5% of patients) and the presentation of drug-induced liver injury is usually symptomatic (jaundice, malaise, abdominal pain), routine hepatic monitoring in healthy adults without known hepatic disease is not required. The dose might need adjustment in patients with reduced creatinine clearance. Itraconazole, 200 mg daily for 12 weeks, or pulse oral itraconazole, 200 mg twice daily for 1 week per month for 3 months, is inferior to standard terbinafine treatments, but it is an acceptable alternative for those unable to take terbinafine. The courses of terbinafine or itraconazole may need to be repeated 6 months after the first treatment cycle if fungal cultures of the nail are still positive. Fluconazole may be used off label at 150 mg weekly until the nail has grown out completely (12–18 month for toenails).

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## DRUG ERUPTION (Dermatitis Medicamentosa)



### ESSENTIALS OF DIAGNOSIS

- ▶ Usually, abrupt onset of widespread, symmetric erythematous eruption.
- ▶ May mimic any inflammatory skin condition.
- ▶ Constitutional symptoms (malaise, arthralgia, headache, and fever) may be present.

### ► General Considerations

Rashes are among the most common adverse reactions to medications and occur in 2–3% of hospitalized patients. There are multiple different types of cutaneous reactions to medications. Penicillins, cephalosporins, and NSAIDs are the most common cause of urticarial drug eruptions. Antibiotics, anticonvulsants, allopurinol, and NSAIDs are common causes of maculopapular or morbilliform reactions. Drug-induced hypersensitivity reaction (DIHS) (also known as drug eruption with eosinophilia and systemic symptoms [DRESS]) is most often caused by anticonvulsants, allopurinol, and sulfonamides. SJS and TEN most commonly occur in response to antibiotics, sulfonamides, anticonvulsants, allopurinol, and NSAIDs. Phenolphthalein, pyrazolone derivatives, tetracyclines, NSAIDs, TMP-SMZ, and barbiturates are the major causes of fixed drug eruptions. Calcium channel blockers are a common cause of pruritus and eczemas in older adults.

Certain genetic polymorphisms of antigen-presenting major histocompatibility (MHC) loci increase the risk for the development of severe drug eruptions, including SJS/TEN and DIHS. Pharmacogenetic testing can help predict who is at risk for and therefore should avoid certain medication exposures.

### ► Clinical Findings

#### A. Symptoms and Signs

Drug eruptions are generally classified as “simple” or “complex,” referring to the risk of morbidity and mortality associated with the specific eruption. Simple morbilliform or maculopapular drug eruptions involve an exanthem, usually appear in the second week of medication therapy, and have no associated constitutional symptoms or abnormal laboratory findings. Complex drug eruptions include DIHS and SJS/TEN.

DIHS occurs later than the simple morbilliform drug eruptions with signs and symptoms developing 2–6 weeks after the medication has been started and has associated constitutional symptoms and abnormal laboratory findings.

These may include fevers, chills, hematologic abnormalities (especially eosinophilia and atypical lymphocytosis), and abnormal liver or kidney function. Coexistent reactivation of certain viruses, especially HHV-6, but also Epstein-Barr virus, cytomegalovirus, HHV-7, and parvovirus B19, may be present and may be important in the pathogenesis of these complex drug eruptions. Table 6–3 summarizes the types of skin reactions, their appearance and distribution, and the common offenders in each case.

#### B. Laboratory Findings

Routinely ordered blood work is of no value in the diagnosis of simple drug eruptions, except upon initial evaluation to ensure that there is no systemic involvement. In complex drug eruptions, the complete blood count, liver biochemical tests, and kidney function tests should be monitored. Skin biopsies may be helpful in making the diagnosis. Serum PCR for HHV-6, HHV-7, Epstein-Barr virus, cytomegalovirus, and parvovirus B19 is performed in some centers.

#### ► Differential Diagnosis

Observation after discontinuation, which may be a slow process, helps establish the diagnosis. Rechallenge, though of theoretical value, may pose a danger to the patient and is best avoided.

#### ► Complications

Some cutaneous drug reactions may be associated with visceral involvement. The organ systems involved depend on the individual medication or drug class. Most common is an infectious mononucleosis-like illness and hepatitis associated with administration of anticonvulsants. Myocarditis may be a serious complication of drug-induced hypersensitivity syndrome and may present acutely or months after initial rash onset. Months after recovering from DIHS, patients may suffer hypothyroidism.

#### ► Treatment

##### A. General Measures

Systemic manifestations are treated as they arise (eg, anemia, icterus, purpura). Antihistamines may be of value in urticarial and angioneurotic reactions. Epinephrine 1:1000, 0.5–1 mL intravenously or subcutaneously, should be used as an emergency measure. In DIHS, corticosteroids are typically required; the most common regimen is oral prednisone, 1–1.5 mg/kg/day tapering slowly over a minimum of 6 weeks, since rapid taper leads to rebound and more recalcitrant disease. In the case of allopurinol-induced DIHS, starting a steroid-sparing agent (eg, mycophenolate mofetil) at the time of prednisone initiation is recommended because allopurinol-induced DIHS tends to rebound after corticosteroid discontinuation. Treatment in this special case often takes up to 12 months.

##### B. Local Measures

SJS/TEN with extensive blistering eruptions resulting in erosions and superficial ulcerations demands hospitalization

**Table 6–3.** Skin reactions due to systemic medications.

| Reaction   | Appearance   | Distribution and Comments   | Common Offenders  |
|--|--|---|---|
| Allergic vasculitis  | The primary lesion is typically a 2–3 mm purpuric papule. Other morphologies include urticaria that lasts over 24 hours, vesicles, bullae, or necrotic ulcers. | Most severe on the legs.  | Sulfonamides, phenytoin, propylthiouracil.  |
| Drug exanthem  | Morbilliform, maculopapular, exanthematous reactions.  | The most common skin reaction to medications. Initially begins on trunk 7–10 days after the medication has been started. Spreads to extremities and begins to clear on the trunk over 3–5 days. In previously exposed patients, the rash may start in 2–3 days. Fever may be present. | Antibiotics (especially ampicillin and TMP-SMZ), sulfonamides and related compounds (including thiazide diuretics, furosemide, and sulfonylurea hypoglycemic agents), and barbiturates. |
| Drug-related subacute cutaneous lupus erythematosus<br>(Drug-induced SLE rarely produces a skin reaction)                            | May present with a photosensitive rash, annular lesions, or psoriasis on upper trunk.  | Less severe than SLE, sparing the kidneys and central nervous system. Recovery often follows medication withdrawal.   | Diltiazem, etanercept, hydrochlorothiazide, infliximab, lisinopril, terbinafine.  |
| Erythema nodosum   | Inflammatory cutaneous nodules.  | Usually limited to the extensor aspects of the legs. May be accompanied by fever, arthralgias, and pain.  | Oral contraceptives.  |
| Exfoliative dermatitis and erythroderma<br>(Drug-induced hypersensitivity syndrome)  | Red and scaly.   | Entire skin surface. Typically associated with elevated liver biochemical tests, eosinophilia, and acute kidney injury. Eruption begins between 2 and 6 weeks after first dose of medication.   | Allopurinol, sulfonamides, isoniazid, anticonvulsants, or carbamazepine.  |
| Fixed drug eruptions   | Single or multiple demarcated, round, erythematous plaques that often become hyperpigmented.   | Recur at the same site when the medication is repeated. Hyperpigmentation, if present, remains after healing.   | Antimicrobials, analgesics (acetaminophen, ibuprofen, and naproxen), barbiturates, heavy metals, antiparasitic agents, antihistamines, phenolphthalein.                                 |
| Lichenoid and lichen planus-like eruptions   | Pruritic, erythematous to violaceous polygonal papules that coalesce or expand to form plaques.  | May be in photo- or nonphotodistributed pattern.  | Carbamazepine, furosemide, hydroxychloroquine, phenothiazines, beta-blockers, quinidine, quinine, sulfonylureas, tetracyclines, thiazides, and triprolidine.                            |
| Photosensitivity: increased sensitivity to light, often of ultraviolet A wavelengths, but may be due to UVB or visible light as well | Sunburn, vesicles, papules in photodistributed pattern.  | Exposed skin of the face, the neck, and the backs of the hands and, in women, the lower legs. Exaggerated response to ultraviolet light.  | Sulfonamides and sulfonamide-related compounds (thiazide diuretics, furosemide, sulfonylureas), tetracyclines, phenothiazines, sulindac, amiodarone, voriconazole, and NSAIDs.          |
| Pigmentary changes   | Flat hyperpigmented areas.   | Forehead and cheeks (chloasma, melasma). The most common pigmentary disorder associated with drug ingestion. Improvement is slow despite stopping the medication.   | Oral contraceptives are the usual cause. Diltiazem causes facial hyperpigmentation that may be difficult to distinguish from melasma.   |
|  | Blue-gray discoloration.   | Light-exposed areas.  | Chlorpromazine and related phenothiazines.  |

(continued)

**Table 6–3.** Skin reactions due to systemic medications. (continued)

| Reaction                        | Appearance   | Distribution and Comments  | Common Offenders   |
|---------------------------------|--|--|--|
|                                 | Brown or blue-gray pigmentation.   | Generalized.   | Heavy metals (silver, gold, bismuth, and arsenic).   |
|                                 | Blue-black patches on the shins.   |  | Minocycline, chloroquine.  |
|                                 | Blue-black pigmentation of the nails and palate and depigmentation of the hair.                        |  | Chloroquine.   |
|                                 | Slate-gray color.  | Primarily in photoexposed areas.   | Amiodarone.  |
|                                 | Brown discoloration of the nails.  | Especially in more darkly pigmented patients.  | Hydroxyurea.   |
| Pityriasis rosea-like eruptions | Oval, red, slightly raised patches with central scale.   | Mainly on the trunk.   | Barbiturates, bismuth, captopril, clonidine, methopromazine, metoprolol, metronidazole, and tripelennamine.  |
| Psoriasiform eruptions          | Scaly red plaques.   | May be located on trunk and extremities. Palms and soles may be hyperkeratotic. May cause psoriasiform eruption or worsen psoriasis. | Antimalarials, lithium, beta-blockers, and TNF inhibitors.   |
| SJS/TEN                         | Target-like lesions. Bullae may occur. Mucosal involvement.  | Usually trunk and proximal extremities.  | Sulfonamides, anticonvulsants, allopurinol, NSAIDs, lamotrigine.   |
| Urticaria                       | Red, itchy wheals that vary in size from < 1 cm to many centimeters. May be accompanied by angioedema. | Chronic urticaria is rarely caused by medications.   | Acute urticaria: penicillins, NSAIDs, sulfonamides, opioids, and salicylates. Angioedema is common in patients receiving ACE inhibitors and angiotensin receptor blockers. |

ACE, angiotensin-converting enzyme; NSAIDs, nonsteroidal anti-inflammatory drugs; SJS/TEN, Stevens-Johnson syndrome/toxic epidermal necrolysis; SLE, systemic lupus erythematosus; TMP-SMZ, trimethoprim-sulfamethoxazole; TNF, tumor necrosis factor.

and nursing care as for burn patients. See Erythema Multiforme/Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis, above.

## ► Prognosis

Drug rash usually disappears upon withdrawal of the medication and proper treatment. DIHS may be associated with autoimmune phenomena, including abnormal thyroid function. This can occur months after the hypersensitivity syndrome has resolved.

Brockow K et al. EAACI position paper on how to classify cutaneous manifestations of drug hypersensitivity. *Allergy*. 2019;74:14. [PMID: 30028512]

Gerogianni K et al. Drug-induced skin adverse reactions: the role of pharmacogenomics in their prevention. *Mol Diagn Ther*. 2018;22:297. [PMID: 29564734]

Martínez-Cabriales SA et al. Drug reaction with eosinophilia and systemic symptoms (DReSS): how far have we come? *Am J Clin Dermatol*. 2019;20:217. [PMID: 30652265]

Zhang C et al. Drug-induced severe cutaneous adverse reactions: determine the cause and prevention. *Ann Allergy Asthma Immunol*. 2019;123:483. [PMID: 31400461]

# Disorders of the Eyes & Lids

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## REFRACTIVE ERRORS

Refractive error is the most common cause of reduced clarity of vision (visual acuity).

Use of a pinhole will overcome most refractive errors and thus allows their identification as a cause of reduced visual acuity. Refractive error can be treated with glasses, contact lenses, or surgery.

### Treatment

#### A. Contact Lenses

An estimated 40.9 million US adults wear contact lenses, mostly for correction of refractive errors, though decorative-colored contact lenses are used.

The major risk from contact lens wear is corneal infection, potentially a blinding condition. Such infections occur more often with soft lenses, particularly extended wear, for which there is at least a fivefold increase in risk of corneal infection compared with daily wear. Decorative contact lenses have a high prevalence of microbial contamination. Contact lens wearers should be made aware of the risks they face and ways to minimize them, such as avoiding overnight wear or use of lenses past their replacement date and maintaining meticulous lens hygiene, including not using tap water or saliva for lens cleaning. Contact lenses should be removed whenever there is ocular discomfort or redness.

Razmaria AA. JAMA patient page. Proper care of contact lenses. JAMA. 2015;314:1534. [PMID: 26462011]

#### B. Surgery

Various surgical techniques are available to reduce refractive errors, particularly nearsightedness. Laser corneal refractive surgery reshapes the middle layer (stroma) of the cornea with an excimer laser. Other refractive surgery techniques are extraction of the clear crystalline lens with insertion of a single vision, multifocal, or accommodative intraocular lens as occurs after cataract extraction; insertion of an intraocular lens without removal of the crystalline lens (phakic intraocular lens); intrastromal corneal

ring segments (INTACS); collagen cross-linking; laser thermal keratoplasty; and conductive keratoplasty (CK).

Wilkinson JM et al. Refractive eye surgery: helping patients make informed decisions about LASIK. Am Fam Physician. 2017;95:637. [PMID: 28671403]

#### C. Reduction of Rate of Progression of Nearsightedness

The rate at which nearsightedness progresses can be reduced by topical atropine and pirenzepine, a selective muscarinic antagonist; rigid contact lens wear during sleep (orthokeratology); and various types of soft contact lenses and spectacles, but their long-term efficacy and safety are uncertain.

### When to Refer

Any contact lens wearer with an acute painful red eye must be referred emergently for ophthalmologic evaluation.

## DISORDERS OF THE LIDS & LACRIMAL APPARATUS

### 1. Hordeolum

Hordeolum is an acute infection that is commonly due to *Staphylococcus aureus*. It is characterized by a localized red, swollen, acutely tender area on the upper or lower lid. Internal hordeolum is a meibomian gland abscess that usually points onto the conjunctival surface of the lid; external hordeolum, or stye, is usually smaller and on the lid margin and is an abscess of the gland of Zeis.

Warm compresses are helpful. Incision may be indicated if resolution does not begin within 48 hours. An antibiotic ointment (bacitracin or erythromycin) applied to the lid every 3 hours may be beneficial during the acute stage. Internal hordeolum may lead to generalized cellulitis of the lid.

### 2. Chalazion

Chalazion is a common granulomatous inflammation of a meibomian gland that may follow an internal hordeolum. It is characterized by a hard, nontender swelling on the

upper or lower lid with redness and swelling of the adjacent conjunctiva. Initial treatment is with warm compresses. If resolution has not occurred by 2–3 weeks, incision and curettage is indicated. Corticosteroid injection may also be effective.

### 3. Blepharitis

Blepharitis is a common chronic bilateral inflammatory condition of the lid margins. **Anterior blepharitis** involves the lid skin, eyelashes, and associated glands. It may be ulcerative because of infection by staphylococci, or seborrheic in association with seborrhea of the scalp, brows, and ears. **Posterior blepharitis** results from inflammation of the meibomian glands. There may be bacterial infection, particularly with staphylococci, or primary glandular dysfunction, which is strongly associated with acne rosacea.

### Clinical Findings

Symptoms are irritation, burning, and itching. In **anterior blepharitis**, the eyes are “red-rimmed” and scales or collerettes can be seen clinging to the lashes. In **posterior blepharitis**, the lid margins are hyperemic with telangiectasias, and the meibomian glands and their orifices are inflamed. The lid margin is frequently rolled inward to produce a mild entropion, and the tear film may be frothy or abnormally greasy.

Blepharitis is a common cause of recurrent conjunctivitis. Both anterior and, especially, posterior blepharitis may be complicated by hordeola or chalazia; abnormal lid or lash positions, producing trichiasis; epithelial keratitis of the lower third of the cornea; marginal corneal infiltrates; and inferior corneal vascularization and thinning.

### Treatment

**Anterior blepharitis** is usually controlled by eyelid hygiene. Warm compresses help soften the scales and warm the meibomian gland secretions. Eyelid cleansing can be achieved by gentle eyelid massage and lid scrubs with baby shampoo or 0.01% hypochlorous acid. In acute exacerbations, an antibiotic eye ointment, such as bacitracin or erythromycin, is applied daily to the lid margins.

Mild **posterior blepharitis** may be controlled with regular meibomian gland expression and warm compresses. Inflammation of the conjunctiva and cornea is treated with long-term low-dose oral antibiotic therapy, eg, tetracycline (250 mg twice daily for 2–4 weeks), doxycycline (100 mg daily for 2–4 weeks), minocycline (50–100 mg daily for 2–4 weeks) erythromycin (250 mg three times daily for 2–4 weeks), or azithromycin (500 mg daily for 3 days in three cycles with 7-day intervals). Short-term (5–7 days) topical corticosteroids, eg, prednisolone, 0.125% twice daily, may also be indicated. Topical therapy with antibiotics, such as ciprofloxacin 0.3% ophthalmic solution twice daily, may be helpful but should be restricted to short courses of 5–7 days.

Amescua G et al; American Academy of Ophthalmology Preferred Practice Pattern Cornea and External Disease Panel. Blepharitis Preferred Practice Pattern<sup>®</sup>. Ophthalmology. 2019;126:P56. [PMID: 30366800]

### 4. Entropion & Ectropion

Entropion (inward turning of usually the lower lid) occurs occasionally in older people as a result of degeneration of the lid fascia or may follow extensive scarring of the conjunctiva and tarsus. Surgery is indicated if the lashes rub on the cornea. Botulinum toxin injections may also be used for temporary correction of the involutional lower lid entropion of older people.

Ectropion (outward turning of the lower lid) is common with advanced age. Surgery is indicated if there is excessive tearing, exposure keratitis, or a cosmetic problem.

### 5. Tumors

Lid tumors are usually benign. Basal cell carcinoma is the most common malignant tumor. Squamous cell carcinoma, meibomian gland carcinoma, and malignant melanoma also occur. Surgery for any lesion involving the lid margin should be performed by an ophthalmologist or suitably trained plastic surgeon to avoid deformity of the lid. Histopathologic examination of eyelid tumors should be routine, since 2% of lesions thought to be benign clinically are found to be malignant. Medications such as vismodegib (an oral inhibitor of the hedgehog pathway), imiquimod (an immunomodulator), and 5-fluorouracil occasionally are used instead of or as an adjunct to surgery for some basal and squamous cell carcinomas.

### 6. Dacryocystitis

Dacryocystitis is infection of the lacrimal sac usually due to congenital or acquired obstruction of the nasolacrimal system. It may be acute or chronic and occurs most often in infants and in persons over 40 years. It is usually unilateral. Infection is typically with *S aureus* and streptococci in acute dacryocystitis and *Staphylococcus epidermidis*, streptococci, or gram-negative bacilli in chronic dacryocystitis.

Acute dacryocystitis is characterized by pain, swelling, tenderness, and redness in the tear sac area; purulent material may be expressed. In chronic dacryocystitis, tearing and discharge are the principal signs, and mucus or pus may also be expressed.

Acute dacryocystitis responds well to systemic antibiotic therapy. To relieve the underlying obstruction, surgery is usually done electively but may be performed urgently in acute cases. The chronic form may be kept latent with systemic antibiotics, but relief of the obstruction is the only cure. In adults, the standard procedure is dacryocystorhinostomy, which involves surgical exploration of the lacrimal sac and formation of a fistula into the nasal cavity and, if necessary, supplemented by nasolacrimal intubation.

Congenital nasolacrimal duct obstruction is common and often resolves spontaneously. It can be treated by probing the nasolacrimal system, supplemented by nasolacrimal intubation or balloon catheter dilation, if necessary; dacryocystorhinostomy is rarely required.

### CONJUNCTIVITIS

Conjunctivitis is inflammation of the mucous membrane that lines the surface of the eyeball and inner eyelids. It may be acute or chronic. Most cases are due to viral or bacterial

(including gonococcal and chlamydial) infection. Other causes include keratoconjunctivitis sicca, allergy, chemical irritants, and trauma. The mode of transmission of infectious conjunctivitis is usually via direct contact of contaminated fingers or objects to the fellow eye or to other persons. It may also be spread through respiratory secretions or contaminated eye drops.

Conjunctivitis must be differentiated from acute uveitis, acute glaucoma, and corneal disorders (Table 7–1).

## 1. Viral Conjunctivitis

Adenovirus is the most common cause of viral conjunctivitis. There is usually sequential bilateral disease with copious watery discharge and a follicular conjunctivitis. Infection spreads easily. Epidemic keratoconjunctivitis, which may result in decreased vision from corneal subepithelial infiltrates, is usually caused by adenovirus types 8, 19, and 37. The active viral conjunctivitis lasts up to 2 weeks, with the immune-mediated keratitis occurring later. Infection with adenovirus types 3, 4, 7, and 11 is typically associated with pharyngitis, fever, malaise, and preauricular adenopathy (pharyngoconjunctival fever). The disease usually lasts 10 days. Contagious acute hemorrhagic conjunctivitis (see Chapter 32) may be caused by enterovirus 70 or coxsackievirus A24. Viral conjunctivitis from herpes simplex virus (HSV) is typically unilateral and may be associated with lid vesicles.

Except for HSV infection for which treatment with topical (eg, ganciclovir 0.15% gel) and/or systemic (eg, oral acyclovir, valacyclovir) antivirals is recommended (Table 32–1), there is no specific treatment for contagious viral conjunctivitis. Artificial tears and cold compresses may help reduce discomfort. The use of topical antibiotics and steroids in the acute infection is discouraged. Frequent hand and linen hygiene is encouraged to minimize spread.

Varu DM et al; American Academy of Ophthalmology Preferred Practice Pattern Cornea and External Disease Panel. Conjunctivitis Preferred Practice Pattern®. Ophthalmology. 2019; 126:P94. [PMID: 30366797]

## 2. Bacterial Conjunctivitis

The organisms isolated most commonly in bacterial conjunctivitis are staphylococci, including methicillin-resistant *S aureus* (MRSA); streptococci, particularly *Streptococcus pneumoniae*; *Haemophilus* species; *Pseudomonas*; and *Moraxella*. All may produce purulent discharge and eyelid matting. Blurring of vision and discomfort are mild. In severe (hyperpurulent) cases, examination of stained conjunctival scrapings and cultures is recommended, particularly to identify gonococcal infection that requires emergent treatment.

The disease is usually self-limited, lasting about 10–14 days if untreated. Most topical antibiotics hasten clinical remission. This infection is typically self-limited, and no topical antibiotic has proven superiority over another.

### A. Gonococcal Conjunctivitis

Gonococcal conjunctivitis, usually acquired through contact with infected genital secretions, typically causes copious purulent discharge. It is an ophthalmologic emergency because corneal involvement may rapidly lead to perforation. The diagnosis should be confirmed by stained smear and culture of the discharge. Systemic treatment is required with a single 1-g dose of intramuscular ceftriaxone plus azithromycin 1000 mg orally (see Chapter 33). Fluoroquinolone resistance is common. Eye irrigation with saline may promote resolution of conjunctivitis. Topical antibiotics such as erythromycin and bacitracin may be added. Other sexually transmitted diseases, including chlamydiosis,

**Table 7–1.** The inflamed eye: differential diagnosis of common causes.

|                          | Acute Conjunctivitis | Acute Anterior Uveitis (Iritis)    | Acute Angle-Closure Glaucoma | Corneal Trauma or Infection               |
|--------------------------|----------------------|------------------------------------|------------------------------|---|
| Incidence                | Extremely common     | Common                             | Uncommon                     | Common                                    |
| Discharge                | Moderate to copious  | None                               | None                         | Watery or purulent                        |
| Vision                   | No effect on vision  | Often blurred                      | Markedly blurred             | Usually blurred                           |
| Pain                     | Mild                 | Moderate                           | Severe                       | Moderate to severe                        |
| Conjunctival injection   | Diffuse              | Mainly circumcorneal               | Mainly circumcorneal         | Mainly circumcorneal                      |
| Cornea                   | Clear                | Usually clear                      | Cloudy                       | Clarity change related to cause           |
| Pupil size               | Normal               | Small                              | Moderately dilated           | Normal or small                           |
| Pupillary light response | Normal               | Poor                               | None                         | Normal                                    |
| Intraocular pressure     | Normal               | Usually normal but may be elevated | Markedly elevated            | Normal                                    |
| Smear                    | Causative organisms  | No organisms                       | No organisms                 | Organisms found only in corneal infection |

syphilis, and HIV infection, should be considered. Routine treatment for chlamydial infection is recommended.

### B. Chlamydial Keratoconjunctivitis

**1. Trachoma**—Trachoma is the most common infectious cause of blindness worldwide, with approximately 40 million people affected and 1.2 million blind. Recurrent episodes of infection in childhood manifest as bilateral follicular conjunctivitis, epithelial keratitis, and corneal vascularization (pannus). Scarring (cicatrization) of the tarsal conjunctiva leads to entropion and trichiasis in adulthood with secondary central corneal scarring.

Immunologic tests or polymerase chain reaction (PCR) on conjunctival samples will confirm the diagnosis but treatment should be started on the basis of clinical findings. A single 1-g dose of oral azithromycin is the preferred drug for mass treatment campaigns. Improvements in hygiene and living conditions probably have contributed more to the marked reduction in the prevalence of trachoma during the past 30 years. Local treatment is not necessary. Surgical treatment includes correction of lid deformities and corneal transplantation.

Godwin W et al. Trachoma prevalence after discontinuation of mass azithromycin distribution. *J Infect Dis.* 2020;221:S519. [PMID: 32052842]

**2. Inclusion conjunctivitis**—The eye becomes infected after contact with genital secretions infected with chlamydia. The disease starts with acute redness, discharge, and irritation. Examination shows follicular conjunctivitis with mild keratitis. A nontender preauricular lymph node can often be palpated. Healing usually leaves no sequelae. Diagnosis can be rapidly confirmed by immunologic tests or PCR on conjunctival samples. Treatment is with a single dose of azithromycin, 1 g orally. All cases should be assessed for genital tract infection and other sexually transmitted diseases.

### 3. Dry Eyes

Dry eye, a common and chronic disorder, is an umbrella term that describes a condition of tear film instability and associated ocular and visual complaints. Dry eye is more common in women than men and increases with age. Hypofunction of the lacrimal glands, causing loss of the aqueous component of tears (keratoconjunctivitis sicca), may be due to aging, hereditary disorders, systemic disease (eg, Sjögren syndrome), or systemic drugs. Excessive evaporation of tears may be due to environmental factors (eg, excessive screen time, windy climate) or abnormalities of the lipid component of the tear film, as in blepharitis. Mucin deficiency may be due to vitamin A deficiency or conjunctival scarring from trachoma, Stevens-Johnson syndrome, mucous membrane pemphigoid, graft-versus-host disease, chemical burns, or topical drug toxicity.

### Clinical Findings

The patient complains of dryness, redness, foreign body sensation, and variable vision. In severe cases, there is persistent marked discomfort, with photophobia, difficulty in moving the lids, and excessive mucus secretion. In many cases, gross inspection reveals no abnormality, but on slit-lamp examination there are abnormalities of tear film stability and reduced tear volume. In more severe cases, damaged corneal and conjunctival cells stain with fluorescein and lissamine green. In the most severe cases, there is marked conjunctival injection, mucoid discharge, loss of the normal conjunctival and corneal luster, and epithelial keratopathy that stains with fluorescein and may progress to frank ulceration. The Schirmer test, which measures the rate of production of the aqueous component of tears, may be helpful.

### Treatment

Aqueous deficiency can be treated with artificial tears drops or ointments. The simplest preparations are physiologic (0.9%) or hypo-osmotic (0.45%) solutions of sodium chloride, which can be used as frequently as every half-hour, but in most cases are needed only three or four times a day. More prolonged duration of action can be achieved with drop preparations containing a mucomimetic such as hydroxypropyl methylcellulose (HPMC) or carboxymethylcellulose (carmellose). If there is tenacious mucus, mucolytic agents (eg, acetylcysteine 10% or 20%, 1 drop six times daily) may be helpful.

Artificial tear preparations are generally safe and, in most cases, are used three or four times a day. However, preservatives included in some preparations to maintain sterility are potentially toxic and allergenic and may cause ocular surface toxicity in frequent users. Such reactions may be misinterpreted as a worsening of the dry eye state requiring more frequent use of the artificial tears and leading in turn to further deterioration, rather than being recognized as a need to change to a preservative-free preparation. Preservative-free preparations are recommended for any frequency of use greater than four times a day. Eye drops claiming to “get the red out” are not recommended as they cause toxicity and rebound hyperemia with prolonged use.

Dry eye is considered an inflammatory ocular surface disease. Accordingly, disease modification may require episodic treatment with low potency corticosteroid drops. All patients using topical corticosteroids should have their intraocular pressure monitored by eye care professionals. Corticosteroid-sparing anti-inflammatory drops such as the calcineurin inhibitor cyclosporine 0.05% ophthalmic emulsion (Restasis) and the integrin antagonist lifitegrast 5% are commonly used with no universal consensus of efficacy. Lacrimal punctal occlusion by canalicular plugs or cautery is useful in severe cases.

Blepharitis is treated as described above.

de Paiva CS et al. Topical cyclosporine A therapy for dry eye syndrome. *Cochrane Database Syst Rev.* 2019;9:CD010051. [PMID: 31517988]

Gonzales JA. . Seitzman GD et al. Ocular clinical signs and diagnostic tests most compatible with keratoconjunctivitis sicca: a latent class approach. *Cornea*. 2020;39:1013. [PMID: 32251167]

## 4. Allergic Eye Disease

Allergic eye disease is common and takes a number of different forms but all are expressions of atopy, which may also manifest as atopic asthma, atopic dermatitis, or allergic rhinitis.

### ► Clinical Findings

Symptoms include itching, tearing, redness, stringy discharge, and occasionally, photophobia and visual loss.

**Allergic conjunctivitis** is common. It may be seasonal (hay fever), developing usually during the spring or summer, or perennial. Clinical signs include conjunctival hyperemia and edema (chemosis), the latter at times being marked and sudden in onset. **Vernal keratoconjunctivitis** also tends to occur in late childhood and early adulthood. It is usually seasonal, with a predilection for the spring. Large “cobblestone” papillae are noted on the upper tarsal conjunctiva. There may be follicles at the limbus. **Atopic keratoconjunctivitis** is a more chronic disorder of adulthood. Both the upper and the lower tarsal conjunctivas exhibit a papillary conjunctivitis. Severe cases demonstrate conjunctival fibrosis, resulting in forniceal shortening and entropion with trichiasis. Corneal involvement, including refractory ulceration, is frequent during exacerbations of both vernal and severe atopic keratoconjunctivitis. The latter may be complicated by herpes simplex keratitis.

### ► Treatment

#### A. Mild and Moderately Severe Allergic Eye Disease

Topical anti-inflammatory agents include mast cell stabilizers and antihistamines (Table 7–2). Mast cell stabilization takes longer to act than antihistamines but can be useful for prophylaxis. Topical vasoconstrictors, such as ephedrine, naphazoline, tetrahydrozoline, and phenylephrine, alone or in combination with antihistamines, are available as over-the-counter medications and not typically used because of limited efficacy, rebound hyperemia, and follicular conjunctivitis. Systemic antihistamines (eg, loratadine 10 mg orally daily) may be useful in prolonged atopic keratoconjunctivitis. In allergic conjunctivitis, specific allergens may be avoidable.

#### B. Acute Exacerbations and Severe Allergic Eye Disease

Topical corticosteroids (Table 7–2) are essential to control acute exacerbations of both vernal and atopic keratoconjunctivitis. Corticosteroid-induced side effects should be monitored by eye care professionals and include cataracts, glaucoma, and exacerbation of herpes simplex keratitis. The lowest potency corticosteroid that controls ocular inflammation should be used. Topical cyclosporine or tacrolimus is also effective. Systemic corticosteroid or

other immunosuppressant therapy may be required in severe atopic keratoconjunctivitis.

Beck KM, Seitzman GD et al. Ocular co-morbidities of atopic dermatitis. part I: associated ocular diseases. *Am J Clin Dermatol*. 2019;20:797. [PMID: 31359350]

Beck KM, Seitzman GD et al. Ocular co-morbidities of atopic dermatitis. part II: ocular disease secondary to treatments. *Am J Clin Dermatol*. 2019;20:807. [PMID: 31352589]

## PINGUECULA & PTERYGium

Pinguecula is a yellowish, elevated conjunctival nodule in the area of the palpebral fissure. It is common in persons over age 35 years. Pterygium is a fleshy, triangular encroachment of the conjunctiva onto the cornea and is usually associated with prolonged exposure to wind, sun, sand, and dust. Pinguecula and pterygium are often bilateral and occur more frequently on the nasal side of the conjunctiva.

Pingueculae rarely grow but may become inflamed (pingueculitis). Pterygia become inflamed and may grow. Treatment is rarely required for inflammation of pinguecula or pterygium, and artificial tears are often beneficial.

The indications for excision of pterygium are growth that threatens vision by encroaching on the visual axis, marked induced astigmatism, or severe ocular irritation.

## CORNEAL ULCER

Corneal ulcers are most commonly due to infection by bacteria, viruses, fungi, or amoebas. Noninfectious causes—all of which may be complicated by infection—include neurotrophic keratitis (resulting from loss of corneal sensation), exposure keratitis (due to inadequate lid closure), severe dry eye, severe allergic eye disease, and inflammatory disorders that may be purely ocular or part of a systemic vasculitis. Delayed or ineffective treatment of corneal ulceration may lead to devastating consequences with corneal scarring and rarely intraocular infection. Prompt referral is essential.

Patients complain of pain, photophobia, tearing, and reduced vision. The conjunctiva is injected, and there may be purulent or watery discharge. The corneal appearance varies according to the underlying cause.

### ► When to Refer

Any patient with an acute painful red eye and corneal abnormality should be referred emergently to an ophthalmologist. Contact lens wearers with acute eye pain, redness, and decreased vision should be referred immediately.

## INFECTIOUS KERATITIS

### 1. Bacterial Keratitis

Risk factors for bacterial keratitis include contact lens wear—especially overnight wear—and corneal trauma, including refractive surgery. The pathogens most commonly isolated are staphylococci, including MRSA; streptococci;

**Table 7–2.** Topical ophthalmic agents (selected list).

| Agent  | Cost/Size <sup>1</sup>         | Recommended Regimen   | Indications  |
|--|--------------------------------|---|--|
| <b>Antibiotic Agents</b>                               |                                |   |  |
| Amikacin 2.5% (fortified) solution                     | Compounding pharmacy           |   |  |
| Azithromycin (AzaSite)                                 | \$247.45/2.5 mL                | 1 drop two times daily for 2 days, then once daily for 5 days   | Bacterial conjunctivitis                                   |
| Bacitracin 500 units/g ointment (various) <sup>2</sup> | \$118.44/3.5 g                 | Apply 0.5 inch into lower conjunctival sac or to eyelids three to four times daily for 7–10 days  | Bacterial conjunctivitis, blepharitis, sty                 |
| Bacitracin/Polymyxin ointment (Polysporin, AK-Poly)    | \$25.70/3.5 g                  | Apply 0.5 inch into lower conjunctival sac and then three to four times daily, then as required   | Corneal abrasion<br>Following corneal foreign body removal |
| Besifloxacin ophthalmic suspension, 0.6% (Besivance)   | \$228.35/5 mL                  | 1–2 drops every 2 hours while awake for 2 days, then every 4 hours for 5 days<br>1 drop every hour during the day and every 2 hours during the night for 48 hours, then gradually reduce  | Bacterial conjunctivitis<br>Bacterial keratitis            |
| Ciprofloxacin HCl 0.3% solution (Ciloxan)              | \$10.20/5 mL                   | 1–2 drops every 2 hours while awake for 2 days, then every 4 hours for 5 days<br>1 drop every hour during the day and every 2 hours during the night for 48 hours, then gradually reduce  | Bacterial conjunctivitis<br>Bacterial keratitis            |
| Ciprofloxacin HCl 0.3% ointment                        | \$257.23/3.5 g                 | Apply 0.5 inch into lower conjunctival sac three times daily for 2 days, then two times daily for 5 days  | Bacterial conjunctivitis                                   |
| Erythromycin 0.5% ointment (various)                   | \$17.96/3.5 g                  | 1-cm ribbon up to six times daily   | Bacterial infection of the conjunctiva or lid margin       |
| Fusidic acid 1% gel (Fucithalmic)                      | Not available in United States | 1 drop two times daily  | Bacterial conjunctivitis, blepharitis, sty, keratitis      |
| Gatifloxacin 0.5% solution (Zymaxid)                   | \$118.16/2.5 mL                | 1 drop every 2 hours while awake, up to eight times on day 1, then two to four times daily while awake, days 2–7<br>1 drop every hour during the day and every 2 hours during the night for 48 hours, then gradually reduce                         | Bacterial conjunctivitis<br>Bacterial keratitis            |
| Gentamicin sulfate 0.3% solution (various)             | \$19.18/5 mL                   | 1–2 drops every 4 hours up to 2 drops every hour for severe infections  | Ocular surface infection                                   |
| Gentamicin sulfate 0.3% ointment (various)             | \$35.44/3.5 g                  | Apply 0.5 inch into lower conjunctival sac two to three times daily   | Ocular surface infection                                   |
| Gentamicin sulfate 1.5% (fortified preparation)        | Compounding pharmacy           | 1 drop every hour during the day and every 2 hours during the night for 48 hours, then gradually reduce   | Bacterial keratitis  |
| Levofloxacin 0.5% solution (various)                   | \$75.00/5 mL                   | 1–2 drops every 2 hours while awake for 2 days (maximum eight times per day), then every 4 hours for 5 days (maximum four times per day)<br>1 drop every hour during the day and every 2 hours during the night for 48 hours, then gradually reduce | Bacterial conjunctivitis<br>Bacterial keratitis            |
| Moxifloxacin 0.5% solution (Vigamox)                   | \$167.35/3 mL                  | 1 drop three times daily for 7 days<br>1 drop every hour during the day and every 2 hours during the night for 48 hours, then gradually reduce  | Bacterial conjunctivitis<br>Bacterial keratitis            |

(continued)

**Table 7–2.** Topical ophthalmic agents (selected list). (continued)

| Agent  | Cost/Size <sup>1</sup>             | Recommended Regimen   | Indications  |
|--|------------------------------------|---|--|
| Neomycin/Polymyxin B/Gramicidin (Neosporin)                                  | \$61.26/10 mL                      | 1–2 drops every 4 hours for 7–10 days or more frequently, as required   | Ocular surface infection   |
| Norfloxacin 0.3% solution  | Not available in United States     | 1 drop every hour during the day and every 2 hours during the night for 48 hours, then gradually reduce   | Ocular surface infection<br>Bacterial keratitis                    |
| Ofloxacin 0.3% solution (Ocuflax)  | \$20.94/5 mL                       | 1–2 drops every 2–4 hours for 2 days, then four times daily for 5 days<br>1 drop every hour during the day and every 2 hours during the night for 48 hours, then gradually reduce                       | Bacterial conjunctivitis<br>Bacterial keratitis                    |
| Polymyxin B 10,000 U/mL/Trimethoprim sulfate 1 mg/mL (Polytrim) <sup>4</sup> | \$12.87/10 mL                      | 1 drop every 3 hours for 7–10 days (maximum of 6 doses per day)   | Ocular surface infection   |
| Propamidine isethionate 0.1% solution  | Not available in the United States | 1–2 drops every 2–4 hours for 2 days, then four times daily for 5 days  | Ocular surface infection (including <i>Acanthamoeba</i> keratitis) |
| Propamidine isethionate 0.1% ointment  | Not available in the United States | Apply 0.5 inch into lower conjunctival sac up to four times daily   |  |
| Sulfacetamide sodium 10% solution (various)                                  | \$55.65/15 mL                      | 1 or 2 drops every 2–3 hours initially; taper by increasing time intervals as condition responds; usual duration 7–10 days  | Bacterial infection of the conjunctiva or lid margin               |
| Sulfacetamide sodium 10% ointment (various)                                  | \$65.86/3.5 g                      | Apply 0.5 inch into lower conjunctival sac once every 3–4 hours and at bedtime; taper by increasing time intervals as condition responds; usual duration 7–10 days                                      | Bacterial infection of the conjunctiva or lid margin               |
| Tobramycin 0.3% solution (various)   | \$6.25/5 mL                        | 1–2 drops every 4 hours for a mild to moderate infection or hourly until improvement (then reduce prior to discontinuation) for a severe infection  |  |
| Tobramycin 1.5% (fortified) solution   | Compounding pharmacy               | 1 drop every hour during the day and every 2 hours during the night for 48 hours, then gradually reduce   | Bacterial keratitis  |
| Tobramycin 0.3% ointment (Tobrex)  | \$257.23/3.5 g                     | Apply 0.5 inch into lower conjunctival sac two to three times daily for a mild to moderate infection or every 3–4 hours until improvement (then reduce prior to discontinuation) for a severe infection |  |
| <b>Antifungal Agents</b>   |                                    |   |  |
| Amphotericin 0.1–0.5% solution   | Compounding pharmacy               |   |  |
| Natamycin 5% suspension (Natacyn)  | \$430.18/15 mL                     | 1 drop every 1–2 hours initially  | Fungal blepharitis, conjunctivitis, keratitis                      |
| Voriconazole 1% solution   | Compounding pharmacy               |   |  |
| <b>Antiviral Agents</b>  |                                    |   |  |
| Acyclovir 3% ointment (Zovirax)  | Not available in United States     | Five times daily  | Herpes simplex virus keratitis                                     |
| Ganciclovir 0.15% gel (Zirgan)   | \$473.62/5 g                       | Five times daily  | Herpetic keratitis   |

(continued)

**Table 7–2.** Topical ophthalmic agents (selected list). (continued)

| Agent  | Cost/Size <sup>1</sup>             | Recommended Regimen  | Indications   |
|--|------------------------------------|--|---|
| Trifluridine 1% solution (Viroptic)                          | \$178.28/7.5 mL                    | 1 drop onto cornea every 2 hours while awake for a maximum daily dose of 9 drops until resolution occurs; then an additional 7 days of 1 drop every 4 hours while awake (minimum five times daily) | Herpes simplex virus keratitis  |
| <b>Anti-Inflammatory Agents</b>                              |                                    |  |   |
| <b>Antihistamines<sup>5</sup></b>                            |                                    |  |   |
| Emedastine difumarate 0.05% solution (Emadine)               | Not available in the United States | 1 drop four times daily  | Allergic eye disease  |
| Levocabastine (Livostin)                                     | Not available in United States     | 1 drop twice daily   |   |
| <b>Mast cell stabilizers</b>                                 |                                    |  |   |
| Cromolyn sodium 4% solution (Crolom)                         | \$37.20/10 mL                      | 1 drop four to six times daily   |   |
| Lodoxamide tromethamine 0.1% solution (Alomide)              | \$205.28/10 mL                     | 1 or 2 drops four times daily (up to 3 months)   |   |
| Nedocromil sodium 2% solution (Alocril)                      | \$269.41/5 mL                      | 1 drop twice daily   |   |
| Pemirolast potassium 0.1% solution (Alamast)                 | Not available in the United States | 1 drop four times daily  |   |
| <b>Combined antihistamines and mast cell stabilizers</b>     |                                    |  |   |
| Alcaftadine 0.25% ophthalmic solution (Lastacift)            | \$283.99/3 mL                      | 1 drop once daily  |   |
| Azelastine HCl 0.05% ophthalmic solution (Optivar)           | \$102.90/6 mL                      | 1 drop two to four times daily (up to 6 weeks)   |   |
| Bepotastine besilate 1.5% solution (Bepreve)                 | \$554.52/10 mL                     | 1 drop twice daily   |   |
| Epinastine hydrochloride 0.05% ophthalmic solution (Elestat) | \$106.95/5 mL                      | 1 drop twice daily (up to 8 weeks)   |   |
| Ketotifen fumarate 0.025% solution (Zaditor)                 | OTC \$7.79/5 mL                    | 1 drop two to four times daily   |   |
| Olopatadine hydrochloride 0.1% solution (Patanol)            | \$108.00/5 mL                      | 1 drop twice daily   |   |
| <b>Nonsteroidal anti-inflammatory agents</b>                 |                                    |  |   |
| Bromfenac 0.09% solution (Xibrom)                            | \$213.69/1.7 mL                    | 1 drop to operated eye twice daily beginning 24 hours after cataract surgery and continuing through first 2 postoperative weeks  | Treatment of postoperative inflammation following cataract extraction   |
| Diclofenac sodium 0.1% solution (Voltaren)                   | \$17.50/5 mL                       | 1 drop to operated eye four times daily beginning 24 hours after surgery and continuing through first 2 postoperative weeks.   | Treatment of postoperative inflammation following cataract extraction and laser corneal surgery                       |
| Flurbiprofen sodium 0.03% solution (various)                 | \$51.50/2.5 mL                     | 1 drop every half hour beginning 2 hours before surgery; 1 drop to operated eye four times daily beginning 24 hours after cataract surgery   | Inhibition of intraoperative miosis; treatment of cystoid macular edema and inflammation after cataract surgery       |
| Indomethacin 1% solution (Indocid)                           | Not available in United States     | 1 drop four times daily  | Treatment of allergic eye disease, postoperative inflammation following cataract extraction and laser corneal surgery |

(continued)

**Table 7–2.** Topical ophthalmic agents (selected list). (continued)

| Agent   | Cost/Size <sup>1</sup> | Recommended Regimen  | Indications   |
|---|------------------------|--|---|
| Ketorolac tromethamine 0.5% solution (Acular)             | \$105.50/5 mL          | 1 drop four times daily  | Treatment of allergic eye disease, postoperative inflammation following cataract extraction and laser corneal surgery |
| Nepafenac 0.1% suspension (Nevanac)                       | \$325.96/3 mL          | 1 drop to operated eye three times daily beginning 24 hours after cataract surgery and continuing through first 2 postoperative weeks  | Treatment of postoperative inflammation following cataract extraction   |
| <b>Corticosteroids<sup>6</sup></b>                        |                        |  |   |
| Dexamethasone sodium phosphate 0.1% solution (various)    | \$21.10/5 mL           | 1 or 2 drops as often as indicated by severity; use every hour during the day and every 2 hours during the night in severe inflammation; taper off as inflammation decreases                 | Treatment of steroid-responsive inflammatory conditions   |
| Dexamethasone sodium phosphate 0.05% ointment             | Compounding pharmacy   | Apply thin coating on lower conjunctival sac three or four times daily   |   |
| Fluorometholone 0.1% suspension (various) <sup>7</sup>    | \$170.50/10 mL         | 1 or 2 drops as often as indicated by severity; use every hour during the day and every 2 hours during the night in severe inflammation; taper off as inflammation decreases                 |   |
| Fluorometholone 0.25% suspension (FML Forte) <sup>7</sup> | \$404.22/10 mL         | 1 drop two to four times daily   |   |
| Fluorometholone 0.1% ointment (FML S.O.P.)                | \$192.48/3.5 g         | Apply thin coating on lower conjunctival sac three or four times daily   |   |
| Loteprednol etabonate 0.5% (Lotemax)                      | \$512.86/10 mL         | 1 or 2 drops four times daily  |   |
| Prednisolone acetate 0.12% suspension (Pred Mild)         | \$384.97/10 mL         | 1 or 2 drops as often as indicated by severity of inflammation; use every hour during the day and every 2 hours during the night in severe inflammation; taper off as inflammation decreases |   |
| Prednisolone sodium phosphate 0.125% solution             | Compounding pharmacy   |  |   |
| Prednisolone acetate 1% suspension (various)              | \$105.60/10 mL         | 2 drops four times daily   |   |
| Prednisolone sodium phosphate 1% solution (various)       | \$63.25/10 mL          | 1–2 drops two to four times daily  |   |
| <b>Immunomodulators</b>                                   |                        |  |   |
| Cyclosporine 0.05% emulsion (Restasis) 0.4 mL/container   | \$368.92/30 containers | 1 drop twice daily   | Dry eyes and severe allergic eye disease  |
| Tacrolimus 0.1% ointment                                  | \$162.60/30 g tube     | Not yet established (no label to support)  | Severe allergic eye disease; no indication in United States   |
| <b>Glaucoma and Ocular Hypertension Agents</b>            |                        |  |   |
| <b>Sympathomimetics</b>                                   |                        |  |   |
| Apraclonidine HCl 0.5% solution (Iopidine)                | \$86.77/5 mL           | 1 drop three times daily   | Reduction of intraocular pressure; expensive; reserve for treatment of resistant cases                                |

(continued)

**Table 7–2.** Topical ophthalmic agents (selected list). (continued)

| Agent  | Cost/Size <sup>1</sup>   | Recommended Regimen   | Indications   |
|--|--|---|---|
| Apraclonidine HCl 1% solution (Iopidine)   | \$33.27/unit dose  | 1 drop 1 hour before and immediately after anterior segment laser surgery | To control or prevent elevations of intraocular pressure after laser trabeculoplasty or iridotomy                   |
| Brimonidine tartrate 0.2% solution (Alphagan, Alphagan P [benzalkonium chloride-free])   | \$18.13/5 mL   | 1 drop two or three times daily   | Reduction of intraocular pressure   |
| <b>Beta-adrenergic blocking agents</b>   |  |   |   |
| Betaxolol HCl 0.5% solution (Betoptic) and 0.25% suspension (Betoptic S) <sup>8</sup>  | 0.5%: \$117.91/10 mL<br>0.25%: \$372.64/10 mL                  | 1 drop twice daily  | Reduction of intraocular pressure   |
| Carteolol HCl 1% and 2% solution (various, Teoptic) <sup>9</sup>   | 1%: \$40.10/10 mL  | 1 drop twice daily  |   |
| Levobunolol HCl 0.25% and 0.5% solution (Betagan) <sup>10</sup>  | 0.5%: \$21.49/5 mL   | 1 drop once or twice daily  |   |
| Metipranolol HCl 0.3% solution (OptiPranolol) <sup>10</sup>  | \$29.67/5 mL   | 1 drop twice daily  |   |
| Timolol 0.25% and 0.5% solution (Betimol) <sup>10</sup>  | 0.5%: \$169.28/5 mL  | 1 drop once or twice daily  |   |
| Timolol maleate 0.25% and 0.5% solution (Istalol, Ocudose [preservative-free], Timoptic) and 0.1%, 0.25%, and 0.5% gel (Timoptic-XE, Timoptic GFS) <sup>10</sup> | 0.5% solution: \$6.56/5 mL<br>0.5% gel: \$266.09/5 mL          | 1 drop once or twice daily  |   |
| <b>Miotics</b>   |  |   |   |
| Pilocarpine HCl 1–4% solution <sup>11</sup>  | 1% solution: \$94.81/15 mL                                     | 1 drop up to four times daily for elevated intraocular pressure           | Reduction of intraocular pressure, treatment of acute or chronic angle-closure glaucoma, and pupillary constriction |
| <b>Carbonic anhydrase inhibitors</b>   |  |   |   |
| Brinzolamide 1% suspension (Azopt)   | \$366.01/10 mL   | 1 drop three times daily  | Reduction of intraocular pressure   |
| Dorzolamide HCl 2% solution (Trusopt)  | \$45.89/10 mL  | 1 drop three times daily  |   |
| <b>Prostaglandin analogs</b>   |  |   |   |
| Bimatoprost 0.03% solution (Lumigan)   | \$134.63/3 mL  | 1 drop once daily at night  | Reduction of intraocular pressure   |
| Latanoprost 0.005% solution (Xalatan, Monopost [preservative-free])  | \$15.00/2.5 mL<br>(Monopost not available in United States)    | 1 drop once or twice daily at night                                       |   |
| Latanoprostene bunod 0.024% solution (Vyzulta)   | \$257.26/2.5 mL  | 1 drop daily at night   |   |
| Tafluprost 0.0015% solution (Saflutan [preservative-free], Taflutan, Zioptan [preservative-free])  | \$255.61/30 units<br>(Saflutan not available in United States) | 1 drop once daily at night  |   |
| Travoprost 0.004% solution (Travatan, Travatan Z [benzalkonium chloride-free])   | \$198.36/2.5 mL  | 1 drop once daily at night  |   |
| Unoprostone isopropyl 0.15% solution (Rescula)   | \$153.84/5 mL  | 1 drop twice daily  |   |
| <b>Rho kinase inhibitor</b>  |  |   |   |
| Netarsudil ophthalmic solution 0.02% (Rhopressa)   | \$339.54/2.5 mL  | 1 drop daily in the evening   | Reduction of intraocular pressure   |

(continued)

**Table 7–2.** Topical ophthalmic agents (selected list). (continued)

| Agent   | Cost/Size <sup>1</sup>         | Recommended Regimen         | Indications                       |
|---|--------------------------------|-----------------------------|-----------------------------------|
| <b>Combined preparations</b>  |                                |                             |                                   |
| Bimatoprost 0.03% and timolol 0.5% (Ganfort)                            | Not available in United States | 1 drop daily in the morning | Reduction of intraocular pressure |
| Brimonidine 0.2% and timolol 0.5% (Combigan)                            | \$466.60/10 mL                 | 1 drop twice daily          |                                   |
| Brimonidine 0.2% and brinzolamide 1% (Simbrinza)                        | \$217.34/8 mL                  | 1 drop three times a day    |                                   |
| Brinzolamide 1% and timolol 0.5% (Azarga)                               | Not available in United States | 1 drop twice daily          |                                   |
| Dorzolamide 2% and timolol 0.5% (Cosopt, Cosopt PF [preservative-free]) | \$238.41/10 mL                 | 1 drop twice daily          |                                   |
| Latanoprost 0.005% and timolol 0.5% (Xalacom)                           | Not available in United States | 1 drop daily in the morning |                                   |
| Tafluprost 0.0015% and timolol 0.5% (Taptiqom [preservative-free])      | Not available in United States | 1 drop daily                |                                   |
| Travoprost 0.004% and timolol 0.5% (DuoTrav)                            | Not available in United States | 1 drop daily                |                                   |

<sup>1</sup>Average wholesale price (AWP, for AB-rated generic when available) for quantity listed. Source: IBM Micromedex Red Book (electronic version) IBM Watson Health. Greenwood Village, CO, USA. Available at <https://www.micromedexsolutions.com>, accessed March 27, 2021. AWP may not accurately represent the actual pharmacy cost because wide contractual variations exist among institutions.

<sup>2</sup>Little efficacy against gram-negative organisms (except *Neisseria*).

<sup>3</sup>Aplastic anemia has been reported with prolonged ophthalmic use.

<sup>4</sup>No gram-positive coverage.

<sup>5</sup>May produce rebound hyperemia and local reactions.

<sup>6</sup>Long-term use increases intraocular pressure, causes cataracts, and predisposes to bacterial, herpes simplex virus, and fungal keratitis. These problems may be attenuated by the ester corticosteroid, loteprednol.

<sup>7</sup>Less likely to elevate intraocular pressure.

<sup>8</sup>Cardioselective (beta-1) beta-blocker.

<sup>9</sup>Teoptic is not available in the United States.

<sup>10</sup>Nonselective (beta-1 and beta-2) beta-blocker. Monitor all patients for systemic side effects, particularly exacerbation of asthma.

<sup>11</sup>Decreased night vision and headaches possible.

and *Pseudomonas aeruginosa*, *Moraxella* species, and other gram-negative bacilli. The cornea has an epithelial defect and an underlying opacity. Hypopyon may be present. Topical fluoroquinolones, such as levofloxacin 0.5%, ofloxacin 0.3%, norfloxacin 0.3%, or ciprofloxacin 0.3%, are commonly used as first-line agents as long as local prevalence of resistant organisms is low (Table 7–2). For severe central ulcers, diagnostic scrapings can be sent for Gram stain and culture. Treatment may include compounded high-concentration topical antibiotic drops applied hourly day and night for at least the first 48 hours. Fourth-generation fluoroquinolones (moxifloxacin 0.5% and gatifloxacin 0.3%) are also frequently used in this setting. Although early adjunctive topical corticosteroid therapy may improve visual outcome, it should be prescribed only by an ophthalmologist.

Lin A et al; American Academy of Ophthalmology Preferred Practice Pattern Cornea and External Disease Panel. Bacterial Preferred Practice Pattern\*. Ophthalmology. 2019;126:P1. [PMID: 30366799]

## 2. Herpes Simplex Keratitis

Primary ocular herpes simplex virus infection may manifest as lid, conjunctival, or corneal ulceration. The ability of the virus to colonize the trigeminal ganglion leads to recurrences that may be precipitated by fever, excessive exposure to sunlight, or immunodeficiency. Herpetic corneal disease is typically unilateral but can be seen bilaterally in the setting of atopy or immunocompromise. The dendritic (branching) corneal ulcer is the most characteristic manifestation of herpetic corneal disease. More extensive (“geographic”) ulcers also occur, particularly if topical corticosteroids have been used. The corneal ulcers are most easily seen after instillation of fluorescein and examination with a cobalt blue light. Resolution of corneal herpetic

### ► When to Refer

Any patient with suspected bacterial keratitis must be referred emergently to an ophthalmologist.

disease is hastened by treatment with topical antiviral agents (eg, trifluridine drops, ganciclovir gel, acyclovir ointment) or oral antiviral agents (eg, acyclovir, 400–800 mg five times daily or valacyclovir 500–1000 mg three times daily for 7–14 days). Topical antiviral agents may cause corneal toxicity after approximately 10–14 days of therapy and for that reason are not commonly used for long-term suppressive therapy.

Stromal herpes simplex keratitis produces increasingly severe corneal opacity with each recurrence. Antiviral agents alone are insufficient to control stromal disease, so topical corticosteroids are also used, but they may enhance viral replication and steroid dependence frequently occurs. Severe stromal scarring may require corneal transplantation; recurrence in the new cornea is common and long-term oral antiviral agents are required.

The rate of recurrent corneal herpetic disease is reduced by using long-term oral acyclovir, 400 mg twice daily; famciclovir, 250 mg once daily; or valacyclovir, 500 mg once daily. Long-term oral antiviral dosing may be adjusted if the disease breaks through suppressive dosing or if kidney dysfunction is present. **Caution:** For patients with known or possible herpetic disease, topical corticosteroids should be prescribed only with ophthalmologic supervision.

## ► When to Refer

Any patient with a history of herpes simplex keratitis and an acute red eye should be referred urgently to an ophthalmologist.

Azher TN et al. Herpes simplex keratitis: challenges in diagnosis and clinical management. Clin Ophthalmol. 2017;11:185. [PMID: 28176902]

## 3. Herpes Zoster Ophthalmicus

Herpes zoster frequently involves the ophthalmic division of the trigeminal nerve. It presents with malaise, fever, headache, and periorbital burning and itching. These symptoms may precede the eruption by a day or more. The rash is initially vesicular, quickly becoming pustular and then crusting. Involvement of the tip of the nose or the lid margin predicts involvement of the eye. Ocular signs include conjunctivitis, keratitis, episcleritis, and anterior uveitis, often with elevated intraocular pressure. Recurrent anterior segment inflammation, neurotrophic keratitis, and posterior subcapsular cataract are long-term complications. Optic neuropathy, cranial nerve palsies, acute retinal necrosis, and cerebral angiitis occur infrequently. HIV infection is an important risk factor for herpes zoster ophthalmicus and increases the likelihood of complications.

High-dose oral acyclovir (800 mg five times a day), valacyclovir (1 g three times a day), or famciclovir (500 mg three times a day) for 7–10 days started within 72 hours after the appearance of the rash reduces the incidence of ocular complications but not of postherpetic neuralgia. Acute keratitis, or a “pseudo-dendrite,” can be treated with a topical antiviral such as ganciclovir 0.15% gel, 1 drop five times daily until healing has occurred and then 1 drop three times daily for 1 more week. Anterior uveitis requires

additional treatment with topical corticosteroids and cycloplegics. Topical corticosteroids, which promote viral replication, may have to be delayed until the keratitis has resolved. Neurotrophic keratitis is an important cause of long-term morbidity.

## ► When to Refer

Any patient with herpes zoster ophthalmicus and ocular symptoms or signs should be referred urgently to an ophthalmologist.

Vrcek I et al. Herpes zoster ophthalmicus: a review for the internist. Am J Med. 2017;130:21 [PMID: 27644149]

## 4. Fungal Keratitis

Fungal keratitis tends to occur after corneal injury involving plant material or in an agricultural setting, in eyes with chronic ocular surface disease, and increasingly in contact lens wearers. It may be an indolent process. The corneal infiltrate may have feathery edges and multiple “satellite” lesions. A hypopyon may be present. Unlike bacterial keratitis, an epithelial defect may or may not be present. Corneal scrapings should be cultured on media suitable for fungi whenever the history or corneal appearance is suggestive of fungal disease. Diagnosis is often delayed and treatment is difficult, commonly requiring 6 months or longer for severe disease. Natamycin 5%, amphotericin 0.1–0.5%, and voriconazole 0.2–1% are the most frequently used topical agents (Table 7–2). Systemic azoles are probably not helpful unless there is scleritis or intraocular infection. Corneal grafting is often required.

Bourcier T et al. Fungal keratitis. J Fr Ophtalmol. 2017;40:e307. [PMID: 28987448]

Prajna NV et al. Effect of oral voriconazole on fungal keratitis in the Mycotic Ulcer Treatment Trial II (MUTT II): a randomized clinical trial. JAMA Ophthalmol. 2016;134:1365. [PMID: 27787540]

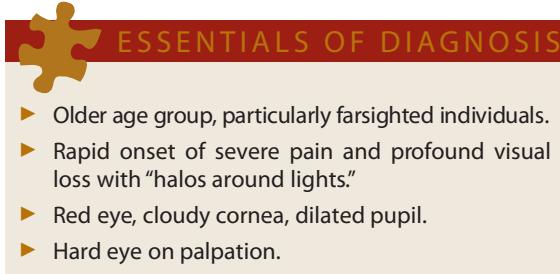
## 5. Amoebic Keratitis

Amoebic infection, usually due to *Acanthamoeba*, is an important cause of keratitis. The two greatest risk factors in developed countries are contact lens wear and fresh-water or hot-tub exposure. Although severe pain with perineural and ring infiltrates in the corneal stroma is characteristic, it is not specific and earlier forms with changes confined to the corneal epithelium are identifiable. Diagnosis is facilitated by confocal microscopy and Giemsa staining of cornea smears. Culture requires specialized media. Intensive topical compounded biguanide (polyhexamethylene or chlorhexidine) is initiated immediately, and long-term treatment is required. Diamidine (propamidine or hexamidine) may be added. Oral miltefosine is FDA approved for the treatment of *Acanthamoeba* keratitis, but indications and efficacy have yet to be established. There should be close monitoring for systemic toxicity (vomiting, diarrhea, elevation of transaminases, and kidney function studies) during its use. Delayed diagnosis and prior treatment with topical corticosteroids

adversely affect the visual outcome. Corneal grafting may be required after resolution of infection to restore vision. If there is scleral involvement, systemic anti-inflammatory and immunosuppressant medication is helpful in controlling pain, but the prognosis is poor.

Carrijo-Carvalho LC et al. Therapeutic agents and biocides for ocular infections by free-living amoebae of *Acanthamoeba* genus. *Surv Ophthalmol*. 2017;62:203. [PMID: 27836717]  
Pinna A et al. Free-living amoebae keratitis. *Cornea*. 2017;36:785. [PMID: 28486311]

## ACUTE ANGLE-CLOSURE GLAUCOMA



### ► General Considerations

**Primary acute angle-closure glaucoma** (acute angle-closure crisis) results from closure of a preexisting narrow anterior chamber angle. The predisposing factors are shallow anterior chamber, which may be associated with farsightedness or a small eye (short axial length); enlargement of the crystalline lens with age; and inheritance, such as among Inuits and Asians. Closure of the angle is precipitated by pupillary dilation and thus can occur from sitting in a darkened theater, during times of stress, following nonocular administration of anticholinergic or sympathomimetic agents (eg, nebulized bronchodilators, atropine, antidepressants, bowel or bladder antispasmodics, nasal decongestants, or tocolytics), or, rarely, from pharmacologic mydriasis (see Precautions in Management of Ocular Disorders, below). Subacute primary angle-closure glaucoma may present as recurrent headache.

**Secondary acute angle-closure glaucoma**, for which the mechanism may differ between cases, does not require a preexisting narrow angle. Secondary acute angle-closure glaucoma may occur in anterior uveitis, with dislocation of the lens, with hemodialysis, or due to various drugs (see Adverse Ocular Effects of Systemic Drugs, below). Symptoms are the same as in primary acute angle-closure glaucoma, but differentiation is important because of differences in management.

### ► Clinical Findings

Patients with acute glaucoma usually seek treatment immediately because of extreme pain and blurred vision, though there are subacute cases. Typically, the blurred vision is

associated with halos around lights. Nausea and abdominal pain may occur. The eye is red, the cornea cloudy, and the pupil moderately dilated and nonreactive to light. Intraocular pressure is usually over 50 mm Hg, producing a hard eye on palpation.

### ► Differential Diagnosis

Acute glaucoma must be differentiated from conjunctivitis, acute uveitis, and corneal disorders (Table 7–1).

### ► Treatment

Initial treatment, regardless of mechanism, is reduction of intraocular pressure. A single 500-mg intravenous dose of acetazolamide, followed by 250 mg orally four times a day, together with topical medications that lower intraocular pressure is usually sufficient. Osmotic diuretics, such as oral glycerin and intravenous urea or mannitol—the dosage of all three being 1–2 g/kg—may be necessary if there is no response to acetazolamide. Definitive treatment depends on the mechanism.

#### A. Primary

In primary acute angle-closure glaucoma, once the intraocular pressure has started to fall, topical 4% pilocarpine, 1 drop every 15 minutes for 1 hour and then four times a day, is used to reverse the underlying angle closure. The definitive treatment is laser peripheral iridotomy, surgical peripheral iridectomy, or cataract extraction. Cataract extraction is becoming more of a first-line treatment for those with primary angle-closure glaucoma.

All patients with primary acute angle closure should undergo prophylactic laser peripheral iridotomy to the unaffected eye, or early cataract extraction should be considered, unless that eye has already undergone cataract or glaucoma surgery.

#### B. Secondary

In secondary acute angle-closure glaucoma, additional treatment is determined by the cause.

### ► Prognosis

Untreated acute angle-closure glaucoma results in severe and permanent visual loss within 2–5 days after onset of symptoms. Affected patients need to be monitored for development of chronic glaucoma.

### ► When to Refer

Any patient with suspected acute angle-closure glaucoma must be referred emergently to an ophthalmologist.

Prum BE Jr et al. Primary Angle Closure Preferred Practice Pattern(\*) Guidelines. *Ophthalmology*. 2016;123:P1. [PMID: 26581557]

Tanner L et al. Has the EAGLE landed for the use of clear lens extraction in angle-closure glaucoma? And how should primary angle-closure suspects be treated? *Eye (Lond)*. 2020; 34:40. [PMID: 31649349]

## CHRONIC GLAUCOMA

### ESSENTIALS OF DIAGNOSIS

- ▶ Three types of chronic glaucoma: open-angle glaucoma, angle-closure glaucoma, and normal-tension glaucoma.
- ▶ No symptoms in early stages.
- ▶ Insidious progressive bilateral loss of peripheral vision, resulting in tunnel vision; visual acuities preserved until advanced disease.
- ▶ Pathologic cupping of the optic disks.
- ▶ Intraocular pressure is usually elevated.

### ► General Considerations

Chronic glaucoma is characterized by gradually progressive excavation (“cupping”) of the optic disk with loss of vision progressing from slight visual field loss to complete blindness. In **chronic open-angle glaucoma**, primary or secondary, intraocular pressure is elevated due to reduced drainage of aqueous fluid through the trabecular meshwork. In **chronic angle-closure glaucoma**, which is particularly common in Inuits and eastern Asians, flow of aqueous fluid into the anterior chamber angle is obstructed. In **normal-tension glaucoma**, intraocular pressure is not elevated but the same pattern of optic nerve damage occurs.

Primary chronic open-angle glaucoma is usually bilateral. There is an increased prevalence in first-degree relatives of affected individuals and in diabetic patients. In Afro-Caribbean and African persons, and probably in Hispanic persons, it is more frequent, occurs at an earlier age, and results in more severe optic nerve damage. Secondary chronic open-angle glaucoma may result from ocular disease, eg, pigment dispersion, pseudoexfoliation, uveitis, or trauma; or corticosteroid therapy, whether it is intraocular, topical, inhaled, intranasal, or systemic.

In the United States, it is estimated that 2% of people over 40 years of age have glaucoma, affecting over 2.5 million individuals. At least 25% of cases are undetected. Over 90% of cases are of the open-angle type. Worldwide, about 45 million people have open-angle glaucoma, of whom about 4.5 million are bilaterally blind. About 4 million people, of whom approximately 50% live in China, are bilaterally blind from chronic angle-closure glaucoma.

### ► Clinical Findings

Because initially there are no symptoms, chronic glaucoma is often first suspected at a routine eye test. Diagnosis requires consistent and reproducible abnormalities in at least two of three parameters—optic disk or retinal nerve fiber layer (or both), visual field, and intraocular pressure.

**1. Optic disk cupping**—Optic disk cupping is identified as an absolute increase or an asymmetry between the two eyes of the ratio of the diameter of the optic cup to the diameter of the whole optic disk (cup-disk ratio). (Cup-disk ratio

greater than 0.5 or asymmetry between eyes of 0.2 or more is suggestive.) Detection of optic disk cupping and associated abnormalities of the retinal nerve fiber layer is facilitated by optical coherence tomography scans.

**2. Visual field abnormalities**—Visual field abnormalities initially develop in the paracentral region, followed by constriction of the peripheral visual field. Central vision remains good until late in the disease.

**3. Intraocular pressure**—The normal range of intraocular pressure is 10–21 mm Hg. In many individuals (about 4.5 million in the United States), elevated intraocular pressure is not associated with optic disk or visual field abnormalities (ocular hypertension). Monitoring for the development of glaucoma is required in all such cases; a significant proportion of eyes with primary open-angle glaucoma have normal intraocular pressure when it is first measured, and only repeated measurements identify the abnormally high pressure. In normal-tension glaucoma, intraocular pressure is always within the normal range.

### ► Prevention

There are many causes of optic disk abnormalities or visual field changes that mimic glaucoma, and visual field testing may prove unreliable in some patients, particularly in the older age group. Hence, the diagnosis of glaucoma is not always straightforward and screening programs need to involve eye care professionals.

Although all persons over age 50 years may benefit from intraocular pressure measurement and optic disk examination every 3–5 years, screening for chronic open-angle glaucoma should be targeted at individuals with an affected first-degree relative, at persons who have diabetes mellitus, and at older individuals with African or Hispanic ancestry. Screening may also be warranted in patients taking long-term oral or combined intranasal and inhaled corticosteroid therapy. Screening for chronic angle-closure glaucoma should be targeted at Inuits and Asians.

### ► Treatment

#### A. Medications

Medical treatment is directed toward lowering intraocular pressure. Prostaglandin analog eye drops are commonly used as first-line therapy because of their efficacy, lack of systemic side effects, and convenient once-daily dose, (except unoprostone) (Table 7–2). All may produce conjunctival hyperemia, permanent darkening of the iris and eyebrow color, increased eyelash growth, and reduction of periorbital fat (prostaglandin-associated periorbitopathy). Latanoprostene bunod is metabolized into latanoprost and another component that releases nitric oxide, which increases trabecular outflow. Topical beta-adrenergic blocking agents may be used alone or in combination with a prostaglandin analog. They may be contraindicated in patients with reactive airway disease or heart failure. Betaxolol is theoretically safer in reactive airway disease but less effective at reducing intraocular pressure. Brimonidine 0.2%, a selective alpha-2-agonist, and topical carbonic

anhydrase inhibitors also can be used in addition to a prostaglandin analog or a beta-blocker (twice daily) or as initial therapy when prostaglandin analogs and betablockers are contraindicated (brimonidine twice daily, carbonic anhydrase inhibitors three times daily). All three are associated with allergic reactions. Brimonidine may cause uveitis. Apraclonidine, 0.5–1%, another alpha-2-agonist, can be used three times a day to postpone the need for surgery in patients receiving maximal medical therapy, but long-term use is limited by adverse reactions. It is more commonly used to control acute rise in intraocular pressure, such as after laser therapy. The topical agent netarsudil ophthalmic solution 0.02% (1 drop into the affected eye once daily in the evening) increases aqueous fluid outflow through the trabecular meshwork. Pilocarpine 1–4% is rarely used because of adverse effects. Oral carbonic anhydrase inhibitors (acetazolamide, methazolamide, and dichlorphenamide) may be used on a long-term basis if topical therapy is inadequate and surgical or laser therapy is inappropriate.

Various eye drop preparations combining two agents (eg, prostaglandin analogs, beta-adrenergic blocking agents, brimonidine, and topical carbonic anhydrase inhibitors) are available to improve compliance when multiple medications are required. Formulations of one or two agents without preservative or not including benzalkonium chloride as the preservative are preferred to reduce adverse ocular effects for patients with allergies or severe dry eyes.

## B. Laser Therapy and Surgery

**1. Open-angle glaucoma**—Laser trabeculoplasty is used as an adjunct to topical therapy to defer surgery and is also advocated as primary treatment, especially when compliance with medications is an issue. Surgery is generally undertaken when intraocular pressure is inadequately controlled by medical and laser therapy, but it may also be used as primary treatment in advanced cases. Trabeculectomy remains the standard procedure. Adjunctive treatment with subconjunctival mitomycin or fluorouracil is used perioperatively or postoperatively in worse prognosis cases. A variety of less invasive procedures that avoid a full-thickness incision into the eye, called microinvasive glaucoma surgery, are appropriate for moderate glaucoma and are associated with fewer complications but can be more difficult to perform.

**2. Angle-closure glaucoma**—In chronic angle-closure glaucoma, laser peripheral iridotomy, surgical peripheral iridectomy, or cataract extraction may be helpful. In patients with asymptomatic narrow anterior chamber angles, which includes about 10% of Chinese adults, prophylactic laser peripheral iridotomy can be performed to reduce the risk of acute and chronic angle-closure glaucoma. However, there are concerns about the efficacy of such treatment and the risk of cataract progression and corneal decompensation. In the United States, about 1% of people over age 35 years have narrow anterior chamber angles, but acute and chronic angle closure are sufficiently uncommon that prophylactic therapy is not generally advised.

## ► Prognosis

Untreated chronic glaucoma that begins at age 40–45 years will probably cause complete blindness by age 60–65. Early diagnosis and treatment can preserve useful vision throughout life. In primary open-angle glaucoma and if treatment is required in ocular hypertension, the aim is to reduce intraocular pressure to a level that will adequately reduce progression of visual field loss. In eyes with marked visual field or optic disk changes, intraocular pressure must be reduced to less than 16 mm Hg. In normal-tension glaucoma with progressive visual field loss, it is necessary to achieve even lower intraocular pressure such that surgery is often required.

## ► When to Refer

All patients with suspected chronic glaucoma should be referred to an ophthalmologist.

Jonas JB et al. Glaucoma. Lancet. 2017;390:2183. [PMID: 28577860]

Pillunat et al. Micro-invasive glaucoma surgery (MIGS): a review of surgical procedures using stents. Clin Ophthalmol. 2017;11:1583. [PMID: 28919702]

Prum BE Jr et al. Primary open-angle glaucoma Preferred Practice Pattern<sup>(\*)</sup> guidelines. Ophthalmology. 2016;123:P41. [PMID: 26581556]

Schehlein EM et al. New classes of glaucoma medications. Curr Opin Ophthalmol. 2017;28:161. [PMID: 27828896]

## UVEITIS



### ESSENTIALS OF DIAGNOSIS

- ▶ Usually immunologic but possibly infective or neoplastic.
- ▶ Inflammation may be confined to the eye or may be systemic.
- ▶ **Acute nongranulomatous anterior uveitis:** pain, redness, photophobia, and visual loss.
- ▶ **Granulomatous anterior uveitis:** blurred vision in a variably painful and inflamed eye.
- ▶ **Posterior uveitis:** gradual loss of vision in a variably inflamed eye.

## ► General Considerations

Intraocular inflammation (uveitis) is classified as acute or chronic and as nongranulomatous or granulomatous, according to the clinical signs, and by its involvement of the anterior, intermediate, posterior, or all (panuveitis) segments of the eye. The common types are acute nongranulomatous anterior, granulomatous anterior, and posterior.

In most cases the pathogenesis of uveitis is primarily immunologic, but infection may be the cause, particularly in immunodeficiency states. The systemic disorders associated with acute nongranulomatous anterior uveitis are the

HLA-B27-related conditions (ankylosing spondylitis, reactive arthritis, psoriasis, ulcerative colitis, and Crohn disease). Chronic nongranulomatous anterior uveitis occurs in juvenile idiopathic arthritis. Behcet syndrome produces both anterior uveitis, with recurrent hypopyon, and posterior uveitis, characteristically with branch retinal vein occlusions. Both herpes simplex and herpes zoster infections may cause nongranulomatous and granulomatous anterior uveitis as well as retinitis (acute retinal necrosis).

Diseases producing granulomatous anterior uveitis also tend to be causes of posterior uveitis. These include sarcoidosis, toxoplasmosis, tuberculosis, syphilis, Vogt-Koyanagi-Harada disease (bilateral uveitis associated with alopecia, poliosis [depigmented eyelashes, eyebrows, or hair], vitiligo, and hearing loss), and sympathetic ophthalmia that occurs after penetrating ocular trauma. In toxoplasmosis, there may be evidence of previous episodes of retinochoroiditis. Syphilis characteristically produces a “salt and pepper” fundus but may present with a wide variety of clinical manifestations. The other principal pathogens responsible for ocular inflammation in HIV infection are cytomegalovirus (CMV), herpes simplex and herpes zoster viruses, mycobacteria, *Cryptococcus*, *Toxoplasma*, and *Candida*.

Retinal vasculitis and intermediate uveitis predominantly manifest as posterior uveitis with central or peripheral retinal abnormalities in retinal vasculitis and far peripheral retinal abnormalities (pars planitis) in intermediate uveitis. Retinal vasculitis can be caused by a wide variety of infectious agents and noninfectious systemic conditions but also may be idiopathic. Intermediate uveitis is often idiopathic but can be due to multiple sclerosis or sarcoidosis.

## ► Clinical Findings

**Anterior uveitis** is characterized by inflammatory cells and flare within the aqueous. In severe cases, there may be hypopyon (layered collection of white cells) and fibrin within the anterior chamber. Cells may also be seen on the corneal endothelium as keratic precipitates (KPs). In granulomatous uveitis, there are large “mutton-fat” KPs, and sometimes iris nodules. In nongranulomatous uveitis, the KPs are smaller with no iris nodules. The pupil is usually small, and with the development of posterior synechiae (adhesions between the iris and anterior lens capsule), it also becomes irregularly shaped and poorly reactive.

Nongranulomatous anterior uveitis tends to present acutely with unilateral pain, redness, photophobia, and visual loss. However, the ocular inflammation associated with juvenile idiopathic arthritis is frequently indolent, commonly asymptomatic initially, and carries a high risk of sight-threatening complications. Granulomatous anterior uveitis is also frequently chronic, recurrent, and indolent, causing blurred vision in a variably inflamed eye.

In **posterior uveitis**, there are cells in the vitreous and there may be inflammatory retinal or choroidal lesions. New retinal lesions are yellow with indistinct margins and there may be retinal hemorrhages. Older lesions have more defined margins and are commonly pigmented. Retinal vessel sheathing may occur adjacent to such lesions or more diffusely. In severe cases, vitreous opacity precludes visualization of retinal details.

Posterior uveitis tends to present bilaterally with floaters and visual loss. Symptoms are commonly slower in onset, though acute presentations can occur. Visual loss may be due to vitreous haze and opacities, inflammatory lesions involving the macula, macular edema, retinal vein occlusion, or rarely, optic neuropathy.

## ► Differential Diagnosis

Retinal detachment, intraocular tumors, and central nervous system lymphoma may all masquerade as uveitis.

## ► Treatment

**Anterior uveitis** usually responds to topical corticosteroids. Occasionally, periocular or intraocular corticosteroid injections or even systemic corticosteroids are required. Dilation of the pupil is important to relieve discomfort and prevent permanent posterior synechiae. **Posterior uveitis** more commonly requires systemic, periocular, or intravitreal corticosteroid therapy. In chronic cases, systemic corticosteroid-sparing immunomodulatory therapy with agents such as azathioprine, cyclosporine, mycophenolate, methotrexate, tacrolimus, or sirolimus is commonly required. Biologic therapies are also often used. Pupillary dilation is not usually necessary.

If an infectious cause is identified, specific antimicrobial therapy is often needed. In general, the prognosis for anterior uveitis, particularly the nongranulomatous type, is better than for posterior uveitis.

## ► When to Refer

- Any patient with suspected acute uveitis should be referred urgently to an ophthalmologist or emergently if visual loss or pain is severe.
- Any patient with suspected chronic uveitis should be referred to an ophthalmologist, urgently if there is more than mild visual loss.

## ► When to Admit

Patients with severe uveitis, particularly those requiring intravenous therapy, may require hospital admission.

Al-Janabi A et al. Long-term outcomes of treatment with biological agents in eyes with refractory, active, noninfectious intermediate uveitis, posterior uveitis, or panuveitis. *Ophthalmology*. 2020;127:410. [PMID: 31607412]

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Krishna U et al. Uveitis: a sight-threatening disease which can impact all systems. *Postgrad Med J*. 2017;93:766. [PMID: 28942431]

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## CATARACT



### ESSENTIALS OF DIAGNOSIS

- ▶ Gradually progressive blurred vision.
- ▶ No pain or redness.
- ▶ Lens opacities (may be grossly visible).

### ► General Considerations

Cataracts are opacities of the crystalline lens and are usually bilateral. They are the leading cause of blindness worldwide. Age-related cataract is by far the most common cause. Other causes include (1) congenital (from intrauterine infections, such as rubella and CMV, or inborn errors of metabolism, such as galactosemia); (2) traumatic; (3) secondary to systemic disease (diabetes mellitus, myotonic dystrophy, atopic dermatitis); (4) topical, systemic, or inhaled corticosteroid treatment; (5) uveitis; or (6) radiation exposure. Most persons over age 60 have some degree of lens opacity. Cigarette smoking increases the risk of cataract formation. Multivitamin/mineral supplements and high dietary antioxidants may prevent the development of age-related cataract.

### ► Clinical Findings

The predominant symptom is progressive blurring of vision. Glare, especially in bright light or with night driving; change of focusing, particularly development of nearsightedness; and monocular double vision may occur.

Even in its early stages, a cataract can be seen through a dilated pupil with an ophthalmoscope or slit lamp. As the cataract matures, the retina will become increasingly difficult to visualize, until finally the fundus reflection is absent and the pupil is white.

### ► Treatment

Functional visual impairment, specifically its effect on daily activities such as increased falls, is the prime criterion for surgery. The cataract is usually removed by one of the techniques in which the posterior lens capsule remains (extracapsular), thus providing support for a prosthetic intraocular lens. Ultrasonic fragmentation (phacoemulsification) of the lens nucleus and foldable intraocular lenses allow cataract surgery to be performed through a small incision without the need for sutures, thus reducing the postoperative complication rate and accelerating visual rehabilitation. The standard monofocal prosthetic intraocular lens can correct near or far vision. Premium intraocular lenses (multifocal, extended depth of focus, and accommodative) reduce the need for both distance and near vision correction. In the developing world, manual small-incision surgery, in which the lens nucleus is removed intact, is popular because less equipment is required. Additional laser treatment may be required

subsequently (months to years after the initial cataract surgery) if the posterior capsule opacifies. The use of topical eye drops to dissolve or prevent cataracts has shown promising results in experimental models; surgery, however, is currently the only treatment option for a visually significant cataract.

### ► Prognosis

Cataract surgery is cost-effective in improving survival and quality of life. In the developed world, it improves visual acuity in 95% of cases. In the other 5%, there is preexisting retinal damage or operative or postoperative complications. In less developed areas, the improvement in visual acuity is not as high, in part due to uncorrected refractive error postoperatively. A large number of drugs, such as alpha-adrenoreceptor antagonists for benign prostatic hyperplasia or systemic hypertension and antipsychotics, increase the risk of complications during surgery (floppy iris syndrome) and in the early postoperative period. Nasolacrimal duct obstruction increases the risk of intraocular infection (endophthalmitis).

The alpha-blocker tamsulosin has been shown to have the greatest risk of floppy iris syndrome. There is no consensus about whether to stop alpha-blockers before surgery because the effects of the drug on the iris can persist for months to years. The surgeon must know if the patient is taking an alpha-blocker to prepare for iris issues during surgery. If the patient has not yet started an alpha-blocker and is planning to have cataract surgery shortly, it is best to wait until after surgery to begin the medication, if possible.

### ► When to Refer

Patients with cataracts should be referred to an ophthalmologist when their visual impairment adversely affects their everyday activities.

Enright JM et al. Floppy iris syndrome and cataract surgery. *Curr Opin Ophthalmol*. 2017;28:29. [PMID: 27653607]

Lian RR et al. The quest for homeopathic and nonsurgical cataract treatment. *Curr Opin Ophthalmol*. 2020;31:61. [PMID: 31770163]

Nanji KC et al. Preventing adverse events in cataract surgery: recommendations from a Massachusetts expert panel. *Anesth Analg*. 2018;126:1537. [PMID: 28991115]

Rampat R et al. Multifocal and extended depth-of-focus intraocular lenses in 2020. *Ophthalmology*. 2020;S0161-6420(20)30931-3. [PMID: 32980397]

## RETINAL DETACHMENT



### ESSENTIALS OF DIAGNOSIS

- ▶ Loss of vision in one eye that is usually rapid, possibly with “curtain” spreading across field of vision.
- ▶ No pain or redness.
- ▶ Detachment seen by ophthalmoscopy.

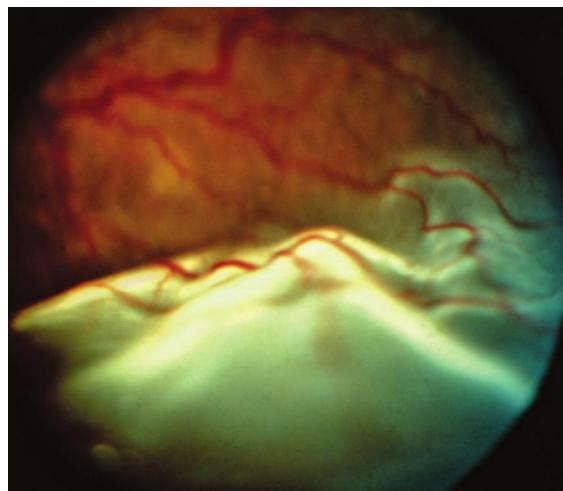
## ► General Considerations

Most cases of retinal detachment are due to development of one or more peripheral retinal tears or holes (rhegmatogenous retinal detachment). This usually results from posterior vitreous detachment, related to degenerative changes in the vitreous, and generally occurs in persons over 50 years of age. Nearsightedness and cataract extraction are the two most common predisposing causes. It may also be caused by penetrating or blunt ocular trauma.

Tractional retinal detachment occurs when there is preretinal fibrosis, such as in proliferative retinopathy due to diabetic retinopathy or retinal vein occlusion, or as a complication of rhegmatogenous retinal detachment. Exudative retinal detachment results from accumulation of subretinal fluid, such as in neovascular age-related macular degeneration or secondary to choroidal tumor.

## ► Clinical Findings

Rhegmatogenous retinal detachment usually starts in the peripheral retina, spreading rapidly to cause visual field loss. Premonitory symptoms of the predisposing vitreous degeneration and vitreo-retinal traction include recent onset of or increase in floaters (moving spots or strands like cobwebs in the visual field) and photopsias (flashes of light). Central vision remains intact until the central macula becomes detached. On ophthalmoscopic examination, the retina may be seen elevated in the vitreous cavity with an irregular surface (Figure 7–1). In tractional retinal detachment, there is irregular retinal elevation adherent to scar tissue on the retinal surface, sometimes extending into the vitreous. Exudative retinal detachments are dome-shaped and the subretinal fluid shifts position with changes in posture. Ocular ultrasonography assists the detection and characterization of retinal detachment.



▲ **Figure 7–1.** Inferior retinal detachment as seen on direct or indirect ophthalmoscopy.

## ► Treatment

Treatment of rhegmatogenous retinal detachments requires closing all of the retinal tears and holes by forming a permanent adhesion between the neurosensory retina, the retinal pigment epithelium, and the choroid with laser photocoagulation to the retina or cryotherapy to the sclera. Certain types of uncomplicated retinal detachment may be treated by pneumatic retinopexy, in which an expansile gas is injected into the vitreous cavity followed by positioning of the patient's head to facilitate apposition between the gas and the hole to permit reattachment of the retina. Once the retina is reattached, the defects are surrounded by laser photocoagulation or cryotherapy scars; these two methods are also used to seal retinal defects without associated detachment.

In complicated retinal detachments, particularly tractional retinal detachments, retinal reattachment can be accomplished only by pars plana vitrectomy, direct manipulation of the retina, and internal tamponade of the retina with air, expansile gas, or silicone oil. The presence of an expansile gas within the eye is a contraindication to air travel, mountaineering at high altitude, and nitrous oxide anesthesia. Such gases persist in the globe for weeks after surgery. (See Chapter 37.) Treatment of exudative retinal detachments is determined by the underlying cause.

## ► Prognosis

About 90% of uncomplicated rhegmatogenous retinal detachments can be cured with one operation. The visual prognosis is worse if the macula is detached or if the detachment is of long duration.

## ► When to Refer

All cases of retinal detachment must be referred urgently to an ophthalmologist, and emergently if central vision is good because this indicates that the macula has not detached. During transportation, the patient's head is positioned so that the retinal tear is placed at the lowest point of the eye. If the inferior retina is detached, the patient should keep the head upright so that the tear is located at the lowest point, whereas if the temporal retina is detached, the patient should keep the temporal side of the head down to reduce the chances that the fluid will extend beneath the central retina, causing the macula to detach. If vision is good and the macula is attached, patients should minimize eye motion; in some patients, patching both eyes can be helpful in preventing the eyes from moving rapidly around until surgery can be performed to repair the retinal detachment.

Bond-Taylor M et al. Posterior vitreous detachment—prevalence of and risk factors for retinal tears. *Clin Ophthalmol*. 2017;11:1689. [PMID: 29075095]

Lahham S et al. Role of point of care ultrasound in the diagnosis of retinal detachment in the emergency department. *Open Access Emerg Med*. 2019;11:265. [PMID: 32009820]

Park DH et al. Factors associated with visual outcome after macula-off rhegmatogenous retinal detachment surgery. *Retina*. 2018;38:137. [PMID: 28099315]

## VITREOUS HEMORRHAGE

Patients with vitreous hemorrhage complain of sudden visual loss, abrupt onset of floaters that may progressively increase in severity, or occasionally, “bleeding within the eye.” Visual acuity ranges from 20/20 (6/6) to light perception. The eye is not inflamed, red, or painful, and clues to diagnosis are inability to see fundus details or localized collection of blood in the vitreous, in front of the retina. Causes of vitreous hemorrhage include retinal tear (with or without detachment), diabetic or sickle cell retinopathy, retinal vein occlusion, retinal vasculitis, neovascular age-related macular degeneration, retinal arterial macroaneurysm, blood dyscrasia, therapeutic anticoagulation, trauma, subarachnoid hemorrhage, and severe straining (Valsalva retinopathy).

### ► When to Refer

All patients with suspected vitreous hemorrhage must be referred urgently to an ophthalmologist to determine the etiology. If the vitreous hemorrhage is caused by a retinal tear or detachment, it must be repaired urgently to prevent permanent vision loss.

Sheih WS et al. Ophthalmic complications associated with direct oral anticoagulant medications. *Semin Ophthalmol*. 2017;32:614. [PMID: 27367495]

Zhang T et al. Early vitrectomy for dense vitreous hemorrhage in adults with non-traumatic and non-diabetic retinopathy. *J Int Med Res*. 2017;45:2065. [PMID: 28627981]

## AGE-RELATED MACULAR DEGENERATION



### ESSENTIALS OF DIAGNOSIS

- ▶ Older age group.
- ▶ In one or both eyes; acute or chronic deterioration of central vision; distortion or abnormal size of images, sometimes developing acutely.
- ▶ No pain or redness.
- ▶ Classified as dry (“atrophic,” “geographic”) or wet (“neovascular,” “exudative”) macular degeneration.
- ▶ Macular abnormalities seen by ophthalmoscopy.

### ► General Considerations

In developed countries, age-related macular degeneration is the leading cause of permanent visual loss in the older population. Its prevalence progressively increases over age 50 years (to almost 30% by age 75). Its occurrence and response to treatment are likely influenced by genetically determined variations, many of which involve the complement pathway. Other associated factors are sex (slight female predominance), family history, hypertension, hypercholesterolemia, cardiovascular disease, farsightedness, light iris color, and cigarette smoking (the most readily modifiable risk factor).

Although both dry and wet age-related macular degeneration are progressive and usually bilateral, they differ in manifestations, prognosis, and management.

### ► Clinical Findings

The precursor to age-related macular degeneration is age-related maculopathy that is characterized by retinal drusen. Hard drusen appear ophthalmoscopically as discrete yellow subretinal deposits. Soft drusen are paler and less distinct. Large, confluent soft drusen are risk factors for neovascular (wet) age-related macular degeneration. Age-related macular degeneration results in loss of central vision only in most patients. Peripheral fields, and hence navigational vision, are maintained, except in patients with severe neovascular age-related macular degeneration.

**“Dry” age-related macular degeneration** is characterized by gradually progressive bilateral visual loss due to atrophy of the outer retina, the retinal pigment epithelium, and the choriocapillaris, which supplies blood to both the outer retina and the retinal pigment epithelium. In **“wet” age-related macular degeneration**, choroidal new vessels grow under either the retina or the retinal pigment epithelial cells, leading to accumulation of exudative fluid, hemorrhage, and fibrosis. The onset of visual loss is more rapid and more severe than in atrophic degeneration. The two eyes are frequently affected sequentially over a period of a few years. Although “dry” age-related macular degeneration is much more common, “wet” age-related macular degeneration accounts for about 90% of all cases of legal blindness due to age-related macular degeneration.

### ► Treatment

No dietary modification has been shown to prevent the development of age-related maculopathy, but its progression may be reduced by oral treatment with antioxidants (vitamins C and E), zinc, copper, and carotenoids (lutein and zeaxanthin, rather than vitamin A [ $\beta$ -carotene]). Oral omega-3 fatty acids do not provide additional benefit.

There is no specific treatment for dry age-related macular degeneration but, as for wet degeneration, rehabilitation including low-vision aids is important. In addition, patients should be advised to stop smoking and to take vitamin supplements as described above.

In wet age-related macular degeneration, inhibitors of vascular endothelial growth factors (VEGF), such as ranibizumab, bevacizumab, afibercept, and brolucizumab, cause regression of choroidal neovascularization with resorption of subretinal fluid and improvement or stabilization of vision. Long-term repeated intraocular injections are required and must be administered in the eye clinic several times a year, if not monthly. Treatment is well tolerated with minimal adverse effects, but there is a risk of infection (1/2000), retinal detachment (1/10,000), vitreous hemorrhage, and cataract. Brolucizumab has been associated with intraocular inflammation and occlusive retinal vasculitis resulting in irreversible vision loss in some patients. A certain percentage of patients do not respond to anti-VEGF injections and up to one-third of eyes lose vision despite regular treatment.

## ► When to Refer

Older patients with sudden visual loss, particularly para-central or central distortion or scotoma with preservation of central acuity, should be referred urgently to an ophthalmologist.

Baurnal CR et al. Retinal vasculitis and intraocular inflammation after intravitreal injection of brolucizumab. *Ophthalmology*. 2020;127:1345. [PMID: 32344075]

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Kataja M et al. Outcome of anti-vascular endothelial growth factor therapy for neovascular age-related macular degeneration in real-life setting. *Br J Ophthalmol*. 2018;102:959. [PMID: 29074495]

Plyukhova AA et al. Comparative safety of bevacizumab, ranibizumab and aflibercept for treatment of neovascular age-related macular degeneration (AMD): A systematic review and network meta-analysis of direct comparative studies. *J Clin Med*. 2020;9:1522. [PMID: 32443612]

## CENTRAL & BRANCH RETINAL VEIN OCCLUSIONS



### ESSENTIALS OF DIAGNOSIS

- ▶ Sudden monocular loss of vision.
- ▶ No pain or redness.
- ▶ Widespread or sectoral retinal hemorrhages.

## ► General Considerations

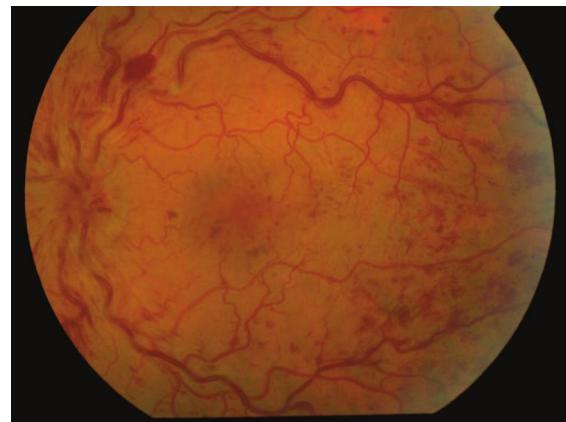
Central and branch retinal vein occlusion are common causes of acute vision loss, with branch vein occlusions being four times more common. The major predisposing factors are the etiologic factors associated with arteriosclerosis, but glaucoma is also a major risk factor.

## ► Clinical Findings

### A. Symptoms and Signs

Ophthalmoscopic signs of **central retinal vein occlusion** include widespread retinal hemorrhages, retinal venous dilation and tortuosity, retinal cotton-wool spots, and optic disk swelling (Figure 7–2).

**Branch retinal vein occlusion** may present in a variety of ways. Sudden loss of vision may occur at the time of occlusion if the fovea is involved, or some time afterward from vitreous hemorrhage due to retinal new vessels. More gradual visual loss may occur with development of macular edema. In acute branch retinal vein occlusion, the retinal abnormalities (hemorrhages, microaneurysms, venous dilation and tortuosity, and cotton-wool spots) are confined to the area drained by the obstructed vein.



▲ **Figure 7–2.** Central retinal vein occlusion.

To assess for possible reversible risk factors, check blood pressure and ask about tobacco smoking in all patients, and ask women about estrogen therapy (including combined oral contraceptives). Patients should also be asked about a history of glaucoma and should undergo a comprehensive eye examination to check intraocular pressure and for signs of open- or narrow-angle glaucoma.

### B. Laboratory Findings

Obtain screening laboratory studies for diabetes mellitus, hyperlipidemia, and hyperviscosity (especially in simultaneous bilateral disease), including serum protein electrophoresis for paraproteinemia. Particularly in younger patients, consider obtaining antiphospholipid antibodies, lupus anticoagulant, tests for inherited thrombophilia, and plasma homocysteine levels.

## ► Complications

If central retinal vein occlusion is associated with widespread retinal ischemia, manifesting as poor visual acuity (20/200 [6/60] or worse), florid retinal abnormalities, and extensive areas of capillary closure on fluorescein angiography, there is a high risk of development of neovascular (rubeotic) glaucoma, typically within the first 3 months after the occlusion. Branch retinal vein occlusion may be complicated by peripheral retinal neovascularization or chronic macular edema.

## ► Treatment

### A. Macular Edema

Intravitreal injection of VEGF inhibitors, including ranibizumab, bevacizumab, or aflibercept, is beneficial in patients with macular edema due to either branch or central retinal vein occlusion. Intravitreal triamcinolone improves vision in chronic macular edema due to nonischemic central retinal vein occlusion, whereas an intravitreal implant containing dexamethasone is beneficial in both central and branch retinal vein occlusion, but carries the risk of glaucoma in 20–65% of patients, and will cause cataract in all patients who have not already had cataract surgery. Retinal

laser photocoagulation may be indicated in chronic macular edema due to branch, but not central, retinal vein occlusion, but most patients are treated with VEGF inhibitor injections rather than laser.

### B. Neovascularization

Eyes at risk for neovascular glaucoma following ischemic central retinal vein occlusion can be treated with panretinal laser photocoagulation prophylactically or as soon as there is evidence of neovascularization, with the latter approach necessitating frequent monitoring. Regression of iris neovascularization can be achieved with intravitreal injections of bevacizumab. In branch retinal vein occlusion complicated by retinal neovascularization, the ischemic retina should be treated with laser photocoagulation.

### ► Prognosis

In central retinal vein occlusion, severity of visual loss initially is a good guide to visual outcome. Initial visual acuity of 20/60 (6/18) or better indicates a good prognosis. Visual prognosis is poor for eyes with neovascular glaucoma. In branch retinal vein occlusion, visual outcome is determined by the severity of glaucoma and macular damage from hemorrhage, ischemia, or edema.

### ► When to Refer

All patients with retinal vein occlusion should be referred urgently to an ophthalmologist.

- Ang JL et al. A systematic review of real-world evidence of the management of macular oedema secondary to branch retinal vein occlusion. *Eye (Lond)*. 2020;34:1770. [PMID: 32313172]
- Ehlers JP et al. Therapies for macular edema associated with branch retinal vein occlusion: a report by the American Academy of Ophthalmology. *Ophthalmology*. 2017;124:1412. [PMID: 28551163]
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- Sinawat S et al. Systemic abnormalities associated with retinal vein occlusion in young patients. *Clin Ophthalmol*. 2017;11:441. [PMID: 28260858]
- Shalchi Z et al. Anti-vascular endothelial growth factor for macular oedema secondary to branch retinal vein occlusion. *Cochrane Database Syst Rev*. 2020;7:CD009510. [PMID: 32633861]

## CENTRAL & BRANCH RETINAL ARTERY OCCLUSIONS



### ESSENTIALS OF DIAGNOSIS

- Sudden monocular loss of vision.
- No pain or redness.
- Widespread or sectoral pale retinal swelling.

### ► General Considerations

In patients 50 years of age or older with central retinal artery occlusion, giant cell arteritis must be considered (see Ischemic Optic Neuropathy and Chapter 20). Otherwise, even if no retinal emboli are identified on ophthalmoscopy, urgent investigation for carotid and cardiac sources of emboli must be undertaken in central and branch retinal artery occlusion so that timely treatment can be given to reduce the risk of stroke (see Chapters 12, 14, and 24). Diabetes mellitus, hyperlipidemia, and systemic hypertension are common etiologic factors. Migraine, oral contraceptives, systemic vasculitis, congenital or acquired thrombophilia, and hyperhomocysteinemia are also causes, particularly in young patients. Internal carotid artery dissection should be considered especially when there is neck pain or a recent history of neck trauma.

### ► Clinical Findings

#### A. Symptoms and Signs

**Central retinal artery occlusion** presents as sudden profound monocular visual loss. Visual acuity is usually reduced to counting fingers or worse, and visual field may be restricted to an island of vision in the temporal field. Ophthalmoscopy reveals pale swelling of the retina with a cherry-red spot at the fovea. The retinal arteries are attenuated, and “box-car” segmentation of blood in the arteries or veins may be seen as the red blood cells separate from serum when blood flow is slowed or arrested. Occasionally, emboli are seen in the central retinal artery or its branches. The retinal swelling subsides over a period of 4–6 weeks, leaving a pale optic disk with thinning of the inner retina on optical coherence tomography scans; these findings can help diagnose unexplained vision loss if the patient is not examined during the acute occlusive event.

**Branch retinal artery occlusion** may also present with sudden loss of vision if the fovea is involved, but more commonly sudden loss of a discrete area in the visual field in one eye is the presenting complaint. Fundus signs of retinal swelling and sometimes adjacent cotton-wool spots are limited to the area of retina supplied by the occluded artery.

Identify risk factors for cardiac sources of emboli including arrhythmia, particularly atrial fibrillation, and cardiac valvular disease, and check the blood pressure. Nonocular clinical features of giant cell arteritis are age 50 years or older, headache, scalp tenderness, jaw claudication, general malaise, weight loss, symptoms of polymyalgia rheumatica, and tenderness, thickening, or absence of pulse of the superficial temporal arteries. Table 20–12 lists the clinical manifestations of vasculitis.

#### B. Laboratory Findings

Giant cell arteritis should be considered in cases of central retinal artery occlusion without visible emboli. Erythrocyte sedimentation rate and C-reactive protein are usually elevated in giant cell arteritis but one or both may be normal (see Chapter 20). Consider screening for other types of vasculitis (see Table 20–11). Screen for diabetes mellitus and hyperlipidemia in all patients. Particularly in younger

patients, consider testing for antiphospholipid antibodies, lupus anticoagulant, inherited thrombophilia, and elevated plasma homocysteine.

### C. Imaging

To identify carotid and cardiac sources of emboli, obtain duplex ultrasonography of the carotid arteries, ECG, and echocardiography with transesophageal studies, if necessary. When indicated, obtain CT or MR studies for internal carotid artery dissection.

### Treatment

Retinal artery occlusions require urgent referral to an emergency department for imaging and clinical assessment to prevent subsequent stroke. If the patient is seen within a few hours after onset, emergency treatment, comprising laying the patient flat, ocular massage, high concentrations of inhaled oxygen, intravenous acetazolamide, and anterior chamber paracentesis, may influence the visual outcome. Early thrombolysis, particularly by local intra-arterial injection, but also intravenously, has shown good results in central retinal artery occlusion not due to giant cell arteritis. However, intra-arterial injection of thrombolytic agents has a high incidence of adverse effects and may be difficult to accomplish quickly enough after the occlusion develops to prevent permanent vision loss due to inner retinal ischemia, which non-human primate studies suggest occurs within 90 minutes of occlusion.

In giant cell arteritis, there is risk of involvement of the other eye without prompt treatment. Recommended initial empiric treatment is intravenous methylprednisolone 1 g/day for 3 days. Whether oral methylprednisolone is similarly effective is unknown. All patients require subsequent long-term corticosteroid therapy (eg, oral prednisone); concomitant administration of long-term low-dose aspirin therapy is controversial. There must be close monitoring to ensure that symptoms resolve and do not recur. Temporal artery biopsy should be performed promptly to confirm the diagnosis, and if necessary, assistance sought from a rheumatologist to guide management (see *Polymyalgia Rheumatica & Giant Cell Arteritis*, Chapter 20).

Patients with embolic retinal artery occlusion with 70–99% ipsilateral carotid artery stenosis, and possibly those with 50–69% stenosis, should be considered for carotid endarterectomy or possibly angioplasty with stenting to be performed within 2 weeks (see Chapters 12 and 24). Retinal embolization due to cardiac disease such as atrial fibrillation or a hypercoagulable state usually requires anticoagulation. Cardiac valvular disease and patent foramen ovale may require surgical treatment.

### When to Refer

- Patients with retinal artery occlusions should be referred immediately to an emergency department to evaluate for stroke manifestations.
- Patients with central retinal artery occlusion should be referred emergently to an ophthalmologist.
- Patients with branch retinal artery occlusion should be referred urgently.

### When to Admit

Patients with visual loss due to giant cell arteritis may require emergency admission for high-dose corticosteroid therapy and close monitoring to ensure adequate treatment.

Abel AS et al. Practice patterns after acute embolic retinal artery occlusion. *Asia Pac J Ophthalmol (Phila)*. 2017;6:37. [PMID: 28161924]

Biousse V et al. Management acute retinal ischemia: follow the guidelines! *Ophthalmology*. 2018;125:1597. [PMID: 29716787]

Soriano A et al. Visual loss and other cranial ischaemic complications in giant cell arteritis. *Nat Rev Rheumatol*. 2017;13:476. [PMID: 28680132]

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## TRANSIENT MONOCULAR VISUAL LOSS



### ESSENTIALS OF DIAGNOSIS

- ▶ Sudden-onset, monocular loss of vision usually lasting a few minutes with complete recovery.

### Clinical Findings

#### A. Symptoms and Signs

Transient monocular visual loss (“ocular transient ischemic attack [TIA]”) is usually caused by a retinal embolus from ipsilateral carotid disease or the heart. The visual loss is characteristically described as a curtain passing vertically across the visual field with complete monocular visual loss lasting a few minutes and a similar curtain effect as the episode passes (amaurosis fugax; also called “fleeting blindness”). An embolus is rarely seen on ophthalmoscopy. Other causes of transient, often recurrent, visual loss due to ocular ischemia are giant cell arteritis, hypercoagulable state (such as antiphospholipid syndrome), hyperviscosity, and severe occlusive carotid disease. More transient visual loss, lasting only a few seconds to 1 minute, usually recurrent, and affecting one or both eyes, occurs in patients with optic disk swelling, for example in those with raised intracranial pressure.

#### B. Diagnostic Studies

In most cases, clinical assessment and investigations are much the same as for retinal artery occlusion with emphasis on identification of a source of emboli, since patients with embolic transient vision loss are at increased risk for stroke, myocardial infarction, and other vascular events. Optic disk swelling requires different investigations.

### Treatment

All patients with possible embolic transient visual loss should be treated immediately with oral aspirin (at least 81 mg daily), or another antiplatelet drug, until the cause has been

determined. Affected patients with 70–99% (and possibly those with 50–69%) ipsilateral carotid artery stenosis should be considered for urgent carotid endarterectomy or possibly angioplasty with stenting (see Chapters 12 and 24). In all patients, vascular risk factors (eg, hypertension) need to be controlled. Retinal embolization due to cardiac arrhythmia, such as atrial fibrillation, or hypercoagulable state usually requires anticoagulation. Cardiac valvular disease and patent foramen ovale may require surgical treatment.

### ► When to Refer

In all cases of episodic visual loss, early ophthalmologic consultation is advisable.

### ► When to Admit

Referral to a stroke center or hospital admission is recommended in embolic transient visual loss if there have been two or more episodes in the preceding week (“crescendo TIA”) or the underlying cause is cardiac or a hypercoagulable state.

Biousse V et al. Management of acute retinal ischemia: follow the guidelines! *Ophthalmology*. 2018;125:1597. [PMID: 29716787]  
 Vodopivec I et al. Management of transient monocular vision loss and retinal artery occlusions. *Semin Ophthalmol*. 2017; 32:125. [PMID: 27780399]

## RETINAL DISORDERS ASSOCIATED WITH SYSTEMIC DISEASES

### 1. Diabetic Retinopathy



#### ESSENTIALS OF DIAGNOSIS

- ▶ Present in ~33% of all diagnosed diabetic patients.
- ▶ Present in ~20% of type 2 diabetic patients at time of diagnosis of diabetes.
- ▶ By 20 years after diagnosis of diabetes, 99% of type 1 diabetic patients and 60% of type 2 diabetic patients will have diabetic retinopathy.
- ▶ Nonproliferative diabetic retinopathy: can be mild, moderate, or severe. Microvascular changes are limited to the retina.
- ▶ Proliferative diabetic retinopathy: new blood vessels grow on the surface of the retina, optic nerve, or iris.
- ▶ Diabetic macular edema: central retinal swelling; can occur with any severity level of diabetic retinopathy; reduces visual acuity if center involved.

### ► General Considerations

Diabetic retinopathy is present in about one-third of patients in whom diabetes has been diagnosed, and about one-third of those have sight-threatening disease. In the United States, it affects about 4 million people; it is the

leading cause of new blindness among adults aged 20–65 years; and the number of affected individuals aged 65 years or older is increasing. Worldwide, there are approximately 93 million people with diabetic retinopathy, including 28 million with vision-threatening disease. Retinopathy increases in prevalence and severity with increasing duration and poorer control of diabetes. In type 1 diabetes, retinopathy is not detectable for the first 5 years after diagnosis. In type 2 diabetes, about 20% of patients have retinopathy at diagnosis likely because they had diabetes for an extensive period of time before diagnosis. Macular involvement is the most common cause of legal blindness in type 2 diabetes.

There are two main categories of diabetic retinopathy: nonproliferative and proliferative. Diabetic macular edema can occur at any stage. **Nonproliferative retinopathy** is subclassified as mild, moderate, or severe; **proliferative retinopathy** is less common but causes more severe visual loss.

**Nonproliferative (“background”) retinopathy** represents the earliest stage of retinal involvement by diabetes. During this stage, the retinal capillaries leak proteins, lipids, or red cells into the retina. When this process occurs in the macula (clinically significant macular edema), the area of greatest concentration of visual cells, there is interference with visual acuity; this is the most common cause of visual impairment in patients with type 2 diabetes.

**Proliferative retinopathy** involves the growth of new capillaries and fibrous tissue on the surface of the retina, extending into the vitreous chamber. It is a consequence of small vessel occlusion, which causes retinal hypoxia; this, in turn, stimulates new vessel growth.

### ► Clinical Findings

Clinical assessment comprises visual acuity testing, stereoscopic examination of the retina, retinal imaging with optical coherence tomography, and sometimes fluorescein angiography.

**Nonproliferative retinopathy** manifests as microaneurysms, retinal hemorrhages, venous beading, retinal edema, and hard exudates. In mild nonproliferative diabetic retinopathy, there are mild retinal abnormalities without visual loss. Reduction of vision is most commonly due to diabetic macular edema, which may be focal or diffuse, but it can also be due to macular ischemia.

**Proliferative retinopathy** is characterized by neovascularization, arising from either the optic disk or the major vascular arcades. Prior to proliferation of new capillaries, a preproliferative phase often occurs in which arteriolar ischemia is manifested as cotton-wool spots (small infarcted areas of retina). Vision is usually normal until macular edema, vitreous hemorrhage, or retinal detachment occurs. Proliferation into the vitreous of blood vessels, with associated fibrosis, may lead to vitreous hemorrhage (common) and tractional retinal detachment (see eFigure 7–42). Severe nonproliferative retinopathy is defined as having any one of the following: severe intraretinal hemorrhages and microaneurysms in four quadrants, venous beading in two or more quadrants, or intraretinal microvascular abnormalities in at least one quadrant.

Diabetic retinopathy may worsen after bariatric surgery or in patients with long-standing hyperglycemia that is

rapidly brought under tight control, such as after receiving an insulin pump with continuous glucose monitoring. Macular edema may be associated with thiazolidinedione (ie, pioglitazone, rosiglitazone) treatment.

## ► Screening

Visual symptoms and visual acuity are poor guides to the presence of diabetic retinopathy. Adult and adolescent patients with diabetes mellitus should undergo regular screening by fundus photography, which can be performed using telemedicine that may involve computer detection software programs or dilated slit-lamp examination of the retina. Patients with type 1 diabetes mellitus should be screened 5 years after the diabetes is diagnosed. Patients with type 2 diabetes mellitus should be screened at or shortly after diagnosis of diabetes. More frequent monitoring is required in women with type 1 or 2 diabetes during pregnancy and in those planning pregnancy.

## ► Treatment

Treatment includes optimizing blood glucose, blood pressure, kidney function, and serum lipids. Glycemic control is the most important modifiable factor in treating patients with diabetic retinopathy, but intensive blood pressure control and avoiding tobacco use also slow retinopathy progression.

Macular edema and exudates, but not macular ischemia, may respond to laser photocoagulation; to intravitreal administration of a VEGF inhibitor (ranibizumab, bevacizumab, afibercept, or brolucizumab) or corticosteroid (triamcinolone, dexamethasone implant, or fluocinolone implant); or to vitrectomy. VEGF inhibitor therapy improves diabetic retinopathy severity in eyes at all levels of nonproliferative diabetic retinopathy and is the mainstay of treatment for diabetic macular edema.

In patients with **severe nonproliferative retinopathy**, fluorescein angiography can help determine whether panretinal laser photocoagulation should be undertaken prophylactically by determining the extent of retinal ischemia. Vitrectomy is necessary for removal of persistent vitreous hemorrhage, to improve vision and allow panretinal laser photocoagulation for the underlying retinal neovascularization, for treatment of tractional retinal detachment involving the macula, and for management of rapidly progressive proliferative disease.

**Proliferative retinopathy** is usually treated by intravitreal injection of a VEGF inhibitor or panretinal laser photocoagulation, preferably before vitreous hemorrhage or tractional detachment has occurred. Proliferative diabetic retinopathy, especially after successful laser treatment, is not a contraindication to treatment with thrombolytic agents, aspirin, or warfarin unless there has been recent intraocular hemorrhage.

## ► When to Refer

- All diabetic patients with sudden loss of vision or retinal detachment should be referred emergently to an ophthalmologist.

- Proliferative retinopathy or macular involvement requires urgent referral to an ophthalmologist.
- Severe nonproliferative retinopathy or unexplained reduction of visual acuity requires early referral to an ophthalmologist.

Flaxel CJ et al. Diabetic Retinopathy Preferred Practice Pattern®. *Ophthalmology*. 2020;127:P66. [PMID: 31757498]

Gross JG et al; Diabetic Retinopathy Clinical Research Network. Five-year outcomes of panretinal photocoagulation vs intravitreous ranibizumab for proliferative diabetic retinopathy: a randomized clinical trial. *JAMA Ophthalmol*. 2018;136:1138. [PMID: 30043039]

Liu Y et al. Risk factors of diabetic retinopathy and sight-threatening diabetic retinopathy: a cross-sectional study of 13 473 patients with type 2 diabetes mellitus in mainland China. *BMJ Open*. 2017;7:e016280. [PMID: 28864696]

Wong TY et al. Strategies to tackle the global burden of diabetic retinopathy: from epidemiology to artificial intelligence. *Ophthalmologica*. 2019;1. [PMID: 31408872]

## 2. Hypertensive Retinochoroidopathy

Systemic hypertension affects both the retinal and choroidal circulations. The clinical manifestations vary according to the degree and rapidity of rise in blood pressure and the underlying state of the ocular circulation (see Chapter 11). The most florid ocular changes occur in young patients with abrupt elevations of blood pressure, such as may occur in pheochromocytoma, malignant hypertension, or preeclampsia-eclampsia.

Chronic hypertension accelerates the development of atherosclerosis. The retinal arterioles become more tortuous and narrower and develop abnormal light reflexes ("silver-wiring" and "copper-wiring") (Figure 11–2). There is increased venous compression at the retinal arteriovenous crossings ("arteriovenous nicking"), predisposing to branch retinal vein occlusions. Flame-shaped hemorrhages occur in the nerve fiber layer of the retina. Detection is aided by nonmydriatic fundus photography.

Acute elevations of blood pressure result in loss of autoregulation in the retinal circulation, leading to breakdown of endothelial integrity and occlusion of precapillary arterioles and capillaries that manifest as cotton-wool spots, retinal hemorrhages, retinal edema, and retinal exudates, often in a stellate appearance at the macula. Vasoconstriction and ischemia in the choroid result in exudative retinal detachments and retinal pigment epithelial infarcts that later develop into pigmented lesions that may be focal, linear, or wedge-shaped. The abnormalities in the choroidal circulation may also affect the optic nerve head, producing ischemic optic neuropathy with optic disk swelling. *Fundus abnormalities are the hallmark of hypertensive crisis with retinopathy (previously known as malignant hypertension) that requires emergency treatment* (see Chapter 11). Marked fundus abnormalities are likely to be associated with permanent retinal, choroidal, or optic nerve damage. Precipitous reduction of blood pressure may exacerbate such damage.

Fraser-Bell S et al. Hypertensive eye disease: a review. *Clin Exp Ophthalmol*. 2017;45:45. [PMID: 27990740]

- Kolman SA et al. Consideration of hypertensive retinopathy as an important end-organ damage in patients with hypertension. *J Hum Hypertens.* 2017;31:121. [PMID: 27465980]
- Tsukikawa M et al. A review of hypertensive retinopathy and chorioretinopathy. *Clin Optom (Auckl).* 2020;12:67. [PMID: 32440245]

### 3. Blood Dyscrasias

Severe thrombocytopenia or anemia may result in various types of retinal or choroidal hemorrhages, including white centered retinal hemorrhages (Roth spots) that occur in leukemia and other situations (eg, bacterial endocarditis). Involvement of the macula may result in permanent visual loss.

Sickle cell retinopathy is particularly common in hemoglobin SC disease but may also occur with other hemoglobin S variants. Manifestations include “salmon-patch” preretinal/intraretinal hemorrhages, “black sunbursts” resulting from intraretinal hemorrhage, and new vessels. Severe visual loss is rare but more common in patients with pulmonary hypertension. Retinal laser photocoagulation reduces the frequency of vitreous hemorrhage from new vessels. Surgery is occasionally needed for persistent vitreous hemorrhage or tractional retinal detachment.

- Alabduljalil T et al. Retinal ultra-wide-field colour imaging versus dilated fundus examination to screen for sickle cell retinopathy. *Br J Ophthalmol.* 2020;31:6779. [PMID: 32816790]
- AlRyalat SA et al. Ocular manifestations of sickle cell disease in different genotypes. *Ophthalmic Epidemiol.* 2021;28:185. [PMID: 32757703]
- Talcott KE et al. Ophthalmic manifestations of leukemia. *Curr Opin Ophthalmol.* 2016;27:545. [PMID: 27585213]

### 4. HIV Infection/AIDS

See Chapter 31. **HIV retinopathy** causes cotton-wool spots, retinal hemorrhages, and microaneurysms but may also lead to reduced contrast sensitivity and retinal nerve fiber layer and outer retinal damage (HIV neuroretinal disorder).

**CMV retinitis** is less common since the availability of antiretroviral therapy (ART) but continues to be prevalent where resources are limited. It usually occurs when CD4 counts are below 50/mcL ( $0.05 \times 10^9/L$ ) and is characterized by progressively enlarging yellowish-white patches of retinal opacification, accompanied by retinal hemorrhages, and usually beginning adjacent to the major retinal vascular arcades. Patients are often asymptomatic until there is involvement of the fovea or optic nerve, or until retinal detachment develops. See Table 31–3 for initial therapeutic recommendations. Maintenance therapy can be achieved with lower-dose therapy or with intravitreal therapy. Systemic therapy has a greater risk of nonocular adverse effects but reduces mortality, incidence of nonocular CMV disease (but this is less common with ART), and incidence of retinitis in the fellow eye and avoids intraocular complications of intravitreal administration. Pharmacologic prophylaxis against CMV retinitis in patients with low CD4 counts or high CMV burdens has not been found to be worthwhile. In all patients with CMV retinitis, ART needs to be instituted or adjusted. This may lead to the immune

reconstitution inflammatory syndrome (IRIS), of which the immune recovery uveitis may lead to visual loss, predominantly due to cystoid macular edema. It may be possible to reduce the likelihood of IRIS by using immunomodulatory therapy to suppress the immune response causing the inflammation. If the CD4 count is maintained above 100/mcL ( $0.1 \times 10^9/L$ ), it may be possible to discontinue maintenance anti-CMV therapy.

Other ophthalmic manifestations of opportunistic infections occurring in AIDS patients include herpes simplex retinitis, which usually manifests as acute retinal necrosis; toxoplasmic and candidal chorioretinitis possibly progressing to endophthalmitis; herpes zoster ophthalmicus and herpes zoster retinitis, which can manifest as acute retinal necrosis or progressive outer retinal necrosis; and various entities due to syphilis, tuberculosis, or cryptococcosis. Kaposi sarcoma of the conjunctiva (see Chapter 31) and orbital lymphoma may also be seen on rare occasions.

Heiden D et al. Active cytomegalovirus retinitis after the start of antiretroviral therapy. *Br J Ophthalmol.* 2019;103:157. [PMID: 30196272]

Kim DY et al. Comparison of visual prognosis and clinical features of cytomegalovirus retinitis in HIV and non-HIV patients. *Retina.* 2017;37:376. [PMID: 28118285]

Munro M et al. Cytomegalovirus retinitis in HIV and non-HIV individuals. *Microorganisms.* 2019;8:55. [PMID: 31905656]

Tang Y et al. Clinical features of cytomegalovirus retinitis in HIV infected patients. *Front Cell Infect Microbiol.* 2020;10:136. [PMID: 32318357]

## ISCHEMIC OPTIC NEUROPATHY



### ESSENTIALS OF DIAGNOSIS

- ▶ Sudden painless visual loss with signs of optic nerve dysfunction.
- ▶ Optic disk swelling in anterior ischemic optic neuropathy.

**Anterior ischemic optic neuropathy**—due to inadequate perfusion of the posterior ciliary arteries that supply the anterior portion of the optic nerve—produces sudden visual loss, usually with an altitudinal field defect, and optic disk swelling. In older patients, it may be caused by giant cell arteritis (arteritic anterior ischemic optic neuropathy). The predominant factor predisposing to nonarteritic anterior ischemic optic neuropathy, which subsequently affects the fellow eye in around 15% of cases, is a congenitally crowded optic disk, compromising optic disk circulation. Other predisposing factors are systemic hypertension, diabetes mellitus, hyperlipidemia, systemic vasculitis, inherited or acquired thrombophilia, interferon-alpha therapy, obstructive sleep apnea; the association with phosphodiesterase type 5 inhibitors is controversial.

**Posterior ischemic optic neuropathy**, involving the retrobulbar optic nerve and thus not causing any optic disk swelling, may occur with severe blood loss; nonocular surgery,

particularly prolonged lumbar spine surgery in the prone position; severe burns; or in association with dialysis. In all such situations, there may be several contributory factors.

## ► Treatment

Arteritic anterior ischemic optic neuropathy necessitates emergency high-dose systemic corticosteroid treatment to prevent visual loss in the other eye. (See Central & Branch Retinal Artery Occlusions, above, and Polymyalgia Rheumatica & Giant Cell Arteritis, Chapter 20.) It is uncertain whether systemic or intravitreal corticosteroid therapy influences the outcome in nonarteritic anterior ischemic optic neuropathy or whether oral low-dose (~81 mg daily) aspirin reduces the risk of fellow eye involvement. In ischemic optic neuropathy after nonocular surgery, treatment of marked anemia by blood transfusion may be beneficial.

## ► When to Refer

Patients with ischemic optic neuropathy should be referred urgently to an ophthalmologist.

## ► When to Admit

Patients with ischemic optic neuropathy due to giant cell arteritis or other vasculitis may require emergency admission for high-dose corticosteroid therapy and close monitoring to ensure that treatment is adequate.

Berry S et al. Nonarteritic anterior ischemic optic neuropathy: cause, effect, and management. *Eye Brain*. 2017;9:23. [PMID: 29033621]

Liub B. The association between phosphodiesterase type 5 inhibitor use and risk of non-arteritic anterior ischemic optic neuropathy: a systematic review and meta-analysis. *Sex Med*. 2018;6:185. [PMID: 29884471]

## OPTIC NEURITIS



### ESSENTIALS OF DIAGNOSIS

- Subacute usually unilateral visual loss.
- Pain exacerbated by eye movements.
- Optic disk usually normal in acute stage but subsequently develops pallor.

## ► General Considerations

Inflammatory optic neuropathy is strongly associated with demyelinating disease (typical optic neuritis), particularly multiple sclerosis but also acute disseminated encephalomyelitis. It also occurs in sarcoidosis; in neuromyelitis optica spectrum disorder, which is characterized by serum antibodies to aquaporin-4; in association with serum antibodies to myelin oligodendrocyte glycoprotein; following viral infection (usually in children); in varicella zoster virus infection; in autoimmune disorders, particularly systemic lupus erythematosus and Sjögren syndrome; during

treatment with biologics; and by spread of inflammation from the meninges, orbital tissues, or paranasal sinuses.

## ► Clinical Findings

Optic neuritis in demyelinating disease is characterized by unilateral loss of vision developing over a few days. Visual acuity ranges from 20/30 (6/9) to no perception of light, with more severe visual loss being associated with low serum vitamin D. In almost all cases there is pain behind the eye, exacerbated by eye movements. Field loss is usually central. There is particular loss of color vision and a relative afferent pupillary defect. In about two-thirds of cases, the optic nerve is normal during the acute stage (retrobulbar optic neuritis). In the remainder, the optic disk is swollen (papillitis) with occasional flame-shaped peripapillary hemorrhages. Visual acuity usually improves within 2–3 weeks and returns to 20/40 (6/12) or better in 95% of previously unaffected eyes. Optic atrophy subsequently develops if there has been damage to sufficient optic nerve fibers. Any patient without a known diagnosis of multiple sclerosis with presumed demyelinating optic neuritis in which visual recovery does not occur or there are other atypical features, including continuing deterioration of vision or persisting pain after 2 weeks, should undergo further investigation; MRI of the head and orbits can look for periventricular white matter demyelination, examine for a lesion compressing the optic nerve, and identify atypical optic neuritis.

## ► Treatment

In acute demyelinating optic neuritis, intravenous methylprednisolone (1 g daily for 3 days followed by a tapering course of oral prednisolone) has been shown to accelerate visual recovery but not to improve final vision. However, in clinical practice, the oral taper is not often prescribed, and oral methylprednisolone may be used. Use in an individual patient is determined by the degree of visual loss, the state of the fellow eye, and the patient's visual requirements. Phenytoin may be neuroprotective in typical optic neuritis.

Atypical optic neuritis due to sarcoidosis, neuromyelitis optica, herpes zoster, or systemic lupus erythematosus generally has a poorer prognosis, requires immediate and more prolonged corticosteroid therapy, may require plasma exchange, and may necessitate long-term immunosuppression.

## ► Prognosis

Among patients with a first episode of clinically isolated optic neuritis, multiple sclerosis will develop in 50% within 15 years; however, the likelihood of developing multiple sclerosis ranges from 25% for patients without demyelinating lesions on brain MRI to 72% in patients with one or more demyelinating lesions. The major risk factors are female sex and multiple white matter lesions on brain MRI. Many disease-modifying drugs are available to reduce the risk of further neurologic episodes and disability, but each has adverse effects that in some instances are life-threatening. Fingolimod is associated with macular edema. Retinal nerve fiber layer optical coherence tomography quantifies axonal damage that can be used to monitor disease progression.

## ► When to Refer

All patients with optic neuritis should be referred urgently for ophthalmologic or neurologic assessment.

- Deschamps R et al. Etiologies of acute demyelinating optic neuritis: an observational study of 110 patients. *Eur J Neurol.* 2017;24:875. [PMID: 28477397]
- Graves JS. Optical coherence tomography in multiple sclerosis. *Semin Neurol.* 2019;39:711. [PMID: 31847042]
- Morrow MJ et al. Should oral corticosteroids be used to treat demyelinating optic neuritis? *J Neuroophthalmol.* 2017; 37:444. [PMID: 28857910]
- Patterson SL et al. Neuromyelitis optica. *Rheum Dis Clin North Am.* 2017;43:579. [PMID: 29061244]

## OPTIC DISK SWELLING

Optic disk swelling may result from any orbital or optic nerve lesion causing nerve compression, severe hypertensive retinochoroidopathy, or raised intracranial pressure, the last necessitating urgent imaging to exclude an intracranial mass or cerebral venous sinus occlusion. Intraocular causes include central retinal vein occlusion, posterior uveitis, and posterior scleritis. Optic nerve lesions causing disk swelling include anterior ischemic optic neuropathy; optic neuritis; optic nerve sheath meningioma; and infiltration by sarcoidosis, leukemia, or lymphoma.

Papilledema (optic disk swelling due to raised intracranial pressure) is usually bilateral and most commonly produces enlargement of the blind spot without loss of acuity. Chronic papilledema, as in idiopathic intracranial hypertension and cerebral venous sinus occlusion, or severe acute papilledema may be associated with visual field loss and occasionally with profound loss of acuity. All patients with chronic papilledema must be monitored carefully—especially their visual fields—and cerebrospinal fluid shunt or optic nerve sheath fenestration should be considered in those with progressive visual failure not controlled by medical therapy (weight loss where appropriate and usually acetazolamide in patients with idiopathic intracranial hypertension). In idiopathic intracranial hypertension, transverse venous sinus stenting is also an option.

Optic disk drusen and congenitally crowded optic disks, which are associated with farsightedness, cause optic disk elevation that may be mistaken for swelling (pseudopapilledema). Exposed optic disk drusen may be obvious clinically or can be demonstrated by their autofluorescence. Buried drusen are best detected by orbital ultrasound or CT scanning. Other family members may be similarly affected.

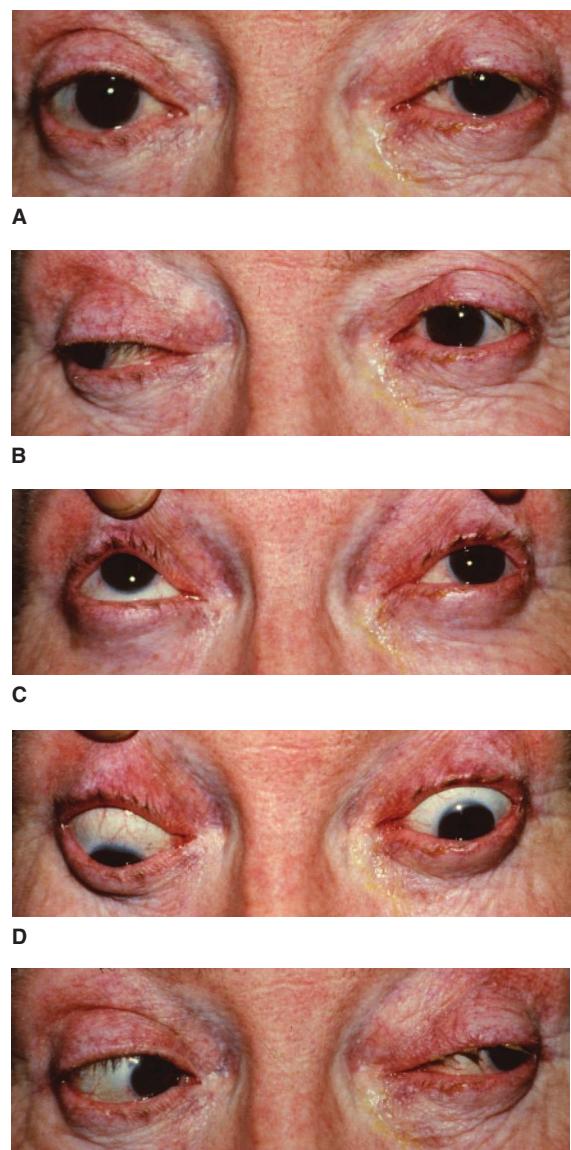
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Wall M et al; NORDIC Idiopathic Intracranial Hypertension Study Group. The longitudinal Idiopathic Intracranial Hypertension Trial: outcomes from months 6–12. *Am J Ophthalmol.* 2017;176:102. [PMID: 28104417]

## CRANIAL NERVE PALSYES

A cranial nerve palsy of any of the three cranial nerves that supply the extraocular muscles can cause double vision.

In a complete **third nerve palsy**, there is ptosis with a divergent and slightly depressed eye (Figure 7–3). Extraocular movements are restricted in all directions except laterally (preserved lateral rectus function) (Figure 7–3E).



**▲ Figure 7-3.** Left partial third nerve palsy with ptosis (**A**), reduced adduction (**B**), reduced elevation (**C**), and reduced depression (**D**) but normal abduction (**E**) of the left eye.

Intact fourth nerve (superior oblique) function is detected by inward rotation on attempted depression of the eye. Pupillary involvement, manifesting as a relatively dilated pupil that does not constrict normally to light, usually means compression, which may be due to aneurysm of the posterior communicating artery or uncal herniation due to a supratentorial mass lesion. In acute painful isolated third nerve palsy with pupillary involvement, posterior communicating artery aneurysm must be excluded. Pituitary apoplexy is a rarer cause. Causes of isolated third nerve palsy without pupillary involvement include diabetes mellitus, hypertension, giant cell arteritis, and herpes zoster.

**Fourth nerve palsy** causes upward deviation of the eye with failure of depression on adduction. In acquired cases, there is vertical and torsional diplopia that is most apparent on looking down. Trauma is a major cause of acquired—particularly bilateral—fourth nerve palsy, but posterior fossa tumor and medical causes, such as in third nerve palsy, should also be considered. Similar clinical features are seen in congenital cases due to developmental anomaly of the nerve, muscle, or tendon.

**Sixth nerve palsy** causes convergent squint in the primary position with failure of abduction of the affected eye, producing horizontal diplopia that increases on gaze to the affected side and on looking into the distance. It is an important sign of raised intracranial pressure and may also be due to trauma, neoplasms, brainstem lesions, petrous apex lesions, or medical causes (such as diabetes mellitus, hypertension, giant cell arteritis, and herpes zoster).

In an isolated cranial nerve palsy presumed to be due a medical cause, brain MRI is not always required initially, but it is necessary if recovery has not begun within 3 months.

A cranial nerve palsy accompanied by other neurologic signs may be due to lesions in the brainstem, cavernous sinus, or orbit. Lesions around the cavernous sinus involve the first and second divisions of the trigeminal nerve, the third, fourth, and sixth cranial nerves, and occasionally the optic chiasm. Orbital apex lesions involve the optic nerve and the three cranial nerves supplying the extraocular muscles.

Myasthenia gravis and thyroid eye disease (see Graves ophthalmopathy) should be considered in the differential diagnosis of disordered extraocular movements.

## ► When to Refer

- In recent-onset isolated third nerve palsy, especially if there is pupillary involvement or pain, immediate referral is required for neurologic assessment and possibly CT, MRI, or catheter angiography for intracranial aneurysm.
- All patients with recent-onset double vision should be referred urgently to a neurologist or ophthalmologist, particularly if there are multiple cranial nerve dysfunctions or other neurologic abnormalities.

## ► When to Admit

Patients with double vision due to giant cell arteritis may require emergency admission for high-dose corticosteroid

therapy and close monitoring to ensure that treatment is adequate. (See Central & Branch Retinal Artery Occlusions and Chapter 20.)

Huff JS et al. Neuro-ophthalmology in emergency medicine. *Emerg Med Clin North Am.* 2016;34:967. [PMID: 27741997]

Prasad S. A window to the brain: neuro-ophthalmology for the primary care practitioner. *Am J Med.* 2018;131:120. [PMID: 29079403]

## THYROID EYE DISEASE (Graves Ophthalmopathy)

See Hyperthyroidism (Thyrotoxicosis) in Chapter 26.

## ORBITAL CELLULITIS

Orbital cellulitis is characterized by fever, proptosis, restriction of extraocular movements, and swelling with redness of the lids. Immediate treatment with intravenous antibiotics is necessary to prevent optic nerve damage and spread of infection to the cavernous sinuses, meninges, and brain. Infection of the paranasal sinuses is the usual underlying cause. Infecting organisms include *S pneumoniae*, the incidence of which has been reduced by the administration of pneumococcal vaccine; other streptococci, such as the anginosus group; *H influenzae*; and, less commonly, *S aureus* including MRSA. Penicillinase-resistant penicillin, such as nafcillin, is recommended, possibly together with metronidazole or clindamycin to treat anaerobic infections. If trauma is the underlying cause, a cephalosporin, such as cefazolin or ceftriaxone, should be added to ensure coverage for *S aureus* and group A beta-hemolytic streptococci. If MRSA infection is a concern, vancomycin or clindamycin may be required. For patients with penicillin hypersensitivity, vancomycin, levofloxacin, and metronidazole are recommended. The response to antibiotics is usually excellent, but surgery may be required to drain the paranasal sinuses or orbital abscess. In immunocompromised patients, zygomycosis must be considered.

## ► When to Refer

All patients with suspected orbital cellulitis must be referred emergently to an ophthalmologist.

Tsiropoulos T et al. Orbital cellulitis. *Surv Ophthalmol.* 2018;63:534. [PMID: 29248536]

## OCULAR TRAUMA

Ocular trauma is an important cause of avoidable severe visual impairment at all ages, and it is the leading cause of monocular blindness in young adult men in the United States. Thorough but safe clinical assessment, supplemented when necessary by imaging, is crucial to effective management. Ocular damage and the possible need for early assessment by an ophthalmologist need to be borne in mind in the assessment of any patient with mid-facial injury.

## 1. Conjunctival & Corneal Foreign Bodies

If a patient complains of “something in my eye” and gives a consistent history, a foreign body is usually present on the cornea or under the upper lid even though it may not be visible. Visual acuity should be tested before treatment is instituted to assess the severity of the injury and as a basis for comparison in the event of complications.

After a local anesthetic (eg, proparacaine, 0.5%) is instilled, the eye is examined with a slit lamp or with a hand flashlight, using oblique illumination, and loupe. The instillation of sterile fluorescein may make corneal foreign bodies more apparent, which are then removed with a sterile wet cotton-tipped applicator or hypodermic needle. Bacitracin-polymyxin ophthalmic ointment should be instilled. It is not necessary to patch the eye. All patients need to be advised to return promptly for reassessment if there is any increase in pain, redness, or impairment of vision.

Iron foreign bodies usually leave a diffuse rust ring. This requires excision and is best done under local anesthesia using a slit lamp. **Caution:** Anesthetic drops should not be given to the patient for self-administration.

If there is no infection, a layer of corneal epithelial cells will line the crater within 24 hours. While the epithelium is defective, the cornea is extremely susceptible to infection. Early infection is manifested by a white necrotic area around the crater and a small amount of gray exudate.

In the case of a foreign body under the upper lid, a local anesthetic is instilled and the lid is everted by grasping the lashes gently and exerting pressure on the mid portion of the outer surface of the upper lid with an applicator. If a foreign body is present, it can easily be removed by passing a wet sterile cotton-tipped applicator across the conjunctival surface.

### ► When to Refer

Refer urgently to an ophthalmologist if a corneal foreign body cannot be removed or if there is suspicion of corneal infection.

Fraenkel A et al. Managing corneal foreign bodies in office-based general practice. *Aust Fam Physician*. 2017;46:89. [PMID: 28260265]

## 2. Intraocular Foreign Body

Intraocular foreign body requires emergency treatment by an ophthalmologist. Patients giving a history of “something hitting the eye”—particularly while hammering on metal or using grinding equipment—must be assessed for this possibility, especially when no corneal foreign body is seen, a corneal or scleral wound is apparent, or there is marked visual loss or media opacity. Such patients must be treated as for open globe injury and referred without delay. Intraocular foreign bodies significantly increase the risk of intraocular infection.

### ► When to Refer

Patients with suspected intraocular foreign body must be referred emergently to an ophthalmologist.

Loporchio D et al. Intraocular foreign bodies: a review. *Surv Ophthalmol*. 2016;61:582. [PMID: 26994871]

## 3. Corneal Abrasions

A patient with a corneal abrasion complains of severe pain and photophobia. There is often a history of trauma to the eye, commonly involving a fingernail, piece of paper, or contact lens. Visual acuity is recorded, and the cornea and conjunctiva are examined with a light and loupe to rule out a foreign body. If an abrasion is suspected but cannot be seen, sterile fluorescein is instilled into the conjunctival sac: the area of corneal abrasion will stain because fluorescein stains areas that are devoid of epithelium.

Treatment includes bacitracin-polymyxin ophthalmic ointment or drops, or a fluoroquinolone topical antibiotic in contact lens wearers, as prophylaxis against infection. A mydriatic (cyclopentolate 1%) and either topical or oral nonsteroidal anti-inflammatory agents can be used for pain control. Patching the eye is probably not helpful for small abrasions. Corneal abrasions heal more slowly in persons who smoke cigarettes. Recurrent corneal erosion may follow corneal abrasions.

Although treatment of pain from a corneal abrasion with topical tetracaine for 24 hours has been reported to be safe and effective, there is a risk of severe corneal disease from misuse of topical anesthetics, so it is not recommended.

Wakai A et al. Topical non-steroidal anti-inflammatory drugs for analgesia in traumatic corneal abrasions. *Cochrane Database Syst Rev*. 2017;5:CD009781. [PMID: 28516471]

## 4. Contusions

Contusion injury of the eye (closed globe injury) and surrounding structures may cause ecchymosis (“black eye”), subconjunctival hemorrhage, edema of the cornea, hemorrhage into the anterior chamber (hyphema), rupture of the root of the iris (iridodialysis), paralysis of the pupillary sphincter, paralysis of the muscles of accommodation, cataract, dislocation of the lens, vitreous hemorrhage, retinal hemorrhage and edema (most common in the macular area), detachment of the retina, rupture of the choroid, fracture of the orbital floor (“blowout fracture”), or optic nerve injury. Many of these injuries are immediately obvious; others may not become apparent for days or weeks. The possibility of globe injury must always be considered in patients with facial injury, particularly if there is an orbital fracture. Patients with moderate to severe contusions should be seen by an ophthalmologist.

Any injury causing hyphema involves the danger of secondary hemorrhage, which may cause intractable glaucoma with permanent visual loss. The patient should be advised to rest until complete resolution has occurred. Frequent ophthalmologic assessment is essential. Aspirin and any drugs inhibiting coagulation increase the risk of secondary hemorrhage and are to be avoided. Sickle cell anemia or trait adversely affects outcome.

## ► When to Refer

Patients with moderate or severe ocular contusion should be referred to an ophthalmologist, emergently if there is hyphema.

### 5. Lacerations

#### A. Lids

If the lid margin is lacerated, the patient should be referred for specialized care, since permanent notching may result. Lacerations of the lower eyelid near the inner canthus often sever the lower canaliculus, for which canalicular intubation is likely to be required. Lid lacerations not involving the margin may be sutured like any skin laceration.

Ko AC et al. Eyelid and periorbital soft tissue trauma. Facial Plast Surg Clin North Am. 2017;25:605. [PMID: 28941512]

#### B. Conjunctiva

In lacerations of the conjunctiva, sutures are not necessary. To prevent infection, topical sulfonamide or other antibiotic is used until the laceration is healed.

#### C. Cornea or Sclera

Patients with suspected corneal or scleral laceration or rupture (open globe injury) must be seen emergently by an ophthalmologist. Manipulation is kept to a minimum, since pressure may result in extrusion of intraocular contents. The eye is bandaged lightly and covered with a shield that rests on the orbital bones above and below. The patient should be instructed not to squeeze the eye shut and to remain still. If there may be a metallic intraocular foreign body, a radiograph or CT scan is obtained to identify and localize it. *MRI is contraindicated because of the risk of movement of any metallic foreign body but may be useful for non-metallic foreign body.* Endophthalmitis occurs in over 5% of open globe injuries.

## ► When to Refer

Patients with suspected open globe injury must be referred emergently to an ophthalmologist.

### ULTRAVIOLET KERATITIS (Actinic Keratitis)

Ultraviolet burns of the cornea are usually caused by use of a sunlamp without eye protection, exposure to a welding arc, or exposure to the sun when skiing (“snow blindness”). There are no immediate symptoms, but about 6–12 hours later the patient complains of agonizing eye pain and severe photophobia. Slit-lamp examination shows diffuse punctate fluorescein staining of both corneas.

Treatment consists of patching and instillation of 1–2 drops of 1% cyclopentolate (to relieve the discomfort of ciliary spasm). Patients typically recover within 24–48 hours

without complications. Local anesthetics should not be prescribed because they delay corneal epithelial healing.

### CHEMICAL CONJUNCTIVITIS & KERATITIS

Chemical burns are treated by copious irrigation of the eyes as soon as possible after exposure, with tap water, saline solution, or buffering solution if available. Neutralization of an acid with an alkali or vice versa may cause further damage. Alkali injuries are more serious and require prolonged irrigation, since alkalies are not precipitated by the proteins of the eye as are acids. It is important to remove any retained particulate matter, such as is typically present in injuries involving cement and building plaster. This often requires eversion of the upper lid. The pupil should be dilated with 1% cyclopentolate, 1 drop twice a day, to relieve discomfort, and prophylactic topical antibiotics should be started (Table 7–2). In moderate to severe injuries, intensive topical corticosteroids and topical and systemic vitamin C are also necessary. Complications include mucus deficiency, scarring of the cornea and conjunctiva, symblepharon (adhesions between the tarsal and bulbar conjunctiva), tear duct obstruction, and secondary infection. It is difficult to assess severity of chemical burns without slit-lamp examination.

Sharma N et al. Treatment of acute ocular chemical burns. Surv Ophthalmol. 2018;63:214. [PMID: 28935121]

### PRECAUTIONS IN MANAGEMENT OF OCULAR DISORDERS

#### 1. Use of Local Anesthetics

Unsupervised self-administration of local anesthetics is dangerous because they are toxic to the corneal epithelium, delay healing, and the patient may further injure an anesthetized eye without knowing it.

Lee MD, Driver TH, Seitzman GD. Cornea specialists do not recommend routine usage of topical anesthetics for corneal abrasions. Ann Emerg Med. 2019;74:463. [PMID: 31445551]

#### 2. Pupillary Dilation

Dilating the pupil can very occasionally precipitate acute glaucoma if the patient has a narrow anterior chamber angle and should be undertaken with caution if the anterior chamber is obviously shallow (readily determined by oblique illumination of the anterior segment of the eye). A short-acting mydriatic, such as tropicamide, should be used and the patient warned to report immediately if ocular discomfort or redness develops. Angle closure is more likely to occur if pilocarpine is used to overcome pupillary dilation than if the pupil is allowed to constrict naturally.

Ah-Kee EY et al. A review of drug-induced acute angle closure glaucoma for non-ophthalmologists. Qatar Med J. 2015; 2015:6. [PMID: 26535174]

### 3. Corticosteroid Therapy

Comanagement with eye specialists is strongly recommended to monitor for ocular complications of corticosteroid therapy. Long-term use of local corticosteroids presents several hazards: ocular hypertension leading to open-angle glaucoma; cataract formation; and exacerbation of ocular infections, such as herpes simplex (dendritic) and fungal keratitis. Furthermore, perforation of the cornea may occur when corticosteroids are used indiscriminately for infectious keratitis. The potential for causing or exacerbating systemic hypertension, diabetes mellitus, gastritis, osteoporosis, or glaucoma must always be borne in mind when systemic corticosteroids are prescribed for such conditions as uveitis or giant cell arteritis.

### 4. Contaminated Eye Medications

Ophthalmic solutions are prepared with the same degree of care as fluids intended for intravenous administration, but once bottles are opened there is always a risk of contamination, particularly with solutions of tetracaine, proparacaine, fluorescein, and any preservative-free preparations. Single-use fluorescein eyedrops or sterile fluorescein filter paper strips are recommended for use in place of multiple-use fluorescein solutions.

Whether in plastic or glass containers, eye solutions should not remain in use for long periods after the bottle is opened. Four weeks after opening is the usual maximum time for use of a solution containing preservatives before discarding. Preservative-free preparations should be kept refrigerated and usually discarded within 1 week after opening. Single-use products should not be reused.

If the eye has been injured by accident or by surgical trauma, it is of the greatest importance to use freshly opened bottles of sterile medications or single-use products.

### 5. Toxic & Hypersensitivity Reactions to Topical Therapy

In patients receiving long-term topical therapy, local toxic or hypersensitivity reactions to the active agent or preservatives may develop (Figure 7–4), especially if there is inadequate tear secretion. Preservatives in contact lens cleaning solutions may produce similar problems. Burning and soreness are exacerbated by drop instillation or contact lens insertion; occasionally, fibrosis and scarring of the conjunctiva and cornea may occur. Preservative-free topical medications and contact lens solutions are available.



**▲ Figure 7–4.** Periorcular contact dermatitis due to eye drop preservative.

An antibiotic instilled into the eye can sensitize the patient to that drug and cause an allergic reaction upon subsequent systemic administration. Potentially fatal anaphylaxis is known to occur in up to 0.3% of patients after intravenous fluorescein for fluorescein angiography. Anaphylaxis also has been reported after topical fluorescein.

### 6. Systemic Effects of Ocular Drugs

The systemic absorption of certain topical drugs (through the conjunctival vessels and lacrimal drainage system) must be considered when there is a systemic medical contraindication to the use of the drug. Ophthalmic solutions of the nonselective beta-blockers, eg, timolol, may worsen bradycardia, heart failure, or asthma. Phenylephrine eye drops may precipitate hypertensive crises and angina. Adverse interactions between systemically administered and ocular drugs should also be considered. Using only 1 or 2 drops at a time and a few minutes of nasolacrimal occlusion or eyelid closure ensures maximum ocular efficacy and decreases systemic side effects of topical agents.

### ADVERSE OCULAR EFFECTS OF SYSTEMIC DRUGS

Systemically administered drugs produce a wide variety of adverse effects on the visual system. Table 7–3 lists the major examples. The likelihood of most complications is rare, but if visual changes develop while the patient is being treated with these medications, the patient should be referred to an eye care professional for an eye examination. Repeated screening for toxic retinopathy is recommended in patients receiving long-term chloroquine or hydroxychloroquine therapy. If no baseline abnormalities are present, screening should be repeated annually beginning after 5 years. More frequent screening is necessary in patients treated with doses greater than 5.0 mg/kg real weight/day of hydroxychloroquine or greater than 2.3 mg/kg/day of chloroquine, or in patients with kidney disease or in those taking tamoxifen.

Pentosan polysulfate (used to treat interstitial cystitis) has been associated with progressive vision loss due to maculopathy. Patients who receive pentosan polysulfate should be monitored with annual eye examinations, including color fundus photography, fundus autofluorescence, and optical coherence tomography images; progressive vision loss can occur after maculopathy develops.

Patients receiving long-term systemic corticosteroids are at increased risk for several ocular complications, including glaucoma, cataract, and central serous retinopathy. They should be referred to an eye care professional for an eye examination at baseline before starting corticosteroids and at any time if reduced or blurry vision develops.

An ophthalmologist should be informed whether a patient is taking alpha-adrenoreceptor antagonists (such as tamsulosin) before cataract surgery because these medications increase the risk of intraoperative floppy iris syndrome, which can make cataract surgery more challenging.

**Table 7–3.** Adverse ophthalmic effects of systemic drugs (selected list).

| Drug   | Possible Ophthalmic Side Effects   |
|--|--|
| <b>Ophthalmic drugs</b>  |  |
| Carbonic anhydrase inhibitors<br>(eg, acetazolamide, methazolamide)                | Nearsightedness, angle-closure glaucoma due to ciliary body swelling   |
| <b>Respiratory drugs</b>   |  |
| Anticholinergic bronchodilators<br>(eg, ipratropium)                               | Angle-closure glaucoma due to mydriasis, blurring of vision due to cycloplegia, dry eyes   |
| Sympathomimetic bronchodilators (eg, salbutamol) and decongestants (eg, ephedrine) | Angle-closure glaucoma due to mydriasis  |
| <b>Cardiovascular system drugs</b>   |  |
| Amiodarone   | Corneal deposits (vortex keratopathy), optic neuropathy, thyroid eye disease   |
| Amlodipine   | Chemosis (conjunctival edema)  |
| Anticoagulants   | Conjunctival, retinal, and vitreous hemorrhage   |
| Chlorthalidone   | Angle-closure glaucoma due to ciliary body swelling  |
| Digitalis  | Disturbance of color vision, photopsia   |
| Furosemide   | Angle-closure glaucoma due to ciliary body swelling  |
| Phosphodiesterase type 5 inhibitors<br>(eg, sildenafil, tadalafil, vardenafil)     | Disturbance of color vision, ischemic optic neuropathy   |
| Statins  | Extraocular muscle palsy (myasthenic syndrome)   |
| Thiazides (eg, indapamide)   | Angle-closure glaucoma due to ciliary body swelling, nearsightedness, xanthopsia (yellow vision)   |
| <b>Gastrointestinal drugs</b>  |  |
| Anticholinergic agents   | Angle-closure glaucoma due to mydriasis, blurring of vision due to cycloplegia, dry eyes   |
| <b>Urinary tract drugs</b>   |  |
| Alpha-adrenoceptor-antagonists (eg, doxazosin, prazosin, tamsulosin, terazosin)    | Floppy iris syndrome during intraocular surgery  |
| Pentosan polysulfate sodium  | Maculopathy  |
| Anticholinergic agents   | Angle-closure glaucoma due to mydriasis, blurring of vision due to cycloplegia, dry eyes   |
| Finasteride  | Floppy iris syndrome during intraocular surgery  |
| <b>Central nervous system drugs</b>  |  |
| Amphetamines   | Widening of palpebral fissure, blurring of vision due to mydriasis, elevated intraocular pressure  |
| Anticholinergic agents including preoperative medications                          | Angle-closure glaucoma due to mydriasis, blurring of vision due to cycloplegia, dry eyes   |
| Aripiprazole   | Nearsightedness  |
| Diazepam   | Nystagmus  |
| Haloperidol  | Capsular cataract  |
| Lithium carbonate  | Proptosis, oculogyric crisis, nystagmus  |
| Monoamine oxidase inhibitors   | Nystagmus  |
| Morphine   | Miosis   |
| Neostigmine  | Nystagmus, miosis  |
| Olanzapine   | Angle-closure glaucoma due to mydriasis  |
| Phenothiazines (eg, chlorpromazine)  | Pigmentary deposits in conjunctiva, cornea, lens, and retina, oculogyric crisis<br>Chlorpromazine causes floppy iris syndrome during intraocular surgery |
| Phenytoin  | Nystagmus  |
| Quetiapine   | Floppy iris syndrome during intraocular surgery  |
| Retigabine   | Ocular pigmentation and retinopathy  |

(continued)

**Table 7–3.** Adverse ophthalmic effects of systemic drugs (selected list). (continued)

| Drug   | Possible Ophthalmic Side Effects   |
|--|--|
| Risperidone, paliperidone  | Floppy iris syndrome during intraocular surgery  |
| Selective serotonin reuptake inhibitors (SSRIs) (eg, paroxetine, sertraline) | Angle-closure glaucoma, optic neuropathy   |
| Serotonin and noradrenaline reuptake inhibitors (eg, venlafaxine)            | Angle-closure glaucoma   |
| Thioridazine   | Corneal and lens deposits, retinopathy, oculogyric crisis  |
| Topiramate   | Angle-closure glaucoma due to ciliary body swelling, nearsightedness, macular folds, anterior uveitis                                  |
| Tricyclic agents (eg, imipramine)  | Angle-closure glaucoma due to mydriasis, blurring of vision due to cycloplegia   |
| Triptans (sumatriptan, zolmitriptan)   | Angle-closure glaucoma due to ciliary body swelling, nearsightedness   |
| Vigabatrin   | Visual field constriction  |
| Zonisamide   | Angle-closure glaucoma due to ciliary body swelling, nearsightedness   |
| <b>Obstetric drugs</b>   |  |
| Sympathomimetic tocolytics   | Angle-closure glaucoma due to mydriasis  |
| <b>Hormonal agents</b>   |  |
| Aromatase inhibitors (eg, anastrozole)                                       | Dry eye, vitreo-retinal traction, retinal hemorrhages  |
| Cabergoline  | Angle-closure glaucoma   |
| Female sex hormones  | Retinal artery occlusion, retinal vein occlusion, papilledema, cranial nerve palsies, ischemic optic neuropathy                        |
| Tamoxifen  | Crystalline retinal and corneal deposits, altered color perception, cataract, optic neuropathy   |
| <b>Immunomodulators</b>  |  |
| Alpha-interferon   | Retinopathy, keratoconjunctivitis, dry eyes, optic neuropathy  |
| Corticosteroids  | Cataract (posterior subcapsular); susceptibility to viral (herpes simplex), bacterial, and fungal infections; steroid-induced glaucoma |
| Cyclosporine   | Posterior reversible leukoencephalopathy   |
| Fingolimod   | Macular edema  |
| Tacrolimus   | Optic neuropathy, posterior reversible leukoencephalopathy   |
| <b>Antibiotics</b>   |  |
| Chloramphenicol  | Optic neuropathy   |
| Clofazimine  | Crystalline deposits (conjunctiva, cornea, iris)   |
| Ethambutol   | Optic neuropathy   |
| Fluoroquinolones   | Diplopia, retinal detachment   |
| Isoniazid  | Optic neuropathy   |
| Linezolid  | Optic neuropathy   |
| Rifabutin  | Uveitis  |
| Streptomycin   | Optic neuropathy, epidermal necrolysis   |
| Sulfonamides   | Nearsightedness, angle-closure glaucoma due to ciliary body swelling   |
| Tetracycline, doxycycline, minocycline                                       | Papilledema  |
| <b>Antivirals</b>  |  |
| Cidofovir  | Uveitis  |
| <b>Antimalarial agents</b>   |  |
| Chloroquine, hydroxychloroquine  | Retinal degeneration principally involving the macula, keratopathy   |
| Quinine  | Retinal toxicity, pupillary abnormalities  |
| <b>Amebicides</b>  |  |
| Iodochlorhydroxyquin   | Optic neuropathy   |

(continued)

**Table 7–3.** Adverse ophthalmic effects of systemic drugs (selected list). (continued)

| Drug  | Possible Ophthalmic Side Effects  |
|---|---|
| <b>Chemotherapeutic agents</b>  |   |
| Bortezomib  | Chalazia  |
| Chlorambucil  | Optic neuropathy  |
| Cisplatin   | Optic neuropathy  |
| Docetaxel   | Lacrimal (canalicular) obstruction  |
| Fluorouracil  | Lacrimal (canalicular) obstruction  |
| MEK inhibitors: trametinib, selumetinib, cobimetinib, pimasertib                      | Multifocal serous retinal detachment, retinal vein occlusion, cystoid macular edema   |
| Vincristine   | Optic neuropathy  |
| <b>Chelating agents</b>   |   |
| Deferoxamine, deferasirox   | Retinopathy, optic neuropathy, lens opacity   |
| Penicillamine   | Ocular pemphigoid, optic neuropathy, extraocular muscle palsy (myasthenic syndrome)   |
| <b>Oral hypoglycemic agents</b>   |   |
| Chlorpropamide  | Refractive error, epidermal necrolysis, optic neuropathy  |
| Thiazolidinediones (glitazones)   | Increase in diabetic macular edema  |
| <b>Vitamins</b>   |   |
| Vitamin A   | Papilledema   |
| Vitamin D   | Band-shaped keratopathy   |
| <b>Rheumatologic agents</b>   |   |
| Chloroquine, hydroxychloroquine   | Retinal degeneration principally involving the macula, vortex keratopathy   |
| Gold salts  | Deposits in the cornea, conjunctiva, and lens   |
| Nonsteroidal anti-inflammatory drugs (NSAIDs) (eg, ibuprofen, naproxen, indomethacin) | Vortex keratopathy (ibuprofen, naproxen), corneal deposits (indomethacin), retinal degeneration principally involving the macula (indomethacin)       |
| Penicillamine   | Ocular pemphigoid, optic neuropathy, extraocular muscle palsy (myasthenic syndrome)   |
| Phenylbutazone  | Retinal hemorrhages   |
| Salicylates   | Subconjunctival and retinal hemorrhages, nystagmus  |
| <b>Dermatologic agents</b>  |   |
| Retinoids (eg, isotretinoin, tretinoin, acitretin, and etretinate)                    | Papilledema, blepharoconjunctivitis, corneal opacities, decreased contact lens tolerance, decreased dark adaptation, teratogenic ocular abnormalities |
| Dupilumab   | Conjunctivitis  |
| <b>Bisphosphonates</b>  |   |
| Alendronate, pamidronate  | Scleritis, episcleritis, uveitis  |

The chemotherapeutic MEK inhibitors are associated with ocular complications including serous retinal detachment, cystoid macular edema, and retinal vein occlusion. Patients receiving MEK inhibitors should have a complete eye examination at baseline before the initiation of these medications and should be referred for an eye examination if blurred or reduced vision develops while taking MEK inhibitors.

Alves C et al. Risk of ophthalmic adverse effects in patients treated with MEK inhibitors: a systematic review and meta-analysis. *Ophthalmic Res.* 2017;57:60. [PMID: 27404571]

Campbell RJ et al. Evolution in the risk of cataract surgical complications among patients exposed to tamsulosin: a population-based study. *Ophthalmology.* 2019;126:490. [PMID: 30648549]  
 Fraunfelder FW et al. Ocular & systemic side effects of drugs. In: Riordan-Eva P, Augsburger JJ. *Vaughan & Asbury's General Ophthalmology*, 19th ed. McGraw-Hill, 2018.

Pearce WA et al. Pigmentary maculopathy associated with chronic exposure to pentosan polysulfate sodium. *Ophthalmology.* 2018;125:1793. [PMID: 29801663]

Raizman MB et al. Drug-induced corneal epithelial changes. *Surv Ophthalmol.* 2017;62:286. [PMID: 27890620]

# Ear, Nose, & Throat Disorders

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# 8

## DISEASES OF THE EAR

### HEARING LOSS



#### ESSENTIALS OF DIAGNOSIS

- ▶ Two main types of hearing loss: conductive and sensorineural.
- ▶ Most commonly due to cerumen impaction, transient eustachian tube dysfunction from upper respiratory tract infection, or age-related hearing loss.

### Classification & Epidemiology

Table 8–1 categorizes hearing loss as normal, mild, moderate, severe, and profound and outlines the vocal equivalent as well as the decibel range.

#### A. Conductive Hearing Loss

Conductive hearing loss results from external or middle ear dysfunction. Four mechanisms each result in impairment of the passage of sound vibrations to the inner ear: (1) obstruction (eg, cerumen impaction), (2) mass loading (eg, middle ear effusion), (3) stiffness (eg, otosclerosis), and (4) discontinuity (eg, ossicular disruption). Conductive losses in adults are most commonly due to cerumen impaction or transient eustachian tube dysfunction from upper respiratory tract infection. Persistent conductive losses usually result from chronic ear infection, trauma, or otosclerosis. Conductive hearing loss is often correctable with medical or surgical therapy, or both.

#### B. Sensorineural Hearing Loss

Sensory and neural causes of hearing loss are difficult to differentiate due to testing methodology and thus are often referred to as “sensorineural.” Sensorineural hearing losses are common in adults.

Sensory hearing loss results from deterioration of the cochlea, usually due to loss of hair cells from the organ of Corti. The most common form is a gradually progressive, predominantly high-frequency loss with advancing age (presbycusis); other causes include excessive noise exposure, head trauma, and systemic diseases. Sensory hearing loss is usually not correctable with medical or surgical therapy but often may be prevented or stabilized. An exception is a sudden sensory hearing loss, which may respond to corticosteroids if delivered within several weeks of onset.

Neural hearing loss lesions involve the eighth cranial nerve, auditory nuclei, ascending tracts, or auditory cortex. Neural hearing loss is much less commonly recognized. Causes include acoustic neuroma, multiple sclerosis, and auditory neuropathy.

Michels TC et al. Hearing loss in adults: differential diagnosis and treatment. Am Fam Physician. 2019;100:98. [PMID: 31305044]  
US Preventive Services Task Force, Krist AH et al. Screening for hearing loss in older adults: US Preventive Services Task Force recommendation statement. JAMA. 2021;325:1196. [PMID: 33755083]

### Evaluation of Hearing (Audiology)

In a quiet room, the hearing level may be estimated by having the patient repeat aloud words presented in a soft whisper, a normal spoken voice, or a shout. A 512-Hz tuning fork is useful in differentiating conductive from sensorineural losses. In the **Weber test**, the tuning fork is placed on the forehead or front teeth. In conductive losses, the sound appears louder in the poorer-hearing ear, whereas in sensorineural losses it radiates to the better side. In the **Rinne test**, the tuning fork is placed alternately on the mastoid bone and in front of the ear canal. In conductive losses greater than 25 dB, bone conduction exceeds air conduction; in sensorineural losses, the opposite is true.

Formal audiometric studies are performed in a sound-proofed room. Pure-tone thresholds in decibels (dB) are obtained over the range of 250–8000 Hz for both air and bone conduction. Conductive losses create a gap between the air and bone thresholds, whereas in sensorineural losses, both air and bone thresholds are equally diminished. Speech discrimination measures the clarity

**Table 8–1.** Hearing loss classification.

| Classification | Vocal Equivalent    | Decibel (dB) Range |
|----------------|---------------------|--------------------|
| Normal         | Soft whisper        | 0–20 dB            |
| Mild           | Soft spoken voice   | 20–40 dB           |
| Moderate       | Normal spoken voice | 40–60 dB           |
| Severe         | Loud spoken voice   | 60–80 dB           |
| Profound       | Shout               | > 80 dB            |

of hearing, reported as percentage correct (90–100% is normal). Auditory brainstem-evoked responses may determine whether the lesion is sensory (cochlea) or neural (central). However, MRI scanning is more sensitive and specific in detecting central lesions.

Every patient who complains of a hearing loss should be referred for audiology evaluation unless the cause is easily remediable (eg, cerumen impaction, otitis media). Immediate audiometric referral is indicated for patients with idiopathic sudden sensorineural hearing loss because it requires treatment (corticosteroids) within a limited several-week time period. Routine audiologic screening is recommended for adults with prior exposure to potentially injurious noise levels or in adults at age 65, and every few years thereafter.

Feltner C et al. Screening for hearing loss in older adults: updated evidence report and systematic review for the US Preventive Services Task Force. *JAMA*. 2021;325:1202. [PMID: 33755082]

## Hearing Amplification

Patients with hearing loss not correctable by medical therapy may benefit from hearing amplification. Contemporary hearing aids are comparatively free of distortion and have been miniaturized to the point where they often may be contained entirely within the ear canal or lie inconspicuously behind the ear.

For patients with conductive loss or unilateral profound sensorineural loss, bone-conducting hearing aids directly stimulate the ipsilateral cochlea (for conductive losses) or contralateral ear (profound unilateral sensorineural loss).

In most adults with severe to profound sensory hearing loss, the cochlear implant—an electronic device that is surgically implanted into the cochlea to stimulate the auditory nerve—offers socially beneficial auditory rehabilitation.

Johnson CE et al. Benefits from, satisfaction with, and self-efficacy for advanced digital hearing aids in users with mild sensorineural hearing loss. *Semin Hear*. 2018;39:158. [PMID: 29915453]

Jolink C et al. Hearing disabilities and the effectiveness of rehabilitation in different age groups. *Otol Neurotol*. 2020;41:e982. [PMID: 33169948]

Jorgensen LE et al. Conventional amplification for children and adults with severe-to-profound hearing loss. *Semin Hear*. 2018;39:364. [PMID: 30374208]

McRackan TR et al. Meta-analysis of quality-of-life improvement after cochlear implantation and associations with speech recognition abilities. *Laryngoscope*. 2018;128:982. [PMID: 28731538]

## DISEASES OF THE AURICLE

Disorders of the auricle include skin cancers due to sun exposure. Traumatic auricular hematoma must be drained to prevent significant cosmetic deformity (cauliflower ear) or canal blockage resulting from dissolution of supporting cartilage. Similarly, cellulitis of the auricle must be treated promptly to prevent perichondritis and resultant deformity. Relapsing polychondritis is characterized by recurrent, frequently bilateral, painful episodes of auricular erythema and edema and sometimes progressive involvement of the cartilaginous tracheobronchial tree. Treatment with corticosteroids may help forestall cartilage dissolution. Polychondritis and perichondritis may be differentiated from cellulitis by sparing of involvement of the lobule, which does not contain cartilage.

Dalal PJ et al. Risk factors for auricular hematoma and recurrence after drainage. *Laryngoscope*. 2020;130:628. [PMID: 31621925]

## DISEASES OF THE EAR CANAL

### 1. Cerumen Impaction

Cerumen is a protective secretion produced by the outer portion of the ear canal. In most persons, the ear canal is self-cleansing. Recommended hygiene consists of cleaning the external opening only with a washcloth over the index finger. Cerumen impaction is most often self-induced through ill-advised cleansing attempts by entering the canal itself. It may be relieved by the patient using detergent ear drops (eg, 3% hydrogen peroxide; 6.5% carbamide peroxide) and irrigation, or by the clinician using mechanical removal, suction, or irrigation. Irrigation is performed with water at body temperature to avoid a vestibular caloric response. The stream should be directed at the posterior ear canal wall adjacent to the cerumen plug. Irrigation should be performed only when the tympanic membrane is known to be intact.

Use of jet irrigators (eg, WaterPik) should be avoided since they may result in tympanic membrane perforations. Following irrigation, the ear canal should be thoroughly dried (eg, by the patient using a hair blow-dryer on low-power setting or by the clinician instilling isopropyl alcohol) to reduce the likelihood of external otitis. Specialty referral is indicated if impaction is frequently recurrent, if it has not responded to routine measures, or if there is tympanic membrane perforation or chronic otitis media.

Horton GA et al. Cerumen management: an updated clinical review and evidence-based approach for primary care physicians. *J Prim Care Community Health*. 2020;11:2150132720904181. [PMID: 31994443]

### 2. Foreign Bodies

Foreign bodies in the ear canal are more frequent in children than in adults. Firm materials may be removed with a loop or a hook, taking care not to displace the object medially toward the tympanic membrane; microscopic guidance

is helpful. Aqueous irrigation should not be performed for organic foreign bodies (eg, beans, insects), because water may cause them to swell. Living insects are best immobilized before removal by filling the ear canal with lidocaine.

Kim KH et al. Clinical characteristics of external auditory canal foreign bodies in children and adolescents. *Ear Nose Throat J*. 2020;99:648. [PMID: 31814447]

### 3. External Otitis



#### ESSENTIALS OF DIAGNOSIS

- ▶ Painful erythema and edema of the ear canal skin.
- ▶ Purulent exudate.
- ▶ In diabetic or immunocompromised patients, osteomyelitis of the skull base ("malignant external otitis") may occur.

#### ► General Considerations

External otitis presents with otalgia, frequently accompanied by pruritus and purulent discharge. There is often a history of recent water exposure (ie, swimmer's ear) or mechanical trauma (eg, scratching, cotton applicators). External otitis is usually caused by gram-negative rods (eg, *Pseudomonas*, *Proteus*) or fungi (eg, *Aspergillus*), which grow in the presence of excessive moisture. In diabetic or immunocompromised patients, persistent external otitis may evolve into osteomyelitis of the skull base (so-called malignant external otitis). Usually caused by *Pseudomonas aeruginosa*, osteomyelitis begins in the floor of the ear canal and may extend into the middle fossa floor, the clivus, and even the contralateral skull base.

#### ► Clinical Findings

Examination reveals erythema and edema of the ear canal skin, often with a purulent exudate (Figure 8–1). Manipulation of the auricle elicits pain. Because the lateral surface of the tympanic membrane is ear canal skin, it is often erythematous. However, in contrast to acute otitis media, it moves normally with pneumatic otoscopy. When the canal skin is very edematous, it may be impossible to visualize the tympanic membrane. Malignant external otitis typically presents with persistent foul aural discharge, granulations in the ear canal, deep otalgia, and in advanced cases, progressive palsies of cranial nerves VI, VII, IX, X, XI, or XII. Diagnosis is confirmed by the demonstration of osseous erosion on CT scanning.

#### ► Treatment

Treatment of external otitis involves protection of the ear from additional moisture and avoidance of further mechanical injury by scratching. In cases of moisture in the ear (eg, swimmer's ear), acidification with a drying agent (ie, a 50/50 mixture of isopropyl alcohol/white vinegar) is



**▲ Figure 8–1.** Malignant external otitis in a 40-year-old woman with diabetes mellitus, with typical swelling and honey-colored crusting of the pinna. Both the external auditory canal and temporal bone were involved in the pseudomonal infection. (Used, with permission, from E.J. Mayeaux Jr, MD, in Usatine RP, Smith MA, Mayeaux EJ Jr, Chumley H. *The Color Atlas of Family Medicine*, 2nd ed. McGraw-Hill, 2013.)

often helpful. When infected, an otic antibiotic solution or suspension of an aminoglycoside (eg, neomycin/polymerin B) or fluoroquinolone (eg, ciprofloxacin), with or without a corticosteroid (eg, hydrocortisone), is usually effective. Purulent debris filling the ear canal should be gently removed to permit entry of the topical medication. Drops should be used abundantly (five or more drops three or four times a day) to penetrate the depths of the canal. When substantial edema of the canal wall prevents entry of drops into the ear canal, a wick is placed to facilitate their entry. In recalcitrant cases—particularly when cellulitis of the periauricular tissue has developed—oral fluoroquinolones (eg, ciprofloxacin, 500 mg twice daily for 1 week) are used because of their effectiveness against *Pseudomonas*. Any case of persistent otitis externa in an immunocompromised or diabetic individual must be referred for specialty evaluation.

Treatment of "malignant external otitis" requires prolonged antipseudomonal antibiotic administration, often for several months. Although intravenous therapy is often required initially (eg, ciprofloxacin 200–400 mg every 12 hours), selected patients may be graduated to oral ciprofloxacin (500–1000 mg twice daily). To avoid relapse, antibiotic therapy should be continued, even in the asymptomatic patient, until gallium scanning indicates marked reduction or resolution of the inflammation.

Surgical debridement of infected bone is reserved for cases of deterioration despite medical therapy.

Mildenhall N et al. Clinician adherence to the clinical practice guideline: acute otitis externa. *Laryngoscope*. 2020;130:1565. [PMID: 31730729]

Peled C et al. Necrotizing otitis externa-analysis of 83 cases: clinical findings and course of disease. *Otol Neurotol*. 2019;40:56. [PMID: 30239427]

Wang X et al. Use of systemic antibiotics for acute otitis externa: impact of a clinical practice guideline. *Otol Neurotol*. 2018; 39:1088. [PMID: 30124617]

#### 4. Pruritus

Pruritus of the external auditory canal, particularly at the meatus, is common. While it may be associated with external otitis or with seborrheic dermatitis or psoriasis, most cases are self-induced from excoriation or overly zealous ear cleaning. To permit regeneration of the protective cerumen blanket, patients should be instructed to avoid use of soap and water or cotton swabs in the ear canal and avoid any scratching. Patients with excessively dry canal skin may benefit from application of mineral oil, which helps counteract dryness and repel moisture. When an inflammatory component is present, topical application of a corticosteroid (eg, 0.1% triamcinolone) may be beneficial.

#### 5. Exostoses & Osteomas

Bony overgrowths of the ear canal are a frequent incidental finding and occasionally have clinical significance. Clinically, they present as skin-covered bony mounds in the medial ear canal obscuring the tympanic membrane to a variable degree. Solitary osteomas are of no significance as long as they do not cause obstruction or infection. Multiple exostoses, which are generally acquired from repeated exposure to cold water (eg, “surfer’s ear”), may progress and require surgical removal.

Simas V et al. Lifetime prevalence of exostoses in New Zealand surfers. *J Prim Health Care*. 2019;11:47. [PMID: 31039989]

#### 6. Neoplasia

The most common neoplasm of the ear canal is squamous cell carcinoma. When an apparent otitis externa does not resolve on therapy, a malignancy should be suspected and biopsy performed. This disease carries a very high 5-year mortality rate because the tumor tends to invade the lymphatics of the cranial base and must be treated with wide surgical resection and radiation therapy. Adenomatous tumors, originating from the ceruminous glands, generally follow a more indolent course.

Komune N et al. Prognostic impact of tumor extension in patients with advanced temporal bone squamous cell carcinoma. *Front Oncol*. 2020;10:1229. [PMID: 32850367]

Piras G et al. Management of squamous cell carcinoma of the temporal bone: long-term results and factors influencing outcomes. *Eur Arch Otorhinolaryngol*. 2020. [Epub ahead of print] [PMID: 32979119]

Seligman KL et al. Temporal bone carcinoma: treatment patterns and survival. *Laryngoscope*. 2020;130:E11. [PMID: 30874314]

### DISEASES OF THE EUSTACHIAN TUBE

#### 1. Eustachian Tube Dysfunction



#### ESSENTIALS OF DIAGNOSIS

- ▶ Aural fullness.
- ▶ Fluctuating hearing.
- ▶ Discomfort with barometric pressure change.
- ▶ At risk for serous otitis media.

The tube that connects the middle ear to the nasopharynx—the eustachian tube—provides ventilation and drainage for the middle ear cleft. It is normally closed, opening only during swallowing or yawning. When eustachian tube function is compromised, air trapped within the middle ear becomes absorbed and negative pressure results. The most common causes of eustachian tube dysfunction are diseases associated with edema of the tubal lining, such as viral upper respiratory tract infections and allergy. The patient usually reports a sense of fullness in the ear and mild to moderate impairment of hearing. When the tube is only partially blocked, swallowing or yawning may elicit a popping or crackling sound. Examination may reveal retraction of the tympanic membrane and decreased mobility on pneumatic otoscopy. Following a viral illness, this disorder is usually transient, lasting days to weeks. Treatment with systemic and intranasal decongestants (eg, pseudoephedrine, 60 mg orally every 4–6 hours; oxy-metazoline, 0.05% spray every 8–12 hours) combined with autoinflation by forced exhalation against closed nostrils may hasten relief. Autoinflation should not be recommended to patients with active intranasal infection, since this maneuver may precipitate middle ear infection. Allergic patients may also benefit from intranasal corticosteroids (eg, beclomethasone dipropionate, two sprays in each nostril twice daily for 2–6 weeks). Air travel, rapid altitude change, and underwater diving should be avoided until resolution.

Conversely, an overly patent eustachian tube (“patulous eustachian tube”) is a relatively uncommon, though quite distressing problem. Typical complaints include fullness in the ear and autophony, an exaggerated ability to hear oneself breathe and speak. A patulous eustachian tube may develop during rapid weight loss, or it may be idiopathic. In contrast to eustachian tube dysfunction, the aural pressure is often made worse by exertion and may diminish during an upper respiratory tract infection. Although physical examination is usually normal, respiratory excursions of the tympanic membrane may occasionally be detected during vigorous breathing. Treatment includes avoidance of decongestant products, insertion of a

ventilating tube to reduce the outward stretch of the eardrum during phonation, and rarely, surgery on the eustachian tube itself.

Huisman JML et al. Treatment of eustachian tube dysfunction with balloon dilation: a systematic review. *Laryngoscope*. 2018;128:237. [PMID: 28799657]

Ikeda R et al. Systematic review of surgical outcomes following repair of patent Eustachian tube. *Otol Neurotol*. 2020;41:1012. [PMID: 33169947]

Meyer TA et al. A randomized controlled trial of balloon dilation as a treatment for persistent Eustachian tube dysfunction with 1-year follow-up. *Otol Neurotol*. 2018;39:894. [PMID: 29912819]

## 2. Serous Otitis Media



### ESSENTIALS OF DIAGNOSIS

- ▶ Eustachian tube remains blocked for a prolonged period.
- ▶ Resultant negative pressure results in transudation of fluid.

Prolonged eustachian tube dysfunction with resultant negative middle ear pressure may cause a transudation of fluid. In adults, serous otitis media usually occurs with an upper respiratory tract infection, with barotrauma, or with chronic allergic rhinitis, but when persistent and unilateral, nasopharyngeal carcinoma must be excluded. The tympanic membrane is dull and hypomobile, occasionally accompanied by air bubbles in the middle ear and conductive hearing loss. The treatment of serous otitis media is similar to that for eustachian tube dysfunction. When medication fails to bring relief after several months, a ventilating tube placed through the tympanic membrane may restore hearing and alleviate the sense of aural fullness. Endoscopically guided laser expansion of the nasopharyngeal orifice of the eustachian tube or balloon dilation may improve function in recalcitrant cases.

Vanneste P et al. Otitis media with effusion in children: pathophysiology, diagnosis, and treatment. A review. *J Otol*. 2019; 14:33. [PMID: 31223299]

## 3. Barotrauma

Persons with poor eustachian tube function (eg, congenital narrowness or acquired mucosal edema) may be unable to equalize the barometric stress exerted on the middle ear by air travel, rapid altitudinal change, or underwater diving. The problem is generally most acute during airplane descent, since the negative middle ear pressure tends to collapse and block the eustachian tube, causing pain. Several measures are useful to enhance eustachian tube function and avoid otic barotrauma. The patient should be advised to swallow, yawn, and autoinflate frequently during descent. Oral decongestants (eg, pseudoephedrine, 60–120 mg) should be taken several hours before

anticipated arrival time so that they will be maximally effective during descent. Topical decongestants such as 1% phenylephrine nasal spray should be administered 1 hour before arrival.

For acute negative middle ear pressure that persists on the ground, treatment includes decongestants and attempts at autoinflation. Myringotomy (creation of a small eardrum perforation) provides immediate relief and is appropriate in the setting of severe otalgia and hearing loss. Repeated episodes of barotrauma in persons who must fly frequently may be alleviated by insertion of ventilating tubes.

Underwater diving may represent an even greater barometric stress to the ear than flying. Patients should be warned to avoid diving when they have an upper respiratory infection or episode of nasal allergy. During the descent phase of the dive, if inflation of the middle ear via the eustachian tube has not occurred, pain will develop within the first 15 feet; the dive must be aborted. In all cases, divers must descend slowly and equilibrate in stages to avoid the development of severely negative pressures in the tympanum that may result in hemorrhage (hemotympanum) or in perilymphatic fistula. In the latter, the oval or round window ruptures, resulting in sensory hearing loss and acute vertigo. During the ascent phase of a saturation dive, sensory hearing loss or vertigo may develop as the first (or only) symptom of decompression sickness. Immediate recompression will return intravascular gas bubbles to solution and restore the inner ear microcirculation.

Tympanic membrane perforation is an absolute contraindication to diving, as the patient will experience an unbalanced thermal stimulus to the semicircular canals and may experience vertigo, disorientation, and even emesis.

Rozycki SW et al. Inner ear barotrauma in divers: an evidence-based tool for evaluation and treatment. *Diving Hyperb Med*. 2018;48:186. [PMID: 30199891]

Ryan P et al. Prevention of otic barotrauma in aviation: a systematic review. *Otol Neurotol*. 2018;39:539. [PMID: 29595579]

## DISEASES OF THE MIDDLE EAR

### 1. Acute Otitis Media



### ESSENTIALS OF DIAGNOSIS

- ▶ Otalgia, often with an upper respiratory tract infection.
- ▶ Erythema and hypomobility of tympanic membrane.

### ► General Considerations

Acute otitis media is a bacterial infection of the mucosally lined air-containing spaces of the temporal bone. Purulent material forms not only within the middle ear cleft but also within the pneumatized mastoid air cells and petrous apex. Acute otitis media is usually precipitated by a viral upper

respiratory tract infection that causes eustachian tube obstruction. This results in accumulation of fluid and mucus, which becomes secondarily infected by bacteria. The most common pathogens are *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Streptococcus pyogenes*.

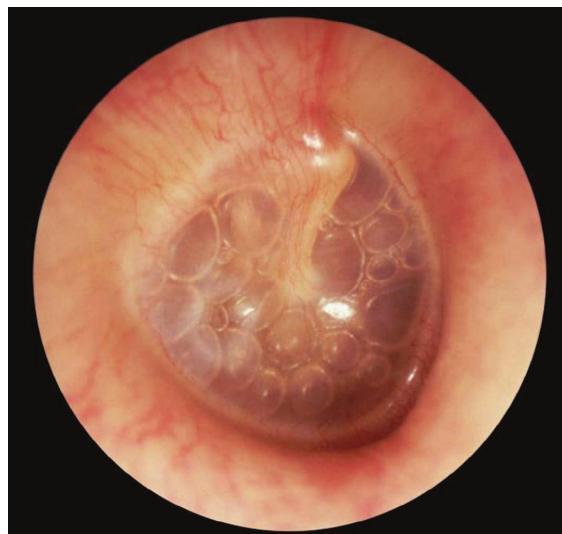
### ► Clinical Findings

Acute otitis media may occur at any age. Presenting symptoms and signs include otalgia, aural pressure, decreased hearing, and often fever. The typical physical findings are erythema and decreased mobility of the tympanic membrane (Figure 8–2). Occasionally, bullae will appear on the tympanic membrane.

Rarely, when middle ear empyema is severe, the tympanic membrane bulges outward. In such cases, tympanic membrane rupture is imminent. Rupture is accompanied by a sudden decrease in pain, followed by the onset of otorrhea. With appropriate therapy, spontaneous healing of the tympanic membrane occurs in most cases. When perforation persists, chronic otitis media may develop. Mastoid tenderness often accompanies acute otitis media and is due to the presence of pus within the mastoid air cells. This alone does not indicate suppurative (surgical) mastoiditis. Frank swelling over the mastoid bone or the association of cranial neuropathies or central findings indicates severe disease requiring urgent care.

### ► Treatment

The treatment of acute otitis media is specific antibiotic therapy, often combined with nasal decongestants. The first-choice antibiotic is amoxicillin 1 g orally every 8 hours for 5–7 days. Alternatives (useful in resistant cases) are



**▲ Figure 8–2.** Acute otitis media with effusion of right ear, with multiple air-fluid levels visible through a translucent, slightly retracted, nonerythematous tympanic membrane. (Used, with permission, from Frank Miller, MD, in Usatine RP, Smith MA, Mayeaux EJ Jr, Chumley H. *The Color Atlas of Family Medicine*, 2nd ed. McGraw-Hill, 2013.)

amoxicillin-clavulanate 875/125 mg or 2 g/125 mg ER every 12 hours for 5–10 days; or cefuroxime 500 mg or cefpodoxime 200 mg orally every 12 hours for 5–7 days.

Tympanocentesis for bacterial (aerobic and anaerobic) and fungal culture may be performed by any experienced physician. A 20-gauge spinal needle bent 90 degrees to the hub attached to a 3-mL syringe is inserted through the inferior portion of the tympanic membrane. Interposition of a pliable connecting tube between the needle and syringe permits an assistant to aspirate without inducing movement of the needle. Tympanocentesis is useful for otitis media in immunocompromised patients and when infection persists or recurs despite multiple courses of antibiotics.

Surgical drainage of the middle ear (myringotomy) is reserved for patients with severe otalgia or when complications of otitis (eg, mastoiditis, meningitis) have occurred.

Recurrent acute otitis media may be managed with long-term antibiotic prophylaxis. Single daily oral doses of sulfamethoxazole (500 mg) or amoxicillin (250 or 500 mg) are given over a period of 1–3 months. Failure of this regimen to control infection is an indication for insertion of ventilating tubes.

Hutz MJ et al. Neurological complications of acute and chronic otitis media. *Curr Neurol Neurosci Rep*. 2018;18:11. [PMID: 29445883]

Szmuilowicz J et al. Infections of the ear. *Emerg Med Clin North Am*. 2019;37:1. [PMID: 30454772]

## 2. Chronic Otitis Media



### ESSENTIALS OF DIAGNOSIS

- ▶ Chronic otorrhea with or without otalgia.
- ▶ Tympanic membrane perforation with conductive hearing loss.
- ▶ Often amenable to surgical correction.

### ► General Considerations

Chronic infection of the middle ear and mastoid generally develops as a consequence of recurrent acute otitis media, although it may follow other diseases and trauma. Perforation of the tympanic membrane is usually present. The bacteriology of chronic otitis media differs from that of acute otitis media. Common organisms include *P aeruginosa*, *Proteus* species, *Staphylococcus aureus*, and mixed anaerobic infections.

### ► Clinical Findings

The clinical hallmark of chronic otitis media is purulent aural discharge. Drainage may be continuous or intermittent, with increased severity during upper respiratory tract infection or following water exposure. Pain is uncommon except during acute exacerbations. Conductive hearing loss results from destruction of the tympanic membrane or ossicular chain, or both.

## ► Treatment

The medical treatment of chronic otitis media includes regular removal of infected debris, use of earplugs to protect against water exposure, and topical antibiotic drops (ofloxacin 0.3% or ciprofloxacin with dexamethasone) for exacerbations. Oral ciprofloxacin, active against *Pseudomonas*, 500 mg twice a day for 1–6 weeks, may help dry a chronically discharging ear.

Definitive management is surgical in most cases. Successful reconstruction of the tympanic membrane may be achieved in about 90% of cases, often with elimination of infection and significant improvement in hearing. When the mastoid air cells are involved by irreversible infection, they should be exenterated at the same time through a mastoideectomy.

Emmett SD et al. Chronic ear disease. *Med Clin North Am*. 2018;102:1063. [PMID: 30342609]

Head K et al. Antibiotics versus topical antiseptics for chronic suppurative otitis media. *Cochrane Database Syst Rev*. 2020;1:CD013056. [PMID: 31902139]

Master A et al. Management of chronic suppurative otitis media and otosclerosis in developing countries. *Otolaryngol Clin North Am*. 2018;51:593. [PMID: 29525390]

and destruction of the ossicular chain. Over time they may erode into the inner ear, involve the facial nerve, and on rare occasions spread intracranially. Otoscopic examination may reveal an epitympanic retraction pocket or a marginal tympanic membrane perforation that exudes keratin debris, or granulation tissue. The treatment of cholesteatoma is surgical marsupialization of the sac or its complete removal. This may require the creation of a “mastoid bowl” in which the ear canal and mastoid are joined into a large common cavity that must be periodically cleaned.

Basonbul RA et al. Systematic review of endoscopic ear surgery outcomes for pediatric cholesteatoma. *Otol Neurotol*. 2021;42:108. [PMID: 33165162]

Luu K et al. Updates in pediatric cholesteatoma: minimizing intervention while maximizing outcomes. *Otolaryngol Clin North Am*. 2019;52:813. [PMID: 31280890]

## B. Mastoiditis

Acute suppurative mastoiditis usually evolves following several weeks of inadequately treated acute otitis media. It is characterized by postauricular pain and erythema accompanied by a spiking fever. CT scan reveals coalescence of the mastoid air cells due to destruction of their bony septa. Initial treatment consists of intravenous antibiotics (eg, cefazolin 0.5–1.5 g every 6–8 hours) directed against the most common offending organisms (*S pneumoniae*, *H influenzae*, and *S pyogenes*), and myringotomy for culture and drainage. Failure of medical therapy indicates the need for surgical drainage (mastoideectomy).

## C. Petrous Apicitis

The medial portion of the petrous bone between the inner ear and clivus may become a site of persistent infection when the drainage of its pneumatic cell tracts becomes blocked. This may cause foul discharge, deep ear and retro-orbital pain, and sixth nerve palsy (Gradenigo syndrome); meningitis may be a complication. Treatment is with prolonged antibiotic therapy (based on culture results) and surgical drainage via petrous apicectomy.

Gadre AK et al. The changing face of petrous apicitis—a 40-year experience. *Laryngoscope*. 2018;128:195. [PMID: 28378370]

McLaren J et al. How well do we know Gradenigo? A comprehensive literature review and proposal for novel diagnostic categories of Gradenigo's syndrome. *Int J Pediatr Otorhinolaryngol*. 2020;132:109942. [PMID: 32065876]

Ren Y et al. Acute otitis media and associated complications in United States emergency departments. *Otol Neurotol*. 2018;39:1005. [PMID: 30113560]

## D. Facial Paralysis

Facial palsy may be associated with either acute or chronic otitis media. In the acute setting, it results from inflammation of the seventh nerve in its middle ear segment. Treatment consists of myringotomy for drainage and culture, followed by intravenous antibiotics (based on culture results). The use of corticosteroids is controversial. The prognosis is excellent, with complete recovery in most cases.



▲ **Figure 8-3.** Cholesteatoma. (Used, with permission, from Vladimir Zlinsky, MD, in Roy F. Sullivan, PhD: Audiology Forum: Video Otoscopy, www.RCSullivan.com; from Usatine RP, Smith MA, Mayeaux EJ Jr, Chumley H. *The Color Atlas of Family Medicine*, 2nd ed. McGraw-Hill, 2013.)

Facial palsy associated with chronic otitis media usually evolves slowly due to chronic pressure on the seventh nerve in the middle ear or mastoid by cholesteatoma. Treatment requires surgical correction of the underlying disease. The prognosis is less favorable than for facial palsy associated with acute otitis media.

Meerwein C et al. An intact bony tympanic facial canal does not protect from secondary facial paresis in adult acute otitis media. *J Laryngol Otol*. 2020;134:409. [PMID: 32425144]  
Owusu JA et al. Facial nerve paralysis. *Med Clin North Am*. 2018;102:1135. [PMID: 30342614]

### E. Sigmoid Sinus Thrombosis

Trapped infection within the mastoid air cells adjacent to the sigmoid sinus may cause septic thrombophlebitis. This is heralded by signs of systemic sepsis (spiking fevers, chills), at times accompanied by signs of increased intracranial pressure (headache, lethargy, nausea and vomiting, papilledema). Diagnosis can be made noninvasively by magnetic resonance venography (MRV). Primary treatment is with intravenous antibiotics (based on culture results). Surgical drainage with ligation of the internal jugular vein may be indicated when embolization is suspected.

Mather M et al. Is anticoagulation beneficial in acute mastoiditis complicated by sigmoid sinus thrombosis? *Laryngoscope*. 2018;128:2435. [PMID: 29521448]

### F. Central Nervous System Infection

Otogenic meningitis is by far the most common intracranial complication of ear infection. In the setting of acute suppurative otitis media, it arises from hematogenous spread of bacteria, most commonly *H influenzae* and *S pneumoniae*. In chronic otitis media, it results either from passage of infection along preformed pathways, such as the petrosquamous suture line, or from direct extension of disease through the dural plates of the petrous pyramid.

Epidural abscesses arise from direct extension of disease in the setting of chronic infection. They are usually asymptomatic but may present with deep local pain, headache, and low-grade fever. They are often discovered as an incidental finding at surgery. Brain abscess may arise in the temporal lobe or cerebellum as a result of septic thrombophlebitis adjacent to an epidural abscess. The predominant causative organisms are *S aureus*, *S pyogenes*, and *S pneumoniae*. Rupture into the subarachnoid space results in meningitis and often death. (See Chapter 30.)

Hutz MJ et al. Neurological complications of acute and chronic otitis media. *Curr Neurol Neurosci Rep*. 2018;18:11. [PMID: 29445883]

Mather M et al. Is anticoagulation beneficial in acute mastoiditis complicated by sigmoid sinus thrombosis? *Laryngoscope*. 2018;128:2435. [PMID: 29521448]

### 3. Otosclerosis

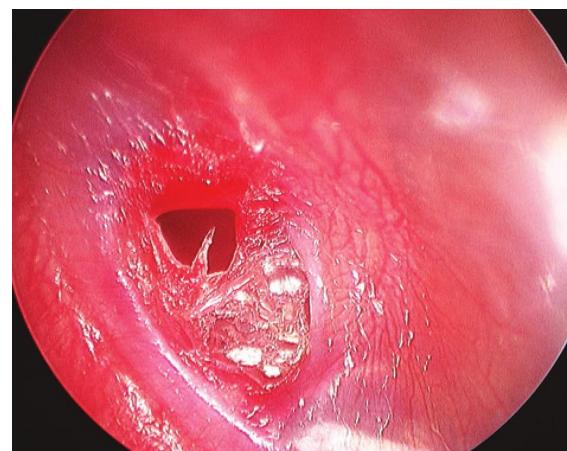
Otosclerosis is a progressive disease with a marked familial tendency that affects the bony otic capsule. Lesions involving the footplate of the stapes result in increased impedance to the passage of sound through the ossicular chain, producing conductive hearing loss. This may be treated either through the use of a hearing aid or surgical replacement of the stapes with a prosthesis (stapedectomy). When otosclerotic lesions involve the cochlea ("cochlear otosclerosis"), permanent sensory hearing loss occurs.

Gillard DM et al. Cost-effectiveness of stapedectomy vs hearing aids in the treatment of otosclerosis. *JAMA Otolaryngol Head Neck Surg*. 2020;146:42. [PMID: 31697352]  
Yeh CF et al. Predictors of hearing outcomes after stapes surgery in otosclerosis. *Acta Otolaryngol*. 2019;139:1058. [PMID: 31617779]

### 4. Trauma to the Middle Ear

Tympanic membrane perforation may result from impact injury or explosive acoustic trauma (Figure 8-4). Spontaneous healing occurs in most cases. Persistent perforation may result from secondary infection brought on by exposure to water. During the healing period, patients should be advised to wear earplugs while swimming or bathing. Hemorrhage behind an intact tympanic membrane (hemotympanum) may follow blunt trauma or extreme barotrauma. Spontaneous resolution over several weeks is the usual course. When a conductive hearing loss greater than 30 dB persists for more than 3 months following trauma, disruption of the ossicular chain should be suspected. Middle ear exploration with reconstruction of the ossicular chain, combined with repair of the tympanic membrane when required, will usually restore hearing.

Sagiv D et al. Traumatic perforation of the tympanic membrane: a review of 80 cases. *J Emerg Med*. 2018;54:186. [PMID: 29110975]



**▲ Figure 8-4.** Traumatic perforation of the left tympanic membrane. (Used, with permission, from William Clark, MD, in Usatine RP, Smith MA, Mayeaux EJ Jr, Chumley H. *The Color Atlas of Family Medicine*, 2nd ed. McGraw-Hill, 2013.)

## 5. Middle Ear Neoplasia

Primary middle ear tumors are rare. Glomus tumors arise either in the middle ear (glomus tympanicum) or in the jugular bulb with upward erosion into the hypotympanum (glomus jugulare). They present clinically with pulsatile tinnitus and hearing loss. A vascular mass may be visible behind an intact tympanic membrane. Large glomus jugulare tumors are often associated with multiple cranial neuropathies, especially involving nerves VII, IX, X, XI, and XII. Treatment usually requires surgery, radiotherapy, or both. Pulsatile tinnitus thus warrants magnetic resonance angiography (MRA) and MRV to rule out a vascular mass.

Appanan VR et al. Glomus tympanicum. *Malays Fam Physician*. 2018;13:45. [PMID: 29796211]

Marinelli JP et al. Adenomatous neuroendocrine tumors of the middle ear: a multi-institutional investigation of 32 cases and development of a staging system. *Otol Neurotol*. 2018;39:e712. [PMID: 30001283]

## EARACHE

Earache can be caused by a variety of otologic problems, but external otitis and acute otitis media are the most common. Differentiation of the two should be apparent by pneumatic otoscopy. Pain out of proportion to the physical findings may be due to herpes zoster oticus, especially when vesicles appear in the ear canal or concha. Persistent pain and discharge from the ear suggest osteomyelitis of the skull base or cancer, and patients with these complaints should be referred for specialty evaluation.

Nonotologic causes of otalgia are numerous. The sensory innervation of the ear is derived from the trigeminal, facial, glossopharyngeal, vagal, and upper cervical nerves. Because of this rich innervation, referred otalgia is quite frequent. Temporomandibular joint dysfunction is a common cause of referred ear pain. Pain is exacerbated by chewing or psychogenic grinding of the teeth (bruxism) and may be associated with dental malocclusion. Repeated episodes of severe lancinating otalgia may occur in glossopharyngeal neuralgia. Infections and neoplasia that involve the oropharynx, hypopharynx, and larynx frequently cause otalgia. Persistent earache demands specialty referral to exclude cancer of the upper aerodigestive tract.

Norris CD et al. Secondary otalgia: referred pain pathways and pathologies. *AJNR Am J Neuroradiol*. 2020;41:2188. [PMID: 33093134]

## DISEASES OF THE INNER EAR

### 1. Sensory Hearing Loss

Diseases of the cochlea result in sensory hearing loss, a condition that is usually irreversible. Most cochlear diseases result in bilateral symmetric hearing loss. The presence of unilateral or asymmetric sensorineural hearing loss suggests a lesion proximal to the cochlea. The primary goals in the management of sensory hearing loss are prevention of further losses and functional improvement with amplification and auditory rehabilitation.

### A. Presbycusis

Presbycusis, or age-related hearing loss, is the most frequent cause of sensory hearing loss and is progressive, predominantly high-frequency, and symmetrical. Various etiologic factors (eg, prior noise trauma, drug exposure, genetic predisposition) may contribute to presbycusis. Most patients notice a loss of speech discrimination that is especially pronounced in noisy environments. About 25% of people between the ages of 65 and 75 years and almost 50% of those over 75 experience hearing difficulties.

Tawfik KO et al. Advances in understanding of presbycusis. *J Neurosci Res*. 2020;98:1685. [PMID: 30950547]

Tu NC et al. Age-related hearing loss: unraveling the pieces. *Laryngoscope Investig Otolaryngol*. 2018;3:68. [PMID: 29721536]

Vaisbuch Y et al. Age-related hearing loss: innovations in hearing augmentation. *Otolaryngol Clin North Am*. 2018;51:705. [PMID: 29735277]

### B. Noise Trauma

Noise trauma is the second most common cause of sensory hearing loss. Sounds exceeding 85 dB are potentially injurious to the cochlea, especially with prolonged exposures. The loss typically begins in the high frequencies (especially 4000 Hz) and, with continuing exposure, progresses to involve the speech frequencies. Among the more common sources of injurious noise are industrial machinery, weapons, and excessively loud music. Personal music devices used at excessive loudness levels may also be injurious. Monitoring noise levels in the workplace by regulatory agencies has led to preventive programs that have reduced the frequency of occupational losses. Individuals of all ages, especially those with existing hearing losses, should wear earplugs when exposed to moderately loud noises and specially designed earmuffs when exposed to explosive noises.

Le Prell CG et al. Noise-induced hearing loss and its prevention: current issues in mammalian hearing. *Curr Opin Physiol*. 2020;18:32. [PMID: 32984667]

Neitzel RL et al. Risk of noise-induced hearing loss due to recreational sound: review and recommendations. *J Acoust Soc Am*. 2019;146:3911. [PMID: 31795675]

### C. Physical Trauma

Head trauma (eg, deployment of air bags during an automobile accident) has effects on the inner ear similar to those of severe acoustic trauma. Some degree of sensory hearing loss may occur following simple concussion and is frequent after skull fracture.

Mizutari K. Update on treatment options for blast-induced hearing loss. *Curr Opin Otolaryngol Head Neck Surg*. 2019;27:376. [PMID: 31348022]

### D. Ototoxicity

Ototoxic substances may affect both the auditory and vestibular systems. The most commonly used ototoxic medications are aminoglycosides; loop diuretics; and several

antineoplastic agents, notably cisplatin. These medications may cause irreversible hearing loss even when administered in therapeutic doses. When using these medications, it is important to identify high-risk patients, such as those with preexisting hearing losses or kidney disease. Patients simultaneously receiving multiple ototoxic agents are at particular risk owing to ototoxic synergy. Useful measures to reduce the risk of ototoxic injury include serial audiometry, monitoring of serum peak and trough levels, and substitution of equivalent nonototoxic drugs whenever possible.

It is possible for topical agents that enter the middle ear to be absorbed into the inner ear via the round window. When the tympanic membrane is perforated, use of potentially ototoxic ear drops (eg, neomycin, gentamicin) is best avoided.

Laurell G. Pharmacological intervention in the field of ototoxicity. *HNO*. 2019;67:434. [PMID: 30993373]

Rybak LP et al. Local drug delivery for prevention of hearing loss. *Front Cell Neurosci*. 2019;13:300. [PMID: 31338024]

## E. Sudden Sensory Hearing Loss

Idiopathic sudden loss of hearing in one ear may occur at any age, but typically it occurs in persons over age 20 years. The cause is unknown; however, one hypothesis is that it results from a viral infection or a sudden vascular occlusion of the internal auditory artery. Prognosis is mixed, with many patients suffering permanent deafness in the involved ear, while others have complete recovery. Prompt treatment with corticosteroids has been shown to improve the odds of recovery. A common regimen is oral prednisone, 1 mg/kg/day, followed by a tapering dose over a 10-day period. Intratympanic administration of corticosteroids alone or in association with oral corticosteroids has been associated with an equal or more favorable prognosis. Because treatment appears to be most effective as close to the onset of the loss as possible, and appears not to be effective after 6 weeks, a prompt audiogram should be obtained in all patients who present with sudden hearing loss without obvious middle ear pathology.

Ahmadzai N et al. A systematic review and network meta-analysis of existing pharmacologic therapies in patients with idiopathic sudden sensorineural hearing loss. *PLoS One*. 2019;14:e0221713. [PMID: 31498809]

Chandrasekhar SS et al. Clinical practice guideline: sudden hearing loss (Update). *Otolaryngol Head Neck Surg*. 2019;161:S1. [PMID: 31369359]

## F. Autoimmune Hearing Loss

Sensory hearing loss may be associated with a wide array of systemic autoimmune disorders, such as systemic lupus erythematosus, granulomatosis with polyangiitis, and Cogan syndrome (hearing loss, keratitis, aortitis). The loss is most often bilateral and progressive. The hearing level often fluctuates, with periods of deterioration alternating with partial or even complete remission. Usually, there is the gradual evolution of permanent hearing loss, which

often stabilizes with some remaining auditory function but occasionally proceeds to complete deafness. Vestibular dysfunction, particularly dysequilibrium and postural instability, may accompany the auditory symptoms.

In many cases, the autoimmune pattern of audiovestibular dysfunction presents in the absence of recognized systemic autoimmune disease. Responsiveness to oral corticosteroid treatment is helpful in making the diagnosis and constitutes first-line therapy. If stabilization of hearing becomes dependent on long-term corticosteroid use, steroid-sparing immunosuppressive regimens may become necessary.

Das S et al. Demystifying autoimmune inner ear disease. *Eur Arch Otorhinolaryngol*. 2019;276:3267. [PMID: 31605190]

Mancini P et al. Hearing loss in autoimmune disorders: prevalence and therapeutic options. *Autoimmun Rev*. 2018;17:644. [PMID: 29729446]

## 2. Tinnitus



- ▶ Perception of abnormal ear or head noises.
- ▶ Persistent tinnitus often, though not always, indicates the presence of sensory hearing loss.
- ▶ Intermittent periods of mild, high-pitched tinnitus lasting seconds to minutes are common in normal-hearing persons.

## ► General Considerations

Tinnitus is defined as the sensation of sound in the absence of an exogenous sound source. Tinnitus can accompany any form of hearing loss, and its presence provides no diagnostic value in determining the cause of a hearing loss. Approximately 15% of the general population experiences some type of tinnitus, with prevalence beyond 20% in aging populations.

## ► Clinical Findings

### A. Symptoms and Signs

Though tinnitus is commonly associated with hearing loss, tinnitus severity correlates poorly with the degree of hearing loss. About one in seven tinnitus sufferers experiences severe annoyance, and 4% are severely disabled. When severe and persistent, tinnitus may interfere with sleep and ability to concentrate, resulting in considerable psychological distress.

Pulsatile tinnitus—often described by the patient as listening to one's own heartbeat—should be distinguished from tonal tinnitus. Although often ascribed to conductive hearing loss, pulsatile tinnitus may be far more serious and may indicate a vascular abnormality, such as glomus tumor, venous sinus stenosis, carotid vaso-occlusive disease,

arteriovenous malformation, or aneurysm. In contrast, a staccato “clicking” tinnitus may result from middle ear muscle spasm, sometimes associated with palatal myoclonus. The patient typically perceives a rapid series of popping noises, lasting seconds to a few minutes, accompanied by a fluttering feeling in the ear.

### B. Diagnostic Testing

For routine, nonpulsatile tinnitus, audiometry should be ordered to rule out an associated hearing loss. For unilateral tinnitus, particularly associated with hearing loss in the absence of an obvious causative factor (ie, noise trauma), an MRI should be obtained to rule out a retrocochlear lesion, such as vestibular schwannoma. MRA and MRV and temporal bone computed tomography (CT) should be considered for patients who have pulsatile tinnitus to exclude a causative vascular lesion or sigmoid sinus abnormality.

### Treatment

The most important treatment of tinnitus is avoidance of exposure to excessive noise, ototoxic agents, and other factors that may cause cochlear damage. Masking the tinnitus with music or through amplification of normal sounds with a hearing aid may also bring some relief. Among the numerous drugs that have been tried, oral antidepressants (eg, nortriptyline at an initial dosage of 50 mg orally at bedtime) have proved to be the most effective. In addition to masking techniques, habituation techniques, such as tinnitus retraining therapy, may prove beneficial in those with refractory symptoms.

- Chari DA et al. Tinnitus. *Med Clin North Am.* 2018;102:1081. [PMID: 30342610]  
 Wu V et al. Approach to tinnitus management. *Can Fam Physician.* 2018;64:491. [PMID: 30002023]

### 3. Hyperacusis

Excessive sensitivity to sound may occur in normal-hearing individuals, either in association with ear disease, following noise trauma, in patients susceptible to migraines, or for psychological reasons. Patients with cochlear dysfunction commonly experience “recruitment,” an abnormal sensitivity to loud sounds despite a reduced sensitivity to softer ones. Fitting hearing aids and other amplification devices to patients with recruitment requires use of compression circuitry to avoid uncomfortable overamplification. For normal-hearing individuals with hyperacusis, use of an earplug in noisy environments may be beneficial, though attempts should be made at habituation.

- Aazh H et al. Insights from the third international conference on hyperacusis: causes, evaluation, diagnosis, and treatment. *Noise Health.* 2018;20:162. [PMID: 30136676]  
 Cederroth CR et al. Association between hyperacusis and tinnitus. *J Clin Med.* 2020;9:2412. [PMID: 32731492]

### 4. Vertigo

#### ESSENTIALS OF DIAGNOSIS

- Either a sensation of motion when there is no motion or an exaggerated sense of motion in response to movement.
- Duration of vertigo episodes and association with hearing loss are the keys to diagnosis.
- Must differentiate peripheral from central etiologies of vestibular dysfunction.
- **Peripheral:** Onset is sudden; often associated with tinnitus and hearing loss; horizontal nystagmus may be present.
- **Central:** Onset is gradual; no associated auditory symptoms.
- Evaluation includes audiogram and electronystagmography (ENG) or videonystagmography (VNG) and head MRI.

### General Considerations

Vertigo can be caused by either a peripheral or central etiology, or both (Table 8–2).

### Clinical Findings

#### A. Symptoms and Signs

Vertigo is the cardinal symptom of vestibular disease. Vertigo is typically experienced as a distinct “spinning” sensation or a sense of tumbling or of falling forward or backward. It should be distinguished from imbalance, light-headedness, and syncope, all of which are nonvestibular in origin (Table 8–3).

**1. Peripheral vestibular disease**—Peripheral vestibulopathy usually causes vertigo of sudden onset, may be so severe that the patient is unable to walk or stand, and is frequently accompanied by nausea and vomiting. Tinnitus and hearing loss may be associated and provide strong support for a peripheral (ie, otologic) origin.

Critical elements of the history include the duration of the discrete vertiginous episodes (seconds, minutes to hours, or days), and associated symptoms (hearing loss). Triggers should be sought, including diet (eg, high salt in the case of Ménière disease), stress, fatigue, and bright lights (eg, migraine-associated dizziness).

The physical examination of the patient with vertigo includes evaluation of the ears, observation of eye motion and nystagmus in response to head turning, cranial nerve examination, and Romberg testing. In acute peripheral lesions, nystagmus is usually horizontal with a rotatory component; the fast phase usually beats away from the diseased side. Visual fixation tends to inhibit nystagmus except in very acute peripheral lesions or with CNS disease. In benign paroxysmal positioning vertigo, Dix-Hallpike

**Table 8–2.** Causes of vertigo.

| Peripheral causes                           |
|---|
| Vestibular neuritis/labyrinthitis           |
| Ménière disease                             |
| Benign paroxysmal positioning vertigo       |
| Ethanol intoxication                        |
| Inner ear barotraumas                       |
| Semicircular canal dehiscence               |
| Central causes                              |
| Seizure                                     |
| Multiple sclerosis                          |
| Wernicke encephalopathy                     |
| Chiari malformation                         |
| Cerebellar ataxia syndromes                 |
| Mixed central and peripheral causes         |
| Migraine                                    |
| Stroke and vascular insufficiency           |
| Posterior inferior cerebellar artery stroke |
| Anterior inferior cerebellar artery stroke  |
| Vertebral artery insufficiency              |
| Vasculitides                                |
| Cogan syndrome                              |
| Susac syndrome                              |
| Granulomatosis with polyangiitis            |
| Behçet disease                              |
| Cerebellopontine angle tumors               |
| Vestibular schwannoma                       |
| Meningioma                                  |
| Infections                                  |
| Lyme disease                                |
| Syphilis                                    |
| Vascular compression                        |
| Hyperviscosity syndromes                    |
| Waldenström macroglobulinemia               |
| Endocrinopathies                            |
| Hypothyroidism                              |
| Pendred syndrome                            |

testing (quickly lowering the patient to the supine position with the head extending over the edge and placed 30 degrees lower than the body, turned either to the left or right) will elicit a delayed-onset (~10 sec) fatigable nystagmus. Nonfatigable nystagmus in this position indicates CNS disease.

Since visual fixation often suppresses observed nystagmus, many of these maneuvers are performed with Frenzel goggles, which prevent visual fixation, and often bring out subtle forms of nystagmus. The Fukuda test can

demonstrate vestibular asymmetry when the patient steps in place with eyes closed and consistently rotates in one direction.

**2. Central disease**—In contrast, vertigo arising from CNS disease (Table 8–2) tends to develop gradually and then becomes progressively more severe and debilitating. Nystagmus is not always present but can occur in any direction, may be dissociated in the two eyes, and is often nonfatigable, vertical rather than horizontal in orientation, without latency, and unsuppressed by visual fixation. ENG is useful in documenting these characteristics. Evaluation of central audiovestibular dysfunction requires MRI of the brain.

Episodic vertigo can occur in patients with diplopia from external ophthalmoplegia and is maximal when the patient looks in the direction where the separation of images is greatest. Cerebral lesions involving the temporal cortex may also produce vertigo; it is sometimes the initial symptom of a seizure. Finally, vertigo may be a feature of a number of systemic disorders and can occur as a side effect of certain anticonvulsant, antibiotic, hypnotic, analgesic, and tranquilizer medications or of alcohol.

Welgampola MS et al. Dizziness demystified. Pract Neurol. 2019;19:492. [PMID: 31326945]

## B. Laboratory Findings

Laboratory investigations, such as audiologic evaluation, caloric stimulation, ENG, VNG, vestibular-evoked myogenic potentials (VEMPs), and MRI, are indicated in patients with persistent vertigo or when CNS disease is suspected. These studies help distinguish between central

**Table 8–3.** Common vestibular disorders: differential diagnosis based on classic presentations.

| Duration of Typical Vertiginous Episodes | Auditory Symptoms Present  | Auditory Symptoms Absent  |
|--|--|---|
| Seconds                                  | Perilymphatic fistula  | Benign paroxysmal positioning vertigo (cupulolithiasis), vertebrobasilar insufficiency, migraine-associated vertigo |
| Hours                                    | Endolymphatic hydrops (Ménière syndrome, syphilis)                   | Migraine-associated vertigo   |
| Days                                     | Labyrinthitis, labyrinthine concussion, autoimmune inner ear disease | Vestibular neuronitis, migraine-associated vertigo  |
| Months                                   | Acoustic neuroma, ototoxicity  | Multiple sclerosis, cerebellar degeneration   |

and peripheral lesions and identify causes requiring specific therapy. ENG consists of objective recording of the nystagmus induced by head and body movements, gaze, and caloric stimulation. It is helpful in quantifying the degree of vestibular hypofunction.

Chan TLH et al. Vestibular lab testing: interpreting the results in the headache patient with dizziness. *Curr Neurol Neurosci Rep.* 2020;20:16. [PMID: 32430768]

Sorathia S et al. Dizziness and the otolaryngology point of view. *Med Clin North Am.* 2018;102:1001. [PMID: 30342604]

## ► Vertigo Syndromes Due to Peripheral Lesions

### A. Endolymphatic Hydrops (Ménière Syndrome)

The cause of Ménière syndrome is unknown. The classic syndrome consists of episodic vertigo, with discrete vertigo spells lasting 20 minutes to several hours in association with fluctuating low-frequency sensorineural hearing loss, tinnitus (usually low-tone and “blowing” in quality), and a sensation of unilateral aural pressure (Table 8–3). These symptoms in the absence of hearing fluctuations suggest migraine-associated dizziness. Symptoms wax and wane as the endolymphatic pressure rises and falls. Caloric testing commonly reveals loss or impairment of thermally induced nystagmus on the involved side. Primary treatment involves a low-salt diet and diuretics (eg, acetazolamide). For symptomatic relief of acute vertigo attacks, oral meclizine (25 mg) or diazepam (2–5 mg) can be used. In refractory cases, patients may undergo intratympanic corticosteroid injections, endolymphatic sac decompression, or vestibular ablation, either through transtympanic gentamicin, vestibular nerve section, or surgical labyrinthectomy.

Gibson WPR. Meniere's disease. *Adv Otorhinolaryngol.* 2019; 82:77. [PMID: 30947172]

### B. Labyrinthitis

Patients with labyrinthitis suffer from acute onset of continuous, usually severe vertigo lasting several days to a week, accompanied by hearing loss and tinnitus. During a recovery period that lasts for several weeks, the vertigo gradually improves. Hearing may return to normal or remain permanently impaired in the involved ear. The cause of labyrinthitis is unknown. Treatment consists of antibiotics, if the patient is febrile or has symptoms of a bacterial infection, and supportive care. Vestibular suppressants are useful during the acute phase of the attack (eg, diazepam or meclizine) but should be discontinued as soon as feasible to avoid long-term dysequilibrium from inadequate compensation.

Welgampola MS et al. Dizziness demystified. *Pract Neurol.* 2019;19:492. [PMID: 31326945]

### C. Benign Paroxysmal Positioning Vertigo

Patients suffering from recurrent spells of vertigo, lasting a few minutes per spell, associated with changes in head

position (often provoked by rolling over in bed), usually have benign paroxysmal positioning vertigo (BPPV). The term “positioning vertigo” is more accurate than “positional vertigo” because it is provoked by changes in head position rather than by the maintenance of a particular posture.

The typical symptoms of BPPV occur in clusters that persist for several days. There is a brief (10–15 sec) latency period following a head movement before symptoms develop, and the acute vertigo subsides within 10–60 seconds, though the patient may remain imbalanced for several hours. Constant repetition of the positional change leads to habituation. Since some CNS disorders can mimic BPPV (eg, vertebrobasilar insufficiency), recurrent cases warrant head MRI/MRA. In central lesions, there is no latent period, fatigability, or habituation of the symptoms and signs. Treatment of BPPV involves physical therapy protocols (eg, the Epley maneuver or Brandt-Daroff exercises), based on the theory that it results from cupulolithiasis (free-floating statoconia, also known as otoconia) within a semicircular canal.

Argaet EC et al. Benign positional vertigo, its diagnosis, treatment and mimics. *Clin Neurophysiol Pract.* 2019;4:97. [PMID: 31193795]

Instrum RS et al. Benign paroxysmal positional vertigo. *Adv Otorhinolaryngol.* 2019;82:67. [PMID: 30947198]

### D. Vestibular Neuritis

In vestibular neuritis, a paroxysmal, usually single attack of vertigo occurs without accompanying impairment of auditory function and will persist for several days to a week before gradually abating. During the acute phase, examination reveals nystagmus and absent responses to caloric stimulation on one or both sides. The cause of the disorder is unclear though presumed to be viral. Treatment consists of supportive care, including oral diazepam, 2–5 mg every 6–12 hours, or meclizine, 25–100 mg divided two to three times daily, during the acute phases of the vertigo only, followed by vestibular therapy if the patient does not completely compensate.

Bronstein AM et al. Long-term clinical outcome in vestibular neuritis. *Curr Opin Neurol.* 2019;32:174. [PMID: 30566414]

Lee JY et al. Clinical characteristics of acute vestibular neuritis according to involvement site. *Otol Neurotol.* 2020;41:143. [PMID: 31789808]

### E. Traumatic Vertigo

Labyrinthine concussion is the most common cause of vertigo following head injury. Symptoms generally diminish within several days but may linger for a month or more. Basilar skull fractures that traverse the inner ear usually result in severe vertigo lasting several days to a week and deafness in the involved ear. Chronic posttraumatic vertigo may result from cupulolithiasis. This occurs when traumatically detached statoconia (otoconia) settle on the ampulla of the posterior semicircular canal and cause an excessive degree of cupular deflection in response to head motion. Clinically, this presents as episodic positioning

vertigo. Treatment consists of supportive care and vestibular suppressant medication (diazepam or meclizine) during the acute phase of the attack, and vestibular therapy.

Marcus HJ et al. Vestibular dysfunction in acute traumatic brain injury. *J Neurol*. 2019;266:2430. [PMID: 31201499]

### F. Perilymphatic Fistula

Leakage of perilymphatic fluid from the inner ear into the tympanic cavity via the round or oval window is a rare cause of vertigo and sensory hearing loss. Most cases result from either physical injury (eg, blunt head trauma, hand slap to ear); extreme barotrauma during airflight, scuba diving, etc; or vigorous Valsalva maneuvers (eg, during weight lifting). Treatment may require middle ear exploration and window sealing with a tissue graft.

Deveze A et al. Diagnosis and treatment of perilymphatic fistula. *Adv Otorhinolaryngol*. 2018;81:133. [PMID: 29794455]

### G. Cervical Vertigo

Position receptors located in the facets of the cervical spine are important physiologically in the coordination of head and eye movements. Cervical proprioceptive dysfunction is a common cause of vertigo triggered by neck movements. This disturbance often commences after neck injury, particularly hyperextension; it is also associated with degenerative cervical spine disease. Although symptoms vary, vertigo may be triggered by assuming a particular head position as opposed to moving to a new head position (the latter typical of labyrinthine dysfunction). Cervical vertigo may often be confused with migraine-associated vertigo, which is also associated with head movement. Management consists of neck movement exercises to the extent permitted by orthopedic considerations.

Devaraja K. Approach to cervicogenic dizziness: a comprehensive review of its aetiopathology and management. *Eur Arch Otorhinolaryngol*. 2018;275:2421. [PMID: 30094486]  
Ranalli P. An overview of central vertigo disorders. *Adv Otorhinolaryngol*. 2019;82:127. [PMID: 30947212]

### H. Migrainous Vertigo

Episodic vertigo is frequently associated with migraine headache. Head trauma may also be a precipitating feature. The vertigo may be temporally related to the headache and last up to several hours, or it may also occur in the absence of any headache. Migrainous vertigo may resemble Ménière disease but without associated hearing loss or tinnitus. Accompanying symptoms may include head pressure; visual, motion, or auditory sensitivity; and photosensitivity. Symptoms typically worsen with lack of sleep and anxiety or stress. Food triggers include caffeine, chocolate, and alcohol, among others. There is often a history of motion intolerance (easily carsick as a child). Migrainous vertigo may be familial. Treatment includes dietary and lifestyle changes (improved sleep pattern, avoidance of stress) and antimigraine prophylactic medication.

Hain T et al. Migraine associated vertigo. *Adv Otorhinolaryngol*. 2019;82:119. [PMID: 30947176]

### I. Superior Semicircular Canal Dehiscence

Deficiency in the bony covering of the superior semicircular canal may be associated with vertigo triggered by loud noise exposure, straining, and an apparent conductive hearing loss. Autophony is also a common feature. Diagnosis is with coronal high-resolution CT scan and VEMPs. Surgically resurfacing or plugging the dehiscent canal can improve symptoms.

Ahmed W et al. Systematic review of round window operations for the treatment of superior semicircular canal dehiscence. *J Int Adv Otol*. 2019;15:209. [PMID: 31418721]  
Naert L et al. Aggregating the symptoms of superior semicircular canal dehiscence syndrome. *Laryngoscope*. 2018;128:1932. [PMID: 29280497]

## ► Vertigo Syndromes Due to Central Lesions

CNS causes of vertigo include brainstem vascular disease, arteriovenous malformations, tumors of the brainstem and cerebellum, multiple sclerosis, and vertebrobasilar migraine (Table 8–2). Vertigo of central origin often becomes unremitting and disabling. The associated nystagmus is often nonfatigable, vertical rather than horizontal in orientation, without latency, and unsuppressed by visual fixation. ENG is useful in documenting these characteristics. There are commonly other signs of brainstem dysfunction (eg, cranial nerve palsies; motor, sensory, or cerebellar deficits in the limbs) or of increased intracranial pressure. Auditory function is generally spared. The underlying cause should be treated.

Choi JY et al. Central vertigo. *Curr Opin Neurol*. 2018;31:81. [PMID: 29084063]  
Ranalli P. An overview of central vertigo disorders. *Adv Otorhinolaryngol*. 2019;82:127. [PMID: 30947212]

## DISEASES OF THE CENTRAL AUDITORY & VESTIBULAR SYSTEMS

Lesions of the eighth cranial nerve and central audiovestibular pathways produce neural hearing loss and vertigo (Table 8–3). One characteristic of neural hearing loss is deterioration of speech discrimination out of proportion to the decrease in pure tone thresholds. Another is auditory adaptation, wherein a steady tone appears to the listener to decay and eventually disappear. Auditory evoked responses are useful in distinguishing cochlear from neural losses and may give insight into the site of lesion within the central pathways.

The evaluation of central audiovestibular disorders usually requires imaging of the internal auditory canal, cerebellopontine angle, and brain with enhanced MRI.

### 1. Vestibular Schwannoma (Acoustic Neuroma)

Eighth cranial nerve schwannomas are among the most common intracranial tumors. Most are unilateral, but

about 5% are associated with the hereditary syndrome neurofibromatosis type 2, in which bilateral eighth nerve tumors may be accompanied by meningiomas and other intracranial and spinal tumors. These benign lesions arise within the internal auditory canal and gradually grow to involve the cerebellopontine angle, eventually compressing the pons and resulting in hydrocephalus. Their typical auditory symptoms are unilateral hearing loss with a deterioration of speech discrimination exceeding that predicted by the degree of pure tone loss. Nonclassic presentations, such as sudden unilateral hearing loss, are fairly common. Any individual with a unilateral or asymmetric sensorineural hearing loss should be evaluated for an intracranial mass lesion. Vestibular dysfunction more often takes the form of continuous dysequilibrium than episodic vertigo. Diagnosis is made by enhanced MRI. Treatment consists of observation, microsurgical excision, or stereotactic radiotherapy, depending on such factors as patient age, underlying health, and size of the tumor. Bevacizumab (vascular endothelial growth factor blocker) has shown promise for treatment of tumors in neurofibromatosis type 2.

Kalogeridi MA et al. Stereotactic radiosurgery and radiotherapy for acoustic neuromas. *Neurosurg Rev*. 2020;43:941. [PMID: 30982152]

Leon J et al. Observation or stereotactic radiosurgery for newly diagnosed vestibular schwannomas: a systematic review and meta-analysis. *J Radiosurg SBRT*. 2019;6:91. [PMID: 31641546]

## 2. Vascular Compromise

Vertebrobasilar insufficiency is a common cause of vertigo in the elderly. It is often triggered by changes in posture or extension of the neck. Reduced flow in the vertebrobasilar system may be demonstrated noninvasively through MRA. Empiric treatment is with vasodilators and aspirin.

Cornelius JF et al. Compression syndromes of the vertebral artery at the craniocervical junction. *Acta Neurochir Suppl*. 2019;125:151. [PMID: 30610316]

## 3. Multiple Sclerosis

Patients with multiple sclerosis may suffer from episodic vertigo and chronic imbalance. Hearing loss in this disease is most commonly unilateral and of rapid onset. Spontaneous recovery may occur.

Kattah JC et al. Eye movements in demyelinating, autoimmune and metabolic disorders. *Curr Opin Neurol*. 2020;33:111. [PMID: 31770124]

## OTOLOGIC MANIFESTATIONS OF AIDS

The otologic manifestations of AIDS are protean. The pinna and external auditory canal may be affected by Kaposi sarcoma and by persistent and potentially invasive fungal infections (particularly *Aspergillus fumigatus*). Serous otitis media due to eustachian tube dysfunction may arise from adenoidal hypertrophy (HIV

lymphadenopathy), recurrent mucosal viral infections, or an obstructing nasopharyngeal tumor (eg, lymphoma). Unfortunately, ventilating tubes are seldom helpful and may trigger profuse watery otorrhea. Acute otitis media is usually caused by typical bacterial organisms, including *Proteus*, *Staphylococcus*, and *Pseudomonas*, and rarely, by *Pneumocystis jirovecii*. Sensorineural hearing loss is common and, in some cases, results from viral CNS infection. In cases of progressive hearing loss, cryptococcal meningitis and syphilis must be excluded. Acute facial paralysis due to herpes zoster infection (Ramsay Hunt syndrome) occurs commonly and follows a clinical course similar to that in nonimmunocompromised patients. Treatment is with high-dose acyclovir (see Chapter 32). Corticosteroids may also be effective as an adjunct.

Bao S et al. Otorhinolaryngological profile and surgical intervention in patients with HIV/AIDS. *Sci Rep*. 2018;8:12045. [PMID: 30104657]

Matas CG et al. Audiological and electrophysiological alterations in HIV-infected individuals subjected or not to antiretroviral therapy. *Braz J Otorhinolaryngol*. 2018;84:574. [PMID: 28823692]

## DISEASES OF THE NOSE & PARANASAL SINUSES

### INFECTIONS OF THE NOSE & PARANASAL SINUSES

#### 1. Acute Viral Rhinosinusitis (Common Cold)



#### ESSENTIALS OF DIAGNOSIS

- ▶ Nasal congestion, clear rhinorrhea, and hyposmia.
- ▶ Associated malaise, headache, and cough.
- ▶ Erythematous, engorged nasal mucosa without intranasal purulence.
- ▶ Symptoms are self-limited, lasting < 4 weeks and typically < 10 days.

#### ► Clinical Findings

Because there are numerous serologic types of rhinoviruses, adenoviruses, and other viruses, patients remain susceptible to the common cold throughout life. These infections, while generally quite benign and self-limited, have been implicated in the development or exacerbation of more serious conditions, such as acute bacterial sinusitis and acute otitis media, asthma, cystic fibrosis, and bronchitis. Nasal congestion, decreased sense of smell, watery rhinorrhea, and sneezing, accompanied by general malaise, throat discomfort and, occasionally, headache, are typical in viral infections. Nasal examination usually shows erythematous, edematous mucosa and a watery discharge. The presence of purulent nasal discharge suggests bacterial rhinosinusitis.

In 2020, the World Health Organization (WHO) designated a novel coronavirus called SARS-CoV-2 as the cause of a respiratory syndrome known as COVID-19. On March 11, 2020, the WHO declared it a global pandemic. While COVID-19 primarily involves the lower respiratory system, the viral prodrome is similar to that of other upper respiratory viruses with fever, nasal inflammation, rhinorrhea, cough, myalgias, and fatigue. Peculiar to SARS-CoV-2 is its propensity to cause hyposmia and anosmia, which are considered pathognomonic for COVID-19. While this altered olfaction was thought to be temporary, it became clear by late 2020 that the loss of the sense of smell could be permanent (see further information from the Centers for Disease Control and Prevention at <https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html> and from the WHO at [https://www.who.int/health-topics/coronavirus#tab=tab\\_3](https://www.who.int/health-topics/coronavirus#tab=tab_3)).

Dhama K et al. Coronavirus disease 2019-COVID-19. *Clin Microbiol Rev*. 2020;33:e00028. [PMID: 32580969]

## 2. Acute Bacterial Rhinosinusitis (Sinusitis)

### ESSENTIALS OF DIAGNOSIS

- ▶ Purulent yellow-green nasal discharge or expectoration.
- ▶ Facial pain or pressure over the affected sinus or sinuses.
- ▶ Nasal obstruction.
- ▶ Acute onset of symptoms (between 1 and 4 weeks' duration).
- ▶ Associated cough, malaise, fever, and headache.

## Treatment

There are no effective antiviral therapies for either the prevention or treatment of most viral rhinitis despite a common misperception among patients that antibiotics are helpful. Prevention of influenza virus infection by boosting the immune system using the annually created vaccine may be the most effective management strategy. Oseltamivir is the first neuraminidase inhibitor approved for the treatment and prevention of influenza virus infection, but its use is generally limited to those patients considered high risk. These high-risk patients include young children, pregnant women, and adults older than 65 years of age. Oseltamivir is hard to use because it must be started within 48 hours for optimal effect. Buffered hypertonic saline (3–5%) nasal irrigation has been shown to improve symptoms and reduce the need for nonsteroidal anti-inflammatory drugs (NSAIDs). Other supportive measures, such as oral decongestants (pseudoephedrine, 30–60 mg every 4–6 hours or 120 mg twice daily), may provide some relief of rhinorrhea and nasal obstruction. Nasal sprays, such as oxymetazoline or phenylephrine, are rapidly effective but should not be used for more than a few days to prevent rebound congestion. Withdrawal of the drug after prolonged use leads to **rhinitis medicamentosa**, an almost addictive need for continuous usage. Treatment of rhinitis medicamentosa requires mandatory cessation of the sprays, and this is often extremely frustrating for patients. Topical intranasal corticosteroids (eg, flunisolide, 2 sprays in each nostril twice daily), intranasal anticholinergic (ipratropium 0.06% nasal spray, 2–3 sprays every 8 hours as needed), or a short tapering course of oral prednisone may help during the withdrawal process.

## Complications

Other than mild eustachian tube dysfunction or transient middle ear effusion, complications of viral rhinitis are unusual. Secondary acute bacterial rhinosinusitis is a well-accepted complication of acute viral rhinitis and is suggested by persistence of symptoms beyond 10 days with purulent green or yellow nasal secretions and unilateral facial or tooth pain.

## General Considerations

Compared with viral rhinitis, acute bacterial rhinosinusitis infections are uncommon, but they still affect nearly 20 million Americans annually and account for over 2 billion dollars in health care expenditures.

Acute bacterial rhinosinusitis is believed to be the result of impaired mucociliary clearance, inflammation of the nasal cavity mucosa, and obstruction of the ostiomeatal complex, or sinus “pore.” Edematous mucosa causes obstruction of the complex, resulting in the accumulation of mucus in the sinus cavity that becomes secondarily infected by bacteria. The largest of these ostiomeatal complexes is deep to the middle turbinate in the middle meatus. This complex is actually a confluence of complexes draining the maxillary, ethmoid, and frontal sinuses. The sphenoid drains from a separate complex between the septum and superior turbinate.

The typical pathogens of bacterial rhinosinusitis are *S pneumoniae*, other streptococci, *H influenzae*, and less commonly, *S aureus* and *Moraxella catarrhalis*. Pathogens vary regionally in both prevalence and drug resistance; about 25% of healthy asymptomatic individuals may, if sinus aspirates are cultured, harbor such bacteria as well.

## Clinical Findings

### A. Symptoms and Signs

There are no agreed-upon criteria for the diagnosis of acute bacterial rhinosinusitis in adults. Major symptoms include purulent nasal drainage, nasal obstruction or congestion, facial pain/pressure, altered smell, cough, and fever. Minor symptoms include headache, otalgia, halitosis, dental pain, and fatigue. Many of the more specific symptoms and signs relate to the affected sinus(es). Bacterial rhinosinusitis can be distinguished from viral rhinitis by persistence of symptoms for more than 10 days after onset or worsening of symptoms within 10 days after initial improvement. Acute rhinosinusitis is defined as lasting less than 4 weeks, and subacute rhinosinusitis, as lasting 4–12 weeks.

**Acute maxillary sinusitis** is the most common form of acute bacterial rhinosinusitis because the maxillary is the largest sinus with a single drainage pathway that is easily obstructed. Unilateral facial fullness, pressure, and tenderness over the cheek are common symptoms, but may not always be present. Pain may refer to the upper incisor and canine teeth via branches of the trigeminal nerve, which traverse the floor of the sinus. Purulent nasal drainage should be noted with nasal airway obstruction or facial pain (pressure). Maxillary sinusitis may result from dental infection, and teeth that are tender should be carefully examined for signs of abscess. Drainage of the periapical abscess or removal of the diseased tooth typically resolves the sinus infection.

**Acute ethmoiditis** in adults is often accompanied by maxillary sinusitis, and symptoms are similar to those described above. Localized ethmoid sinusitis may present with pain and pressure over the high lateral wall of the nose between the eyes that may radiate to the orbit.

**Sphenoid sinusitis** is usually seen in the setting of pansinusitis or infection of all the paranasal sinuses on at least one side. The patient may complain of a headache “in the middle of the head” and often points to the vertex.

**Acute frontal sinusitis** may cause pain and tenderness of the forehead. This is most easily elicited by palpation of the orbital roof just below the medial end of the eyebrow.

**Hospital-associated sinusitis** is a form of acute bacterial rhinosinusitis that may present without the usual symptoms. Instead, it may be a cause of fever in critically ill patients. It is often associated with prolonged presence of a nasogastric or, rarely, nasotracheal tube causing nasal mucosal inflammation and ostiomeatal complex obstruction. Pansinusitis on the side of the tube is common on imaging studies.

## B. Imaging

The diagnosis of acute bacterial rhinosinusitis can usually be made on clinical grounds alone. Although more sensitive than clinical examination, routine radiographs are not cost-effective and are not recommended by the Agency for Health Care Policy and Research or American Association of Otolaryngology Guidelines. Consensus guidelines recommend imaging when clinical criteria are difficult to evaluate, when the patient does not respond to appropriate therapy or has been treated repeatedly with antibiotics, when intracranial involvement or cerebrospinal fluid rhinorrhea is suspected, when complicated dental infection is suspected, or when symptoms of more serious infection are noted.

When necessary, noncontrast screening coronal CT scans are more cost-effective and provide more information than conventional sinus films. CT provides a rapid and effective means to assess all of the paranasal sinuses, identify areas of greater concern (such as bony dehiscence, periosteal elevation, or maxillary tooth root exposure within the sinus), and speed appropriate therapy.

CT scans are reasonably sensitive but are not specific. Swollen soft tissue and fluid may be difficult to distinguish when opacification of the sinus is due to other conditions, such as chronic rhinosinusitis, nasal polyposis, or mucus retention cysts. Sinus abnormalities can be seen in most

patients with an upper respiratory infection, while bacterial rhinosinusitis develops in only 2%.

If malignancy, intracranial extension, or opportunistic infection is suspected, MRI with gadolinium should be ordered instead of, or in addition to, CT. MRI will distinguish tumor from fluid, inflammation, and inspissated mucus far better than CT, and will better delineate tumor extent (eg, involvement of adjacent structures, such as the orbit, skull base, and palate). Bone destruction can be demonstrated as well by MRI as by CT.

## Treatment

All patients with acute bacterial rhinosinusitis should have careful evaluation of pain. For symptom reduction in viral rhinitis and bacterial rhinosinusitis without complication, the European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS) 2012 recommends NSAIDs, saline nasal sprays, and nasal decongestants (pseudoephedrine, 30–60 mg every 6 hours, up to 240 mg/day; nasal oxymetazoline, 0.05% or oxymetazoline, 0.05–0.1%, one or two sprays in each nostril every 6–8 hours for up to 3 days). In cases of suspected bacterial rhinosinusitis, intranasal corticosteroids (eg, high-dose mometasone furoate 200 mcg each nostril twice daily for 21 days) have demonstrated efficacy in reducing nasal symptoms and are recommended. Other medications, such as mucolytics, vitamin C, probiotics, and antihistamines, have not demonstrated efficacy in the management of acute rhinosinusitis.

Antibiotic therapy should be reserved for complicated or protracted acute bacterial rhinosinusitis. Between 40% and 69% of patients with acute bacterial rhinosinusitis improve symptomatically within 2 weeks without antibiotic therapy. Antibiotic treatment is controversial in uncomplicated cases of clinically diagnosed acute bacterial rhinosinusitis because only 5% of patients will note a shorter duration of illness with treatment, and antibiotic treatment is associated with nearly twice the number of adverse events compared with placebo. Antibiotics may be considered when symptoms last more than 10 days or when symptoms (including fever, facial pain, and swelling of the face) are severe or when cases are complicated (such as immunodeficiency). In these patients, administration of antibiotics does reduce the incidence of clinical failure by 50% and represents the most cost-effective treatment strategy.

Selection of antibiotics is usually empiric and based on a number of factors, including regional patterns of antibiotic resistance, antibiotic allergy, cost, and patient tolerance. For adults younger than 65 years with mild to moderate acute bacterial rhinosinusitis, the recommended first-line therapy is amoxicillin-clavulanate (500 mg/125 mg orally three times daily or 875 mg/125 mg orally twice daily for 5–7 days), or in those with severe sinusitis, high-dose amoxicillin-clavulanate (2000 mg/125 mg extended-release orally twice daily for 7–10 days). In patients with a high risk for penicillin-resistant *S pneumoniae* (age over 65 years, hospitalization in the prior 5 days, antibiotic use in the prior month, immunocompromised status, multiple comorbidities, or severe sinus infection), the recommended first-line therapy is the high-dose amoxicillin-clavulanate option (2000 mg/125 mg extended-release

orally twice daily for 7–10 days). For those with penicillin allergy or hepatic impairment, doxycycline (100 mg orally twice daily or 200 mg orally once daily for 5–7 days), or clindamycin (150–300 mg every 6 hours) plus a cephalosporin (cefixime 400 mg orally once daily or cefpodoxime proxetil 200 mg orally twice daily) for 10 days are options. Macrolides, trimethoprim-sulfamethoxazole, and second- or third-generation cephalosporins are not recommended for empiric therapy.

Hospital-associated infections in critically ill patients are treated differently from community-acquired infections. Removal of a nasogastric tube and improved nasal hygiene (nasal saline sprays, humidification of supplemental nasal oxygen, and nasal decongestants) are critical interventions and often curative in mild cases without aggressive antibiotic use. Endoscopic or transantral cultures may help direct medical therapy in complicated cases. In addition, broad-spectrum antibiotic coverage directed at *P aeruginosa*, *S aureus* (including methicillin-resistant strains), and anaerobes may be required.

## ► Complications

Local complications of acute bacterial rhinosinusitis include orbital cellulitis and abscess, osteomyelitis, cavernous sinus thrombosis, and intracranial extension.

Orbital complications typically occur by extension of ethmoid sinusitis through the lamina papyracea, a thin layer of bone that comprises the medial orbital wall. Any change in the ocular examination necessitates immediate CT imaging. Extension in this area may cause orbital cellulitis leading to proptosis, gaze restriction, and orbital pain. Select cases are responsive to intravenous antibiotics, with or without corticosteroids, and should be managed in close conjunction with an ophthalmologist or otolaryngologist, or both. Extension through the lamina papyracea can also lead to subperiosteal abscess formation (orbital abscess). Such abscesses cause marked proptosis, ophthalmoplegia, and pain with medial gaze. While some cases respond to antibiotics, such findings should prompt an immediate referral to a specialist for consideration of decompression and evacuation. Failure to intervene quickly may lead to permanent visual impairment and a “frozen globe.”

Osteomyelitis requires prolonged antibiotics as well as removal of necrotic bone. The frontal sinus is most commonly affected, with bone involvement suggested by a tender swelling of the forehead (Pott puffy tumor). Following treatment, secondary cosmetic reconstructive procedures may be necessary.

Intracranial complications of sinusitis can occur either through hematogenous spread, as in cavernous sinus thrombosis and meningitis, or by direct extension, as in epidural and intraparenchymal brain abscesses. Fortunately, they are rare today. Cavernous sinus thrombosis is heralded by ophthalmoplegia, chemosis, and visual loss; the diagnosis is most commonly confirmed by MRI. When identified early, cavernous sinus thrombosis typically responds to intravenous antibiotics. Frontal epidural and intracranial abscesses are often clinically silent, but may

present with altered mental status, persistent fever, or severe headache.

## ► When to Refer

Failure of acute bacterial rhinosinusitis to resolve after an adequate course of oral antibiotics necessitates referral to an otolaryngologist for evaluation. Endoscopic cultures may direct further treatment choices. Nasal endoscopy and CT scan are indicated when symptoms persist longer than 4–12 weeks. Any patients with suspected extension of disease outside the sinuses should be evaluated urgently by an otolaryngologist and imaging should be obtained.

## ► When to Admit

- Facial swelling and erythema indicative of facial cellulitis.
- Proptosis.
- Vision change or gaze abnormality indicative of orbital cellulitis.
- Abscess or cavernous sinus involvement.
- Mental status changes suggestive of intracranial extension.
- Immunocompromised status.
- Failure to respond to appropriate first-line treatment or symptoms persisting longer than 4 weeks.

Dhama K et al. Coronavirus disease 2019-COVID-19. *Clin Microbiol Rev*. 2020;33:e00028. [PMID: 32580969]

Ebell MH et al. Accuracy of signs and symptoms for the diagnosis of acute rhinosinusitis and acute bacterial rhinosinusitis. *Ann Fam Med*. 2019;17:164. [PMID: 30858261]

Lemire MB et al. Antibiotics for acute rhinosinusitis in adults. *Cochrane Database Syst Rev*. 2018;9:CD006089. [PMID: 30198548]

## 3. Nasal Vestibulitis & *S aureus* Nasal Colonization

Inflammation of the nasal vestibule may result from folliculitis of the hairs that line this orifice and is usually the result of nasal manipulation or hair trimming. Systemic antibiotics effective against *S aureus* (such as dicloxacillin, 250 mg orally four times daily for 7–10 days) are indicated. Topical mupirocin 2% nasal ointment (applied two or three times daily) may be a helpful addition and may prevent future occurrences. If recurrent, the addition of rifampin (10 mg/kg orally twice daily for the last 4 days of dicloxacillin treatment) may eliminate the *S aureus* carrier state. If a furuncle exists, it should be incised and drained, preferably intranasally. Adequate treatment of these infections is important to prevent retrograde spread of infection through valveless veins into the cavernous sinus and intracranial structures.

*S aureus* is the leading nosocomial pathogen, and nasal carriage is a well-defined risk factor in the development and spread of nosocomial infections. Nasal and extranasal methicillin-resistant *S aureus* (MRSA) colonizations are associated with a 30% risk of developing an invasive MRSA infection during hospital stays. While the vast majority

have no vestibulitis symptoms, screening by nasal swabs and polymerase chain reaction (PCR)-based assays has demonstrated a 30% rate of *S aureus* colonization in hospital patients and an 11% rate of MRSA colonization in intensive care unit patients. Elimination of the carrier state is challenging, but studies of mupirocin 2% nasal ointment application with chlorhexidine facial washing (40 mg/mL) twice daily for 5 days have demonstrated decolonization in 39% of patients.

Septimus EJ. Nasal decolonization: what antimicrobials are most effective prior to surgery? Am J Infect Control. 2019;47S:A53. [PMID: 31146851]

#### 4. Invasive Fungal Sinusitis

Invasive fungal sinusitis is rare and includes both rhinocerebral mucormycosis (*Mucor*, *Absidia*, and *Rhizopus* spp.) and other invasive fungal infections, such as *Aspergillus*. The fungus spreads rapidly through vascular channels and may be lethal if not detected early. Patients with mucormycosis almost invariably have some degree of immunocompromise, such as diabetes mellitus, long-term corticosteroid therapy, neutropenia associated with chemotherapy for hematologic malignancy, or end-stage renal disease. Occasional cases of sinonasal infection with *Aspergillus* spp. have been reported in patients with untreated HIV/AIDS. The initial symptoms may be similar to those of acute bacterial rhinosinusitis, although facial pain is often more severe. Nasal drainage is typically clear or straw-colored, rather than purulent, and visual symptoms may be noted at presentation in the absence of significant nasal findings. On examination, the classic finding of mucormycosis is a black eschar on the middle turbinate, but this finding is not universal and may not be apparent if the infection is deep or high within the nasal bones. Often the mucosa appears normal or simply pale and dry. This may be noted on the hard palate as well. Early diagnosis requires suspicion of the disease and nasal biopsy with silver stains, revealing broad nonseptate hyphae within tissues and necrosis with vascular occlusion. Because CT or MRI may initially show only soft tissue changes, biopsy and ultimate debridement should be based on the clinical setting rather than radiographic demonstration of bony destruction or intracranial changes.

Invasive fungal sinusitis represents a medical and surgical emergency. Once recognized, voriconazole may be started by intravenous infusion, and prompt wide surgical debridement is indicated for patients with reversible immune deficiency (eg, poorly controlled hyperglycemia in diabetes). Other antifungals, including amphotericin or the less nephrotoxic lipid-based amphotericin B (Ambisome) and caspofungin, are alternatives to voriconazole and may be added to voriconazole depending on the fungus. Surgical management, while necessary for any possibility of cure, often results in tremendous disfigurement and functional deficits (eg, often resulting in the loss of at least one eye). Even with early diagnosis and immediate appropriate intervention, the prognosis is guarded. In persons with diabetes, the mortality rate is about 20%. If kidney disease is present or develops, mortality is over 50%; in

the setting of AIDS or hematologic malignancy with neutropenia, mortality approaches 100%. Whether to undertake aggressive surgical management should be considered carefully because many patients are gravely ill at the time of diagnosis, and overall disease-specific survival is only about 57%.

Craig JR. Updates in management of acute invasive fungal rhinosinusitis. Curr Opin Otolaryngol Head Neck Surg. 2019;27:29. [PMID: 30585877]

Kashkouli MB et al. Outcomes and factors affecting them in patients with rhino-orbito-cerebral mucormycosis. Br J Ophthalmol. 2019;103:1460. [PMID: 30514712]

#### ALLERGIC RHINITIS

##### ESSENTIALS OF DIAGNOSIS

- ▶ Clear rhinorrhea, sneezing, tearing, eye irritation, and pruritus.
- ▶ Associated symptoms include cough, bronchospasm, and eczematous dermatitis.
- ▶ Environmental allergen exposure in the presence of allergen-specific IgE.

##### ► General Considerations

Allergic rhinitis is very common in the United States with population studies reporting a prevalence of 20–30% of adults and up to 40% of children. Allergic rhinitis adversely affects school and work performance, costing about \$6 billion annually in the United States through direct costs of therapy as well as the indirect costs of sleep deprivation, fatigue and reduced productivity, or absenteeism. Seasonal allergic rhinitis is most commonly caused by pollens and spores. Flowering shrub and tree pollens are most common in the spring, flowering plants and grasses in the summer, and ragweed and molds in the fall. Interestingly, climate change may have an impact on the occurrence of allergic rhinitis since increased temperature and carbon dioxide exposure cause increased pollen production in ragweed plants and since the extended duration of summer correlates with longer periods of pollen production in these and other flowering weeds. Dust, household mites, air pollution, and pet dander may produce year-round symptoms, termed “perennial rhinitis.”

##### ► Clinical Findings

The symptoms of “hay fever” are similar to those of viral rhinitis but are usually persistent and may show seasonal variation. Nasal symptoms are often accompanied by eye irritation, pruritus, conjunctival erythema, and excessive tearing. Many patients have a strong family history of atopy or allergy.

The clinician should be careful to distinguish allergic rhinitis from other types of nonallergic rhinitis. **Vasomotor rhinitis** (sometimes called **senile rhinitis**) is caused by

increased sensitivity of the vidian nerve and is a common cause of clear rhinorrhea in elderly persons. Often patients will report that they have troubling rhinorrhea in response to numerous nasal stimuli, including warm or cold air, odors or scents, light, or particulate matter. Other types of rhinitis, including gustatory, atrophic, and drug-induced rhinorrhea, have also been described.

On physical examination, the mucosa of the turbinates is usually pale or violaceous because of venous engorgement. This is in contrast to the erythema of viral rhinitis. Nasal polyps, which are yellowish boggy masses of hypertrophic mucosa, are associated with long-standing allergic rhinitis.

## ► Treatment

### A. Intranasal Corticosteroids

Intranasal corticosteroid sprays remain the mainstay of treatment of allergic rhinitis. They are more effective—and frequently less expensive—than nonsedating antihistamines, though patients should be reminded that there may be a delay in onset of relief of 2 or more weeks. Corticosteroid sprays may also shrink hypertrophic nasal mucosa and nasal polyps, thereby providing an improved nasal airway and ostiomeatal complex drainage. Because of this effect, intranasal corticosteroids are critical in treating allergy in patients prone to recurrent acute bacterial rhinosinusitis or chronic rhinosinusitis. Available preparations include beclomethasone (42 mcg/spray twice daily per nostril), flunisolide (25 mcg/spray twice daily per nostril), mometasone furoate (200 mcg once daily per nostril), budesonide (100 mcg twice daily per nostril), and fluticasone propionate (200 mcg once daily per nostril). All are considered equally effective. Probably the most critical factors are compliance with regular use and proper introduction into the nasal cavity. In order to deliver medication to the region of the middle meatus, proper application involves holding the bottle straight up with the head tilted forward and pointing the bottle toward the ipsilateral ear when spraying. Side effects are limited, the most annoying being epistaxis (perhaps related to incorrect delivery of the drug toward the nasal septum).

### B. Antihistamines

Antihistamines offer temporary, but immediate, control of many of the most troubling symptoms of allergic rhinitis. Effective oral antihistamines include nonsedating loratadine (10 mg once daily), desloratadine (5 mg once daily), and fexofenadine (60 mg twice daily or 120 mg once daily), and minimally sedating cetirizine (10 mg once daily). Brompheniramine or chlorpheniramine (4 mg orally every 6–8 hours, or 8–12 mg orally every 8–12 hours as a sustained-release tablet) and clemastine (1.34–2.68 mg orally twice daily) may be less expensive but are usually associated with some drowsiness. The safety and efficacy of the newer, less-sedating antihistamines is so compelling that one of them, the H<sub>1</sub>-receptor antagonist nasal spray azelastine (1–2 sprays per nostril daily), is now included in the treatment guidelines of many consensus statements;

however, some patients object to its bitter taste. Other side effects of oral antihistamines besides sedation include xerostomia and antihistamine tolerance (with eventual return of allergy symptoms despite initial benefit after several months of use). In such patients, typically those with perennial allergy, alternating effective antihistamines periodically can control symptoms over the long term.

### C. Adjunctive Treatment Measures

Antileukotriene medications, such as montelukast (10 mg/day orally), alone or with cetirizine (10 mg/day orally) or loratadine (10 mg/day orally), may improve nasal rhinorrhea, sneezing, and congestion. Cromolyn sodium and sodium nedocromil may be useful adjunct agents for allergic rhinitis. They work by stabilizing mast cells and preventing proinflammatory mediator release. As topical agents, they have very few side effects, but they must be initiated well before allergen exposure (up to 4 weeks before). The most useful form of cromolyn is probably the ophthalmologic preparation placed dropwise into the nasal cavity. Intranasal cromolyn is cleared rapidly and must be administered four times daily for continued symptom relief. In practice, it is not nearly as effective as inhaled corticosteroid.

Intranasal anticholinergic agents, such as ipratropium bromide 0.03% or 0.06% sprays (42–84 mcg per nostril three times daily), may be helpful adjuncts when rhinorrhea is a major symptom. They are not as effective for treating allergic rhinitis but are more useful for treating vasomotor rhinitis.

Avoiding or reducing exposure to airborne allergens is the most effective means of alleviating symptoms of allergic rhinitis. Depending on the allergen, this can be extremely difficult. Maintaining an allergen-free environment by covering pillows and mattresses with plastic covers, substituting synthetic materials (foam mattress, acrylics) for animal products (wool, horsehair), and removing dust-collecting household fixtures (carpets, drapes, bedspreads, wicker) is worth the attempt to help more troubled patients. Air purifiers and dust filters may also aid in maintaining an allergen-free environment. Nasal saline irrigations are a useful adjunct in the treatment of allergic rhinitis to mechanically flush the allergens from the nasal cavity. When symptoms are extremely bothersome, a search for offending allergens may prove helpful. This can either be done by serum radioallergosorbent test (RAST) testing or skin testing by an allergist.

In some cases, allergic rhinitis symptoms are inadequately relieved by medication and avoidance measures. Often, such patients have a strong family history of atopy and may also have lower respiratory manifestations, such as allergic asthma. Referral to an allergist for immunotherapy may be appropriate. Such treatment involves proper identification of offending allergens, progressively increasing doses of allergen(s), and eventual maintenance dose administration over a period of 3–5 years. Immunotherapy has been proven to reduce circulating IgE levels in patients with allergic rhinitis and reduce the need for allergy medications. Both subcutaneous and topical immunotherapy have been

shown to be effective in the long-term treatment of refractory allergic rhinitis. Emerging evidence demonstrating the safety and efficacy of sublingual and intranasal immunotherapy may allow these outpatient treatment options to replace more traditional parenteral allergen desensitization for allergic rhinitis in the near future.

Fein MN et al. CSACI position statement: Newer generation H<sub>1</sub>-antihistamines are safer than first-generation H<sub>1</sub>-antihistamines and should be the first-line antihistamines for the treatment of allergic rhinitis and urticaria. *Allergy Asthma Clin Immunol*. 2019;15:61. [PMID: 3158299]

Meng Y et al. Recent developments and highlights in allergic rhinitis. *Allergy*. 2019;74:2320. [PMID: 31571226]

Reitsma S et al. Recent developments and highlights in rhinitis and allergen immunotherapy. *Allergy*. 2018;73:2306. [PMID: 30260494]

Small P et al. Allergic rhinitis. *Allergy Asthma Clin Immunol*. 2018;14:51. [PMID: 30263033]

nervous system. Nasal obstruction (from polyps, trauma, foreign bodies, or nasal masses) can cause functional hyposmia. Most clinical offices are not set up to test olfaction, but such tests may at times be worthwhile if only to assess whether a patient possesses any sense of smell at all. The University of Pennsylvania Smell Identification Test (UPSIT) is available commercially and is a simple, self-administered “scratch-and-sniff” test that is useful in differentiating hyposmia, anosmia, and malingering.

## ► Treatment

Hyposmia secondary to nasal polyposis, obstruction, and chronic rhinosinusitis may respond to endoscopic sinus surgery. Unfortunately, there is no specific treatment for primary disruption of olfaction; some disturbances spontaneously resolve. The degree of hyposmia is the greatest predictor of recovery, with less severe hyposmia recovering at a much higher rate. In permanent hyposmia, counseling should be offered about seasoning foods (such as using pepper that stimulates the trigeminal as well as olfactory chemoreceptors, rather than table salt) and safety issues (such as installing home smoke alarms and using electric rather than gas appliances).

## OLFACTORY DYSFUNCTION

### ESSENTIALS OF DIAGNOSIS

- ▶ Subjective diminished smell or taste sensation.
- ▶ Lack of objective nasal obstruction.
- ▶ Objective decrease in olfaction demonstrated by testing.

## ► General Considerations

Anatomic blockage of the nasal cavity with subsequent airflow disruption is the most common cause of olfactory dysfunction (hyposmia or anosmia). Polyps, septal deformities, and nasal tumors may be the cause. Transient olfactory dysfunction often accompanies the common cold, nasal allergies, and perennial rhinitis through changes in the nasal and olfactory epithelium. About 20% of olfactory dysfunction is idiopathic, although it often follows a viral illness. Hyposmia and anosmia are cardinal early manifestations of the COVID-19 illness caused by the novel SARS-CoV-2 coronavirus; the olfactory symptoms may linger and even be permanent sequelae of this viral infection. Central nervous system neoplasms, especially those that involve the olfactory groove or temporal lobe, may affect olfaction and must be considered in patients with no other explanation for their hyposmia or for other neurologic signs. Head trauma is a rare but severe cause of olfactory dysfunction. Shearing of the olfactory neurites is more commonly associated with anosmia. Absent, diminished, or distorted smell or taste has been reported in a wide variety of endocrine, nutritional, and nervous disorders.

## ► Clinical Findings

Evaluation of olfactory dysfunction should include a thorough history of systemic illnesses and medication use as well as a physical examination focusing on the nose and

Doty RL. Age-related deficits in taste and smell. *Otolaryngol Clin North Am*. 2018;51:815. [PMID: 30001793]

Howell J et al. Head trauma and olfactory function. *World J Otorhinolaryngol Head Neck Surg*. 2018;4:39. [PMID: 30035260]

Karimi-Galouaghi M et al. Anosmia and the need for COVID-19 screening during the pandemic. *Otolaryngol Head Neck Surg*. 2020;163:96. [PMID: 32366195]

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## EPISTAXIS

### ESSENTIALS OF DIAGNOSIS

- ▶ Bleeding from a unilateral anterior nasal cavity most common.
- ▶ Most cases may be successfully treated by direct pressure on the bleeding site for 15 minutes. When this is inadequate, topical sympathomimetics and various nasal tamponade methods are usually effective.
- ▶ Posterior, bilateral, or large-volume epistaxis should be triaged immediately to a specialist in a critical care setting.

## ► General Considerations

Epistaxis is an extremely common problem in the primary care setting. Bleeding is most common in the anterior septum where a confluence of veins creates a superficial venous plexus (Kiesselbach plexus). Predisposing factors

include nasal trauma (nose picking, foreign bodies, forceful nose blowing), rhinitis, nasal mucosal drying from low humidity or supplemental nasal oxygen, deviation of the nasal septum, atherosclerotic disease, hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu syndrome), inhaled nasal cocaine (or other illicit drug), and alcohol abuse. Poorly controlled hypertension is associated with epistaxis. Anticoagulation or antiplatelet medications may be associated with a higher incidence, more frequent recurrence, and greater difficulty in control of epistaxis, but they do not cause it.

## Clinical Findings

Laboratory assessment of bleeding parameters may be indicated, especially in recurrent epistaxis. Once the acute episode has passed, careful examination of the nose and paranasal sinuses is indicated to rule out neoplasia and hereditary hemorrhagic telangiectasia.

Repeated evaluation for diagnosis and treatment of clinically significant hypertension should be performed following control of epistaxis and removal of any packing.

## Treatment

Most cases of anterior epistaxis may be successfully treated by direct pressure on the site by compression of the nares continuously for 15 minutes. Venous pressure is reduced in the sitting position, and slight leaning forward lessens the swallowing of blood. Short-acting topical nasal decongestants (eg, phenylephrine, 0.125–1% solution, one or two sprays), which act as vasoconstrictors, may also help. When the bleeding does not readily subside, the nose should be examined, using good illumination and suction, in an attempt to locate the bleeding site. Topical 4% cocaine applied either as a spray or on a cotton strip serves both as an anesthetic and a vasoconstrictor. If cocaine is unavailable, a topical decongestant (eg, oxymetazoline) and a topical anesthetic (eg, tetracaine or lidocaine) provide similar results. When visible, the bleeding site may be cauterized with silver nitrate, diathermy, or electrocautery. A supplemental patch of Surgicel or Gelfoam may be helpful with a moisture barrier, such as petroleum-based ointment, to prevent drying and crusting. Warfarin may be continued in the setting of controlled epistaxis, although resorbable packing may be preferable in these patients.

Occasionally, a site of bleeding may be inaccessible to direct control, or attempts at direct control may be unsuccessful. In such cases, there are a number of alternatives. When the site of bleeding is anterior, a hemostatic sealant, pneumatic or other nasal tamponade, or anterior packing may suffice as the latter may be accomplished with several feet of lubricated iodoform packing systematically placed in the floor of the nose and then the vault of the nose.

About 5% of nasal bleeding originates in the posterior nasal cavity, commonly associated with atherosclerotic disease and hypertension. In such cases, it may be necessary to consult an otolaryngologist for a pack to occlude the choana before placing a pack anteriorly. In emergency settings, double balloon packs (Epistat) may facilitate rapid control of bleeding with little or no mucosal trauma.

Because such packing is uncomfortable, bleeding may persist, and vasovagal syncope is possible, hospitalization for monitoring and stabilization is indicated. Posterior nasal packing is quite uncomfortable and may require an opioid analgesic for pain control.

Surgical management of epistaxis, through ligation of the nasal arterial supply (internal maxillary artery and ethmoid arteries) is indicated when direct pressure and nasal packing fail. The most common approach to surgical treatment is endoscopic sphenopalatine artery ligation. This method has a reported efficacy of 73–100% in studies; however, it may miss bleeds caused by the ethmoid arterial supply. Alternatively, endovascular epistaxis control is highly effective (75–92%) and can address all sources of intranasal bleeding except those from the anterior ethmoid artery. Its use may be reserved for when a surgical approach fails because it is associated with a 1.1–1.5% risk of stroke.

After control of epistaxis, the patient is advised to avoid straining and vigorous exercise for several days. Nasal saline should be applied to the packing frequently to keep the packing moist. Avoidance of hot or spicy foods and tobacco is also advisable, since these may cause nasal vaso-dilation. Avoiding nasal trauma, including nose picking, is an obvious necessity. Lubrication with petroleum jelly or bacitracin ointment and increased home humidity may also be useful ancillary measures. Finally, antistaphylococcal antibiotics (eg, cephalexin, 500 mg orally four times daily, or clindamycin, 150 mg orally four times daily) are indicated to reduce the risk of toxic shock syndrome developing while the packing remains in place (at least 5 days).

## When to Refer

- Patients with recurrent epistaxis, large-volume epistaxis, and episodic epistaxis with associated nasal obstruction should be referred to an otolaryngologist for endoscopic evaluation and possible imaging.
- Those with ongoing bleeding beyond 15 minutes should be taken to a local emergency department if the clinician is not prepared to manage acute epistaxis.

D'Aguanno V et al. Clinical recommendations for epistaxis management during the COVID-19 pandemic. *Otolaryngol Head Neck Surg.* 2020;163:75. [PMID: 32366173]

Krulewitz NA et al. Epistaxis. *Emerg Med Clin North Am.* 2019;37:29. [PMID: 30454778]

Tran QK et al. Prophylactic antibiotics for anterior nasal packing in emergency department: a systematic review and meta-analysis of clinically-significant infections. *Am J Emerg Med.* 2020;38:983. [PMID: 31839514]

Tunkel DE et al. Clinical practice guideline: nosebleed (epistaxis) executive summary. *Otolaryngol Head Neck Surg.* 2020;162:8. [PMID: 31910122]

Wojak JC. Endovascular treatment of epistaxis. *Semin Intervent Radiol.* 2020;37:150. [PMID: 32419727]

## NASAL TRAUMA

The nasal pyramid is the most frequently fractured bone in the body. Fracture is suggested by crepitance or palpably mobile bony segments. Epistaxis and pain are common, as are soft-tissue hematomas (“black eye”). It is important to

make certain that there is no palpable step-off of the infraorbital rim, which would indicate the presence of a zygomatic complex fracture. Radiologic confirmation may at times be helpful but is not necessary in uncomplicated nasal fractures. It is also important to assess for possible concomitant additional facial, spine, pulmonary, or intracranial injuries when the circumstances of injury are suggestive, as in the case of automobile and motorcycle accidents.

Treatment is aimed at maintaining long-term nasal airway patency and cosmesis. Closed reduction can be performed under local or general anesthesia; closed reduction under general anesthesia appears to afford better patient satisfaction and decreased need for subsequent revision septoplasty or rhinoplasty.

Intranasal examination should be performed in all cases to rule out septal hematoma, which appears as a widening of the anterior septum, visible just posterior to the columella. The septal cartilage receives its only nutrition from its closely adherent mucoperichondrium. An untreated subperichondrial hematoma will result in loss of the nasal cartilage with resultant saddle nose deformity. Septal hematomas may become infected, with *S aureus* most commonly, and should be drained with an incision in the inferior mucoperichondrium on both sides. The drained fluid should be sent for culture.

Packing for 2–5 days is often helpful to help prevent reformation of the hematoma. Antibiotics with antistaphylococcal efficacy (eg, cephalexin, 500 mg four times daily, or clindamycin, 150 mg four times daily) should be given for 3–5 days or the duration of the packing to reduce the risk of toxic shock syndrome.

## TUMORS & GRANULOMATOUS DISEASE

### 1. Benign Nasal Tumors

#### A. Nasal Polyps

Nasal polyps are pale, edematous, mucosally covered masses commonly seen in patients with allergic rhinitis. They may result in chronic nasal obstruction and a diminished sense of smell. In patients with nasal polyps and a history of asthma, aspirin should be avoided as it may precipitate a severe episode of bronchospasm, known as **triad asthma** (Samter triad). Such patients may have an immunologic salicylate sensitivity.

Use of topical intranasal corticosteroids improves the quality of life in patients with nasal polyposis and chronic rhinosinusitis. Initial treatment with topical nasal corticosteroids (see Allergic Rhinitis section for specific drugs) for 1–3 months is usually successful for small polyps and may reduce the need for operation. A short course of oral corticosteroids (eg, prednisone, 6-day course using 21 [5-mg] tablets; 6 tablets [30 mg] on day 1 and tapering by 1 tablet [5 mg] each day) may also be of benefit, but when polyps are massive or medical management is unsuccessful obstructing polyps may be removed surgically. In healthy persons, this is a minor outpatient procedure. In recurrent polyposis, it may be necessary to remove polyps from the ethmoid, sphenoid, and maxillary sinuses to provide longer-lasting relief and open the affected sinuses. Intranasal

corticosteroids should be continued following polyp removal to prevent recurrence, and the clinician should consider allergen testing to determine the offending allergen and avoidance measures.

Brescia G. Role of blood inflammatory cells in chronic rhinosinusitis with nasal polyps. *Acta Otolaryngol.* 2019;139:48. [PMID: 30686139]

Song WJ et al. Chronic rhinosinusitis with nasal polyps in older adults: clinical presentation, pathophysiology, and comorbidity. *Curr Allergy Asthma Rep.* 2019;19:46. [PMID: 31486905]

### B. Inverted Papillomas

Inverted papillomas are benign tumors caused by human papillomavirus (HPV) that usually arise on the lateral nasal wall. They present with unilateral nasal obstruction and occasionally hemorrhage. They are often easily seen on anterior rhinoscopy as cauliflower-like growths in or around the middle meatus. Because squamous cell carcinoma is seen in about 10% of inverted or schneiderian papillomas, complete excision is strongly recommended. This usually requires an endoscopic medial maxillectomy. While rare, very extensive disease may require an open inferior or total maxillectomy for complete removal. Because recurrence rates for inverted papillomas are reported to be as high as 20%, subsequent clinical and radiologic follow-up is imperative. All excised tissue (not just a portion) should be carefully reviewed by the pathologist to be sure no carcinoma is present.

Peng R et al. Outcomes of sinonasal inverted papilloma resection by surgical approach: an updated systematic review and meta-analysis. *Int Forum Allergy Rhinol.* 2019;9:573. [PMID: 30748098]

### 2. Malignant Nasopharyngeal & Paranasal Sinus Tumors

Though rare, malignant tumors of the nose, nasopharynx, and paranasal sinuses are quite problematic because they tend to remain asymptomatic until late in their course. Squamous cell carcinoma is the most common cancer found in the sinuses and nasopharynx. It is especially common in the nasopharynx, where it obstructs the eustachian tube and results in serous otitis media. Nasopharyngeal carcinoma (nonkeratinizing squamous cell carcinoma or lymphoepithelioma) is usually associated with elevated IgA antibody to the viral capsid antigen of the Epstein-Barr virus (EBV). It is particularly common in patients of southern Chinese descent and has a weaker association with tobacco exposure than other head and neck squamous cell carcinomas. Adenocarcinomas, mucosal melanomas, sarcomas, and non-Hodgkin lymphomas are less commonly encountered neoplasms of this area.

Early symptoms are nonspecific, mimicking those of rhinitis or sinusitis. Unilateral nasal obstruction, otitis media, and discharge are common, with pain and recurrent hemorrhage often clues to the diagnosis of cancer. Any adult with persistent unilateral nasal symptoms or new otitis media should be thoroughly evaluated with nasal endoscopy and nasopharyngoscopy. A high index of

suspicion remains a key to early diagnosis of these tumors. Patients often present with advanced symptoms, such as proptosis, expansion of a cheek, or ill-fitting maxillary dentures. Malar hypesthesia, due to involvement of the infraorbital nerve, is common in maxillary sinus tumors. Biopsy is necessary for definitive diagnosis, and MRI is the best imaging study to delineate the extent of disease and plan appropriate surgery and radiation.

Treatment depends on the tumor type and the extent of disease. Very early stage disease may be treated with megavoltage radiation therapy alone, but advanced nasopharyngeal carcinoma is best treated with concurrent radiation and cisplatin followed by adjuvant chemotherapy with cisplatin and fluorouracil. This chemoradiation therapy protocol significantly decreases local, nodal, and distant failures and increases progression-free and overall survival in advanced stage disease. Locally recurrent nasopharyngeal carcinoma may in selected cases be treated with repeat irradiation protocols or surgery with moderate success and a high degree of concern about local wound healing. Other squamous cell carcinomas are best treated—when resectable—with a combination of surgery and irradiation. Cranial base surgery, which can be done endoscopically using image navigation, appears to be an effective modality in improving the overall prognosis in paranasal sinus malignancies eroding the ethmoid roof. Although the prognosis is poor for advanced tumors, the results of treating resectable tumors of paranasal sinus origin have improved with the wider use of skull base resections and intensity-modulated radiation therapy. Cure rates are often 45–60%.

El-Sharkawy A et al. Epstein-Barr virus-associated malignancies: roles of viral oncoproteins in carcinogenesis. *Front Oncol*. 2018;8:265. [PMID: 30116721]

Lam WKJ et al. Recent advances in the management of nasopharyngeal carcinoma. *F1000Res*. 2018;7:1829. [PMID: 30519454]

Vartanian JG et al. Orbital exenteration for sinonasal malignancies: indications, rehabilitation and oncologic outcomes. *Curr Opin Otolaryngol Head Neck Surg*. 2018;26:122. [PMID: 29465436]

### 3. Sinonasal Inflammatory Disease (Granulomatosis with Polyangiitis & Sarcoidosis)

The nose and paranasal sinuses are involved in over 90% of cases of **granulomatosis with polyangiitis**. It is often not realized that involvement at these sites is more common than involvement of lungs or kidneys. Examination shows blood-stained crusts and friable mucosa. Biopsy, when positive, shows necrotizing granulomas and vasculitis. Other recognized sites of granulomatosis with polyangiitis in the head and neck include the subglottis and the middle ear. For treatment of granulomatosis with polyangiitis, see Chapter 20.

**Sarcoidosis** commonly involves the paranasal sinuses and is clinically similar to other chronic sinonasal inflammatory processes. Sinonasal symptoms, including rhinorrhea, nasal obstruction, and hyposmia or anosmia, may precede diagnosis of sarcoidosis in other organ systems. Clinically, the turbinates appear engorged with small white granulomas. Biopsy shows classic noncaseating granulomas. Notably,

patients with sinonasal involvement generally have more trouble managing sarcoidosis in other organ systems.

**Polymorphic reticulosis** (midline malignant reticulosis, idiopathic midline destructive disease, lethal midline granuloma)—as the multitude of apt descriptive terms suggests—is not well understood but appears to be a nasal T-cell or NK-cell lymphoma. In contrast to granulomatosis with polyangiitis, involvement is limited to the mid-face, and there may be extensive bone destruction. Many destructive lesions of the mucosa and nasal structures labeled as polymorphic reticulosis are in fact non-Hodgkin lymphoma of either NK-cell or T-cell origin. Immunophenotyping, especially for CD56 expression, is essential in the histologic evaluation. Even when apparently localized, these lymphomas have a poor prognosis, with progression and death within a year the rule.

Edriss H et al. Sinonasal and laryngeal sarcoidosis—an uncommon presentation and management challenge. *Am J Med Sci*. 2019;357:93. [PMID: 30665498]

Felicetti M et al. Ear, nose and throat involvement in granulomatosis with polyangiitis: how it presents and how it determines disease severity and long-term outcomes. *Clin Rheumatol*. 2018;37:1075. [PMID: 29460094]

Kühn D et al. Manifestation of granulomatosis with polyangiitis in head and neck. *Clin Exp Rheumatol*. 2018;36:78. [PMID: 29799391]

## DISEASES OF THE ORAL CAVITY & PHARYNX

### LEUKOPLAKIA, ERYTHROPLAKIA, ORAL LICHEN PLANUS, & ORAL CANCER



#### ESSENTIALS OF DIAGNOSIS

- ▶ **Leukoplakia:** A white lesion that cannot be removed by rubbing the mucosal surface.
- ▶ **Erythroplakia:** Similar to leukoplakia except that it has a definite erythematous component.
- ▶ **Oral Lichen Planus:** Most commonly presents as lacy leukoplakia but may be erosive; definitive diagnosis requires biopsy.
- ▶ **Oral Cancer:** Early lesions appear as leukoplakia or erythroplakia; more advanced lesions will be larger, with invasion into the tongue such that a mass lesion is palpable. Ulceration may be present.
- ▶ **Oropharynx Cancer:** Unilateral throat masses, typically presenting with painful swallowing and weight loss.

**Leukoplakic regions** range from small to several centimeters in diameter (Figure 8–5). Histologically, they are often hyperkeratoses occurring in response to chronic irritation (eg, from dentures, tobacco, lichen planus); about 2–6%, however, represent either dysplasia or early



**▲ Figure 8–5.** Leukoplakia with moderate dysplasia on the lateral border of the tongue. (Used, with permission, from Ellen Eisenberg, DMD, in Usatine RP, Smith MA, Mayeaux EJ Jr, Chumley H. *The Color Atlas of Family Medicine*, 2nd ed. McGraw-Hill, 2013.)

invasive squamous cell carcinoma. Distinguishing between **leukoplakia** and **erythroplakia** is important because about 90% of cases of erythroplakia are either dysplasia or carcinoma. **Squamous cell carcinoma** accounts for 90% of oral cancer. Alcohol and tobacco use are the major epidemiologic risk factors.

The differential diagnosis may include oral candidiasis, necrotizing sialometaplasia, pseudoepitheliomatous hyperplasia, median rhomboid glossitis, and vesiculocro erosive inflammatory disease, such as erosive lichen planus. This should not be confused with the brown-black gingival melanin pigmentation—diffuse or speckled—common in non-Whites, blue-black embedded fragments of dental amalgam, or other systemic disorders associated with general pigmentation (neurofibromatosis, familial polyposis, Addison disease). Intraoral melanoma is extremely rare and carries a dismal prognosis.

Any area of **erythroplakia**, enlarging area of **leukoplakia**, or a lesion that has submucosal depth on palpation should have an incisional biopsy or an exfoliative cytologic examination. Ulcerative lesions are particularly suspicious and worrisome. Specialty referral should be sought early both for diagnosis and treatment. A systematic intraoral examination—including the lateral tongue, floor of the mouth, gingiva, buccal area, palate, and tonsillar fossae—and palpation of the neck for enlarged lymph nodes should be part of any general physical examination, especially in patients over the age of 45 who smoke tobacco or drink immoderately. Indirect or fiberoptic examination of the nasopharynx, oropharynx, hypopharynx, and larynx by an otolaryngologist, head and neck surgeon, or radiation oncologist should also be considered for such patients when there is unexplained or persistent throat or ear pain, oral or nasal bleeding, or oral erythroplakia. Fine-needle aspiration (FNA) biopsy may expedite the diagnosis if an enlarged lymph node is found.

To date, there remain no approved therapies for reversing or stabilizing leukoplakia or erythroplakia. Clinical trials have suggested a role for beta-carotene, celecoxib,

vitamin E, and retinoids in producing regression of leukoplakia and reducing the incidence of recurrent squamous cell carcinomas. None have demonstrated benefit in large studies and these agents are not in general use today. The mainstays of management are surveillance following elimination of carcinogenic irritants (eg, smoking tobacco, chewing tobacco or betel nut, drinking alcohol) along with serial biopsies and excisions.

**Oral lichen planus** is a relatively common (0.5–2% of the population) chronic inflammatory autoimmune disease that may be difficult to diagnose clinically because of its numerous distinct phenotypic subtypes. For example, the reticular pattern may mimic candidiasis or hyperkeratosis, while the erosive pattern may mimic squamous cell carcinoma. Management begins with distinguishing it from other oral lesions. Exfoliative cytology or a small incisional or excisional biopsy is indicated, especially if squamous cell carcinoma is suspected. Therapy of lichen planus is aimed at managing pain and discomfort. Daily topical corticosteroid remains the most effective treatment for symptomatic lichen planus, but cyclosporines, retinoids, and tacrolimus have also been used. Many experts think there is a low rate (1%) of squamous cell carcinoma arising within lichen planus (in addition to the possibility of clinical misdiagnosis) and prevention of malignant transformation remains a goal of treatment. Photodynamic therapy is being studied as an approach to both treatment of symptomatic lichen planus as well as prevention of malignant transformation, but there is no compelling evidence to argue for widespread application of this technique at this time.

**Hairy leukoplakia** occurs on the lateral border of the tongue and is a common early finding in HIV infection (see Chapter 31). It often develops quickly and appears as slightly raised leukoplakic areas with a corrugated or “hairy” surface (Figure 8–6). While much more prevalent in HIV-positive patients, hairy leukoplakia can occur following solid organ transplantation and is associated with Epstein-Barr virus infection and long-term systemic corticosteroid use. Hairy leukoplakia waxes and wanes over time with generally modest irritative symptoms. Acyclovir,



**▲ Figure 8–6.** Oral hairy leukoplakia on the side of the tongue in AIDS. (Used, with permission, from Richard P. Usatine, MD, in Usatine RP, Smith MA, Mayeaux EJ Jr, Chumley H. *The Color Atlas of Family Medicine*, 2nd ed. McGraw-Hill, 2013.)



**▲ Figure 8–7.** Squamous cell carcinoma of the palate. (Used, with permission, from Frank Miller, MD, in Usatine RP, Smith MA, Mayeaux EJ Jr, Chumley H. *The Color Atlas of Family Medicine*, 2nd ed. McGraw-Hill, 2013.)

valacyclovir, and famciclovir have all been used for treatment but produce only temporary resolution of the condition. It does not appear to predispose to malignant transformation.

**Oral cavity squamous cell carcinoma** can be hard to distinguish from other oral lesions, but early detection is the key to successful management (Figure 8–7). Raised, firm, white lesions with ulcers at the base are highly suspicious and generally quite painful on even gentle palpation. Lesions less than 4 mm in depth have a low propensity to metastasize. Most patients in whom the tumor is detected before it is 2 cm in diameter are cured by local resection. Radiation is reserved for patients with positive margins or metastatic disease. Large tumors are usually treated with a combination of resection, neck dissection, and external beam radiation. Reconstruction, if required, is done at the time of resection and can involve the use of myocutaneous flaps or vascularized free flaps with or without bone.

**Oropharyngeal squamous cell carcinoma** generally presents later than oral cavity squamous cell carcinoma. The lesions tend to be larger and are often buried within the lymphoid tissue of the palatine or lingual tonsils. Most patients note only unilateral odynophagia and weight loss, but ipsilateral cervical lymphadenopathy is often identified by the careful clinician. While these tumors are typically associated with known carcinogens such as tobacco and alcohol, their epidemiology has changed dramatically over the past 20 years. Despite demonstrated reductions in tobacco and alcohol use within developed nations, the incidence of oropharyngeal squamous cell carcinoma has not declined over this period. Known as a possible cause of head and neck cancer since 1983, the human papillomavirus (HPV)—most commonly, type 16—is now believed to be the cause of up

to 70% of all oropharyngeal squamous cell carcinoma. HPV-positive tumors are readily distinguished by immunostaining of primary tumor or FNA biopsy specimens for the p16 protein, a tumor suppressor protein that is highly correlated with the presence of HPV. These tumors often present in advanced stages of the disease with regional cervical lymph node metastases (stages III and IV), but have a better prognosis than similarly staged lesions in tobacco and alcohol users. This difference in disease control is so apparent in multicenter studies that, based on the presence or absence of the p16 protein, two distinct staging systems for oropharyngeal squamous cell carcinoma were introduced in 2018. Ongoing clinical trials are trying to determine if a reduction in treatment intensity is warranted for HPV-associated cancers.

Awadallah M et al. Management update of potentially premalignant oral epithelial lesions. *Oral Surg Oral Med Oral Pathol Oral Radiol*. 2018;125:628. [PMID: 29656948]

Chera BS et al. Current status and future directions of treatment deintensification in human papilloma virus-associated oropharyngeal squamous cell carcinoma. *Semin Radiat Oncol*. 2018;28:27. [PMID: 29173753]

Mello FW et al. Prevalence of oral potentially malignant disorders: a systematic review and meta-analysis. *J Oral Pathol Med*. 2018;47:633. [PMID: 29738071]

## ORAL CANDIDIASIS



### ESSENTIALS OF DIAGNOSIS

- ▶ Fluctuating throat or mouth discomfort.
- ▶ Systemic or local immunosuppression, such as recent corticosteroid, chemotherapy, or antibiotic use.
- ▶ Erythema of the oral cavity or oropharynx with creamy-white, curd-like patches.
- ▶ Rapid resolution of symptoms with appropriate treatment.

## Clinical Findings

### A. Symptoms and Signs

Oral candidiasis (thrush) is usually painful and looks like creamy-white curd-like patches overlying erythematous mucosa (see Figure 6–22). Because these white areas are easily rubbed off (eg, by a tongue depressor)—unlike leukoplakia or lichen planus—only the underlying irregular erythema may be seen. Oral candidiasis is commonly associated with the following risk factors: (1) use of dentures, (2) debilitated state with poor oral hygiene, (3) diabetes mellitus, (4) anemia, (5) chemotherapy or local irradiation, (6) corticosteroid use (oral or systemic), or (7) broad-spectrum antibiotics. Another manifestation of candidiasis is angular cheilitis (also seen in nutritional deficiencies) (Figure 8–8).



**▲ Figure 8–8.** Severe angular cheilitis in HIV-positive man with oral thrush. (Used, with permission, from Richard P. Usatine, MD, in Usatine RP, Smith MA, Mayeaux EJ Jr, Chumley H. *The Color Atlas of Family Medicine*, 2nd ed. McGraw-Hill, 2013.)

## B. Diagnostic Studies

The diagnosis is made clinically. A wet preparation using potassium hydroxide will reveal spores and may show non-septate mycelia. Biopsy will show intraepithelial pseudo-mycelia of *Candida albicans*.

Candidiasis is often the first manifestation of HIV infection, and HIV testing should be considered in patients with no known predisposing cause for *Candida* overgrowth (see also Chapter 31). The US Department of Health Services Clinical Practice Guideline for Evaluation and Management of Early HIV Infection recommends examination of the oral mucosa with each clinician visit as well as at a dental examination every 6 months for individuals infected with HIV.

## ► Treatment

Effective antifungal therapy may be achieved with any of the following: fluconazole (100 mg orally daily for 7 days), ketoconazole (200–400 mg orally with breakfast [requires acidic gastric environment for absorption] for 7–14 days), clotrimazole troches (10 mg dissolved orally five times daily), or nystatin mouth rinses (500,000 units [5 mL of 100,000 units/mL] held in the mouth before swallowing three times daily). In patients with HIV infection, however, longer courses of therapy with fluconazole may be needed, and oral itraconazole (200 mg/day) may be indicated in fluconazole-refractory cases. Many of the *Candida* species in these patients are resistant to first-line azoles and may require newer drugs, such as voriconazole. In addition, 0.12% chlorhexidine or half-strength hydrogen peroxide mouth rinses may provide local relief. Nystatin powder (100,000 units/g) applied to dentures three or four times daily and rinsed off for several weeks may help denture wearers.

- Fang J et al. Efficacy of antifungal drugs in the treatment of oral candidiasis: a Bayesian network meta-analysis. *J Prosthet Dent.* 2020;S0022-3913(20)30076. [PMID: 32165010]
- Vila T et al. Oral candidiasis: a disease of opportunity. *J Fungi (Basel).* 2020;16:6:15. [PMID: 31963180]

## GLOSSITIS, GLOSSODYNIA, DYSGEUSIA, & BURNING MOUTH SYNDROME

Inflammation of the tongue with loss of filiform papillae leads to a red, smooth-surfaced tongue (glossitis). Rarely painful, it may be secondary to nutritional deficiencies (eg, niacin, riboflavin, iron, or vitamin E), drug reactions, dehydration, irritants, or foods and liquids, and possibly to autoimmune reactions or psoriasis. If the primary cause cannot be identified and corrected, empiric nutritional replacement therapy may be of value.

Glossodynia is burning and pain of the tongue, which may occur with or without glossitis. In the absence of any clinical findings, it has been termed “burning mouth syndrome.” Glossodynia with glossitis has been associated with diabetes mellitus, drugs (eg, diuretics), tobacco, xerostomia, and candidiasis as well as the listed causes of glossitis. The burning mouth syndrome typically has no identifiable associated risk factors and seems to be most common in postmenopausal women. Treating possible underlying causes, changing long-term medications to alternative ones, and smoking cessation may resolve symptoms of glossitis. Effective treatments for the burning mouth syndrome include alpha-lipoic acid and clonazepam. Clonazepam is most effective as a rapid-dissolving tablet placed on the tongue in doses from 0.25 mg to 0.5 mg every 8–12 hours. Both glossodynia and the burning mouth syndrome are benign, and reassurance that there is no infection or tumor is likely to be appreciated. Unilateral symptoms, symptoms that cannot be related to a specific medication, and symptoms and signs involving regions supplied by other cranial nerves all may suggest neuropathology, and imaging of the brain, brainstem, and skull base with MRI should be considered.

de Campos WG et al. Treatment of symptomatic benign migratory glossitis: a systematic review. *Clin Oral Investig.* 2018; 22:2487. [PMID: 29982968]

Liu YF et al. Burning mouth syndrome: a systematic review of treatments. *Oral Dis.* 2018;24:325. [PMID: 28247977]

## INTRAORAL ULCERATIVE LESIONS

### 1. Necrotizing Ulcerative Gingivitis (Trench Mouth, Vincent Angina)

Necrotizing ulcerative gingivitis, often caused by an infection with both spirochetes and fusiform bacilli, is common in young adults under stress (classically in students at examination time). Underlying systemic diseases may also predispose to this disorder. Clinically, there is painful acute gingival inflammation and necrosis, often with bleeding, halitosis, fever, and cervical lymphadenopathy. Warm half-strength peroxide rinses and oral penicillin (250 mg three times daily for 10 days) may help. Dental gingival curettage may prove necessary.

Reddy R et al. Seventeen new cases of chronic ulcerative stomatitis with literature review. *Head Neck Pathol.* 2019;13:386. [PMID: 30374883]

## 2. Aphthous Ulcer (Canker Sore, Ulcerative Stomatitis)

Aphthous ulcers are very common and easy to recognize. Their cause remains uncertain, although an association with human herpesvirus 6 has been suggested. Found on freely moving, nonkeratinized mucosa (eg, buccal and labial mucosa and not attached gingiva or palate), they may be single or multiple, are usually recurrent, and appear as painful small round ulcerations with yellow-gray fibrinoid centers surrounded by red halos. Minor aphthous ulcers are less than 1 cm in diameter and generally heal in 10–14 days. Major aphthous ulcers are greater than 1 cm in diameter and can be disabling due to the degree of associated oral pain. Stress seems to be a major predisposing factor to the eruptions of aphthous ulcers. A study found that the frequency of viral rhinitis and bedtime after 11 PM were independent predictors of aphthous ulcer frequency and severity in college students.

Treatment is challenging because no single systemic treatment has proven effective. Topical corticosteroids (triamcinolone acetonide, 0.1%, or fluocinonide ointment, 0.05%) in an adhesive base (Orabase Plain) do appear to provide symptomatic relief in many patients. Other topical therapies shown to be effective in controlled studies include diclofenac 3% in hyaluronan 2.5%, doxymycine-cyanoacrylate, mouthwashes containing the enzymes amyloglucosidase and glucose oxidase, and amlexanox 5% oral paste. A 1-week tapering course of prednisone (40–60 mg/day) has also been used successfully. Cimetidine maintenance therapy may be useful in patients with recurrent aphthous ulcers. Thalidomide has been used selectively in recurrent aphthous ulcerations in HIV-positive patients.

Large or persistent areas of ulcerative stomatitis may be secondary to erythema multiforme or drug allergies, acute herpes simplex, pemphigus, pemphigoid, epidermolysis bullosa acquisita, bullous lichen planus, Behcet disease, or inflammatory bowel disease. Squamous cell carcinoma may occasionally present in this fashion. When the diagnosis is not clear, incisional biopsy is indicated.

Fitzpatrick SG et al. Ulcerated lesions of the oral mucosa: clinical and histologic review. Head Neck Pathol. 2019;13:91. [PMID: 30701449]

Saikaly SK et al. Recurrent aphthous ulceration: a review of potential causes and novel treatments. J Dermatolog Treat. 2018;29:542. [PMID: 29278022]

## 3. Herpes Stomatitis

Herpes gingivostomatitis is common, mild, and short-lived and requires no intervention in most adults. In immunocompromised persons, however, reactivation of herpes simplex virus infection is frequent and may be severe. Clinically, there is initial burning, followed by typical small vesicles that rupture and form scabs. Lesions are most commonly found on the attached gingiva and mucocutaneous junction of the lip, but lesions can also form on the tongue, buccal mucosa, and soft palate. Acyclovir (200–800 mg orally five times daily for 7–10 days) or valacyclovir (1000 mg orally twice daily for 7–10 days) may shorten the course and reduce

postherpetic pain. These treatments may be effective only when started within 24–48 hours of the onset of initial symptoms (pain, itching, burning) and are not effective once vesicles have erupted. Differential diagnosis includes aphthous stomatitis, erythema multiforme, syphilitic chancre, and carcinoma.

Mazzarello V et al. Do sunscreens prevent recurrent herpes labialis in summer? J Dermatolog Treat. 2019;30:179. [PMID: 29804485]

Petti S et al. The controversial natural history of oral herpes simplex virus type 1 infection. Oral Dis. 2019;25:1850. [PMID: 31733122]

## PHARYNGITIS & TONSILLITIS



- ▶ Centor criteria: sore throat, fever, anterior cervical adenopathy, tonsillar exudate. Sore throat.
- ▶ Goal is to treat group A beta-hemolytic streptococcal infection to prevent subsequent rheumatic fever (rash, arthralgias, myocarditis) and other sequelae (glomerulonephritis, posterior pharyngeal abscess).

### General Considerations

Pharyngitis and tonsillitis account for over 10% of all office visits to primary care clinicians and 50% of outpatient antibiotic use. The main concern is determining who is likely to have a group A beta-hemolytic streptococcal (GABHS) infection, since this can lead to subsequent complications, such as rheumatic fever and glomerulonephritis. A second public health policy concern is reducing the extraordinary cost (both in dollars and in the development of antibiotic-resistant *S pneumoniae*) in the United States associated with unnecessary antibiotic use. Questions being asked include: Have the rapid antigen tests supplanted the need to culture a throat under most circumstances? Are clinical criteria alone a sufficient basis for decisions about which patients should be given antibiotics? Should any patient receive any antibiotic other than penicillin (or erythromycin if penicillin-allergic)? For how long should treatment be continued? Numerous well-done studies and experience with rapid laboratory tests for detection of streptococci (eliminating the delay caused by culturing) have informed a consensus experience.

### Clinical Findings

#### A. Symptoms and Signs

The clinical features most suggestive of GABHS pharyngitis include fever over 38°C, tender anterior cervical adenopathy, lack of a cough, and pharyngotonsillar exudate (Figure 8–9). These four features (the Centor criteria), when present, strongly suggest GABHS. When two or three of the four are present, there is an intermediate likelihood of GABHS. When only one criterion is present, GABHS is



**▲ Figure 8–9.** Marked exudative pharyngitis and tonsillitis due to group A beta-hemolytic streptococci.

(Used, with permission, from Lawrence B. Stack, MD, in Knoop KJ, Stack LB, Storrow AB, Thurman RJ. *The Atlas of Emergency Medicine*, 5th ed. McGraw Hill, 2021.)

unlikely. Sore throat may be severe, with odynophagia, tender adenopathy, and a scarlatiniform rash. An elevated white count and left shift are also possible. Hoarseness, cough, and coryza are not suggestive of this disease.

Marked lymphadenopathy and a shaggy, white-purple tonsillar exudate, often extending into the nasopharynx, suggest mononucleosis, especially if present in a young adult. With about 90% sensitivity, lymphocyte-to-white-blood-cell ratios of greater than 35% suggest EBV infection and not tonsillitis. Hepatosplenomegaly and a positive heterophile agglutination test or elevated anti-EBV titer are corroborative. However, about one-third of patients with infectious mononucleosis have secondary streptococcal tonsillitis, requiring treatment. Ampicillin should routinely be avoided if mononucleosis is suspected because it induces a rash that might be misinterpreted by the patient as a penicillin allergy. Diphtheria (extremely rare but described in the alcoholic population) presents with low-grade fever and an ill patient with a gray tonsillar pseudomembrane.

The most common pathogens other than GABHS in the differential diagnosis of "sore throat" are viruses, *Neisseria gonorrhoeae*, *Mycoplasma*, and *Chlamydia trachomatis*. Rhinorrhea and lack of exudate would suggest a virus, but in practice it is not possible to confidently distinguish viral upper respiratory infection from GABHS on clinical grounds alone. Infections with *Corynebacterium diphtheriae*, anaerobic streptococci, and *Corynebacterium haemolyticum* (which responds better to erythromycin than penicillin) may also mimic pharyngitis due to GABHS.

## B. Laboratory Findings

A single-swab throat culture is 90–95% sensitive and the rapid antigen detection testing (RADT) is 90–99% sensitive for GABHS. Results from the RADT are available in about 15 minutes.

## ► Treatment

The Infectious Diseases Society of America recommends laboratory confirmation of the clinical diagnosis by means

of either throat culture or RADT of the throat swab. The American College of Physicians-American Society of Internal Medicine (ACP-ASIM), in collaboration with the Centers for Disease Control and Prevention, advocates use of a clinical algorithm alone—in lieu of microbiologic testing—for confirmation of the diagnosis in adults for whom the suspicion of streptococcal infection is high. Others examine the assumptions of the ACP-ASIM guideline for using a clinical algorithm alone and question whether those recommendations will achieve the stated objective of dramatically decreasing excess antibiotic use. A reasonable strategy to follow is that patients with zero or one Centor criterion are at very low risk for GABHS and therefore do not need throat cultures or RADT of the throat swab and should not receive antibiotics. Patients with two or three Centor criterion need throat cultures or RADT of the throat swab, since positive results would warrant antibiotic treatment. Patients who have all four Centor criteria are likely to have GABHS and can receive empiric therapy without throat culture or RADT.

A single intramuscular injection of benzathine penicillin or procaine penicillin, 1.2 million units is an effective antibiotic treatment, but the injection is painful. It is now used for patients if compliance with an oral regimen is an issue. Currently, oral treatment is effective and preferred. Penicillin V potassium (250 mg orally three times daily or 500 mg twice daily for 10 days) or cefuroxime axetil (250 mg orally twice daily for 5–10 days) are both effective. The efficacy of a 5-day regimen of penicillin V potassium appears to be similar to that of a 10-day course, with a 94% clinical response rate and an 84% streptococcal eradication rate. Erythromycin (also active against *Mycoplasma* and *Chlamydia*) is a reasonable alternative to penicillin in allergic patients. Cephalosporins are somewhat more effective than penicillin in producing bacteriologic cures; 5-day courses of cefpodoxime and cefuroxime have been successful. The macrolide antibiotics have also been reported to be successful in shorter-duration regimens. Azithromycin (500 mg once daily), because of its long half-life, needs to be taken for only 3 days.

Adequate antibiotic treatment usually avoids the streptococcal complications of scarlet fever, rheumatic myocarditis, glomerulonephritis, and local abscess formation.

Antibiotics for treatment failures are also somewhat controversial. Surprisingly, penicillin-tolerant strains are not isolated more frequently in those who fail treatment than in those treated successfully with penicillin. The reasons for failure appear to be complex, and a second course of treatment with the same drug is reasonable. Alternatives to penicillin include cefuroxime and other cephalosporins, dicloxacillin (which is beta-lactamase-resistant), and amoxicillin with clavulanate. When there is a history of penicillin allergy, alternatives should be used, such as erythromycin. Erythromycin resistance—with failure rates of about 25%—is an increasing problem in many areas. In cases of severe penicillin allergy, cephalosporins should be avoided since cross-reaction occurs in greater than 8% of cases.

Ancillary treatment of pharyngitis includes analgesics and anti-inflammatory agents, such as aspirin, acetaminophen,

and corticosteroids. In meta-analysis, corticosteroids increased the likelihood of complete pain resolution at 24 hours by threefold without an increase in recurrence or adverse events. Some patients find that salt water gargling is soothing. In severe cases, anesthetic gargles and lozenges (eg, benzocaine) may provide additional symptomatic relief. Occasionally, odynophagia is so intense that hospitalization for intravenous hydration and antibiotics is necessary. (See Chapter 33.)

Patients who have had rheumatic fever should be treated with a continuous course of antimicrobial prophylaxis (penicillin G, 500 mg once daily orally, or erythromycin, 250 mg twice daily orally) for at least 5 years.

- Berkley J. Management of pharyngitis. *Circulation*. 2018; 138:1920. [PMID: 30372134]  
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 Munck H et al. Antibiotics for recurrent acute pharyngotonsillitis: systematic review. *Eur J Clin Microbiol Infect Dis*. 2018;37:1221. [PMID: 29651614]  
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## PERITONSILLAR ABSCESS & CELLULITIS

When infection penetrates the tonsillar capsule and involves the surrounding tissues, peritonsillar cellulitis results. Peritonsillar abscess (**quinsy**) and cellulitis present with severe sore throat, odynophagia, trismus, medial deviation of the soft palate and peritonsillar fold, and an abnormal muffled ("hot potato") voice. Following therapy, peritonsillar cellulitis usually either resolves over several days or evolves into peritonsillar abscess. Ultrasound may be a useful adjunct to clinical suspicion, but imaging is not required for the diagnosis. The existence of an abscess may be confirmed by aspirating pus from the peritonsillar fold just superior and medial to the upper pole of the tonsil. A 19-gauge or 21-gauge needle should be passed medial to the molar and no deeper than 1 cm, because the internal carotid artery may lie more medially than its usual location and pass posterior and deep to the tonsillar fossa. Most commonly, patients with peritonsillar abscess present to the emergency department and receive a dose of parenteral amoxicillin (1 g), amoxicillin-sulbactam (3 g), or clindamycin (600–900 mg). Less severe cases and patients who are able to tolerate oral intake may be treated for 7–10 days with oral antibiotics, including amoxicillin, 500 mg three times a day; amoxicillin-clavulanate, 875 mg twice a day; or clindamycin, 300 mg four times daily. Although antibiotic treatment is generally undisputed, there is controversy regarding the surgical management of peritonsillar abscess. Methods include needle aspiration, incision and drainage, and tonsillectomy. Some clinicians incise and drain the area and continue with parenteral antibiotics, whereas others aspirate only and monitor as an outpatient. To drain the abscess and avoid recurrence, it may be appropriate to consider immediate tonsillectomy (quinsy tonsillectomy).

About 10% of patients with peritonsillar abscess exhibit relative indications for tonsillectomy. All three approaches are effective. Regardless of the method used, one must be sure the abscess is adequately treated, since complications such as extension to the retropharyngeal, deep neck, and posterior mediastinal spaces are possible. Bacteria may also be aspirated into the lungs, resulting in pneumonia. There is controversy about whether a single abscess is a sufficient indication for tonsillectomy; about 30% of patients aged 17–30 who do not undergo early planned tonsillectomy following peritonsillar abscess ultimately undergo surgery, and only about 13% of those over 30 have their tonsils removed.

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Luo MS et al. Needle aspiration versus incision and drainage under local anaesthesia for the treatment of peritonsillar abscess. *Eur Arch Otorhinolaryngol*. 2020;277:645. [PMID: 31555918]

## DEEP NECK INFECTIONS

### ESSENTIALS OF DIAGNOSIS

- ▶ Marked acute neck pain and swelling.
- ▶ Abscesses are emergencies because rapid airway compromise may occur.
- ▶ May spread to the mediastinum or cause sepsis.

### General Considerations

**Ludwig angina** is the most commonly encountered neck space infection. It is a cellulitis of the sublingual and submaxillary spaces, often arising from infection of the mandibular dentition. **Deep neck abscesses** most commonly originate from odontogenic infections. Other causes include suppurative lymphadenitis, direct spread of pharyngeal infection, penetrating trauma, pharyngoesophageal foreign bodies, cervical osteomyelitis, and intravenous injection of the internal jugular vein, especially in drug abusers. Recurrent deep neck infection may suggest an underlying congenital lesion, such as a branchial cleft cyst. Suppurative lymphadenopathy in middle-aged persons who smoke and drink alcohol regularly should be considered a manifestation of malignancy (typically metastatic squamous cell carcinoma) until proven otherwise.

### Clinical Findings

Patients with **Ludwig angina** have edema and erythema of the upper neck under the chin and often of the floor of the mouth. The tongue may be displaced upward and backward by the posterior spread of cellulitis, and coalescence of pus is often present in the floor of mouth. This may lead to occlusion of the airway. Microbiologic isolates include streptococci, staphylococci, *Bacteroides*, and *Fusobacterium*. Patients with diabetes may have different

flora, including *Klebsiella*, and a more aggressive clinical course.

Patients with **deep neck abscesses** usually present with marked neck pain and swelling. Fever is common but not always present. *Deep neck abscesses are emergencies because they may rapidly compromise the airway.* Untreated or inadequately treated, they may spread to the mediastinum or cause sepsis.

Contrast-enhanced CT usually augments the clinical examination in defining the extent of the infection. It often will distinguish inflammation and phlegmon (requiring antibiotics) from abscess (requiring drainage) and define for the surgeon the extent of an abscess. CT with MRI may also identify thrombophlebitis of the internal jugular vein secondary to oropharyngeal inflammation. This condition, known as **Lemierre syndrome**, is rare and usually associated with severe headache. The presence of pulmonary infiltrates consistent with septic emboli in the setting of a neck abscess should lead one to suspect Lemierre syndrome or injection drug use, or both.

## ► Treatment

Usual doses of penicillin plus metronidazole, ampicillin-sulbactam, clindamycin, or selective cephalosporins are good initial choices for treatment of **Ludwig angina**. Culture and sensitivity data are then used to refine the choice. Dental consultation is advisable to address the offending tooth or teeth. External drainage via bilateral submental incisions is required if the airway is threatened or when medical therapy has not reversed the process.

Treatment of **deep neck abscesses** includes securing the airway, intravenous antibiotics, and incision and drainage. When the infection involves the floor of the mouth, base of the tongue, or the supraglottic or paraglottic space, the airway may be secured either by intubation or tracheotomy. Tracheotomy is preferable in the patients with substantial pharyngeal edema, since attempts at intubation may precipitate acute airway obstruction. Bleeding in association with a deep neck abscess is very rare but suggests carotid artery or internal jugular vein involvement and requires prompt neck exploration both for drainage of pus and for vascular control.

Patients with **Lemierre syndrome** require prompt institution of antibiotics appropriate for *Fusobacterium necrophorum* as well as the more usual upper airway pathogens. The use of anticoagulation in treatment is of no proven benefit.

Fiorella ML et al. New laboratory predictive tools in deep neck space infections. *Acta Otorhinolaryngol Ital.* 2020;40:332. [PMID: 3329922]

Lee WS et al. Lemierre's syndrome: a forgotten and re-emerging infection. *J Microbiol Immunol Infect.* 2020;53:513. [PMID: 32303484]

Li RM et al. Infections of the neck. *Emerg Med Clin North Am.* 2019;37:95. [PMID: 30454783]

Velhonoja J et al. Deep neck space infections: an upward trend and changing characteristics. *Eur Arch Otorhinolaryngol.* 2020;277:863. [PMID: 31797041]

## SNORING



### ESSENTIALS OF DIAGNOSIS

- ▶ Noise produced on inspiration during sleep.
- ▶ Snoring is associated with obstructive sleep apnea (OSA) but has no disruption of sleep on clinical sleep evaluation.

## ► General Considerations

Ventilation disorders during sleep are extremely common. While OSA occurs in 5–10% of Americans, clinically relevant snoring may occur in as many as 59%. In general, sleep-disordered breathing problems are attributed to narrowing of the upper aerodigestive tract during sleep due to changes in position, muscle tone, and soft tissue hypertrophy or laxity. The most common sites of obstruction are the oropharynx and the base of the tongue. The spectrum of the problem ranges from simple snoring without cessation of airflow to OSA with long periods of apnea and life-threatening physiologic sequelae. OSA is discussed in Chapter 9. In contrast to OSA, snoring is almost exclusively a social problem, and despite its prevalence and association with OSA, there is comparatively little known about the management of this problem.

## ► Clinical Findings

### A. Symptoms and Signs

All patients who complain of snoring should be evaluated for OSA as discussed in Chapter 9. Symptoms of OSA (including snoring, excessive daytime somnolence, daytime headaches, and weight gain) may be present in as many as 30% of patients without demonstrable apnea or hypopnea on formal testing. Clinical examination should include examination of the nasal cavity, nasopharynx, oropharynx, and larynx to help exclude other causes of dynamic airway obstruction. In many cases of isolated snoring, the palate and uvula appear enlarged and elongated with excessive mucosa hanging below the muscular portion of the soft palate.

### B. Imaging and Diagnostic Testing

Sleep examination with polysomnography is strongly advised in the evaluation of a patient with complaints of snoring. Radiographic imaging of the head or neck is generally not necessary.

## ► Treatment

Expedited and inexpensive management solutions of snoring are sought, often with little or no benefit. Diet modification and physical exercise can lead to improvement in snoring through the weight loss and improvement in pharyngeal tone that accompanies overall physical conditioning. Position change during sleep can be effective, and time-honored treatments, such as placing a golf or

tennis ball into a pocket sewn on the back of the pajama top worn during sleep, may satisfactorily eliminate symptoms by ensuring recumbency on one side. Although numerous pharmacologic therapies have been endorsed, none demonstrate any significant utility when scrutinized.

Anatomic management of snoring can be challenging. As with OSA, snoring can come from a number of sites in the upper aerodigestive tract. While medical or surgical correction of nasal obstruction may help alleviate snoring problems, most interventions aim to improve airflow through the nasopharynx and oropharynx. Nonsurgical options include mandibular advancement appliances designed to pull the base of the tongue forward and continuous positive airway pressure via face or nasal mask. Compliance with both of these treatment options is problematic because snorers without OSA do not notice the physiologic benefits of these devices noted by patients with sleep apnea.

Surgical correction of snoring is most commonly directed at the soft palate. Historical approaches involved resection of redundant mucosa and the uvula similar to uvulopalatopharyngoplasty that is used for OSA. Regardless of how limited the procedure or what technique was used, the postoperative pain, expense of general anesthesia, and high recurrence rates limit the utility of these procedures. Office-based approaches are more widely used because of these limitations. Most of these procedures aim to stiffen the palate to prevent vibration rather than remove it. A series of procedures, including injection snoreplasty, radiofrequency thermal fibrosis, and an implantable palatal device, have been used with variable success and patient tolerance. The techniques can be technically challenging. Persistent symptoms may occur following initial treatment necessitating costly (and sometimes painful) repeat procedures. The durability of these procedures in alleviating symptoms is also poorly understood, and late failures can lead to patient and clinician frustration.

De Meyer MMD et al. Systematic review of the different aspects of primary snoring. *Sleep Med Rev*. 2019;45:88. [PMID: 30978609]

Demko BG. The evolution of oral appliance therapy for snoring and sleep apnea: where did we come from, where are we, and where are we going? *Sleep Med Clin*. 2018;13:467. [PMID: 30396442]

in association with chronic illness. Underlying Sjögren syndrome and chronic periodontitis may contribute. Ductal obstruction, often by an inspissated mucous plug, is followed by salivary stasis and secondary infection. The most common organism recovered from purulent draining saliva is *S aureus*. Treatment consists of intravenous antibiotics, such as nafcillin (1 g intravenously every 4–6 hours), and measures to increase salivary flow, including hydration, warm compresses, sialagogues (eg, lemon drops), and massage of the gland. Treatment can usually then be switched to an oral agent based on clinical improvement and microbiologic results to complete a 10-day treatment course. Less severe cases can often be treated with oral antibiotics with similar spectrum. Complete resolution of parotid swelling and pain can take 2–3 weeks. Failure of the process to improve and ultimately resolve on this regimen suggests abscess formation, ductal stricture, stone, or tumor causing obstruction. Ultrasound or CT scan may be helpful in establishing the diagnosis. In the setting of acute illness, a severe and potentially life-threatening form of sialadenitis, sometimes called suppurative sialadenitis, may develop. The causative organism is usually *S aureus*, but often no pus will drain from Stensen papilla. These patients often do not respond to rehydration and intravenous antibiotics and thus may require operative incision and drainage to resolve the infection.

## 2. Sialolithiasis

Calculus formation is more common in the Wharton duct (draining the submandibular glands) than in the Stensen duct (draining the parotid glands). Clinically, a patient may note postprandial pain and local swelling, often with a history of recurrent acute sialadenitis. Stones in the Wharton duct are usually large and radiopaque, whereas those in the Stensen duct are usually radiolucent and smaller. Those very close to the orifice of the Wharton duct may be palpated manually in the anterior floor of the mouth and removed intraorally by dilating or incising the distal duct. Those more than 1.5–2 cm from the duct are too close to the lingual nerve to be removed safely in this manner. Similarly, dilation of the Stensen duct, located on the buccal surface opposite the second maxillary molar, may relieve distal stricture or allow a small stone to pass. Sialendoscopy for the management of chronic sialolithiasis is superior to extracorporeal shock-wave lithotripsy and fluoroscopically guided basket retrieval. Repeated episodes of sialadenitis are usually associated with stricture and chronic infection. If the obstruction cannot be safely removed or dilated, excision of the gland may be necessary to relieve recurrent symptoms.

Kessler AT et al. Review of the major and minor salivary glands, Part 1: anatomy, infectious, and inflammatory processes. *J Clin Imaging Sci*. 2018;8:47. [PMID: 30546931]

Plonowska KA et al. One-year outcomes of sialendoscopic-assisted salivary duct surgery for sialadenitis without sialolithiasis. *Laryngoscope*. 2019;129:890. [PMID: 30152080]

Ryan WR et al. One-year symptom outcomes after sialolithiasis treatment with sialendoscopy-assisted salivary duct surgery. *Laryngoscope*. 2019;129:396. [PMID: 30151855]

## DISEASES OF THE SALIVARY GLANDS

### ACUTE INFLAMMATORY SALIVARY GLAND DISORDERS

#### 1. Sialadenitis

Acute bacterial sialadenitis most commonly affects either the parotid or submandibular gland. It typically presents with acute swelling of the gland, increased pain and swelling with meals, and tenderness and erythema of the duct opening. Pus often can be massaged from the duct. Sialadenitis often occurs in the setting of dehydration or

## CHRONIC INFLAMMATORY & INFILTRATIVE DISORDERS OF THE SALIVARY GLANDS

Numerous infiltrative disorders may cause unilateral or bilateral parotid gland enlargement. Sjögren syndrome and sarcoidosis are examples of lymphoepithelial and granulomatous diseases that may affect the salivary glands. Metabolic disorders, including alcoholism, diabetes mellitus, and vitamin deficiencies, may also cause diffuse enlargement. Several drugs have been associated with parotid enlargement, including thioureas, iodine, and drugs with cholinergic effects (eg, phenothiazines), which stimulate salivary flow and cause more viscous saliva.

## SALIVARY GLAND TUMORS

Approximately 80% of salivary gland tumors occur in the parotid gland. In adults, about 80% of these are benign. In the submandibular triangle, it is sometimes difficult to distinguish a primary submandibular gland tumor from a metastatic submandibular space node. Only 50–60% of primary submandibular tumors are benign. Tumors of the minor salivary glands are most likely to be malignant, with adenoid cystic carcinoma predominating, and may be found throughout the oral cavity or oropharynx.

Most parotid tumors present as an asymptomatic mass in the superficial part of the gland. Their presence may have been noted by the patient for months or years. Facial nerve involvement correlates strongly with malignancy. Tumors may extend deep to the plane of the facial nerve or may originate in the parapharyngeal space. In such cases, medial deviation of the soft palate is visible on intraoral examination. MRI and CT scans have largely replaced sialography in defining the extent of tumor. At least one new study demonstrates the potential benefit of enhanced MRI imaging in distinguishing among Warthin tumors and pleomorphic adenomas and malignant salivary gland tumors.

When the clinician encounters a patient with an otherwise asymptomatic salivary gland mass where tumor is the most likely diagnosis, the choice is whether to simply excise the mass via a parotidectomy with facial nerve dissection or submandibular gland excision or to first obtain an FNA biopsy. Although the accuracy of FNA biopsy for malignancy has been reported to be quite high, results vary among institutions. If a negative FNA biopsy would lead to a decision not to proceed to surgery, then it should be considered. Poor overall health of the patient and the possibility of inflammatory disease as the cause of the mass are situations where FNA biopsy might be helpful. In otherwise straightforward nonrecurrent cases, excision is indicated. In benign and small, low-grade malignant tumors, no additional treatment is needed. Postoperative irradiation is indicated for larger and high-grade cancers.

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Ogawa T et al. Clinical utility of dynamic-enhanced MRI in salivary gland tumors: retrospective study and literature review. Eur Arch Otorhinolaryngol. 2018;275:1613. [PMID: 29623392]

## DISEASES OF THE LARYNX

### DYSPHONIA, HOARSENESS, & STRIDOR

The primary symptoms of laryngeal disease are hoarseness and stridor. Hoarseness is caused by an abnormal vibration of the vocal folds. The voice is breathy when too much air passes incompletely apposed vocal folds, as in unilateral vocal fold paralysis or vocal fold mass. The voice is harsh when the vocal folds are stiff and vibrate irregularly, as is the case in laryngitis or malignancy. Heavy, edematous vocal folds produce a rough, low-pitched vocal quality. Stridor (a high-pitched, typically inspiratory, sound) is the result of turbulent airflow from a narrowed upper airway. Airway narrowing at or above the vocal folds produces inspiratory stridor. Airway narrowing below the vocal fold level produces either expiratory or biphasic stridor. The timing and rapidity of onset of stridor are critically important in determining the seriousness of the airway problem. All cases of stridor should be evaluated by a specialist and rapid-onset stridor should be evaluated emergently.

Evaluation of an abnormal voice begins with obtaining a history of the circumstances preceding its onset and an examination of the airway. Any patient with hoarseness that has persisted beyond 2 weeks should be evaluated by an otolaryngologist with laryngoscopy. Especially when the patient has a history of tobacco use, laryngeal cancer or lung cancer (leading to paralysis of a recurrent laryngeal nerve) must be strongly considered. In addition to structural causes of dysphonia, laryngoscopy can help identify functional problems with the voice, including vocal fold paralysis, muscle tension dysphonia, and spasmodic dysphonia.

Ross J et al. Utility of audiometry in the evaluation of patients presenting with dysphonia. Ann Otol Rhinol Laryngol. 2020;129:333. [PMID: 31731878]

Stachler RJ et al. Clinical Practice Guideline: hoarseness (dysphonia) (update). Otolaryngol Head Neck Surg. 2018;158:S1. [PMID: 29494321]

## COMMON LARYNGEAL DISORDERS

### 1. Acute Laryngitis

Acute laryngitis is probably the most common cause of hoarseness, which may persist for a week or so after other symptoms of an upper respiratory infection have cleared. The patient should be warned to avoid vigorous use of the voice (singing, shouting) until their voice returns to normal, since persistent use may lead to the formation of traumatic vocal fold hemorrhage, polyps, and cysts. Although thought to be usually viral in origin, both *M catarrhalis* and *H influenzae* may be isolated from the nasopharynx at higher than expected frequencies. Despite this finding, a meta-analysis has failed to demonstrate any convincing evidence that antibiotics significantly alter the natural resolution of acute laryngitis. Erythromycin may speed improvement of hoarseness at 1 week and cough at 2 weeks when measured subjectively. Oral or intramuscular

corticosteroids may be used in highly selected cases of professional vocalists to speed recovery and allow scheduled performances. Examination of the vocal folds and assessment of vocal technique are mandatory prior to corticosteroid initiation, since inflamed vocal folds are at greater risk for hemorrhage and the subsequent development of traumatic vocal fold pathology.

Jaworek AJ et al. Acute infectious laryngitis: a case series. Ear Nose Throat J. 2018;97:306. [PMID: 30273430]

## 2. Laryngopharyngeal Reflux



### ESSENTIALS OF DIAGNOSIS

- ▶ Commonly associated with hoarseness, throat irritation, and chronic cough.
- ▶ Symptoms typically occur when upright, and half of patients do not experience heartburn.
- ▶ Laryngoscopy is critical to exclude other causes of hoarseness.
- ▶ Diagnosis is made based on response to proton-pump inhibitor therapy.
- ▶ Treatment failure with proton-pump inhibitors is common and suggests other etiologies.

Gastroesophageal reflux into the larynx (laryngopharyngeal reflux) is considered a cause of chronic hoarseness when other causes of abnormal vocal fold vibration (such as tumor or nodules) have been excluded by laryngoscopy. Gastroesophageal reflux disease (GERD) has also been suggested as a contributing factor to other symptoms, such as throat clearing, throat discomfort, chronic cough, a sensation of postnasal drip, esophageal spasm, and some cases of asthma. Since less than half of patients with laryngeal acid exposure have typical symptoms of heartburn and regurgitation, the lack of such symptoms should not be construed as eliminating this cause. Indeed, most patients with symptomatic laryngopharyngeal reflux, as it is now called, do not meet criteria for GERD by pH probe testing and these entities must be considered separately. The prevalence of this condition is hotly debated in the literature, and laryngopharyngeal reflux may not be as common as once thought.

Evaluation should initially exclude other causes of dysphonia through laryngoscopy; consultation with an otolaryngologist is advisable. Many clinicians opt for an empiric trial of a proton-pump inhibitor since no gold standard exists for diagnosing this condition. Such an empiric trial should not precede visualization of the vocal folds to exclude other causes of hoarseness. When used, the American Academy of Otolaryngology–Head and Neck Surgery recommends twice-daily therapy with full-strength proton-pump inhibitor (eg, omeprazole 40 mg orally twice daily, or equivalent) for a minimum of 3 months. Patients may note improvement in symptoms after 3 months, but the changes

in the larynx often take 6 months to resolve. If symptoms improve and cessation of therapy leads to symptoms again, then a proton-pump inhibitor is resumed at the lowest dose effective for remission, usually daily but at times on a demand basis. Although H<sub>2</sub>-receptor antagonists are an alternative to proton-pump inhibitors, they are generally both less clinically effective and less cost-effective. Nonresponders should undergo pH testing and manometry. Twenty-four-hour pH monitoring of the pharynx should best document laryngopharyngeal reflux and is advocated by some as the initial management step, but it is costly, more difficult, and less available than lower esophageal monitoring alone. Double pH probe (proximal and distal esophageal probes) testing is the best option for evaluation, since lower esophageal pH monitoring alone does not correlate well with laryngopharyngeal reflux symptoms. Oropharyngeal pH probe testing is available, but its ability to predict response to reflux treatment in patients with laryngopharyngeal reflux is not known.

Chae M et al. A prospective randomized clinical trial of combination therapy with proton pump inhibitors and mucolytics in patients with laryngopharyngeal reflux. Ann Otol Rhinol Laryngol. 2020;129:781. [PMID: 32186395]

Lechien JR et al. Laryngopharyngeal reflux disease: clinical presentation, diagnosis and therapeutic challenges in 2018. Curr Opin Otolaryngol Head Neck Surg. 2018;26:392. [PMID: 30234664]

Lechien JR et al. Association between laryngopharyngeal reflux and benign vocal folds lesions: a systematic review. Laryngoscope. 2019;129:E329. [PMID: 30892725]

## 3. Recurrent Respiratory Papillomatosis

Papillomas are common lesions of the larynx and other sites where ciliated and squamous epithelia meet. Unlike oral papillomas, recurrent respiratory papillomatosis typically becomes symptomatic, with hoarseness that occasionally progresses over weeks to months. These papillomas are almost always due to HPV types 6 and 11. Repeated laser vaporizations or cold knife resections via operative laryngoscopy are the mainstay of treatment. Severe cases can cause airway compromise in adults and may require treatment as often as every 6 weeks to maintain airway patency. Extension can occur into the trachea and lungs. Tracheotomy should be avoided, if possible, since it introduces an additional squamociliary junction for which papillomas appear to have an affinity. Interferon treatment has been under investigation for many years but is only indicated in severe cases with pulmonary involvement. Rarely, cases of malignant transformation have been reported (often in smokers), but recurrent respiratory papillomatosis should generally be thought of as a benign condition. Cidofovir (a cytosine nucleotide analog in use to treat cytomegalovirus retinitis) has been used with success as intralesional therapy for recurrent respiratory papillomatosis. Because cidofovir causes adenocarcinomas in laboratory animals, its potential for carcinogenesis is being monitored. The quadrivalent and new 9 serotype recombinant human HPV vaccines (Gardasil and Gardasil 9) offer hope for the eventual prevention of this benign, but terribly morbid, disease.

Ivancic R et al. Current and future management of recurrent respiratory papillomatosis. *Laryngoscope Investig Otolaryngol.* 2018;3:22. [PMID: 29492465]

Jackowska J et al. Voice improvement in patients with recurrent respiratory papillomatosis after combined treatment with cidofovir and CO(2) laser surgery. *Lasers Med Sci.* 2019;34:1433. [PMID: 30762194]

#### 4. Epiglottitis

Epiglottitis (or, more correctly, supraglottitis) should be suspected when a patient presents with a rapidly developing sore throat or when odynophagia (pain on swallowing) is out of proportion to apparently minimal oropharyngeal findings on examination. It is more common in diabetic patients and may be viral or bacterial in origin. Rarely in the era of *H influenzae* type b vaccine is this bacterium isolated in adults. Unlike in children, indirect laryngoscopy is generally safe and may demonstrate a swollen, erythematous epiglottis. Lateral plain radiographs may demonstrate an enlarged epiglottis (the epiglottis “thumb sign”). Initial treatment is hospitalization for intravenous antibiotics—eg, ceftizoxime, 1–2 g intravenously every 8–12 hours; or cefuroxime, 750–1500 mg intravenously every 8 hours; and dexamethasone, usually 4–10 mg as initial bolus, then 4 mg intravenously every 6 hours—and observation of the airway. Corticosteroids may be tapered as symptoms and signs resolve. Similarly, substitution of oral antibiotics may be appropriate to complete a 10-day course. Less than 10% of adults require intubation. Indications for intubation are dyspnea, rapid pace of sore throat (where progression to airway compromise may occur before the effects of corticosteroids and antibiotics), and endolaryngeal abscess noted on CT imaging. If the patient is not intubated, prudence suggests monitoring oxygen saturation with continuous pulse oximetry and initial admission to a monitored unit.

Baiu I et al. Epiglottitis. *JAMA.* 2019;321:1946. [PMID: 31112260]  
Sideris A et al. A systematic review and meta-analysis of predictors of airway intervention in adult epiglottitis. *Laryngoscope.* 2020;130:465. [PMID: 31173373]

### MASSES OF THE LARYNX

#### 1. Traumatic Lesions of the Vocal Folds

**Vocal fold nodules** are smooth, paired lesions that form at the junction of the anterior one-third and posterior two-thirds of the vocal folds. They are a common cause of hoarseness resulting from vocal abuse. In adults, they are referred to as “singer’s nodules” and in children as “screamer’s nodules.” Treatment requires modification of voice habits, and referral to a speech therapist is indicated. While nearly all true nodules will resolve with behavior modification, recalcitrant nodules may require surgical excision. Often, additional pathology, such as a polyp or cyst, may be encountered.

**Vocal fold polyps** are unilateral masses that form within the superficial lamina propria of the vocal fold. They are related to vocal trauma and seem to follow resolution of vocal fold hemorrhage. Small, sessile polyps may

resolve with conservative measures, such as voice rest and corticosteroids, but larger polyps are often irreversible and require operative removal to restore normal voice.

**Vocal fold cysts** are also considered traumatic lesions of the vocal folds and are either true cysts with an epithelial lining or pseudocysts. They typically form from mucus-secreting glands on the inferior aspect of the vocal folds. Cysts may fluctuate in size from week to week and cause a variable degree of hoarseness. They rarely, if ever, resolve completely and may leave behind a sulcus, or vocal fold scar, if they decompress or are marsupialized. Such scarring can be a frustrating cause of permanent dysphonia.

**Polypoid corditis** is different from vocal fold polyps and may form from loss of elastin fibers and loosening of the intracellular junctions within the lamina propria. This loss allows swelling of the gelatinous matrix of the superficial lamina propria (called **Reinke edema**). These changes in the vocal folds are strongly associated with smoking, but also with vocal abuse, chemical industrial irritants, and hypothyroidism. While this problem is common in both male and female smokers, women seem more troubled by the characteristic decline in modal pitch caused by the increased mass of the vocal folds. If the patient stops smoking or the lesions cause stridor and airway obstruction, surgical resection of the hyperplastic vocal fold mucosa may be indicated to improve the voice or airway, or both.

A common but often unrecognized cause of hoarseness and odynophonia are **contact ulcers** or their close relatives, **granulomas**. Both lesions form on the vocal processes of the arytenoid cartilages, and patients often can correctly inform the clinician which side is affected. The cause of these ulcers and granulomas is disputed, but they are clearly related to trauma and may be related to exposure of the underlying perichondrium. They are common following intubation and generally resolve quite quickly. Chronic ulceration or granuloma formation has been associated with gastroesophageal reflux but is also common in patients with muscle tension dysphonia. Treatment is often multimodal, and an inhaled corticosteroid (eg, fluticasone 440 mcg twice daily) may be the most effective pharmacologic therapy. Adjunctive treatment measures include proton-pump inhibitor therapy (omeprazole 40 mg orally twice daily, or equivalent) and voice therapy with special attention to vocal hygiene. Rare cases can be quite stubborn and persistent without efficacious therapy. Surgical removal is rarely, if ever, required for nonobstructive lesions.

Ramavat AS et al. Efficacy of intralesional steroid injection in small benign vocal fold lesions. *J Voice.* 2019;33:767. [PMID: 30077419]

White A. Management of benign vocal fold lesions: current perspectives on the role for voice therapy. *Curr Opin Otolaryngol Head Neck Surg.* 2019;27:185. [PMID: 30893134]

#### 2. Laryngeal Leukoplakia

Leukoplakia of the vocal folds is commonly found in association with hoarseness in smokers. Direct laryngoscopy with biopsy is advised in almost all cases. Histologic examination usually demonstrates mild, moderate, or severe dysplasia. In some cases, invasive squamous cell carcinoma

is present in the initial biopsy specimen. Cessation of smoking may reverse or stabilize mild or moderate dysplasia. Some patients—estimated to be less than 5% of those with mild dysplasia and about 35–60% of those with severe dysplasia—will subsequently develop squamous cell carcinoma. Treatment options include proton-pump inhibitor therapy, close follow-up with laryngovideostroboscopy, serial resection, and external beam radiation therapy.

Sezen Goktas S et al. A new approach to vocal cord leukoplakia and evaluation of proton pump inhibitor treatment. Eur Arch Otorhinolaryngol. 2019;276:467. [PMID: 30607560]

### 3. Squamous Cell Carcinoma of the Larynx



#### ESSENTIALS OF DIAGNOSIS

- ▶ New and persistent (> 2 weeks' duration) hoarseness in a smoker.
- ▶ Persistent throat or ear pain, especially with swallowing.
- ▶ Neck mass.
- ▶ Hemoptysis.
- ▶ Stridor or other symptoms of a compromised airway.

#### ► General Considerations

Squamous cell carcinoma of the larynx, the most common malignancy of the larynx, occurs almost exclusively in patients with a history of significant tobacco use. Squamous cell carcinoma is usually seen in men aged 50–70 years; an estimated 13,150 new cases in both sexes (10,490 in men) will be seen in the United States in 2018. There may be an association between laryngeal cancer and HPV type 16 or 18 infection, but this association is much less strong than that between HPV 16 or 18 and oropharyngeal cancer. In both cancer types, the association with HPV seems to be strongest in nonsmokers. Laryngeal cancer is very treatable and early detection is the key to maximizing posttreatment voice, swallowing, and breathing function.

#### ► Clinical Findings

##### A. Symptoms and Signs

A change in voice quality is most often the presenting complaint, although throat or ear pain, hemoptysis, dysphagia, weight loss, and airway compromise may occur. Because of their early impact on vocal quality, glottic cancers are among the smallest detectable human malignancies and treatment success is very high with early lesions. Neck metastases are not common in early glottic (true vocal fold) cancer in which the vocal folds are mobile, but a third of patients in whom there is impaired fold mobility will also have involved lymph nodes at neck dissection. Supraglottic carcinoma (false vocal folds, aryepiglottic folds,

epiglottis), on the other hand, often metastasizes to both sides of the neck early in the disease. Complete head and neck examination, including laryngoscopy, by an experienced clinician is mandated for any person with the concerning symptoms listed under Essentials of Diagnosis.

#### B. Imaging and Laboratory Studies

Radiologic evaluation by CT or MRI is helpful in assessing tumor extent. Imaging evaluates neck nodes, tumor volume, and cartilage sclerosis or destruction. A chest CT scan is indicated if there are level VI enlarged nodes (around the trachea and the thyroid gland) or level IV enlarged nodes (inferior to the cricoid cartilage along the internal jugular vein), or if a chest film is concerning for a second primary lesion or metastases. Laboratory evaluation includes complete blood count and liver biochemical tests. Formal cardiopulmonary evaluation may be indicated, especially if partial laryngeal surgery is being considered. All partial laryngectomy candidates should have good to excellent lung function and exercise tolerance because chronic microaspiration may be expected following the procedure. A positron emission tomography (PET) scan or CT-PET scan may be indicated to assess for distant metastases when there appears to be advanced local or regional disease.

#### C. Biopsy

Diagnosis is made by biopsy at the time of laryngoscopy when true fold mobility and arytenoid fixation, as well as surface tumor extent, can be evaluated. Most otolaryngologists recommend esophagoscopy and bronchoscopy at the same time to exclude synchronous primary tumor. Although an FNA biopsy of an enlarged neck node may have already been done, it is generally acceptable to assume radiographically enlarged neck nodes (greater than 1–1.5 cm) or nodes with necrotic centers are neck metastases. Open biopsies of nodal metastases should be discouraged because they may lead to higher rates of tumor treatment failure.

#### D. Tumor Staging

The American Joint Committee on Cancer (AJCC) staging of laryngeal cancers uses the TNM system to describe tumor extent and can be used for prognosis. Early laryngeal cancers, T1 and T2 (stage I and II) lesions, involve 1–2 laryngeal subsites locally and have no nodal metastases or profound functional abnormalities. T3 and T4 lesions may involve multiple laryngeal subsites with limitation of laryngeal mobility. These locally advanced lesions are stage III or IV cancers, and any size tumor with regional nodal metastases is at least a stage III tumor. Stage I and II lesions are generally treated with single-modality therapy (surgery or radiation), while multimodality therapy, usually including chemotherapy with radiation therapy, is reserved for more advanced stage III and IV lesions.

#### ► Treatment

Treatment of laryngeal carcinoma has four goals: cure, preservation of safe and effective swallowing, preservation

of useful voice, and avoidance of a permanent tracheostoma. For early glottic and supraglottic cancers, radiation therapy is the standard of care since cure rates are greater than 95% and 80%, respectively. That said, radiation therapy carries substantial morbidity, and many early tumors (T1 and T2 lesions, without involved nodes) and selected advanced tumors (T3 and T4) may be treated with partial laryngectomy if at least one cricoarytenoid unit can be preserved. Five-year locoregional cure rates exceed 80–90% with surgery, and patient-reported satisfaction is excellent. In supraglottic tumors, even when clinically N0, elective limited neck dissection is indicated following surgical resection because of the high risk of neck node involvement.

Advanced stage III and IV tumors represent a challenging and ever-changing treatment dilemma. Twenty-five years ago, total laryngectomy was often recommended for such patients. However, the 1994 VA study (with induction cisplatin and 5-fluorouracil followed by irradiation alone in responders) demonstrated that two-thirds of patients could preserve their larynx. Subsequent studies have further defined multimodal therapy. Cisplatin-based chemotherapy concomitant with radiation therapy has been shown to be superior to either irradiation alone or induction chemotherapy followed by radiation. The same benefits have been demonstrated with the epidermal growth factor receptor blocker cetuximab with lower overall systemic toxicity and better patient tolerance. However, chemoradiation using either cetuximab or cisplatin is associated with prolonged gastrostomy-dependent dysphagia.

The high rate of dysphagia and morbidity associated with severe laryngeal stenosis following chemoradiation has prompted a reevaluation of the role of extended, but less-than-total, laryngeal resection for selected advanced laryngeal carcinoma in which at least one cricoarytenoid unit is intact (organ preservation surgery). In addition to the late complications, clinicians have noted that the overall success in the treatment of larynx cancer has declined in parallel with the increase in organ preservation chemoradiation therapy over the past 20 years. Some experts have proposed that this decline is the direct result of the shift in management of advanced laryngeal cancer away from surgery. Organ preservation surgery should be considered and discussed as an alternative to chemoradiation but may require referral to an appropriate regional center where such techniques are offered. After thorough evaluation of candidacy and discussion of the treatment options, patient choice plays a critical role in the ultimate decision to pursue surgery or chemoradiation as a definitive treatment modality. The patient and treating clinicians must carefully consider different early and late side effects and complications associated with different treatment modalities.

The presence of malignant adenopathy in the neck affects the prognosis greatly. Supraglottic tumors metastasize early and bilaterally to the neck, and this must be included in the treatment plans even when the neck is apparently uninvolved. Glottic tumors in which the true vocal folds are mobile (T1 or T2) have less than a 5% rate of nodal involvement; when a fold is immobile, the rate of ipsilateral nodal involvement climbs to about 30%. An

involved neck is treated by surgery or chemoradiation, or both. This decision will depend on the treatment chosen for the larynx and the extent of neck involvement.

Total laryngectomy is largely reserved for patients with advanced resectable tumors with extralaryngeal spread or cartilage involvement, for those with persistent tumor following chemoradiation, and for patients with recurrent or second primary tumor following previous radiation therapy. Voice rehabilitation via a primary (or at times secondary) tracheoesophageal puncture produces intelligible and serviceable speech in about 75–85% of patients. Indwelling prostheses that are changed every 3–6 months are a common alternative to patient-inserted prostheses, which need changing more frequently.

Long-term follow-up is critical in head and neck cancer patients. In addition to the 3–4% annual rate of second tumors and monitoring for recurrence, psychosocial aspects of treatment are common. Dysphagia, impaired communication, and altered appearance may result in patient difficulties adapting to the workplace and to social interactions. In addition, smoking cessation and alcohol abatement are common challenges. Nevertheless, about 65% of patients with larynx cancer are cured, most have useful speech, and many resume their prior livelihoods with adaptations.

### ► When to Refer

- Specialty referral should be sought early for diagnosis and treatment.
- Indirect or fiberoptic examination of the nasopharynx, oropharynx, hypopharynx, and larynx by an otolaryngologist-head and neck surgeon should be considered for patients with oral erythroplakia, unexplained throat or ear pain, unexplained oral or nasal bleeding, firm neck mass, or visible oral cavity or oropharyngeal mass.

### ► When to Admit

- Airway compromise, hemorrhage, dehydration.
- To determine an effective pain management regimen for severe pain.

Moskovitz J et al. Immunotherapy for head and neck squamous cell carcinoma. *Curr Oncol Rep.* 2018;20:22. [PMID: 29502288]

Patel KB et al. Treatment of early stage supraglottic squamous cell carcinoma: meta-analysis comparing primary surgery versus primary radiotherapy. *J Otolaryngol Head Neck Surg.* 2018;47:19. [PMID: 29506564]

## VOCAL FOLD PARALYSIS

Vocal fold paralysis can result from a lesion or damage to either the vagus or recurrent laryngeal nerve and usually results in breathy dysphonia and effortful voicing. Common causes of **unilateral recurrent laryngeal nerve** involvement include thyroid surgery (and occasionally thyroid cancer), other neck surgery (anterior discectomy and carotid endarterectomy), and mediastinal or apical

involvement by lung cancer. Skull base tumors often involve or abut upon lower cranial nerves and may affect the vagus nerve directly, or the vagus nerve may be damaged during surgical management of the lesion. While iatrogenic injury is the most common cause of unilateral vocal fold paralysis, the second most common cause is idiopathic. However, before deciding whether the paralysis is due to iatrogenic injury or is idiopathic, the clinician must exclude other causes, such as malignancy. In the absence of other cranial neuropathies, a CT scan with contrast from the skull base to the aorto-pulmonary window (the span of the recurrent laryngeal nerve) should be performed. If other cranial nerve deficits or high vagal weakness with palate paralysis is noted, an MRI scan of the brain and brainstem is warranted.

Unlike unilateral fold paralysis, **bilateral fold paralysis** usually causes inspiratory stridor with deep inspiration. If the onset of bilateral fold paralysis is insidious, it may be asymptomatic at rest, and the patient may have a normal voice. However, the acute onset of bilateral vocal fold paralysis with inspiratory stridor at rest should be managed by a specialist immediately in a critical care environment. Causes of bilateral fold paralysis include thyroid surgery, esophageal cancer, and ventricular shunt malfunction. Unilateral or bilateral fold immobility may also be seen in cricoarytenoid arthritis secondary to advanced rheumatoid arthritis, intubation injuries, glottic and subglottic stenosis, and, of course, laryngeal cancer. The goal of intervention is the creation of a safe airway with minimal reduction in voice quality and airway protection from aspiration. A number of fold lateralization procedures for bilateral paralysis have been advocated as a means of removing the tracheotomy tube.

Unilateral vocal fold paralysis is occasionally temporary and may take over a year to resolve spontaneously. Surgical management of persistent or irrecoverable symptomatic unilateral vocal fold paralysis has evolved over the last several decades. The primary goal is medialization of the paralyzed fold in order to create a stable platform for vocal fold vibration. Additional goals include advancing diet and improving pulmonary toilet by facilitating cough. Success has been reported for years with injection laryngoplasty using Teflon, Gelfoam, fat, and collagen. Teflon is the only permanent injectable material, but its use is discouraged because of granuloma formation within the vocal folds of some patients. Temporary injectable materials, such as collagen or fat, provide excellent temporary restoration of voice and can be placed under local or general anesthesia. Once the paralysis is determined to be permanent, formal medialization thyroplasty may be performed by creating a small window in the thyroid cartilage and placing an implant between the thyroarytenoid muscle and inner table of the thyroid cartilage. This procedure moves the vocal fold medially and creates a stable platform for bilateral, symmetric mucosal vibration.

Desuter G et al. Voice outcome indicators for unilateral vocal fold paralysis surgery: a review of the literature. *Eur Arch Otorhinolaryngol.* 2018;275:459. [PMID: 29264655]

Miyamaru S et al. Phonatory function in patients with well-differentiated thyroid carcinoma following meticulous resection of tumors adhering to the recurrent laryngeal nerve. *Int J Clin Oncol.* 2019;24:1536. [PMID: 31236741]

## TRACHEOSTOMY & CRICOHYROTOMY

There are two primary indications for tracheotomy: airway obstruction at or above the level of the larynx and respiratory failure requiring prolonged mechanical ventilation. In an acute emergency, cricothyrotomy secures an airway more rapidly than tracheotomy, with fewer potential immediate complications, such as pneumothorax and hemorrhage. Percutaneous dilatational tracheotomy as an elective bedside (or intensive care unit) procedure has undergone scrutiny in recent years as an alternative to tracheotomy. In experienced hands, the various methods of percutaneous tracheotomy have been documented to be safe for carefully selected patients. Simultaneous videobronchoscopy can reduce the incidence of major complications. The major cost reduction comes from avoiding the operating room. Bedside tracheotomy (in the intensive care unit) achieves similar cost reduction and is advocated by some experts as slightly less costly than the percutaneous procedures.

The most common indication for elective tracheotomy is the need for prolonged mechanical ventilation. There is no firm rule about how many days a patient must be intubated before conversion to tracheotomy should be advised. The incidence of serious complications, such as subglottic stenosis, increases with extended endotracheal intubation. As soon as it is apparent that the patient will require protracted ventilatory support, tracheotomy should replace the endotracheal tube. Less frequent indications for tracheostomy are life-threatening aspiration pneumonia, the need to improve pulmonary toilet to correct problems related to insufficient clearing of tracheobronchial secretions, and obstructive sleep apnea.

Posttracheotomy care requires humidified air to prevent secretions from crusting and occluding the inner cannula of the tracheotomy tube. The tracheotomy tube should be cleaned several times daily. The most frequent early complication of tracheotomy is dislodgment of the tracheotomy tube. Surgical creation of an inferiorly based tracheal flap sutured to the inferior neck skin may make reinsertion of a dislodged tube easier. It should be recalled that the act of swallowing requires elevation of the larynx, which is limited by tracheotomy. Therefore, frequent tracheal and bronchial suctioning is often required to clear the aspirated saliva as well as the increased tracheobronchial secretions. Care of the skin around the stoma is important to prevent maceration and secondary infection.

Adly A et al. Timing of tracheostomy in patients with prolonged endotracheal intubation: a systematic review. *Eur Arch Otorhinolaryngol.* 2018;275:679. [PMID: 29255970]  
 Bontempo LJ. Tracheostomy emergencies. *Emerg Med Clin North Am.* 2019;37:109. [PMID: 30454773]  
 Cinotti R et al. Tracheostomy and long-term mortality in ICU patients undergoing prolonged mechanical ventilation. *PLoS One.* 2019;14:e0220399. [PMID: 31577804]

Cooper JD. Tracheal injuries complicating prolonged intubation and tracheostomy. *Thorac Surg Clin.* 2018;28:139. [PMID: 29627046]

D'Souza A et al. Tracheostomy intervention in intubated COVID positive patients: a survey of current clinical practice among ENT surgeons. *Head Neck.* 2020;42:1382. [PMID: 32501600]

Chirica M et al. Esophageal emergencies: WSES guidelines. *World J Emerg Surg.* 2019;14:26. [PMID: 31164915]

## FOREIGN BODIES IN THE UPPER AERODIGESTIVE TRACT

### FOREIGN BODIES IN THE TRACHEA & BRONCHI

Aspiration of foreign bodies occurs much less frequently in adults than in children. Older adults and denture wearers appear to be at greatest risk. Wider familiarity with the Heimlich maneuver has reduced deaths. If the maneuver is unsuccessful, cricothyrotomy may be necessary. Plain chest radiographs may reveal a radiopaque foreign body. Detection of radiolucent foreign bodies may be aided by inspiration-expiration films that demonstrate air trapping distal to the obstructed segment. Atelectasis and pneumonia may occur later.

Tracheal and bronchial foreign bodies should be removed under general anesthesia with rigid bronchoscopy by a skilled endoscopist working with an experienced anesthesiologist.

### FOREIGN BODIES IN THE ESOPHAGUS

Foreign bodies in the esophagus create urgent but not life-threatening situations as long as the airway is not compromised. There is probably time to consult an experienced clinician for management. It is a useful diagnostic sign of complete obstruction if the patient is drooling or cannot handle secretions. Patients may often point to the exact level of the obstruction. Indirect laryngoscopy often shows pooling of saliva at the esophageal inlet. Plain films may detect radiopaque foreign bodies, such as chicken bones. Coins tend to align in the coronal plane in the esophagus and sagittally in the trachea. If a foreign body is suspected, a barium swallow may help make the diagnosis.

The treatment of an esophageal foreign body depends very much on identification of its nature. In children, swallowed nonfood objects are common. In adults, however, food foreign bodies are more common, and there is the greater possibility of underlying esophageal pathology. Endoscopic removal and examination are usually best via flexible esophagoscopy or rigid laryngoscopy and esophagoscopy. If there is nothing sharp, such as a bone, some clinicians advocate a hospitalized 24-hour observation period prior to esophagoscopy, noting that spontaneous passage of the foreign body will occur in 50% of adult patients. In the management of meat obstruction, the use of papain (meat tenderizer) should be discouraged because it can damage the esophageal mucosa and lead to stenosis or perforation.

### DISEASES PRESENTING AS NECK MASSES

The differential diagnosis of neck masses is heavily dependent on the location in the neck, the age of the patient, and the presence of associated disease processes. Rapid growth and tenderness suggest an inflammatory process, while firm, painless, and slowly enlarging masses are often neoplastic. In young adults, most neck masses are benign (branchial cleft cyst, thyroglossal duct cyst, reactive lymphadenitis), although malignancy should always be considered (lymphoma, metastatic thyroid carcinoma). Lymphadenopathy is common in HIV-positive persons, but a growing or dominant mass may well represent lymphoma. In adults over age 40, cancer is the most common cause of persistent neck mass. A metastasis from squamous cell carcinoma arising within the mouth, pharynx, larynx, or upper esophagus should be suspected, especially if there is a history of tobacco or significant alcohol use. Especially among patients younger than 30 or older than 70, lymphoma should be considered. In any case, a comprehensive otolaryngologic examination is needed. Cytologic evaluation of the neck mass via FNA biopsy is likely to be the next step if a primary tumor is not obvious on physical examination.

### CONGENITAL LESIONS PRESENTING AS NECK MASSES IN ADULTS

#### 1. Branchial Cleft Cysts

Branchial cleft cysts usually present as a soft cystic mass along the anterior border of the sternocleidomastoid muscle. These lesions are usually recognized in the second or third decades of life, often when they suddenly swell or become infected. To prevent recurrent infection and possible carcinoma, they should be completely excised, along with their fistulous tracts.

First branchial cleft cysts present high in the neck, sometimes just below the ear. A fistulous connection with the floor of the external auditory canal may be present. Second branchial cleft cysts, which are far more common, may communicate with the tonsillar fossa. Third branchial cleft cysts, which may communicate with the piriform sinus, are rare and present low in the neck.

#### 2. Thyroglossal Duct Cysts

Thyroglossal duct cysts occur along the embryologic course of the thyroid's descent from the tuberculum impar of the tongue base to its usual position in the low neck. Although they may occur at any age, they are most common before age 20. They present as a midline neck mass, often just below the hyoid bone, which moves with swallowing. Surgical excision is recommended to prevent recurrent infection. This requires removal of the entire fistulous tract along with the middle portion of the hyoid bone through which many of the fistulas pass. Preoperative evaluation should include a thyroid ultrasound to confirm anatomic position of the thyroid.

## INFECTIOUS & INFLAMMATORY NECK MASSES

### 1. Reactive Cervical Lymphadenopathy

Normal lymph nodes in the neck are usually less than 1 cm in length. Infections involving the pharynx, salivary glands, and scalp often cause tender enlargement of neck nodes. Enlarged nodes are common in HIV-infected persons. Except for the occasional node that suppurates and requires incision and drainage, treatment is directed against the underlying infection. An enlarged node (larger than 1.5 cm) or node with a necrotic center that is not associated with an obvious infection should be further evaluated, especially if the patient has a history of smoking, alcohol use, or prior cancer. Other common indications for FNA biopsy of a node include its persistence or continued enlargement. Common causes of cervical adenopathy include cancer (eg, squamous cell carcinoma, lymphoma, occasional metastases from non-head and neck sites) and infection (eg, reactive nodes, mycobacteria, and cat-scratch disease). Rare causes of adenopathy include Kikuchi disease (histiocytic necrotizing lymphadenitis) and autoimmune adenopathy.

### 2. Tuberculous & Nontuberculous Mycobacterial Lymphadenitis

Granulomatous neck masses are not uncommon. The differential diagnosis includes mycobacterial adenitis, sarcoidosis, and cat-scratch disease due to *Bartonella henselae*. The incidence of mycobacterial lymphadenitis is on the rise both in immunocompromised and immunocompetent individuals. The usual presentation of granulomatous disease in the neck is simply single or matted nodes. Although mycobacterial adenitis can extend to the skin and drain externally (as described for atypical mycobacteria and referred to as scrofula), this late presentation is no longer common.

FNA biopsy is usually the best initial diagnostic approach: cytology, smear for acid-fast bacilli, mycobacterial culture, and a sensitivity test can all be done. PCR from FNA (or from excised tissue) is the most sensitive test and is particularly useful when conventional methods have not been diagnostic but clinical impression remains consistent for tuberculous infection. While FNA has a high sensitivity (about 88%), its specificity is low (49%); thus, an excisional biopsy is often required to confirm the diagnosis.

See Tables 9-14 and 9-15 for current recommended treatment of tuberculosis infection, which includes infection of the lymph nodes (tuberculous lymphadenopathy). For atypical (nontuberculous) infection of the lymph nodes, treatment depends on the sensitivity results of culture, but antibiotics likely to be useful include 6 months of isoniazid and rifampin and, for at least the first 2 months, ethambutol—all in standard dosages. Some would totally excise the involved nodes prior to chemotherapy, depending on location and other factors, but this can lead to chronic draining fistulas.

Pang P et al. Clinical study of tuberculosis in the head and neck region—11 years' experience and a review of the literature. *Emerg Microbes Infect*. 2018;7:4. [PMID: 29323108]

### 3. Lyme Disease

Lyme disease, caused by the spirochete *Borrelia burgdorferi* and transmitted by ticks of the *Ixodes* genus, may have protean manifestations, but over 75% of patients have symptoms involving the head and neck. Facial paralysis, dysesthesias, dysgeusia, or other cranial neuropathies are most common. Headache, pain, and cervical lymphadenopathy may occur. See Chapter 34 for a more detailed discussion.

Bush LM et al. Tick-borne illness—Lyme disease. *Dis Mon*. 2018; 64:195. [PMID: 29402399]

Cruickshank M et al; Guideline Committee. Lyme disease: summary of NICE guidance. *BMJ*. 2018;361:k1261. [PMID: 29650513]

Shapiro ED et al. Lyme disease in 2018: what is new (and what is not). *JAMA*. 2018;320:635. [PMID: 30073279]

## CANCER METASTASES

In older adults, 80% of firm, persistent, and enlarging neck masses are metastatic in origin. The great majority of these arise from squamous cell carcinoma of the upper aerodigestive tract. A complete head and neck examination may reveal the cancer of origin, but examination under anesthesia with direct laryngoscopy, esophagoscopy, and bronchoscopy is usually required to fully evaluate the cancer and exclude second primaries.

It is often helpful to obtain a cytologic diagnosis if initial head and neck examination fails to reveal the primary cancer. An open biopsy should be done only when neither physical examination by an experienced clinician specializing in head and neck cancer nor FNA biopsy performed by an experienced cytopathologist yields a diagnosis. In such a setting, one should strongly consider obtaining an MRI or PET scan prior to open biopsy, as these methods may yield valuable information about a possible presumed primary site or another site for FNA.

With the exception of papillary thyroid carcinoma, non-squamous cell metastases to the neck are infrequent. While cancers that are not primary in the head or neck seldom metastasize to the cervical lymph nodes, the supraclavicular lymph nodes are quite often involved by lung, gastroesophageal, and breast cancers. Infradiaphragmatic cancers, with the exception of renal cell carcinoma and testicular cancer, rarely metastasize to the neck.

Bochner T et al. Diagnosis and management of metastatic neoplasms with unknown primary. *Semin Diagn Pathol*. 2018; 35:199. [PMID: 29203116]

Payabvash S et al. Differentiation of lymphomatous, metastatic, and non-malignant lymphadenopathy in the neck with quantitative diffusion-weighted imaging: systematic review and meta-analysis. *Neuroradiology*. 2019;61:897. [PMID: 31175398]

Rahimi-Nedjat RK et al. Sentinel lymph node biopsy in malignant melanoma of the head and neck. *J Craniomaxillofac Surg*. 2018;46:1027. [PMID: 29735384]

## LYMPHOMA

About 10% of lymphomas present in the head and neck. Multiple rubbery nodes, especially in young adults or in patients who have AIDS, are suggestive of lymphoma. A thorough physical examination may demonstrate other sites of nodal or organ involvement. FNA biopsy may be diagnostic, but open biopsy is often required to determine architecture and an appropriate treatment course.

Cabeçadas J et al. Lymphomas of the head and neck region: an update. *Virchows Arch.* 2019;474:649. [PMID: 30778677]  
Payabvash S et al. Differentiation of lymphomatous, metastatic, and non-malignant lymphadenopathy in the neck with quantitative diffusion-weighted imaging: systematic review and meta-analysis. *Neuroradiology.* 2019;61:897. [PMID: 31175398]

# 9

# Pulmonary Disorders

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## DISORDERS OF THE AIRWAYS

Airway disorders have diverse causes but share certain common pathophysiologic and clinical features. Airflow limitation is characteristic and frequently causes dyspnea and cough. Other symptoms are typically disease specific. Disorders of the airways can be classified as those that involve the upper airways—loosely defined as those above and including the vocal folds—and those that involve the lower airways.

### DISORDERS OF THE UPPER AIRWAYS

**Acute obstruction of the upper airway** can be immediately life-threatening and must be relieved promptly to avoid asphyxia. Causes of acute upper airway obstruction include trauma to the larynx or pharynx, foreign body aspiration, laryngospasm, laryngeal edema from thermal injury or angioedema, infections (acute epiglottitis, Ludwig angina, pharyngeal or retropharyngeal abscess), and acute allergic laryngitis.

**Chronic obstruction of the upper airway** may be caused by goiter, carcinoma of the pharynx or larynx, laryngeal or subglottic stenosis, laryngeal granulomas or webs, or bilateral vocal fold paralysis. Laryngeal or subglottic stenosis may become evident weeks or months after translaryngeal endotracheal intubation. Laryngomalacia refers to the collapse of the supraglottic structures during inspiration. It is the most common congenital anomaly of the larynx, manifests in infancy, and is usually resolved by 12–18 months. Inspiratory stridor, intercostal retractions on inspiration, a palpable inspiratory thrill over the larynx, and wheezing localized to the neck or trachea on auscultation are characteristic findings. Flow-volume loops may show characteristic flow limitations. Soft-tissue radiographs of the neck may show supraglottic or infraglottic narrowing. CT and MRI scans can reveal exact sites of obstruction. Flexible endoscopy may be diagnostic, but caution is necessary to avoid exacerbating upper airway edema and precipitating critical airway narrowing.

**Vocal fold dysfunction syndrome**, a type of inducible laryngeal obstruction, is characterized by paradoxical vocal fold adduction causing acute or chronic upper airway obstruction, or both. It presents as dyspnea and wheezing

that may mimic asthma but may be distinguished from asthma or exercise-induced asthma by the lack of response to bronchodilator therapy, normal spirometry immediately after an attack, spirometric evidence of upper airway obstruction, or a negative bronchial provocation test. However, vocal cord dysfunction may also coexist with asthma, be induced by exercise, be triggered by inhalational irritant exposures, laryngopharyngeal reflux of gastric contents, or psychological stress. Definitive diagnosis requires direct visualization of adduction of the vocal folds on inspiration. Treatment consists of addressing underlying precipitants (including psychogenic contributors) in addition to speech therapy, which results in significant decrease in asthma medication use.

Eskander A et al. Acute upper airway obstruction. *N Engl J Med.* 2019;381:1940. [PMID: 31722154]

Petrov AA. Vocal cord dysfunction: the spectrum across the ages. *Immunol Allergy Clin North Am.* 2019;39:547. [PMID: 31563188]

Shaffer M et al. Speech-language pathology as a primary treatment for exercise-induced laryngeal obstruction. *Immunol Allergy Clin North Am.* 2018;38:293. [PMID: 29631737]

## DISORDERS OF THE LOWER AIRWAYS

**Tracheal obstruction** may be intrathoracic (below the suprasternal notch) or extrathoracic. Fixed tracheal obstruction may be caused by acquired or congenital tracheal stenosis, primary or secondary tracheal neoplasms, extrinsic compression (tumors of the lung, thymus, or thyroid; lymphadenopathy; congenital vascular rings; aneurysms; etc), foreign body aspiration, tracheal granulomas and papillomas, and tracheal trauma. Variable or dynamic tracheal obstruction may be caused by tracheomalacia, foreign body aspiration, and retained secretions.

Acquired **tracheal stenosis** is usually secondary to previous tracheotomy or endotracheal intubation. Dyspnea, cough, and inability to clear pulmonary secretions occur weeks to months after tracheal decannulation or extubation. Physical findings may be absent until tracheal diameter is reduced 50% or more, when wheezing, a palpable tracheal thrill, and harsh breath sounds may be detected. The diagnosis is usually confirmed by plain films or CT of

the trachea. Complications include recurring pulmonary infection and life-threatening respiratory failure. Management is directed toward ensuring adequate ventilation and oxygenation and avoiding manipulative procedures that may increase edema of the tracheal mucosa. Surgical reconstruction, endotracheal stent placement, or laser photoresection may be required.

Idiopathic subglottic stenosis is a fibrotic disease of unclear etiology that causes obstruction of the central airway under the glottis. Because it is a diagnosis of exclusion, its diagnosis is usually delayed. Endoscopic procedures and surgery are the most common management modalities.

**Bronchial obstruction** may be caused by retained pulmonary secretions, aspiration, foreign bodies, bronchomalacia, bronchogenic carcinoma, compression by extrinsic masses, and tumors metastatic to the airway. Clinical and radiographic findings vary depending on the location of the obstruction and the degree of airway narrowing. Symptoms include dyspnea, cough, wheezing, and, if infection is present, fever and chills. A history of recurrent pneumonia in the same lobe or segment or slow resolution (more than 3 months) of pneumonia on successive radiographs suggests the possibility of bronchial obstruction and the need for bronchoscopy.

Radiographic findings include atelectasis (local parenchymal collapse), postobstructive infiltrates, and air trapping caused by unidirectional expiratory obstruction. CT scanning may demonstrate the nature and exact location of obstruction of the central bronchi. MRI may be superior to CT for delineating the extent of underlying disease in the hilum, but it is usually reserved for cases in which CT findings are equivocal. Bronchoscopy is the definitive diagnostic study, particularly if tumor or foreign body aspiration is suspected. The finding of bronchial breath sounds on physical examination or an air bronchogram on chest radiograph in an area of atelectasis rules out complete airway obstruction. Management includes the use of bronchoscopic electrocautery, argon plasma coagulation, and laser and radiofrequency ablation.

Aravena C et al. Idiopathic subglottic stenosis: a review. *J Thorac Dis*. 2020;12:1100. [PMID: 32274178]

Mahajan AK et al. Electrosurgical and laser therapy tools for the treatment of malignant central airway obstructions. *Chest*. 2020;157:446. [PMID: 31472155]

Murgu SD et al. Central airway obstruction: benign strictures, tracheobronchomalacia, and malignancy-related obstruction. *Chest*. 2016;150:426. [PMID: 26874192]

Shroff GS et al. Pathology of the trachea and central bronchi. *Semin Ultrasound CT MR*. 2016;37:177. [PMID: 27261343]

## ASTHMA

### ESSENTIALS OF DIAGNOSIS

- ▶ Episodic or chronic symptoms of wheezing, dyspnea, or cough.
- ▶ Symptoms frequently worse at night or in the early morning.

- ▶ Prolonged expiration and diffuse wheezes on physical examination.
- ▶ Limitation of airflow on pulmonary function testing or positive bronchoprovocation challenge.
- ▶ Reversibility of airflow obstruction, either spontaneously or following bronchodilator therapy.

## ► General Considerations

Asthma is a common disease, affecting approximately 8–10% of the population. It is slightly more common in male children (younger than 14 years) and in female adults. There is a genetic predisposition to asthma. Prevalence, hospitalizations, and fatal asthma have all increased in the United States over the past 20 years. Each year, approximately 10 million office visits, 1.8 million emergency department visits, and more than 3500 deaths in the United States are attributed to asthma. Hospitalization rates are highest among Blacks and children, and death rates are consistently highest among Blacks aged 15–24 years. The 2020 Global Initiative for Asthma (GINA) Report entitled *Global Strategy for Asthma Management and Prevention* is a comprehensive and practical resource that addresses asthma diagnosis, assessment, management, and exacerbations.

## ► Definition & Pathogenesis

Asthma is a chronic disorder of the airways characterized by variable airway obstruction, airway hyperresponsiveness, and airway inflammation. No single histopathologic feature is pathognomonic but common findings include airway inflammatory cell infiltration with eosinophils, neutrophils, and lymphocytes (especially T cells); goblet cell hyperplasia; plugging of small airways with mucus; collagen deposition beneath the basement membrane; bronchial smooth muscle hypertrophy; airway edema; mast cell activation; and denudation of airway epithelium. The pathophysiology of asthma is heterogeneous, but a division into T2-high and T2-low endotypes (marked by high and low levels, respectively, of classic Th2 cytokines such as IL-4, IL-5, and IL-13) has been shown to be important regarding the selection of therapies.

Many clinical phenotypes of asthma have been identified. The most common is **allergic asthma**, which usually begins in childhood and is associated with other allergic diseases such as eczema, allergic rhinitis, or food allergy. Exposure of sensitive patients to inhaled allergens may cause symptoms immediately (immediate asthmatic response) or 4–6 hours after allergen exposure (late asthmatic response). Common allergens include house dust mites (often found in pillows, mattresses, upholstered furniture, carpets, and drapes), cockroaches, cat dander, and seasonal pollens. Substantially reducing exposure reduces pathologic findings and clinical symptoms. **Allergic asthma** falls into the T2-high endotype, as do **late-onset T2-high asthma** and **aspirin/NSAID-associated respiratory disease**. T2-low asthma phenotypes include **nonallergic asthma**, which tends to occur in adults and be marked by

neutrophilic inflammation and variable response to standard therapies. **Asthma with persistent airflow limitation** is thought to be due to airway remodeling. **Asthma with obesity** refers to prominent respiratory symptoms in obese patients with little airway inflammation.

**Nonspecific precipitants** of asthma include upper respiratory tract infections, rhinosinusitis, postnasal drip, aspiration, gastroesophageal reflux, changes in the weather, stress, and exercise. Exposure to **products of combustion** (eg, from tobacco, methamphetamines, diesel fuel, and other agents) increases asthma symptoms and the need for medications and reduces lung function. **Air pollution** (increased air levels of respirable particles, ozone,  $\text{SO}_2$ , and  $\text{NO}_2$ ) precipitates asthma symptoms and increases emergency department visits and hospitalizations. Selected individuals may experience asthma symptoms after exposure to aspirin (aspirin-exacerbated respiratory disease), NSAIDs, or tartrazine dyes. Other **medications** may precipitate asthma symptoms (see Table 9–23). **Occupational asthma** is triggered by various agents in the workplace and may occur weeks to years after initial exposure and sensitization. Women may experience **catamenial asthma** at predictable times during the menstrual cycle. **Exercise-induced bronchoconstriction** begins during exercise or within 3 minutes after its end, peaks within 10–15 minutes, and then resolves by 60 minutes. This phenomenon is thought to be a consequence of the airways' warming and humidifying an increased volume of expired air during exercise. **Cough-variant asthma** has cough instead of wheezing as the predominant symptom of bronchial hyperreactivity. Other diseases may mimic asthma; “**cardiac asthma**” is wheezing precipitated by pulmonary edema in the setting of decompensated heart failure, while **upper airway obstruction** and **paradoxical vocal fold motion** may also present with wheezing and dyspnea.

### A. Symptoms and Signs

Asthma is characterized by episodic wheezing, shortness of breath, chest tightness, and cough. Symptoms vary over time and in intensity and are often worse at night or in the early morning. Asthma symptoms may occur spontaneously or be precipitated or exacerbated by many different triggers, as discussed above. The following features decrease the likelihood that respiratory symptoms are due to asthma: isolated cough with no other symptoms, chronic sputum production, chest pain, shortness of breath with paresthesias.

Some physical examination findings increase the probability of asthma. Nasal mucosal swelling, increased secretions, and polyps are often seen in patients with allergic asthma. Eczema, atopic dermatitis, or other allergic skin disorders may also be present. Wheezing or a prolonged expiratory phase during normal breathing correlates well with the presence of airflow obstruction; wheezing during forced expiration does not. Chest examination may be normal between exacerbations in patients with mild asthma. During severe asthma exacerbations, airflow may be too limited to produce wheezing, and the only diagnostic clue on auscultation may be globally reduced breath sounds with prolonged expiration. Hunched shoulders and use of accessory muscles of respiration suggest an increased work of breathing.

### B. Laboratory Findings

Arterial blood gas (ABG) measurements may be normal during a mild asthma exacerbation, but respiratory alkalosis and an increase in the alveolar-arterial oxygen difference ( $\text{A-a-DO}_2$ ) are common. During severe exacerbations, hypoxemia develops and the  $\text{Paco}_2$  returns to normal. The combination of an increased  $\text{Paco}_2$  and respiratory acidosis may indicate impending respiratory failure and the need for mechanical ventilation.

### C. Pulmonary Function Testing

Clinicians correctly identify airflow obstruction on examination but have limited ability to gauge its severity or to predict whether it is reversible. The evaluation for asthma should therefore include **spirometry** (forced expiratory volume in 1 second [ $\text{FEV}_1$ ], forced vital capacity [ $\text{FVC}$ ]),

**Table 9–1.** Assessing asthma control.

| Components of Asthma Control                              | Classification of Asthma Control             |  |  |
|---|--|--|--|
|   | Well Controlled                              | Partly Controlled                              | Not Controlled                                 |
| Daytime asthma symptoms > 2 ×/week                        |  |  |  |
| Nighttime awakenings due to asthma                        |  |  |  |
| Interference with normal activity due to asthma           |  |  |  |
| Reliever medication needed for asthma symptoms > 2 ×/week | None of these components within past 4 weeks | 1 or 2 of these components within past 4 weeks | 3 or 4 of these components within past 4 weeks |

Adapted from National Asthma Education and Prevention Program. Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma. National Institutes of Health Pub. No. 08-4051. Bethesda, MD, 2007, and Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2019. (Available from: [www.ginasthma.org](http://www.ginasthma.org))

and  $\text{FEV}_1/\text{FVC}$ ) before and after the administration of a short-acting bronchodilator. These measurements help determine the presence and extent of airflow obstruction and whether it is immediately reversible. Airflow obstruction is indicated by a reduced  $\text{FEV}_1/\text{FVC}$  ratio, generally below 0.7. Significant reversibility of airflow obstruction is defined by an increase of 12% or more and 200 mL in  $\text{FEV}_1$  or FVC after inhaling a short-acting bronchodilator. A positive bronchodilator response strongly supports the diagnosis of asthma but a lack of responsiveness in the pulmonary function laboratory does not preclude success in a clinical trial of bronchodilator therapy. Severe airflow obstruction results in significant air trapping, with an increase in residual volume and consequent reduction in FVC, resulting in a pattern that may mimic a restrictive ventilatory defect.

**Bronchoprovocation testing** with inhaled histamine or methacholine may be useful when asthma is suspected but spirometry is nondiagnostic. Bronchial provocation is not recommended if the  $\text{FEV}_1$  is less than 65% of predicted. A positive methacholine test is defined as a fall in the  $\text{FEV}_1$  of 20% or more at exposure to a methacholine concentration of less than or equal to 8 mg/mL. A negative methacholine test has a negative predictive value for asthma of 95%. Exercise challenge testing may be useful in patients with symptoms of exercise-induced bronchospasm.

**Peak expiratory flow (PEF)** meters are handheld devices designed as personal monitoring tools. PEF monitoring can establish peak flow variability, quantify asthma severity, and provide both patient and clinician with objective measurements on which to base treatment decisions. There are conflicting data about whether measuring PEF improves asthma outcomes but doing so is recommended to help confirm the diagnosis of asthma, to improve asthma control in patients with poor perception of airflow obstruction, and to identify environmental and occupational causes of symptoms. Predicted values for PEF vary with age, height, and sex but are poorly standardized. Comparison with reference values is less helpful than comparison with the patient's own baseline. PEF shows diurnal variation; it is generally lowest on first awakening and highest several hours before the midpoint of the waking day. PEF should be measured in the morning before the administration of a bronchodilator and in the afternoon after taking a bronchodilator. A 20% change in PEF values from morning to afternoon or from day to day suggests inadequately controlled asthma. PEF values less than 200 L/min indicate severe airflow obstruction.

#### D. Additional Testing

Routine chest radiographs in patients with asthma are usually normal or show only hyperinflation. Other findings may include bronchial wall thickening and diminished peripheral lung vascular shadows. Chest imaging is indicated when pneumonia, another disorder mimicking asthma, or a complication of asthma such as pneumothorax is suspected.

Skin testing or in vitro testing, including total serum IgE and allergen-specific IgE, to assess sensitivity to environmental allergens can identify atopy in patients with

persistent asthma who may benefit from therapies directed at their allergic diathesis. Evaluations for paranasal sinus disease or gastroesophageal reflux should be considered in patients with persistent, severe, or refractory asthma symptoms. An absolute eosinophil count can identify patients eligible for anti-interleukin-5 therapy to manage eosinophilic airway disease.

#### ► Complications

Complications of asthma include exhaustion, dehydration, airway infection, and tussive syncope. Pneumothorax occurs but is rare. Acute hypercapnic and hypoxic respiratory failure occurs in severe disease.

#### ► Differential Diagnosis

Patients who have atypical symptoms or poor response to therapy may have one of several conditions that mimic asthma. These disorders typically fall into upper airway disorders, lower airway disorders, systemic vasculitides, cardiac disorders, and psychiatric disorders. **Upper airway disorders** that mimic asthma include vocal fold paralysis, vocal fold dysfunction syndrome, narrowing of the supraglottic airway, and laryngeal masses or dysfunction. **Lower airway disorders** include foreign body aspiration, tracheal masses or narrowing, tracheobronchomalacia, airway edema (eg, angioedema or inhalation injury), nonasthmatic chronic obstructive pulmonary disease (COPD) (chronic bronchitis or emphysema), bronchiectasis, allergic bronchopulmonary mycosis, cystic fibrosis, eosinophilic pneumonia, hypersensitivity pneumonitis, sarcoidosis, and bronchiolitis obliterans. A **systemic vasculitis** with pulmonary involvement may have an asthmatic component, such as eosinophilic granulomatosis with polyangiitis. **Cardiac disorders** include heart failure and pulmonary hypertension. **Psychiatric causes** include conversion disorders ("functional" asthma), emotional laryngeal wheezing, or episodic laryngeal dyskinesia. Rarely, Münchausen syndrome or malingering may explain a patient's complaints.

#### ► Approach to Management

The 2020 GINA Report *Global Strategy for Asthma Management and Prevention* provides guidelines for the management of asthma and identifies five important aspects of chronic asthma management: (1) assessing asthma control and severity, (2) distinguishing between severe asthma and uncontrolled asthma, (3) personalized pharmacologic therapy for asthma, (4) treatment of modifiable risk factors and control of environmental factors, and (5) guided self-management education and skills training.

**1. Assessing asthma control and severity**—Asthma control is assessed by evaluating symptoms, activity limitations, and risk of future exacerbations. Asthma symptoms are assessed by asking patients about their past 4 weeks including frequency of symptoms (days per week), awakening from sleep, and frequency of short-acting beta-agonist (SABA) reliever use for relief of symptoms (Table 9–1). Future risk of exacerbations is increased by poor symptom

control as well as several other risk factors: more than one exacerbation in the previous year, poor asthma medication adherence, incorrect inhaler technique, chronic sinusitis, and smoking. **Asthma severity** is evaluated retrospectively from the level of treatment needed to control symptoms and exacerbations. For example, a patient who requires Step 3 treatment to achieve control has moderate disease. Figure 9–1 describes the step therapy in a personalized asthma management plan. Typically, mild asthma responds to Step 1 or 2 treatments, moderate asthma, to Step 3 treatment, and severe asthma, to Step 4 or 5 treatments.

**2. Severe vs uncontrolled asthma**—It is important to distinguish between severe and uncontrolled asthma in patients who are using Step 4 or Step 5 treatments. The clinician must assess inhaler technique, medication adherence, comorbidities such as obstructive sleep apnea or gastroesophageal reflux disease (GERD), and ongoing exposure to allergens as causes of poor asthma control. If the patient still requires Step 4 or 5 therapy after these issues have been addressed, then the patient has severe asthma and should be referred to a pulmonary or asthma specialist.

**3. Pharmacotherapy for asthma**—The goals of pharmacologic therapy are to minimize chronic symptoms that interfere with normal activity (including exercise), to prevent recurrent exacerbations, to reduce or eliminate the need for emergency department visits or hospitalizations, and to maintain normal or near-normal pulmonary function. Personalized asthma management is a continuous cycle that involves assessment, treatment and review with the goals of symptom control and minimizing future risk. These goals should be met while providing therapeutic agents with the fewest adverse effects and while satisfying patients' expectations of asthma care. Management should include stepping up therapy if asthma remains uncontrolled despite adherence and good inhaler technique, and stepping down to find the minimum effective therapeutic dose.

**4. Treat modifiable risk factors and control environmental factors**—Significant reduction in exposure to nonspecific airway irritants in all patients or to inhaled allergens in atopic patients may reduce symptoms and medication needs. Comorbid conditions that impair asthma management, such as smoking, rhinosinusitis, gastroesophageal reflux, obesity, and obstructive sleep apnea, should be identified and treated. Nonpharmacologic interventions include increasing physical activity and breathing exercises.

**5. Guided asthma self-management education and skills training**—Self-management includes self-monitoring of symptoms or peak flow, a written action plan, and regular review of asthma control, treatment, and skills with a health care professional.

(Table 9–3) used on an as-needed basis to relieve breakthrough symptoms, and (3) **add-on therapies** for severe asthma. Figure 9–1 shows a personalized management plan for asthma to control symptoms and minimize future risk.

Most asthma medications are administered by inhalation or by oral dosing. Inhalation of an appropriate agent results in a more rapid onset of pulmonary effects as well as fewer systemic effects compared with the oral dose required to achieve the same effect on the airways. Proper inhaler technique and the use of an inhalation chamber (a "spacer") with metered-dose inhalers (MDIs) improve drug delivery to the lung and decrease oropharyngeal drug deposition. Nebulizer therapy is reserved for patients who are acutely ill and those who cannot use inhalers because of difficulties with coordination, understanding, or cooperation.

**1. Inhaled corticosteroids**—Inhaled corticosteroids are essential controller medications (Tables 9–3 and 9–4). Once the diagnosis of asthma is made, early initiation of inhaled corticosteroid therapy leads to a greater improvement in lung function than delayed therapy. Prescribing as-needed or daily controller inhaled corticosteroids at the start of asthma therapy conveys a message to patients that both symptom control and risk reduction are the mainstays of asthma treatment. The most important determinants of medication choice, device and dose are a patient's symptoms and risk factors, along with practical issues (such as cost and delivery mechanism). Inhaled corticosteroid dosages are classified as low-, medium-, and high-dose strengths in various published sources including GINA, but low-dose inhaled corticosteroid provides clinical benefit and is sufficient for most patients with asthma. Dosages for inhaled corticosteroids vary depending on the specific agent and delivery device (Table 9–4). For patients who require high-dose inhaled corticosteroids to achieve adequate symptom control, after 3 months of good control the dose of inhaled corticosteroid should be decreased to the lowest dose that preserves symptom control and minimizes exacerbation risk.

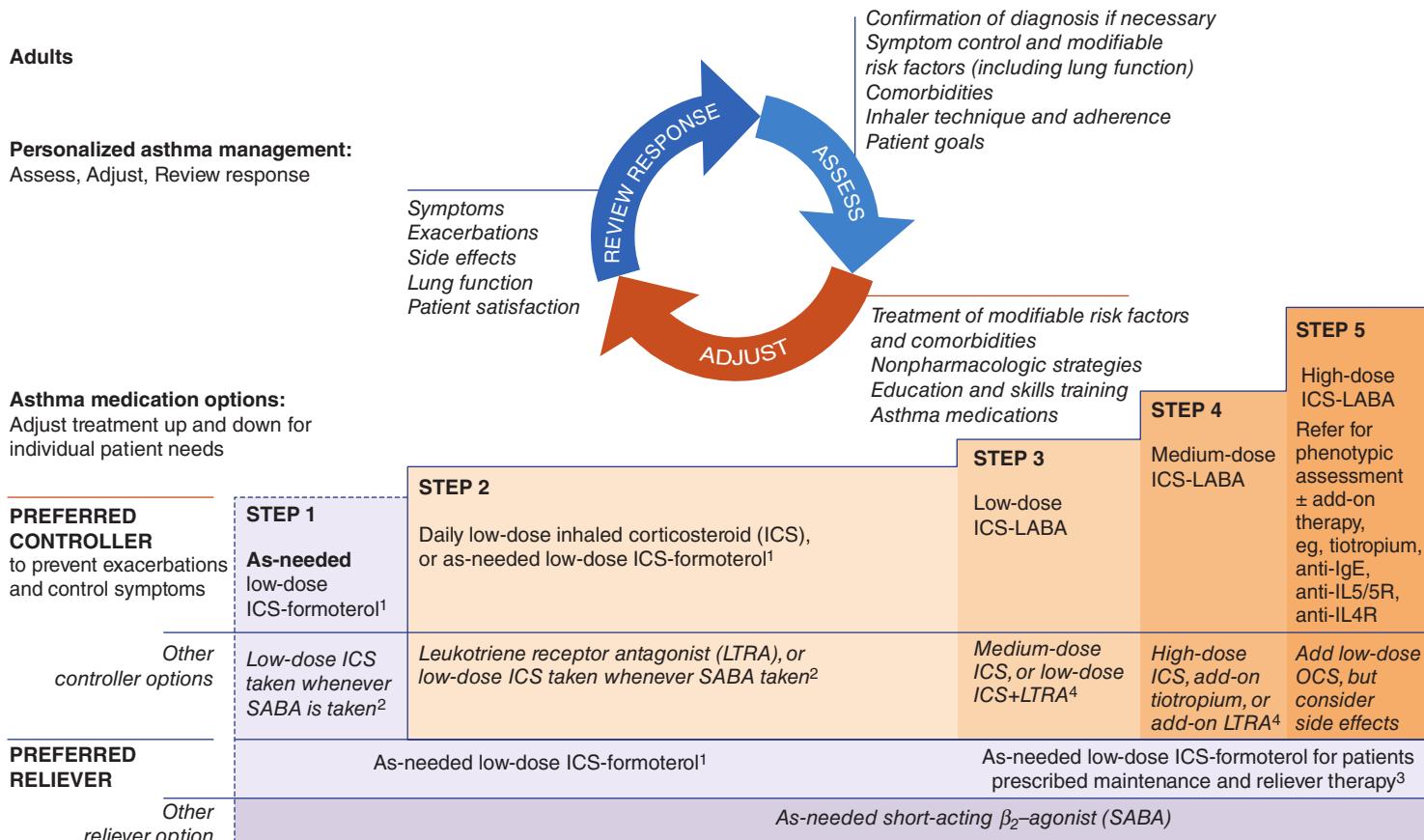
Concomitant use of a MDI and an inhalation chamber coupled with mouth washing after inhaled corticosteroid use decreases systemic absorption and local side effects (cough, dysphonia, oropharyngeal candidiasis). Dry powder inhalers (DPIs) are not used with an inhalation chamber. Systemic effects (adrenal suppression, osteoporosis, skin thinning, easy bruising, and cataracts) may occur with high-dose inhaled corticosteroid therapy. Combination inhalers with an inhaled corticosteroid and a long-acting beta-2-agonist (LABA) offer convenient treatment of asthma. The GINA report recommends low-dose inhaled corticosteroid/formoterol as its preferred agent due to clinical evidence but notes that its cost and availability in different countries must be taken into consideration. Budesonide/formoterol is listed as a World Health Organization (WHO) essential medication.

**2. Beta-adrenergic agonists**—Beta-agonists are divided into SABAs and LABAs. SABAs (Table 9–3), including agents such as albuterol, levalbuterol, bitolterol, pirbuterol, and terbutaline, are mainstays of reliever or

## ► Treatment

### A. Pharmacologic Agents

Asthma medications can be divided into three categories: (1) **long-term controller** medications (Table 9–2) used long-term to reduce airway inflammation, symptoms, and risk of future exacerbations, (2) **reliever** medications



<sup>1</sup>Off-label; data only with budesonide-formoterol (bud-form)

<sup>2</sup>Off-label; separate or combination ICS and SABA inhalers

<sup>3</sup>Low-dose ICS-form is the reliever for patients prescribed bud-form of BDP-form maintenance and reliever therapy

<sup>4</sup>Consider adding HDM SLIT for sensitized patients with allergic rhinitis and FEV<sub>1</sub> > 70% predicted

**Figure 9–1.** Personalized management to control asthma symptoms and to minimize future risk. BDP, beclomethasone dipropionate; HDM SLIT, house dust mite sublingual immunotherapy; LABA, long-acting beta-2-agonist; OCS, oral corticosteroids; SABA, short-acting beta-2-agonist. (Adapted with permission from Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2019, ©2019 Global Initiative for Asthma. Available from: [www.ginasthma.org/](http://www.ginasthma.org/).)

**Table 9–2.** Long-term controller medications for asthma.

| Medication                           | Dosage Form   | Adult Dose  | Comments  |
|--------------------------------------|---|---|---|
| <b>Inhaled Corticosteroids (ICS)</b> |   |   | (See Table 9–4)   |
| <b>Systemic Corticosteroids</b>      |   |   | (Applies to all three corticosteroids)  |
| Methylprednisolone                   | 2-, 4-, 6-, 8-, 16-, 32-mg tablets  | 40–60 mg  |   |
| Prednisolone                         | 5-mg tablets; 5 mg/5 mL, 15 mg/5 mL oral solution   | 40–60 mg  |   |
| Prednisone                           | 1-, 2.5-, 5-, 10-, 20-, 50-mg tablets; 5 mg/mL oral solution  | 7.5–60 mg   | <ul style="list-style-type: none"> <li>Administer single dose in am either daily or on alternate days (alternate-day therapy may produce less adrenal suppression) as needed for control.</li> <li>Short courses or “bursts” as single or two divided doses for 3–10 days are effective for establishing control when initiating therapy or during a period of gradual deterioration.</li> <li>There is no evidence that tapering the dose following improvement in symptom control and pulmonary function prevents relapse.</li> </ul> |
| <b>Inhaled LABA</b>                  |   |   | Should not be used for symptom relief or exacerbations. Use with inhaled corticosteroids.   |
| Formoterol                           | Inhalation: 20 mcg/2 mL nebulizer (DPI discontinued by FDA in United States)                                      | 20 mcg every 12 hours   | <ul style="list-style-type: none"> <li>Additional doses should not be administered for at least 12 hours.</li> <li>Agents should be used only with their specific inhaler and should not be taken orally.</li> <li>Decreased duration of protection against EIB may occur with regular use.</li> </ul>  |
| Salmeterol                           | DPI: 50 mcg/actuation   | 1 blister every 12 hours                                      |   |
| <b>Combined Medication</b>           |   |   |   |
| Budesonide/formoterol                | HFA MDI: 80 mcg/4.5 mcg<br>160 mcg/4.5 mcg  | 2 inhalations twice daily; dose depends on severity of asthma | <ul style="list-style-type: none"> <li>80/4.5 mcg for asthma not controlled on low- to medium-dose ICS.</li> <li>160/4.5 mcg for asthma not controlled on medium- to high-dose ICS.</li> </ul>  |
| Fluticasone/salmeterol               | DPI: 100 mcg/50 mcg<br>250 mcg/50 mcg<br>500 mcg/50 mcg<br>HFA: 45 mcg/21 mcg<br>115 mcg/21 mcg<br>230 mcg/21 mcg | 1 inhalation twice daily; dose depends on severity of asthma  | <ul style="list-style-type: none"> <li>100/50 mcg DPI or 45/21 mcg HFA for asthma not controlled on low- to medium-dose ICS.</li> <li>250/50 mcg DPI or 115/21 mcg HFA for asthma not controlled on medium- to high-dose ICS.</li> </ul>  |
| Fluticasone furoate/vilanterol       | DPI: 100 mcg/25 mcg or 200 mcg/25 mcg per blister   | 1 puff inhaled daily  | <ul style="list-style-type: none"> <li>Once-daily asthma maintenance.</li> </ul>  |
| Mometasone/formoterol                | 100 mcg/5 mcg/spray<br>200 mcg/5 mcg/spray  | 2 inhalations twice daily                                     |   |
| <b>Cromolyn and Nedocromil</b>       |   |   |   |
| Cromolyn                             | MDI: 0.8 mg/puff<br>Nebulizer: 20 mg/ampule   | 2 puffs four times daily<br>1 ampule four times daily         | <ul style="list-style-type: none"> <li>4- to 6-week trial may be needed to determine maximum benefit.</li> <li>Dose by MDI may be inadequate to affect hyperresponsiveness.</li> <li>One dose before exercise or allergen exposure provides effective prophylaxis for 1–2 hours. Not as effective for EIB as SABA.</li> <li>Once control is achieved, the frequency of dosing may be reduced.</li> </ul>  |
| Nedocromil                           | MDI: 1.75 mg/puff   | 2 puffs four times daily                                      |   |

(continued)

**Table 9–2.** Long-term controller medications for asthma. (continued)

| Medication                                 | Dosage Form                                      | Adult Dose   | Comments   |
|--|--|--|--|
| <b>Inhaled Long-Acting Anticholinergic</b> |  |  | Should not be used for symptom relief or exacerbations. Use with ICS.  |
| Tiotropium                                 | DPI: 18 mcg/blister                              | 1 blister daily  |  |
| <b>Leukotriene Modifiers</b>               |  |  |  |
| <b>Leukotriene Receptor Antagonists</b>    |  |  |  |
| Montelukast                                | 4- or 5-mg chewable tablet; 10-mg tablet         | 10 mg daily at bedtime   | <ul style="list-style-type: none"> <li>Exhibits a flat dose-response curve. Doses &gt; 10 mg will not produce a greater response in adults.</li> </ul>   |
| Zafirlukast                                | 10- or 20-mg tablet                              | 20-mg tablet twice daily   | <ul style="list-style-type: none"> <li>Administration with meals decreases bioavailability; take at least 1 hour before or 2 hours after meals.</li> <li>Monitor for symptoms and signs of hepatic dysfunction.</li> </ul>   |
| <b>5-Lipoxygenase Inhibitor</b>            |  |  |  |
| Zileuton                                   | 600-mg tablet                                    | 600 mg four times daily  | <ul style="list-style-type: none"> <li>Monitor hepatic enzyme (ALT).</li> </ul>  |
| <b>Methylxanthines</b>                     |  |  |  |
| Theophylline                               | Liquids, sustained-release tablets, and capsules | Starting dose: 10 mg/kg/day up to 300 mg maximum<br>Usual maximum dose: 800 mg/day | <ul style="list-style-type: none"> <li>Adjust dose to achieve serum concentration of 5–15 mcg/mL after at least 48 hours on same dose.</li> <li>Due to wide interpatient variability in theophylline metabolic clearance, routine serum theophylline level monitoring is important.</li> </ul> |
| <b>Monoclonal Antibodies</b>               |  |  |  |
| Omalizumab                                 | Subcutaneous injection                           | Dependent on pretreatment IgE level; up to 375 mg every 2 weeks                    | <ul style="list-style-type: none"> <li>Binds to IgE; prevents interaction with IgE receptor on mast cells and basophils</li> <li>Carries black-box warning of anaphylaxis</li> <li>Suggested IgE level 30–1500 international units/mL</li> </ul>   |
| Mepolizumab                                | Subcutaneous injection                           | 100 mg every 4 weeks   | <ul style="list-style-type: none"> <li>Binds to IL-5; prevents interaction with receptor</li> <li>Suggested AEC ≥ 150–300/mcL (0.15–0.3 × 10<sup>9</sup>/L)</li> </ul>   |
| Reslizumab                                 | Intravenous injection                            | 3 mg/kg every 4 weeks  | <ul style="list-style-type: none"> <li>Binds to IL-5; prevents interaction with receptor</li> <li>Carries black-box warning of anaphylaxis</li> <li>Suggested AEC ≥ 400/mcL (0.4 × 10<sup>9</sup>/L)</li> </ul>  |
| Benralizumab                               | Subcutaneous injection                           | 30 mg every 4 weeks for 3 doses, then every 8 weeks                                | <ul style="list-style-type: none"> <li>Binds to IL-5 receptor; blocks receptor-ligand interaction and also causes apoptosis of basophils and eosinophils</li> <li>Suggested AEC ≥ 300/mcL (0.3 × 10<sup>9</sup>/L)</li> </ul>  |
| Dupilumab                                  | Subcutaneous injection                           | 200 or 300 mg every 2 weeks  | <ul style="list-style-type: none"> <li>Binds to IL-4Ralpha; blocks IL-4 and IL-13 signaling</li> <li>Suggested AEC ≥ 150/mcL (0.15 × 10<sup>9</sup>/L) and/or FENO ≥ 25 ppb</li> </ul>   |

AEC, absolute eosinophil count; ALT, alanine aminotransferase; DPI, dry powder inhaler; EIB, exercise-induced bronchospasm; FDA, US Food and Drug Administration; FENO, fractional exhaled nitric oxide; HFA, hydrofluoroalkane; LABA, long-acting beta-2-agonist; MDI, metered-dose inhaler; SABA, short-acting beta-2-agonist.

**Table 9–3.** Reliever medications for asthma.

| Medication   | Dosage Form  | Adult Dose   | Comments   |
|--|--|--|--|
| <b>Inhaled Short-Acting Beta-2-Agonists (SABA)</b> |  |  |  |
| Albuterol CFC                                      | MDI: 90 mcg/puff,<br>200 puffs/canister  | 2 puffs 5 minutes before exercise<br>2 puffs every 4–6 hours as needed | <ul style="list-style-type: none"> <li>An increasing use or lack of expected effect indicates diminished control of asthma.</li> </ul>   |
| Albuterol HFA                                      | MDI: 90 mcg/puff,<br>200 puffs/canister  | 2 puffs 5 minutes before exercise<br>2 puffs every 4–6 hours as needed | <ul style="list-style-type: none"> <li>Not recommended for long-term daily treatment. Regular use exceeding 2 days/week for symptom control (not prevention of EIB) indicates the need to step up therapy.</li> </ul>  |
| Pirbuterol CFC                                     | MDI: 200 mcg/puff,<br>400 puffs/canister   | 2 puffs 5 minutes before exercise<br>2 puffs every 4–6 hours as needed | <ul style="list-style-type: none"> <li>Differences in potency exist, but all products are essentially comparable on a per-puff basis.</li> </ul>   |
| Levalbuterol HFA                                   | MDI: 45 mcg/puff,<br>200 puffs/canister  | 2 puffs 5 minutes before exercise<br>2 puffs every 4–6 hours as needed | <ul style="list-style-type: none"> <li>May double usual dose for mild exacerbations.</li> <li>Prime the inhaler by releasing four actuations prior to use.</li> <li>Periodically clean HFA activator, as drug may block/plug orifice.</li> </ul>   |
| Albuterol  | Nebulizer solution:<br>0.63 mg/3 mL<br>1.25 mg/3 mL<br>2.5 mg/3 mL<br>5 mg/mL (0.5%)     | 1.25–5 mg in 3 mL of saline every 4–8 hours as needed                  | <ul style="list-style-type: none"> <li>May mix with budesonide inhalant suspension, cromolyn, or ipratropium nebulizer solutions.</li> <li>May double dose for severe exacerbations.</li> </ul>  |
| Levalbuterol (R-albuterol)                         | Nebulizer solution:<br>0.31 mg/3 mL<br>0.63 mg/3 mL<br>1.25 mg/0.5 mL<br>1.25 mg/3 mL    | 0.63–1.25 mg every 8 hours as needed                                   | <ul style="list-style-type: none"> <li>Compatible with budesonide inhalant suspension. The product is a sterile-filled, preservative-free, unit dose vial.</li> </ul>  |
| <b>Anticholinergics</b>                            |  |  |  |
| Ipratropium HFA                                    | MDI: 17 mcg/puff,<br>200 puffs/canister  | 2–3 puffs every 6 hours  | <ul style="list-style-type: none"> <li>Evidence is lacking for anticholinergics producing added benefit to beta-2-agonists in long-term asthma control therapy.</li> </ul>   |
|  | Nebulizer solution:<br>0.25 mg/mL (0.025%)   | 0.25 mg every 6 hours  |  |
| Ipratropium with albuterol                         | MDI: 18 mcg/puff of ipratropium bromide and 90 mcg/puff of albuterol, 200 puffs/canister | 2–3 puffs every 6 hours  |  |
|  | Nebulizer solution:<br>0.5 mg/3 mL ipratropium bromide and 2.5 mg/3 mL albuterol         | 3 mL every 4–6 hours   | <ul style="list-style-type: none"> <li>Contains EDTA to prevent discolorations of the solution. This additive does not induce bronchospasm.</li> </ul>   |
| <b>Systemic Corticosteroids</b>                    |  |  |  |
| Methylprednisolone                                 | 2-, 4-, 6-, 8-, 16-, 32-mg tablets   | 40–60 mg/day as single or 2 divided doses                              | <ul style="list-style-type: none"> <li>Short courses or “bursts” are effective for establishing control when initiating therapy or during a period of gradual deterioration.</li> <li>The burst should be continued until symptoms resolve and the PEF is at least 80% of personal best. This usually requires 3–10 days but may require longer. There is no evidence that tapering the dose following improvements prevents relapse.</li> </ul> |
| Prednisolone                                       | 5-mg tablets;<br>5 mg/5 mL, 15 mg/5 mL oral solution                                     | 40–60 mg/day as single or 2 divided doses                              |  |

(continued)

**Table 9–3.** Reliever medications for asthma. (continued)

| Medication                 | Dosage Form  | Adult Dose                                | Comments   |
|----------------------------|--|---|--|
| Prednisone                 | 1-, 2.5-, 5-, 10-, 20-, 50-mg tablets; 5 mg/mL oral solution | 40–60 mg/day as single or 2 divided doses |  |
| Methylprednisolone acetate | Repository injection:<br>40 mg/mL<br>80 mg/mL                | 240 mg intramuscularly once               | • May be used in place of a short burst of oral corticosteroids in patients who are vomiting or if adherence is a problem. |

CFC, chlorofluorocarbon; EIb, exercise-induced bronchospasm; HFA, hydrofluoroalkane; MDI, metered-dose inhaler; PEF, peak expiratory flow.

Adapted from National Asthma Education and Prevention Program. Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma. National Institutes of Health Pub. No. 08-4051. Bethesda, MD, 2007.

rescue therapy for asthma patients. There is no convincing evidence to support the use of one agent over another. All asthmatics should have immediate access to a SABA because they are the most effective bronchodilators during exacerbations and provide immediate relief of symptoms. Administration before exercise effectively prevents exercise-induced bronchoconstriction.

Inhaled SABA therapy is as effective as oral or parenteral beta-agonist therapy in relaxing airway smooth muscle and improving acute asthma and offers the advantages of rapid onset of action (less than 5 minutes) with fewer systemic side effects. Repetitive administration produces incremental bronchodilation. One or two inhalations of a SABA from an MDI are usually sufficient for mild to

**Table 9–4.** Estimated clinically comparable daily dosages for inhaled corticosteroids for adults with asthma.

| Medication   | Low Daily Dose            | Medium Daily Dose              | High Daily Dose        |
|--|---------------------------|--------------------------------|------------------------|
| Beclomethasone dipropionate HFA<br>40 or 80 mcg/puff   | 80–240 mcg                | > 240–480 mcg                  | > 480 mcg              |
| Budesonide dipropionate DPI<br>90, 180, or 200 mcg/inhalation                                      | 180–400 mcg               | > 400–800 mcg                  | > 800 mcg              |
| Flunisolide<br>250 mcg/puff  | 500–1000 mcg              | > 1000–2000 mcg                | > 2000 mcg             |
| Flunisolide HFA<br>80 mcg/puff   | 320 mcg                   | > 320–640 mcg                  | > 640 mcg              |
| Fluticasone propionate<br>HFA/MDI: 44, 110, or 220 mcg/puff<br>DPI: 50, 100, or 250 mcg/inhalation | 88–264 mcg<br>100–300 mcg | > 264–440 mcg<br>> 300–500 mcg | > 440 mcg<br>> 500 mcg |
| Mometasone furoate DPI<br>200 mcg/puff   | 200 mcg                   | 400 mcg                        | > 400 mcg              |
| Triamcinolone acetonide<br>75 mcg/puff   | 300–750 mcg               | > 750–1500 mcg                 | > 1500 mcg             |

DPI, dry powder inhaler; HFA, hydrofluoroalkane; MDI, metered-dose inhaler.

Notes:

- The most important determinant of appropriate dosing is the clinician's judgment of the patient's response to therapy. Most of clinical benefit from inhaled corticosteroid therapy is seen at low doses; responsiveness varies among patients.
- Potential drug interactions:

A number of the inhaled corticosteroids, including fluticasone, budesonide, and mometasone, are metabolized in the gastrointestinal tract and liver by CYP 3A4 isoenzymes. Potent inhibitors of CYP 3A4, such as ritonavir and ketoconazole, have the potential for increasing systemic concentrations of these inhaled corticosteroids by increasing oral availability and decreasing systemic clearance. Some cases of clinically significant Cushing syndrome and secondary adrenal insufficiency have been reported.

Adapted from National Asthma Education and Prevention Program. Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma. National Institutes of Health Pub. No. 08-4051. Bethesda, MD, 2007, and Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2019. (Available from: [www.ginasthma.org](http://www.ginasthma.org))

moderate symptoms. Severe exacerbations frequently require higher doses: 6–12 puffs every 30–60 minutes of albuterol by MDI with an inhalation chamber or 2.5 mg by nebulizer provide equivalent bronchodilation. Administration by nebulization does not offer more effective delivery than MDIs used correctly but does provide higher doses. With most SABAs, the recommended dose by nebulizer for acute asthma (albuterol, 2.5 mg) is 25–30 times that delivered by a single activation of the MDI (albuterol, 0.09 mg). This difference suggests that standard dosing of inhalations from an MDI may be insufficient in the setting of an acute exacerbation. Independent of dose, nebulizer therapy may be more effective in patients who are unable to coordinate inhalation of medication from an MDI because of age, agitation, or severity of the exacerbation.

GINA does not recommend SABA-only treatment of asthma in adults or adolescents and does not recommend scheduled daily use of SABAs. Although SABA is effective as a quick relief medication, patients who are treated with SABA alone are at increased risk for asthma-related death and urgent health care even if their symptoms are controlled. Increased use (more than one canister a month) or lack of expected effect indicates diminished asthma control and the need for additional long-term controller therapy.

LABAs provide bronchodilation for up to 12 hours after a single dose. Salmeterol and formoterol are LABAs available for asthma in the United States. In combination with an inhaled corticosteroid they are indicated for long-term prevention of asthma symptoms (including nocturnal symptoms) and for prevention of exercise-induced bronchospasm. LABAs should not be used as monotherapy because they have no anti-inflammatory effect and because monotherapy has been associated with a small but statistically significant increased risk of severe or fatal asthma attacks in two large studies. Combination inhalers containing formoterol and low-dose budesonide are the preferred option because of a large study in mild asthma that showed a 64% reduction in severe exacerbations compared with SABA-only treatment, and two large studies in mild asthma that showed noninferiority for severe exacerbations compared to low-dose inhaled corticosteroid alone.

**3. Systemic corticosteroids**—Systemic corticosteroids (oral prednisone or prednisolone or parenteral methylprednisolone) are most effective in achieving prompt control of asthma during acute exacerbations. Systemic corticosteroids are effective as primary treatments for patients with moderate to severe asthma exacerbations and for patients with exacerbations that do not respond promptly and completely to inhaled SABA therapy. These medications speed the resolution of airflow obstruction and reduce the rate of relapse. Delays in administering corticosteroids may result in progressive impairment. Therefore, patients with moderate to severe asthma should be prescribed oral corticosteroids so they are available for early, at-home administration. The minimal effective dose of systemic corticosteroids for asthma patients has not been identified. Outpatient prednisone “burst” therapy is 0.5–1 mg/kg/day (typically 40–60 mg) in 1–2 doses for 3–7 days. Severe

exacerbations requiring hospitalization typically require 1 mg/kg of prednisone or methylprednisolone every 6–12 hours for 48 hours or until the FEV<sub>1</sub> (or PEF rate) returns to 50% of predicted (or 50% of baseline). The dose is then decreased to 0.5 mg/kg/day until the PEF reaches 70% of predicted or personal best. No clear advantage has been found for higher doses of corticosteroids. It may be prudent to administer corticosteroids intravenously to critically ill patients to avoid concerns about altered gastrointestinal absorption.

In patients with refractory, poorly controlled asthma, systemic corticosteroids may be required for the long-term suppression of symptoms. Repeated efforts should be made to reduce the dose to the minimum needed to control symptoms. Concurrent treatment with calcium supplements and vitamin D should be initiated to prevent corticosteroid-induced bone mineral loss with long-term administration. Bone mineral density testing after 3 or more months of cumulative systemic corticosteroid exposure can guide the use of bisphosphonates for treatment of steroid-induced osteoporosis. Rapid discontinuation of systemic corticosteroids after long-term use may precipitate adrenal insufficiency.

**4. Anticholinergics**—Anticholinergic agents reverse vagally mediated bronchospasm but not allergen- or exercise-induced bronchospasm. They may decrease mucous gland hypersecretion. Both **short-acting muscarinic agents** (SAMAs) and **long-acting muscarinic agents** (LAMAs) are available. Ipratropium bromide, a SAMA, is less effective than SABA for relief of acute bronchospasm, but it is the inhaled drug of choice for patients with intolerance to SABA or with bronchospasm due to beta-blocker medications. Ipratropium bromide reduces the rate of hospital admissions when added to inhaled SABAs in patients with moderate to severe asthma exacerbations. Although LAMAs have long been the cornerstone of therapy for COPD, their role in asthma continues to evolve. Studies have shown that the addition of tiotropium to medium-dose inhaled corticosteroid and salmeterol improves lung function and reduces the frequency of asthma exacerbations.

**5. Leukotriene modifiers**—Leukotrienes are potent mediators that contribute to airway obstruction and asthma symptoms by contracting airway smooth muscle, increasing vascular permeability and mucous secretion, and attracting and activating airway inflammatory cells. Zileuton is a 5-lipoxygenase inhibitor that decreases leukotriene production, and zafirlukast and montelukast are cysteinyl leukotriene receptor antagonists. In randomized controlled trials (RCTs), these agents caused modest improvements in lung function and reductions in asthma symptoms and lessened the need for SABA rescue therapy. These agents are less effective than inhaled corticosteroid for exacerbation reduction but may be considered as alternatives in patients with asthma who are unable to take inhaled corticosteroid or have undesirable side effects.

**6. Phosphodiesterase inhibitor**—Theophylline provides mild bronchodilation in asthmatic patients. It also has anti-inflammatory and immunomodulatory properties,

enhances mucociliary clearance, and strengthens diaphragmatic contractility. Sustained-release theophylline preparations are effective in controlling nocturnal symptoms and as added therapy in patients with moderate or severe persistent asthma whose symptoms are inadequately controlled by inhaled corticosteroids. Low-dose sustained-release theophylline is included as a less effective option in Step 3 treatment. Neither theophylline nor aminophylline is recommended for therapy of acute asthma exacerbations.

Theophylline has a notably narrow therapeutic-toxic range. At therapeutic doses, potential adverse effects include insomnia, aggravation of dyspepsia and gastroesophageal reflux, and urination difficulties in men with prostatic hyperplasia. Dose-related toxicities include nausea, vomiting, tachyarrhythmias, headache, seizures, hyperglycemia, and hypokalemia. Theophylline serum levels are highly variable due to many factors that alter drug absorption, significant individual differences in metabolism, and multiple drug-drug interactions. Therefore, serum concentrations need to be monitored closely.

**7. Mediator inhibitors**—Cromolyn sodium and nedocromil are long-term control medications that prevent asthma symptoms and improve airway function in patients with mild persistent or exercise-induced asthma. These agents modulate mast cell mediator release and eosinophil recruitment and inhibit both early and late asthmatic responses to allergen challenge and exercise-induced bronchospasm. The clinical response to these agents is less predictable than to inhaled corticosteroids. Both agents have excellent safety profiles.

**8. Monoclonal antibody agents**—Asthmatic patients who require monoclonal antibody therapies should be evaluated by either a pulmonologist or allergist experienced in their use. Omalizumab is a recombinant antibody that binds IgE without activating mast cells. In clinical trials in patients with moderate to severe asthma and elevated serum IgE levels, omalizumab reduced the need for corticosteroids. Reslizumab, mepolizumab, and benralizumab are interleukin-5 antagonist monoclonal antibodies (anti IL-5/5R) approved for the treatment of severe asthma with peripheral blood eosinophilia that has not responded to standard treatments. Dupilumab is a self-administered monoclonal antibody (anti-IL-4Ralpha) that inhibits overactive signaling of interleukin-4 and interleukin-13.

## B. Desensitization

Immunotherapy for specific allergens may be considered in selected asthma patients who have exacerbations when exposed to allergens to which they are sensitive and when unresponsive to environmental control measures or other therapies. Studies show a reduction in asthma symptoms in patients treated with single-allergen immunotherapy. Because of the risk of immunotherapy-induced bronchoconstriction, it should be administered only in a setting where such complications can be immediately treated.

## C. Vaccination

Adult patients aged 19–64 with asthma should receive the 23-valent pneumococcal polysaccharide vaccine (Pneumovax 23) and annual influenza vaccinations. Inactive vaccines (Pneumovax) are associated with few side effects. However, the use of the intranasal live attenuated influenza vaccine may be associated with asthma exacerbations in young children.

## ► Treatment of Asthma Exacerbations

GINA asthma treatment algorithms begin with an assessment of the severity of a patient's baseline asthma. Adjustments to that algorithm follow a stepwise approach based on a careful assessment of asthma control. Educating patients to recognize symptoms of an exacerbation and to use their action plan are important aspects of asthma management. Symptoms of exacerbations include progressive breathlessness, increasing chest tightness, decreased peak flow, and lack of improvement after SABA therapy (Table 9–5). Most instances of uncontrolled asthma are mild and can be managed successfully by patients at home with self-management plans. More severe exacerbations require evaluation and management in a primary care office (Figure 9–2) or emergency department setting (Figure 9–3).

## A. Mild to Moderate Exacerbations

Mild asthma exacerbations are characterized by only minor changes in airway function (PEF greater than 60% of best) with minimal symptoms and signs of airway dysfunction. Many such patients respond quickly and fully to an inhaled SABA alone. However, an inhaled SABA may need to be continued at increased doses, eg, every 3–4 hours for 24–48 hours. Patients may also require a short-term increase in inhaled corticosteroid to four times the usual dose. In patients not improving after 48 hours, a 5- to 7-day course of oral corticosteroids (eg, prednisone 0.5–1.0 mg/kg/day) may be necessary.

The principal goals for treating moderate asthma exacerbations are correcting hypoxemia, reversing airflow obstruction, and reducing the likelihood of obstruction recurrence. Early intervention may lessen the severity and shorten the duration of an exacerbation. Airflow obstruction is treated with continuous administration of an inhaled SABA and the early administration of systemic corticosteroids. Systemic corticosteroids should be given to patients who have a peak flow less than 70% of baseline or who do not respond to several treatments of SABA. Serial measurements of lung function to quantify the severity of airflow obstruction and its response to treatment are useful. The improvement in FEV<sub>1</sub> after 30–60 minutes of treatment correlates significantly with the severity of the asthma exacerbation. Serial measurement of airflow in the emergency department may reduce the rate of hospital admissions for asthma exacerbations. Post-exacerbation care planning is important. All patients, regardless of severity, should be provided with (1) necessary medications and taught how to use them, (2) instruction in

**Table 9–5.** Evaluation and classification of severity of asthma exacerbations.

|  | Mild                                | Moderate                    | Severe   | Respiratory Arrest Imminent                 |
|--|-------------------------------------|-----------------------------|--|---|
| <b>Symptoms</b>  |                                     |                             |  |   |
| Breathlessness   | While walking                       | At rest, limits activity    | At rest, interferes with conversation              | While at rest, mute                         |
| Talks in   | Sentences                           | Phrases                     | Words  | Silent                                      |
| Alertness  | May be agitated                     | Usually agitated            | Usually agitated                                   | Drowsy or confused                          |
| <b>Signs</b>   |                                     |                             |  |   |
| Respiratory rate   | Increased                           | Increased                   | Often > 30/minute                                  | > 30/minute                                 |
| Body position  | Can lie down                        | Prefers sitting             | Sits upright                                       | Unable to recline                           |
| Use of accessory muscles, suprasternal retractions       | Usually not                         | Commonly                    | Usually  | Paradoxical thoracoabdominal movement       |
| Wheeze   | Moderate, often only end expiratory | Loud; throughout exhalation | Usually loud; throughout inhalation and exhalation | Absent                                      |
| Pulse/minute   | < 100                               | 100–120                     | > 120  | Bradycardia                                 |
| Pulsus paradoxus   | Absent < 10 mm Hg                   | May be present 10–25 mm Hg  | Often present > 25 mm Hg                           | Absence suggests respiratory muscle fatigue |
| <b>Functional Assessment</b>                             |                                     |                             |  |   |
| PEF or FEV <sub>1</sub> , % predicted or % personal best | ≥ 70%                               | 40–69%                      | < 40%  | < 25%                                       |
| Pao <sub>2</sub> (on air, mm Hg)                         | Normal <sup>1</sup>                 | ≥ 60 <sup>1</sup>           | < 60: possible cyanosis                            | < 60: possible cyanosis                     |
| PCO <sub>2</sub> (mm Hg)                                 | < 42 <sup>1</sup>                   | < 42 <sup>1</sup>           | ≥ 42 <sup>1</sup>                                  | ≥ 42 <sup>1</sup>                           |
| Sao <sub>2</sub> (on air)                                | > 95% <sup>1</sup>                  | 90–95% <sup>1</sup>         | < 90% <sup>1</sup>                                 | < 90% <sup>1</sup>                          |

<sup>1</sup>Test not usually necessary.

FEV<sub>1</sub>, forced expiratory volume in 1 second; PEF, peak expiratory flow; Sao<sub>2</sub>, oxygen saturation.

Adapted from National Asthma Education and Prevention Program. Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma. National Institutes of Health Pub. No. 08-4051. Bethesda, MD, 2007.

self-assessment, (3) a follow-up appointment, and (4) an action plan for managing recurrence.

## B. Severe Exacerbations

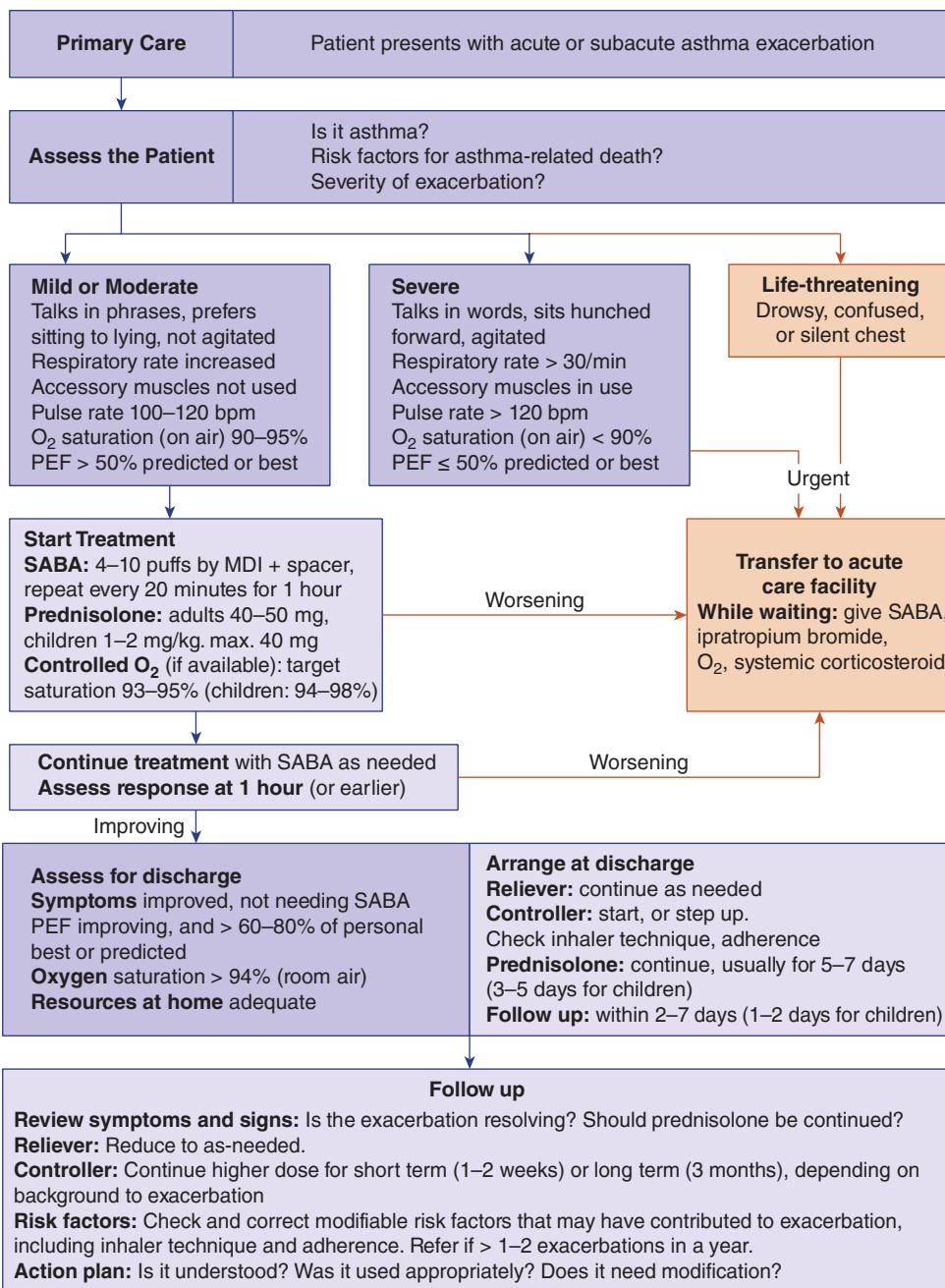
Severe exacerbations of asthma can be life-threatening, so treatment should be started immediately. All patients with a severe exacerbation should immediately receive oxygen, high doses of an inhaled SABA, and systemic corticosteroids. A brief history pertinent to the exacerbation can be completed while such treatment is being initiated. More detailed assessments, including laboratory studies, usually add little early on and so should be postponed until after therapy is instituted. Early initiation of **oxygen therapy** is paramount because asphyxia is a common cause of asthma deaths. Supplemental oxygen should be given to maintain an Sao<sub>2</sub> greater than 90% or a Pao<sub>2</sub> greater than 60 mm Hg. Oxygen-induced hypoventilation is extremely rare in asthmatic patients, and concern for hypercapnia should never delay correction of hypoxemia.

Frequent high-dose delivery of an **inhaled SABA** is indicated and usually well tolerated in severe airway obstruction. At least three MDI or nebulizer treatments

should be given in the first hour of therapy. Some studies suggest that continuous therapy is more effective than intermittent administration of these agents, but there is no clear consensus as long as similar doses are administered. After the first hour, the frequency of administration varies according to improvements in airflow and symptoms and occurrence of side effects. Ipratropium bromide reduces the rate of hospital admissions when added to inhaled SBAs in patients with moderate to severe asthma exacerbations.

**Systemic corticosteroids** are administered as detailed above. **Intravenous magnesium sulfate** (2 g intravenously over 20 minutes) is not recommended for routine use in asthma exacerbations. However, a 2-g infusion over 20 minutes may reduce hospitalization rates in acute severe asthma (FEV<sub>1</sub> less than 25% of predicted on presentation or failure to respond to initial treatment).

Mucolytic agents (eg, acetylcysteine, potassium iodide) may worsen cough or airflow obstruction. Anxiolytic and hypnotic drugs are generally contraindicated in severe asthma exacerbations because of their potential respiratory depressant effects.

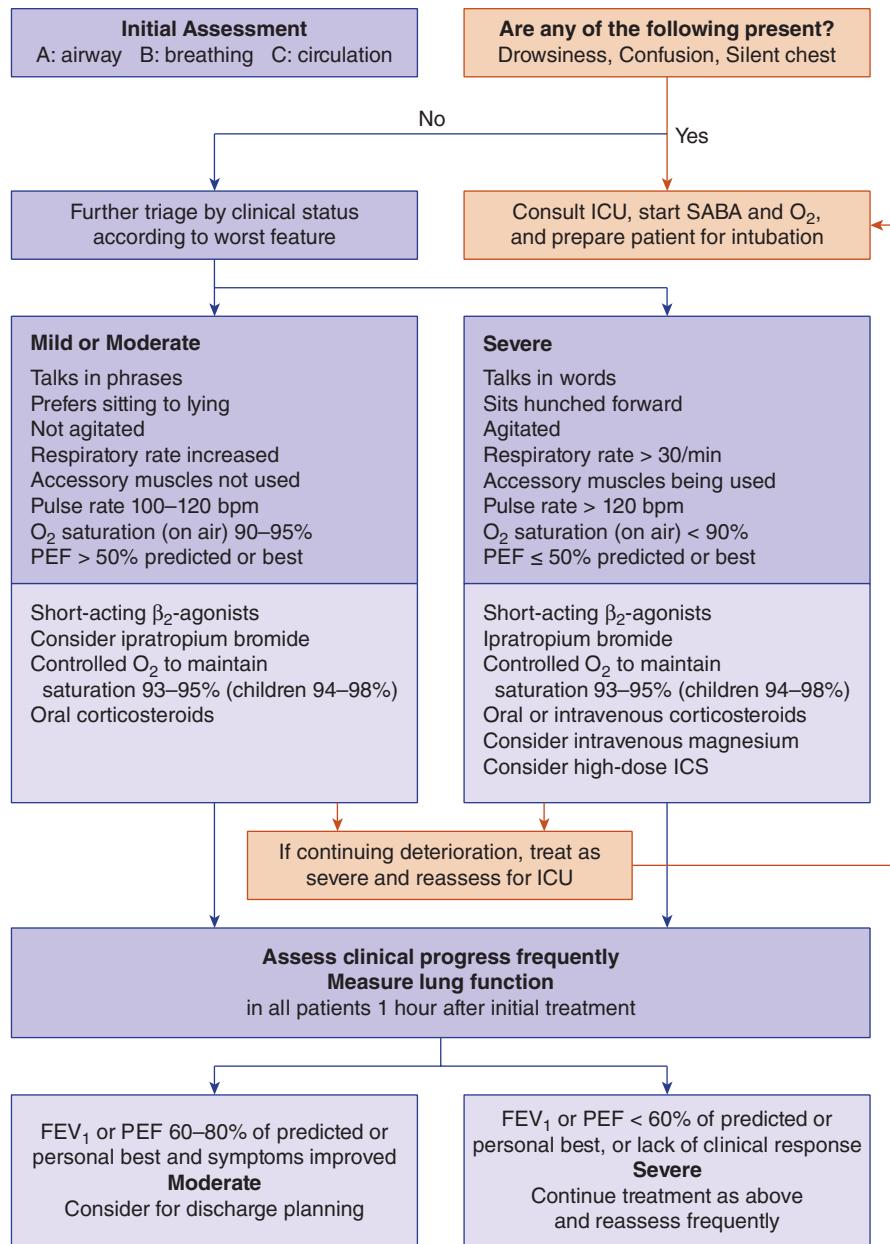


▲ **Figure 9–2.** Management of asthma exacerbations in primary care.  $O_2$ , oxygen; PEF, peak expiratory flow; SABA, short-acting beta-2-agonist (doses are for salbutamol). (Adapted with permission from Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2019, ©2019 Global Initiative for Asthma. Available from: [www.ginasthma.org/](http://www.ginasthma.org/).)

Multiple studies suggest that infections with viruses (rhinovirus) and bacteria (*Mycoplasma pneumoniae*, *Chlamydophila pneumoniae*) predispose to acute exacerbations of asthma and may underlie chronic, severe asthma. The use of empiric antibiotics is, however, not recommended in routine asthma exacerbations because there is no consistent evidence to support improved clinical outcomes.

Antibiotics should be considered when there is a high likelihood of acute bacterial respiratory tract infection, such as when patients have fever or purulent sputum and evidence of pneumonia or bacterial sinusitis.

In the **emergency department setting**, repeat assessment of patients with severe exacerbations should be done after the initial dose of an inhaled SABA and again after



**▲ Figure 9–3.** Management of asthma exacerbations in acute care facility (eg, emergency department). FEV<sub>1</sub>, forced expiratory volume in 1 second; ICS, inhaled corticosteroids; ICU, intensive care unit; O<sub>2</sub>, oxygen; PEF, peak expiratory flow; SABA, short-acting beta-2-agonist. (Adapted with permission from Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2019, ©2019 Global Initiative for Asthma. Available from: [www.ginasthma.org/](http://www.ginasthma.org/).)

3 doses of an inhaled SABA (60–90 minutes after initiating treatment). The response to initial treatment is a better predictor of the need for hospitalization than is the severity of the exacerbation on presentation. The decision to hospitalize a patient should be based on the duration and severity of symptoms, severity of airflow obstruction, ABG results (if available), course and severity of prior exacerbations, medication use at the time of the exacerbation, access to medical care and medications, adequacy of social support and home conditions, and presence of psychiatric

illness. In general, discharge to home is appropriate if the PEF or FEV<sub>1</sub> has returned to 60% or more of predicted or personal best and if symptoms are minimal or absent. Patients with a rapid response to treatment should be observed for 30 minutes after the most recent dose of bronchodilator to ensure stability of response before discharge.

In the **intensive care setting**, a small subset of patients will not respond to treatment and will progress to impending respiratory failure due to a combination of worsening airflow obstruction and respiratory muscle fatigue

(see Figure 9–3 and Table 9–5). Since such patients can deteriorate rapidly, they must be monitored in a critical care setting. Intubation of an acutely ill asthma patient is technically difficult and is best done semi-electively before the crisis of a respiratory arrest. At the time of intubation, the patient's intravascular volume should be closely monitored because hypotension commonly follows the administration of sedative medications and the initiation of positive-pressure ventilation; these patients are often dehydrated due to poor recent oral intake and high insensible losses.

The main goals of mechanical ventilation are to ensure adequate oxygenation and to avoid barotrauma. Controlled hypoventilation with permissive hypercapnia is often required to limit airway pressures. Frequent high-dose delivery of inhaled SABAs should be continued along with anti-inflammatory agents as discussed above. Many questions remain regarding the optimal delivery of inhaled SABAs to intubated, mechanically ventilated patients.

### ► When to Refer

- Atypical presentation or uncertain diagnosis of asthma, particularly if additional diagnostic testing is required (bronchoprovocation challenge, allergy skin testing, rhinoscopy, consideration of occupational exposure).
- Complicating comorbid problems, such as rhinosinusitis, tobacco use, multiple environmental allergies, suspected allergic bronchopulmonary mycosis.
- Occupational asthma.
- Uncontrolled symptoms despite a moderate-dose inhaled corticosteroid and a LABA.
- Patient not meeting goals of asthma therapy after 3–6 months of treatment.
- Frequent asthma-related health care utilization.
- More than two courses of oral prednisone therapy in the past 12 months.
- Any life-threatening asthma exacerbation or exacerbation requiring hospitalization in the past 12 months.
- Presence of social or psychological issues interfering with asthma management.

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## CHRONIC OBSTRUCTIVE PULMONARY DISEASE

### ESSENTIALS OF DIAGNOSIS

- ▶ History of cigarette smoking or other chronic inhalational exposure.
- ▶ Chronic cough, dyspnea, and sputum production.
- ▶ Rhonchi, decreased intensity of breath sounds, and prolonged expiration on physical examination.
- ▶ Airflow limitation on pulmonary function testing that is not fully reversible and is most often progressive.

### ► General Considerations

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) defines COPD as a common, preventable, and treatable disease state characterized by persistent respiratory symptoms and airflow limitation due to airway and alveolar abnormalities usually caused by significant exposure to noxious particles or gases. The term "COPD" has evolved from an umbrella term for chronic bronchitis and emphysema to one that refers to a clinical syndrome of chronic respiratory symptoms, structural pulmonary abnormalities (airways or alveoli), and impaired lung function arising from multiple causes that result in airflow limitation that is not fully reversible. Symptoms include cough, dyspnea, and sputum production. COPD is a major cause of chronic morbidity and is the third leading cause of death worldwide.

The most important causes of COPD are cigarette smoking in the developed world and biomass fuel cooking in the developing world. The majority of smokers suffer an accelerated decline in lung function that is dose- and duration-dependent. One major study of active smokers reported yearly decreases in FEV<sub>1</sub> of 66 mL per year in men and 54 mL per year in women compared to 30 mL per year in men and 22 mL per year in women who sustained smoking cessation. Fifteen percent of smokers develop progressively disabling symptoms in their 40s and 50s. Approximately two-thirds of patients seen for COPD have significant exposure to tobacco smoke. The remaining one-third may have a combination of exposures to environmental tobacco smoke, occupational dusts and chemicals, and indoor air pollution from biomass fuel used for cooking and heating in poorly ventilated buildings. Outdoor air pollution, airway infection, environmental factors, and allergy have also been implicated, along with hereditary factors (most notably, deficiency of alpha-1-antitrypsin). Atopy and bronchoconstriction in response to non-specific airway stimuli may be important risk factors. There is evidence that lung exposures to pollution and allergens early in life can lead to poor lung growth in childhood and expiratory airflow limitation, resulting in lower than predicted spirometric values in midlife.

## Clinical Findings

### A. Symptoms and Signs

Patients with COPD characteristically present in the fifth or sixth decade of life complaining of excessive cough, sputum production, and shortness of breath. Symptoms have often been present for 10 years or more, yet if diagnosed early, smoking cessation can reduce the decline in lung function. Dyspnea is noted initially only on heavy exertion, but as the condition progresses it occurs with mild activity. In severe disease, dyspnea occurs at rest. As the disease progresses, two symptom patterns tend to emerge, historically referred to as “pink puffers” and “blue bloaters” (Table 9–6). Most COPD patients have features of both disorders, and their clinical course and severity may involve other factors, such as central control of ventilation and concomitant sleep-disordered breathing.

A hallmark of COPD is the acute exacerbation of symptoms beyond normal day-to-day variation, often including increased dyspnea, an increased frequency or severity of cough, and increased sputum volume or change in sputum character. These exacerbations are commonly precipitated by infection (more often viral than bacterial) or

environmental factors. Pneumonia, pulmonary hypertension, cor pulmonale, and chronic respiratory failure characterize the late stage of COPD.

### B. Laboratory Findings

Spirometry provides objective information about pulmonary function and assesses the response to therapy. Pulmonary function tests early in the course of COPD may reveal only abnormal closing volume and reduced mid-expiratory flow rates. Reductions in FEV<sub>1</sub> and in the ratio of FEV<sub>1</sub> to vital capacity (FEV<sub>1</sub>% or FEV<sub>1</sub>/FVC ratio) establish the presence of airflow obstruction. In severe disease, the FVC is markedly reduced. Lung volume measurements reveal an increase in residual volume (RV) and in total lung capacity (TLC), and an elevation of the RV/TLC ratio, indicative of air trapping, particularly common in patients with emphysema. In the setting of airflow obstruction, a reduction in the single breath diffusing capacity (DL<sub>CO</sub>) predicts emphysema. A severely reduced DL<sub>CO</sub> predicts exertional oxyhemoglobin desaturation and is associated with coexisting pulmonary hypertension. A 6-minute walking distance of less than 350 m is associated with increased mortality.

**Table 9–6.** Patterns of disease in advanced COPD.

|                                  | Type A: Pink Puffer (Emphysema Predominant)  | Type B: Blue Blander (Bronchitis Predominant)  |
|----------------------------------|--|--|
| History and physical examination | Major complaint is dyspnea, often severe, usually presenting after age 50. Cough is rare, with scant clear, mucoid sputum. Patients are thin, with recent weight loss common. They appear uncomfortable, with evident use of accessory muscles of respiration. Chest is very quiet without adventitious sounds. No peripheral edema. | Major complaint is chronic cough, productive of mucopurulent sputum, with frequent exacerbations due to chest infections. Often presents in late 30s and 40s. Dyspnea usually mild, though patients may note limitations to exercise. Patients frequently overweight and cyanotic but seem comfortable at rest. Peripheral edema is common. Chest is noisy, with rhonchi invariably present; wheezes are common. |
| Laboratory studies               | Hemoglobin usually normal (12–15 g/dL). Pao <sub>2</sub> normal to slightly reduced (65–75 mm Hg) but SaO <sub>2</sub> normal at rest. Paco <sub>2</sub> normal to slightly reduced (35–40 mm Hg). Chest radiograph shows hyperinflation with flattened diaphragms. Vascular markings are diminished, particularly at the apices.    | Hemoglobin usually elevated (15–18 g/dL). Pao <sub>2</sub> reduced (45–60 mm Hg) and Paco <sub>2</sub> slightly to markedly elevated (50–60 mm Hg). Chest radiograph shows increased interstitial markings (“dirty lungs”), especially at bases. Diaphragms are not flattened.   |
| Pulmonary function tests         | Airflow obstruction ubiquitous. TLC increased, sometimes markedly so. DL <sub>CO</sub> reduced. Static lung compliance increased.  | Airflow obstruction ubiquitous. TLC generally normal but may be slightly increased. DL <sub>CO</sub> normal. Static lung compliance normal.  |
| Special Evaluations              |  |  |
| Ventilation-perfusion testing    | Increased ventilation to high V/Q areas, ie, high dead space ventilation.  | Increased perfusion to low V/Q areas.  |
| Hemodynamics                     | Cardiac output normal to slightly low. Pulmonary artery pressures mildly elevated and increase with exercise.  | Cardiac output normal. Pulmonary artery pressures elevated, sometimes markedly so, and worsen with exercise.   |
| Nocturnal ventilation            | Mild to moderate degree of oxygen desaturation not usually associated with obstructive sleep apnea.  | Severe oxygen desaturation, frequently associated with obstructive sleep apnea.  |
| Exercise ventilation             | Increased minute ventilation for level of oxygen consumption; Pao <sub>2</sub> tends to fall; Paco <sub>2</sub> rises slightly.  | Decreased minute ventilation for level of oxygen consumption. Pao <sub>2</sub> may rise; Paco <sub>2</sub> may rise significantly.   |

DL<sub>CO</sub>, single-breath diffusing capacity for carbon monoxide; TLC, total lung capacity; V/Q, ventilation-perfusion.

ABG measurement characteristically shows no abnormalities early in COPD other than an increased A-a- $\text{DO}_2$ . Indeed, ABG measurement is unnecessary unless (1) hypoxemia or hypercapnia is suspected, (2) the FEV<sub>1</sub> or DL<sub>CO</sub> is less than 40% of predicted, or (3) there are clinical signs of right heart failure. Hypoxemia occurs in advanced disease, particularly when chronic bronchitis predominates. Compensated respiratory acidosis occurs in patients with chronic respiratory failure, particularly in chronic bronchitis, with worsening of acidemia during acute exacerbations.

Positive sputum cultures are poorly correlated with acute exacerbations, and research techniques demonstrate evidence of preceding viral infection in most patients with exacerbations. The ECG may show sinus tachycardia and, in advanced disease, chronic pulmonary hypertension may produce electrocardiographic abnormalities typical of cor pulmonale. Supraventricular arrhythmias (multifocal atrial tachycardia, atrial flutter, and atrial fibrillation) and ventricular irritability also occur.

### C. Imaging

Radiographs of patients with chronic bronchitis typically show only nonspecific peribronchial and perivasculär markings. Plain radiographs are insensitive for the diagnosis of emphysema; they show hyperinflation with flattening of the diaphragm or peripheral arterial deficiency in about half of cases. CT of the chest identifies and can quantify the emphysema phenotype associated with loss of tissue. Chest CT also detects airway narrowing and wall thickening characteristic of the bronchitic phenotype. In advanced disease, pulmonary hypertension may be suggested by enlargement of central pulmonary arteries on chest radiographs or chest CTs, and Doppler echocardiography provides an estimate of pulmonary artery pressure.

### Differential Diagnosis

Clinical, imaging, and laboratory findings should enable the clinician to distinguish COPD from other obstructive pulmonary disorders, such as asthma, bronchiectasis, cystic fibrosis, bronchopulmonary mycosis, and central airflow obstruction. Asthma is characterized by complete or near-complete reversibility of airflow obstruction. Bronchiectasis is distinguished from COPD by recurrent pneumonia and hemoptysis, digital clubbing, and characteristic imaging abnormalities. Cystic fibrosis occurs in children, adolescents, and young adults and has characteristic imaging as well as endocrine and hepatic abnormalities. Bronchopulmonary mycosis is characterized by eosinophilia; elevated levels of immunoglobulin E; and episodic worsening marked by fever, malaise, productive cough, and radiographic infiltrates. Mechanical obstruction of the central airways can be distinguished from COPD by flow-volume loops.

### Complications

Acute bronchitis, pneumonia, pulmonary thromboembolism, atrial dysrhythmias (such as atrial fibrillation, atrial flutter, and multifocal atrial tachycardia), and concomitant

left ventricular failure may worsen otherwise stable COPD. Pulmonary hypertension, cor pulmonale, and chronic respiratory failure are common in advanced COPD. Spontaneous pneumothorax occurs in a small fraction of patients with emphysema. Hemoptysis may result from chronic bronchitis or may signal bronchogenic carcinoma.

### Prevention

COPD is largely preventable through elimination of long-term exposure to tobacco smoke, products of combustion of biomass fuels, and other inhaled toxins. Smokers with early evidence of airflow limitation can significantly alter the course of their disease by smoking cessation. Influenza vaccination reduces the frequency and severity of influenza-like illness as well as the number of COPD exacerbations. Pneumococcal vaccination appears to reduce both the frequency of community-acquired pneumonia and the number of COPD exacerbations.

### Treatment

The treatment of COPD is guided by the severity of symptoms or the presence of an exacerbation of stable symptoms. Standards for the management of patients with stable COPD and COPD exacerbations from the American Thoracic Society and GOLD, a joint expert committee of the National Heart, Lung, and Blood Institute and the WHO, are incorporated in the recommendations below. There are three commonly used ways to identify high-risk COPD patients who may require more intense treatment: (1) FEV<sub>1</sub> less than 50% predicted, (2) more than two exacerbations within the previous year, and (3) one or more hospitalizations for COPD exacerbation in the previous year.

#### A. Ambulatory Patients

**1. Smoking cessation**—The single most important intervention in smokers with COPD is to encourage smoking cessation (see Chapter 1). Simply telling a patient to quit succeeds 5% of the time. Behavioral approaches, ranging from clinician advice to intensive group programs, may improve cessation rates. Pharmacologic therapy includes bupropion, nicotine replacement (transdermal patch, gum, lozenge, inhaler, or nasal spray), and varenicline (a partial agonist of nicotinic acetylcholine receptors). Combined pharmacotherapies (two forms of nicotine replacement, or nicotine replacement and bupropion), with or without behavioral approaches, have been recommended. Varenicline is effective but use has been limited by concerns about neuropsychiatric side effects. Electronic cigarettes are not recommended as a smoking cessation aid, due in part to concern for e-cigarette and vaping-associated lung injury (EVALI).

**2. Oxygen therapy**—Supplemental oxygen for patients with resting hypoxemia ( $\text{PaO}_2 < 56 \text{ mm Hg}$ ) is the only therapy with evidence of improvement in the natural history of COPD. Proven benefits of home oxygen therapy in hypoxic patients include longer survival, reduced hospitalizations, and better quality of life. Survival in hypoxic patients with COPD treated with supplemental oxygen

therapy is directly proportionate to the number of hours per day oxygen is administered: in hypoxicemic COPD patients treated with continuous oxygen for 24 hours daily, the survival after 36 months is about 65%—significantly better than the survival rate of about 45% in those treated with only nocturnal oxygen. Oxygen by nasal prongs must be given for at least 15 hours a day unless therapy is specifically intended only for exercise or sleep. However, several studies of supplemental oxygen therapy showed no survival benefit in COPD patients with borderline low-normal resting oxygen levels ( $\text{PaO}_2$  between 56 mm Hg and 69 mm Hg). In a study of patients with stable COPD and resting or exercise-induced moderate desaturation, the prescription of long-term supplemental oxygen did not result in a longer time to first hospitalization or death than no long-term supplemental oxygen, nor did it provide sustained benefit in any other measured outcomes. Requirements for US Medicare coverage for a patient's home use of oxygen and oxygen equipment are listed in Table 9–7. ABG analysis is preferred over oximetry to guide initial oxygen therapy. Hypoxicemic patients with pulmonary hypertension, chronic cor pulmonale, erythrocytosis, impaired cognitive function, exercise intolerance, nocturnal restlessness, or morning headache are particularly likely to benefit from home oxygen therapy.

Home oxygen may be supplied by liquid oxygen systems, compressed gas cylinders, or oxygen concentrators. Most patients benefit from having both stationary and portable systems. For most patients, a flow rate of 1–3 L/min achieves a  $\text{PaO}_2$  greater than 55 mm Hg. Reservoir nasal cannulas or “pendants” and demand (pulse) oxygen delivery systems are available to conserve oxygen.

**Table 9–7.** Home oxygen therapy: requirements for Medicare coverage.<sup>1</sup>

**Group I (any of the following):**

1.  $\text{PaO}_2 \leq 55$  mm Hg or  $\text{SaO}_2 \leq 88\%$  taken while awake, at rest, breathing room air.
2. During sleep (prescription for nocturnal oxygen use only):  $\text{PaO}_2 \leq 55$  mm Hg or  $\text{SaO}_2 \leq 88\%$  for a patient whose awake, resting, room air  $\text{PaO}_2$  is  $\geq 56$  mm Hg or  $\text{SaO}_2 \geq 89\%$ , or Decrease in  $\text{PaO}_2 > 10$  mm Hg or decrease in  $\text{SaO}_2 > 5\%$  associated with symptoms or signs reasonably attributed to hypoxemia (eg, impaired cognitive processes, nocturnal restlessness, insomnia).
3. During exercise (prescription for oxygen use only during exercise):  $\text{PaO}_2 \leq 55$  mg Hg or  $\text{SaO}_2 \leq 88\%$  taken during exercise for a patient whose awake, resting, room air  $\text{PaO}_2$  is  $\geq 56$  mm Hg or  $\text{SaO}_2 \geq 89\%$ , and there is evidence that the use of supplemental oxygen during exercise improves the hypoxemia that was demonstrated during exercise while breathing room air.

**Group II:**

$\text{PaO}_2 = 56\text{--}59$  mm Hg or  $\text{SaO}_2 = 89\%$  if there is evidence of any of the following:

1. Dependent edema suggesting heart failure.
2. P pulmonale on ECG (P wave  $> 3$  mm in standard leads II, III, or aVF).
3. Hematocrit  $> 56\%$ .

**3. Inhaled bronchodilators**—Bronchodilators do not alter the inexorable decline in lung function that is a hallmark of COPD, but they improve symptoms, exercise tolerance,  $\text{FEV}_1$ , and overall health status. Aggressiveness of bronchodilator therapy should be matched to the severity of the patient's disease. In patients who experience no symptomatic improvement, bronchodilators should be discontinued.

The most commonly prescribed short-acting bronchodilators are the SAMA ipratropium bromide and the SABAs (eg, albuterol/salbutamol), delivered by MDI or as an inhalation solution by nebulizer. Some clinicians prefer ipratropium as a first-line agent because of its longer duration of action and absence of sympathomimetic side effects. Some studies have suggested that ipratropium achieves superior bronchodilation in COPD patients. Typical doses are 2–4 puffs (36–72 mcg) every 6 hours. Other clinicians prefer SABAs because they are less expensive and have a more rapid onset of action, commonly leading to greater patient satisfaction. At maximal doses, beta-2-agonists have bronchodilator action equivalent to that of ipratropium but may cause tachycardia, tremor, or hypokalemia. There does not appear to be any advantage of scheduled use of SABAs compared with as-needed administration. There has been no consistent difference in efficacy demonstrated between SABAs and SAMAs. Using the SABAs and the SAMAs at submaximal doses leads to improved bronchodilation compared with either agent alone but does not improve dyspnea.

LAMAs (eg, tiotropium, aclidinium, umeclidinium, glycopyrrolate) and LABAs (eg, formoterol, salmeterol, indacaterol, arformoterol, vilanterol, olodaterol) appear to achieve bronchodilation that is equivalent or superior to what is experienced with ipratropium, in addition to similar improvements in health status. Although more expensive than short-acting agents, long-acting bronchodilators may have superior clinical efficacy in persons with advanced disease. One RCT of long-term administration of tiotropium added to standard therapy reported fewer exacerbations or hospitalizations and improved dyspnea scores—but no long-term effect on lung function—in the tiotropium group. Another RCT comparing the effects of tiotropium with those of salmeterol-fluticasone over 2 years reported no difference in the risk of COPD exacerbation. The incidence of pneumonia was higher in the salmeterol-fluticasone group, yet dyspnea scores were lower and there was a mortality benefit compared with tiotropium. The combination of tiotropium and formoterol (LAMA/LABA) has been shown to improve  $\text{FEV}_1$  and FVC more than the inhaled corticosteroid/LABA combination salmeterol and fluticasone in patients with a baseline  $\text{FEV}_1$  of less than 55% predicted. The initial drug of choice for patients with mild disease and no exacerbations is a LAMA. If the patient has more severe dyspnea and airflow obstruction, LAMA/LABA can be initiated.

The symptomatic benefits of long-acting bronchodilators are firmly established. Increased exacerbations and mortality reported in some asthmatic patients treated with salmeterol have not been observed in COPD patients, and several studies report a trend toward lower mortality in patients treated with salmeterol alone, compared with placebo. In addition, a 4-year tiotropium trial reported fewer

<sup>1</sup>Centers for Medicare & Medicaid Services, 2003.

<sup>2</sup>Patients in this group must have a second oxygen test 3 months after the initial oxygen setup.

cardiovascular events in the intervention group. Subsequent meta-analyses that include the 4-year tiotropium trial did not find an increase in cardiovascular events in treated patients. Most practitioners believe that the documented benefits of anticholinergic therapy outweigh any potential risks.

**4. Corticosteroids**—Multiple large clinical trials have reported a reduction in the frequency of COPD exacerbations and an increase in self-reported functional status in COPD patients treated with inhaled corticosteroids. These same trials demonstrate no effect of inhaled corticosteroids on mortality or the characteristic decline in lung function experienced by COPD patients. Thus, inhaled corticosteroids alone should not be considered first-line therapy in stable COPD patients.

Three large clinical trials of combination therapy with an inhaled corticosteroid added to a LABA demonstrated a reduced frequency of exacerbations and modest improvements in lung function. The benefits of inhaled corticosteroids must be weighed against the increased risk of bacterial pneumonia, however (relative risk was increased 1.57-fold in one study). Withdrawal of inhaled corticosteroids should be considered when patients have been stable for 2 years.

Apart from acute exacerbations, COPD is not generally responsive to oral corticosteroid therapy. Given the risks of adverse side effects, oral corticosteroids are not recommended for long-term treatment of COPD.

**5. Theophylline**—Oral theophylline is a fourth-line agent for treating COPD patients who do not achieve adequate symptom control with inhaled anticholinergic, beta-2-agonist, and corticosteroid therapies. Theophylline improves dyspnea ratings, exercise performance, and pulmonary function in many patients with stable COPD. Its benefits result from bronchodilation; anti-inflammatory properties; and extrapulmonary effects on diaphragm strength, myocardial contractility, and kidney function. Theophylline toxicity is a significant concern due to the medication's narrow therapeutic window, and long-term administration requires careful monitoring of serum levels. GOLD guidelines recommend theophylline only as a last resort if other bronchodilators are unavailable or unaffordable.

**6. Antibiotics**—Antibiotics are commonly prescribed to outpatients with COPD for the following indications: (1) to treat an acute exacerbation, (2) to treat acute bronchitis, and (3) to prevent acute exacerbations of chronic bronchitis (prophylactic antibiotics). In patients with COPD, antibiotics appear to improve outcomes slightly in all three situations. Patients with a COPD exacerbation associated with increased sputum purulence accompanied by dyspnea or an increase in the quantity of sputum are thought to benefit the most from antibiotic therapy. The choice of antibiotic depends on local bacterial resistance patterns and individual risk of *Pseudomonas aeruginosa* infection (history of *Pseudomonas* isolation, FEV<sub>1</sub> less than 50% of predicted, recent hospitalization [2 or more days in the past 3 months], more than three courses of antibiotics within the past year, use of systemic corticosteroids). Oral antibiotic options include doxycycline (100 mg every 12 hours),

trimethoprim-sulfamethoxazole (160/800 mg every 12 hours), a cephalosporin (eg, cefpodoxime 200 mg every 12 hours or cefprozil 500 mg every 12 hours), a macrolide (eg, azithromycin 500 mg followed by 250 mg daily for 5 days), a fluoroquinolone (eg, ciprofloxacin 500 mg every 12 hours), and amoxicillin-clavulanate (875/125 mg every 12 hours). Suggested duration of therapy is 3–5 days and depends on response to therapy. There are few controlled trials of antibiotics in severe COPD exacerbations, but prompt administration is appropriate, particularly in persons with risk factors for poor outcomes (age older than 65 years, FEV<sub>1</sub> less than 50% of predicted, three or more exacerbations in the past year, antibiotic therapy within the past 3 months, comorbid conditions, such as cardiac disease). In COPD patients subject to frequent exacerbations despite optimal medical therapy, azithromycin (daily or three times weekly) and moxifloxacin (a 5-day course 1 week in 8 over 48 weeks) were modestly effective in clinical trials at reducing the frequency of exacerbations; monitoring for hearing loss and QT prolongation is essential.

**7. Pulmonary rehabilitation**—Graded aerobic physical exercise programs (eg, walking 20 minutes three times weekly or bicycling) are helpful to prevent deterioration of physical condition and to improve patients' ability to carry out daily activities. Training of inspiratory muscles by inspiring against progressively larger resistive loads reduces dyspnea and improves exercise tolerance, health status, and respiratory muscle strength in some but not all patients. Pursed-lip breathing to slow the rate of breathing and abdominal breathing exercises to relieve fatigue of accessory muscles of respiration may reduce dyspnea in some patients. Many patients undergo these exercise and educational interventions in a structured rehabilitation program. Pulmonary rehabilitation has been shown in multiple studies to improve exercise capacity, decrease hospitalizations, and enhance quality of life. Referral to a comprehensive rehabilitation program is recommended in patients who have severe dyspnea, reduced quality of life, or frequent hospitalizations despite optimal medical therapy.

**8. Phosphodiesterase 4 inhibitor**—Roflumilast has been shown to reduce exacerbation frequency in patients who have moderate or severe (FEV<sub>1</sub> less than 50% of predicted) COPD and chronic bronchitis, with frequent exacerbations, and are taking LABA/inhaled corticosteroid with or without a LAMA.

**9. Other measures**—In patients with chronic bronchitis, increased mobilization of secretions may be accomplished through adequate systemic hydration, effective cough training methods, or the use of a handheld flutter device and postural drainage, sometimes with chest percussion or vibration. Postural drainage and chest percussion should be used only in selected patients with excessive amounts of retained secretions that cannot be cleared by coughing and other methods; these measures are of no benefit in pure emphysema. Expectorant-mucolytic therapy has generally been regarded as unhelpful in patients with chronic bronchitis. Cough suppressants and sedatives should be avoided. Morphine can reduce chronic dyspnea in patients with very severe COPD.

Human alpha-1-antitrypsin is available for replacement therapy in emphysema due to congenital deficiency (PiZZ or null genotype) of alpha-1-antiprotease (alpha-1-antitrypsin). Patients over 18 years of age with airflow obstruction by spirometry and serum levels less than 11 mmol/L (~50 mg/dL) are potential candidates for replacement therapy. Alpha-1-antitrypsin is administered intravenously in a dose of 60 mg/kg body weight once weekly.

Severe dyspnea in spite of optimal medical management may warrant a clinical trial of an opioid (eg, morphine 5–10 mg orally every 3–4 hours, oxycodone 5–10 mg orally every 4–6 hours, sustained-release morphine 10 mg orally once daily). Sedative-hypnotic drugs (eg, diazepam, 5 mg three times daily) marginally improve intractable dyspnea but cause significant drowsiness; they may benefit very anxious patients. Transnasal positive-pressure ventilation at home to rest the respiratory muscles is an approach to improve respiratory muscle function and reduce dyspnea in patients with severe COPD.

See Chapter 37 for a discussion of air travel in patients with lung disease.

## B. Hospitalized Patients

Management of the hospitalized patient with an acute exacerbation of COPD includes (1) supplemental oxygen (titrated to maintain  $\text{Sao}_2$  between 90% and 94% or  $\text{PaO}_2$  between 60 mm Hg and 70 mm Hg); (2) inhaled beta-2-agonists (eg, albuterol 2.5 mg diluted with saline to a total of 3 mL by nebulizer, or MDI, 90 mcg per puff, four to eight puffs via spacer, every 1–4 hours as needed) with or without inhaled ipratropium bromide (500 mcg by nebulizer, or 36 mcg by MDI with spacer, every 4 hours as needed); (3) corticosteroids (prednisone 0.5 mg/kg/day orally for 7–10 days is usually sufficient, and even 5 days may be adequate); (4) broad-spectrum antibiotics; and (5) in selected cases, chest physiotherapy.

For patients without risk factors for *Pseudomonas*, management options include a fluoroquinolone (eg, levofloxacin 750 mg orally or intravenously per day, or moxifloxacin 400 mg orally or intravenously every 24 hours) or a third-generation cephalosporin (eg, ceftriaxone 1 g intravenously per day, or cefotaxime 1 g intravenously every 8 hours).

For patients with risk factors for *Pseudomonas*, therapeutic options include piperacillin-tazobactam (4.5 g intravenously every 6 hours), ceftazidime (1 g intravenously every 8 hours), cefepime (1 g intravenously every 12 hours), or levofloxacin (750 mg orally or intravenously per day for 3–7 days).

Oxygen therapy should *not* be withheld for fear of worsening respiratory acidemia; hypoxemia is more detrimental than hypercapnia. Cor pulmonale usually responds to measures that reduce pulmonary artery pressure, such as supplemental oxygen and correction of acidemia; bed rest, salt restriction, and diuretics may add some benefit. Cardiac dysrhythmias, particularly multifocal atrial tachycardia, usually respond to aggressive treatment of COPD itself. Atrial fibrillation and flutter may require DC cardioversion after initiation of the above therapy. Theophylline should not be initiated in the acute setting, but patients taking theophylline prior to acute hospitalization should

have their theophylline serum levels measured and maintained in the therapeutic range. If progressive respiratory failure ensues, tracheal intubation and mechanical ventilation are necessary. In clinical trials of COPD patients with hypercapnic acute respiratory failure, **noninvasive positive-pressure ventilation** (NIPPV) delivered via face mask reduced the need for intubation and shortened lengths of stay in the intensive care unit (ICU). Other studies have suggested a lower risk of nosocomial infections and less use of antibiotics in COPD patients treated with NIPPV.

## C. Procedures for COPD

**1. Lung transplantation**—Requirements for lung transplantation are severe lung disease, limited activities of daily living, exhaustion of medical therapy, ambulatory status, potential for pulmonary rehabilitation, limited life expectancy without transplantation, adequate function of other organ systems, and a good social support system. Two-year survival rate after lung transplantation for COPD is 75%. Complications include acute rejection, opportunistic infection, and obliterative bronchiolitis. Substantial improvements in pulmonary function and exercise performance have been noted after transplantation.

**2. Lung volume reduction surgery**—Lung volume reduction surgery, or reduction pneumoplasty, is a surgical approach to relieve dyspnea and improve exercise tolerance in patients with advanced diffuse emphysema and lung hyperinflation. Bilateral resection of 20–30% of lung volume in selected patients results in modest improvements in pulmonary function, exercise performance, and dyspnea. The duration of improvement as well as any mortality benefit remains uncertain. Prolonged air leaks occur in up to 50% of patients postoperatively. Mortality rates in centers with the largest experience with lung volume reduction surgery range from 4% to 10%.

The National Emphysema Treatment Trial compared lung volume reduction surgery with medical treatment in a randomized, multicenter clinical trial of 1218 patients with severe emphysema. Overall, surgery improved exercise capacity but not mortality when compared with medical therapy. The persistence of this benefit remains to be defined. Subgroup analysis suggested that patients with upper lobe-predominant emphysema and low exercise capacity might have improved survival, while other groups suffered excess mortality when randomized to surgery.

**3. Bullectomy**—Bullectomy is an older surgical procedure for palliation of dyspnea in patients with severe bullous emphysema. Bullectomy is most commonly pursued when a single bulla occupies at least 30–50% of the hemithorax.

## ► Prognosis

The outlook for patients with clinically significant COPD is poor. The degree of pulmonary dysfunction at the time the patient is first seen is an important predictor of survival: median survival of patients with  $\text{FEV}_1 = 1 \text{ L}$  or less is about 4 years. A multidimensional index (the BODE index), which includes body mass index, airway obstruction ( $\text{FEV}_1$ ), dyspnea (modified Medical Research Council

dyspnea score), and exercise capacity, is a tool that predicts death and hospitalization better than FEV<sub>1</sub> alone. Comprehensive care programs, cessation of smoking, and supplemental oxygen may reduce the rate of decline of pulmonary function, but therapy with bronchodilators and other approaches probably have little, if any, impact on the natural course of COPD.

Dyspnea at the end of life can be extremely uncomfortable and distressing to the patient and family. As patients near the end of life, meticulous attention to palliative care is essential to effectively manage dyspnea (see Chapter 5).

### ► When to Refer

- COPD onset occurs before the age of 40.
- Frequent exacerbations (two or more a year) despite optimal treatment.
- Severe or rapidly progressive COPD.
- Symptoms disproportionate to the severity of airflow obstruction.
- Need for long-term oxygen therapy.
- Onset of comorbid illnesses (eg, bronchiectasis, heart failure, or lung cancer).

### ► When to Admit

- Severe symptoms or acute worsening that fails to respond to outpatient management.
- Acute or worsening hypoxemia, hypercapnia, peripheral edema, or change in mental status.
- Inadequate home care, or inability to sleep or maintain nutrition/hydration due to symptoms.
- The presence of high-risk comorbid conditions.

Agustí A et al. Update on the pathogenesis of chronic obstructive pulmonary disease. *N Engl J Med.* 2019;381:1248. [PMID: 31553836]

Celli BR et al. Update on clinical aspects of chronic obstructive pulmonary disease. *N Engl J Med.* 2019;381:1257. [PMID: 31553837]

Global Initiative for Chronic Obstructive Lung Disease (GOLD). 2020 Global strategy for the prevention, diagnosis, and management of chronic obstructive lung disease. <https://goldcopd.org/gold-reports/>

## BRONCHIECTASIS



### ESSENTIALS OF DIAGNOSIS

- ▶ Chronic productive cough with dyspnea and wheezing.
- ▶ Radiographic findings of dilated, thickened airways and scattered, irregular opacities.

### ► General Considerations

Bronchiectasis is a congenital or acquired disorder of the large bronchi characterized by permanent, abnormal

dilation and destruction of bronchial walls. It may be caused by recurrent inflammation or infection of the airways and may be localized or diffuse. Cystic fibrosis causes about half of all cases of bronchiectasis. Other causes include (1) lung infections (tuberculosis, fungal infections, lung abscess, pneumonia), (2) immunodeficiencies (congenital or acquired hypogammaglobulinemia; common variable immunodeficiency; selective IgA, IgM, and IgG subclass deficiencies; AIDS; lymphoma; plasma cell myeloma; leukemia), (3) alpha-1-antitrypsin deficiency, (4) primary ciliary dyskinesia, (5) rheumatic diseases (rheumatoid arthritis, Sjögren syndrome), and (6) localized airway obstruction (foreign body, tumor, mucoid impaction).

### ► Clinical Findings

#### A. Symptoms and Signs

Symptoms of bronchiectasis include chronic cough with production of copious amounts of purulent sputum, hemoptysis, pleuritic chest pain, dyspnea, and weight loss. Physical findings may include crackles at the lung bases and wheezing.

#### B. Laboratory Findings and Imaging

Laboratory tests include immunoglobulin quantification; testing for cystic fibrosis; and sputum culture, including for nontuberculous mycobacteria. Obstructive pulmonary dysfunction with hypoxemia is seen in moderate or severe disease. Radiographic abnormalities include dilated and thickened bronchi that may appear as “tram tracks” or as ring-like markings. Scattered irregular opacities, atelectasis, and focal consolidation may be present. High-resolution CT is the diagnostic study of choice.

#### C. Microbiology

*Haemophilus influenzae* is the most common organism recovered from non-cystic fibrosis patients with bronchiectasis. *P. aeruginosa*, *Streptococcus pneumoniae*, and *Staphylococcus aureus* are commonly identified. Nontuberculous mycobacteria are seen less commonly. Patients with *Pseudomonas* infection experience an accelerated course, with more frequent exacerbations and more rapid decline in lung function.

### ► Treatment

Treatment of acute exacerbations consists of antibiotics, daily chest physiotherapy with postural drainage and chest percussion, and inhaled bronchodilators. Handheld flutter valve devices may be as effective as chest physiotherapy in clearing secretions. Antibiotic therapy should be guided by sputum smears and prior cultures. If a specific bacterial pathogen cannot be isolated, then empiric oral antibiotic therapy for 10–14 days is appropriate. Common medications include amoxicillin or amoxicillin-clavulanate, ampicillin, a second- or third-generation cephalosporin, doxycycline, or a fluoroquinolone. For recurrent exacerbations, preventive macrolide therapy for 6–12 months has

been found to decrease the frequency of exacerbations. Alternatively, a trial of inhaled antibiotics may be given. Alternating cycles of oral antibiotics may also be considered, although data are inconclusive.

Complications of bronchiectasis include hemoptysis, cor pulmonale, amyloidosis, and secondary visceral abscesses at distant sites (eg, brain). Bronchoscopy is sometimes necessary to evaluate hemoptysis, remove retained secretions, and rule out obstructing airway lesions. Massive hemoptysis may require embolization of bronchial arteries or surgical resection.

- Chalmers JD et al. Long-term macrolide antibiotics for the treatment of bronchiectasis in adults: an individual participant data meta-analysis. *Lancet Respir Med*. 2019;7:845. [PMID: 31405828]
- Gruffydd-Jones K et al. Primary care implications of the British Thoracic Society Guidelines for bronchiectasis in adults 2019. *NPJ Prim Care Respir Med*. 2019;29:24. [PMID: 31249313]
- King CS et al. Critical care of the adult patient with cystic fibrosis. *Chest*. 2019;155:202. [PMID: 30077689]
- Lesan A et al. Short review on the diagnosis and treatment of bronchiectasis. *Med Pharm Rep*. 2019;92:111. [PMID: 31086836]
- McShane PJ et al. Bronchiectasis. *Chest*. 2019;155:825. [PMID: 30403962]

## ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS (Mycosis)

Allergic bronchopulmonary aspergillosis (ABPA) (or mycosis) is a pulmonary hypersensitivity disorder caused by allergy to fungal antigens that colonize the tracheobronchial tree. It usually occurs in atopic asthmatic individuals who are 20–40 years of age or those with cystic fibrosis, in response to antigens of *Aspergillus* species. Primary criteria for the diagnosis of ABPA include (1) a clinical history of asthma or cystic fibrosis; (2) elevated serum total IgE levels (typically greater than 1000 international units/mL; a value less than 1000 international units/mL may be acceptable if all other criteria are met); (3) immediate cutaneous hypersensitivity to *Aspergillus* antigens or elevated serum IgE levels specific to *Aspergillus fumigatus*; and (4) at least two of the following: (a) precipitating serum antibodies to *Aspergillus* antigen or elevated serum *Aspergillus* IgG by immunoassay, (b) radiographic pulmonary opacities consistent with ABPA, or (c) peripheral blood eosinophil count greater than 500 cells/mcL (greater than  $0.5 \times 10^9/L$ ). High-dose corticosteroids (eg, prednisone 0.5–1 mg/kg orally per day) for at least 2 weeks is the treatment of choice. Depending on the clinical situation, the corticosteroid dose can then be reduced and tapered over 3–6 months. Relapses are frequent, and repeated treatment with corticosteroid is not uncommon. Patients with corticosteroid-dependent disease may benefit from itraconazole or voriconazole. Bronchodilators (see Table 9–3) may also be helpful. Complications include hemoptysis, severe bronchiectasis, and pulmonary fibrosis.

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Muthu V et al. Diagnostic cutoffs and clinical utility of recombinant *Aspergillus fumigatus* antigens in the diagnosis of allergic bronchopulmonary aspergillosis. *J Allergy Clin Immunol Pract*. 2020;8:579. [PMID: 31520840]

Periselneris J et al. Posaconazole for the treatment of allergic bronchopulmonary aspergillosis in patients with cystic fibrosis. *J Antimicrob Chemother*. 2019;74:1701. [PMID: 30805605]

## CYSTIC FIBROSIS

### ESSENTIALS OF DIAGNOSIS

- Pulmonary disease: chronic or recurrent productive cough, dyspnea, and wheezing; recurrent airway infections or chronic colonization of the airways with *H influenzae*, *P aeruginosa*, *S aureus*, or *Burkholderia cenocepacia*; bronchiectasis and scarring on chest radiographs; airflow obstruction on spirometry.
- Extrapulmonary disease: sinus disease; gastrointestinal disease (pancreatic insufficiency, recurrent pancreatitis, hepatobiliary disease, meconium ileus, and distal intestinal obstruction); genitourinary problems (male infertility and urogenital abnormalities)
- Sweat chloride concentration > 60 mEq/L on two occasions.
- Presence of two disease-causing mutations in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene.
- Abnormal nasal potential difference.

### General Considerations

Cystic fibrosis is the most common cause of severe chronic lung disease in young adults and the most common fatal hereditary disorder of Whites in the United States. It is an autosomal-recessive disorder affecting about 1 in 3000 Whites; 1 in 25 is a carrier. Cystic fibrosis is caused by abnormalities in a membrane chloride channel (the cystic fibrosis transmembrane conductance regulator [*CFTR*] protein) that results in altered chloride transport and water flux across the apical surface of epithelial cells. Almost all exocrine glands produce an abnormal mucus that obstructs glands and ducts and leads to tissue damage. In the respiratory tract, inadequate hydration of the tracheobronchial epithelium impairs mucociliary function. High concentration of extracellular DNA in airway secretions (due to chronic airway inflammation and autolysis of neutrophils) increases sputum viscosity.

Over one-third of the nearly 30,000 cystic fibrosis patients in the United States are adults. Adult patients with cystic fibrosis have an increased risk of osteopenia, arthropathies, and malignancies of the gastrointestinal tract, among others.

## ► Clinical Findings

### A. Symptoms and Signs

Cystic fibrosis should be suspected in an adult with a history of chronic lung disease (especially bronchiectasis), pancreatitis, or infertility. Cough, sputum production, decreased exercise tolerance, and recurrent hemoptysis are typical complaints. Patients also often complain of chronic rhinosinusitis symptoms, steatorrhea, diarrhea, and abdominal pain. Patients with cystic fibrosis are often malnourished with low body mass index. Digital clubbing (Figure 6–42), increased anteroposterior chest diameter, hyperresonance to percussion, and apical crackles are noted on physical examination. Sinus tenderness, purulent nasal secretions, and nasal polyps may also be seen. Nearly all men with cystic fibrosis have congenital bilateral absence of the vas deferens with azoospermia. Biliary cirrhosis and gallstones may occur.

### B. Laboratory Findings

ABG studies often reveal hypoxemia and, in advanced disease, a chronic, compensated respiratory acidosis. Pulmonary function studies show a mixed obstructive and restrictive pattern. There is a reduction in FVC, airflow rates, and TLC. Air trapping (high ratio of RV to TLC) and reduction in pulmonary diffusing capacity are common.

### C. Imaging

Hyperinflation is seen early in the disease process. Peribronchial cuffing, mucus plugging, bronchiectasis (ring shadows and cysts), increased interstitial markings, small rounded peripheral opacities, and focal atelectasis are common findings. Pneumothorax can also be seen. Thin-section CT scanning often confirms the presence of bronchiectasis.

### D. Diagnosis

The **quantitative pilocarpine iontophoresis sweat test** reveals elevated sodium and chloride levels (greater than 60 mEq/L) in the sweat of patients with cystic fibrosis. Two tests on different days performed in experienced laboratories are required for accurate diagnosis. A normal sweat chloride test does not exclude the diagnosis, in which case *CFTR* genotyping or other alternative diagnostic studies (such as measurement of nasal membrane potential difference, semen analysis, or assessment of pancreatic function) should be pursued, especially if there is a high clinical suspicion of cystic fibrosis. Additionally, all patients with cystic fibrosis should undergo *CFTR* genotyping.

## ► Treatment

Early recognition and comprehensive multidisciplinary therapy improve symptom control and survival. Referral to a regional cystic fibrosis center is strongly recommended. Treatment programs focus on the following areas: *CFTR* modulator medications, clearance and reduction of lower airway secretions, reversal of bronchoconstriction, treatment of respiratory tract infections and airway bacterial

burden, pancreatic enzyme replacement, and nutritional and psychosocial support (including genetic and occupational counseling).

**CFTR modulators** include medications that alter *CFTR* trafficking, folding, or function. These medications are only available for patients with specific *CFTR* mutations. Examples are ivacaftor, a potentiator of the *CFTR* channel that works by increasing the time the channel remains open after being activated; and lumacaftor, tezacaftor, and elexacaftor that work by improving *CFTR* protein folding and cell-surface trafficking.

**Airway clearance** can be promoted by postural drainage, chest percussion or vibration techniques, positive expiratory pressure or flutter valve breathing devices, directed cough, and other breathing techniques. Inhaled recombinant human deoxyribonuclease (rhDNase, dornase alpha) cleaves extracellular DNA in sputum, decreasing sputum viscosity; when administered long-term at a daily nebulized dose of 2.5 mg, this therapy leads to improved FEV<sub>1</sub> and reduces the risk of cystic fibrosis-related respiratory exacerbations as well as the need for intravenous antibiotics. Inhalation of hypertonic (7%) saline improves clearance of mucus from the airway and has been associated with small improvements in pulmonary function and fewer pulmonary exacerbations.

**Short-term antibiotics** are used to treat active airway infections based on results of culture and susceptibility testing of sputum. *S aureus* (including methicillin-resistant strains) and a mucoid variant of *P aeruginosa* are commonly present. *H influenzae*, *Stenotrophomonas maltophilia*, and *B cenocepacia* (a highly drug-resistant organism) are occasionally isolated. **Long-term antibiotic therapy**, such as azithromycin (which has immunomodulatory properties) and various inhaled antibiotics (eg, tobramycin, aztreonam, colistin, and levofloxacin) taken two to three times a day, helps slow disease progression and reduce exacerbations in patients with sputum cultures positive for *P aeruginosa*. The length of therapy depends on the persistent presence of *P aeruginosa* in the sputum. The incidence of atypical mycobacterial colonization is higher in cystic fibrosis patients, and directed antibiotic treatment is recommended for frequent exacerbations, progressive decline in lung function, or failure to thrive. Yearly screening with sputum acid-fast bacilli cultures is advised.

**Inhaled bronchodilators** (eg, albuterol) should be considered in patients who demonstrate an increase of at least 12% in FEV<sub>1</sub> after an inhaled bronchodilator. An inhaled corticosteroid should be added to the treatment regimen for patients who have cystic fibrosis with persistent asthma or allergic bronchopulmonary mycosis.

**Lung transplantation** is the only definitive treatment for advanced cystic fibrosis.

**Vaccination** against pneumococcal infection and annual influenza vaccination are advised. **Screening** of family members and genetic counseling are suggested.

## ► Prognosis

The longevity of patients with cystic fibrosis is increasing, and the median survival age is now over 39 years. Death occurs from pulmonary complications (eg, pneumonia,

pneumothorax, or hemoptysis) or as a result of terminal chronic respiratory failure and cor pulmonale.

Bienvenu T et al. Current and future diagnosis of cystic fibrosis: performance and limitations. *Arch Pediatr*. 2020;27:eS19. [PMID: 32172931]

De Boeck K. Cystic fibrosis in the year 2020: a disease with a new face. *Acta Paediatr*. 2020;109:893. [PMID: 31899933]

Lopes-Pacheco M. CFTR modulators: the changing face of cystic fibrosis in the era of precision medicine. *Front Pharmacol*. 2020;10:1662. [PMID: 32153386]

Turcios NL. Cystic fibrosis lung disease: an overview. *Respir Care*. 2020;65:233. [PMID: 31772069]

airflow obstruction and air trapping on spirometry; unremarkable plain chest radiographs but heterogeneous airflow obstruction and air trapping on chest CT scans; and a progressive, deteriorating clinical course.

**Proliferative bronchiolitis** is associated with diverse pulmonary disorders, including infection, aspiration, acute respiratory distress syndrome (ARDS), hypersensitivity pneumonitis, connective tissue diseases, and organ transplantation. Compared with constrictive bronchiolitis, proliferative bronchiolitis is more likely to have an abnormal chest radiograph. Chest CT scan may show patchy consolidation, ground-glass opacities, or peripheral nodular appearance.

**Cryptogenic organizing pneumonitis (COP)** affects men and women between the ages of 50 and 70 years, typically with a dry cough, dyspnea, and constitutional symptoms that may be present for weeks to months prior to seeking medical attention. A history of a preceding viral illness is present in half of cases. Pulmonary function testing typically reveals a restrictive ventilatory defect and impaired oxygenation. The chest radiograph frequently shows bilateral patchy, ground-glass or alveolar infiltrates, although other patterns have been described.

**Follicular bronchiolitis** is most commonly associated with connective tissue disease, especially rheumatoid arthritis and Sjögren syndrome, and with immunodeficiency states, such as HIV or AIDS. Chest CT scan may show centrilobular and peribronchial nodules. It may be seen in lymphoid interstitial pneumonia.

**Respiratory bronchiolitis** is the most common form of bronchiolitis in adults and is usually related to cigarette smoking. It usually occurs without symptoms or physiologic evidence of lung impairment. It may be seen in respiratory bronchiolitis-associated interstitial lung disease (RB-ILD).

**Diffuse panbronchiolitis** is most frequently diagnosed in Japan. Men are affected about twice as often as women, two-thirds are nonsmokers, and most patients have a history of chronic pansinusitis. Patients complain of dyspnea, cough, and sputum production, and chest examination shows crackles and rhonchi. Pulmonary function tests reveal obstructive abnormalities, and the chest radiograph shows a distinct pattern of diffuse, small, nodular shadows with hyperinflation.

## Treatment

**Constrictive bronchiolitis** is relatively unresponsive to corticosteroids and is frequently progressive. Corticosteroids are usually effective in **proliferative bronchiolitis** and **COP**, and improvement can be prompt. Therapy is initiated with prednisone at 1 mg/kg/day orally for 1–3 months. The dose is then tapered slowly to 20–40 mg/day, depending on the response, and weaned over the subsequent 3–6 months as tolerated. Relapses are common if corticosteroids are stopped prematurely or tapered too quickly. Azithromycin may be used to effectively treat **diffuse panbronchiolitis** and, additionally, it may slow down the progression of bronchiolitis obliterans syndrome in lung transplant recipients.

## BRONCHIOLITIS



### ESSENTIALS OF DIAGNOSIS

- ▶ Insidious onset of cough and dyspnea.
- ▶ Irreversible airflow obstruction and air trapping on pulmonary function testing.
- ▶ Minimal findings on chest radiograph, heterogeneous airflow obstruction, and air trapping on chest CT scan.
- ▶ Relevant exposure or risk factors: toxic fumes, viral infections, organ transplantation, connective tissue disease.

### General Considerations

Bronchiolitis is a generic term applied to varied inflammatory processes that affect the bronchioles, which are small conducting airways less than 2 mm in diameter. Bronchiolitis is less common in adults than in children, but it is encountered in multiple clinical settings, such as postinfectious, inhalational injury (such as vaping), organ transplantation, connective tissue diseases, and hypersensitivity pneumonitis.

The clinical approach to bronchiolitis divides patients into groups based on etiology, but different clinical syndromes may have identical histopathologic findings. As a result, no single classification scheme has been widely accepted, and there is an overlapping array of terms to describe these disorders from the viewpoints of the clinician, the pathologist, and the radiologist.

### Clinical Findings

**Acute bronchiolitis** can be seen following viral infections.

**Constrictive bronchiolitis** (also referred to as obliterative bronchiolitis or bronchiolitis obliterans) is relatively infrequent, although it is the most common finding following inhalation injury (ammonia, welding fumes, and heavy metals). It may also be seen in rheumatoid arthritis; medication reactions (busulfan, gold, and penicillamine); and chronic rejection following heart-lung, lung, or hematopoietic stem cell transplantation (bronchiolitis obliterans syndrome). Patients with constrictive bronchiolitis have

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- Ruttens D et al. Montelukast for bronchiolitis obliterans syndrome after lung transplantation: a randomized controlled trial. *PLoS One.* 2018;13:e0193564. [PMID: 29624575]
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## PULMONARY INFECTIONS

### PNEUMONIA

Pneumonia has classically been considered in terms of the infecting organism (Table 9–8). This approach facilitates discussion of characteristic clinical presentations but is a limited guide to patient management since specific

microbiologic information is usually not available at initial presentation. Current classification schemes emphasize epidemiologic factors that predict etiology and guide initial therapy. Pneumonia may be classified as **community-acquired (CAP)** or **nosocomial** and, within the latter, as **hospital-acquired (HAP)** or **ventilator-associated (VAP)**. These categories are based on differing settings and infectious agents and require different diagnostic and therapeutic interventions. **Anaerobic pneumonia** and **lung abscess** can occur in both hospital and community settings and warrant separate consideration.

This section sets forth the evaluation and management of pulmonary infiltrates in immunocompetent persons separately from the approach to immunocompromised persons—defined as those with HIV disease, absolute neutrophil counts less than 1000/mcL ( $1.0 \times 10^9/L$ ), or current or recent exposure to myelosuppressive or immunosuppressive medications, or those currently taking prednisone in a dosage greater than 5 mg/day.

**Table 9–8.** Characteristics of selected pneumonias.

| Organism; Appearance on Smear of Sputum                                   | Clinical Setting   | Complications   |
|---|--|---|
| <i>Streptococcus pneumoniae</i> (pneumococcus). Gram-positive diplococci. | Chronic cardiopulmonary disease; follows upper respiratory tract infection   | Bacteremia, meningitis, endocarditis, pericarditis, empyema                                   |
| <i>Haemophilus influenzae</i> . Pleomorphic gram-negative coccobacilli.   | Chronic cardiopulmonary disease; follows upper respiratory tract infection   | Empyema, endocarditis   |
| <i>Staphylococcus aureus</i> . Plump gram-positive cocci in clumps.       | Residence in long-term care facility, hospital-associated, influenza epidemics, cystic fibrosis, bronchiectasis, injection drug use  | Empyema, cavitation   |
| <i>Klebsiella pneumoniae</i> . Plump gram-negative encapsulated rods.     | Alcohol abuse, diabetes mellitus; hospital-associated  | Cavitation, empyema   |
| <i>Escherichia coli</i> . Gram-negative rods.                             | Hospital-associated; rarely, community-acquired  | Empyema   |
| <i>Pseudomonas aeruginosa</i> . Gram-negative rods.                       | Hospital-associated; cystic fibrosis, bronchiectasis   | Cavitation  |
| Anaerobes. Mixed flora.   | Aspiration, poor dental hygiene  | Necrotizing pneumonia, abscess, empyema   |
| <i>Mycoplasma pneumoniae</i> . PMNs and monocytes; no bacteria.           | Young adults; summer and fall  | Skin rashes, bullous myringitis; hemolytic anemia   |
| <i>Legionella</i> species. Few PMNs; no bacteria.                         | Summer and fall; exposure to contaminated construction site, water source, air conditioner; community-acquired or hospital-associated  | Empyema, cavitation, endocarditis, pericarditis   |
| <i>Chlamydophila pneumoniae</i> . Nonspecific.                            | Clinically similar to <i>M pneumoniae</i> , but prodromal symptoms last longer (up to 2 weeks); sore throat with hoarseness common; mild pneumonia in teenagers and young adults | Reinfection in older adults with underlying COPD or heart failure may be severe or even fatal |
| <i>Moraxella catarrhalis</i> . Gram-negative diplococci.                  | Preexisting lung disease; elderly patients; corticosteroid or immunosuppressive therapy  | Rarely, pleural effusions and bacteremia  |
| <i>Pneumocystis jirovecii</i> . Nonspecific.                              | AIDS, immunosuppressive or cytotoxic drug therapy, cancer  | Pneumothorax, respiratory failure, ARDS, death  |
| SARS-CoV-2. Nonspecific.  | Pandemic. Milder pneumonia (teenagers, young adults); more severe pneumonia (elderly, immunocompromised, multiple comorbidly ill adults)   | Respiratory failure, ARDS, death  |

ARDS, acute respiratory distress syndrome; COPD, chronic obstructive pulmonary disease; PMN, polymorphonuclear leukocyte; SARS-CoV-2, severe acute respiratory syndrome due to coronavirus-2 (see COVID-19 discussion, Chapter 32, and consult <https://www.coronavirus.gov> for the latest from the CDC).

## 1. Community-Acquired Pneumonia



### ESSENTIALS OF DIAGNOSIS

- ▶ Fever or hypothermia, tachypnea, cough with or without sputum, dyspnea, chest discomfort, sweats or rigors (or both).
- ▶ Bronchial breath sounds or inspiratory crackles on chest auscultation.
- ▶ Parenchymal opacity on chest radiograph (occasionally not evident at presentation).
- ▶ Occurs outside of the hospital or within 48 hours of hospital admission.

### ► General Considerations

Community-acquired pneumonia (CAP) is a common disorder, with approximately 4–5 million cases diagnosed each year in the United States, 25% of which require hospitalization. It is the deadliest infectious disease in the United States and the eighth leading cause of death. Mortality in milder cases treated as outpatients is less than 1%. Among patients hospitalized for CAP, in-hospital mortality is approximately 10–12% and 1-year mortality (in those over age 65) is greater than 40%. Risk factors for the development of CAP include advanced age; alcoholism; tobacco use; comorbid medical conditions, especially asthma or COPD; and immunosuppression.

The patient's history, physical examination, and imaging studies are essential to establishing a diagnosis of CAP. None of these efforts identifies a specific microbiologic cause, however. Sputum examination may be helpful in selected patients but 40% of patients cannot produce an evaluable sputum sample; sputum Gram stain and culture lack sensitivity for the most common causes of pneumonia. Since patient outcomes improve when the initial antibiotic choice is appropriate for the infecting organism, the American Thoracic Society and the Infectious Diseases Society of America recommend empiric treatment based on epidemiologic data (Table 9–9). Such treatment improves initial antibiotic coverage, reduces unnecessary hospitalization, and appears to improve 30-day survival.

### ► Definition & Pathogenesis

CAP is diagnosed outside of the hospital setting or within the first 48 hours of hospital admission. Pulmonary defense mechanisms (cough reflex, mucociliary clearance system, immune responses) normally prevent the development of lower respiratory tract infections following aspiration of oropharyngeal secretions containing bacteria or inhalation of infected aerosols. CAP occurs when there is a defect in one or more of these normal defense mechanisms or when a large infectious inoculum or a virulent pathogen overwhelms the immune response.

Prospective studies fail to identify the cause of CAP in 30–60% of cases; two or more causes are identified in up to one-third of cases. The most common bacterial pathogen

identified in most studies of CAP is *S pneumoniae*, accounting for approximately two-thirds of bacterial isolates. Other common bacterial pathogens include *H influenzae*, *M pneumoniae*, *C pneumoniae*, *S aureus*, *Moraxella catarrhalis*, *Klebsiella pneumoniae*, other gram-negative rods, and *Legionella* species. Common viral causes of CAP include coronaviruses (SARS-CoV-2, MERS), influenza virus, respiratory syncytial virus, adenovirus, and parainfluenza virus. A detailed assessment of epidemiologic risk factors may aid in diagnosing pneumonias due to the following uncommon causes: *Chlamydophila psittaci* (psittacosis); *Coxiella burnetii* (Q fever); *Francisella tularensis* (tularemia); *Blastomyces*, *Coccidioides*, *Histoplasma* (endemic fungi); and (Sin Nombre virus [hantavirus pulmonary syndrome]).

### ► Clinical Findings

#### A. Symptoms and Signs

Most patients with CAP experience an acute or subacute onset of fever, cough with or without sputum production, and dyspnea. Other common symptoms include sweats, chills, rigors, chest discomfort, pleurisy, hemoptysis, fatigue, myalgias, anorexia, headache, and abdominal pain.

Common physical findings include fever or hypothermia, tachypnea, tachycardia, and arterial oxygen desaturation. Many patients appear acutely ill. Chest examination often reveals inspiratory crackles and bronchial breath sounds. Dullness to percussion may be observed if lobar consolidation or a parapneumonic pleural effusion is present. The clinical evaluation is less than 50% sensitive compared to chest imaging for the diagnosis of CAP (see Imaging section below). In most patients, therefore, a chest radiograph is essential to the evaluation of suspected CAP.

#### B. Diagnostic Testing

Diagnostic testing for a specific infectious cause of CAP is not generally indicated in ambulatory patients treated as outpatients because empiric antibiotic therapy is almost always effective in this population. In ambulatory outpatients whose presentation (travel history, exposure) suggests an etiology not covered by standard therapy (eg, *Coccidioides*) or public health concerns (eg, SARS-CoV-2, *Mycobacterium tuberculosis*, influenza), diagnostic testing is appropriate. Diagnostic testing is recommended in hospitalized CAP patients for multiple reasons: the likelihood of an infectious cause unresponsive to standard therapy is higher in more severe illness, the inpatient setting allows narrowing of antibiotic coverage as specific diagnostic information is available, and the yield of testing is improved in more acutely ill patients.

Diagnostic tests are used to permit adjustment of empirically chosen therapy to a specific infectious cause or resistance pattern and facilitate epidemiologic analysis. Three widely available diagnostic tests may guide therapy: the sputum Gram stain and culture, urinary antigen tests for *S pneumoniae* and *Legionella* species, and tests for viruses such as influenza and SARS-CoV-2 (see COVID-19 discussion, Chapter 32, and consult <https://www.cdc.gov> for the latest from the CDC). Sputum Gram stain is

**Table 9–9.** Recommended empiric antibiotics for community-acquired bacterial pneumonia.

| <b>Outpatient management</b>   |
|--|
| 1. For previously healthy patients with no risk factors for MRSA or <i>Pseudomonas</i> :   |
| a. Amoxicillin, 1 g orally three times daily, or   |
| b. Doxycycline, 100 mg orally twice a day, or  |
| c. In regions with a low rate (< 25%) of infection with high level (MIC ≥ 16 mcg/mL) macrolide-resistant <i>Streptococcus pneumoniae</i> , then a macrolide (clarithromycin, 500 mg orally twice a day; or azithromycin, 500 mg orally as a first dose and then 250 mg orally daily for 4 days, or 500 mg orally daily for 3 days).  |
| 2. For patients with comorbid medical conditions such as chronic heart, lung, liver, or kidney disease; diabetes mellitus; alcohol use disorder; malignancy; asplenia; immunosuppressant conditions or use of immunosuppressive drugs; or use of antibiotics within the previous 3 months (in which case an agent from a different antibiotic class should be selected):   |
| a. A macrolide or doxycycline (as above) <i>plus</i> an oral beta-lactam (amoxicillin/clavulanate 500 mg/125 mg three times daily, amoxicillin/clavulanate 875 mg/125 mg twice daily, amoxicillin/clavulanate 2 g/125 mg twice daily; cefpodoxime, 200 mg twice daily; cefuroxime, 500 mg twice daily).  |
| b. Monotherapy with an oral fluoroquinolone (moxifloxacin, 400 mg daily; gemifloxacin, 320 mg daily; levofloxacin, 750 mg daily).  |
| <b>Inpatient management of nonsevere pneumonia (typically not requiring intensive care)</b>  |
| 1. A respiratory fluoroquinolone. Oral and intravenous doses equivalent: moxifloxacin, 400 mg daily or levofloxacin, 500–750 mg daily or   |
| 2. A macrolide (see above for oral therapy) <i>plus</i> a beta-lactam (see above for oral beta-lactam therapy). For intravenous therapy: ampicillin/sulbactam, 1.5–3 g every 6 hours; cefotaxime, 1–2 g every 8 hours; ceftriaxone, 1–2 g every 12–24 hours; ceftaroline, 600 mg every 12 hours.   |
| 3. For patients with prior respiratory isolation of MRSA, strongly consider adding coverage for MRSA and obtain cultures or nasal PCR to confirm infection or to allow de-escalation of therapy: vancomycin, typically starting at 15 mg/kg intravenously every 12 h with interval dosing based on kidney function to achieve serum trough concentration 15–20 mcg/mL or linezolid, 600 mg orally or intravenously every 12 h. |
| 4. For patients with prior respiratory isolation of <i>Pseudomonas aeruginosa</i> , strongly consider adding coverage for <i>P aeruginosa</i> and obtain cultures to confirm infection or to allow de-escalation of therapy. Intravenous therapy only: piperacillin-tazobactam, 3.375–4.5 g every 6 h; ceferipime, 1–2 g every 8 h; imipenem, 0.5–1 g every 6 h; meropenem, 1 g every 8 h; or aztreonam 2 g every 8 h.         |
| <b>Inpatient management of severe pneumonia (typically requiring intensive care). All agents administered intravenously, except as noted.</b>  |
| 1. Azithromycin (500 mg orally as a first dose and then 250 mg orally daily for 4 days, or 500 mg orally daily for 3 days) <i>or</i> a respiratory fluoroquinolone (as above) <i>plus</i> an intravenous anti-pneumococcal beta-lactam (as above).   |
| 2. For patients allergic to beta-lactam antibiotics, a fluoroquinolone <i>plus</i> aztreonam (2 g every 8 h).  |
| 3. For patients at risk for <i>P aeruginosa</i> , add coverage for <i>P aeruginosa</i> and obtain cultures to confirm infection or to allow de-escalation of therapy: piperacillin-tazobactam, 3.375–4.5 g every 6 h; ceferipime, 1–2 g every 8 h; imipenem, 0.5–1 g every 6 h; meropenem, 1 g every 8 h; or aztreonam 2 g every 8 h.  |
| 4. For patients at risk for <i>Pseudomonas</i> infection AND who are critically ill, at increased risk for drug resistance, or if local incidence of monotherapy-resistant <i>Pseudomonas</i> is > 10%, consider adding either   |
| a. An anti-pseudomonal fluoroquinolone (ciprofloxacin 400 mg every 8–12 h or levofloxacin 750 mg daily) <i>or</i>  |
| b. An aminoglycoside (gentamicin, tobramycin, amikacin, all weight-based dosing administered daily adjusted to appropriate trough levels).   |
| 5. For patients at risk for MRSA infection, add coverage for MRSA and obtain cultures and/or nasal PCR to confirm infection or to allow de-escalation of therapy: vancomycin, typically starting at 15 mg/kg intravenously every 12 h with interval dosing based on kidney function to achieve serum trough concentration 15–20 mcg/mL or linezolid, 600 mg every 12 h.  |

MIC, minimum inhibitory concentration; MRSA, methicillin-resistant *Staphylococcus aureus*; PCR, polymerase chain reaction.

Recommendations assembled from Metlay JP et al; Diagnosis and treatment of adults with community-acquired pneumonia. An official clinical practice guideline of the American Thoracic Society and Infectious Diseases Society of America. Am J Respir Crit Care Med. 2019;200(7):e45–e67.

neither sensitive nor specific for *S pneumoniae*, the most common cause of CAP. The usefulness of a sputum Gram stain lies in broadening initial coverage in patients to be hospitalized for CAP, most commonly to cover *S aureus* (including community-acquired methicillin-resistant *S aureus* [CA-MRSA] strains) or gram-negative rods (including *P aeruginosa* and Enterobacteriaceae). Urinary antigen assays for *Legionella pneumophila* and *S pneumoniae* are at least as sensitive and specific as sputum Gram stain and culture. Results are not affected by early initiation of antibiotic therapy, and positive tests may allow narrowing of initial antibiotic coverage. Urinary antigen assay for *S pneumoniae* should be ordered for patients

with leukopenia or asplenia or those with severe disease. Urinary antigen assay for *L pneumophila* should be ordered for patients in an area with an outbreak, with recent travel, with severe disease, or in whom a high clinical index of suspicion exists. Rapid influenza and SARS-CoV-2 testing has intermediate sensitivity but high specificity, with sensitivity depending on the method of detection (nucleic acid or polymerase chain reaction [PCR]-based tests have higher sensitivity than antigen-based detection). Positive tests may reduce direct isolation of hospitalized patients but do not necessarily reduce the need for antibacterial therapy, since viral coinfection with a bacterial pathogen is common.

Rapid turnaround multiplex-PCR amplification is widely available. Different commercial products can identify multiple strains of bacteria and viruses, in addition to genes that encode for antibiotic resistance, with results available in 60–90 minutes. Early experience with multiplex-PCR shows improved overall diagnostic yield, particularly for viral infections, and a higher incidence of bacterial/viral coinfection than previously recognized. Given the lack of effective treatment for most respiratory viral infections, the value of multiplex-PCR may be to avoid antibacterial therapy in viral infections, and early adjustment of empiric antibiotic therapy according to resistance patterns. Limitations of multiplex-PCR include cost and availability, in addition to the challenge of interpreting potentially false-positive results from a highly sensitive test. Testing for pandemic SARS-CoV-2 is reviewed in Chapter 32.

Additional microbiologic testing including pre-antibiotic sputum and blood cultures (at least two sets with needle sticks at separate sites) has been standard practice for patients with CAP who require hospitalization. The yield of blood and sputum cultures is low, however; false-positive results are common, and the impact of culture results on patient outcomes is small. As a result, targeted testing is recommended for patients with severe disease and for those treated empirically for MRSA or *P aeruginosa* infection. Culture results are not available prior to initiation of antibiotic therapy. Their role is to allow narrowing of initial empiric antibiotic coverage, adjustment of coverage based on specific antibiotic resistance patterns, to identify unsuspected pathogens not covered by initial therapy, and to provide information for epidemiologic analysis.

Apart from microbiologic testing, hospitalized patients should undergo complete blood count with differential and a chemistry panel (including serum glucose, electrolytes, urea nitrogen, creatinine, bilirubin, and liver enzymes). Hypoxemic patients should have ABGs sampled. Test results help assess severity of illness and guide evaluation and management. HIV testing should be considered in all adult patients and performed in those with risk factors.

## C. Imaging

A pulmonary opacity on chest radiography or CT scan is required to establish a diagnosis of CAP. Chest CT scan is more sensitive and specific than chest radiography and may be indicated in selected cases. Radiographic findings range from patchy airspace opacities to lobar consolidation with air bronchograms to diffuse alveolar or interstitial opacities. Additional findings can include pleural effusions and cavitation. Chest imaging cannot identify a specific microbiologic cause of CAP, however. No pattern of radiographic abnormalities is pathognomonic of any infectious cause.

Chest imaging may help assess severity and response to therapy over time. Progression of pulmonary opacities during antibiotic therapy or lack of radiographic improvement over time are poor prognostic signs and raise concerns about secondary or alternative pulmonary processes. Clearing of pulmonary opacities in patients with CAP can take 6 weeks or longer. Clearance is usually quickest in younger patients, nonsmokers, and those with only single-lobe involvement.

## D. Special Examinations

Patients with CAP who have significant pleural fluid collections may require diagnostic thoracentesis (with pleural fluid sent for glucose, lactate dehydrogenase [LD], and total protein levels; leukocyte count with differential; pH determination; and Gram stain and culture). Positive pleural cultures indicate the need for tube thoracostomy drainage.

Patients with cavitary opacities should have sputum fungal and mycobacterial cultures.

Sputum induction and fiberoptic bronchoscopy to obtain samples of lower respiratory secretions are indicated in patients who cannot provide expectorated sputum samples or who may have pneumonia caused by *P jirovecii*, SARS-CoV-2, or *M tuberculosis* infection.

Procalcitonin is a calcitonin precursor released in response to bacterial toxins and inhibited by viral infections. This divergent response to bacterial and viral infections offers laboratory support for a clinical judgment of a viral process in patients with lower respiratory symptoms; however, studies have not found a threshold at which bacterial pneumonia can be reliably distinguished from viral pneumonia. Therefore, procalcitonin is not recommended as a “rule-out” test for bacterial pneumonia, and empiric antibacterial agents are recommended regardless of procalcitonin level at time of presentation.

## ► Differential Diagnosis

The differential diagnosis of lower respiratory tract infection is extensive and includes upper respiratory tract infections, reactive airway diseases, heart failure, cryptogenic organizing pneumonitis, lung cancer, pulmonary vasculitis, pulmonary thromboembolic disease, and atelectasis.

## ► Treatment

Two general principles guide antibiotic therapy once the diagnosis of CAP is established: **prompt** initiation of a medication to which the etiologic pathogen is **susceptible**.

In patients who require specific diagnostic evaluation, sputum and blood culture specimens should be obtained prior to initiation of antibiotics. Since early administration of antibiotics to acutely ill patients is associated with improved outcomes, obtaining other diagnostic specimens or test results should not delay the initial dose of antibiotics.

Optimal antibiotic therapy would be pathogen directed, but a definitive microbiologic diagnosis is not typically available on presentation. A syndromic approach to therapy, based on clinical presentation and chest imaging, does not reliably predict the microbiology of CAP. Therefore, initial antibiotic choices are typically empiric, based on acuity (treatment as an outpatient, inpatient, or in the ICU), patient risk factors for specific pathogens, and local antibiotic resistance patterns (Table 9–9).

Since *S pneumoniae* remains a common cause of CAP in all patient groups, local prevalence of drug-resistant *S pneumoniae* significantly affects initial antibiotic choice. Prior treatment with one antibiotic in a pharmacologic class (eg, beta-lactam, macrolide, fluoroquinolone) predisposes

to the emergence of drug-resistant *S pneumoniae*, with resistance developing against that class of antibiotics to which the pathogen was previously exposed. Definitions of resistance have shifted based on observations of continued clinical efficacy at achievable serum levels. In CAP, for parenteral penicillin G or oral amoxicillin, susceptible strains have a minimum inhibitory concentration (MIC) of 2 mcg/mL or less; intermediate resistance is defined as an MIC between 2 mcg/mL and 4 mcg/mL because treatment failures are uncommon with MIC of 4 mcg/mL or less. Macrolide resistance has increased; approximately one-third of *S pneumoniae* isolates now show in vitro resistance to macrolides. Treatment failures have been reported but remain rare compared to the number of patients treated. Current in vivo efficacy appears to justify maintaining macrolides as first-line therapy except in areas where there is a high prevalence of resistant strains. *S pneumoniae* resistant to fluoroquinolones is rare in the United States (1% to levofloxacin, 2% to ciprofloxacin) but is increasing.

CA-MRSA is genetically and phenotypically different from hospital-acquired MRSA strains. CA-MRSA is a rare cause of necrotizing pneumonia, empyema, respiratory failure, and shock; it appears to be associated with prior influenza infection. Linezolid may be preferred to vancomycin in treatment of CA-MRSA pulmonary infection. For expanded discussions of specific antibiotics, see Chapters 30 and e1.

### A. Treatment of Outpatients

See Table 9–9 for specific medication dosages. The most common etiologies of CAP in outpatients who do not require hospitalization are *S pneumoniae*; *M pneumoniae*; *C pneumoniae*; and respiratory viruses, including influenza. For previously healthy patients with no recent (90 days) use of antibiotics, the recommended treatment is a macrolide (clarithromycin or azithromycin), doxycycline, or amoxicillin. In areas with a high incidence of macrolide-resistant *S pneumoniae*, initial therapy in patients with no comorbidities may include the combination of a beta-lactam *plus* a macrolide, or a respiratory fluoroquinolone.

In outpatients with chronic heart, lung, liver, or kidney disease; diabetes mellitus; alcoholism; malignancy; or asplenia or who received antibiotic therapy within the past 90 days, the recommended treatment is a macrolide or doxycycline plus a beta-lactam (high-dose amoxicillin and amoxicillin-clavulanate are preferred to cefpodoxime and cefuroxime) or monotherapy with a respiratory fluoroquinolone (moxifloxacin, gemifloxacin, or levofloxacin).

The default duration of antibiotic therapy for CAP should be 5 days; factors that may affect therapy duration are clinical stability, etiology (MRSA and *P aeruginosa* require 7 days of therapy, for example), severity of illness, complications, and comorbid medical problems.

### B. Treatment of Hospitalized and ICU Patients

**1. Antibiotics**—The most common etiologies of CAP in patients who require hospitalization but not intensive care are *S pneumoniae*, *M pneumoniae*, *C pneumoniae*, *H influenzae*, *Legionella* species, and respiratory viruses.

Some patients have aspiration as an immediate precipitant to the CAP without a specific bacterial etiology. First-line therapy in hospitalized patients is the combination of a macrolide (clarithromycin or azithromycin) plus a beta-lactam (cefotaxime, ceftriaxone, ceftaroline, or ampicillin-sulbactam) or monotherapy with a respiratory fluoroquinolone (eg, moxifloxacin, gemifloxacin, or levofloxacin) (see Table 9–9).

Almost all patients admitted to a hospital for treatment of CAP receive intravenous antibiotics. However, no studies in hospitalized patients demonstrated superior outcomes with intravenous antibiotics compared with oral antibiotics, provided patients were able to tolerate oral therapy and the medication was well absorbed. Duration of inpatient antibiotic treatment is the same as for outpatients.

The most common etiologies of CAP in patients who require admission to intensive care are *S pneumoniae*, *Legionella* species, *H influenzae*, Enterobacteriaceae species, *S aureus*, *Pseudomonas* species, and respiratory viruses. First-line therapy in ICU patients with CAP is an anti-pneumococcal beta-lactam (cefotaxime, ceftriaxone, ceftaroline, or ampicillin-sulbactam) *plus* either azithromycin or a respiratory fluoroquinolone (moxifloxacin, gemifloxacin, or levofloxacin).

Risk factors for *Pseudomonas*, Enterobacteriaceae, or MRSA infection must be considered when choosing empiric antibiotic therapy for inpatients with CAP. Specific risk factors for these organisms include (1) prior isolation of the pathogen, (2) inpatient hospitalization within the last 90 days, or (3) exposure to intravenous antibiotics within the last 90 days. In patients with specific risk factors for *Pseudomonas* infection, combine an anti-pneumococcal, anti-pseudomonal beta-lactam (piperacillin-tazobactam, cefepime, imipenem, meropenem) with either azithromycin or a respiratory fluoroquinolone (moxifloxacin, gemifloxacin, or levofloxacin). In critically ill patients, in those at increased risk for drug resistance, or if the unit incidence of monotherapy-resistant *Pseudomonas* is greater than 10%, consider use of two agents with anti-pseudomonal efficacy: either ciprofloxacin or levofloxacin plus the above anti-pneumococcal, anti-pseudomonal beta-lactam **or** an anti-pneumococcal, anti-pseudomonal beta-lactam plus an aminoglycoside (gentamicin, tobramycin, amikacin) plus either azithromycin or a respiratory fluoroquinolone. Patients with specific risk factors for MRSA should be treated with vancomycin or linezolid. Patients with very severe disease (respiratory failure requiring mechanical ventilation or septic shock) should also be strongly considered for MRSA therapy. Provided the patient is clinically improving, negative sputum and blood cultures obtained prior to initiation of antibiotics can support de-escalation of antibiotic therapy. Additionally, all patients prescribed vancomycin or linezolid should have swabs of the nasal passages for MRSA; if the swab results are negative, MRSA coverage can be safely de-escalated, even when adequate sputum samples have not been obtained.

Patients with CAP in whom influenza is detected should be treated with the antiviral oseltamavir, whether influenza is identified as a single pathogen or as a coinfection along with a bacterial pathogen. Oseltamavir

treatment is most effective when begun within 2 days but may still be beneficial within several days after symptom onset, particularly in severe cases of CAP.

**2. Adjunctive treatment**—Conflicting data have emerged from RCTs regarding adjunctive treatment with corticosteroids in CAP. Meta-analyses of large studies have failed to find a mortality benefit in association with corticosteroid use in mild or moderate CAP, though there may be benefit in severe disease. Based on limited data and because of the potential for complications (eg, hyperglycemia), the 2019 Infectious Diseases Society of America/American Thoracic Society (IDSA/ATS) guidelines recommend against corticosteroids in the treatment CAP of any severity. Corticosteroid treatment of viral (influenza) pneumonia may be associated with higher mortality and should be avoided. Corticosteroids are recommended to be started or continued in patients with CAP who may also have severe septic shock, acute exacerbation of asthma or COPD, or adrenal insufficiency.

## ► When to Admit

Once a diagnosis of CAP is made, the first management decision is to determine the site of care: Is it safe to treat the patient at home or does he or she require hospital or intensive care admission? There are two widely used clinical prediction rules available to guide admission and triage decisions, the **Pneumonia Severity Index (PSI)** and the **CURB-65**.

### A. Hospital Admission Decision

The PSI is a validated prediction model that uses 20 items from demographics, medical history, physical examination, laboratory results, and imaging to stratify patients into five risk groups. The PSI is weighted toward discrimination at low predicted mortality. In conjunction with clinical judgment, it facilitates safe decisions to treat CAP in the outpatient setting. An online PSI risk calculator is available at [https://www.thecalculator.co/health/Pneumonia-Severity-Index-\(PSI\)-Calculator-977.html](https://www.thecalculator.co/health/Pneumonia-Severity-Index-(PSI)-Calculator-977.html). The CURB-65 assesses five simple, independent predictors of increased mortality (confusion, uremia, respiratory rate, blood pressure, and age greater than 65) to calculate a 30-day predicted mortality (<https://www.mdcalc.com/curb-65-score-pneumonia-severity>). Compared with the PSI, the simpler CURB-65 is less discriminating at low mortality but excellent at identifying patients with high mortality who may benefit from ICU-level care. A modified version (CRB-65) dispenses with blood urea nitrogen and eliminates the need for laboratory testing. Both have the advantage of simplicity: patients with zero CRB-65 predictors have a low predicted mortality (less than 1%) and usually do not need hospitalization; hospitalization should be considered for those with one or two predictors, since they have an increased risk of death; and urgent hospitalization (with consideration of ICU admission) is required for those with three or four predictors.

Hospital admission decision should also include circumstances of care independent of pneumonia severity, including comorbidities and the patient's ability to care for themselves effectively at home.

### B. Intensive Care Unit Admission Decision

Expert opinion has defined major and minor criteria to identify patients at high risk for death. Major criteria are septic shock with need for vasopressor support and respiratory failure with need for mechanical ventilation. Minor criteria are respiratory rate = 30 breaths or more per minute, hypoxemia (defined as  $\text{PaO}_2/\text{FiO}_2 = 250$  or less), hypothermia (core temperature less than  $36.0^\circ\text{C}$ ), hypotension requiring aggressive fluid resuscitation, confusion/disorientation, multilobar pulmonary opacities, leukopenia due to infection with WBC less than  $4000/\text{mCL}$  (less than  $4.0 \times 10^9/\text{L}$ ), thrombocytopenia with platelet count less than  $100,000/\text{mCL}$  (less than  $100 \times 10^9/\text{L}$ ), uremia with blood urea nitrogen =  $20 \text{ mg/dL}$  or more ( $7.1 \text{ mmol/L}$  or more), metabolic acidosis, or elevated serum lactate level. Either one major criterion or three or more minor criteria of illness severity generally require ICU-level care.

## ► Prevention

Pneumococcal vaccines have the potential to prevent or lessen the severity of pneumococcal infections in immunocompetent patients. Two pneumococcal vaccines for adults are available and approved for use in the United States: one containing capsular polysaccharide antigens of 23 common strains of *S pneumoniae* in use for many years (Pneumovax 23) and a conjugate vaccine containing 13 common strains approved for adult use in 2011 (Prevnar-13). Current recommendations are for sequential administration of the two vaccines in those aged 65 years or older and in immunocompromised persons, starting with Prevnar-13. Adults with chronic illness that increases the risk of CAP (see Chapter 30) should receive the 23-valent vaccine regardless of age. Immunocompromised patients and those at highest risk for fatal pneumococcal infections should receive a single revaccination of the 23-valent vaccine 5 years after the first vaccination regardless of age. Immunocompetent persons 65 years of age or older should receive a second dose of the 23-valent vaccine if the patient first received the vaccine 6 or more years previously and was under 65 years old at the time of first vaccination.

The seasonal influenza vaccine is effective in preventing severe disease due to influenza virus with a resulting positive impact on both primary influenza pneumonia and secondary bacterial pneumonias. The seasonal influenza vaccine is administered annually to persons at risk for complications of influenza infection (aged 65 years or older, residents of long-term care facilities, patients with pulmonary or cardiovascular disorders, patients recently hospitalized with chronic metabolic disorders) as well as health care workers and others who may transmit influenza to high-risk patients.

Hospitalized patients who would benefit from pneumococcal and influenza vaccines should be vaccinated during hospitalization. The two vaccines may be administered simultaneously as soon as the patient has stabilized.

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## 2. Nosocomial Pneumonia (Hospital-Acquired & Ventilator-Associated)



- ▶ **Hospital-acquired pneumonia (HAP)** is diagnosed in patients with clinical features and imaging consistent with pneumonia, occurring  $> 48$  hours after admission to the hospital and excluding any infections present at the time of admission.
- ▶ **Ventilator-associated pneumonia (VAP)** requires clinical features concerning for new pneumonia with positive respiratory samples developing  $> 48$  hours following endotracheal intubation and mechanical ventilation.

### ► General Considerations

Hospitalized patients carry different flora with different resistance patterns than healthy patients in the community, and their health status may place them at higher risk for more severe infection. The diagnostic approach and antibiotic treatment of patients with HAP is, therefore, different from patients with CAP. Similarly, management of patients in whom VAP develops following endotracheal intubation and mechanical ventilation should address issues specific to this group of patients.

Considered together, these nosocomial pneumonias (HAP or VAP) represent an important cause of morbidity and mortality despite widespread use of preventive measures, advances in diagnostic testing, and potent new antimicrobial agents. HAP is one of the most common causes of infection among hospital inpatients and carries the highest burden of morbidity and mortality. Patients in ICUs and those who are being mechanically ventilated are at the highest risk for HAP (and VAP) and experience higher morbidity and mortality from them than other inpatients. Definitive identification of the infectious cause of a lower respiratory infection is rarely available on presentation; initial antibiotic

treatment is therefore empiric and informed by epidemiologic and patient data rather than pathogen directed.

### ► Definition & Pathogenesis

HAP develops more than 48 hours after admission to the hospital and VAP develops in a mechanically ventilated patient more than 48 hours after endotracheal intubation. Three factors distinguish nosocomial pneumonia from CAP: (1) different infectious causes; (2) different antibiotic susceptibility patterns, specifically, a higher incidence of drug resistance; and (3) poorer underlying health status of patients putting them at risk for more severe infections. Since access to the lower respiratory tract occurs primarily through microaspiration, nosocomial pneumonia starts with a change in upper respiratory tract flora. Colonization of the pharynx and possibly the stomach with bacteria is the most important step in the pathogenesis of nosocomial pneumonia. Pharyngeal colonization is promoted by exogenous factors (eg, instrumentation of the upper airway with nasogastric and endotracheal tubes; contact with personnel, equipment, and contaminated aerosols; treatment with broad-spectrum antibiotics that promote the emergence of drug-resistant organisms); and patient factors (eg, malnutrition, advanced age, altered consciousness, swallowing disorders, and underlying pulmonary and systemic diseases). Impaired cellular and mechanical defense mechanisms in the lungs of hospitalized patients raise the risk of infection after aspiration has occurred.

Gastric acid may play a role in protection against nosocomial pneumonias. Observational studies have suggested that elevation of gastric pH due to antacids,  $\text{H}_2$ -receptor antagonists, proton-pump inhibitors (PPIs), or enteral feeding is associated with gastric microbial overgrowth, tracheobronchial colonization, and HAP/VAP. Moreover, a 2018 meta-analysis of randomized controlled trials suggested an increased risk of HAP among enterally fed patients receiving stress ulcer prophylaxis. The IDSA and other professional organizations recommend that acid-suppressive medications ( $\text{H}_2$ -receptor antagonists and PPIs) be given only to patients at high risk for stress gastritis.

The microbiology of the nosocomial pneumonias differs from CAP but is substantially the same among HAP and VAP. The most common organisms responsible for HAP and VAP include *S aureus* (both methicillin-sensitive *S aureus* and MRSA), *P aeruginosa*, gram-negative rods, including extended spectrum beta-lactamase (ESBL)-producing organisms (*Enterobacter* species, *K pneumoniae*, and *Escherichia coli*) and non-ESBL-producing organisms. VAP patients may be infected with *Acinetobacter* species and *S maltophilia*. Anaerobic organisms (*Bacteroides*, anaerobic streptococci, *Fusobacterium*) may also cause pneumonia in the hospitalized patient; when these organisms are isolated, they are commonly part of a polymicrobial flora. VAP occurring before hospital day 4 in a previous healthy person with no antibiotic exposure is more likely to involve oral flora with a minimal resistance profile than multidrug-resistant pathogens. However, multidrug-resistant pathogens may complicate early-onset VAP in patients

with antibiotic exposure in preceding 90 days, recent hospitalization, or prior colonization with multidrug-resistant pathogens.

## ► Clinical Findings

### A. Symptoms and Signs

The symptoms and signs associated with nosocomial pneumonias are nonspecific. However, two or more clinical findings (fever, leukocytosis, purulent sputum, worsening respiratory status) along with one or more new or progressive pulmonary opacities on chest imaging are characteristic features of nosocomial pneumonia. Other findings include those listed above for CAP.

The differential diagnosis of new lower respiratory tract symptoms and signs in hospitalized patients includes heart failure, atelectasis, aspiration, ARDS, pulmonary thromboembolism, pulmonary hemorrhage, and medication reactions.

### B. Laboratory Findings

Diagnostic evaluation for suspected nosocomial pneumonia includes blood cultures from two different sites. Blood cultures can identify the pathogen in 15–20% of patients with nosocomial pneumonias; positivity is associated with increased risk of complications and other sites of infection. Blood counts and clinical chemistry tests do not establish a specific diagnosis; however, they help define the severity of illness and identify complications. Serum procalcitonin levels are not sufficiently sensitive to rule out HAP or VAP but may allow discontinuation of antibiotic therapy. Thoracentesis for pleural fluid analysis should be considered in patients with pleural effusions.

Examination of lower respiratory tract secretions is attended by the same disadvantages as in CAP. Gram stains and cultures of sputum are neither sensitive nor specific in the diagnosis of nosocomial pneumonias; sensitivity of sputum results further decreases following antibiotic therapy, particularly after 72 hours of antibiotics. The identification of a bacterial organism by culture of lower respiratory tract secretions does not prove that the organism is a lower respiratory tract pathogen; however, it can be used to help identify bacterial antibiotic sensitivity patterns and as a guide to adjusting empiric therapy. Nasal swab for PCR detection of MRSA is recommended to guide de-escalation of broad-spectrum antibiotic therapy in patients with HAP and VAP.

### C. Imaging

Radiographic findings in HAP/VAP are nonspecific and often confounded by other processes that led initially to hospitalization or ICU admission. (See CAP above.)

### D. Special Examinations

When HAP is suspected in a patient who subsequently requires mechanical ventilation, secretions may be obtained by spontaneous expectoration, sputum induction, nasotracheal suctioning, and endotracheal aspiration (qualitative or semiquantitative samples), or more invasively via

bronchoscopic sampling of the lower airways secretions (quantitative samples). The best approach remains a matter of debate, since qualitative or semiquantitative samples are more likely to return nonpathogenic organisms and are, thus, associated with higher antibiotic exposure (without improvement in mortality), while invasive quantitative sampling increases cost and patient risk. Invasive qualitative sampling is universally recommended when the patient does not improve during initial therapy directed at expected or isolated pathogens, or in immunocompromised persons in whom an opportunistic pathogen is suspected.

## ► Treatment

The initial treatment of HAP and VAP is usually empiric, based on risk factors for MRSA and multiple drug-resistant pathogens (Table 9–10) as well as local antibiograms and mortality risk (Table 9–11). Each hospital should generate antibiograms to guide the optimal choice of antibiotics with the goals of reducing exposure to unnecessary antibiotics and the development of antibiotic resistance, thus

**Table 9–10.** Risk factors for multidrug-resistant (MDR) pathogens, methicillin-resistant *Staphylococcus aureus* (MRSA), and *Pseudomonas* and other gram-negative bacilli in patients with hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP).

#### Risk factors for MDR pathogens

- Antibiotic therapy in the preceding 90 days
- Septic shock
- Acute respiratory distress syndrome preceding VAP
- ≥ 5 days in hospital prior to occurrence of HAP/VAP
- Acute renal replacement therapy prior to HAP/VAP onset
- Treatment in a unit where > 10% of gram-negative isolates are resistant to an agent being considered for monotherapy
- Treatment in a unit where local antibiotic susceptibility rates are not known

#### Risk factors for MRSA

- Antibiotic therapy in the preceding 90 days
- Renal replacement therapy in the preceding 30 days
- Use of gastric acid suppressive agents
- Positive culture or prior MRSA colonization, especially in the preceding 90 days
- Hospitalization in a unit where > 20% of *S aureus* isolates are MRSA
- Hospitalization in a unit where prevalence of MRSA is not known

#### Risk factors for *Pseudomonas aeruginosa* and other gram-negative bacilli

- Antibiotic therapy in the preceding 90 days
- Structural lung disease (COPD, especially with recurrent exacerbations; bronchiectasis; or cystic fibrosis)
- Recent hospitalizations, especially with manipulation of the aerodigestive tract (nasoenteric nutrition, intubation)
- High-quality Gram stain of respiratory secretions with numerous and predominant gram-negative bacilli
- Positive culture for *P aeruginosa* in the past year

COPD, chronic obstructive pulmonary disease.

Data from Kalil AC et al. Management of adults with hospital-acquired and ventilator-associated pneumonia: 2016 Clinical Practice Guidelines by the Infectious Diseases Society of America and the American Thoracic Society. Clin Infect Dis. 2016;63:e61.

**Table 9–11.** Recommended initial empiric antibiotics for hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP).

**HAP not at high risk for mortality, or VAP with no risk factors for MRSA, MDR, or *Pseudomonas* and other gram-negative bacilli**

USE **one** of the following:

- Piperacillin-tazobactam, 4.5 g intravenously every 6 hours<sup>1</sup>
- Cefepime, 2 g intravenously every 8 hours<sup>1</sup>
- Levofloxacin, 750 mg intravenously daily
- Imipenem, 500 mg intravenously every 6 hours<sup>1</sup>
- Meropenem, 1 g intravenously every 8 hours<sup>1</sup>

**HAP or VAP with risk factors for MRSA but no risk factors for MDR, *Pseudomonas*, and other gram-negative bacilli**

USE **one** of the following:

- Piperacillin-tazobactam, 4.5 g intravenously every 6 hours<sup>1</sup>
- Cefepime, 2 g intravenously every 8 hours<sup>1</sup>
- Ceftazidime, 2 g intravenously every 8 hours
- Levofloxacin, 750 mg intravenously daily
- Ciprofloxacin, 400 mg intravenously every 8 hours
- Imipenem, 500 mg intravenously every 6 hours<sup>1</sup>
- Meropenem, 1 g intravenously every 8 hours<sup>1</sup>
- Aztreonam, 2 g intravenously every 8 hours

PLUS **one** of the following:

- Vancomycin, 15 mg/kg intravenously every 8–12 hours with goal to target trough level = 15–20 mg/mL (consider a loading dose of 25–30 mg/kg once for severe illness)<sup>2</sup>
- Linezolid, 600 mg intravenously every 12 hours

**HAP with risk factors for *Pseudomonas* and other gram-negative bacilli, but no risk factors for MRSA and not at high risk for mortality**

USE **one** of the following:

- Piperacillin-tazobactam, 4.5 g intravenously every 6 hours<sup>1</sup>
- Cefepime, 2 g intravenously every 8 hours<sup>1</sup>
- Ceftazidime, 2 g intravenously every 8 hours
- Imipenem, 500 mg intravenously every 6 hours<sup>1</sup>
- Meropenem, 1 g intravenously every 8 hours<sup>1</sup>
- Aztreonam, 2 g intravenously every 8 hours

PLUS **one** of the following:

- Levofloxacin, 750 mg intravenously daily
- Ciprofloxacin, 400 mg intravenously every 8 hours
- Gentamicin, 5–7 mg/kg intravenously daily<sup>2</sup>
- Tobramycin, 5–7 mg/kg intravenously daily<sup>2</sup>
- Aztreonam, 2 g intravenously every 8 hours

**HAP at high risk for mortality or VAP with risk factors for MRSA and risk factors for MDR, *Pseudomonas*, and other gram-negative bacilli**

USE **one** of the following:

- Piperacillin-tazobactam, 4.5 g intravenously every 6 hours<sup>1</sup>
- Cefepime, 2 g intravenously every 8 hours<sup>1</sup>
- Ceftazidime, 2 g intravenously every 8 hours
- Imipenem, 500 mg intravenously every 6 hours<sup>1</sup>
- Meropenem, 1 g intravenously every 8 hours<sup>1</sup>
- Aztreonam, 2 g intravenously every 8 hours

PLUS **one** of the following:

- Levofloxacin, 750 mg intravenously daily
- Ciprofloxacin, 400 mg intravenously every 8 hours
- Amikacin, 15–20 mg/kg intravenously daily<sup>2</sup>
- Gentamicin, 5–7 mg/kg intravenously daily<sup>2</sup>
- Tobramycin, 5–7 mg/kg intravenously daily<sup>2</sup>
- Meropenem, 1 g intravenously every 8 hours<sup>1</sup>
- Polymyxin B, 2.5–3.0 mg/kg per day divided in 2 daily intravenous doses
- Colistin: consult clinical pharmacist for assistance with dosing

PLUS **one** of the following:

- Vancomycin, 15 mg/kg intravenously every 8–12 hours with goal to target trough level = 15–20 mg/mL (consider a loading dose of 25–30 mg/kg once for severe illness)<sup>2</sup>
- Linezolid, 600 mg intravenously every 12 hours

CrCl, creatinine clearance; MDR, multidrug resistant; MRSA, methicillin-resistant *Staphylococcus aureus*.

<sup>1</sup>Extended infusions may be appropriate.

<sup>2</sup>Drug level monitoring and adjustment of dosing are required.

Data from Kalil AC et al. Management of adults with hospital-acquired and ventilator-associated pneumonia: 2016 Clinical Practice Guidelines by the Infectious Diseases Society of America and the American Thoracic Society. Clin Infect Dis. 2016;63:e61.

minimizing patient harm. Because of the high mortality rate, therapy should be started as soon as HAP or VAP is suspected. After results of cultures are available, it may be possible to narrow initially broad therapy to more specific agents. Endotracheal aspiration cultures have significant negative predictive value but limited positive predictive value in the diagnosis of specific infectious causes of HAP/VAP. If an invasive diagnostic approach to suspected VAP using quantitative culture of bronchoalveolar lavage (BAL), protected specimen brush (PSB), or blind bronchial sampling (BBS) is used, antibiotics can be withheld when results are below a diagnostic threshold (BAL less than  $10^4$  CFU/mL, PSB or BBS less than  $10^3$  CFU/mL). Duration of antibiotic therapy is 7 days, consistent with clinical response, but should be individualized based on the pathogen, severity of illness, response to therapy, and comorbid conditions.

For expanded discussions of specific antibiotics, see Chapter 30.

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### 3. Anaerobic Pneumonia & Lung Abscess



► History of or predisposition to aspiration.

► Indolent symptoms, including fever, weight loss, and malaise.

► Poor dentition.

► Foul-smelling purulent sputum (in many patients).

► Infiltrate in dependent lung zone, with single or multiple areas of cavitation or pleural effusion.

#### ► General Considerations

Aspiration of small amounts of oropharyngeal secretions occurs during sleep in normal individuals but rarely causes disease. Sequelae of aspiration of larger amounts of

material include nocturnal asthma, chemical pneumonitis, mechanical obstruction of airways by particulate matter, bronchiectasis, and pleuropulmonary infection. Individuals predisposed to disease induced by aspiration include those with depressed levels of consciousness due to drug or alcohol use, seizures, general anesthesia, or central nervous system disease; those with impaired deglutition due to esophageal disease or neurologic disorders; and those with tracheal or nasogastric tubes, which disrupt the mechanical defenses of the airways.

Periodontal disease and poor dental hygiene, which increase the number of anaerobic bacteria in aspirated material, are associated with a greater likelihood of anaerobic pleuropulmonary infection. Aspiration of infected oropharyngeal contents initially leads to pneumonia in dependent lung zones, such as the posterior segments of the upper lobes and superior and basilar segments of the lower lobes. Body position at the time of aspiration determines which lung zones are dependent. The onset of symptoms is insidious. By the time the patient seeks medical attention, necrotizing pneumonia, lung abscess, or empyema may be apparent.

In most cases of aspiration and necrotizing pneumonia, lung abscess, and empyema, multiple species of anaerobic bacteria are causing the infection. Most of the remaining cases are caused by infection with both anaerobic and aerobic bacteria. *Prevotella melaninogenica*, *Peptostreptococcus*, *Fusobacterium nucleatum*, and *Bacteroides* species are commonly isolated anaerobic bacteria.

#### ► Clinical Findings

##### A. Symptoms and Signs

Patients with anaerobic pleuropulmonary infection usually present with constitutional symptoms, such as fever, weight loss, and malaise. Cough with expectoration of foul-smelling purulent sputum suggests anaerobic infection, though the absence of productive cough does not rule out such an infection. Dentition is often poor. Patients are rarely edentulous; if so, an obstructing bronchial lesion may be present.

##### B. Laboratory Findings

Expectorated sputum cultures may be difficult to interpret due to contaminating upper respiratory tract flora, but high colony count of a particular microorganism on Gram stain or in culture likely represents a true pathogen. Anaerobes and facultative anaerobes are difficult to recover on any culture, particularly following initiation of antibiotics; pleural fluid from empyema may be revealing.

##### C. Imaging

The different types of anaerobic pleuropulmonary infection are distinguished by their radiographic appearance. **Lung abscess** appears as a thick-walled solitary cavity surrounded by consolidation. An air-fluid level is usually present. Other causes of cavitary lung disease (tuberculosis, mycosis, cancer, infarction, necrobiotic nodules in rheumatoid arthritis, and pulmonary vasculitides) should be excluded. **Necrotizing pneumonia** is distinguished by

multiple areas of cavitation within an area of consolidation. **Empyema** is characterized by the presence of purulent pleural fluid and may accompany either of the other two radiographic findings. Ultrasonography is of value in locating fluid and may also reveal pleural loculations.

## ► Treatment

Medications of choice are directed at anaerobic organisms or facultative anaerobic streptococci and include a beta-lactam/lactamase inhibitor combination, carbapenem, or clindamycin. Second-line therapy includes a combination of penicillin and metronidazole. Duration of antibiotic therapy for anaerobic pneumonia is controversial, but it is usually given for a minimum of 3 weeks, with some experts recommending treatment until the abscess cavity has resolved on imaging.

Peripheral lung abscess must be carefully distinguished from empyema because empyema requires tube thoracostomy; if tube thoracostomy is placed inadvertently into an abscess cavity, complications, such as a bronchopleural fistula, may result. Thoracic surgery consultation is recommended for large or nonresolving abscesses or for abscesses that rupture into the pleural space. Rarely, a large abscess requires surgical intervention (percutaneous drainage, segmentectomy, lobectomy, or pneumonectomy).

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## PULMONARY INFILTRATES IN IMMUNOCOMPROMISED PATIENTS

Pulmonary infiltrates in immunocompromised patients (patients with HIV disease, absolute neutrophil counts less than 1000/mcL [less than  $1.0 \times 10^9/L$ ], current or recent exposure to myelosuppressive or immunosuppressive medications, or those currently taking more than 20 mg/day of prednisone) may arise from infectious or noninfectious causes. Infection may be due to bacterial, mycobacterial, fungal, protozoal, helminthic, or viral pathogens. Noninfectious processes, such as pulmonary edema, alveolar hemorrhage, medication reactions, pulmonary thromboembolic disease, malignancy, and radiation pneumonitis, may mimic infection.

Although almost any pathogen can cause pneumonia in an immunocompromised patient, two clinical tools help the clinician narrow the differential diagnosis. The first is knowledge of the underlying immunologic defect. Specific immunologic defects are associated with particular infections. Defects in humoral immunity predispose to bacterial infections; defects in cellular immunity lead to infections with viruses, fungi, mycobacteria, and protozoa. Neutropenia and impaired granulocyte function predispose to infections from *S aureus*, *Aspergillus*, gram-negative bacilli, and *Candida*. Second, the time

course of infection also provides clues to the etiology of pneumonia in immunocompromised patients. A fulminant pneumonia is often caused by bacterial infection, whereas an insidious pneumonia is more apt to be caused by viral, fungal, protozoal, or mycobacterial infection. Pneumonia occurring within 2–4 weeks after organ transplantation is usually bacterial, whereas several months or more after transplantation *P jirovecii*, viruses (eg, cytomegalovirus) and fungi (eg, *Aspergillus*) are encountered more often.

## ► Clinical Findings

Chest radiography is rarely helpful in narrowing the differential diagnosis. Examination of expectorated sputum for bacteria, fungi, mycobacteria, *Legionella*, and *P jirovecii* is important and may preclude the need for expensive, invasive diagnostic procedures. Sputum induction is often necessary for diagnosis. The sensitivity of induced sputum for detection of *P jirovecii* depends on institutional expertise, number of specimens analyzed, and detection methods.

Routine evaluation frequently fails to identify a causative organism. The clinician may begin empiric antimicrobial therapy before proceeding to invasive procedures, such as bronchoscopy, transthoracic needle aspiration, or open lung biopsy. The approach to management must be based on the severity of the pulmonary infection, the underlying disease, the risks of empiric therapy, and local expertise and experience with diagnostic procedures. BAL using flexible bronchoscopy is a safe and effective method for obtaining representative pulmonary secretions for microbiologic studies. It involves less risk of bleeding and other complications than transbronchial biopsy. BAL is especially suitable for the diagnosis of *P jirovecii* pneumonia in patients with HIV/AIDS when induced sputum analysis is negative. Surgical lung biopsy, now often performed by video-assisted thoracoscopy, provides the definitive option for diagnosis of pulmonary infiltrates in immunocompromised patients; however, a specific diagnosis is obtained in only about two-thirds of cases, and the information obtained may not affect the outcome.

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 Ghembaza A et al. Risk factors and prevention of *Pneumocystis jirovecii* pneumonia in patients with autoimmune and inflammatory diseases. *Chest.* 2020;158:2323. [PMID: 32502592]  
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## PULMONARY TUBERCULOSIS



### ESSENTIALS OF DIAGNOSIS

- ▶ Fatigue, weight loss, fever, night sweats, and productive cough.
- ▶ Risk factors for acquisition of infection: household exposure, incarceration, drug use, travel to or residence in endemic area.
- ▶ Chest radiograph: pulmonary opacities, including nodular or cavitating.
- ▶ Acid-fast bacilli on smear of sputum, rapid molecular testing positive, or sputum culture positive for *M tuberculosis*.

### ► General Considerations

Tuberculosis is one of the world's most widespread and deadly illnesses and is the most deadly infectious disease. *M tuberculosis*, the organism that causes tuberculosis infection and disease, infects one-quarter of the world's population, nearly 2 billion people. In 2019, there were 10 million new cases of tuberculosis worldwide with 1.4 million people dying of the disease. While most incident cases occur in low- and middle-income countries, tuberculosis is present in all regions of the world. In the United States, an estimated 13 million people are infected with *M tuberculosis*, and in 2019, there were 8914 reported active cases (a decrease from prior years), with the majority of incident cases in New York, California, Florida, and Texas. Tuberculosis occurs disproportionately among disadvantaged populations, such as the malnourished, homeless, and those living in overcrowded and substandard housing. There is an increased occurrence of tuberculosis among HIV-positive individuals.

Infection with *M tuberculosis* begins when a susceptible person inhales airborne droplet nuclei containing viable organisms. Tubercle bacilli that reach the alveoli are ingested by alveolar macrophages. Infection follows if the inoculum escapes alveolar macrophage microbial activity. Once infection is established, lymphatic and hematogenous dissemination of tuberculosis typically occurs before the development of an effective immune response. This stage of infection, **primary tuberculosis**, is usually clinically and radiographically silent. In most persons with intact cell-mediated immunity, T-cells and macrophages surround the organisms in granulomas that limit their multiplication and spread. The infection is contained but not eradicated, since viable organisms may lie dormant within granulomas for years to decades.

Individuals with **latent tuberculosis infection** do not have active disease and cannot transmit the organism to others. However, reactivation of disease may occur if the patient's immune defenses are impaired. **Active tuberculosis** will develop in 5–15% of individuals with latent tuberculosis infection who are not given preventive therapy; half of these cases occur in the 2 years following primary infection. Diverse conditions such as gastrectomy, silicosis,

diabetes mellitus, and an impaired immune response (eg, HIV infection; therapy with corticosteroids, tumor necrosis factor inhibitors or other immunosuppressive drugs) are associated with an increased risk of reactivation.

In approximately 5% of cases, the immune response is inadequate to contain the primary infection and **progressive primary tuberculosis** develops, accompanied by both pulmonary and constitutional symptoms. The clinical presentation does not definitively distinguish primary disease from reactivation of latent tuberculosis infection. Standard teaching has held that 90% of tuberculosis in adults represents activation of latent disease. However, DNA fingerprinting of the bacillus suggests that as many as one-third of new cases of tuberculosis in urban populations are primary infections resulting from person-to-person transmission.

The prevalence of drug-resistant strains is increasing worldwide, with a 10% increase in multidrug-resistant strains between 2018 and 2019; however, in the United States, the rate of multidrug-resistant isolates has fallen to less than 1%. Risk factors for drug resistance include immigration from countries with a high prevalence of drug-resistant tuberculosis, close and prolonged contact with individuals with drug-resistant tuberculosis, unsuccessful previous therapy, and nonadherence to treatment. Drug resistance may be single or multiple. **Drug-resistant tuberculosis** is resistant to one first-line antituberculous drug, either isoniazid or rifampin. **Multidrug-resistant tuberculosis** is resistant to isoniazid and rifampin, and possibly additional agents. **Extensively drug-resistant tuberculosis** is resistant to isoniazid, rifampin, fluoroquinolones, and either aminoglycosides or capreomycin or both. Outcomes of drug-resistant tuberculosis treatment are worse than when the isolate is drug-sensitive, and outcomes appear to vary with HIV status. In a review of extensively drug-resistant tuberculosis cases in the United States, mortality was 10% and 68% in HIV-negative and HIV-positive patients, respectively.

### ► Clinical Findings

#### A. Symptoms and Signs

The patient with pulmonary tuberculosis typically presents with slowly progressive constitutional symptoms of malaise, anorexia, weight loss, fever, and night sweats. Chronic cough is the most common pulmonary symptom. It may be dry at first but typically becomes productive of purulent sputum as the disease progresses. Blood-streaked sputum is common, but significant hemoptysis is rarely a presenting symptom; life-threatening hemoptysis may occur in advanced disease. Dyspnea is unusual unless there is extensive disease. On physical examination, the patient appears chronically ill and malnourished. On chest examination, there are no physical findings specific for tuberculosis infection. The examination may be normal or may reveal classic findings such as posttussive apical rales.

#### B. Laboratory Findings

Definitive diagnosis depends on recovery of *M tuberculosis* from cultures or identification of the organism by DNA or RNA amplification techniques (in concert with appropriate

clinical context). At least three consecutive morning sputum specimens are advised, and samples should be collected 8 hours apart. Acid-fast staining of a sputum smear is performed initially as a screening method, with sensitivity and negative predictive values that are low (50–80%) with a single smear but may improve to 90% with serial sampling. Smear sensitivity is lower in HIV-coinfected patients. Demonstration of acid-fast bacilli on sputum smear does not establish a diagnosis of *M tuberculosis*, since nontuberculous mycobacteria may colonize the airways and are increasingly recognized to cause clinical illness in patients with underlying structural lung disease.

In patients thought to have tuberculosis who cannot produce satisfactory specimens or when the smear of the spontaneously expectorated sputum is negative for acid-fast bacilli, sputum induction with 3% hypertonic saline should be performed. Flexible bronchoscopy with bronchial washings has similar diagnostic yield to induced sputum; transbronchial lung biopsies do not significantly increase the diagnostic yield but may lead to earlier diagnosis by identifying tissue granulomas. Post-bronchoscopy expectorated sputum specimens should be collected. Positive blood cultures for *M tuberculosis* are uncommon in patients with normal CD4 cell counts, but the organism

may be cultured from blood in up to 50% of HIV-seropositive patients with tuberculosis whose CD4 cell counts are less than 100/mcL (less than  $0.1 \times 10^9/L$ ); mycobacterial blood cultures should be obtained in such patients.

The slow rate of mycobacterial growth; the urgency to provide early, appropriate treatment to patients to improve their outcomes and limit community spread; and concerns about potential drug toxicities in patients treated empirically who do not have tuberculosis infection have fostered the use of rapid diagnostic techniques (Table 9–12). Molecular diagnostics offer multiple options and many advantages, though at increased expense. Nucleic acid amplification testing not only detects *M tuberculosis* (NAAT-TB) but also identifies resistance markers (NAAT-R). NAAT-TB can identify *M tuberculosis* within hours of sputum processing, allowing early isolation and treatment, though the negative predictive value is lower in smear-negative patients. NAAT-R allows rapid identification of primary drug resistance and has previously been indicated in the following patients: (1) those treated previously for tuberculosis, (2) those born (or who lived for more than 1 year) in a country with moderate tuberculosis incidence or a high incidence of multiple drug-resistant isolates, (3) contacts of patients with multidrug-resistant tuberculosis,

**Table 9–12.** Essential laboratory tests for the detection of *Mycobacterium tuberculosis*.<sup>1</sup>

| Test  | Time to Result                                     | Test Characteristics   |
|---|--|--|
| Acid-fast bacilli light microscopy  | 1 day  | Three morning specimens recommended. Combined sensitivity of 70% (54% for the first specimen, 11% for the second specimen, and 5% for the third specimen). First morning specimen increased yield by 12% compared to spot specimen.  |
| Nucleic acid amplification test, detection (NAAT-TB)  | 1 day  | Sensitivity/specifity high for smear-positive specimens, 85–97% for both; sensitivity falls in smear-negative specimens to ~66%. A positive NAAT in smear-negative patients with intermediate to high (> 30%) pretest probability of <i>M tuberculosis</i> infection is helpful while a negative NAAT is not. Should not be ordered in patients with low pretest probability of <i>M tuberculosis</i> infection. |
| Nucleic acid amplification test, resistance markers (NAAT-R)  | 1–2 days   | Multiple assays for rifampin and isoniazid are available. Specificity uniformly high, > 98%. Sensitivity varies from about 84% to 96%, increases with multiple specimens. See text for indications for testing.  |
| Mycobacterial growth detection<br>Liquid (broth based) medium<br>Solid (agar or egg based) medium                             | Up to 6–8 weeks<br>Avg 10–14 days<br>Avg 3–4 weeks | Liquid culture methods are more sensitive than solid culture methods (~90% and 76%, respectively) with shorter time to detection but higher contamination with bacterial growth. Specificity exceeds 99% for all methods.  |
| Identification of <i>M tuberculosis</i> complex by DNA probe or high-performance liquid chromatography                        | 1 day <sup>1</sup>                                 | May be useful in areas of low <i>M tuberculosis</i> incidence where nontuberculous mycobacteria are commonly isolated.   |
| First-line drug susceptibility testing (liquid medium)  | 1–2 weeks <sup>1</sup>                             | Gold standard. Should be performed routinely on the initial isolate.   |
| Second-line and novel compound drug susceptibility testing<br>Liquid (broth based) medium<br>Solid (agar or egg based) medium | 1–2 weeks <sup>1</sup><br>3–4 weeks <sup>1</sup>   |  |

<sup>1</sup>Following detection of mycobacterial growth.

Adapted from Diagnostic Standards and Classification of Tuberculosis in Adults and Children. This official statement of the American Thoracic Society and the Centers for Disease Control and Prevention was adopted by the ATS Board of Directors, July 1999. This statement was endorsed by the Council of the Infectious Disease Society of America, September 1999. Am J Respir Crit Care Med. 2000;161:1376.

or (4) those who are HIV seropositive. In view of the rapidity of result in concert with rifampin resistance identification, the WHO issued continued guidance in 2020 that rapid molecular testing is the ideal initial test for diagnosis and resistance profiling in persons in whom pulmonary or extrapulmonary tuberculosis is suspected.

Needle biopsy of the pleura reveals granulomatous inflammation in approximately 60% of patients with pleural effusions caused by *M tuberculosis*. Pleural fluid cultures are positive for *M tuberculosis* in 23–58% of cases of pleural tuberculosis. Culture of three pleural biopsy specimens combined with microscopic examination of a pleural biopsy yields a diagnosis in up to 90% of patients with pleural tuberculosis. Tests for pleural fluid adenosine deaminase (approximately 90% sensitivity and specificity for pleural tuberculosis at levels greater than 70 units/L) and interferon-gamma (89% sensitivity, 97% specificity in a recent meta-analysis) can be extremely helpful diagnostic aids, particularly in making decisions to pursue invasive testing in complex cases.

### C. Imaging

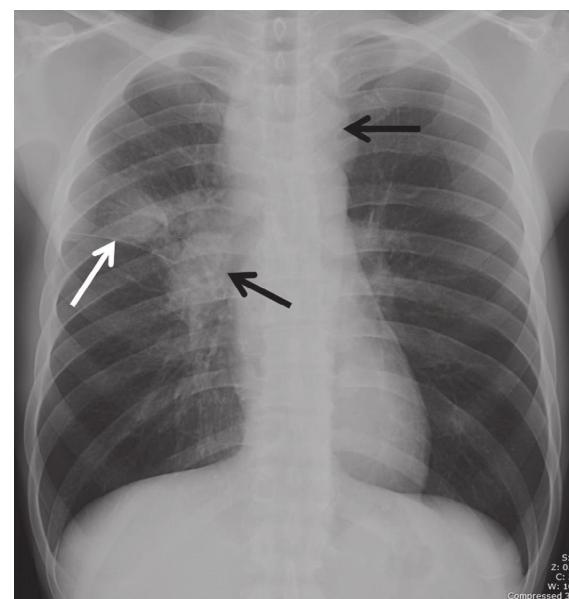
Contrary to traditional teaching, molecular analysis demonstrates that radiographic abnormalities in pulmonary tuberculosis do not distinguish primary disease from reactivation of latent tuberculosis (Figure 9–4). The only independent predictor of an atypical pattern on chest radiograph—that is, not associated with upper lobe or cavitary disease—is an impaired patient immune response. The chest imaging pattern traditionally associated with primary disease includes small unilateral infiltrates, hilar and paratracheal lymph node enlargement, and segmental atelectasis. Pleural effusion is present in 30–40% of patients, sometimes as the sole radiographic abnormality. Reactivation tuberculosis traditionally has been associated with fibrocavitory apical disease, discrete nodules, and pneumonic infiltrates, usually in the apical or posterior segments of the upper lobes or in the superior segments of the lower lobes. Radiographic evidence of disease in other locations may be present in up to 30% of patients.

In elderly patients, lower lobe infiltrates with or without pleural effusion are frequently encountered. A “miliary” pattern (diffuse small nodular densities) can be seen with hematologic or lymphatic dissemination of the organism. Immunocompromised patients—particularly those with late-stage HIV infection—often display lower lung zone, diffuse, or miliary infiltrates; pleural effusions; and involvement of hilar and, in particular, mediastinal lymph nodes.

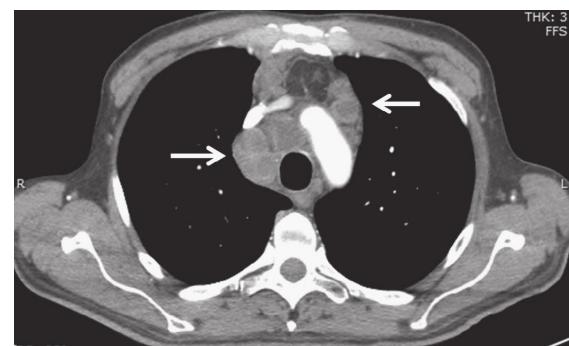
Resolution of active tuberculosis leaves characteristic radiographic findings. Dense nodules in the pulmonary hila, with or without obvious calcification, upper lobe fibronodular scarring, and bronchiectasis with volume loss are common findings. Ghon (calcified primary focus) and Ranke (calcified primary focus and calcified hilar lymph node) complexes are seen in a minority of patients.

### D. Special Examinations

Testing for latent tuberculosis infection is used to evaluate an asymptomatic person in whom *M tuberculosis* infection



A



B

**▲ Figure 9–4.** Pulmonary tuberculosis. Primary pulmonary tuberculosis in a 20-year-old man with chest radiograph (A) showing right upper lobe consolidation (white arrow) and right hilar and mediastinal lymphadenopathy (black arrows) and contrast-enhanced CT scan (B) showing mediastinal lymphadenopathy (arrows). (Used, with permission, from Carlos Santiago Restrepo, MD, in Usatine RP, Smith MA, Mayeaux EJ Jr, Chumley H. *The Color Atlas of Family Medicine*, 2nd ed. McGraw-Hill, 2013.)

is suspected (eg, following contact exposure) or to establish the prevalence of tuberculosis infection in a population. Testing may be used in a person with symptoms of active tuberculosis, but a positive test does not distinguish between active and latent infection, and a negative test does not rule out active disease. Routine testing of individuals at low risk for tuberculosis is not recommended. Empiric treatment of latent tuberculosis without testing is considered appropriate in HIV-infected persons or in young (less than 5 years old) household contacts of persons with active tuberculosis in endemic areas.

The traditional approach to testing for latent tuberculosis infection is the **tuberculin skin test**. The Mantoux test

**Table 9–13.** Classification of positive tuberculin skin test reactions.<sup>1</sup>

| Induration Size | Group   |
|-----------------|---|
| ≥ 5 mm          | <ol style="list-style-type: none"> <li>1. HIV-positive persons.</li> <li>2. Recent contacts of a person with infectious tuberculosis.</li> <li>3. Persons with fibrotic changes on chest radiographs suggestive of prior tuberculosis.</li> <li>4. Patients with organ transplants and other immunosuppressed patients (receiving the equivalent of &gt; 15 mg/day of prednisone for 1 month or more, or those taking TNF-alpha antagonists).</li> </ol>  |
| ≥ 10 mm         | <ol style="list-style-type: none"> <li>1. Recent immigrants (&lt; 5 years) from countries with a high prevalence of tuberculosis (eg, Asia, Africa, Latin America).</li> <li>2. HIV-negative injection drug users.</li> <li>3. Mycobacteriology laboratory personnel.</li> <li>4. Residents of and employees in high-risk congregate settings: correctional institutions; long-term care facilities; hospitals and other health care facilities; residential facilities for HIV/AIDS patients; and homeless shelters.</li> <li>5. Persons with medical conditions that increase the risk of progression to tuberculosis disease: gastrectomy, weight loss to ≥ 10% below ideal body weight, jeunoileal bypass, diabetes mellitus, silicosis, advanced chronic kidney disease, some hematologic disorders (eg, leukemias, lymphomas), and other specific malignancies (eg, carcinoma of the head or neck and lung).</li> <li>6. Children younger than 4 years or infants, children, and adolescents exposed to adults at high risk.</li> </ol> |
| ≥ 15 mm         | <ol style="list-style-type: none"> <li>1. Persons with no known risk factors for tuberculosis.</li> </ol>   |

<sup>1</sup>A tuberculin skin test reaction is considered positive if the transverse diameter of the *indurated* area reaches the size required for the specific group. All other reactions are considered negative.

Data from <https://www.cdc.gov/tb/publications/factsheets/testing/skintesting.htm>.

is the preferred method: 0.1 mL of purified protein derivative (PPD) containing 5 tuberculin units is injected intradermally on the volar surface of the forearm using a 27-gauge needle on a tuberculin syringe. The **transverse width in millimeters of induration** at the skin test site is measured after 48–72 hours. To optimize test performance, criteria for determining a positive reaction vary depending on the likelihood of infection. Table 9–13 summarizes the criteria established by the Centers for Disease Control and Prevention (CDC) for interpretation of the Mantoux tuberculin skin test. Sensitivity and specificity of the tuberculin skin test are high: 77% and 97%, respectively. Specificity falls to 59% in populations previously vaccinated with bacillus Calmette-Guérin (BCG, an attenuated form of *Mycobacterium bovis*). False-negative tuberculin skin test reactions may result from improper testing technique; concurrent infections, including fulminant tuberculosis; malnutrition; advanced age; immunologic disorders; malignancy; corticosteroid therapy; chronic kidney disease; and HIV infection. Some individuals with latent tuberculosis infection may have a negative tuberculin skin test when tested many years after exposure. Anergy testing is not recommended for routine use to distinguish a true-negative result from anergy. Poor anergy test standardization and lack of outcome data limit the evaluation of its effectiveness. Interpretation of the tuberculin skin test in persons who have previously received BCG vaccination is the same as in those who have not had BCG.

**Interferon gamma release assays** (including the QuantiFERON and T-SPOT tests) are in vitro assays of CD4+ T-cell-mediated interferon gamma release in response to stimulation by specific *M tuberculosis* antigens. The antigens are absent from all BCG strains and most

nontuberculous mycobacteria; therefore, in whole blood, the specificity of interferon gamma release assays is superior to the tuberculin skin test in BCG-vaccinated individuals. Sensitivity is comparable to the tuberculin skin test: 60–90% depending on the specific assay and study population. Sensitivity is reduced by HIV infection, particularly in patients with low CD4 counts. Specificity is high, greater than 95%. Potential advantages of interferon gamma release assay testing include fewer false-positive results from prior BCG vaccination, better discrimination of positive responses due to nontuberculous mycobacteria, and the requirement for only one patient contact (ie, no need for the patient to return to have the tuberculin skin test read 48–72 hours later). Disadvantages include the need for specialized laboratory equipment and personnel, and the substantially increased cost compared to the tuberculin skin test.

In endemic areas, interferon gamma release assays are no more sensitive than the tuberculin skin test in active tuberculosis (20–40% false-negative rate) and cannot distinguish active from latent disease. Interferon gamma release assays should not be used to exclude active tuberculosis.

Guidelines established by the CDC allow interferon gamma release assays to be used interchangeably with the tuberculin skin testing in the diagnosis of latent tuberculosis infection. Interferon gamma release assays are preferred in patients with prior BCG vaccination; the tuberculin skin test is preferred in children under 5 years old. Routine use of both tests is not recommended. In individuals with a positive tuberculin skin test but a low prior probability of latent tuberculosis infection and low-risk for progression to active disease, the interferon gamma release assay may be helpful as a confirmatory test to exclude a false-positive tuberculin skin test.

## ► Treatment

### A. General Measures

The goals of therapy are to cure the individual patient, minimize risk of morbidity and mortality related to treatment, reduce transmission of *M tuberculosis* to other persons, and prevent the emergence of clinically significant drug resistance in tubercle bacilli. The basic principles of antituberculous treatment are (1) to administer multiple medications to which the organisms are susceptible; (2) to provide the safest, most effective therapy for the shortest period of time; (3) to ensure adherence to therapy; and (4) to add at least two new antituberculous agents to a regimen when treatment failure is suspected.

All suspected and confirmed cases of tuberculosis should be reported promptly to local and state public health authorities. Patients with tuberculosis should be treated by clinicians who are skilled in the management of this infection. Clinical expertise is especially important in cases of drug-resistant tuberculosis.

Nonadherence to antituberculous treatment is a major cause of treatment failure, continued transmission of tuberculosis, and development of medication resistance. Adherence to treatment can be improved by providing detailed patient education about tuberculosis and its treatment in addition to a case manager who oversees all aspects of an individual patient's care. **Directly observed therapy (DOT)**, which requires that a health care worker physically observe the patient ingest antituberculous medications in the home, clinic, hospital, or elsewhere, also improves adherence to treatment. The importance of direct observation of therapy cannot be overemphasized. The CDC recommends DOT for all patients with drug-resistant tuberculosis and for those receiving intermittent (twice- or thrice-weekly) therapy.

Hospitalization for initial therapy of tuberculosis is not necessary for most patients. It should be considered if a patient is incapable of self-care or is likely to expose new, susceptible individuals to tuberculosis. Hospitalized patients with active disease require a private room with appropriate environmental controls, including negative-pressure ventilation where available, until tubercle bacilli are no longer found in their sputum ("smear-negative") on three consecutive smears taken on separate days.

Characteristics of antituberculous drugs are provided in Table 9–14. Additional treatment considerations can be found in Chapter 33. More complete information can be obtained from the CDC's Division of Tuberculosis Elimination website at <https://www.cdc.gov/tb/topic/treatment/default.htm> or the WHO tuberculosis website at <https://www.who.int/health-topics/tuberculosis/>.

### B. Treatment of Tuberculosis in HIV-Negative Persons

Most patients with previously untreated pulmonary tuberculosis can be effectively treated with either a 6-month or a 9-month regimen, though the 6-month regimen is preferred. The initial phase of a 6-month regimen consists of 2 months of daily isoniazid, rifampin, pyrazinamide, and

ethambutol. Once the isolate is determined to be isoniazid-sensitive, ethambutol may be discontinued. If the *M tuberculosis* isolate is susceptible to isoniazid and rifampin, the second phase of therapy consists of isoniazid and rifampin for a minimum of 4 additional months, with treatment to extend at least 3 months beyond documentation of conversion of sputum cultures to negative for *M tuberculosis*. If DOT is used, medications may be given intermittently using one of three regimens: (1) Daily isoniazid, rifampin, pyrazinamide, and ethambutol for 2 months, followed by isoniazid and rifampin two or three times each week for 4 months if susceptibility to isoniazid and rifampin is demonstrated. (2) Daily isoniazid, rifampin, pyrazinamide, and ethambutol for 2 weeks, then administration of the same agents twice a week for 6 weeks followed by administration of isoniazid and rifampin twice each week for 4 months if susceptibility to isoniazid and rifampin is demonstrated. (3) Isoniazid, rifampin, pyrazinamide, and ethambutol three times a week for 6 months.

Patients who cannot or should not (eg, pregnant women) take pyrazinamide should receive daily isoniazid and rifampin along with ethambutol for 4–8 weeks. If susceptibility to isoniazid and rifampin is demonstrated or drug resistance is unlikely, ethambutol can be discontinued, and isoniazid and rifampin may be given for a total of 9 months of therapy. If drug resistance is a concern, patients should receive isoniazid, rifampin, and ethambutol for 9 months. Patients with smear- and culture-negative disease (eg, pulmonary tuberculosis diagnosed on clinical grounds) and patients for whom drug susceptibility testing is not available can be treated with 6 months of isoniazid and rifampin combined with pyrazinamide for the first 2 months. This regimen assumes low prevalence of drug resistance. Previous guidelines have used streptomycin interchangeably with ethambutol. Increasing worldwide streptomycin resistance has made this medication less useful as empiric therapy.

When a twice-weekly or thrice-weekly regimen is used instead of a daily regimen, the dosages of isoniazid, pyrazinamide, and ethambutol or streptomycin must be increased. Recommended dosages for the initial treatment of tuberculosis are listed in Table 9–15. Fixed-dose combinations of isoniazid and rifampin (Rifamate) and of isoniazid, rifampin, and pyrazinamide (Rifater) are available to simplify treatment. Single tablets improve compliance but are more expensive than the individual medications purchased separately.

### C. Treatment of Tuberculosis in HIV-Positive Persons

Management of tuberculosis is complex in patients with concomitant HIV disease. Experts in the management of both tuberculosis and HIV disease should be involved in the care of such patients. The CDC has published detailed recommendations for the treatment of tuberculosis in HIV-positive patients (<https://www.cdc.gov/tb/topic/treatment/tbhiv.htm>).

The basic approach to HIV-positive patients with tuberculosis is similar to that detailed above for patients

**Table 9–14.** Characteristics of antituberculous medications.

| Medication   | Most Common Side Effects   | Tests for Side Effects                                | Drug Interactions   | Remarks   |
|--------------|--|---|---|---|
| Isoniazid    | Peripheral neuropathy, hepatitis, rash, mild CNS effects.  | AST and ALT; neurologic examination.                  | Phenytoin (synergistic); disulfiram.  | Bactericidal to both extracellular and intracellular organisms. Pyridoxine, 25–50 mg orally daily is given as prophylaxis for neuropathy; 50–100 mg orally daily as treatment for it.                                     |
| Rifampin     | Hepatitis, fever, rash, flu-like illness, gastrointestinal upset, bleeding problems, kidney failure. | CBC, platelets, AST and ALT.                          | Rifampin inhibits the effect of oral contraceptives, quinidine, corticosteroids, warfarin, methadone, digoxin, oral hypoglycemics; aminosalicylic acid may interfere with absorption of rifampin. Significant interactions with protease inhibitors and nonnucleoside reverse transcriptase inhibitors. | Bactericidal to all populations of organisms. Colors urine and other body secretions orange. May discolor contact lenses.   |
| Rifapentine  | Bone marrow suppression, hematuria/pyuria, hepatitis, gastrointestinal upset, flu-like illness.      | CBC, platelets, AST and ALT.                          | Strong cytochrome P450 inducer with multiple drug interactions. Use in HIV patients receiving antiretroviral therapy should be limited to experts in antiretroviral therapy.  | Bactericidal to both extracellular and intracellular organisms. Colors urine and other body secretions orange. Long half-life, can be administered weekly in LTBI prophylaxis. Not for use in induction phase of therapy. |
| Pyrazinamide | Hyperuricemia, hepatotoxicity, rash, gastrointestinal upset, joint aches.                            | Uric acid, AST, ALT.                                  | Rare.   | Bactericidal to intracellular organisms.  |
| Ethambutol   | Optic neuritis (reversible with discontinuance of drug; rare at 15 mg/kg); rash.                     | Red-green color discrimination and visual acuity.     | Rare.   | Bacteriostatic to both intracellular and extracellular organisms. Mainly used to inhibit development of resistant mutants. Use with caution in kidney disease or when ophthalmologic testing is not feasible.             |
| Streptomycin | Eighth nerve damage, nephrotoxicity.   | Vestibular function (audiograms); BUN and creatinine. | Neuromuscular blocking agents may be potentiated and cause prolonged paralysis.   | Bactericidal to extracellular organisms. Use with caution in older patients or those with kidney disease.   |

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CBC, complete blood count; LTBI, latent tuberculosis infection.

without HIV disease. Additional considerations in HIV-positive patients include (1) longer duration of therapy and (2) drug interactions between rifamycin derivatives such as rifampin and rifabutin used to treat tuberculosis and some of the protease inhibitors and nonnucleoside reverse transcriptase inhibitors (NNRTIs) used to treat HIV (see <https://www.cdc.gov/tb/topic/treatment/tbhiv.htm>). DOT should be used for all HIV-positive tuberculosis patients. Pyridoxine (vitamin B<sub>6</sub>), 25–50 mg orally each day, should be administered to all HIV-positive patients being treated with isoniazid to reduce central and peripheral nervous system side effects.

#### D. Treatment of Drug-Resistant Tuberculosis

Patients with drug-resistant *M. tuberculosis* infection require careful supervision and management. Clinicians who are unfamiliar with the treatment of drug-resistant tuberculosis should seek expert advice. Tuberculosis resistant only to isoniazid can be successfully treated with a 6-month regimen of rifampin, pyrazinamide, and ethambutol or streptomycin or a 12-month regimen of rifampin and ethambutol. When isoniazid resistance is documented during a 9-month regimen without pyrazinamide, isoniazid should be discontinued. If ethambutol was part of the

**Table 9–15.** Recommended dosages for the initial treatment of tuberculosis.<sup>1</sup>

| Medication   | Daily <sup>2</sup>                 | Cost <sup>3</sup> /Day | Twice a Week <sup>2</sup>                                 | Cost <sup>3</sup> /Wk | Three Times a Week <sup>2</sup>                           | Cost <sup>3</sup> /Wk |
|--------------|------------------------------------|------------------------|---|-----------------------|---|-----------------------|
| Isoniazid    | 5 mg/kg<br>Max: 300 mg/dose        | \$0.31/300 mg          | 15 mg/kg<br>Max: 900 mg/dose                              | \$1.86                | 15 mg/kg<br>Max: 900 mg/dose                              | \$2.79                |
| Rifampin     | 10 mg/kg<br>Max: 600 mg/dose       | \$2.66/600 mg          | 10 mg/kg<br>Max: 600 mg/dose                              | \$5.32                | 10 mg/kg<br>Max: 600 mg/dose                              | \$7.98                |
| Pyrazinamide | 18.2–26.3 mg/kg<br>Max: 2 g/dose   | \$24.33/2 g            | Weight-based dosing:<br>see references below <sup>1</sup> | —                     | Weight-based dosing: see<br>references below <sup>1</sup> | —                     |
| Ethambutol   | 14.5–21.1 mg/kg<br>Max: 1.6 g/dose | \$3.74/1.6 g           | Weight-based dosing:<br>see references below <sup>1</sup> | —                     | Weight-based dosing: see<br>references below <sup>1</sup> | —                     |

<sup>1</sup>Data from Nahid P et al. Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America Clinical Practice Guidelines: Treatment of drug-susceptible tuberculosis. Clin Infect Dis. 2016;63:e147.

<sup>2</sup>All dosing regimens should be used with directly observed therapy.

<sup>3</sup>Average wholesale price (AWP, for AB-rated generic when available) for quantity listed. Source: IBM Micromedex. Red Book (electronic version). IBM Watson Health, Greenwood Village, CO, USA. Available at <https://www.micromedexsolutions.com/> (cited March 27, 2021). AWP may not accurately represent the actual pharmacy cost because wide contractual variations exist among institutions.

Also available at <https://www.cdc.gov/tb/topic/treatment/tbdisease.htm>.

initial regimen, rifampin and ethambutol should be continued for a minimum of 12 months. If ethambutol was not part of the initial regimen, susceptibility tests should be repeated and two other medications to which the organism is susceptible should be added. Treatment of *M tuberculosis* isolates resistant to agents other than isoniazid and treatment of drug resistance in HIV-infected patients require expert consultation.

Multidrug-resistant tuberculosis and extensively drug-resistant tuberculosis call for an individualized daily DOT plan under the supervision of an experienced clinician. Treatment regimens are based on the patient's overall status and the results of susceptibility studies. Most drug-resistant isolates are resistant to at least isoniazid and rifampin and require a minimum of three drugs to which the organism is susceptible; expert recommendation is often for an intensive five-drug phase of treatment, followed by a two- or three-drug continuation phase of treatment for at least another 12 months. Some experts recommend at least 18–24 months of therapy.

### E. Treatment of Extrapulmonary Tuberculosis

In most cases, regimens that are effective for treating pulmonary tuberculosis are also effective for treating extrapulmonary disease. However, many experts recommend 9–12 months of therapy when miliary, meningeal, or bone and joint disease is present. Treatment of skeletal tuberculosis is enhanced by early surgical drainage and debridement of necrotic bone. Corticosteroid therapy has been shown to help prevent constrictive pericarditis from tuberculous pericarditis and to reduce neurologic complications from tuberculous meningitis (Chapter 33).

### F. Treatment of Pregnant or Lactating Women

Tuberculosis in pregnancy is usually treated with isoniazid, rifampin, and ethambutol for 2 months, followed by isoniazid

and rifampin for an additional 7 months. Ethambutol can be stopped after the first month if isoniazid and rifampin susceptibility is confirmed. Since the risk of teratogenicity with pyrazinamide has not been clearly defined, pyrazinamide should be used only if resistance to other drugs is documented and susceptibility to pyrazinamide is likely. Streptomycin is contraindicated in pregnancy because it may cause congenital deafness. Pregnant women taking isoniazid should receive pyridoxine (vitamin B<sub>6</sub>), 10–25 mg orally once a day, to prevent peripheral neuropathy.

Small concentrations of antituberculous drugs are present in breast milk. First-line therapy is not known to be harmful to nursing newborns at these concentrations. Therefore, breastfeeding is not contraindicated while receiving first-line antituberculous therapy. Lactating women receiving other agents should consult a tuberculosis expert.

### G. Treatment Monitoring

Adults should have measurements of a complete blood count (including platelets) and serum bilirubin, hepatic enzymes, urea nitrogen, and creatinine before starting therapy for tuberculosis. Visual acuity and red-green color vision tests are recommended before initiation of ethambutol, and serum uric acid is recommended before starting pyrazinamide. Audiometry should be performed if streptomycin therapy is initiated.

Routine monitoring of laboratory tests for evidence of medication toxicity during therapy is not recommended, unless baseline results are abnormal or liver disease is suspected. Monthly questioning for symptoms of medication toxicity is advised. Patients should be educated about common side effects of antituberculous medications and instructed to seek medical attention should these symptoms occur. Monthly follow-up of outpatients is recommended, including sputum smear and culture for

*M tuberculosis*, until cultures convert to negative. Patients with negative sputum cultures after 2 months of treatment should have at least one additional sputum smear and culture performed at the end of therapy. Patients with drug-resistant isolates should have sputum cultures performed monthly during the entire course of treatment. A chest radiograph at the end of therapy provides a useful baseline for any future films.

Patients whose cultures do not become negative or whose symptoms do not resolve despite 3 months of therapy should be evaluated for nonadherence to the regimen and for drug-resistant organisms. DOT is required for the remainder of the treatment regimen, and the addition of at least two drugs not previously given should be considered pending repeat drug susceptibility testing. The clinician should seek expert assistance if drug resistance is newly found, if the patient remains symptomatic, or if smears or cultures remain positive.

Patients with only a clinical diagnosis of pulmonary tuberculosis (smears and cultures negative for *M tuberculosis*) whose symptoms and radiographic abnormalities are unchanged after 3 months of treatment usually either have another process or have had tuberculosis in the past.

### H. Treatment of Latent Tuberculosis

Treatment of latent tuberculous infection is essential to controlling and eliminating tuberculosis and substantially reduces the risk that infection will progress to active disease. Targeted testing with the tuberculin skin test or interferon gamma release assays is used to identify persons who are at high risk for tuberculosis and who stand to benefit from treatment of latent infection. Table 9–13 gives the tuberculin skin test criteria for treatment of latent tuberculous infection. In general, patients with a positive tuberculin skin test or interferon gamma release assay who are at increased risk for exposure or disease are treated. It is essential that each person who meets the criteria for treatment of latent tuberculous infection undergo a careful assessment to exclude active disease. A history of past treatment for tuberculosis and contraindications to treatment should be sought. All patients at risk for HIV infection should have an HIV test. Patients suspected of having tuberculosis should receive one of the recommended multidrug regimens for active disease until the diagnosis is confirmed or excluded.

Some close contacts of persons with active tuberculosis should be evaluated for treatment of latent tuberculous infection despite a negative tuberculin skin test reaction (less than 5 mm induration). These include immunosuppressed persons and those in whom disease may develop quickly after tuberculous infection. Close contacts who have a negative tuberculin skin test reaction on initial testing should be retested 10–12 weeks later.

Several treatment regimens for both HIV-negative and HIV-positive persons are available for the treatment of latent tuberculous infection: (1) **Isoniazid:** A 9-month oral regimen (minimum of 270 doses administered within 12 months) is preferable to 6 months of therapy. Dosing options include a daily dose of 300 mg or twice-weekly

doses of 15 mg/kg. Persons at risk for developing isoniazid-associated peripheral neuropathy (those with diabetes mellitus, uremia, malnutrition, alcoholism, HIV infection, pregnancy, or seizure disorder) may be given supplemental pyridoxine (vitamin B<sub>6</sub>), 10–50 mg/day. (2) **Isoniazid and rifampin:** A 3-month oral regimen of daily isoniazid (300 mg) and rifampin (600 mg). (3) **Isoniazid and rifapentine:** A 3-month oral regimen of once weekly isoniazid at 15 mg/kg and rifapentine at 15–30 mg/kg. (4) **Rifampin:** Patients who cannot tolerate isoniazid can be considered for a 4-month oral regimen of rifampin at 600 mg daily. HIV-positive patients receiving protease inhibitors or NNRTIs who are given rifampin or rifapentine require management by experts in both tuberculosis and HIV disease (see Treatment of Tuberculosis in HIV-Positive Persons, above).

Contacts of persons with isoniazid-resistant, rifampin-sensitive tuberculosis should receive a 2-month regimen of rifampin and pyrazinamide or a 4-month regimen of daily rifampin alone. Contacts of persons with drug-resistant tuberculosis should receive two drugs to which the infecting organism has demonstrated susceptibility. Contacts in whom the tuberculin skin test or interferon gamma release assay is negative and contacts who are HIV seronegative may be observed without treatment or treated for 6 months. HIV-positive contacts should be treated for 12 months. All contacts of persons with multidrug-resistant tuberculosis or extensively drug-resistant tuberculosis should have 2 years of follow-up regardless of type of treatment.

Persons with a positive tuberculin skin test (5 mm or more of induration) and fibrotic lesions suggestive of old tuberculosis on chest radiographs who have no evidence of active disease and no history of treatment for tuberculosis should receive 9 months of isoniazid or 4 months of rifampin (with or without isoniazid). Pregnant or breastfeeding women with latent tuberculosis should receive either daily or twice-weekly isoniazid with pyridoxine (vitamin B<sub>6</sub>).

Baseline laboratory testing is indicated for patients at risk for liver disease, patients with HIV infection, women who are pregnant or within 3 months of delivery, and persons who use alcohol regularly. Patients receiving treatment for latent tuberculous infection should be evaluated once a month to assess for symptoms and signs of active tuberculosis and hepatitis and for adherence to their treatment regimen. Routine laboratory testing during treatment is indicated for those with abnormal baseline laboratory tests and for those at risk for developing liver disease.

**BCG vaccine** is an antimycobacterial vaccine developed from an attenuated strain of *M bovis*. Millions of individuals worldwide have been vaccinated with BCG. The vaccine is not generally recommended in the United States because of the low prevalence of tuberculous infection, the vaccine's interference with the ability to determine latent tuberculous infection using tuberculin skin test reactivity, and its variable effectiveness in prophylaxis of pulmonary tuberculosis. BCG vaccination in the United States should be undertaken only after consultation with local health officials and tuberculosis experts. Vaccination of health care workers should be considered on an

individual basis in settings in which a high percentage of tuberculosis patients are infected with strains resistant to both isoniazid and rifampin, in which transmission of such drug-resistant *M. tuberculosis* and subsequent infection are likely, and in which comprehensive tuberculous infection-control precautions have been implemented but have not been successful. The BCG vaccine is contraindicated in persons with impaired immune responses due to disease or medications.

## ► Prognosis

Almost all properly treated immunocompetent patients with tuberculosis can be cured. Relapse rates are less than 5% with current regimens. The main cause of treatment failure is nonadherence to therapy.

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## PULMONARY DISEASE CAUSED BY NONTUBERCULOUS MYCOBACTERIA



### ESSENTIALS OF DIAGNOSIS

- ▶ Chronic cough, sputum production, and fatigue; less commonly: malaise, dyspnea, fever, hemoptysis, and weight loss.
- ▶ Parenchymal opacities on chest radiograph, most often thin-walled cavities or multiple small nodules associated with bronchiectasis.
- ▶ Isolation of nontuberculous mycobacteria in a sputum culture.

## ► General Considerations

Mycobacteria other than *M. tuberculosis*—nontuberculous mycobacteria (NTM), sometimes referred to as “atypical” mycobacteria—are ubiquitous in water and soil and have

been isolated from tap water. Marked geographic variability exists, both in the NTM species responsible for disease and in the prevalence of disease. These organisms are not considered communicable from person to person, have distinct laboratory characteristics, and are often resistant to most antituberculous medications (Chapter 33). Long-term epidemiologic data suggest that NTM disease has been increasing in the United States.

## ► Definition & Pathogenesis

The diagnosis of lung disease caused by NTM is based on a combination of clinical, radiographic, and bacteriologic criteria and the exclusion of other diseases that can resemble the condition. Specific diagnostic criteria are discussed below. Complementary data are important for diagnosis because NTM organisms can reside in or colonize the airways without causing clinical disease.

*Mycobacterium avium* complex (MAC) is the most frequent cause of NTM pulmonary disease in humans in the United States. *Mycobacterium kansasii* is the next most frequent pulmonary pathogen. Other NTM causes of pulmonary disease include *Mycobacterium abscessus*, *Mycobacterium xenopi*, and *Mycobacterium malmoense*; the list of more unusual etiologic NTM species is long. Most NTM cause a chronic pulmonary infection that resembles tuberculosis but tends to progress more slowly. Disseminated disease is rare in immunocompetent persons; however, disseminated MAC disease is common in patients with AIDS.

## ► Clinical Findings

### A. Symptoms and Signs

NTM infection among immunocompetent persons frequently presents in one of three prototypical patterns: cavitary, upper lobe lesions in older male smokers that may mimic *M. tuberculosis*; nodular bronchiectasis affecting the mid lung zones in middle-aged women with chronic cough; and hypersensitivity pneumonitis following environmental exposure. Most patients with NTM infection experience a chronic cough, sputum production, and fatigue. Less common symptoms include malaise, dyspnea, fever, hemoptysis, and weight loss. Symptoms from coexisting lung disease (COPD, bronchiectasis, previous mycobacterial disease, cystic fibrosis, and pneumoconiosis) may confound the evaluation. In patients with bronchiectasis, coinfection with NTM and *Aspergillus* is a negative prognostic factor. New or worsening infiltrates as well as adenopathy or pleural effusion (or both) are described in HIV-positive patients with NTM infection as part of the immune reconstitution inflammatory syndrome following institution of antiretroviral therapy.

### B. Laboratory Findings

The diagnosis of NTM infection rests on recovery of the pathogen from cultures. Sputum cultures positive for atypical mycobacteria do not prove infection because NTM may exist as saprophytes colonizing the airways or may be environmental contaminants. Bronchial washings are

considered to be more sensitive than expectorated sputum samples; however, their specificity for clinical disease is not known.

Bacteriologic criteria have been proposed based on studies of patients with cavitary disease with MAC or *M kansasii*. Diagnostic criteria in immunocompetent persons include the following: positive culture results from at least two separate expectorated sputum samples; or positive culture from at least one bronchial wash; or a positive culture from pleural fluid or any other normally sterile site. The diagnosis can also be established by demonstrating NTM cultured from a lung biopsy, bronchial wash, or sputum plus histopathologic changes, such as granulomatous inflammation in a lung biopsy. Rapid species identification of some NTM is possible using DNA probes or high-pressure liquid chromatography.

Diagnostic criteria are less stringent for patients with severe immunosuppression. HIV-infected patients may show significant MAC growth on culture of bronchial washings without clinical infection; therefore, HIV patients being evaluated for MAC infection must be considered individually.

Medication susceptibility testing on cultures of NTM is recommended for the following NTM: (1) *Mycobacterium avium intracellulare* to macrolides only (clarithromycin and azithromycin); (2) *M kansasii* to rifampin; and (3) rapid growers (such as *Mycobacterium fortuitum*, *Mycobacterium chelonae*, and *M abscessus*) to amikacin, doxycycline, imipenem, fluoroquinolones, clarithromycin, cefoxitin, and sulfonamides.

### C. Imaging

Chest radiographic findings include infiltrates that are progressive or persist for at least 2 months, cavitary lesions, and multiple nodular densities. The cavities are often thin-walled and have less surrounding parenchymal infiltrate than is commonly seen with MTB infections. Evidence of contiguous spread and pleural involvement is often present. High-resolution CT of the chest may show multiple small nodules with or without multifocal bronchiectasis. Progression of pulmonary infiltrates during therapy or lack of radiographic improvement over time are poor prognostic signs and also raise concerns about secondary or alternative pulmonary processes. Clearing of pulmonary infiltrates due to NTM is slow.

### Treatment

Establishing NTM infection does not mandate treatment in all cases, for two reasons. First, clinical disease may never develop in some patients, particularly asymptomatic patients with few organisms isolated from single specimens. Second, the spectrum of clinical disease severity is very wide; in patients with mild or slowly progressive symptoms, traditional chemotherapeutic regimens using a combination of agents may lead to drug-induced side effects worse than the disease itself.

Specific treatment regimens and responses to therapy vary with the species of NTM. HIV-seronegative patients with MAC pulmonary disease usually receive a

combination of daily clarithromycin or azithromycin, rifampin or rifabutin, and ethambutol (Table 9–15). For patients with severe fibrocavitory disease, streptomycin or amikacin is added for the first 2 months. The optimal duration of treatment is unknown, but therapy should be continued for 12 months after sputum conversion. Medical treatment is initially successful in about two-thirds of cases, but relapses after treatment are common; long-term benefit is demonstrated in about half of all patients. Those who do not respond favorably generally have active but stable disease. Surgical resection is an alternative for the patient with progressive disease that responds poorly to chemotherapy. Disease caused by *M kansasii* responds well to drug therapy. A daily regimen of rifampin, isoniazid, and ethambutol for at least 18 months with a minimum of 12 months of negative cultures is usually successful. Rapidly growing mycobacteria (*M abscessus*, *M fortuitum*, *M chelonae*) are generally resistant to standard antituberculous therapy.

### ► When to Refer

Patients with rapidly growing mycobacteria infection should be referred for expert management.

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## PULMONARY NEOPLASMS

See Chapter 39 for discussions of Lung Cancer, Secondary Lung Cancer, and Mesothelioma.

### SCREENING FOR LUNG CANCER

Lung cancer remains the leading cause of cancer-related mortality, in large part secondary to advanced stage at diagnosis (Chapter 39). Two large RCTs reported findings in 2011 regarding the utility of lung cancer screening. The Prostate, Lung, Colorectal and Ovarian Randomized Trial (PLCO) randomized 154,901 adults (52% current or former smokers) between the ages of 55 and 74 years to receive either no screening or annual posterior-anterior chest radiographs for 4 consecutive years. The investigators monitored the participants after screening for an average of 12 years. Results showed no mortality benefit from four annual chest radiographs either in the whole

cohort or in a subset of heavy smokers who met the entry criteria for the other major trial, the National Lung Screening Trial (NLST). The NLST enrolled 53,454 current or former smokers (minimum 30-pack year exposure history) between the ages of 55 and 74 years who were randomly assigned to one of two screening modalities: three annual posterior-anterior chest radiographs or three annual low-dose chest CT scans. They were monitored for an additional 6.5 years after screening. Compared with chest radiography, low-dose chest CT detected more early-stage lung cancers and fewer advanced-stage lung cancers, indicating that CT screening systematically shifted the time of diagnosis to earlier stages, thereby providing more persons the opportunity for effective treatment. Furthermore, compared with chest radiographs, the cohort that received three annual CT scans had a statistically significant mortality benefit, with reductions in both lung cancer deaths (20.0%) and all-cause mortality (6.7%). This was the first evidence from an RCT demonstrating that lung cancer screening reduced all-cause mortality.

Additional information from PLCO, the NLST, and multiple other ongoing randomized trials is available. Trials in the Netherlands and Belgium (NELSON), Germany (LUSI), Denmark (DLCST), the United Kingdom (UKLS), and Italy (MILD, DANTE, ITALUNG) have been completed. These have revealed variable findings depending on the risk profile of the included patients, but the broad results are that screening is most likely to be effective, with reduction in lung cancer-specific mortality, if performed at short intervals in a high-risk population, as was done in NLST. Some studies indicate that the mortality benefit may be higher among women than among men. Issues that remain of concern regarding lung cancer screening include the following: (1) **Generalizability to practice:** NLST-participating institutions demonstrated a high level of expertise in imaging interpretation and diagnostic evaluation. Ninety-six percent of findings on CT were false positives but the vast majority of patients were monitored with serial imaging. Invasive diagnostic evaluations were uncommon and were associated with a low complication rate (1.4%). (2) **Duration of screening:** The rate of detection of new lung cancers did not fall with each subsequent annual screening over 3 years. Since new lung cancers become detectable during each year-long screening interval, the optimal number of annual CT scans is unknown as is the optimal screening interval. (3) **Overdiagnosis:** After 6.4 years of post-screening observation, there were more lung cancers in the NLST CT cohort than the chest radiography cohort (1089 and 969, respectively). Since the groups were randomized and well matched, lung cancer incidence should have been identical. Therefore, 18.5% of the lung cancers detected by CT remained clinically silent and invisible on chest radiograph for 6.4 years. Many, perhaps most, of these lung cancers would never cause clinical disease and represent overdiagnosis. (4) **Cost effectiveness:** Studies in the United States, Canada, and Europe suggest screening for lung cancer is cost effective; however, whether it is cost effective in all countries has not been determined.

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## SOLITARY PULMONARY NODULE

A solitary pulmonary nodule, sometimes referred to as a “coin lesion,” is a less-than-3-cm isolated, rounded opacity on chest imaging outlined by normal lung and not associated with infiltrate, atelectasis, or adenopathy. Most are asymptomatic and represent an incidental finding on chest radiography or CT scanning. The finding is important because it carries a significant risk of malignancy. The frequency of malignancy in surgical series ranges from 10% to 68% depending on patient population. Benign neoplasms, such as hamartomas, account for less than 5% of solitary nodules. Most benign nodules are infectious granulomas.

The goals of evaluation are to identify and resect malignant tumors in patients who will benefit from resection while avoiding invasive procedures in benign disease. The task is to identify nodules with a sufficiently high probability of malignancy to warrant biopsy or resection or a sufficiently low probability of malignancy to justify observation.

Symptoms alone rarely establish the cause, but clinical and imaging data can be used to assess the probability of malignancy. Malignant nodules are rare in persons under age 30. Above age 30, the likelihood of malignancy increases with age. Smokers are at increased risk, and the likelihood of malignancy increases with the number of cigarettes smoked daily. Patients with a prior malignancy have a higher likelihood of having a malignant solitary nodule.

The first step in the imaging evaluation is to review old imaging studies. Comparison with prior studies allows estimation of doubling time, which is an important marker for malignancy. Rapid progression (doubling time less than 30 days) suggests infection, while long-term stability (doubling time greater than 465 days) suggests benignity. Certain radiographic features help in estimating the probability of malignancy. Size is correlated with malignancy. A study

of solitary nodules identified by CT scan showed a 1% malignancy rate in those measuring 2–5 mm, 24% in 6–10 mm, 33% in 11–20 mm, and 80% in 21–45 mm nodules. The appearance of a smooth, well-defined edge is characteristic of a benign process. Ill-defined margins or a lobular appearance suggest malignancy. A high-resolution CT finding of spiculated margins and a peripheral halo are both highly associated with malignancy. Calcification and its pattern are also helpful clues. Benign lesions tend to have dense calcification in a central or laminated pattern. Malignant lesions are associated with sparser calcification that is typically stippled or eccentric. Cavitary lesions with thick (greater than 16 mm) walls are much more likely to be malignant. High-resolution CT offers better resolution of these characteristics than chest radiography and is more likely to detect lymphadenopathy or the presence of multiple lesions. Chest CT is indicated for any suspicious solitary pulmonary nodule.

## Treatment

Based on clinical and radiologic data, the clinician should assign a specific probability of malignancy to the lesion. The decision whether to recommend a biopsy or surgical excision depends on the interpretation of this probability in light of the patient's unique clinical situation. Quantitative prediction models (Brock model, VA Cooperative model) are available to assess risk of malignancy. The probabilities in parentheses below represent guidelines only and should not be interpreted as definitive.

In the case of solitary pulmonary nodules, a continuous probability function may be grouped into three categories. In patients with a **low probability (less than 5%) of malignancy** (eg, age under 30, lesions stable for more than 2 years, characteristic pattern of benign calcification), watchful waiting is appropriate. Management consists of serial imaging studies at intervals that could identify growth suggestive of malignancy. Three-dimensional reconstruction of high-resolution CT images provides a more sensitive test for growth.

Patients with a **high probability (greater than 60%) of malignancy** should proceed directly to resection following staging, provided the surgical risk is acceptable. Biopsies rarely yield a specific benign diagnosis and are not indicated.

Optimal management of patients with an **intermediate probability of malignancy (5–60%)** remains controversial. The traditional approach is to obtain a diagnostic biopsy, either through transthoracic needle aspiration (TTNA) or bronchoscopy. Bronchoscopy yields a diagnosis in 10–80% of procedures depending on the size of the nodule and its location. In general, the bronchoscopic yield for nodules that are less than 2 cm and peripheral is low, although complications are generally rare. Newer bronchoscopic modalities, such as electromagnetic navigation and ultrathin bronchoscopy are being studied, although their impact upon diagnostic yield remains uncertain. TTNA has a higher diagnostic yield, reported to be between 50% and 97%. The yield is

strongly operator-dependent, however, and is affected by the location and size of the lesion. Complications are higher than bronchoscopy, with pneumothorax occurring in up to 30% of patients, with up to one-third of these patients requiring placement of a chest tube.

Disappointing diagnostic yields and a high false-negative rate (up to 20–30% in TTNA) have prompted alternative approaches. **Positron emission tomography (PET)** detects increased glucose metabolism within malignant lesions with high sensitivity (85–97%) and specificity (70–85%). Many diagnostic algorithms have incorporated PET into the assessment of patients with inconclusive high-resolution CT findings. A positive PET increases the likelihood of malignancy, and a negative PET excludes most cancers. False-negative PET scans can occur with tumors with low metabolic activity (most notably, carcinoid tumors and adenocarcinomas, particularly minimally invasive or *in situ* adenocarcinomas), and follow-up CT imaging is typically performed at discrete intervals to ensure absence of growth. PET has several drawbacks, however: resolution below 1 cm is poor, the test is expensive, and availability remains limited.

**Sputum cytology** is highly specific but lacks sensitivity. It is used in central lesions and in patients who are poor candidates for invasive diagnostic procedures.

Some centers recommend **video-assisted thoracoscopic surgery (VATS)** resection of all solitary pulmonary nodules with intermediate probability of malignancy. In some cases, the surgeon will remove the nodule and evaluate it in the operating room with frozen section. If the nodule is malignant, he or she will proceed to lobectomy and lymph node sampling, either thoracoscopically or through conversion to standard thoracotomy. This approach is less common when PET scanning is available.

All patients should be provided with an estimate of the likelihood of malignancy, and their preferences should be used to help guide diagnostic and therapeutic decisions. A strategy that recommends observation may not be preferred by a patient who desires a definitive diagnosis. Similarly, a surgical approach may not be agreeable to all patients unless the presence of cancer is definitive. Patient preferences should be elicited, and patients should be well informed regarding the specific risks and benefits associated with the recommended approach as well as the alternative strategies.

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## RIGHT MIDDLE LOBE SYNDROME

Right middle lobe syndrome is recurrent or persistent atelectasis of the right middle lobe. This collapse is related to the relatively long length and narrow diameter of the right middle lobe bronchus and the oval (“fish mouth”) opening to the lobe, in the setting of impaired collateral ventilation. Fiberoptic bronchoscopy or CT scan is often necessary to rule out obstructing tumor. Foreign body or other benign causes are common.

## BRONCHIAL CARCINOID TUMORS

Carcinoid and bronchial gland tumors are sometimes termed “bronchial adenomas.” This term should be avoided because it implies that the lesions are benign when, in fact, carcinoid tumors and bronchial gland carcinomas are low-grade malignant neoplasms.

**Carcinoid tumors** are about six times more common than bronchial gland carcinomas, and most of them occur as pedunculated or sessile growths in central bronchi. Men and women are equally affected. Most patients are under 60 years of age. Common symptoms of bronchial carcinoid tumors are hemoptysis, cough, focal wheezing, and recurrent pneumonia. Peripherally located bronchial carcinoid tumors are rare and present as asymptomatic solitary pulmonary nodules. **Carcinoid syndrome** (flushing, diarrhea, wheezing, hypotension) is rare. Fiberoptic bronchoscopy may reveal a pink or purple tumor in a central airway. These lesions have a well-vascularized stroma, and biopsy may be complicated by significant bleeding. CT scanning is helpful to localize the lesion and to follow its growth over time. Octreotide scintigraphy is also available for localization of these tumors.

Bronchial carcinoid tumors grow slowly and rarely metastasize. Complications involve bleeding and airway obstruction rather than invasion by tumor and metastases. Surgical excision of clinically symptomatic lesions is often necessary, and the prognosis is generally favorable. Most bronchial carcinoid tumors are resistant to radiation and chemotherapy (see Chapter 39).

Adenomas, carcinomas, and other malignancies may rarely metastasize to the bronchi and present with endobronchial lesions. Hamartomas, myxomas, and amyloid are other rarer entities in the differential diagnosis of endobronchial mass lesions.

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## MEDIASTINAL MASSES

Various developmental, neoplastic, infectious, traumatic, and cardiovascular disorders may cause masses that appear in the mediastinum on chest radiograph. A useful convention arbitrarily divides the mediastinum into three compartments—anterior, middle, and posterior—in order to classify mediastinal masses and assist in differential diagnosis based on contents of these anatomic regions. The anterior compartment is bounded by the sternum anteriorly and the surface of the great vessels and pericardium posteriorly. The middle compartment extends from the anterior pericardium to the anterior surface of the thoracic spine. The posterior compartment is paravertebral. Specific mediastinal masses have a predilection for one or more of these compartments; most are located in the anterior or middle compartment.

The differential diagnosis of an **anterior mediastinal mass** includes thymoma, teratoma, thyroid lesions, lymphoma, and mesenchymal tumors (lipoma, fibroma). The differential diagnosis of a **middle mediastinal mass** includes lymphadenopathy, pulmonary artery enlargement, aneurysm of the aorta or innominate artery, developmental cyst (bronchogenic, enteric, pleuropericardial), dilated azygous or hemiazygous vein, and foramen of Morgagni hernia. The differential diagnosis of a **posterior mediastinal mass** includes hiatal hernia, neurogenic tumor, meningocele, esophageal tumor, foramen of Bochdalek hernia, thoracic spine disease, and extramedullary hematopoiesis. The neurogenic tumor group includes neurilemmoma, neurofibroma, neurosarcoma, ganglioneuroma, and pheochromocytoma.

Symptoms and signs of mediastinal masses are nonspecific and are usually caused by the effects of the mass on surrounding structures. Insidious onset of retrosternal chest pain, dysphagia, or dyspnea is often an important clue to the presence of a mediastinal mass. In about half of cases, symptoms are absent, and the mass is detected on routine chest radiograph. Physical findings vary depending on the nature and location of the mass.

CT scanning is helpful in management; additional radiographic studies of benefit include barium swallow if esophageal disease is suspected, Doppler sonography or venography of brachiocephalic veins and the superior vena cava, and angiography. MRI is useful; its advantages include better delineation of hilar structures and distinction between vessels and masses. Tissue diagnosis via either needle or excisional biopsy is generally necessary when a neoplastic process is considered. Treatment and prognosis depend on the underlying cause of the mediastinal mass.

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## INTERSTITIAL LUNG DISEASE (Diffuse Parenchymal Lung Disease)



### ESSENTIALS OF DIAGNOSIS

- ▶ Insidious onset of progressive dyspnea and non-productive chronic cough.
- ▶ Tachypnea, small lung volumes, bibasilar dry rales; digital clubbing and right heart failure with advanced disease.
- ▶ Chest radiographs with low lung volumes and patchy distribution of ground glass, reticular, nodular, reticulonodular, or cystic opacities.
- ▶ Reduced lung volumes, pulmonary diffusing capacity, and 6-minute walk distance; hypoxemia with exercise.

Interstitial lung disease, or diffuse parenchymal lung disease, comprises a heterogeneous group of disorders that share common presentations (dyspnea), physical findings (late inspiratory crackles), and chest radiographs (septal thickening and reticulonodular changes).

The term “interstitial” is misleading since the pathologic process usually begins with injury to the alveolar epithelial or capillary endothelial cells (alveolitis). Persistent alveolitis may lead to obliteration of alveolar capillaries and reorganization of the lung parenchyma, accompanied by irreversible fibrosis. The process does not affect the airways proximal to the respiratory bronchioles. At least 180 disease entities may present as interstitial lung disease. Table 9–16 outlines a selected list of differential diagnoses of interstitial lung disease. In most patients, no specific cause can be identified. In the remainder, medications, a variety of organic and inorganic dusts, and connective tissue disease are the principal causes. The history—particularly the occupational and medication history—may provide evidence of a specific

**Table 9–16.** Differential diagnosis of interstitial lung disease (listed alphabetically within category).

#### Medication-related

- Antiarrhythmic agents (amiodarone)
- Antibacterial agents (nitrofurantoin, sulfonamides)
- Antineoplastic agents (bleomycin, cyclophosphamide, methotrexate, nitrosoureas)
- Antirheumatic agents (gold salts, penicillamine)
- Phenytoin

#### Environmental and occupational (inhalation exposures)

- Dust, inorganic (asbestos, beryllium, hard metals, silica)
- Dust, organic (thermophilic actinomycetes, avian antigens, *Aspergillus* species)
- Gases, fumes, and vapors (chlorine, isocyanates, paraquat, sulfur dioxide)
- Ionizing radiation
- Talc (injection drug users)

#### Infections

- Fungus, disseminated (*Blastomyces dermatitidis*, *Coccidioides immitis*, *Histoplasma capsulatum*)
- Mycobacteria, disseminated
- Pneumocystis jirovecii*
- Viruses

#### Primary pulmonary disorders

- Cryptogenic organizing pneumonia
- Idiopathic interstitial pneumonia: acute interstitial pneumonia, desquamative interstitial pneumonia, nonspecific interstitial pneumonia, usual interstitial pneumonia, respiratory bronchiolitis-associated interstitial lung disease
- Pulmonary alveolar proteinosis

#### Systemic disorders

- Acute respiratory distress syndrome
- Amyloidosis
- Ankylosing spondylitis
- Autoimmune disease: dermatomyositis, polymyositis, rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis (scleroderma)
- Chronic eosinophilic pneumonia
- Goodpasture syndrome
- Granulomatosis polyangiitis
- Idiopathic pulmonary hemosiderosis
- Inflammatory bowel disease
- Langerhans cell histiocytosis (eosinophilic granuloma)
- Lymphangitic spread of cancer (lymphangitic carcinomatosis)
- Lymphangioleiomyomatosis
- Pulmonary edema
- Pulmonary venous hypertension, chronic
- Sarcoidosis

cause. The presence of diffuse parenchymal lung disease in the setting of an established connective tissue disease, such as rheumatoid arthritis, systemic lupus erythematosus, scleroderma, polymyositis-dermatomyositis, Sjögren syndrome, and other overlap conditions, is suggestive of the cause. In some cases, lung disease precedes the more typical manifestations of the underlying connective tissue disease by months or years.

Known causes of interstitial lung disease are dealt with in their specific sections. The important idiopathic forms are discussed below.

## DIFFUSE INTERSTITIAL PNEUMONIAS



### ESSENTIALS OF DIAGNOSIS

- ▶ Important to identify specific fibrosing disorders.
- ▶ Idiopathic disease may require biopsy for diagnosis.
- ▶ Accurate diagnosis identifies patients most likely to benefit from therapy.

### ► General Considerations

The most common diagnosis among patients with diffuse interstitial lung disease is one of the interstitial pneumonias, including all the entities described in Table 9–17. Historically, a diagnosis of interstitial lung disease was based on clinical and radiographic criteria with only a small number of patients undergoing surgical lung biopsy. When biopsies were obtained, the common element of fibrosis led to the grouping together of several histologic patterns under the category of interstitial pneumonia or idiopathic pulmonary fibrosis (IPF). Distinct histopathologic features are now understood to represent different natural histories and responses to therapy (Table 9–17). Therefore, in the evaluation of patients with diffuse interstitial lung disease, clinicians should attempt to identify specific disorders.

Patients with diffuse interstitial pneumonia may have any of the histologic patterns described in Table 9–17. The first step in evaluation is to identify patients whose disease is truly idiopathic. As indicated in Table 9–16, most identifiable causes of diffuse interstitial pneumonia are medication-related, environmental or occupational agent exposure, or infectious. Interstitial lung diseases associated with other systemic disorders (pulmonary renal syndromes, autoimmune disease) may be identified through a careful medical history. Apart from acute interstitial pneumonia, the clinical presentations of the diffuse interstitial pneumonias are sufficiently similar to preclude a specific diagnosis. Chest radiographs and high-resolution CT scans are diagnostic in some patients. Ultimately, many patients with apparently idiopathic disease require surgical lung biopsy to make a definitive diagnosis. The importance of accurate diagnosis is twofold. First, it allows the clinician to provide accurate information about the cause and natural history of the illness. Second,

accurate diagnosis helps distinguish patients most likely to benefit from therapy.

### ► Clinical Findings

#### A. Symptoms, Signs, and Imaging

The most common of the diffuse interstitial pneumonias is pulmonary fibrosis associated with the histopathologic pattern of **usual interstitial pneumonia (UIP)**. When no associated cause is evident, this is IPF. A diagnosis of IPF/UIP can be made with 90% confidence in patients over 65 years of age who have (1) idiopathic disease by history and inspiratory crackles on physical examination; (2) restrictive physiology on pulmonary function testing; (3) characteristic UIP pattern on high-resolution chest CT (peripheral, basilar predominant opacities associated with honeycombing and traction bronchiectasis) (Figure 9–5). Such patients do not need surgical lung biopsy. Assessment of pulmonary hypertension is recommended in advanced disease.

#### B. Special Studies

Three diagnostic techniques are in common use: BAL, transbronchial biopsy, and surgical lung biopsy, either through an open procedure or using VATS.

**BAL** may provide a specific diagnosis in cases of infection, particularly with *P jirovecii* or mycobacteria, or when cytologic examination reveals the presence of malignant cells. Additionally, BAL may be diagnostic of eosinophilic pneumonia, Langerhans cell histiocytosis, or alveolar proteinosis.

**Transbronchial biopsy** through the flexible bronchoscope is easily performed in most patients. The risks of pneumothorax (5%) and hemorrhage (1–10%) are low. However, the tissue specimens recovered are small, sampling error is common, and crush artifact may complicate diagnosis. Transbronchial biopsy can make a definitive diagnosis of sarcoidosis, lymphangitic spread of carcinoma, pulmonary alveolar proteinosis, miliary tuberculosis, and Langerhans cell histiocytosis. Note that the diagnosis of IPF cannot be confirmed on transbronchial lung biopsy since the histologic diagnosis requires a pattern of changes rather than a single pathognomonic finding. Transbronchial biopsy may exclude IPF and idiopathic interstitial pneumonia by confirming a specific alternative diagnosis. These patients generally require surgical lung biopsy.

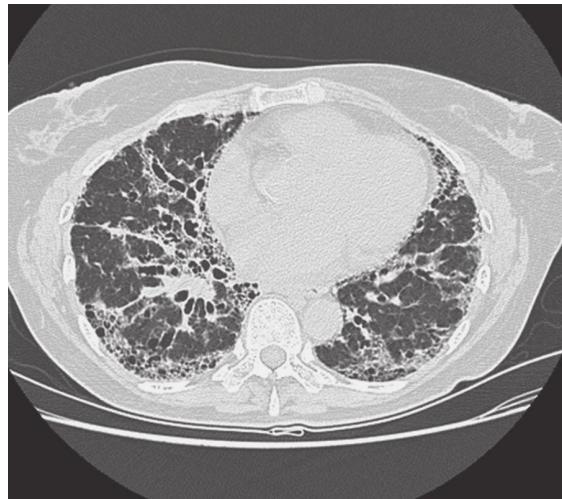
**Surgical lung biopsy** is the standard for diagnosis of diffuse interstitial lung disease. Two or three biopsies taken from multiple sites in the same lung, including apparently normal tissue, may yield a specific diagnosis as well as prognostic information regarding the extent of fibrosis versus active inflammation. Patients under age 60 without a specific diagnosis generally should undergo surgical lung biopsy. In older and sicker patients, the risks and benefits must be weighed carefully for three reasons: (1) the morbidity of the procedure can be significant; (2) a definitive diagnosis may not be possible even with surgical lung biopsy; and (3) when a specific diagnosis is made, there may be no effective treatment. Empiric therapy or no treatment may be preferable to surgical lung biopsy in some patients.

**Table 9–17.** Idiopathic interstitial pneumonias.

| Name and Clinical Presentation  | Histopathology   | Radiographic Pattern  | Response to Therapy and Prognosis  |
|---|--|---|--|
| <b>Usual interstitial pneumonia (UIP)</b><br>Age 55–60, slight male predominance. Insidious dry cough and dyspnea lasting months to years. Clubbing present at diagnosis in 25–50%. Diffuse fine late inspiratory crackles on lung auscultation. Restrictive ventilatory defect and reduced diffusing capacity on pulmonary function tests. ANA and RF positive in ~25% in the absence of documented collagen-vascular disease. | Patchy, temporally and geographically nonuniform distribution of fibrosis, honeycomb change, and normal lung. Type I pneumocytes are lost, and there is proliferation of alveolar type II cells. “Fibroblast foci” of actively proliferating fibroblasts and myofibroblasts. Inflammation is generally mild and consists of small lymphocytes. Intra-alveolar macrophage accumulation is present but is not a prominent feature. | Diminished lung volume. High-resolution CT scanning shows increased linear or reticular bibasilar and subpleural opacities, with associated honeycombing. Unilateral disease is rare. Minimal ground-glass. Areas of normal lung may be adjacent to areas of advanced fibrosis.     | No randomized study has demonstrated improved survival compared with untreated patients. Inexorably progressive. Median survival ~3 years, depending on stage at presentation. Nintedanib and pirenade reduce rate of decline in lung function. Refer early for lung transplantation evaluation.     |
| <b>Respiratory bronchiolitis-associated interstitial lung disease (RB-ILD)<sup>1</sup></b><br>Age 40–45. Presentation similar to that of UIP though in younger patients. Similar results on pulmonary function tests, but less severe abnormalities. Patients with respiratory bronchiolitis are invariably heavy smokers.  | Increased numbers of macrophages evenly dispersed within the alveolar spaces. Rare fibroblast foci, little fibrosis, minimal honeycomb change. In RB-ILD the accumulation of macrophages is localized within the peribronchiolar air spaces; in DIP <sup>1</sup> , it is diffuse. Alveolar architecture is preserved.  | High-resolution CT shows nodular or reticulonodular pattern, more likely to reveal diffuse ground-glass opacities. Honeycombing is rare. May also show upper lobe emphysema.  | Spontaneous remission occurs in up to 20% of patients, so natural history unclear. Smoking cessation is essential. Prognosis clearly better than that of UIP: median survival > 10 years. Corticosteroids thought to be effective, but there are no randomized clinical trials to support this view. |
| <b>Acute interstitial pneumonia (AIP)</b><br>Clinically known as Hamman-Rich syndrome. Wide age range, many young patients. Acute onset of dyspnea followed by rapid development of respiratory failure. Half of patients report a viral syndrome preceding lung disease. Clinical course indistinguishable from that of idiopathic ARDS.   | Pathologic changes reflect acute response to injury within days to weeks. Resembles organizing phase of diffuse alveolar damage. Fibrosis and minimal collagen deposition. May appear similar to UIP but more homogeneous and there is no honeycomb change—though this may appear if the process persists for more than a month in a patient on mechanical ventilation.  | Diffuse bilateral airspace consolidation with areas of ground-glass attenuation on high-resolution CT scan.   | Supportive care (mechanical ventilation) critical but effect of specific therapies unclear. High initial mortality: 50–90% die within 2 months after diagnosis. Not progressive if patient survives. Lung function may return to normal or may be permanently impaired.                              |
| <b>Nonspecific interstitial pneumonia (NSIP)</b><br>Age 45–55. Slight female predominance. Similar to UIP but onset of cough and dyspnea over months, not years.  | Nonspecific in that histopathology does not fit into better-established categories. Varying degrees of inflammation and fibrosis, patchy in distribution but uniform in time, suggesting response to single injury. Most have lymphocytic and plasma cell inflammation without fibrosis. Honeycombing present but scant. Some have advocated division into cellular and fibrotic subtypes.                                       | May be indistinguishable from UIP. Most typical picture is bilateral areas of ground-glass attenuation and fibrosis on high-resolution CT. Honeycombing is rare.  | Treatment with corticosteroids thought to be effective, but no prospective clinical studies have been published. Overall prognosis good but depends on the extent of fibrosis at diagnosis. Median survival > 10 years.  |
| <b>Cryptogenic organizing pneumonia (COP)</b><br>Typically age 50–60 but wide variation. Abrupt onset, frequently weeks to a few months following a flu-like illness. Dyspnea and dry cough prominent, but constitutional symptoms are common: fatigue, fever, and weight loss. Pulmonary function tests usually show restriction, but up to 25% show concomitant obstruction.  | Included in the idiopathic interstitial pneumonias on clinical grounds. Buds of loose connective tissue (Masson bodies) and inflammatory cells fill alveoli and distal bronchioles.  | Lung volumes normal. Chest radiograph typically shows interstitial and parenchymal disease with discrete, peripheral alveolar and ground-glass infiltrates. Nodular opacities common. High-resolution CT shows subpleural consolidation and bronchial wall thickening and dilation. | Rapid response to corticosteroids in two-thirds of patients. Long-term prognosis generally good for those who respond. Relapses are common.  |

<sup>1</sup>Includes desquamative interstitial pneumonia (DIP).

ANA, antinuclear antibody; ARDS, acute respiratory distress syndrome; RF, rheumatoid factor; UIP, usual interstitial pneumonia.



**▲ Figure 9–5.** Idiopathic pulmonary fibrosis. CT scan of the lungs showing the typical radiographic pattern of idiopathic pulmonary fibrosis, with a predominantly basilar, peripheral pattern of traction bronchiectasis, reticulation, and early honeycombing.

## ► Treatment

Patients with diffuse interstitial pneumonia should be treated by a pulmonologist. Clinical experience suggests that patients with RB-ILD, nonspecific interstitial pneumonia (NSIP), or COP (Table 9–17) frequently respond to corticosteroids and should be given a trial of therapy—typically prednisone, 1–2 mg/kg/day for a minimum of 2 months. Corticosteroid therapy is ineffective in patients with IPF and is not recommended. Nintedanib and pirfenidone are approved for the treatment of IPF based on controlled trials in highly selected patients showing a significant reduction in their rate of decline in lung function. Neither agent improved survival or quality of life compared with no treatment, however. The only definitive treatment for IPF is lung transplantation, with a 5-year survival rate estimated at 50%.

## ► When to Refer

Patients with diffuse interstitial pneumonia should be referred early to a pulmonologist for expert diagnosis and management. Patients with IPF should be referred early to a lung transplant program for evaluation.

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## SARCOIDOSIS



### ESSENTIALS OF DIAGNOSIS

- ▶ Symptoms related to the lung, skin, eyes, peripheral nerves, liver, kidney, heart, and other tissues.
- ▶ Demonstration of noncaseating granulomas in a biopsy specimen.
- ▶ Exclusion of other granulomatous disorders.

## ► General Considerations

Sarcoidosis is a systemic disease of unknown etiology characterized in about 90% of patients by granulomatous inflammation of the lung. The incidence is highest in North American Blacks and northern European Whites; among Blacks, women are more frequently affected than men. Onset of disease is usually in the third or fourth decade.

## ► Clinical Findings

### A. Symptoms and Signs

Patients may have malaise, fever, and dyspnea of insidious onset. Symptoms caused by skin involvement (erythema nodosum, lupus pernio [Figure 9–6]), iritis, peripheral neuropathy, arthritis (Chapter 20), or cardiomyopathy may also prompt the patient to seek care. Some individuals are asymptomatic and come to medical attention after abnormal findings on chest radiographs (typically bilateral hilar and right paratracheal lymphadenopathy). Physical findings are atypical of interstitial lung disease in that crackles are uncommon on chest examination. Other symptoms



**▲ Figure 9–6.** Skin involvement in sarcoidosis (lupus pernio), here involving the nasal rim. (Used, with permission, from Richard P. Usatine, MD, in Usatine RP, Smith MA, Mayeaux EJ Jr, Chumley H. *The Color Atlas and Synopsis of Family Medicine*, 3rd ed. McGraw-Hill, 2019.)

and findings may include parotid gland enlargement, hepatosplenomegaly, and lymphadenopathy.

### B. Laboratory Findings

Laboratory tests may show leukopenia, an elevated erythrocyte sedimentation rate, and hypercalcemia (about 5% of patients) or hypercalciuria (20%). Angiotensin-converting enzyme (ACE) levels are elevated in 40–80% of patients with active disease. This finding is neither sensitive nor specific enough to have diagnostic significance. Physiologic testing may reveal evidence of airflow obstruction, but restrictive changes with decreased lung volumes and diffusing capacity are more common. Skin test anergy is present in 70%. ECG may show conduction disturbances and dysrhythmias.

### C. Imaging

Radiographic findings are variable and include bilateral hilar adenopathy alone (radiographic stage I), hilar adenopathy and parenchymal involvement (radiographic stage II), or parenchymal involvement alone (radiographic stage III). Parenchymal involvement is usually manifested radiographically by diffuse reticular infiltrates, but focal infiltrates, acinar shadows, nodules, and, rarely, cavitation may be seen. Pleural effusion is noted in less than 10% of patients. Stage IV disease refers to advanced fibrotic changes principally in the upper lobes.

### D. Special Examinations

The diagnosis of sarcoidosis generally requires histologic demonstration of noncaseating granulomas in biopsies from a patient with other typical associated manifestations. Other granulomatous diseases (eg, berylliosis, tuberculosis, fungal infections) and lymphoma must be excluded. Biopsy of easily accessible sites (eg, palpable lymph nodes, skin lesions, or salivary glands) is likely to be positive. Transbronchial lung biopsy has a high yield (75–90%) as well, especially in patients with radiographic evidence of parenchymal involvement. Some clinicians believe that tissue biopsy is not necessary when stage I radiographic findings are detected in a clinical situation that strongly favors the diagnosis of sarcoidosis (eg, a young Black woman with erythema nodosum). Biopsy is essential whenever clinical and radiographic findings suggest the possibility of an alternative diagnosis, such as lymphoma. BAL fluid in sarcoidosis is usually characterized by an increase in lymphocytes and a high CD4/CD8 cell ratio. BAL does not establish a diagnosis but may be useful in following the activity of sarcoidosis in selected patients. All patients require a complete ophthalmologic evaluation. Cardiac magnetic resonance imaging (MRI) is favored over positron emission tomography (PET) scan for patients with suspected cardiac involvement.

### ► Treatment

Indications for treatment with oral corticosteroids (prednisone, 0.5–1.0 mg/kg/day) include disabling constitutional symptoms, hypercalcemia, iritis, uveitis, arthritis, central

nervous system involvement, cardiac involvement, granulomatous hepatitis, cutaneous lesions other than erythema nodosum, and progressive pulmonary lesions. Long-term therapy is usually required over months to years. Immunosuppressive medications, most commonly methotrexate, azathioprine, or infliximab, are used in patients who are intolerant of corticosteroids or who have corticosteroid-refractory disease, but sound clinical research to support specific agents is lacking. A favorable response is defined by a decrease in symptoms, reduction of radiographic abnormalities, and improvement in pulmonary function tests.

### ► Prognosis

The outlook is best for patients with hilar adenopathy alone; radiographic involvement of the lung parenchyma is associated with a worse prognosis. Erythema nodosum portends a good outcome. About 20% of patients with lung involvement suffer irreversible lung impairment, characterized by progressive fibrosis, bronchiectasis, and cavitation. Pneumothorax, hemoptysis, mycetoma formation in lung cavities, and respiratory failure often complicate this advanced stage. Myocardial sarcoidosis occurs in about 5% of patients, sometimes leading to restrictive cardiomyopathy, cardiac dysrhythmias, and conduction disturbances. Death from respiratory insufficiency occurs in about 5% of patients.

Patients require long-term follow-up. At a minimum, patients should undergo physical examination, pulmonary function tests, chemistry panel, ophthalmologic evaluation, chest radiograph, and ECG yearly. Assessment of pulmonary hypertension is recommended in advanced disease.

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## PULMONARY ALVEOLAR PROTEINOSIS

Pulmonary alveolar proteinosis is a rare disease in which periodic acid-Schiff (PAS)-positive phospholipids accumulate within alveolar spaces. The condition may be primary (idiopathic) or secondary (occurring in immunodeficiency; hematologic malignancies; inhalation of mineral dusts; or following lung infections, including tuberculosis and viral infections). Progressive dyspnea is the usual presenting symptom, and chest radiograph shows bilateral

alveolar infiltrates suggestive of pulmonary edema. The diagnosis is based on demonstration of characteristic findings on BAL (milky appearance and PAS-positive lipoproteinaceous material) in association with typical clinical and radiographic features. In secondary disease, an elevated anti-GM-CSF (anti-granulocyte-macrophage colony-stimulating factor) titer in serum or BAL fluid is highly sensitive and specific. In some cases, transbronchial or surgical lung biopsy (revealing amorphous intra-alveolar phospholipid) is necessary.

The course of the disease varies. Some patients experience spontaneous remission; others develop progressive respiratory insufficiency. Pulmonary infection with *Nocardia* or fungi may occur. Therapy for alveolar proteinosis consists of periodic whole-lung lavage. Patients who cannot tolerate whole lung lavage or who fail to respond may benefit from inhalational or subcutaneous GM-CSF.

Kumar A et al. Pulmonary alveolar proteinosis in adults: pathophysiology and clinical approach. *Lancet Respir Med*. 2018;6: 554. [PMID: 29397349]

Salvaterra E et al. Pulmonary alveolar proteinosis: from classification to therapy. *Breathe (Sheff)*. 2020;16:200018. [PMID: 32684997]

Trapnell BC et al. Pulmonary alveolar proteinosis. *Nat Rev Dis Primers*. 2019;5:16. [PMID: 30846703]

pulmonary edema. BAL typically has a marked eosinophilia; peripheral blood eosinophilia is present in greater than 80%. Therapy with oral prednisone (1 mg/kg/day for 1–2 weeks, followed by a gradual taper over many months) usually results in dramatic improvement; however, most patients require at least 10–15 mg of prednisone every other day for a year or more (sometimes indefinitely) to prevent relapses.

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## DISORDERS OF THE PULMONARY CIRCULATION

### PULMONARY VENOUS THROMBOEMBOLISM



#### ESSENTIALS OF DIAGNOSIS

- ▶ Third most common cardiovascular cause of death in the United States.
- ▶ May present with one or more of the following: dyspnea, pleuritic chest pain, hemoptysis, syncope.
- ▶ Tachypnea, tachycardia, hypoxia (alone or in any combination).
- ▶ Risk stratification with clinical scores, cardiac biomarkers, and right ventricular imaging is key for management.

#### General Considerations

Pulmonary venous thromboembolism (VTE), often referred to as pulmonary embolism (PE), is a common, serious, and potentially fatal complication of thrombus formation within the deep venous circulation. PE is the third leading cause of death among hospitalized patients. Despite this prevalence, most cases are not recognized antemortem, and less than 10% of patients with fatal emboli have received specific treatment for the condition. Management demands a vigilant systematic approach to diagnosis and an understanding of risk factors so that appropriate therapy can be initiated.

Many substances can embolize to the pulmonary circulation, including air (during neurosurgery, from central venous catheters), amniotic fluid (during active labor), fat (long bone fractures), foreign bodies (talc in injection drug

## EOSINOPHILIC PULMONARY SYNDROMES

Eosinophilic pulmonary syndromes are a diverse group of disorders typically characterized by eosinophilic pulmonary infiltrates, dyspnea, and cough. Many patients have constitutional symptoms, including fever. Common causes include exposure to medications (nitrofurantoin, phenytoin, ampicillin, acetaminophen) or infection with helminths (eg, *Ascaris*, hookworms, *Strongyloides*) or filariae (eg, *Wuchereria bancrofti*, *Brugia malayi*, tropical pulmonary eosinophilia). **Löffler syndrome** refers to acute eosinophilic pulmonary infiltrates in response to transpulmonary passage of helminth larvae. Pulmonary eosinophilia can also be a feature of other illnesses, including allergic bronchopulmonary mycosis, eosinophilic granulomatosis with polyangiitis, systemic hypereosinophilic syndromes, eosinophilic granuloma of the lung (properly referred to as pulmonary Langerhans cell histiocytosis), neoplasms, and numerous interstitial lung diseases. If an extrinsic cause is identified, therapy consists of removal of the offending medication or treatment of the underlying parasitic infection.

One-third of cases are idiopathic, and there are two common syndromes. **Acute eosinophilic pneumonia** is an acute, febrile illness characterized by cough and dyspnea, sometimes rapidly progressing to respiratory failure. The chest radiograph is abnormal but nonspecific. BAL fluid frequently shows eosinophilia but peripheral blood eosinophilia is rare at the onset of symptoms. The response to corticosteroids is usually dramatic. **Chronic eosinophilic pneumonia** is seen predominantly in women and is characterized by fever, night sweats, weight loss, and dyspnea. Asthma is present in half of cases. Chest radiographs often show peripheral infiltrates, the “photographic negative” of

users), parasite eggs (schistosomiasis), septic emboli (acute infective endocarditis), and tumor cells (renal cell carcinoma). The most common embolus is thrombus, which may arise anywhere in the venous circulation or right heart but most often originates in the deep veins of the lower extremities. Thrombi confined to the calf rarely embolize to the pulmonary circulation. However, about 20% of calf vein thrombi propagate proximally to the popliteal and iliofemoral veins, at which point they may break off and embolize to the pulmonary circulation. Pulmonary emboli will develop in 50–60% of patients with proximal deep venous thrombosis (DVT); half of these embolic events will be asymptomatic. Approximately 50–70% of patients who have symptomatic pulmonary emboli will have lower extremity DVT when evaluated.

PE and DVT are two manifestations of the same disease. The risk factors for PE are the risk factors for thrombus formation within the venous circulation: venous stasis, injury to the vessel wall, and hypercoagulability (Virchow triad). Venous stasis increases with immobility (obesity, stroke, bed rest—especially postoperative), hyperviscosity (polycythemia), and increased central venous pressures (low cardiac output states, pregnancy). Vessels may be damaged by prior episodes of thrombosis, orthopedic surgery, or trauma. Hypercoagulability can be caused by medications (oral contraceptives, hormonal replacement therapy) or disease (malignancy, surgery) or may be the result of inherited gene defects. The most common inherited cause in White populations is resistance to activated protein C, also known as factor V Leiden. The trait (heterozygous) is present in approximately 3% of healthy American men, but many of these individuals will never have a VTE. Other thrombophilias include deficiencies or dysfunction of protein C, protein S, and antithrombin; prothrombin gene mutation; and the presence of antiphospholipid antibodies (lupus anticoagulant and anticardiolipin antibody).

PE has multiple physiologic effects. Physical obstruction of the vascular bed and vasoconstriction from neurohumoral reflexes both increase pulmonary vascular resistance. Thrombus occlusion of greater than 20–25% of vascular bed causes right ventricular dilation or dysfunction. Vascular obstruction increases physiologic dead space (wasted ventilation) and leads to hypoxemia through right-to-left shunting, decreased cardiac output, and surfactant depletion causing atelectasis. Reflex bronchoconstriction promotes wheezing and increased work of breathing.

## Clinical Findings

### A. Symptoms and Signs

The clinical diagnosis of PE is notoriously difficult for two reasons. First, the clinical symptoms depend on both the size of the embolus and the patient's preexisting cardiopulmonary status. Second, common symptoms and signs of pulmonary emboli are not specific to this disorder (Table 9–18).

Some findings are fairly sensitive: dyspnea and pain on inspiration occur in 75–85% and 65–75% of patients, respectively, but no single symptom or sign or combination of clinical findings is specific to PE. Diagnosis primarily

relies on clinical prediction scores to calculate the pretest probability of PE. Wells score is most commonly used and quantifies clinical risk assessment, allowing separation of patients into low, intermediate, or high probability groups, or PE-likely or PE-unlikely groups (Table 9–19).

### B. Laboratory Findings

The ECG is abnormal in 70% of patients with PE. However, the most common abnormalities are sinus tachycardia and nonspecific ST and T wave changes, each seen in approximately 40% of patients. Five percent or less of patients in the PIOPED I study had P pulmonale, right ventricular hypertrophy, right axis deviation, and right bundle branch block.

ABGs usually reveal acute respiratory alkalosis due to hyperventilation. The arterial  $\text{Po}_2$  and the alveolar-arterial oxygen difference ( $\text{A-a}-\text{DO}_2$ ) are usually abnormal in patients with PE compared with healthy, age-matched controls. However, ABGs are not diagnostic: among patients who were evaluated in the PIOPED I study, neither the  $\text{Po}_2$  nor the  $\text{A-a}-\text{DO}_2$  differentiated between those with and those without pulmonary emboli. Profound hypoxia with a normal chest radiograph in the absence of preexisting lung disease is highly suspicious for PE.

Plasma levels of **D-dimer**, a degradation product of cross-linked fibrin, are elevated in the presence of thrombus. A D-dimer of less than 500 ng/mL may be used to exclude the diagnosis of PE in those patients who have low pretest probability of PE or are PE-unlikely on Wells score. Additionally, an age-adjusted D-dimer value has increased specificity than the usually specified cutoff. Due to much higher false-positive rates, D-dimer is not useful in the hospital setting.

Serum troponin I, troponin T, and plasma B-type natriuretic peptide (BNP) levels are elevated in approximately 25% of patients with PE and are useful in the risk stratification of PE because they correlate with adverse outcomes, including mechanical ventilation, prolonged hospitalization, and death.

### C. Imaging and Special Examinations

**1. Chest radiography**—The chest radiograph is necessary to exclude other common lung diseases, but it does not establish the diagnosis of PE by itself. The chest radiograph was normal in only 12% of patients with confirmed PE in the PIOPED I study. The most frequent findings were atelectasis, parenchymal infiltrates, and pleural effusions. However, the prevalence of these findings was the same in hospitalized patients without PE. A prominent central pulmonary artery with local oligemia (Westerman sign) or pleural-based areas of increased opacity that represent intraparenchymal hemorrhage (Hampton hump) are uncommon. Paradoxically, the chest radiograph may be most suggestive of PE when normal in the setting of hypoxemia.

**2. Pulmonary CT-angiography**—Helical CT-PA is the gold standard diagnostic study in North America for suspected PE due to its high sensitivity and specificity as well as wide availability across hospitals. CT-PA requires administration

**Table 9–18.** Frequency of specific symptoms and signs in patients at risk for pulmonary thromboembolism.

|  | UPET <sup>1</sup><br>PE+ (n = 327) | PIOPED I <sup>2</sup><br>PE+ (n = 117) | PIOPED I <sup>2</sup><br>PE- (n = 248) |
|--|------------------------------------|--|--|
| <b>Symptoms</b>  |                                    |  |  |
| Dyspnea  | 84%                                | 73%                                    | 72%                                    |
| Respirophasic chest pain   | 74%                                | 66%                                    | 59%                                    |
| Cough  | 53%                                | 37%                                    | 36%                                    |
| Leg pain   | NR                                 | 26%                                    | 24%                                    |
| Hemoptysis   | 30%                                | 13%                                    | 8%                                     |
| Palpitations   | NR                                 | 10%                                    | 18%                                    |
| Wheezing   | NR                                 | 9%                                     | 11%                                    |
| Anginal pain   | 14%                                | 4%                                     | 6%                                     |
| <b>Signs</b>   |                                    |  |  |
| Respiratory rate ≥ 16 UPET, ≥ 20 PIOPED I                                | 92%                                | 70%                                    | 68%                                    |
| Crackles (rales)   | 58%                                | 51%                                    | 40% <sup>3</sup>                       |
| Heart rate ≥ 100/min   | 44%                                | 30%                                    | 24%                                    |
| Fourth heart sound (S <sub>4</sub> )                                     | NR                                 | 24%                                    | 13% <sup>3</sup>                       |
| Accentuated pulmonary component of second heart sound (S <sub>2</sub> P) | 53%                                | 23%                                    | 13% <sup>3</sup>                       |
| T ≥ 37.5°C UPET, ≥ 38.5°C PIOPED   | 43%                                | 7%                                     | 12%                                    |
| Homans sign  | NR                                 | 4%                                     | 2%                                     |
| Pleural friction rub   | NR                                 | 3%                                     | 2%                                     |
| Third heart sound (S <sub>3</sub> )                                      | NR                                 | 3%                                     | 4%                                     |
| Cyanosis   | 19%                                | 1%                                     | 2%                                     |

<sup>1</sup>Data from the Urokinase-Streptokinase Pulmonary Embolism Trial (UPET), as reported in Bell WR et al. The clinical features of submassive and massive pulmonary emboli. Am J Med. 1977;62:355.

<sup>2</sup>Data from patients enrolled in the PIOPED I study, as reported in Stein PD et al. Clinical, laboratory, roentgenographic, and electrocardiographic findings in patients with acute pulmonary embolism and no preexisting cardiac or pulmonary disease. Chest. 1991;100:598.

<sup>3</sup>P < 0.05 comparing to patients in the PIOPED I study.

PE+, confirmed diagnosis of pulmonary embolism; PE-, diagnosis of pulmonary embolism ruled out; NR, not reported.

of intravenous radiocontrast dye but is otherwise noninvasive. Patients with intermediate- or high-pretest probability of PE (or PE-likely) or those with an elevated D-dimer should undergo a CT-PA.

**3. Ventilation-perfusion (V/Q) lung scanning**—V/Q scanning may be used as an alternative to CT-PA in patients in whom contrast is contraindicated, such as severe contrast-induced anaphylaxis or kidney dysfunction. V/Q scanning is performed by injecting radiolabeled microaggregated albumin into the venous system, allowing the particles to embolize to the pulmonary capillary bed (perfusion); the patient breathes a radioactive gas or aerosol while the distribution of radioactivity in the lungs is recorded (ventilation). A defect in perfusion without a corresponding defect in ventilation may indicate a PE but is not specific for the diagnosis. In PIOPED, V/Q scans were interpreted as high, intermediate, or low probability of PE. A normal V/Q scan excludes the diagnosis of clinically significant PE (negative predictive value of 91% in the PIOPED I study). Therefore, V/Q scans are most helpful when they are either normal or indicate a high probability of PE.

**4. Venous thrombosis studies**—Seventy percent of patients with PE will have DVT on evaluation. **Venous ultrasonography** is the test of choice to detect proximal DVT. Inability to compress the common femoral or popliteal veins in symptomatic patients is diagnostic (positive predictive value of 97%); full compressibility of both sites excludes proximal DVT (negative predictive value of 98%). The test is less accurate in distal thrombi, recurrent thrombi, or in asymptomatic patients.

Contrast venography may be used to diagnose intraluminal filling defects, though the test is very infrequently used except in complex situations when there is discrepancy between clinical suspicion and venous ultrasound results.

**5. Pulmonary angiography**—Pulmonary angiography is the historical reference standard for the diagnosis of PE. At present, pulmonary angiography is only used during catheter-directed therapy (for administration of a thrombolytic or for mechanical thrombectomy) in the treatment of acute PE or to confirm the diagnosis of chronic PE in chronic thromboembolic pulmonary hypertension.

## ► Integrated Approach to Diagnosis of Pulmonary Embolism

The diagnosis of PE uses the clinical likelihood derived from clinical prediction rules, such as Wells score (Table 9–19) along with the results of diagnostic tests, such as D-dimer, to establish a pretest probability of PE. The ideal diagnostic approach is a cost-effective, stepwise sequence to come to these decision points at minimal risk to the patient.

In patients with low pretest probability, a normal D-dimer rules out presence of PE. The Pulmonary Embolism Rule-out Criteria (PERC) may be used to identify patients for whom no testing is indicated (Table 9–20). Imaging is recommended for patients with low or intermediate pretest probability (or PE-unlikely) and a positive D-dimer or those with high pretest probability (or PE-likely).

## ► Risk Stratification of Pulmonary Embolism

After a PE diagnosis is made, the next step is risk stratification, since this will guide management. There are three categories based on mortality data: high-risk, intermediate-risk, and low-risk PE. Patients with high-risk PE, also known as massive PE, have hemodynamic compromise, defined as systolic blood pressure less than 90 mm Hg or a systolic blood pressure drop by 40 mm Hg or more for longer than

**Table 9–20.** Pulmonary embolism rule-out criteria (PERC) for low-risk patients.

For patients with a Modified Wells Score  $\leq 4^1$  who meet ALL of the following criteria, PE is excluded, monitor off anticoagulation, and search for alternative diagnoses.

- Age  $< 50$  years
- Heart rate  $< 100$  bpm
- Oxyhemoglobin saturation on room air  $\geq 95\%$
- No prior history of venous thromboembolism
- No recent (within 4 weeks) trauma or surgery requiring hospitalization
- No presenting hemoptysis
- No estrogen therapy
- No unilateral leg swelling

<sup>1</sup>See Table 9–19.

Data from Kline JA et al. Impact of a rapid rule-out protocol for pulmonary embolism on the rate of screening, missed cases, and pulmonary vascular imaging in an urban US emergency room. Ann Emerg Med. 2004;44:490.

15 minutes, requiring a vasopressor, or causing a cardiac arrest. Patients with an intermediate-risk PE, also known as submassive PE, are hemodynamically stable but do have signs of right ventricular strain or dysfunction, either by imaging (CT-PA or echocardiogram) or cardiac biomarkers (troponin or BNP). Patients with low-risk PE have normotension without signs of right ventricular dysfunction.

PE severity scores, such as PE Severity Score Index (PESI) or the simplified PESI, compile useful patient characteristics that predict patient outcome. Such scores may also be used to decide which patients may be appropriate for outpatient PE treatment. Imaging of the right ventricle, usually using CT-PA or echocardiogram and cardiac biomarkers (troponin and/or BNP) are other useful tools that may help predict adverse outcomes.

## ► Prevention

VTE is often clinically silent until it presents with significant morbidity or mortality. It is a prevalent disease, clearly associated with identifiable risk factors. Patients at highest risk include those with critical illness, cancer, stroke, myocardial infarction, old age (greater than 75 years), prolonged immobility, obesity, kidney disease, previous VTE, and hypercoagulable states. Hospitalized patients with one or more of these risk factors and an acute medical illness should receive pharmacologic thromboprophylaxis.

Discussion of strategies for the prevention of VTE can be found in Chapter 14.

## ► Treatment

### A. Anticoagulation

Anticoagulation is the mainstay therapy for VTE. It impedes additional thrombus formation, allowing endogenous fibrinolytic mechanisms to lyse existing clot, decreasing mortality and recurrence of PE. Initiation of anticoagulation should be considered even prior to a confirmed diagnosis when there is high clinical suspicion and low risk of bleeding.

**Table 9–19.** Clinical prediction rule for pulmonary embolism (PE).

| Variable   | Points               |
|--|----------------------|
| Clinical symptoms and signs of deep venous thrombosis (DVT) (leg swelling and pain with palpation of deep veins) | 3.0                  |
| Alternative diagnosis less likely than PE  | 3.0                  |
| Heart rate $> 100$ beats/min   | 1.5                  |
| Immobilization for $> 3$ days or surgery in previous 4 weeks   | 1.5                  |
| Previous PE or DVT   | 1.5                  |
| Hemoptysis   | 1.0                  |
| Cancer (with treatment within past 6 months or palliative care)  | 1.0                  |
| <b>Three-tiered clinical probability assessment (Wells criteria)</b>   | <b>Score</b>         |
| High   | $> 6.0$              |
| Moderate   | 2.0 to 6.0           |
| Low  | $< 2.0$              |
| <b>Dichotomous clinical probability assessment (Modified Wells criteria)</b>                                     | <b>Score</b>         |
| PE likely  | $> 4.0$              |
| PE unlikely  | $< \text{or } = 4.0$ |

Data from Wells PS et al. Derivation of a simple clinical model to categorize patients' probability of pulmonary embolism: increasing the models' utility with the SimpliRED D-dimer. Thromb Haemost. 2000;83:416.

Unfractionated heparin binds to and accelerates the ability of antithrombin to inactivate thrombin, factor Xa, and factor IXa. Compared to unfractionated heparin, low-molecular-weight heparins (LMWHs) are as effective but have faster therapeutic activity in the treatment of VTE. Direct-acting oral anticoagulants (DOACs) offer predictable pharmacokinetics and pharmacodynamics with fixed dosing, few drug interactions, and relatively short half-life. DOACs are recommended as first-line anticoagulation for most patients.

The optimal duration of anticoagulation therapy for venous thromboembolism depends on the risk factors for VTE recurrence. Extended anticoagulation should be considered for patients with no identifiable risk factor for the index PE event, those with a persistent risk factor, recurrent VTE, or those with a minor risk factor (such as immobility due to prolonged car or air travel, obesity, pregnancy, or increased age). However, those with major transient/reversible risk factors (such as fracture of lower limb; hip or knee surgery; or hospitalization for heart failure, atrial fibrillation, or myocardial infarction) may be considered for discontinuation of anticoagulation after 3 months. Additionally, duration of therapy needs to take into consideration the patient's age, likelihood and potential consequences of hemorrhage, and preferences for continued therapy. The D-dimer level measured a month after stopping anticoagulant therapy as well as the patient's sex may influence whether to discontinue or restart treatment. Patients who continue to receive anticoagulation long term should be reassessed for venous thrombosis periodically (at least annually).

The major complication of anticoagulation is hemorrhage. Risk factors for hemorrhage include the intensity of the anticoagulation; duration of therapy; concomitant administration of medications, such as aspirin, that interfere with platelet function; and patient characteristics, particularly increased age, previous gastrointestinal hemorrhage, and coexistent kidney or liver disease.

## B. Thrombolytic Therapy

Streptokinase, urokinase, and recombinant tissue plasminogen activator (rt-PA; alteplase) increase plasmin levels and thereby directly lyse intravascular thrombi accelerating resolution of emboli. Guidelines support systemic thrombolysis for high-risk or massive PE (hemodynamically unstable) with low risk of bleeding. Intermediate-risk or submassive PE patients (hemodynamically stable with evidence of right heart strain) do not have a mortality benefit with thrombolytic therapy but do have a significant decrease in incidence of hemodynamic collapse, although they do have an increase in major hemorrhagic complications, including intracranial hemorrhage. Absolute contraindications to thrombolytic therapy include active bleeding and stroke within the past 3 months. Relative contraindications include uncontrolled hypertension and surgery or trauma within the past 4 weeks.

Catheter-directed thrombolysis delivers low-dose thrombolytic directly into the PE, thereby reversing right ventricular dilation faster than anticoagulation alone. This procedure may be considered for patients with high-risk

PE (though with higher risks of bleeding) and for those with intermediate-risk PE at increased risk of hemodynamic collapse.

## C. Additional Measures

Mechanical pulmonary embolectomy or surgical embolectomy may be considered for selected patients with contraindications to thrombolysis or failure of thrombolysis.

Inferior vena cava filters should be inserted in patients with contraindications to anticoagulation and those with recurrent PE despite adequate anticoagulation. Consideration should be given for those with acute PE and presence of free-floating proximal end DVT, since it carries an increased risk of embolization. Once placed, it must be assessed for removal at the earliest opportunity.

## ► Prognosis

PE is estimated to cause more than 50,000–100,000 deaths annually in the United States. Statistics highlight the importance of preventive therapy in high-risk patients (Chapter 14). The outlook for most patients is generally good. However, mortality for intermediate-risk (submassive) PE or high-risk (massive) PE may be as high as 20% and 50%, respectively. Therefore, early diagnosis and risk stratification are key. Survivors may have long-term sequelae of PE, such as exercise intolerance, chronic thromboembolic disease, and chronic thromboembolic pulmonary hypertension. Therefore, follow-up care to assess whether patients have persistent or recurrent symptoms is very important.

## ► When to Admit

Most patients with acute PE require hospitalization. The decision to admit patients with acute PE requires assessment of factors placing them at high risk, including their severity of illness (eg, severe hypoxemia), comorbidities (eg, DVT, cardiac dysfunction), educational needs (eg, lack of knowledge about PE and its management), and/or problematic social situations (eg, prior noncompliance with follow-up care). Carefully selected patients with low-risk PE can be safely and effectively managed as outpatients with the aid of integrated clinical decision support systems.

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## PULMONARY HYPERTENSION



### ESSENTIALS OF DIAGNOSIS

- ▶ Dyspnea, fatigue, chest pain, and syncope on exertion.
- ▶ Narrow splitting of second heart sound with loud pulmonary component; findings of right ventricular hypertrophy and heart failure in advanced disease.
- ▶ Electrocardiographic evidence of right ventricular strain or hypertrophy and right atrial enlargement.
- ▶ Enlarged central pulmonary arteries on chest radiograph.
- ▶ Elevated right ventricular systolic pressure, right ventricular dilation or dysfunction on two-dimensional echocardiography with Doppler flow studies.

### ► General Considerations

Pulmonary hypertension is a complex problem characterized by pathologic elevation in pulmonary arterial pressure. Normal pulmonary artery systolic pressure at rest is 15–30 mm Hg, with a mean pressure between 10 mm Hg and 18 mm Hg. The pulmonary circulation is a low-pressure, low-resistance system due to its large cross-sectional area, and it can accommodate significant increase in blood flow during exercise. The primary pathologic mechanism in pulmonary hypertension is an increase in pulmonary vascular resistance that leads to an increase in the pulmonary systolic pressure. Pulmonary hypertension is defined by a mean pulmonary arterial pressure of 20 mm Hg or more on a resting cardiac catheterization.

The WHO/New York Heart Association (NYHA) functional class currently classifies pulmonary hypertension based on similarities in pathologic mechanisms and includes the following five groups.

**Group 1** (pulmonary arterial hypertension [PAH]): This group gathers diseases that localize directly to the pulmonary arteries leading to structural changes, smooth muscle hypertrophy, and endothelial dysfunction. This group includes idiopathic (formerly primary) PAH; heritable PAH; drug- and toxin-induced PAH; PAH associated with HIV infection, portal hypertension, connective tissue disorders (most commonly scleroderma), congenital heart disease, schistosomiasis; and PAH with features of veno-occlusive disease and pulmonary capillary hemangiomatosis. PAH is defined on a resting cardiac catheterization by a mean pulmonary arterial pressure of 20 mm Hg or more with a pulmonary capillary wedge pressure of 15 mm Hg or less and a pulmonary vascular resistance of 3 Wood units (WU) or more.

**Group 2** (pulmonary venous hypertension due to left heart disease): This group includes left ventricular systolic or diastolic dysfunction and valvular heart disease.

**Group 3** (pulmonary hypertension due to lung disease or hypoxemia): This group is caused by advanced

obstructive and restrictive lung disease, including COPD, interstitial lung disease, pulmonary fibrosis as well as other causes of chronic hypoxemia, such as sleep-disordered breathing, alveolar hypoventilation syndromes, and high-altitude exposure.

**Group 4** (pulmonary hypertension due to pulmonary obstruction): This group primarily includes chronic thromboembolic pulmonary hypertension but also includes other causes of pulmonary obstructions, such as sarcoma, metastatic malignancies, and congenital pulmonary artery stenosis.

**Group 5** (pulmonary hypertension secondary to unclear or multifactorial mechanisms): These patients have pulmonary hypertension secondary to hematologic disorders (eg, chronic hemolytic anemia, sickle cell anemia, myeloproliferative disorders, splenectomy), systemic disorders (eg, sarcoidosis, vasculitis, pulmonary Langerhans cell histiocytosis, neurofibromatosis type 1), metabolic disorders (eg, glycogen storage disease, Gaucher disease, thyroid disease), and miscellaneous causes (eg, end-stage renal disease with or without hemodialysis, fibrosing mediastinitis).

The clinical severity of pulmonary hypertension is classified according to the NYHA classification system, which was originally developed for heart failure but subsequently modified by the WHO; it is based primarily on symptoms and functional status.

**Class I:** No limitation of physical activity; no dyspnea, fatigue, chest pain, or near syncope is present with exertion.

**Class II:** Slight limitation of physical activity; no symptoms at rest, but ordinary physical activity causes dyspnea, fatigue, chest pain, or near syncope.

**Class III:** Marked limitation of physical activity; no symptoms at rest, but less than ordinary activity causes dyspnea, fatigue, chest pain, or near syncope.

**Class IV:** Inability to perform any physical activity without symptoms; dyspnea and fatigue are present at rest and symptoms worsen with any activity.

### ► Clinical Findings

#### A. Symptoms and Signs

There are no specific symptoms or signs of pulmonary hypertension, which may delay its diagnosis and significantly affect its mortality. Typical symptoms include dyspnea with exertion and with advanced disease, at rest. Patients may have anginal pain, nonproductive cough, malaise, and fatigue. Syncope may occur with exertion when there is insufficient cardiac output or if there is an arrhythmia.

Findings on physical examination can include jugular venous distention, accentuated pulmonary valve component of the second heart sound, right-sided third heart sound, tricuspid regurgitation murmur, hepatomegaly, and lower extremity edema.

#### B. Laboratory Findings

Routine blood work is often normal. BNP or pro-BNP may be elevated. All patients should be evaluated for HIV, liver dysfunction, and connective tissue disorders.

The ECG is typically normal except in advanced disease, where right ventricular hypertrophy (right axis deviation, incomplete right bundle branch block) and right atrial enlargement (peaked P wave in the inferior and right-sided leads) can be noted.

### C. Imaging and Special Examinations

Radiographs and CT scans of the chest are useful in diagnosis. Enlargement of the right and left main pulmonary arteries is common; right ventricular and right atrial enlargement is seen in advanced disease. Chest CT scanning and pulmonary function testing are also useful in determining the cause of pulmonary hypertension for patients in Group 3 (pulmonary hypertension due to lung disease). On pulmonary function testing, the combination of normal FVC on spirometry, normal TLC on lung volume measurement, and significantly decreased single-breath diffusing capacity may be suggestive of PAH. However, FVC and TLC may be also reduced in pulmonary hypertension due to lung disease (Group 3).

Echocardiography is the best screening study. Right ventricular assessment is made by measuring right ventricular size and function as well as right ventricular systolic pressure, which is estimated based on tricuspid jet velocity and right atrial pressure. Additionally, the echocardiogram is useful for assessing underlying cardiac disease (eg, pulmonary hypertension due to left heart disease).

Right-sided cardiac catheterization remains the gold standard for the diagnosis and quantification of pulmonary hypertension and should be performed prior to initiation of advanced therapies. Estimated pressures on echocardiogram correlate with right heart catheterization measurement but can vary by at least 10 mm Hg in more than 50% of cases so should not be used to direct therapy. Cardiac catheterization is particularly helpful in differentiating PAH from pulmonary venous hypertension by assessment of the drop in pressure across the pulmonary circulation, also known as the transpulmonary gradient. A vasodilator challenge can be performed during right heart catheterization and a significant acute vasodilator response consists of a drop in mean pulmonary pressure of greater than 10 mm Hg (or 20%) to less than 40 mm Hg.

In patients with unexplained pulmonary hypertension or in those with a history of PE or risk factors for thromboembolic disease, chronic thromboembolic pulmonary hypertension (Group 4) should be excluded prior to diagnosing idiopathic pulmonary hypertension.  $\dot{V}/\dot{Q}$  lung scanning is a very sensitive test that can differentiate these two disorders. If abnormal, CT-PA or pulmonary angiography is the next step in confirming the diagnosis and establishing the distribution and extent of disease.

## Treatment

Advanced therapies, such as pulmonary vasodilators, are available to treat pulmonary hypertension. Such therapies are chosen based on the patient's functional status according to the NYHA/WHO classification. The mechanisms of action for pulmonary vasodilators follow three main pathways: (1) the nitric oxide pathway: phosphodiesterase

inhibitors (sildenafil, tadalafil) and soluble guanylate cyclase stimulators (riociguat); (2) the endothelin pathway: endothelin receptor antagonists (bosentan, ambrisentan, macitentan); and (3) the prostacyclin pathway: prostacyclin analogs (intravenous epoprostenol; intravenous, subcutaneous, inhaled, or oral treprostinil; inhaled iloprost) and prostacyclin receptor agonist (selexipag). These vasodilators are only FDA approved for patients with Group 1 PAH based on their improvement in symptoms, 6-minute walk distance, WHO functional status, and hemodynamic measurements. More recently, a major RCT showed reduction in a composite outcome (death, hospitalization, progression, or unsatisfactory response) for combination therapy (using tadalafil and ambrisentan) compared to monotherapy. As a result, patients with WHO/NYHA functional class II and III are frequently given a combination of endothelin receptor antagonists and phosphodiesterase inhibitors initially. For patients in WHO/NYHA functional class IV, a more aggressive approach is recommended with continuous intravenous or subcutaneous prostacyclin analog infusion. Oral calcium channel blockers may be used in patients with a significant vasodilator response during cardiac catheterization. Anticoagulation was commonly used in the past but has fallen out of favor.

Treatment of patients with Group 2 pulmonary hypertension (due to left heart failure) is discussed in Chapter 10. The main goal is to decrease pulmonary venous pressure by treating heart failure and volume overload, primarily with the use of diuretics.

Patients with Group 3 pulmonary hypertension (due to lung disease) should be assessed for hypoxemia at rest or with physical activity and, if present, should receive supplemental oxygen. In patients with COPD or interstitial lung disease, treatment should focus on supportive care for underlying disease.

For patients with Group 4 pulmonary hypertension (due to chronic thromboembolic disease), long-term anticoagulation is recommended. Additionally, patients with surgically accessible lesions and acceptable perioperative risk should undergo pulmonary thromboendarterectomy. For patients unable to undergo surgery or those with residual pulmonary hypertension postoperatively, medical therapy with riociguat or pulmonary artery balloon angioplasty should be considered.

Lung transplantation is a treatment option for selected patients with pulmonary hypertension when medical therapy is no longer effective. Double-lung transplant is the preferred method, although single-lung transplant is routinely done as well. In some cases, transplantation of the heart and both lungs is needed.

## Prognosis

The prognosis of pulmonary hypertension varies by group. The prognosis of Group 1 patients has improved with the advent of pulmonary hypertension-specific therapy. Factors associated with poor prognosis include age older than 50 years, male sex, WHO/NYHA functional class III or IV, failure to improve to a lower functional class with therapy, and right ventricular dysfunction.

## ► When to Refer

Patients in whom pulmonary hypertension is suspected or has been diagnosed should be referred early to a specialized pulmonary hypertension center for expert management.

## ► When to Admit

- Patients with pulmonary hypertension, severe symptoms, and evidence of decompensated right heart failure with volume overload should be admitted to the hospital for aggressive diuresis.
- Patients with Group 1 pulmonary hypertension and functional class IV symptoms should be admitted to a specialized center for initiation of advanced therapies, such as intravenous prostacyclins.

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## PULMONARY VASCULITIS

**Antineutrophil cytoplasmic autoantibody (ANCA)-associated vasculitides** include granulomatosis with polyangiitis, microscopic polyangiitis, and eosinophilic granulomatosis with polyangiitis. All are associated with ANCA and similar features of glomerulonephritis.

**Granulomatosis with polyangiitis** is a small vessel vasculitis manifested in the upper and lower respiratory tracts. Chronic sinusitis, arthralgias, fever, skin rash, and weight loss are frequent presenting symptoms. Specific pulmonary complaints occur less often. The most common sign of lung disease is nodular pulmonary infiltrates, often with cavitation, seen on chest radiography. Tracheal stenosis and endobronchial disease are sometimes seen. The diagnosis is most often based on serologic testing and biopsy of lung, sinus tissue, or kidney with demonstration of necrotizing granulomatous vasculitis (Chapter 20).

**Eosinophilic granulomatosis with polyangiitis** is an idiopathic multisystem vasculitis of small and

medium-sized arteries that occurs in patients with asthma. The skin and lungs are most often involved, but other organs, including the paranasal sinuses, the heart, gastrointestinal tract, liver, and peripheral nerves, may also be affected. Peripheral eosinophilia greater than 1500 cells/mCL (greater than  $1.5 \times 10^9/L$ ) or greater than 10% of peripheral WBCs is the rule. Abnormalities on chest radiographs range from transient opacities to multiple nodules. This illness may be part of a spectrum that includes polyarteritis nodosa. The diagnosis requires demonstration of histologic features, including fibrinoid necrotizing epithelioid granulomas and eosinophilic granulomas.

## ► Treatment

Treatment of pulmonary vasculitis requires immunosuppressive therapy. Combination therapy with corticosteroids and either rituximab or cyclophosphamide is recommended for those with organ- or life-threatening disease. After complete remission is obtained, then maintenance therapy with rituximab, methotrexate, azathioprine, or mycophenolate is used.

## ► Prognosis

Five-year survival rates in patients with these vasculitis syndromes have been improved by combination therapy. Complete remission can be achieved in over 90% of patients with granulomatosis with polyangiitis. The addition of trimethoprim-sulfamethoxazole (one double-strength tablet by mouth twice daily) to standard therapy may help prevent relapses.

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## ALVEOLAR HEMORRHAGE SYNDROMES

Diffuse alveolar hemorrhage may occur in a variety of immune and nonimmune disorders. Alveolar infiltrates on chest radiograph, dyspnea, anemia, hemoptysis and, occasionally, fever are characteristic. Rapid clearing of diffuse lung infiltrates within 2 days is a clue to the diagnosis of diffuse alveolar hemorrhage. Pulmonary hemorrhage can be associated with an increased single-breath diffusing capacity for carbon monoxide ( $D_{LCO}$ ), although this test is infrequently obtained. Sequential BAL on bronchoscopy is the preferred method for diagnosis. Diffuse alveolar hemorrhage is confirmed when lavage aliquots are progressively more hemorrhagic.

Causes of diffuse **immune alveolar hemorrhage** include anti-basement membrane antibody disease (Goodpasture syndrome), granulomatosis with polyangiitis,

systemic necrotizing vasculitis, pulmonary capillaritis associated with idiopathic rapidly progressive glomerulonephritis, systemic lupus erythematosus, and other vasculitic and collagen vascular diseases. **Nonimmune causes** of diffuse hemorrhage include coagulopathy, mitral stenosis, necrotizing pulmonary infection, drugs (penicillamine), toxins (trimellitic anhydride), and idiopathic pulmonary hemosiderosis.

**Goodpasture syndrome** is idiopathic recurrent alveolar hemorrhage and rapidly progressive glomerulonephritis. The disease is mediated by anti-glomerular basement membrane antibodies. Goodpasture syndrome occurs mainly in men who are in their 30s and 40s. Hemoptysis is the usual presenting symptom, but pulmonary hemorrhage may be occult. Dyspnea, cough, hypoxemia, and diffuse bilateral alveolar infiltrates are typical features. Iron deficiency anemia and microscopic hematuria are usually present. The diagnosis is based on characteristic linear IgG deposits detected by immunofluorescence in glomeruli or alveoli and on the presence of anti-glomerular basement membrane antibody in serum. The combination of plasmapheresis plus immunosuppressive therapy is recommended, rather than immunosuppressive therapy alone. Immunosuppression with the combination of corticosteroids and cyclophosphamide is recommended.

**Idiopathic pulmonary hemosiderosis** is a disease of children or young adults characterized by recurrent pulmonary hemorrhage; in contrast to Goodpasture syndrome, renal involvement and anti-glomerular basement membrane antibodies are absent, but iron deficiency is typical. It is frequently associated with celiac disease. Treatment of acute episodes of hemorrhage with corticosteroids may be useful. Recurrent episodes of pulmonary hemorrhage may result in interstitial fibrosis and pulmonary failure.

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burns themselves. The death rate of patients with both severe burns and smoke inhalation exceeds 50%.

All patients in whom significant smoke inhalation is suspected must be assessed for three consequences of smoke inhalation: impaired tissue oxygenation, thermal injury to the upper airway, and injury to the lower airways and lung parenchyma. Impaired tissue oxygenation may result from inhalation of a hypoxic gas mixture, carbon monoxide or cyanide, or from alterations in  $\dot{V}/\dot{Q}$  matching, and is an immediate threat to life. Immediate treatment with 100% oxygen is essential. The management of patients with carbon monoxide and cyanide poisoning is discussed in Chapter 38. The clinician must recognize that patients with carbon monoxide poisoning display a normal partial pressure of oxygen in arterial blood ( $Pao_2$ ), but have a low measured (ie, not oximetric) hemoglobin saturation ( $Sao_2$ ). Treatment with 100% oxygen should be continued until the measured carboxyhemoglobin level falls to less than 10% and concomitant metabolic acidosis has resolved.

Thermal injury to the mucosal surfaces of the upper airway occurs from inhalation of super-heated gases. Complications, including mucosal edema, upper airway obstruction, and impaired ability to clear oral secretions, usually become evident by 18–24 hours and produce inspiratory stridor. Respiratory failure occurs in severe cases. Early management (Chapter 37) includes the use of a high-humidity face mask with supplemental oxygen, gentle suctioning to evacuate oral secretions, elevation of the head 30 degrees to promote clearing of secretions, and topical epinephrine to reduce edema of the oropharyngeal mucous membrane. Helium-oxygen gas mixtures (Heliox) may reduce labored breathing due to critical upper airway narrowing. Close monitoring with ABGs and later with oximetry is important. Examination of the upper airway with a fiberoptic laryngoscope or bronchoscope is superior to routine physical examination. Endotracheal intubation is often necessary to maintain airway patency and is likely to be necessary in patients with deep facial burns or oropharyngeal or laryngeal edema. Tracheotomy should be avoided, if possible, because of an increased risk of pneumonia and death from sepsis.

Injury to the lower airways and lung parenchyma results from inhalation of toxic gases and products of combustion, including aldehydes and organic acids. The site of lung injury depends on the solubility of the gases inhaled, the duration of exposure, and the size of inhaled particles that transport noxious gases to distal lung units. Bronchorrhea and bronchospasm are seen early after exposure along with dyspnea, tachypnea, and tachycardia. Labored breathing and cyanosis may follow. Physical examination at this stage reveals diffuse wheezing and rhonchi. Bronchiolar and alveolar edema (eg, ARDS) may develop within 1–2 days after exposure. Sloughing of the bronchiolar mucosa may occur within 2–3 days, leading to airway obstruction, atelectasis, and worsening hypoxemia. Bacterial colonization and pneumonia are common by 5–7 days after the exposure.

Treatment of smoke inhalation consists of supplemental oxygen, bronchodilators, suctioning of mucosal debris and mucopurulent secretions via an indwelling endotracheal tube, chest physical therapy to aid clearance of secretions, and adequate humidification of inspired gases. Positive

## ENVIRONMENTAL & OCCUPATIONAL LUNG DISORDERS

### SMOKE INHALATION

The inhalation of products of combustion may cause serious respiratory complications. As many as one-third of patients admitted to burn treatment units have pulmonary injury from smoke inhalation. Morbidity and mortality due to smoke inhalation may exceed those attributed to the

end-expiratory pressure (PEEP) has been advocated to treat bronchiolar edema. Judicious fluid management and close monitoring for secondary bacterial infection round out the management protocol.

The routine use of corticosteroids for lung injury from smoke inhalation has been shown to be ineffective and may even be harmful. Routine or prophylactic use of antibiotics is not recommended.

Patients who survive should be watched for the late development of bronchiolitis obliterans.

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## E-CIGARETTE- OR VAPING PRODUCT-ASSOCIATED LUNG INJURY

### General Considerations

An outbreak of e-cigarette- or vaping product-associated lung injury (EVALI) began in the United States in 2019. Approximately 66% of patients have been male and 80% are under age 35. Over 95% of reported cases required hospitalization: 47% were admitted to intensive care, 22% were intubated, and many died. Based on the characteristics of these patients, the diagnosis of EVALI requires reported use of e-cigarette or vaping products within 3 months of symptom onset, compatible chest imaging findings, and an evaluation that excludes infectious etiologies.

No single causative agent has been identified. The majority of cases involved vaping products containing tetrahydrocannabinol (THC) or nicotine or both. Postulated factors contributing to the development of EVALI include e-cigarette flavorings, exposure to diacetyl (a popcorn flavoring that has been associated with lung injury), THC, adulteration of THC, adulteration of delivery devices, and vitamin E acetate (used as a thickening agent).

### Clinical Findings

#### A. Symptoms and Signs

Patients with EVALI have respiratory symptoms (95%), including cough, shortness of breath, and chest pain; gastrointestinal symptoms (77%), including nausea, vomiting, and diarrhea; and constitutional symptoms (85%), including fever, chills, and weight loss). The illness is usually acute to subacute with patients having symptoms for days to weeks before seeking health care.

Tachycardia and tachypnea are present in 55% and 45% of patients, respectively. Of note, 57% of cases have a recorded room air oxygen saturation of less than 95%. Given the nonspecific nature of the presentation especially during influenza season and the COVID-19 pandemic, providers must have a high degree of clinical suspicion and ask patients specifically about vaping.

### B. Laboratory Findings

There are no laboratory findings specific for the diagnosis of EVALI. There may be leukocytosis, elevated C-reactive protein, and elevated erythrocyte sedimentation rate.

### C. Imaging

Case series of chest imaging findings in EVALI show various patterns of lung injury. Chest radiographs typically show bilateral pulmonary opacities. Chest CT scans are nonspecific and may show patterns seen in other disorders, such as hypersensitivity pneumonitis, ARDS, diffuse alveolar hemorrhage, acute eosinophilic pneumonia, lipoid pneumonia, giant cell interstitial pneumonia, and organizing pneumonia.

### Differential Diagnosis

The differential diagnosis is broad for a patient with respiratory and gastrointestinal symptoms and bilateral pulmonary infiltrates. The first diagnostic considerations are CAP and COVID-19. The EVALI case definition requires a negative work-up for infectious causes. Other diagnoses to consider include acute eosinophilic pneumonia, ARDS, hypersensitivity pneumonitis, lipoid pneumonia, and organizing pneumonia. Influenza testing should be done in season, and SARS-CoV-2 testing, as indicated.

### Treatment

The natural progression of EVALI is not known. In published reports of hospitalized patients with EVALI who have received corticosteroids, rapid improvement has been described.

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## PULMONARY ASPIRATION SYNDROMES

Aspiration of material into the tracheobronchial tree results from various disorders that impair normal deglutition, especially disturbances of consciousness and esophageal dysfunction.

### 1. Acute Aspiration of Gastric Contents (Mendelson Syndrome)

Acute aspiration of gastric contents may be catastrophic. The pulmonary response depends on the characteristics and amount of gastric contents aspirated. The more acidic

the material, the greater the degree of chemical pneumonitis. Aspiration of pure gastric acid ( $\text{pH} < 2.5$ ) causes extensive desquamation of the bronchial epithelium, bronchiolitis, hemorrhage, and pulmonary edema. Acute gastric aspiration is one of the most common causes of ARDS. The clinical picture is one of abrupt onset of respiratory distress, with cough, wheezing, fever, and tachypnea. Crackles may be audible at the bases of the lungs. Hypoxemia may be noted immediately after aspiration occurs. Radiographic abnormalities, consisting of patchy alveolar opacities in dependent lung zones, appear within a few hours. If particulate food matter has been aspirated along with gastric acid, radiographic features of bronchial obstruction may be observed. Fever and leukocytosis are common even in the absence of infection.

Treatment of acute aspiration of gastric contents consists of supplemental oxygen, measures to maintain the airway, and the usual measures for treatment of acute respiratory failure. There is no evidence to support the routine use of prophylactic antibiotics or corticosteroids. Secondary pulmonary infection, which occurs in about one-fourth of patients, typically appears 2–3 days after aspiration. Management of infection depends on the observed flora from the tracheobronchial tree. Hypotension secondary to alveolar capillary membrane injury and intravascular volume depletion is common and is managed with the judicious administration of intravenous fluids.

## 2. Chronic Aspiration of Gastric Contents

Chronic aspiration of gastric contents may result from primary disorders of the larynx or the esophagus, such as achalasia, esophageal stricture, systemic sclerosis (scleroderma), esophageal carcinoma, esophagitis, and GERD. In GERD, relaxation of the tone of the lower esophageal sphincter allows reflux of gastric contents into the esophagus and predisposes to chronic pulmonary aspiration, especially when supine. Cigarette smoking, consumption of alcohol or caffeine, and theophylline use are all known to relax the lower esophageal sphincter. Pulmonary disorders linked to GERD and chronic aspiration include asthma, chronic cough, bronchiectasis, and pulmonary fibrosis. Even in the absence of aspiration, acid in the esophagus may trigger bronchospasm or bronchial hyperreactivity through reflex mechanisms.

The diagnosis and management of gastroesophageal reflux and chronic aspiration are challenging. A discussion of strategies for the evaluation, prevention, and management of extraesophageal reflux manifestations can be found in Chapter 15.

## 3. "Café Coronary"

Acute obstruction of the upper airway by food is associated with difficulty swallowing, old age, dental problems that impair chewing, and use of alcohol and sedative drugs. The Heimlich procedure is lifesaving in many cases.

## 4. Retention of an Aspirated Foreign Body

Retention of an aspirated foreign body in the tracheobronchial tree may produce both acute and chronic conditions, including atelectasis, postobstructive hyperinflation, both

acute and recurrent pneumonia, bronchiectasis, and lung abscess. Occasionally, a misdiagnosis of asthma, COPD, or lung cancer is made in adult patients who have aspirated a foreign body. The plain chest radiograph usually suggests the site of the foreign body. In some cases, an expiratory film, demonstrating regional hyperinflation due to a check-valve effect, is helpful. Bronchoscopy is usually necessary to establish the diagnosis and attempt removal of the foreign body.

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## OCCUPATIONAL PULMONARY DISEASES

Many acute and chronic pulmonary diseases are directly related to inhalation of noxious substances encountered in the workplace. Disorders that are linked to occupational exposures may be classified as follows: (1) pneumoconioses, (2) hypersensitivity pneumonitis, (3) obstructive airway disorders, (4) toxic lung injury, (5) lung cancer, (6) pleural diseases, and (7) other occupational pulmonary diseases.

### 1. Pneumoconioses

Pneumoconioses are chronic fibrotic lung diseases caused by the inhalation of inert inorganic dusts. Pneumoconioses range from asymptomatic disorders with diffuse nodular opacities on chest radiograph to severe, symptomatic, life-shortening disorders. Clinically important pneumoconioses include coal worker's pneumoconiosis, silicosis, and asbestosis (Table 9–21). Treatment for each is supportive; pulmonary rehabilitation may be considered.

#### A. Coal Worker's Pneumoconiosis

In coal worker's pneumoconiosis, ingestion of inhaled coal dust by alveolar macrophages leads to the formation of coal macules, usually 2–5 mm in diameter, that appear on chest radiograph as diffuse small opacities that are especially prominent in the upper lung. Simple coal worker's pneumoconiosis is usually asymptomatic; pulmonary function abnormalities are unimpressive. In complicated coal worker's pneumoconiosis ("progressive massive fibrosis"), conglomeration and contraction in the upper lung zones occur, with radiographic features resembling complicated silicosis. **Caplan syndrome** is a rare condition characterized by the presence of necrobiotic rheumatoid nodules (1–5 cm in diameter) in the periphery of the lung in coal workers with rheumatoid arthritis.

#### B. Silicosis

In silicosis, extensive or prolonged inhalation of free silica (silicon dioxide) particles in the respirable range (0.3–5  $\mu\text{m}$ ) causes the formation of small rounded opacities (silicotic nodules) throughout the lung. Calcification of the

**Table 9–21.** Selected pneumoconioses.

| Disease                      | Agent                         | Occupations   |
|------------------------------|-------------------------------|---|
| Asbestosis                   | Asbestos                      | Mining, insulation, construction, shipbuilding  |
| Baritosis                    | Barium salts                  | Glass and insecticide manufacturing   |
| Coal worker's pneumoconiosis | Coal dust                     | Coal mining   |
| Kaolin pneumoconiosis        | Sand, mica, aluminum silicate | Mining of china clay; pottery and cement work   |
| Shaver disease               | Aluminum powder               | Manufacture of corundum   |
| Siderosis                    | Metallic iron or iron oxide   | Mining, welding, foundry work   |
| Silicosis                    | Free silica (silicon dioxide) | Rock mining, quarrying, stone cutting, tunneling, sandblasting, pottery, diatomaceous earth |
| Stannosis                    | Tin, tin oxide                | Mining, tin-working, smelting   |
| Talcosis                     | Magnesium silicate            | Mining, insulation, construction, shipbuilding  |

periphery of hilar lymph nodes ("eggshell" calcification) is an unusual radiographic finding that strongly suggests silicosis. Simple silicosis is usually asymptomatic and has no effect on routine pulmonary function tests; in complicated silicosis, large conglomerate densities appear in the upper lung and are accompanied by dyspnea and obstructive and restrictive pulmonary dysfunction. The incidence of pulmonary tuberculosis is increased in patients with silicosis. All patients with silicosis should have a tuberculin skin test and a current chest radiograph. If old, healed pulmonary tuberculosis is suspected, multidrug treatment for tuberculosis (not single-agent preventive therapy) should be instituted.

### C. Asbestosis

Asbestosis is a nodular interstitial fibrosis occurring in workers exposed to asbestos fibers (shipyard and construction workers, pipe fitters, insulators) over many years (typically 10–20 years). Patients with asbestosis usually first seek medical attention at least 15 years after exposure with the following symptoms and signs: progressive dyspnea, inspiratory crackles, and in some cases, clubbing and cyanosis. The radiographic features of asbestosis include linear streaking at the lung bases, opacities of various shapes and sizes, and honeycomb changes in advanced cases. The presence of pleural calcifications may be a clue to diagnosis. High-resolution CT scanning is the best imaging method for asbestosis because of its ability to detect parenchymal fibrosis and define the presence of coexisting pleural plaques. Cigarette smoking in asbestos workers increases the prevalence of radiographic pleural and parenchymal changes and markedly increases the incidence of lung carcinoma. It may also interfere with the clearance of short asbestos fibers from the lung. Pulmonary function studies show restrictive dysfunction and reduced diffusing capacity. The presence of a ferruginous body in tissue suggests significant asbestos exposure; however, other histologic features must be present for diagnosis. There is no specific treatment.

Leonard R et al. Coal mining and lung disease in the 21st century. *Curr Opin Pulm Med.* 2020;26:135. [PMID: 31815751]

Mandrioli D et al. WHO/ILO work-related burden of disease and injury: protocol for systematic reviews of occupational exposure to dusts and/or fibres and of the effect of occupational exposure to dusts and/or fibres on pneumoconiosis. *Environ Int.* 2018;119:174. [PMID: 29958118]

Zhao H et al. Pulmonary rehabilitation can improve the functional capacity and quality of life for pneumoconiosis patients: a systematic review and meta-analysis. *Biomed Res Int.* 2020;2020:6174936. [PMID: 32802860]

## 2. Hypersensitivity Pneumonitis

Hypersensitivity pneumonitis (also called extrinsic allergic alveolitis) is a nonatopic, nonasthmatic inflammatory pulmonary disease. It is manifested mainly as an occupational disease (Table 9–22), in which exposure to inhaled organic antigens leads to an acute illness. Prompt diagnosis is essential since symptoms are usually reversible if the offending antigen is removed from the patient's environment early in the course of illness. Continued exposure may lead to progressive disease. The histopathology of acute hypersensitivity pneumonitis is characterized by interstitial infiltrates of lymphocytes and plasma cells, with noncaseating granulomas in the interstitium and air spaces.

### ► Clinical Findings

#### A. Acute Illness

The symptoms are characterized by sudden onset of malaise, chills, fever, cough, dyspnea, and nausea 4–8 hours after exposure to the offending antigen. Bibasilar crackles, tachypnea, tachycardia, and (occasionally) cyanosis are noted. Small nodular densities sparing the apices and bases of the lungs are noted on chest radiograph. Laboratory studies reveal an increase in the white blood cell count with a shift to the left, hypoxemia, and the presence of precipitating antibodies to the offending agent in serum. Hypersensitivity pneumonitis antibody panels against common offending antigens are available; positive results, while supportive, do not establish a definitive diagnosis. Pulmonary function studies reveal restrictive dysfunction and reduced diffusing capacity.

**Table 9–22.** Selected causes of hypersensitivity pneumonitis.

| Disease                       | Antigen   | Source   |
|-------------------------------|---|--|
| Farmer's lung                 | <i>Micropolyspora faeni</i> , <i>Thermoactinomyces vulgaris</i> | Moldy hay  |
| "Humidifier" lung             | Thermophilic actinomycetes                                      | Contaminated humidifiers, heating systems, or air conditioners |
| Bird fancier's lung           | Avian proteins  | Bird serum and excreta   |
| Bagassosis                    | <i>Thermoactinomyces sacchari</i> and <i>T vulgaris</i>         | Moldy sugar cane fiber (bagasse)                               |
| Sequoiosis                    | <i>Graphium</i> , <i>Aureobasidium</i> , and other fungi        | Moldy redwood sawdust  |
| Maple bark stripper's disease | <i>Cryptostroma (Coniosporium) corticale</i>                    | Rotting maple tree logs or bark                                |
| Mushroom picker's disease     | Same as farmer's lung   | Moldy compost  |
| Suberosis                     | <i>Penicillium frequentans</i>                                  | Moldy cork dust  |
| Detergent worker's lung       | <i>Bacillus subtilis</i> enzyme                                 | Enzyme additives   |

## B. Subacute and Chronic Illness

A subacute hypersensitivity pneumonitis syndrome (15% of cases) is characterized by the insidious onset of chronic cough and slowly progressive dyspnea, anorexia, and weight loss. Chronic exposure leads to progressive respiratory insufficiency and the appearance of pulmonary fibrosis on chest imaging. Surgical lung biopsy may be necessary for the diagnosis of subacute and chronic hypersensitivity pneumonitis. Even with surgical lung biopsy, however, chronic hypersensitivity pneumonitis may be difficult to diagnose because histopathologic patterns overlap with several idiopathic interstitial pneumonias.

## Treatment

Treatment of acute hypersensitivity pneumonitis consists of identification of the offending agent and avoidance of further exposure. In severe acute or protracted cases, oral corticosteroids (prednisone, 0.5 mg/kg daily as a single morning dose for 2 weeks, tapered to nil over 4–6 weeks) may be given. Change in occupation is often unavoidable.

- Creamer AW et al. Prognostic factors in chronic hypersensitivity pneumonitis. Eur Respir Rev. 2020;29:190167. [PMID: 32414744]  
 Nogueira R et al. Hypersensitivity pneumonitis: antigen diversity and disease implications. Pulmonology. 2019;25:97. [PMID: 30126802]  
 Soumagne T et al. Current and emerging techniques for the diagnosis of hypersensitivity pneumonitis. Expert Rev Respir Med. 2018;12:493. [PMID: 29727203]

## 3. Other Occupational Pulmonary Diseases

Occupational diseases of the pleura may result from exposure to asbestos or talc. Inhalation of talc causes pleural plaques that are similar to those caused by asbestos. Benign asbestos pleural effusion occurs in some asbestos workers and may cause chronic blunting of the costophrenic angle on chest radiograph.

Occupational agents are also responsible for other pulmonary disorders, with a range of pathologies including occupational asthma, occupational COPD, interstitial lung diseases, and lung cancer. For this reason, it is important to obtain a thorough occupational history in any patient presenting with pulmonary symptoms.

Specific examples of inorganic agents associated with interstitial lung disease include anthracite coal dust (coal workers' pneumoconiosis), crystalline and nonfibrous silicates (silicosis), asbestos (asbestosis, pleural plaques, benign pleural effusion, adenoma, malignant mesothelioma), beryllium (berylliosis, which is very similar to sarcoidosis), and cobalt (hard metal lung disease). Organic dust from farm work, animal or bird exposure, or vegetable stores may cause extrinsic allergic alveolitis or hypersensitivity pneumonitis.

Unusual outbreaks (including "popcorn-worker's lung" and other diacetyl flavoring exposure causing bronchiolitis obliterans, "flock worker's lung" following synthetic fiber exposure) are occasionally reported.

Perlman DM et al. Occupational lung disease. Med Clin North Am. 2019;103:535. [PMID: 30955520]

Wyman AE et al. Update on metal-induced occupational lung disease. Curr Opin Allergy Clin Immunol. 2018;18:73. [PMID: 29337701]

## MEDICATION-INDUCED LUNG DISEASE

Typical patterns of pulmonary response to medications implicated in medication-induced respiratory disease are summarized in Table 9–23. Pulmonary injury due to medications occurs as a result of allergic reactions, idiosyncratic reactions, overdose, or undesirable side effects. In most patients, the mechanism of pulmonary injury is unknown.

Precise diagnosis of medication-induced pulmonary disease is often difficult because results of routine laboratory studies are not helpful and radiographic findings are not specific. A high index of suspicion and a thorough history of medication usage are critical to establishing the diagnosis of medication-induced lung disease. The clinical response to cessation of the suspected offending agent is also helpful. Acute episodes of medication-induced pulmonary disease may disappear 24–48 hours after the medication has been discontinued, but chronic syndromes may take longer to resolve. Challenge tests to confirm the diagnosis are risky and rarely performed.

Treatment of medication-induced lung disease consists of discontinuing the offending agent immediately, managing the pulmonary symptoms appropriately, and occasionally treating with corticosteroids if pulmonary toxicity is

**Table 9–23.** Pulmonary manifestations of selected medication toxicities.

|  |  |
|--|--|
| <b>Asthma</b>                                    | <b>Pulmonary edema</b>   |
| Beta-blockers                                    | Noncardiogenic   |
| Aspirin  | Aspirin  |
| Nonsteroidal anti-inflammatory drugs             | Chlordiazepoxide   |
| Histamine  | Cocaine  |
| Methacholine                                     | Ethchlorvynol  |
| Acetylcysteine                                   | Heroin/opiates   |
| Aerosolized pentamidine                          | Cardiogenic  |
| Any nebulized medication                         | Beta-blockers  |
| <b>Chronic cough</b>                             | <b>Pleural effusion</b>  |
| Angiotensin-converting enzyme inhibitors         | Bromocriptine  |
| <b>Pulmonary infiltration</b>                    | Nitrofurantoin   |
| Without eosinophilia                             | Any drug inducing systemic lupus erythematosus   |
| Amitriptyline                                    | Methysergide   |
| Azathioprine                                     | Chemotherapeutic agents (eg, carmustine, cyclophosphamide, dasatinib, docetaxel, GM-CSF, methotrexate) |
| Amiodarone                                       | Tyrosine kinase inhibitors   |
| With eosinophilia                                | <b>Mediastinal widening</b>  |
| Sulfonamides                                     | Phenytoin  |
| L-Tryptophan                                     | Corticosteroids  |
| Nitrofurantoin                                   | Methotrexate   |
| Penicillin                                       | <b>Respiratory failure</b>   |
| Methotrexate                                     | Neuromuscular blockade   |
| Crack cocaine                                    | Aminoglycosides  |
| <b>Drug-induced systemic lupus erythematosus</b> | Paralytic agents   |
| Hydralazine                                      | <b>Central nervous system depression</b>   |
| Procainamide                                     | Sedatives  |
| Isoniazid  | Hypnotics  |
| Chlorpromazine                                   | Opioids  |
| Phenytoin  | Alcohol  |
| <b>Interstitial pneumonitis/fibrosis</b>         | Tricyclic antidepressants  |
| Nitrofurantoin                                   |  |
| Bleomycin  |  |
| Busulfan   |  |
| Cyclophosphamide                                 |  |
| Immune checkpoint inhibitors                     |  |
| Methysergide                                     |  |
| Phenytoin  |  |

GM-CSF, granulocyte-macrophage colony-stimulating factor.

rapidly progressive. Randomized data supporting the use of corticosteroids in medication-associated pneumonitis is lacking, but observational data supports use in severe cases. Immune checkpoint inhibitors, now commonly used treatments for a variety of malignant and nonmalignant conditions, are associated with at least a 5% risk of pneumonitis, which carries mortality of up to 20% when severe. Observational data support corticosteroid treatment in these cases.

**Inhalation of crack cocaine** may cause a spectrum of acute pulmonary syndromes, including pulmonary infiltration with eosinophilia, pneumothorax and pneumomediastinum, bronchiolitis obliterans, and acute respiratory failure associated with diffuse alveolar damage and alveolar hemorrhage. Corticosteroids have been used with variable success to treat alveolar hemorrhage.

- Long K et al. Pulmonary toxicity of systemic lung cancer therapy. *Respirology*. 2020;25:72. [PMID: 32729207]  
 Suresh K. Immune checkpoint immunotherapy for non-small cell lung cancer: benefits and pulmonary toxicities. *Chest*. 2018;154:1416. [PMID: 301891190]

## RADIATION LUNG INJURY

The lung is an exquisitely radiosensitive organ that can be damaged by external beam radiation therapy. The degree of pulmonary injury is determined by the volume of lung irradiated, the dose and rate of exposure, and potentiating factors (eg, concurrent chemotherapy, previous radiation therapy in the same area, and simultaneous withdrawal of corticosteroid therapy). Symptomatic radiation lung injury occurs in about 10% of patients treated for carcinoma of the breast, 5–15% of patients treated for carcinoma of the lung, and 5–35% of patients treated for lymphoma. Two phases of the pulmonary response to radiation are apparent: an acute phase (radiation pneumonitis) and a chronic phase (radiation fibrosis).

### 1. Radiation Pneumonitis

Acute radiation pneumonitis usually occurs 2–3 months (range 1–6 months) after completion of radiotherapy and is characterized by insidious onset of dyspnea, intractable dry cough, chest fullness or pain, weakness, and fever. Late radiation pneumonitis may develop 6–12 months after completion of radiation. Occasionally, patients who are months to years removed from radiation therapy will experience “radiation recall” with an inflammatory reaction in the radiated region after treatment with a new round of chemotherapy; this phenomenon has also been reported with immune checkpoint inhibitors. The pathogenesis of acute radiation pneumonitis is unknown, but there is speculation that hypersensitivity mechanisms are involved. The dominant histopathologic findings are a lymphocytic interstitial pneumonitis progressing to an exudative alveolitis. Inspiratory crackles may be heard in the involved area. In severe disease, respiratory distress and cyanosis occur that are characteristic of ARDS. An increased white blood cell count and elevated sedimentation rate are common. Pulmonary function studies reveal reduced lung volumes, reduced lung compliance, hypoxemia, reduced diffusing capacity, and reduced maximum voluntary ventilation. Chest radiography, which correlates poorly with the presence of symptoms, usually demonstrates alveolar or nodular opacities limited to the irradiated area. Air bronchograms are often observed. Sharp borders of an opacity may help distinguish radiation pneumonitis from other conditions, such as infectious pneumonia, lymphangitic spread of carcinoma, and recurrent tumor; however, the opacity may extend beyond the radiation field. No specific therapy is proved to be effective in radiation pneumonitis, but prednisone (1 mg/kg/day orally) is commonly given immediately for about 1 week; higher doses may be given in patients who are critically ill. The dose is reduced and maintained at 20–40 mg/day for several weeks, then slowly tapered. Radiation pneumonitis may improve in 2–3 weeks following onset of symptoms as the exudative phase

resolves. Acute respiratory failure, if present, is treated supportively. Death from ARDS is unusual in radiation pneumonitis.

- Giuranno L et al. Radiation-induced lung injury (RILI). *Front Oncol*. 2019;9:877. [PMID: 31555602]
- Hanania AN et al. Radiation-induced lung injury: assessment and management. *Chest*. 2019;156:150. [PMID: 30998908]
- Kasemann L et al. Radiation-induced lung toxicity—cellular and molecular mechanisms of pathogenesis, management, and literature review. *Radiat Oncol*. 2020;15:214. [PMID: 32912295]
- Lu L et al. Radiation-induced lung injury: latest molecular developments, therapeutic approaches, and clinical guidance. *Clin Exp Med*. 2019;19:417. [PMID: 31313081]
- Teng F et al. Radiation recall pneumonitis induced by PD-1/PD-L1 blockades: mechanisms and therapeutic implications. *BMC Med*. 2020;18:275. [PMID: 32943072]

## 2. Pulmonary Radiation Fibrosis

Radiation fibrosis may occur with or without antecedent radiation pneumonitis. Radiographic findings include obliteration of normal lung markings, dense interstitial and pleural fibrosis, reduced lung volumes, tenting of the diaphragm, and sharp delineation of the irradiated area. No specific therapy is proven effective, and corticosteroids have no value. Pulmonary fibrosis may develop after an intervening period (6–12 months) of well-being in patients who experience radiation pneumonitis. Pulmonary radiation fibrosis occurs in most patients who receive a full course of radiation therapy for cancer of the lung or breast. Most patients are asymptomatic, although slowly progressive dyspnea may occur.

- Giuranno L et al. Radiation-induced lung injury (RILI). *Front Oncol*. 2019;9:877. [PMID: 31555602]

## 3. Other Complications of Radiation Therapy

Other complications of radiation therapy directed to the thorax include pericardial effusion, constrictive pericarditis, coronary artery disease, fibrotic damage to cardiac valves, tracheoesophageal fistula, esophageal candidiasis, radiation dermatitis, and rib fractures. Small pleural effusions, radiation pneumonitis outside the irradiated area, spontaneous pneumothorax, and complete obstruction of central airways are unusual occurrences.

- Giuranno L et al. Radiation-induced lung injury (RILI). *Front Oncol*. 2019;9:877. [PMID: 31555602]

## PLEURAL DISEASES

### PLEURITIS

Pleuritic pain due to inflammation of the parietal pleura is generally localized, sharp, and fleeting; it is made worse by coughing, sneezing, deep breathing, or movement. When the central portion of the diaphragmatic parietal pleura is irritated, pain may be referred to the ipsilateral shoulder.

There are numerous causes of pleuritis. The setting in which pleuritic pain develops helps narrow the differential diagnosis. In young, otherwise healthy individuals, pleuritis is usually caused by viral respiratory infections or pneumonia (including tuberculosis in endemic regions), while PE, inflammatory disorders (serositis), malignancy, and drug reactions may also be considered in the proper context. The presence of pleural effusion, pleural thickening, or air in the pleural space requires further diagnostic and therapeutic measures.

Treatment of pleuritis consists of treating the underlying condition. Anti-inflammatory analgesic medications are often helpful for pain relief. Opioids may be used if NSAIDs are ineffective or are contraindicated, provided retention of airway secretions is not a concern.

- Shaw JA et al. Pleural tuberculosis: a concise clinical review. *Clin Respir J*. 2018;12:1779. [PMID: 29660258]

## PLEURAL EFFUSION



### ESSENTIALS OF DIAGNOSIS

- ▶ May be asymptomatic; chest pain frequently seen in the setting of pleuritis, trauma, or infection; dyspnea is common with large effusions.
- ▶ Dullness to percussion and decreased breath sounds over the effusion.
- ▶ Radiographic evidence of pleural effusion.
- ▶ Diagnostic findings on thoracentesis.

## General Considerations

There is constant movement of fluid from parietal pleural capillaries into the pleural space at a rate of 0.01 mL/kg body weight/h. Absorption of pleural fluid occurs through parietal pleural lymphatics. The resultant homeostasis leaves 5–15 mL of fluid in the normal pleural space. A pleural effusion is an abnormal accumulation of fluid in the pleural space. Pleural effusions may be classified by differential diagnosis (Table 9–24) or by underlying pathophysiology. Five pathophysiologic processes account for most pleural effusions: increased production of fluid in the setting of normal capillaries due to increased hydrostatic or decreased oncotic pressures (**transudates**); increased production of fluid due to abnormal capillary permeability (**exudates**); decreased lymphatic clearance of fluid from the pleural space (**exudates**); infection in the pleural space (**empyema**); and bleeding into the pleural space (**hemothorax**).

**Diagnostic thoracentesis** should be performed whenever there is a new pleural effusion and no clinically apparent cause. Observation is appropriate in some situations (eg, symmetric bilateral pleural effusions in the setting of heart failure), but an atypical presentation or failure of an effusion to resolve as expected warrants thoracentesis to identify the underlying process.

**Table 9–24.** Causes of pleural fluid transudates and exudates.

| Transudates                    | Exudates  |
|--------------------------------|---|
| Heart failure                  | Pneumonia (parapneumonic effusion, including empyema) |
| Cirrhosis with ascites         | Cancer  |
| Nephrotic syndrome             | Pulmonary embolism                                    |
| Peritoneal dialysis            | Bacterial infection (including empyema)               |
| Myxedema                       | Tuberculosis  |
| Atelectasis (acute)            | Connective tissue disease                             |
| Constrictive pericarditis      | Viral infection                                       |
| Superior vena cava obstruction | Fungal infection                                      |
| Pulmonary embolism             | Rickettsial infection                                 |

## ► Clinical Findings

### A. Symptoms and Signs

Patients with pleural effusions most often report dyspnea, cough, or respirophasic chest pain. Symptoms are more common in patients with existing cardiopulmonary disease. Small pleural effusions are less likely to be symptomatic than larger effusions. Physical findings are usually absent in small effusions. Larger effusions may present with dullness to percussion and diminished or absent breath sounds over the effusion. Compressive atelectasis may cause bronchial breath sounds and egophony just above the effusion. A massive effusion with increased intrapleural pressure may cause contralateral shift of the trachea and bulging of the intercostal spaces. A pleural friction rub indicates pulmonary infarction or pleuritis.

### B. Laboratory Findings

The gross appearance of pleural fluid helps identify several types of pleural effusion. Grossly purulent fluid signifies empyema. Milky white pleural fluid should be centrifuged. A clear supernatant above a pellet of white cells indicates empyema, whereas a persistently turbid supernatant suggests a **chyloous effusion**; analysis of this supernatant reveals chylomicrons and a high triglyceride level (greater than 100 mg/dL [1 mmol/L]), often from disruption of the thoracic duct. **Hemorrhagic pleural effusion** is a mixture of blood and pleural fluid. Ten thousand red cells per microliter create blood-tinged pleural fluid; 100,000 red cells/mcL ( $100 \times 10^6/\text{L}$ ) create grossly bloody pleural fluid. **Hemothorax** is the presence of gross blood in the pleural

space, usually following chest trauma or instrumentation. It is defined as a ratio of pleural fluid hematocrit to peripheral blood hematocrit greater than 0.5.

Pleural fluid samples should be sent for measurement of protein, glucose, and LD in addition to total and differential white blood cell counts. Chemistry determinations are used to classify effusions as transudates or exudates. This classification is important because the differential diagnosis and subsequent evaluation for each entity varies (Table 9–24). A **pleural exudate** is an effusion that has one or more of the following laboratory features: (1) ratio of pleural fluid protein to serum protein greater than 0.5; (2) ratio of pleural fluid LD to serum LD greater than 0.6; (3) pleural fluid LD greater than two-thirds the upper limit of normal serum LD. Alternative diagnostic criteria that do not require the simultaneous sampling of serum but that perform similarly include the “two-test” (pleural fluid cholesterol greater than 45 mg/dL, pleural fluid LD greater than 0.45 times upper limit of normal serum LD) and the “three-test” (which adds pleural fluid protein greater than 2.9 g/dL). **Pleural transudates** occur in the setting of normal capillary integrity and demonstrate none of the laboratory features of exudates. A transudate suggests the absence of local pleural disease; characteristic laboratory findings include a glucose near to serum glucose, pH between 7.40 and 7.55 (if properly measured), and fewer than 1000 white blood cells/mcL ( $1.0 \times 10^9/\text{L}$ ) with a predominance of mononuclear cells. It is worthwhile to note that discrimination of exudate from transudate is less reliable near the cutoff values for any of the criteria, and that effective diuresis may increase the protein or LD concentration in the pleural fluid as water is reabsorbed, thus creating a borderline “pseudoexudative” chemistry in transudative states such as heart failure.

Heart failure accounts for the majority of transudates. Bacterial pneumonia, cancer, and tuberculosis (in endemic regions) are the most common causes of exudative effusion. Other causes of exudates with characteristic laboratory findings are summarized in Table 9–25.

Pleural fluid pH (normal = 7.60) is useful in the assessment of parapneumonic effusions, provided that it can be reliably measured, and is more useful than glucose measurement in determining need for drainage. A pH less than 7.20 suggests the need for drainage of the pleural space. An elevated amylase level in pleural fluid suggests pancreatitis, pancreatic pseudocyst, adenocarcinoma of the lung or pancreas, or esophageal rupture.

Suspected tuberculous pleural effusion should be evaluated by thoracentesis with culture, although pleural fluid culture positivity for *M tuberculosis* is low. Tests for pleural fluid adenosine deaminase (approximately 90% sensitivity and specificity for pleural tuberculosis at levels greater than 60 units/L, tuberculosis rare if level is less than 40 units/L) and interferon-gamma (89% sensitivity, 97% specificity in a meta-analysis) can be helpful diagnostic aids, particularly in making decisions to pursue invasive testing in complex patients. Closed pleural biopsy is more sensitive than pleural fluid culture for diagnosis, revealing granulomatous inflammation in approximately 60% of patients, and culture of three pleural biopsy specimens combined with

**Table 9–25.** Characteristics of important exudative pleural effusions.

| Etiology or Type of Effusion | Gross Appearance                      | White Blood Cell Count (cells/mcL)  | Red Blood Cell Count (cells/mcL)  | Glucose  | Comments   |
|------------------------------|---------------------------------------|---|---|--|--|
| Malignancy                   | Turbid to bloody; occasionally serous | 1000–100,000<br>(1.0–100 × 10 <sup>9</sup> /L)<br>M                             | 100 (0.1 × 10 <sup>9</sup> /L) to several hundred thousand                | Equal to serum levels;<br>< 60 mg/dL in 15% of cases | Eosinophilia uncommon; positive results on cytologic examination   |
| Uncomplicated parapneumonic  | Clear to turbid                       | 5000–25,000<br>(5.0–25 × 10 <sup>9</sup> /L)<br>P                               | < 5000 (5.0 × 10 <sup>9</sup> /L)   | Equal to serum levels                                | Tube thoracostomy unnecessary  |
| Empyema                      | Turbid to purulent                    | 25,000–100,000<br>(25–100 × 10 <sup>9</sup> /L)<br>P                            | < 5000 (5.0 × 10 <sup>9</sup> /L)   | Less than serum levels; often very low               | Drainage necessary; putrid odor suggests anaerobic infection   |
| Tuberculosis                 | Serous to serosanguineous             | 5000–10,000<br>(5.0–10 × 10 <sup>9</sup> /L)<br>M                               | < 10,000 (10 × 10 <sup>9</sup> /L)  | Equal to serum levels; occasionally < 60 mg/dL       | Protein > 4.0 g/dL (may exceed 5 g/dL); frequently lymphocyte predominant (> 50%); eosinophils (> 10%) or mesothelial cells (> 5%) make diagnosis unlikely; see text for additional diagnostic tests |
| Rheumatoid                   | Turbid; greenish yellow               | 1000–20,000<br>(1.0–20 × 10 <sup>9</sup> /L)<br>M or P                          | < 1000 (1.0 × 10 <sup>9</sup> /L)   | < 40 mg/dL   | Secondary empyema common; high LD, low complement, high rheumatoid factor, cholesterol crystals are characteristic   |
| Pulmonary infarction         | Serous to grossly bloody              | 1000–50,000<br>(1.0–50 × 10 <sup>9</sup> /L)<br>M or P                          | 100 (0.1 × 10 <sup>9</sup> /L) to > 100,000<br>(100 × 10 <sup>9</sup> /L) | Equal to serum levels                                | Variable findings; no pathognomonic features   |
| Esophageal rupture           | Turbid to purulent; red-brown         | < 5000 (5.0 × 10 <sup>9</sup> /L) to > 50,000<br>(50 × 10 <sup>9</sup> /L)<br>P | 1000–10,000<br>(10–10 × 10 <sup>9</sup> /L)                               | Usually low  | High amylase level (salivary origin); pneumothorax in 25% of cases; effusion usually on left side; pH < 6.0 strongly suggests diagnosis  |
| Pancreatitis                 | Turbid to serosanguineous             | 1000–50,000<br>(1.0–50 × 10 <sup>9</sup> /L)<br>P                               | 1000–10,000<br>(1.0–10 × 10 <sup>9</sup> /L)                              | Equal to serum levels                                | Usually left-sided; high amylase level   |

LD, lactate dehydrogenase; M, mononuclear cell predominance; P, polymorphonuclear leukocyte predominance.

histologic examination of a pleural biopsy for granulomas yields a diagnosis in up to 90% of patients.

Between 40% and 80% of exudative pleural effusions are malignant, while over 90% of malignant pleural effusions are exudative. Almost any form of cancer may cause effusions, but the most common causes are lung cancer (one-third of cases) and breast cancer. In 5–10% of malignant pleural effusions, no primary tumor is identified.

Pleural fluid specimens should be sent for cytologic examination in all cases of exudative effusions in patients suspected of harboring an underlying malignancy. The diagnostic yield depends on the nature and extent of the underlying malignancy. Sensitivity is between 50% and 65% and increases with serial sampling. In a patient with a high prior probability of malignancy, a negative cytologic examination should be followed by one repeat thoracentesis. If that examination is negative, thoracoscopy is preferred to closed pleural biopsy. The sensitivity of thoracoscopy is 92–96%.

The term **paramalignant** pleural effusion refers to an effusion in a patient with cancer when repeated attempts to identify tumor cells in the pleura or pleural fluid are non-diagnostic but when there is a presumptive relation to the underlying malignancy. For example, superior vena cava syndrome with elevated systemic venous pressures causing a transudative effusion would be “paramalignant.”

### C. Imaging

The lung is less dense than water and floats on pleural fluid that accumulates in dependent regions. Subpulmonic fluid may appear as lateral displacement of the apex of the diaphragm with an abrupt slope to the costophrenic sulcus or a greater than 2-cm separation between the gastric air bubble and the lung. On a standard upright chest radiograph (Figure 9–7), approximately 75–100 mL of pleural fluid must accumulate in the posterior costophrenic sulcus



▲ **Figure 9–7.** Left pleural effusion. Frontal chest radiograph showing a meniscus-shaped density at the left costophrenic angle sulcus indicative of a moderate-sized pleural effusion. (Reproduced, with permission, from Lechner AJ, Matuschak GM, Brink DS. *Respiratory: An Integrated Approach to Disease*. McGraw-Hill, 2012.)

to be visible on the lateral view, and 175–200 mL must be present in the lateral costophrenic sulcus to be visible on the frontal view. Chest CT scans may identify as little as 10 mL of fluid. At least 1 cm of fluid on the decubitus view is necessary to permit blind thoracentesis. Ultrasonography increases the safety of thoracentesis and should be incorporated routinely by trained users.

Pleural fluid may become trapped (loculated) by pleural adhesions, thereby forming unusual collections along the lateral chest wall or within lung fissures. Round or oval fluid collections in fissures that resemble intraparenchymal masses are called pseudotumors.

## ► Treatment

### A. Transudative Pleural Effusion

Transudative pleural effusions characteristically occur in the absence of pleural disease. Therefore, treatment is directed at the underlying condition. Therapeutic thoracentesis for severe dyspnea typically offers only transient benefit. Pleurodesis or indwelling pleural catheters are rarely indicated but are appropriate for management of symptoms in selected patients whose symptoms respond to drainage and whose effusions are refractory to maximal medical therapy.

### B. Malignant Pleural Effusion

Chemotherapy, radiation therapy, or both offer temporary control in some malignant effusions but are generally ineffective in lung cancer in the pleural space except for small-cell lung cancer. Asymptomatic malignant effusions usually do not require specific treatment. Symptomatic patients should be offered pleural drainage, either via initial

therapeutic thoracentesis to determine symptomatic response to drainage, following which an indwelling pleural catheter can be placed, or via immediate placement of an indwelling pleural catheter. Indwelling pleural catheter placement is associated with shorter hospital stays than pleurodesis. Indwelling pleural catheters often effect a pleurodesis over time, at which point the catheter can be removed.

### C. Parapneumonic Pleural Effusion

Parapneumonic pleural effusions are divided into three categories, the classification of which can only be determined by sampling the fluid: simple or uncomplicated, complicated, and empyema. **Uncomplicated parapneumonic effusions** are free-flowing sterile exudates of modest size that resolve quickly with antibiotic treatment of pneumonia. They do not need drainage.

**Complicated parapneumonic effusions** present the most difficult management decisions. They tend to be larger than simple parapneumonic effusions and to show more evidence of inflammatory stimuli, such as low glucose level, low pH, or evidence of loculation. Inflammation probably reflects ongoing bacterial invasion of the pleural space despite rare positive bacterial cultures. Tube thoracostomy is indicated when pleural fluid glucose is less than 60 mg/dL (less than 3.3 mmol/L) or the pH is less than 7.2. These thresholds have not been prospectively validated and should not be interpreted strictly. The clinician should consider drainage of a complicated effusion if the pleural fluid pH is between 7.2 and 7.3 or the LD is greater than 1000 units/L (greater than 20 mckat/L). Pleural fluid cell count and protein have little diagnostic value in this setting.

**Empyema** is gross infection of the pleural space indicated by positive Gram stain or culture. Empyema should be drained, and the patient referred to a thoracic specialist to determine whether tube thoracostomy versus decortication is needed to facilitate clearance of infection and to reduce the probability of permanent fibrous encasement of the lung.

Tube thoracostomy drainage of empyema or complicated parapneumonic effusions is frequently complicated by loculation that prevents adequate drainage. Intrapleural instillation of fibrinolytic agents alone has not been shown in controlled trials to improve drainage. The combination of intrapleural tissue plasminogen activator and deoxyribonuclease (DNase), an enzyme that catalyzes extracellular DNA and degrades biofilm formation within the pleural cavity, has been found to improve clinical outcome (increased drainage, decreased length of stay, and decreased surgical referral) compared with placebo or either agent alone, and should be considered when fever, leukocytosis, or anorexia persist despite antibiotics and tube thoracostomy, or when the lung fails to reexpand.

### D. Hemothorax

A small-volume hemothorax that is stable or improving on chest radiographs may be managed by close observation. In all other cases, hemothorax is treated by immediate insertion of a thoracostomy tube to (1) drain existing blood and clot, (2) quantify the amount of bleeding, (3) reduce the risk

of fibrothorax, and (4) permit apposition of the pleural surfaces in an attempt to reduce hemorrhage. Thoracic surgery consultation is indicated. Thoracotomy may be required to control hemorrhage, remove clot, and treat complications.

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## PNEUMOTHORAX



### ESSENTIALS OF DIAGNOSIS

- ▶ Acute onset of unilateral chest pain and dyspnea.
- ▶ Minimal physical findings in mild cases; unilateral chest expansion, decreased tactile fremitus, hyperresonance, diminished breath sounds, mediastinal shift, cyanosis and hypotension in tension pneumothorax.
- ▶ Presence of pleural air on chest radiograph.

### ► General Considerations

Pneumothorax, or accumulation of air in the pleural space, is classified as spontaneous (primary or secondary), traumatic, or iatrogenic. **Primary spontaneous pneumothorax** occurs in the absence of an underlying lung disease, whereas **secondary spontaneous pneumothorax** is a complication of preexisting pulmonary disease. **Traumatic pneumothorax** results from penetrating or blunt trauma and includes **iatrogenic pneumothorax** following procedures, such as thoracentesis, pleural biopsy, subclavian or internal jugular vein catheter placement, percutaneous lung biopsy, bronchoscopy with transbronchial biopsy, and positive-pressure mechanical ventilation. **Tension pneumothorax** usually occurs in the setting of penetrating trauma, lung infection, cardiopulmonary resuscitation, or positive-pressure mechanical ventilation. In tension pneumothorax, the pressure of air in the pleural space exceeds alveolar and venous pressures throughout the respiratory cycle, resulting in compression of lung and reduction of venous return to the hemithorax; a check-valve mechanism may allow air to enter the pleural space on inspiration and to prevent egress of air on expiration.

Primary spontaneous pneumothorax is more likely among tall, thin individuals, more common in men, typically occurring at a young age (less than 45 years). It is thought to occur from rupture of subpleural apical blebs in

response to high negative intrapleural pressures. Cigarette smoking is correlated with occurrence of primary spontaneous pneumothorax, as are connective tissue disorders such as Marfan and Ehlers-Danlos syndromes.

Secondary pneumothorax occurs as a complication of COPD, interstitial lung disease, asthma, cystic fibrosis, tuberculosis, *Pneumocystis* pneumonia, necrotizing bacterial pneumonia, menstruation (catamenial pneumothorax), and a wide variety of cystic lung diseases, including lymphangioleiomyomatosis, tuberous sclerosis, Langerhans cell histiocytosis, and Birt-Hogg-Dube syndrome (a hereditary condition with multiple benign skin tumors, lung cysts, and increased risk of both benign and malignant kidney tumors). Secondary pneumothorax, particularly in patients with underlying symptomatic lung disease, is more poorly tolerated due to the decreased respiratory reserve in this group.

### ► Clinical Findings

#### A. Symptoms and Signs

Chest pain ranging from minimal to severe on the affected side and dyspnea occur in nearly all patients, and cough is commonly reported. Pneumothorax may present with life-threatening respiratory failure if underlying lung disease is present or if tension pneumothorax physiology ensues.

If pneumothorax is small (less than 15% of a hemithorax), physical findings, other than mild tachycardia, are normal. If pneumothorax is large, diminished breath sounds, decreased tactile fremitus, decreased movement of the chest, and hyperresonant percussion note are often found. Tension pneumothorax should be suspected in the presence of marked tachycardia, hypotension, and mediastinal or tracheal shift.

#### B. Laboratory Findings

ABG analysis is often unnecessary but reveals hypoxemia and acute respiratory alkalosis in most patients. Left-sided primary pneumothorax may produce QRS axis and precordial T-wave changes on the ECG that may be misinterpreted as acute myocardial infarction.

#### C. Imaging

Demonstration on chest radiograph of lucency without lung markings between the chest wall and lung, and visualization of the visceral pleura (a “pleural line”) is diagnostic. A few patients have secondary pleural effusion that demonstrates a characteristic air-fluid level on chest radiography. In supine patients, pneumothorax on a conventional chest radiograph may appear as an abnormally radiolucent costophrenic sulcus (the “deep sulcus” sign). In patients with tension pneumothorax, chest radiographs show a large amount of air in the affected hemithorax and contralateral shift of the mediastinum.

Chest ultrasonography, performed at the bedside by experienced clinicians or technicians, demonstrates characteristic findings in the region of the pneumothorax. These findings include absent “lung sliding” or absent “lung pulse,” or presence of a “lung point,” all of which demonstrate a

region of lung where the parietal and visceral pleural are not in normal apposition. Ultrasound may be more sensitive than supine chest radiograph (supine positioning necessitated by clinical circumstance) for detecting pneumothorax in trauma patients, and is frequently used in critical care, though comparisons of ultrasound to chest radiograph or to CT scan report variable test characteristics.

High-resolution CT may be considered with the first spontaneous pneumothorax to evaluate for underlying cystic lung disease.

## Differential Diagnosis

If the patient is young with typical clinical characteristics, the diagnosis of primary spontaneous pneumothorax is usually obvious and can be confirmed by chest radiograph. Occasionally, pneumothorax may mimic myocardial infarction, pulmonary embolism, or pneumonia.

## Complications

Tension pneumothorax may be life-threatening. Pneumomediastinum and subcutaneous emphysema may occur as complications of spontaneous pneumothorax. If pneumomediastinum is detected, rupture of the esophagus or a bronchus should be considered in the differential diagnosis.

## Treatment

Treatment depends on the severity of the pneumothorax and the nature of the underlying disease. In a reliable patient with a stable, spontaneous primary pneumothorax, observation alone may be appropriate; many cases resolve spontaneously as air is absorbed from the pleural space. In fact, a 2020 US study demonstrated that even moderate to large pneumothoraces in a stable patient (no oxygen requirement, no limitation to ambulation, and no increase in size of pneumothorax over 4 hours of monitoring) can be managed without intervention provided the patient is reliable. Simple aspiration drainage of pleural air with a small-bore catheter (eg, 16-gauge angiocatheter or larger drainage catheter) can be performed for spontaneous primary pneumothoraces that are large or progressive. Placement of a small-bore chest tube (7F to 14F) attached to a one-way Heimlich valve provides protection against development of tension pneumothorax and may permit observation from home. The patient should be treated symptomatically for cough and chest pain and monitored with serial chest radiographs every 24 hours.

Patients with secondary pneumothorax, tension pneumothorax, or severe symptoms or those who have a pneumothorax on mechanical ventilation should undergo chest tube placement (tube thoracostomy). The chest tube is placed under water-seal drainage, and suction is applied until the lung expands. The chest tube can be removed after the air leak subsides.

All patients who smoke should be advised to discontinue smoking and warned that the risk of recurrence is higher if cigarette smoking is continued.

Indications for surgical management (video-assisted thoracoscopic surgery) include recurrences of spontaneous

pneumothorax, any occurrence of bilateral pneumothorax, and failure of tube thoracostomy for the first episode (failure of lung to reexpand or persistent air leak). Surgical intervention is also generally recommended for any patient with a secondary pneumothorax (presence of underlying lung disease) because the risk of recurrence is high, and the consequences of recurrences are greater. Surgery permits resection or repair of blebs or bullae responsible for the pneumothorax as well as mechanical or chemical pleurodesis. Patients who are not acceptable surgical candidates can be treated with chemical pleurodesis via a chest tube.

## Prognosis

An average of 30% of patients with spontaneous pneumothorax experience recurrence of the disorder after either observation or tube thoracostomy for the first episode. Recurrence after surgical therapy is less frequent. Following successful therapy, there are no long-term complications. Secondary pneumothorax has up to a 50% likelihood of recurrence following the first event if surgical intervention is not undertaken.

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## DISORDERS OF CONTROL OF VENTILATION

The principal influences on ventilatory control are arterial  $\text{PCO}_2$ , pH,  $\text{PO}_2$ , and brainstem tissue pH. These variables are monitored by peripheral and central chemoreceptors. Under normal conditions, the ventilatory control system maintains arterial pH and  $\text{PCO}_2$  within narrow limits; arterial  $\text{PO}_2$  is more loosely controlled.

Abnormal control of ventilation can be seen with a variety of conditions ranging from rare disorders, such as primary alveolar hypoventilation, neuromuscular disorders, myxedema, starvation, and carotid body resection to more common disorders, such as asthma, COPD, obesity, heart failure, and sleep-related breathing disorders. A few of these disorders will be discussed in this section.

## HYPERVENTILATION SYNDROMES

Hyperventilation is an increase in alveolar minute ventilation that leads to hypcapnia. It may be caused by a variety of conditions, such as pregnancy, hypoxemia, obstructive and infiltrative lung diseases, sepsis, liver dysfunction, fever, and pain. Functional hyperventilation may be acute or chronic. **Acute hyperventilation** presents with

hyperpnea, anxiety, paresthesias, carpopedal spasm, and tetany. **Chronic hyperventilation** may present with various nonspecific symptoms, including fatigue, dyspnea, anxiety, palpitations, and dizziness. The diagnosis of chronic hyperventilation syndrome is established if symptoms are reproduced during voluntary hyperventilation. Once organic causes of hyperventilation have been excluded, treatment of acute hyperventilation consists of breathing through pursed lips or through the nose with one nostril pinched or rebreathing expired gas from a paper bag held over the face in order to decrease respiratory alkalemia and its associated symptoms. Anxiolytic drugs may also be useful.

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## OBESITY-HYPOVENTILATION SYNDROME (Pickwickian Syndrome)

In obesity-hypoventilation syndrome, awake alveolar hypoventilation appears to result from a combination of blunted ventilatory drive and increased mechanical load imposed upon the chest by obesity. Voluntary hyperventilation returns the  $\text{PCO}_2$  and the  $\text{PO}_2$  toward normal values, a correction not seen in lung diseases causing chronic respiratory failure, such as COPD. Diagnostic criteria include a body mass index greater than 30, an arterial partial pressure of carbon dioxide greater than 45 mm Hg, and exclusion of other causes of alveolar hypoventilation. Most patients with obesity-hypoventilation syndrome also suffer from obstructive sleep apnea, which must be treated aggressively if identified as a comorbid disorder. Therapy of obesity-hypoventilation syndrome consists mainly of weight loss, which improves hypercapnia and hypoxemia as well as the ventilatory responses to hypoxia and hypercapnia. Avoidance of sedative-hypnotics, opioids, and alcohol is also recommended. NIPPV is helpful in many patients. Patients with obesity-hypoventilation syndrome have a higher risk of complications in the perioperative period, including respiratory failure, intubation, and cardiac failure. Recognition of these patients in the perioperative period is an important safety measure.

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## SLEEP-RELATED BREATHING DISORDERS

Abnormal ventilation during sleep is manifested by apnea (breath cessation for at least 10 seconds) or hypopnea (decrement in airflow with drop in hemoglobin saturation of at

least 4%). Episodes of apnea are **central** if ventilatory effort is absent for the duration of the apneic episode, **obstructive** if ventilatory effort persists throughout the apneic episode but no airflow occurs because of transient obstruction of the upper airway, and **mixed** if absent ventilatory effort precedes upper airway obstruction during the apneic episode. Pure central sleep apnea is uncommon; it may be an isolated finding or may occur in patients with primary alveolar hypoventilation or with lesions of the brainstem. Obstructive and mixed sleep apneas are more common and may be associated with life-threatening cardiac arrhythmias, severe hypoxemia during sleep, daytime somnolence, pulmonary hypertension, cor pulmonale, systemic hypertension, and secondary erythrocytosis.

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## OBSTRUCTIVE SLEEP APNEA



### ESSENTIALS OF DIAGNOSIS

- ▶ Daytime somnolence or fatigue.
- ▶ A history of loud snoring with witnessed apneic events.
- ▶ Overnight polysomnography demonstrating apneic episodes with hypoxemia.

### General Considerations

Upper airway obstruction during sleep occurs when loss of normal pharyngeal muscle tone allows the pharynx to collapse passively during inspiration. Patients with anatomically narrowed upper airways (eg, micrognathia, macroglossia, obesity, tonsillar hypertrophy) are predisposed to the development of obstructive sleep apnea. Ingestion of alcohol or sedatives before sleeping or nasal obstruction of any type, including the common cold, may precipitate or worsen the condition. Hypothyroidism and cigarette smoking are additional risk factors for obstructive sleep apnea. Before making the diagnosis of obstructive sleep apnea, a drug history should be obtained and a seizure disorder, narcolepsy, and depression should be excluded.

### Clinical Findings

#### A. Symptoms and Signs

Most patients with obstructive or mixed sleep apnea are obese, middle-aged men. Arterial hypertension is common. Patients may complain of excessive daytime somnolence, morning sluggishness and headaches, daytime fatigue, cognitive impairment, recent weight gain, and impotence. Bed partners usually report loud cyclical

snoring, breath cessation, witnessed apneas, restlessness, and thrashing movements of the extremities during sleep. Personality changes, poor judgment, work-related problems, depression, and intellectual deterioration (memory impairment, inability to concentrate) may also be observed. The US Preventive Services Task Force does not recommend screening asymptomatic adults for sleep apnea.

Physical examination may be normal or may reveal systemic and pulmonary hypertension with cor pulmonale. The patient may appear sleepy or even fall asleep during the evaluation. The oropharynx is frequently found to be narrowed by excessive soft tissue folds, large tonsils, elongated uvula, or prominent tongue. Nasal obstruction by a deviated nasal septum, poor nasal airflow, and a nasal twang to the speech may be observed. A “bull neck” appearance is common.

### B. Laboratory Findings

Erythrocytosis is common. Thyroid function tests (serum TSH, FT<sub>4</sub>) should be obtained to exclude hypothyroidism.

### C. Other Studies

Observation of the sleeping patient may reveal loud snoring interrupted by episodes of increasingly strong ventilatory effort that fail to produce airflow. A loud snort often accompanies the first breath following an apneic episode. Definitive diagnostic evaluation for suspected sleep apnea includes otorhinolaryngologic examination and overnight polysomnography (the monitoring of multiple physiologic factors during sleep). A complete polysomnography examination includes electroencephalography, electrooculography, electromyography, ECG, pulse oximetry, and measurement of respiratory effort and airflow. Polysomnography reveals apneic episodes lasting as long as 60 seconds. Oxygen saturation falls, often to very low levels. Bradydysrhythmias, such as sinus bradycardia, sinus arrest, or atrioventricular block, may occur. Tachydysrhythmias, including paroxysmal supraventricular tachycardia, atrial fibrillation, and ventricular tachycardia, may be seen once airflow is reestablished. Home sleep studies can be done for the person without comorbidities and a moderate to high pretest probability of obstructive sleep apnea. While home studies cannot quantify the stages of sleep, they can provide a reliable index of respiratory and desaturation events.

## Treatment

**Weight loss** and strict avoidance of alcohol and hypnotic medications are the first steps in management. Weight loss may be curative, but most patients are unable to lose the 10–20% of body weight required. **Continuous positive airway pressure (CPAP)** at night is curative in many patients. Auto-titrating CPAP machines allow a range of pressures to be prescribed (5–15 cm H<sub>2</sub>O). Polysomnography is frequently necessary to optimize the level of CPAP necessary to abolish obstructive apneas and manage hypoxemia. Unfortunately, only about 75% of patients continue to use nasal CPAP after 1 year. Supplemental oxygen may lessen the severity of nocturnal desaturation but may also lengthen apneas; it should not be routinely prescribed without polysomnography to assess the effects of oxygen

therapy. Mechanical devices inserted into the mouth at bedtime to hold the jaw forward and prevent pharyngeal occlusion have modest effectiveness in relieving apnea; however, patient compliance is not optimal.

**Uvulopalatopharyngoplasty (UPPP)**, a procedure consisting of resection of pharyngeal soft tissue and amputation of approximately 15 mm of the free edge of the soft palate and uvula, is helpful in approximately 50% of selected patients. It is more effective in eliminating snoring than apneic episodes. UPPP may be performed on an outpatient basis with a laser. **Nasal septoplasty** is performed if gross anatomic nasal septal deformity is present. **Tracheostomy** relieves upper airway obstruction and its physiologic consequences and represents the definitive treatment for obstructive sleep apnea. However, it has numerous adverse effects, including granuloma formation, difficulty with speech, and stoma and airway infection. Furthermore, the long-term care of the tracheostomy, especially in obese patients, can be difficult. Tracheostomy and other maxillofacial surgery approaches are reserved for patients with life-threatening arrhythmias or severe disability who have not responded to conservative therapy. **Hypoglossal nerve stimulation** can be an option for select patients who do not respond to CPAP and have certain anatomic features, including non-concentric airway collapse; a 5-year follow-up study showed improvement in sleepiness, quality of life, and respiratory outcomes in the treatment cohort. For patients who are unable or unwilling to use CPAP, and who may not be surgical candidates, the H<sub>3</sub>-receptor antagonist/inverse agonist pitolisant has been shown to improve sleepiness and fatigue. Full normalization of breathing patterns is not necessarily the therapeutic goal. A randomized trial of adaptive servo-ventilation in sleep apnea patients with predominant central apnea and impaired left ventricular ejection fraction (less than 45%) reported increased cardiovascular and all-cause mortality in the treatment group.

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## ACUTE RESPIRATORY FAILURE

Respiratory failure is defined as respiratory dysfunction resulting in abnormalities of oxygenation or ventilation (CO<sub>2</sub> elimination) severe enough to threaten the function of vital organs. ABG criteria for respiratory failure are not absolute but may be arbitrarily established as a Po<sub>2</sub> under

60 mm Hg (7.8 kPa) or a  $\text{PCO}_2$  over 50 mm Hg (6.5 kPa). Acute respiratory failure may occur in a variety of pulmonary and nonpulmonary disorders (Table 9–26). Only a few selected general principles of management will be reviewed here.

## Clinical Findings

Symptoms and signs of acute respiratory failure are those of the underlying disease combined with those of

**Table 9–26.** Selected causes of acute respiratory failure in adults.

| Airway disorders   | Neuromuscular and related disorders   |
|--|---|
| Asthma   | Primary neuromuscular diseases  |
| Acute exacerbation of chronic bronchitis or emphysema  | Guillain-Barré syndrome   |
| Obstruction of pharynx, larynx, trachea, mainstem bronchus, or lobar bronchus by edema, mucus, mass, or foreign body | Myasthenia gravis   |
| Pulmonary edema  | Poliomyelitis   |
| Increased hydrostatic pressure   | Polymyositis  |
| Left ventricular dysfunction (eg, myocardial ischemia, heart failure)  | Drug- or toxin-induced  |
| Mitral regurgitation   | Botulism  |
| Left atrial outflow obstruction (eg, mitral stenosis)  | Organophosphates  |
| Volume overload states   | Neuromuscular blocking agents   |
| Increased pulmonary capillary permeability   | Aminoglycosides   |
| Acute respiratory distress syndrome  | Spinal cord injury  |
| Acute lung injury  | Phrenic nerve injury or dysfunction   |
| Unclear etiology   | Electrolyte disturbances  |
| Neurogenic   | Hypokalemia   |
| Negative pressure (inspiratory airway obstruction)   | Hypophosphatemia  |
| Re-expansion   | Myxedema  |
| Tocolytic-associated   |   |
| Parenchymal lung disorders   | <b>Central nervous system disorders</b>   |
| Pneumonia  | Drugs: sedatives, hypnotics, opioids, anesthetics   |
| Interstitial lung diseases   | Brainstem respiratory center disorders: trauma, tumor, vascular disorders, hypothyroidism |
| Diffuse alveolar hemorrhage syndromes  | Intracranial hypertension   |
| Aspiration   | Central nervous system infections   |
| Lung contusion   |   |
| Pulmonary vascular disorders   | <b>Increased <math>\text{CO}_2</math> production</b>                                      |
| Thromboembolism  | Fever   |
| Air embolism   | Infection   |
| Amniotic fluid embolism  | Hyperalimentation with excess caloric and carbohydrate intake                             |
| Chest wall, diaphragm, and pleural disorders   | Hyperthyroidism   |
| Rib fracture   | Seizures  |
| Flail chest  | Rigors  |
| Pneumothorax   | Drugs   |
| Pleural effusion   |   |
| Massive ascites  |   |
| Abdominal distention and abdominal compartment syndrome  |   |

hypoxemia or hypercapnia. The chief symptom of hypoxemia is dyspnea, though profound hypoxemia may exist in the absence of complaints. Signs of hypoxemia include cyanosis, restlessness, confusion, anxiety, delirium, tachypnea, bradycardia or tachycardia, hypotension or hypertension, cardiac dysrhythmias, and tremor. Dyspnea and headache are the cardinal symptoms of hypercapnia. Signs of hypercapnia include peripheral and conjunctival hyperemia, hypertension, tachycardia, tachypnea, impaired consciousness, papilledema, myoclonus, and asterixis. The symptoms and signs of acute respiratory failure are both insensitive and nonspecific; therefore, the clinician must maintain a high index of suspicion and obtain ABG analysis if respiratory failure is suspected.

## Treatment

Treatment of the patient with acute respiratory failure consists of (1) specific therapy directed toward the underlying disease, (2) respiratory supportive care directed toward the maintenance of adequate gas exchange, and (3) general supportive care. Only the last two aspects are discussed below.

### A. Respiratory Support

Respiratory support has both nonventilatory and ventilatory aspects.

**1. Nonventilatory aspects**—The main therapeutic goal in acute hypoxic respiratory failure is to ensure adequate oxygenation of vital organs. Inspired oxygen concentration should be the lowest value that results in an arterial hemoglobin saturation of 88% or more ( $\text{Po}_2$  55 mm Hg or more [7.3 kPa or more]). Higher arterial oxygen tensions are of no proven benefit and may be deleterious. Restoration of normoxemia may rarely cause hypoventilation in patients with chronic hypercapnia; however, oxygen therapy should not be withheld for fear of causing progressive respiratory acidemia. Hypoxemia in patients with obstructive airway disease is usually easily corrected by administering low-flow oxygen by nasal cannula (1–3 L/min) or Venturi mask (24–40%). Higher concentrations of oxygen are necessary to correct hypoxemia in patients with ARDS, pneumonia, and other parenchymal lung diseases. Humidified, high-flow nasal cannulae provide adjustable oxygen delivery and flow-dependent clearance of carbon dioxide from the upper airway, resulting in reduced work of breathing and better matching of respiratory demand during respiratory distress. In hypoxemia due to acute respiratory failure, oxygenation with use of humidified, high-flow nasal cannulae has been shown to be similar and, in some cases, superior to conventional low-flow oxygen supplementation and to NIPPV.

**2. Ventilatory aspects**—Ventilatory support consists of maintaining patency of the airway and ensuring adequate alveolar ventilation. Mechanical ventilation may be provided via mask (noninvasive) or through tracheal intubation.

**A. NONINVASIVE POSITIVE-PRESSURE VENTILATION**—NIPPV delivered via a full-face mask or nasal mask

is first-line therapy in COPD patients with hypercapnic respiratory failure who can protect and maintain the patency of their airway, handle their own secretions, and tolerate the mask apparatus. Several studies have demonstrated the effectiveness of this therapy in reducing intubation rates and ICU stays in patients with ventilatory failure. A bilevel positive-pressure ventilation mode is preferred for most patients. Patients with acute lung injury or ARDS or those who suffer from severely impaired oxygenation are less likely to benefit and should be intubated if they require mechanical ventilation.

**B. TRACHEAL INTUBATION**—Indications for tracheal intubation include (1) hypoxemia despite supplemental oxygen; (2) upper airway obstruction; (3) impaired airway protection; (4) inability to clear secretions; (5) respiratory acidosis; (6) progressive general fatigue, tachypnea, use of accessory respiratory muscles, or mental status deterioration; and (7) apnea. Patients in respiratory failure who undergo a trial of NIPPV and do not improve within 30–90 minutes should be intubated. In general, orotracheal intubation is preferred to nasotracheal intubation in urgent or emergency situations because it is easier, faster, and less traumatic. The tip of the endotracheal tube should be positioned 2–4 cm above the carina and be verified by chest radiograph immediately following intubation. Only tracheal tubes with high-volume, low-pressure air-filled cuffs should be used. Cuff inflation pressure should be kept below 20 mm Hg, if possible, to minimize tracheal mucosal injury.

**C. MECHANICAL VENTILATION**—Indications for mechanical ventilation include (1) apnea, (2) acute hypercapnia that is not quickly reversed by appropriate specific therapy, (3) severe hypoxemia, and (4) progressive patient fatigue despite appropriate treatment.

Several modes of positive-pressure ventilation are available. Controlled mechanical ventilation (CMV; also known as assist-control [A-C]) and synchronized intermittent mandatory ventilation (SIMV) are ventilatory modes in which the ventilator delivers a minimum number of breaths of a specified tidal volume each minute. In both CMV and SIMV, the patient may trigger the ventilator to deliver additional breaths. In CMV, the ventilator responds to breaths initiated by the patient above the set rate by delivering additional full tidal volume breaths. In SIMV, additional breaths are not supported by the ventilator unless the pressure support mode is added. Numerous alternative modes of mechanical ventilation now exist, the most popular being pressure support ventilation (PSV), pressure control ventilation (PCV), and CPAP.

PEEP is useful in improving oxygenation in patients with diffuse parenchymal lung disease, such as ARDS. It should be used cautiously in patients with localized parenchymal disease, emphysema, hyperinflation, or very high airway pressure requirements during mechanical ventilation.

**D. COMPLICATIONS OF MECHANICAL VENTILATION**—Potential complications of mechanical ventilation are numerous. Migration of the tip of the endotracheal tube into a main bronchus can cause atelectasis of the contralateral lung and overdistention of the intubated lung.

Barotrauma refers to rupture and loss of integrity of the alveolar space secondary to high transmural pressures applied during positive-pressure ventilation. Barotrauma is manifested by subcutaneous emphysema, pneumomediastinum, subpleural air cysts, pneumothorax, or systemic gas embolism. Volutrauma is sometimes used to refer to subtle parenchymal injury due to overdistention of alveoli from excessive tidal volumes without alveolar rupture, mediated through inflammatory rather than physical mechanisms. The principal strategy to avoid volutrauma is the use of low tidal volume ventilation (a tidal volume of 6 mL/kg of ideal body weight is supported by the ARDS literature).

Acute respiratory alkalosis caused by overventilation is common. Hypotension induced by elevated intrathoracic pressure that results in decreased return of systemic venous blood to the heart may occur in patients treated with PEEP, particularly those with intravascular volume depletion, and in patients with severe airflow obstruction at high respiratory rates that promote “breath stacking” (dynamic hyperinflation). Ventilator-associated pneumonia is another serious complication of mechanical ventilation.

## B. General Supportive Care

Hypokalemia and hypophosphatemia may worsen hypoventilation due to respiratory muscle weakness. Sedative-hypnotics and opioid analgesics should be titrated carefully to avoid oversedation, leading to prolongation of intubation. Temporary paralysis with a nondepolarizing neuromuscular blocking agent is used to facilitate mechanical ventilation and to lower oxygen consumption. Prolonged muscle weakness due to an acute myopathy is a potential complication of these agents. Myopathy is more common in patients with kidney injury and in those given concomitant corticosteroids.

Psychological and emotional support of the patient and family, skin care to avoid pressure injuries (previously called pressure ulcers), and meticulous avoidance of health care-associated infection and complications of endotracheal tubes are vital aspects of comprehensive care for patients with acute respiratory failure.

Attention must also be paid to preventing complications associated with serious illness. Stress gastritis and ulcers may be avoided by administering sucralfate, histamine H<sub>2</sub>-receptor antagonists, or proton pump inhibitors. Meta-analyses have demonstrated that proton pump inhibitors are most effective. The risk of DVT and PE may be reduced by subcutaneous administration of heparin, the use of LMWH (see Table 14–14), or placement of sequential compression devices on the lower extremities.

## ► Course & Prognosis

The course and prognosis of acute respiratory failure vary and depend on the underlying disease. The prognosis of acute respiratory failure caused by uncomplicated sedative or opioid overdose is excellent. Acute respiratory failure in patients with COPD who do not require intubation and mechanical ventilation has a good immediate prognosis. On the other hand, ARDS and respiratory failure associated with sepsis have a poor prognosis.

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David-João PG et al. Noninvasive ventilation in acute hypoxic respiratory failure: a systematic review and meta-analysis. *J Crit Care*. 2019;49:84. [PMID: 30388493]

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Rochwerg B et al. High flow nasal cannula compared with conventional oxygen therapy for acute hypoxic respiratory failure: a systematic review and meta-analysis. *Intensive Care Med*. 2019;45:563. [PMID: 30888444]

Wiersinga WJ et al. Pathophysiology, transmission, diagnosis, and treatment of coronavirus disease 2019 (COVID-19): a review. *JAMA*. 2020;324:782. [PMID: 32648899]

## ACUTE RESPIRATORY DISTRESS SYNDROME



- ▶ Onset of respiratory distress, often progressing to respiratory failure, within 7 days of a known clinical insult.
- ▶ New, bilateral radiographic pulmonary opacities not explained by pleural effusion, atelectasis, or nodules.
- ▶ Respiratory failure not fully explained by heart failure or volume overload.
- ▶ Impaired oxygenation, with ratio of partial pressure of oxygen in arterial blood ( $\text{PaO}_2$ ) to fractional concentration of inspired oxygen ( $\text{FiO}_2$ )  $< 300 \text{ mm Hg}$ , with  $\text{PEEP} \geq 5 \text{ cm H}_2\text{O}$ .

## General Considerations

Acute respiratory distress syndrome (ARDS) as a clinical syndrome is based on three inclusion criteria plus one exclusion criterion, as detailed above. The severity of ARDS is based on the level of oxygenation impairment: **mild**,  $\text{PaO}_2/\text{FiO}_2$  ratio between 200 mm Hg and 300 mm Hg; **moderate**,  $\text{PaO}_2/\text{FiO}_2$  ratio between 100 mm Hg and 200 mm Hg; and **severe**,  $\text{PaO}_2/\text{FiO}_2$  ratio less than 100 mm Hg.

ARDS may follow a wide variety of clinical events (Table 9–27). Common risk factors for ARDS include sepsis, aspiration of gastric contents, shock, infection, lung contusion, nonthoracic trauma, toxic inhalation, near-drowning, and multiple blood transfusions. About one-third of ARDS patients initially have sepsis syndrome. Damage to capillary endothelial cells and alveolar epithelial cells is common to ARDS regardless of cause or mechanism of lung injury and results in increased vascular permeability and decreased production and activity of surfactant. These abnormalities in turn lead to interstitial and alveolar pulmonary edema, alveolar collapse, and hypoxemia.

**Table 9–27.** Selected disorders associated with ARDS.

| Systemic Insults                       | Pulmonary Insults                                 |
|--|---|
| Trauma                                 | Aspiration of gastric contents                    |
| Sepsis                                 | Embolism of thrombus, fat, air, or amniotic fluid |
| Pancreatitis                           | Miliary tuberculosis                              |
| Shock                                  | Diffuse pneumonia (eg, SARS, COVID-19)            |
| Multiple transfusions                  | Acute eosinophilic pneumonia                      |
| Disseminated intravascular coagulation | Cryptogenic organizing pneumonitis                |
| Burns                                  | Upper airway obstruction                          |
| Drugs and drug overdose                | Free-base cocaine smoking                         |
| Opioids                                | Near-drowning                                     |
| Aspirin                                | Toxic gas inhalation                              |
| Phenothiazines                         | Nitrogen dioxide                                  |
| Tricyclic antidepressants              | Chlorine  |
| Amiodarone                             | Sulfur dioxide                                    |
| Chemotherapeutic agents                | Ammonia   |
| Nitrofurantoin                         | Smoke   |
| Protamine                              | Oxygen toxicity                                   |
| Thrombotic thrombocytopenic purpura    | Lung contusion                                    |
| Cardiopulmonary bypass                 | Radiation exposure                                |
| Head injury                            | High-altitude exposure                            |
| Paraquat                               | Lung reexpansion or reperfusion                   |

ARDS, acute respiratory distress syndrome; COVID-19, coronavirus 19; SARS, severe acute respiratory syndrome.

## Clinical Findings

ARDS is marked by the rapid onset of profound dyspnea that usually occurs 12–48 hours after the initiating event. Labored breathing, tachypnea, intercostal retractions, and crackles are noted on physical examination. Chest radiography shows diffuse or patchy bilateral infiltrates that rapidly become confluent; these characteristically spare the costophrenic angles. Air bronchograms occur in about 80% of cases. Heart size is usually normal, and pleural effusions are small or nonexistent. Marked hypoxemia occurs that is refractory to treatment with supplemental oxygen. Many patients with ARDS demonstrate multiple organ failure, particularly involving the kidneys, liver, gut, central nervous system, and cardiovascular system.

## Differential Diagnosis

Since ARDS is a physiologic and radiographic syndrome rather than a specific disease, the concept of differential diagnosis does not strictly apply. Normal-permeability (“cardiogenic” or hydrostatic) pulmonary edema must be excluded, however, because specific therapy is available for that disorder. Emergent echocardiogram or measurement of pulmonary capillary wedge pressure by means of a flow-directed pulmonary artery catheter may be required in selected patients with suspected cardiac dysfunction; routine use in ARDS is discouraged.

## ► Prevention

No measures that effectively prevent ARDS have been identified. Specifically, neither PEEP nor aspirin when used prophylactically has been shown to be effective in patients at risk for ARDS. Intravenous methylprednisolone does not prevent ARDS when given early to patients with sepsis syndrome or septic shock.

## ► Treatment

The first principle in management is to identify and treat the primary condition that has led to ARDS. Meticulous supportive care must then be provided to compensate for the severe dysfunction of the respiratory system associated with ARDS and to prevent complications.

Treatment of the hypoxemia seen in ARDS usually requires tracheal intubation and positive-pressure mechanical ventilation. The lowest levels of PEEP (used to recruit atelectatic alveoli) and supplemental oxygen required to maintain the  $\text{PaO}_2$  above 55 mm Hg (7.13 kPa) or the  $\text{SaO}_2$  above 88% should be used. Efforts should be made to decrease  $\text{FiO}_2$  as soon as possible in order to avoid oxygen toxicity. PEEP can be increased as needed as long as cardiac output and oxygen delivery do not decrease and airway pressures do not increase excessively (ie, plateau pressures remain below 30 cm  $\text{H}_2\text{O}$ ). Prone positioning frequently improves oxygenation by helping recruit atelectatic alveoli and has been shown in some (although not all) trials to provide a mortality benefit in severe ARDS. Routine use of neuromuscular blockade is controversial; one major trial showed improved mortality and more ventilator-free days in patients with  $\text{PaO}_2/\text{FiO}_2$  ratio less than 120 mm Hg but a subsequent trial (intended to be confirmatory) did not demonstrate a mortality benefit.

A variety of mechanical ventilation strategies are available. The most significant advance in the treatment of ARDS over the past 20 years has been the recognition of the potential for excessive alveolar stretch to cause lung injury, and the widespread adoption of low tidal volume ventilation. A multicenter study of 800 patients demonstrated that a protocol using volume-control ventilation with low tidal volumes (6 mL/kg of ideal body weight) resulted in an 8.8% absolute mortality reduction over therapy with standard tidal volumes (defined as 12 mL/kg of ideal body weight). Varying ventilator modes have been used; conventional modes of ventilation are essentially equivalent, while high-frequency oscillatory ventilation should not be used as initial mode.

Approaches to hemodynamic monitoring and fluid management in patients with acute lung injury have been carefully studied. A prospective RCT comparing hemodynamic management guided either by a pulmonary artery catheter or a central venous catheter using an explicit management protocol demonstrated that a pulmonary artery catheter should not be routinely used for the management of acute lung injury. A subsequent randomized, prospective clinical study of restrictive fluid intake and diuresis as needed to maintain central venous pressure less than 4 mm Hg or pulmonary artery occlusion pressure less than

8 mm Hg (conservative strategy group) versus a fluid management protocol to target a central venous pressure of 10–14 mm Hg or a pulmonary artery occlusion pressure 14–18 mm Hg (liberal strategy group) showed that patients in the conservative strategy group experienced faster improvement in lung function and spent significantly fewer days on mechanical ventilation and in the ICU without an improvement in death by 60 days or worsening nonpulmonary organ failure at 28 days. Oxygen delivery can be increased in anemic patients by ensuring that hemoglobin concentrations are at least 7 g/dL (70 g/L); patients are not likely to benefit from higher levels. Increasing oxygen delivery to supranormal levels through the use of inotropes and high hemoglobin concentrations is not clinically useful and may be harmful. Strategies to decrease oxygen consumption include the appropriate use of sedatives, analgesics, and antipyretics.

A large number of innovative therapeutic interventions to improve outcomes in ARDS patients have been or are being investigated. Unfortunately, to date, none has consistently shown benefit in clinical trials. Systemic corticosteroids have been studied extensively with variable and inconsistent results. While a few small studies suggest some specific improved outcomes when given within the first 2 weeks after the onset of ARDS, mortality appears increased when corticosteroids are started more than 2 weeks after the onset of ARDS. Therefore, routine use of corticosteroids is not recommended.

Another therapeutic intervention is extracorporeal membrane oxygenation (ECMO). The technique has been in use since the 1970s but has been gaining wider acceptance. The EOLIA trial, published in May 2018, compared the early use of ECMO in very severe ARDS with conventional strategies built on low-tidal-volume ventilation. Results failed to show a difference in 60-day mortality; however, 28% of the control group crossed over to receive ECMO. As a result, ECMO seems unlikely to become a standard first-line therapy but is likely to remain a salvage option for patients with very severe ARDS.

## ► Course & Prognosis

Overall, ARDS mortality with low tidal volume ventilation is around 30% in ARDSnet studies. The major causes of death are the primary illness and secondary complications, such as multiple organ system failure or sepsis. Many patients who die of ARDS and its complications die after withdrawal of mechanical ventilation (see Chapter 5). One troubling aspect of ARDS care is that the actual mortality of ARDS in community hospitals continues to be higher than at academic hospitals. This may reflect the fact that a significant number of community hospital-based clinicians have not adopted low tidal volume ventilation.

Different clinical syndromes that lead to ARDS carry different prognoses. For example, patients with trauma-associated ARDS have better prognosis, with a mortality rate close to 20%, whereas those with end-stage liver disease have an 80% mortality rate. This likely reflects both the effects of significant comorbidities (trauma patients tend to be younger and healthier) as well as phenotypic

differences within ARDS associated with different precipitants. Post-hoc analyses of data from several major trials have shown that a hyperinflammatory phenotype associated with high levels of interleukin-6 and soluble tumor necrosis factor receptor in ARDS patients precipitated by sepsis is associated with more multiorgan dysfunction and higher mortality. This may have implications for precision-medicine treatment of ARDS.

Failure to improve in the first week of treatment is a poor prognostic sign. Survivors tend to be young and pulmonary function generally recovers over 6–12 months, although residual abnormalities often remain, including restrictive or obstructive defects, low diffusion capacity, and impaired gas exchange with exercise. Survivors of ARDS also have diminished health-related and pulmonary disease-specific quality of life as well as systemic effects, such as muscle wasting, weakness, and fatigue.

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National Heart, Lung, and Blood Institute PETAL Clinical Trials Network; Moss M et al. Early neuromuscular blockade in the acute respiratory distress syndrome. *N Engl J Med.* 2019;380:1997. [PMID: 31112383]

Papazian L et al. Formal guidelines: management of acute respiratory distress syndrome. *Ann Intensive Care.* 2019;9:69. [PMID: 31197492]

substance abuse, uncontrolled infection, active malignancy, significant organ dysfunction (eg, cirrhosis, chronic kidney disease, heart failure, unrevascularizable coronary disease), and medical noncompliance. Each transplant center has a slightly different selection process; however, common practice includes a detailed multidisciplinary evaluation. Patients should ideally be referred to transplant centers early, before the need for transplant is emergent.

## ► Care After Transplantation

As with other solid organ transplantation, care of the post-lung transplant patient is particularly concerned with immunosuppression and prophylaxis against infection, as well as with management of the side effects of immunosuppression. Most patients are immunosuppressed with a combination of a calcineurin inhibitor (eg, tacrolimus), a cell-cycle inhibitor (eg, mycophenolate mofetil), and glucocorticoids. Most centers screen for rejection with regular pulmonary function testing as well as bronchoscopies and biopsies, particularly in the first 1–2 years after transplantation.

Common complications include acute cellular rejection (treated with intensified immunosuppression), infection, chronic rejection (for which few effective treatments exist), and sequelae of immunosuppression. These include hypertension, dyslipidemia, diabetes mellitus, chronic kidney disease, osteopenia/osteoporosis, and increased risk of malignancy, especially skin cancers. Post-transplant care thus necessitates close cooperation between the patient's transplant team and his or her other physicians.

## ► Outcomes After Transplantation

While lung transplantation can be transformative for those suffering from advanced lung disease, long-term survival remains limited to those receiving kidney or liver transplants. As of the 2019 The International Society of Heart and Lung Transplantation Report, median survival after lung transplantation was 6.7 years. Survival is affected by many variables; two consistent findings have been that survival is improved in double (versus single) lung transplant patients, and in those transplanted for cystic fibrosis (versus other indications).

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Chambers DC et al. The International Thoracic Organ Transplant Registry of the International Society for Heart and Lung Transplantation: Thirty-Sixth Adult Lung and Heart-Lung Transplantation Report—2019; Focus theme: Donor and recipient size match. *J Heart Lung Transplant.* 2019;38:1042. [PMID: 31548030]

van der Mark SC et al. Developments in lung transplantation over the past decade. *Eur Respir Rev.* 2020;29:190132. [PMID: 32699023]

## LUNG TRANSPLANTATION

### ► Introduction

Lung transplantation is a therapeutic option for patients with end-stage lung disease who have not responded to other therapies. The full topic is beyond the scope of this text, therefore only issues related to candidate selection and post-transplant care will be discussed.

### ► Candidate Selection

Patients should be considered for lung transplantation if they have advanced, progressive lung disease despite appropriate medical therapy. The most common indications are interstitial lung disease, COPD, cystic fibrosis, and PAH. The International Society of Heart and Lung Transplantation has produced guidelines for candidate selection; broadly speaking, the ideal candidate has a high (greater than 50%) risk of dying within 2 years without lung transplantation, has minimal other comorbidities, is very likely to survive transplantation, and has good social support. Contraindications are numerous and include obesity (generally BMI greater than 30 is a relative, and greater than 35 a nearly absolute, contraindication), active smoking or

# Heart Disease

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# 10

## ADULT CONGENITAL HEART DISEASE

In the United States, there are many more adults with congenital heart disease than children, with an estimated 2 million adults in the United States surviving with congenital heart disease. In 2018, the American College of Cardiology (ACC) and American Heart Association (AHA) released updated guidelines for the assessment and treatment of patients with adult congenital heart disease. The European Society of Cardiology (ESC) completed their update on the same topic in 2020. As the number of patients with adult congenital heart disease has grown, there has been an increased appreciation of the need for more training and guidelines. A specific subspecialty board and training program has been established. The AHA also issued a scientific statement in 2015 reviewing common issues for adults with underlying congenital heart disease, another statement in 2017 for pregnant patients with congenital heart disease, and a statement in 2017 regarding noncardiac issues in these patients.

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Canobbio MM et al; American Heart Association Council on Cardiovascular and Stroke Nursing; Council on Clinical Cardiology; Council on Cardiovascular Disease in the Young; Council on Functional Genomics and Translational Biology; and Council on Quality of Care and Outcomes Research. Management of pregnancy in patients with complex congenital heart disease: a scientific statement for healthcare professionals from the American Heart Association. Circulation. 2017;135:e50. [PMID: 28082385]

Lui GK et al; American Heart Association Adult Congenital Heart Disease Committee of the Council on Clinical Cardiology and Council on Cardiovascular Disease in the Young; Council on Cardiovascular Radiology and Intervention; and Council on Quality of Care and Outcomes Research. Diagnosis and management of noncardiac complications in adults with congenital heart disease: a scientific statement from the American Heart Association. Circulation. 2017;136:e348. [PMID: 28993401]

Stout KK et al. 2018 AHA/ACC guideline for the management of adults with congenital heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2019;73:e81. [PMID: 30121239]

## PULMONARY VALVE STENOSIS

### ESSENTIALS OF DIAGNOSIS

- ▶ Severe cases may present with right-sided heart failure.
- ▶  $P_2$  delayed and soft or absent.
- ▶ Pulmonary ejection click often present and decreases with inspiration—the only right heart sound that *decreases* with inspiration; all other right heart sounds increase.
- ▶ Echocardiography/Doppler is diagnostic.
- ▶ Patients with peak pulmonic valve gradient greater than 64 mm Hg or a mean of 35 mm Hg by echocardiography/Doppler should undergo intervention regardless of symptoms. Otherwise, operate for symptoms or evidence for right ventricular (RV) dysfunction.

### General Considerations

Stenosis of the pulmonary valve or RV infundibulum increases the resistance to RV outflow, raises the RV pressure, and limits pulmonary blood flow. Pulmonic stenosis is often congenital and associated with other cardiac lesions. Pulmonary blood flow preferentially goes to the left lung in valvular pulmonic stenosis. In the absence of associated shunts, arterial saturation is normal. Peripheral pulmonic stenosis can accompany valvular pulmonic stenosis and may be part of a variety of clinical syndromes, including the congenital rubella syndrome. Patients who have had the **Ross procedure** for aortic valve disease (transfer of the pulmonary valve to the aortic position with a homograft pulmonary valve placed in the pulmonary

position) may experience noncongenital postoperative pulmonic valvular or main pulmonary artery (PA) stenosis due to an immune response in the homograft. RV outflow obstructions can also occur when there is a conduit from the RV to the pulmonary artery that becomes stenotic from degenerative changes over time or when there is degeneration of a bioprosthetic replacement pulmonary valve.

## ► Clinical Findings

### A. Symptoms and Signs

Mild cases of pulmonic stenosis are asymptomatic; moderate to severe pulmonic stenosis may cause symptoms of dyspnea on exertion, syncope, chest pain, and eventually RV failure.

On examination, there is often a palpable parasternal lift due to right ventricular hypertrophy (RVH) and the pulmonary outflow tract may be palpable if the PA is enlarged. A loud, harsh systolic murmur and occasionally a prominent thrill are present in the left second and third interspaces parasternally. The murmur radiates toward the left shoulder due to the flow pattern within the main PA and increases with inspiration. In mild to moderate pulmonic stenosis, a loud ejection click can be heard to precede the murmur; this sound decreases with inspiration as the increased RV filling from inspiration prematurely opens the valve during atrial systole when inspiratory increased blood flow to the right heart occurs. The valve excursion during systole is thus less with inspiration than with expiration, and the click is therefore less audible with inspiration. *This is the only right-sided auscultatory event that decreases with inspiration.* All of the other auscultatory events increase with the increased right heart output that occurs with inspiration. In severe pulmonic stenosis, the second sound is obscured by the murmur and the pulmonary component of  $S_2$  may be diminished, delayed, or absent. A right-sided  $S_4$  and a prominent  $a$  wave in the venous pulse are present when there is RV diastolic dysfunction or a  $c-v$  wave may be observed in the jugular venous pressure if tricuspid regurgitation is present. Pulmonary valve regurgitation is relatively uncommon in primary pulmonic stenosis and may be very difficult to hear, as the gradient between the reduced PA diastolic pressure and the elevated RV diastolic pressure may be quite small (low-pressure pulmonary valve regurgitation).

### B. ECG and Chest Radiography

Right axis deviation or RVH is noted; peaked P waves provide evidence of right atrial (RA) overload. Heart size may be normal on radiographs, or there may be a prominent RV and RA or gross cardiac enlargement, depending on the severity. There is often poststenotic dilation of the main and left pulmonary arteries. Pulmonary vascularity is usually normal, although there tends to be preferential flow to the left lung.

### C. Diagnostic Studies

Echocardiography/Doppler is the diagnostic tool of choice, can provide evidence for a doming valve versus a dysplastic

valve, can determine the gradient across the valve, and can provide information regarding subvalvular obstruction and the presence or absence of tricuspid or pulmonic valvular regurgitation. Mild pulmonic stenosis is present if the peak gradient by echocardiography/Doppler is less than 36 mm Hg, moderate pulmonic stenosis is present if the peak gradient is between 36 mm Hg and 64 mm Hg, and severe pulmonic stenosis is present if the peak gradient is greater than 64 mm Hg or the mean gradient is greater than 35 mm Hg. A lower gradient may be significant if there is RV dysfunction. Catheterization is usually unnecessary for the diagnosis; it should be used only if the data are unclear or in preparation for either percutaneous intervention or surgery.

## ► Prognosis & Treatment

Patients with mild pulmonic stenosis have a normal life span with no intervention. Moderate stenosis may be asymptomatic in childhood and adolescence, but symptoms often appear as patients grow older. The degree of stenosis does worsen with time in a few patients, so serial follow-up is important. Severe stenosis is rarely associated with sudden death but can cause right heart failure in patients as early as in their 20s and 30s. Pregnancy and exercise tend to be well tolerated except in severe stenosis.

The AHA/ACC guidelines and the ESC guidelines generally agree, though the ESC suggests severe pulmonic stenosis should be considered if the RV systolic pressure is greater than 80 mm Hg. Class I (definitive) indications for intervention include all symptomatic patients and all those with a resting peak-to-peak gradient greater than 64 mm Hg or a mean greater than 35 mm Hg, regardless of symptoms. Symptoms can include cyanosis due to right-to-left shunting via a patent foramen ovale (PFO) or atrial septal defect (ASD). Percutaneous balloon valvuloplasty is highly successful in domed valve patients and is the treatment of choice. Surgical commissurotomy can also be done, or pulmonary valve replacement (with either a bioprosthetic valve or homograft) when pulmonary valve regurgitation is too severe or the valve is dysplastic. Pulmonary outflow tract obstruction due to RV to PA conduit obstruction or to homograft pulmonary valve stenosis can often be relieved with a percutaneously implanted pulmonary valve (both the Medtronic Melody valve and the Edwards Sapien XT valve are FDA approved). Frequently the seating of these valves is facilitated by placing a stent within the pulmonary artery first, then the transcatheter device within this stent. Because the new catheter valve may result in compression of the coronary artery, it is a class I requirement to assess the effect of the device on the coronary by use of a temporary balloon inflation prior to delivery of the device. Percutaneous pulmonary valve replacement is also FDA approved for those with conduit stenosis or following the Ross procedure. Percutaneous valve replacements have also been performed off-label for patients with native pulmonary valve disease, including those who have had tetralogy of Fallot repair (assuming the PA root size is small enough to seat a percutaneous valve).

Endocarditis prophylaxis is unnecessary for native valves even after valvuloplasty unless there has been prior

pulmonary valve endocarditis (an unusual occurrence) (see Table 33–3). It should be used if surgical or percutaneous valve replacement has occurred. There appears to be more pulmonary valve endocarditis following percutaneous pulmonary valve replacement with the Melody valve than expected, and this is being closely monitored by the FDA.

### ► When to Refer

All symptomatic patients (regardless of gradient) and all asymptomatic patients whose peak pulmonary valve gradient is greater than 64 mm Hg or whose mean gradient is greater than 35 mm Hg should be referred to a cardiologist with expertise in adult congenital heart disease. Patients also require intervention if cyanosis occurs due to a PFO or ASD or if there is exercise intolerance.

Baumgartner H et al. 2020 ESC Guidelines for the management of adult congenital heart disease. Eur Heart J. 2021;42:563. [PMID: 32860028]

Hansen RL et al. Long-term outcomes up to 25 years following balloon pulmonary valvuloplasty: a multicenter study. Congenit Heart Dis. 2019;14:1037. [PMID: 31250555]

## COARCTATION OF THE AORTA

### ESSENTIALS OF DIAGNOSIS

- ▶ Usual presentation is systemic hypertension.
- ▶ Echocardiography/Doppler is diagnostic; a peak gradient of > 20 mm Hg may be significant due to collaterals around the coarctation reducing gradient despite severe obstruction.
- ▶ Associated bicuspid aortic valve in 50–80% of patients.
- ▶ Delayed pulse in femoral artery compared to brachial artery.
- ▶ Systolic pressure is higher in upper extremities than in lower extremities; diastolic pressures are similar.

### ► General Considerations

Coarctation of the aorta consists of localized narrowing of the aortic arch just distal to the origin of the left subclavian artery. If the stenosis is severe, collateral circulation develops around the coarctation site through the intercostal arteries and the branches of the subclavian arteries and can result in a lower trans-coarctation gradient by enabling blood flow to bypass the obstruction. **Coarctation is a cause of secondary hypertension and should be considered in young patients with elevated blood pressure (BP).** The renin-angiotensin system is often abnormal, however, and contributes to the hypertension occasionally seen even after coarctation repair. A bicuspid valve is seen in approximately 50–80% of the cases, and there is an increased incidence of cerebral berry aneurysms.

Significant native or recurrent aortic coarctation has been defined as follows: upper extremity/lower extremity resting peak-to-peak gradient greater than 20 mm Hg or mean Doppler systolic gradient greater than 20 mm Hg; upper extremity/lower extremity gradient greater than 10 mm Hg or mean Doppler gradient greater than 10 mm Hg when there is either decreased left ventricular (LV) systolic function or aortic regurgitation (AR); or upper extremity/lower extremity gradient greater than 10 mm Hg or mean Doppler gradient greater than 10 mm Hg when there is evidence for collateral flow around the coarctation. This should be coupled with anatomic evidence for coarctation of the aorta, typically defined by advanced imaging (cardiac magnetic resonance, CT angiography). The ESC guidelines have expanded the severity criteria and suggest stenting is appropriate if the patient is normotensive but has a peak gradient of greater than 20 mm Hg (class IIa) or if the stenosis by angiography is more than 50% (class IIb).

### ► Clinical Findings

#### A. Symptoms and Signs

If cardiac failure does not occur in infancy, there are usually no symptoms until the hypertension produces LV failure. Cerebral hemorrhage, though rare, may occur. Approximately 10% of patients with coarctation of the aorta have intracranial aneurysms identified on magnetic resonance angiography or CT angiography. Increasing age has been identified as a risk factor. Strong arterial pulsations are seen in the neck and suprasternal notch. Hypertension is present in the arms, but the pressure is normal or low in the legs. This difference is exaggerated by exercise. Femoral pulsations are weak and are delayed in comparison with the brachial or radial pulse. A continuous murmur heard superiorly and midline in the back or over the left anterior chest may be present when large collaterals are present and is a clue that the coarctation is severe. The coarctation itself may result in systolic ejection murmurs heard in the left upper lung field anteriorly and near the spine on the left side posteriorly. There may be an aortic regurgitation or stenosis murmur due to an associated bicuspid aortic valve. Coarctation is associated with Turner syndrome (a sex chromosomal abnormality [XO]); a webbed neck may be present in these patients.

#### B. ECG and Chest Radiography

The ECG usually shows LV hypertrophy (LVH). Radiography may show scalloping of the inferior portion of the ribs (**rib notching**) due to enlarged collateral intercostal arteries. Dilatation of the left subclavian artery and poststenotic aortic dilation along with LV enlargement may be present. The coarctation region and the poststenotic dilation of the descending aorta may result in a “**3**” sign along the aortic shadow on the PA chest radiograph (the notch in the “**3**” representing the area of coarctation).

#### C. Diagnostic Studies

Echocardiography/Doppler is usually diagnostic and may provide additional evidence for a bicuspid aortic valve.

Both MRI and CT can provide excellent images of the coarctation anatomy, and one or the other should always be done to define the coarctation anatomic structure. MRI and echocardiography/Doppler can also provide estimates of the gradient across the lesion. Cardiac catheterization provides definitive gradient information and is obviously necessary if percutaneous stenting is to be considered.

### ► Prognosis & Treatment

Cardiac failure is common in infancy and in older untreated patients when the coarctation is severe. Patients with a demonstrated peak gradient of greater than 20 mm Hg should be considered for intervention, especially if there is evidence of collateral blood vessels. As noted above, the ESC guidelines incorporate the stenosis severity (greater than 50%) as defining severe coarctation as well. Many untreated patients with severe coarctation die of hypertension, rupture of the aorta, infective endarteritis, or cerebral hemorrhage before the age of 50. Aortic dissection also occurs with increased frequency. Coarctation of any significance may be poorly tolerated in pregnancy because of the inability to support the placental flow.

Resection of the coarctation site has a surgical mortality rate of 1–4% and includes risk of spinal cord injury. The percutaneous interventional procedure of choice is endovascular stenting; when anatomically feasible, self-expanding and balloon-expandable covered stents have been shown to be advantageous over bare metal stents. These covered stents are FDA approved. Most coarctation repair in adults is percutaneous. Otherwise, surgical resection (usually with end-to-end anastomosis) should be performed. About 25–50% of surgically corrected patients continue to be hypertensive years after surgery because of permanent changes in the renin-angiotensin system, endothelial dysfunction, aortic stiffness, altered arch morphology, and increased ventricular stiffness. Whether the repair was by balloon dilatation, stenting, or surgical resection may make a difference in the development of hypertension. Recurrence of the coarctation stenosis following intervention requires long-term follow-up.

### ► When to Refer

All patients with aortic coarctation and any detectable gradient should be referred to a cardiologist with expertise in adult congenital heart disease.

## ATRIAL SEPTAL DEFECT & PATENT FORAMEN OVALE



### ESSENTIALS OF DIAGNOSIS

- ▶ Often asymptomatic and discovered on routine physical examination.
- ▶ With an ASD and left-to-right shunt: RV lift; S2 widely split and fixed.
- ▶ Echocardiography/Doppler is diagnostic.
- ▶ ASDs should be closed if there is evidence of an RV volume overload regardless of symptoms.
- ▶ A PFO, present in 25% of the population, rarely can lead to paradoxical emboli.

### ► General Considerations

The most common form of ASD (80% of cases) is persistence of the ostium secundum in the mid-septum. A less common abnormality is persistence of the ostium primum (low in the septum). In most patients with an ostium primum defect, there are mitral or tricuspid valve “clefts” as well as a ventricular septal defect (VSD) as part of the atrioventricular (AV) septal defect. A sinus venosus defect is a hole, usually at the upper (or rarely the lower) part of the atrial septum, due to failure of the embryonic superior vena cava or the inferior vena cava to merge with the atria properly. The superior vena cava sinus venosus defect is usually associated with an anomalous connection of the right upper pulmonary vein into the superior vena cava. The coronary sinus ASD is rare and is basically an unroofed coronary sinus that results in shunting from the left atrium (LA) to the coronary sinus and then to the RA.

In all cases, normally oxygenated blood from the higher-pressure LA shunts into the RA, increasing RV output and pulmonary blood flow. In children, the degree of shunting across these defects may be quite large (pulmonary to systemic blood flow ratios of 3:1 or so). As the RV compliance worsens from the chronic volume overload, the RA pressure may rise and the degree of left-to-right shunting may decrease over time. Eventually, if the RA pressure exceeds the LA, the shunt may reverse and be primarily right-to-left. When this happens, systemic cyanosis appears. The major factor in the direction of shunt flow is thus the compliance of the respective atrial chambers.

The pulmonary pressures are modestly elevated in most patients with an ASD due to the high pulmonary blood flow, but severe pulmonary hypertension with cyanosis (**Eisenmenger physiology**) is actually unusual, occurring in only about 15% of the patients with an ASD alone. Increased pulmonary vascular resistance (PVR) and pulmonary hypertension secondary to pulmonary vascular disease rarely occur in childhood or young adult life in secundum defects and are more common in primum defects, especially if there is an associated VSD. Eventual RV failure may occur with any atrial shunt of significant size, and most shunts should be corrected unless they are

Baumgartner H et al. 2020 ESC Guidelines for the management of adult congenital heart disease. Eur Heart J. 2021;42:563. [PMID: 32860028]

Fedchenko M et al. Cardiovascular risk factors in adults with coarctation of the aorta. Congenit Heart Dis. 2019;14:549. [PMID: 31099471]

Lee MGY et al. Long-term mortality and cardiovascular burden for adult survivors of coarctation of the aorta. Heart. 2019;105:1190. [PMID: 30923175]

quite small (less than 1.5:1 left-to-right shunt). In adults, a large left-to-right shunt may have begun to reverse, so the absolute left-to-right shunt measurement ( $Qp/Qs$ , where  $Qp$  = pulmonary flow and  $Qs$  = systemic flow) at the time the patient is studied may underestimate the original shunt size. In addition, in most people the LV and LA compliance normally declines more over time than the RV and RA compliance; for this reason, the natural history of small atrial septal shunts is to increase the left-to-right shunting as the patient ages. There is generally only trivial shunting with a PFO compared to a true ASD. ASDs predispose to atrial fibrillation due to RA enlargement, and paradoxical right-to-left emboli do occur. If pulmonary hypertension does occur, the 2018 guidelines recommend that the shunt should still be closed as long as the left-to-right shunt is still greater than 1.5:1 and the systolic PA pressure is less than one-half the systemic arterial pressure and the PVR calculation is less than one-third systemic vascular resistance.

Interestingly, paradoxical emboli may be more common in patients with a PFO than a true ASD, especially when there is an atrial septal aneurysm. An aneurysm of the atrial septum is not a true aneurysm but rather simply a redundancy of the atrial septum that causes it to swing back and forth (greater than 10 mm). When present with a PFO, the back-and-forth swinging tends to pull open the PFO, encouraging shunting. This may help explain why more right-to-left shunting occurs in patients with an atrial septal aneurysm and PFO than in those with a PFO alone. This creates the anatomic substrate for the occurrence of paradoxical emboli. Other factors may distort the atrial septum (such as an enlarged aorta) and result in an increased shunting in patients with a PFO. Right-to-left PFO shunting may be more prominent upright than supine, creating orthostatic hypoxemia (**platypnea orthodeoxia**). There may also be increased shunting in patients with a PFO and sleep apnea as the RA compliance may worsen during apneic spells when pulmonary pressures increase.

## ► Clinical Findings

### A. Symptoms and Signs

Patients with a small or moderate ASD or with a PFO are asymptomatic unless a complication occurs. There is only trivial shunting in a PFO unless the RA pressure increases for some other reason or the atrial septum is distorted. With larger ASD shunts, exertional dyspnea or heart failure may develop, most commonly in the fourth decade of life or later. Prominent RV and PA pulsations are then readily visible and palpable. A moderately loud systolic ejection murmur can be heard in the second and third interspaces parasternally as a result of increased flow through the pulmonary valve.  $S_2$  is widely split and does not vary with respiration. The left-to-right shunt across the defect decreases with inspiration (as the RA pressure increases) and then increases with expiration (as the RA pressure decreases), thus keeping the RV stroke volume relatively constant in inspiration and expiration. A “**fixed**” splitting of the second sound results. In very large left-to-right shunts, a tricuspid rumble may be heard due to the high flow across the tricuspid valve in diastole.

### B. ECG and Chest Radiography

Right axis deviation or RVH may be present depending on the size of the RV volume overload. Incomplete or complete right bundle branch block is present in nearly all cases of ASD, and superior axis deviation (left anterior fascicular block) is noted in the complete AV septal defect, where complete heart block is often seen as well. With sinus venosus defects, the P axis is leftward of +15° due to abnormal atrial activation with loss of the upper RA tissue from around the sinus node. This creates the negative P waves in the inferior leads. The chest radiograph shows large pulmonary arteries, increased pulmonary vascularity, and an enlarged RA and RV as with all pre-tricuspid valve cardiac left-to-right shunts. The LA is not traditionally enlarged due to an ASD shunt because the chamber is being decompressed.

### C. Diagnostic Studies

Echocardiography demonstrates evidence of RA and RV volume overload. The atrial defect is usually observed by echocardiography, although sinus venosus defects may be elusive since they are high in the atrial septum. Many patients with a PFO also have an atrial septal aneurysm (defined as greater than 10-mm excursion of the septum from the static position). Echocardiography with saline injection (**bubble contrast**) can demonstrate the right-to-left component of the shunt, and both pulsed and color flow Doppler flow studies can demonstrate shunting in either direction. In platypnea orthodeoxia, the shunt may primarily result from inferior vena cava blood, and a femoral vein saline injection may be required to demonstrate the shunt. Transesophageal echocardiography (TEE) is helpful when transthoracic echocardiography quality is not optimal because it improves the sensitivity for detection of small shunts and provides a better assessment of PFO or ASD anatomy. Both CT and MRI can elucidate the atrial septal anatomy, better detect multiple fenestrations, and demonstrate associated lesions such as anomalous pulmonary venous connections. Atrial septal anatomy can be complex, and either MRI, TEE, or CT can reveal whether there is an adequate rim around the defect to allow for safe positioning of an atrial septal occluder device. These studies can also help identify any anomalous pulmonary venous connections. Cardiac catheterization can define the size and location of the shunt and determine the pulmonary pressure and PVR.

## ► Prognosis & Treatment

Patients with small atrial shunts live a normal life span with no intervention. Large shunts usually cause disability by age 40 years. Because left-to-right shunts and RV overload tend to increase with normal age-related reduction in LV (and subsequently LA) compliance, both AHA/ACC and the ESC guidelines suggest that closure of all left-to-right shunts greater than 1.5:1 should be accomplished either by a percutaneous device or by surgery if any right heart structures are enlarged at all. If the pulmonary systolic pressure is more than two-thirds the systemic systolic

pressure, then pulmonary hypertension may preclude ASD closure. The ESC guidelines add the pulmonary vascular resistance to the criteria and consider it a class IIa indication if the PVR is between 3 and 5 Wood units, and the guidelines preclude the use of closure if the PVR is greater than or equal to 5 Wood units. Testing with transient balloon occlusion of the shunt, with pulmonary vasodilators, or with both may be required in the presence of pulmonary hypertension. Preservation of the cardiac output after transient balloon occlusion and evidence for preserved pulmonary vasoreactivity with pulmonary vasodilator testing all favor closure when pulmonary hypertension and at least a 1.5:1 left-to-right shunt are present. ESC guidelines favor bringing the patient back to the catheterization laboratory for retesting on pulmonary vasodilators, rather than using acute testing, to see if the PVR can be reduced below 5 Wood units. The ESC guidelines also suggest considering fenestrated closure in the face of pulmonary hypertension. The use of bosentan or sildenafil is recommended if the PVR is over 5 Wood units and there is a right-to-left shunt. After age 40 years, cardiac arrhythmias (especially atrial fibrillation) and heart failure occur with increased frequency due to the chronic right heart volume overload. Paradoxical systemic arterial embolization also becomes more of a concern as RV compliance is lost and the left-to-right shunt begins to reverse.

PFOs are usually *not* associated with significant shunting, and therefore the patients are hemodynamically asymptomatic and the heart size is normal. However, PFOs can be responsible for paradoxical emboli and are a possible cause of **cryptogenic strokes** in patients under age 55 years. Some shunting may occur with exercise if the right heart is enlarged or stiff. Interestingly, the risk of *recurrent* paradoxical emboli is low regardless of whether the PFO is closed or not, and that observation has reduced the value of closing these defects in cryptogenic stroke. Further confounding the advantage of PFO closure for cryptogenic stroke or transient ischemic attack (TIA) has been the discovery of frequent bouts of paroxysmal atrial fibrillation using 30-day monitoring in these patients, suggesting atrial fibrillation is actually the real stroke/TIA risk factor in some patients.

Occasionally, a PFO that has not been pathologic may become responsible for cyanosis, especially if the RA pressure is elevated from pulmonary or RV hypertension or from severe tricuspid regurgitation.

Surgery involves stitching or patching of the foramen. For ostium secundum ASDs, percutaneous closure by use of a variety of devices is preferred over surgery when the anatomy is appropriate (usually this means there must be an adequate atrial septal rim around the defect to secure the occluder device).

Patients who have hypoxemia (especially upon standing or with exercise) should have the PFO closed if no other cause for hypoxemia is evident and there is right-to-left shunting demonstrated through the PFO. For patients with cryptogenic stroke or TIA, it remains uncertain whether closure of the PFO, either by open surgical or percutaneous techniques, has any advantage over anticoagulation with either warfarin, a direct-acting oral anticoagulant (DOAC), or aspirin.

From a practical standpoint, patients younger than 55 years with cryptogenic stroke/TIA and no other identifiable cause except for the presence of a PFO should still be considered for PFO closure. A 2020 update from the guideline subcommittee of the American Academy of Neurology reaffirms no change in this overall policy. The presence of an atrial septal aneurysm (with the septum appearing "floppy" on echocardiogram) has been associated with a higher risk of recurrent stroke/TIA in patients with cryptogenic stroke/TIA. A workup for any causes for hypercoagulability and a 30-day monitor should be part of the clinical assessment to exclude other potential causes for cryptogenic stroke/TIA. In meta-analysis of data in patients with cryptogenic stroke/TIA and PFO who have their PFO closed, ischemic stroke recurrence is less frequent compared with patients receiving medical treatment. Atrial fibrillation is more frequent but mostly transient in patients who have device closure. There is no difference in TIA, all-cause mortality, or myocardial infarction (MI) between those treated with medicine versus a closure device. In a large, multicenter trial in France among patients who had had a recent cryptogenic stroke attributed to PFO with an associated atrial septal aneurysm or large interatrial shunt, the rate of stroke recurrence was lower among those assigned to PFO closure combined with antiplatelet therapy than among those assigned to antiplatelet therapy alone. PFO closure was associated with an increased risk of atrial fibrillation. Residual shunting after device closure is also present in up to 25% of patients. A report from Massachusetts General Hospital found a medium to large residual shunt increased the risk of a recurrent stroke or TIA threefold.

## ► When to Refer

- All patients with an ASD should be evaluated by a cardiologist with expertise in adult congenital disease to ensure no other structural disease is present and to investigate whether the RV is enlarged.
- If the RA and RV sizes remain normal, serial echocardiography should be performed every 3–5 years.
- If the RA and RV volumes are increased, then referral to a cardiologist who performs percutaneous closure is warranted.
- Patients younger than 55 years with cryptogenic stroke when no other source is identified except for a PFO with right-to-left shunting should be considered for PFO closure or medical therapy. An associated atrial septal aneurysm or evidence for hypercoagulability increases risk. Aspirin alone appears not to be effective. DOACs with or without device closure of the PFO may have a role in preventing recurrent stroke.
- Patients with cyanosis and a PFO with evidence of a right-to-left shunt by agitated saline bubble contrast on echocardiography, especially if the cyanosis is worsened upon assuming the upright posture.

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## VENTRICULAR SEPTAL DEFECT



### ESSENTIALS OF DIAGNOSIS

- ▶ A restrictive VSD is small and makes a louder murmur than an unrestricted one, often with an accompanying thrill. The higher the gradient across the septum, the smaller the left-to-right shunt.
- ▶ Small defects may be asymptomatic.
- ▶ Larger defects result in pulmonary hypertension (Eisenmenger physiology) if not repaired or if the pulmonary circuit is not protected by RV outflow tract obstruction.
- ▶ Echocardiography/Doppler is diagnostic.

## General Considerations

Congenital VSDs occur in various parts of the ventricular septum. Membranous and muscular septal defects may spontaneously close in childhood as the septum grows and hypertrophies. A left-to-right shunt is present, with the degree depending on associated systolic RV pressure. The smaller the defect, the greater is the gradient from the LV to the RV and the louder the murmur. The presentation in adults depends on the size of the shunt and whether there is associated pulmonic or subpulmonic stenosis that has protected the lung from the systemic pressure and volume. Unprotected lungs with large shunts invariably lead to pulmonary vascular disease and severe pulmonary hypertension (Eisenmenger physiology). VSD sizes are defined by comparison to the aortic root size; a small or restrictive VSD diameter is less than 25% of the aortic root diameter, a moderately restrictive VSD diameter is 25–75% of the aorta, and an unrestricted VSD size is greater than 75% of the aortic diameter. The size can also be quantitated based

on the Qp/Qs (left-to-right shunt), with a restrictive lesion being less than 1.5:1, moderately restrictive VSD being 1.5–2.2:1, and an unrestricted lesion being greater than 2.2:1.

## ► Clinical Findings

### A. Symptoms and Signs

The clinical features depend on the size of the defect and the presence or absence of RV outflow obstruction or increased PVR. Small shunts are associated with loud, harsh holosystolic murmurs in the left third and fourth intercostal spaces along the sternum. A systolic thrill is common. Larger shunts may create both LV and RV volume and pressure overload. If pulmonary hypertension occurs, high-pressure pulmonary valve regurgitation may result. Right heart failure may gradually become evident late in the course, and the shunt will begin to balance or reverse as RV and LV systolic pressures equalize with the advent of pulmonary hypertension. Cyanosis from a developing right-to-left shunt may then occur. Cyanosis with pulmonary hypertension and an intracardiac shunt define the **Eisenmenger syndrome**.

### B. ECG and Chest Radiography

The ECG may be normal or may show right, left, or biventricular hypertrophy, depending on the size of the defect and the PVR. With large shunts, the LV, the LA, and the pulmonary arteries are enlarged and pulmonary vascularity is increased on chest radiographs. The RV is often normal until late in the process. If an increased PVR (pulmonary hypertension) evolves, an enlarged PA with pruning of the distal pulmonary vascular bed is seen. In rare cases of a VSD high in the ventricular septum, an aortic cusp (right coronary cusp) may prolapse into the VSD and reduce the VSD shunt but result in acute aortic regurgitation and acute heart failure.

### C. Diagnostic Studies

Echocardiography can demonstrate the size of the overloaded chambers and can usually define the defect anatomy. Doppler can qualitatively assess the magnitude of shunting by noting the gradient from LV to RV and, if some tricuspid regurgitation is present, the RV systolic pressure can be estimated. The septal leaflet of the tricuspid valve may be part of the VSD anatomy and the complex appears as a ventricular septal "aneurysm." These membranous septal aneurysms resemble a "windsock" and may fenestrate and result in a VSD shunt being present or they may remain intact. Color flow Doppler helps delineate the shunt severity and the presence of valvular regurgitation. MRI and cardiac CT can often visualize the defect and describe any other anatomic abnormalities. MRI can provide quantitative shunt data as well.

Cardiac catheterization is usually reserved for those with at least moderate shunting, to quantitate the PVR and the degree of pulmonary hypertension. The 2018 adult congenital heart disease guidelines suggest that if there is still at least a 1.5:1 left-to-right shunt and if the PVR is less

than one-third that of the systemic vascular resistance, and the PA systolic pressure is more than one-half of the aortic systolic pressure, then the risk of VSD closure despite some pulmonary hypertension is acceptable and it should be done. If the PVR/systemic vascular resistance ratio or the systolic PA pressure/systolic aortic pressure ratio is greater than two-thirds or there is a net right-to-left shunt, then closure is contraindicated.

The vasoreactivity of the pulmonary circuit may be tested at catheterization using agents such as inhaled nitric oxide. The AHA/ACC guidelines suggest that if the pulmonary pressures can be lowered enough and the above ratios fall below the two-thirds value, then repair is reasonable as long as the left-to-right VSD shunt is greater than 1.5:1. The 2020 ESC guidelines focus not on the pulmonary to systemic systolic BP ratio, but on the pulmonary pressure and the PVR. A PVR of greater than or equal to 5 Wood units is considered inoperable unless pulmonary vasodilators can reduce the PVR to below that value. Bosentan, an endothelial receptor blocker that reduces pulmonary pressure in Eisenmenger syndrome, has been given a class I indication in these patients in both guidelines.

### ► Prognosis & Treatment

Patients with a small VSD have a normal life expectancy except for the small risk of infective endocarditis. Antibiotic prophylaxis after dental work is recommended only when the VSD is residual from a prior patch closure or when there is associated pulmonary hypertension and cyanosis (see Tables 33–3, 33–4, and 33–5). With large VSD shunts, heart failure may develop early in life, and survival beyond age 40 years is unusual without intervention.

Small shunts (pulmonary-to-systemic flow ratio less than 1.5) in asymptomatic patients do not require surgery or other intervention. The presence of RV infundibular stenosis or pulmonary valve stenosis may protect the pulmonary circuit such that some patients, even with a large VSD, may still be surgical candidates as adults if there is no pulmonary hypertension.

Surgical repair of a VSD is generally a low-risk procedure unless there is significant Eisenmenger physiology. Devices for nonsurgical closure of muscular VSDs are approved and those for membranous VSDs are being implanted with promising results; however, conduction disturbance is a major complication. The percutaneous devices are also approved for closure of a VSD related to acute MI, although the results in this very high-risk patient population have not been encouraging. In the acute MI setting, the devices have also been put across the ventricular septum at surgery to help provide a firm base on which to sew a pericardial patch, given the VSD in acute MI is often associated with widespread necrosis and multiple, serpiginous pathways. A novel percutaneous method, wherein the two sides of the device are sewn together using a subxiphoid approach, has been described. The medications used to treat pulmonary hypertension secondary to a VSD are similar to those used to treat idiopathic (“primary”) pulmonary hypertension and at times can be quite effective in relieving symptoms and reducing the degree of cyanosis. **All patients who have a right-to-left shunt**

**present should have filters placed on any intravenous lines to avoid any contamination or air bubbles from becoming systemic.**

### ► When to Refer

All patients with a VSD should be referred to a cardiologist with expertise in adult congenital disease to decide if long-term follow-up or further studies are warranted.

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## TETRALOGY OF FALLOT

### ► ESSENTIALS OF DIAGNOSIS

- ▶ Five features are characteristic:
  - VSD.
  - Concentric RVH.
  - RV outflow obstruction due to infundibular stenosis.
  - Septal overriding of the aorta in half the patients.
  - A right-sided aortic arch in 25%.
- ▶ Most adult patients with tetralogy of Fallot have been operated on, usually with an RV outflow patch and VSD closure. If patch overrides the pulmonary valve annulus, pulmonary regurgitation is common.
- ▶ Physical examination may be deceptive after classic tetralogy repair, with severe pulmonary valve regurgitation difficult to detect.
- ▶ Echocardiography/Doppler may underestimate significant pulmonary valve regurgitation. Be wary if the RV is enlarged or enlarging.
- ▶ Arrhythmias are common; periodic ambulatory monitoring is recommended.
- ▶ Serious arrhythmias and sudden death may occur if the QRS is wide or the RV becomes quite large, or both.

### ► General Considerations

Patients with tetralogy of Fallot have a VSD, RV infundibular stenosis, RVH, and a dilated aorta (in about half of patients it overrides the septum). If there is an associated ASD, the complex is referred to as pentalogy of Fallot. The basic lesion is a large VSD with migration of the septum above the VSD and under the pulmonary valve. There may

be pulmonary valve stenosis as well, usually due to either a bicuspid pulmonary valve or RV outflow hypoplasia. The aorta can be quite enlarged and aortic regurgitation may occur. If more than 50% of the aorta overrides the ventricular septum, it is called double outlet RV. Two vascular abnormalities are common: a right-sided aortic arch (in 25%) and an anomalous left anterior descending coronary artery from the right cusp (7–9%). The latter is important in that surgical correction must avoid injuring the coronary artery when repairing the RV outflow obstruction. Pulmonary branch stenosis may also be present.

Most adult patients have undergone prior surgery. If significant RV outflow obstruction is present in the neonatal period, a systemic arterial to pulmonary artery shunt may be the initial surgical procedure to improve pulmonary blood flow, though many infants undergo repair without this first step. Most adults will have had this initial palliative repair, however. The palliative procedure enables blood to reach the underperfused lung either by directly attaching one of the subclavian arteries to a main PA branch (**classic Blalock shunt**) or, more likely, by creating a conduit between the two (**modified Blalock shunt**). Total repair of the tetralogy of Fallot generally includes a VSD patch and usually an enlarging RV outflow tract patch, as well as a take-down of any prior arterial-pulmonary artery shunt. If the RV outflow tract patch extends through the pulmonary valve into the PA (transannular patch), varying degrees of pulmonary valve regurgitation develop. Most surgeons approach the inside of the RV via the right atrium and through the tricuspid valve and try to avoid a transannular patch if possible. Over the years, the volume overload from residual severe pulmonary valve regurgitation becomes the major hemodynamic problem to deal with in adults. A large RV outflow patch contributes to a relative RV volume load. Ventricular arrhythmias can originate from the edge of either the VSD or outflow tract patch and tend to increase in frequency as the size of the RV increases.

## ► Clinical Findings

Most adult patients in whom tetralogy of Fallot has been repaired are relatively asymptomatic unless right heart failure occurs or arrhythmias become an issue. Patients can be active and generally require no specific therapy.

### A. Symptoms and Signs

Physical examination should include checking both arms for any loss of pulse from a prior shunt procedure in infancy. The jugular venous pulsations (JVP) may reveal an increased *a* wave from poor RV compliance or rarely a *c-v* wave due to tricuspid regurgitation. The right-sided arch has no consequence. The precordium may be active, often with a persistent pulmonary outflow murmur.  $P_2$  may or may not be audible. A right-sided gallop may be heard. A residual VSD or an aortic regurgitation murmur may be present.

### B. ECG and Chest Radiography

The ECG reveals RVH and right axis deviation; in repaired tetralogy, there is often a right bundle branch block

pattern. The chest radiograph shows a classic boot-shaped heart with prominence of the RV and a concavity in the RV outflow tract. This may be less impressive following repair. The aorta may be enlarged and right sided. Importantly, the width of the QRS should be examined yearly because a QRS width of more than 180 msec is one of the risks for sudden death, although newer data suggest that this cutoff is not as specific as once thought. Most experts recommend ambulatory monitoring periodically as well, especially if the patient experiences palpitations. Other identified risk factors for ventricular arrhythmias include having multiple prior cardiac surgeries, an elevated LV end-diastolic pressure (LVEDP), and older age at time of repair. In fact, it appears that the more the left side of the heart is involved, the higher the risk of sudden death.

### C. Diagnostic Studies

Echocardiography/Doppler usually establishes the diagnosis by noting the unrestricted (large) VSD, the RV infundibular stenosis, and the enlarged aorta. In patients who have had tetralogy of Fallot repaired, echocardiography/Doppler also provides data regarding the amount of residual pulmonary valve regurgitation if a transannular patch is present, RV and LV function, and the presence of aortic regurgitation. Elevated N-terminal pro B-type natriuretic peptide (NT-proBNP) blood levels have also been correlated with increasing RV enlargement.

Cardiac MRI and CT can quantitate both the pulmonary regurgitation and the RV volumes. In addition, cardiac MRI and CT can identify whether there is either a native pulmonary arterial branch stenosis or a stenosis at the distal site of a prior arterial-to-PA shunt or other anomalies, such as an ASD. The ability of cardiac MRI to accurately quantitate the pulmonary regurgitation severity and provide more accurate RV volume measurements gives it an advantage over other imaging studies. Cardiac catheterization may be required to document the degree of pulmonary valve regurgitation because noninvasive studies depend on velocity gradients. Pulmonary angiography demonstrates the degree of pulmonary valve regurgitation, and RV angiography helps assess any postoperative outflow tract aneurysm.

The need for electrophysiologic studies with ventricular stimulation and potential ventricular tachycardia ablation has been suggested by some experts for patients who have had evidence for ventricular tachycardia, unexplained syncope, a wide QRS, are older, or who are about to undergo pulmonary valve replacement.

### ► Prognosis & Treatment

A few patients with “just the right amount” of subpulmonic stenosis enter adulthood without having had surgical correction. However, most adult patients have had surgical repair, including VSD closure, resection of infundibular muscle, and insertion of an outflow tract patch to relieve the subpulmonic obstruction. Patients with pulmonary valve regurgitation should be monitored to ensure the RV volume does not progressively increase. Low-pressure pulmonary valve regurgitation is difficult to diagnose due to

the fact that the RV diastolic pressures tend to be high and the pulmonary arterial diastolic pressure low. This means there is little gradient between the PA and the RV in diastole, so that there may be little murmur or evidence of turbulence on color flow Doppler. If the RV begins to enlarge, it must be assumed that this is due to pulmonary valve regurgitation until proven otherwise. Early surgical pulmonary valve replacement is increasingly being favored. The RV volumes from cardiac MRI are important in deciding when to intervene if the patient is not very symptomatic; an RV end-diastolic volume index of greater than 160 mm/m<sup>2</sup> or an RV end-systolic volume index of greater than 80 mm/m<sup>2</sup> is recommended as the cutoff. There are also a number of other triggers for intervention, details of which can be found in the AHA/ACC and ESC guidelines. A percutaneous approach to pulmonary valve regurgitation remains limited as the available percutaneous valve diameters are frequently too small for the size of the pulmonary annulus. The Melody valve is a bovine jugular vein prosthesis with the largest size being 22 mm in diameter. Percutaneous stented valves, particularly the Edwards SAPIEN XT, have been used successfully and can be used in patients with larger pulmonary root sizes. Often, a regular stent is placed within the PA first, with the stented valve then placed within this first stent. The expansion of the PA must not impede flow down any coronary artery; this is tested by a trial balloon expansion while imaging the coronary artery at the same time (class I requirement). There has been an increase in stented valve endocarditis noted after the placement of the Melody valve; this is being closely monitored.

If an anomalous coronary artery is present, then an extracardiac conduit around it from the RV to the PA may be necessary as part of the tetralogy repair. By 20-year follow-up, reoperation of the common tetralogy repair is needed in about 10–15%, not only for severe pulmonary valve regurgitation but also for residual infundibular stenosis. Usually the pulmonary valve is replaced with a pulmonary homograft, although a porcine bioprosthetic valve is also suitable. Percutaneous valve-in-valve stented bioprosthetic valves have successfully been used when there is surgical bioprosthetic valve dysfunction. Cryoablation of the tissue giving rise to arrhythmias is sometimes performed at the time of reoperation. Branch pulmonary stenosis may be percutaneously opened by stenting. If a conduit has been used already for repair of the RV outflow obstruction, a percutaneous approach with a stented pulmonary valve may be possible. All patients require endocarditis prophylaxis (see Tables 33–3, 33–4, and 33–5). Most adults with stable hemodynamics can be quite active, and most women can carry a pregnancy adequately if RV function is preserved.

Atrial fibrillation, reentrant atrial arrhythmias, and ventricular ectopy are common, especially after the age of 45. Left heart disease appears to cause arrhythmias more often than right heart disease. Biventricular dysfunction is not an uncommon consequence as the patient ages. The cause of associated LV dysfunction is often multifactorial and frequently unclear. Similarly, the aorta may enlarge with accompanying aortic regurgitation, and these lesions can

become severe enough to warrant surgical intervention. Patients with RV or LV dysfunction or with dysfunction of both ventricles may require a prophylactic defibrillator.

## ► When to Refer

All patients with tetralogy of Fallot should be referred to a cardiologist with expertise in adult congenital heart disease.

Haas NA et al. Early outcomes of percutaneous pulmonary valve implantation using the Edwards SAPIEN XT transcatheter heart valve system. *Int J Cardiol.* 2018;250:86. [PMID: 29017776]

He F et al. Whether pulmonary valve replacement in asymptomatic patients with moderate or severe regurgitation after tetralogy of Fallot repair is appropriate: a case-control study. *J Am Heart Assoc.* 2019;8:e010689. [PMID: 30587056]

Ros D et al. Infectious endocarditis after percutaneous pulmonary valve implantation with a stent mounted bovine jugular vein valve. Clinical experience and the evaluation of the modified Duke criteria. *Int J Cardiol.* 2021;323:40. [PMID: 32860844]

Smith CA et al. Long-term outcome of tetralogy of Fallot: a study from the Pediatric Cardiac Care Consortium. *JAMA Cardiol.* 2019;4:34. [PMID: 30566184]

## VALVULAR HEART DISEASE

The typical findings of each native valve lesion are described in Table 10–1. Table 10–2 outlines bedside maneuvers to distinguish among the various systolic murmurs.

The 2017 ACC/AHA valvular heart disease guidelines suggest all lesions may be best classified clinically into one of six categories based on anatomy and symptoms.

**Stage A:** Patients at risk for valvular heart disease.

**Stage B:** Patients with progressive valvular heart disease (mild to moderate severity) and asymptomatic.

**Stage C:** Asymptomatic patients who have reached criteria for severe valvular heart disease.

**C1:** Severe valve lesion. Asymptomatic. Normal LV function.

**C2:** Severe valve lesion. Asymptomatic. Abnormal LV function.

**Stage D:** Symptomatic patients as a result of valvular heart disease.

In 2020, the ACC/AHA guideline for the management of patients with valvular heart disease was published and this chapter will highlight the changes and additions from the prior guidelines, first published in 2014 and then updated in 2017.

Nishimura RA et al. 2017 AHA/ACC focused update of the 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation.* 2017;135:e1159. [PMID: 28298458]

Otto CM et al. 2020 ACC/AHA guideline for the management of patients with valvular heart disease. *J Am Coll Cardiol.* 2021; 77:450. [PMID: 33342587]

**Table 10–1.** Differential diagnosis of valvular heart disease.

|  | Mitral Stenosis  | Mitral Regurgitation  | Aortic Stenosis  | Aortic Regurgitation   | Tricuspid Stenosis  | Tricuspid Regurgitation  |
|--|--|---|--|--|---|--|
| Inspection                               | Malar flush, precordial bulge, and diffuse pulsation in young patients.  | Usually prominent and hyperdynamic apical impulse to left of MCL.   | Sustained PMI, prominent atrial filling wave.  | Hyperdynamic PMI to left of MCL and downward. Visible carotid pulsations. Pulsating nailbeds (Quincke sign), head bob (deMusset sign).   | Giant <i>a</i> wave in jugular pulse with sinus rhythm. Peripheral edema or ascites, or both. | Large <i>v</i> wave in jugular pulse; time with carotid pulsation. Peripheral edema or ascites, or both.   |
| Palpation                                | "Tapping" sensation over area of expected PMI. Right ventricular pulsation in left third to fifth ICS parasternally when pulmonary hypertension is present. $P_2$ may be palpable.   | Forceful, brisk PMI; systolic thrill over PMI. Pulse normal, small, or slightly collapsing.   | Powerful, heaving PMI to left and slightly below MCL. Systolic thrill over aortic area, sternal notch, or carotid arteries in severe disease. Small and slowly rising carotid pulse. If bicuspid AS, check for delay at femoral artery to exclude coarctation. | Apical impulse forceful and displaced significantly to left and downward. Prominent carotid pulses. Rapidly rising and collapsing pulses (Corrigan pulse).   | Pulsating, enlarged liver in ventricular systole.   | Right ventricular pulsation. Systolic pulsation of liver.  |
| Heart sounds, rhythm, and blood pressure | $S_1$ loud if valve mobile. Opening snap following $S_2$ . The worse the disease, the closer the $S_2$ -opening snap interval.   | $S_1$ normal or buried in early part of murmur (exception in mitral prolapse where murmur may be late). Prominent third heart sound when severe MR. Atrial fibrillation common. Blood pressure normal. Midsystolic clicks may be present and may be multiple.   | $A_2$ normal, soft, or absent. Prominent $S_4$ . Blood pressure normal, or systolic pressure normal with high diastolic pressure.  | $S_1$ normal or reduced, $A_2$ loud. Wide pulse pressure with diastolic pressure < 60 mm Hg. When severe, gentle compression of femoral artery with diaphragm of stethoscope may reveal diastolic flow (Duroziez) and pressure in leg on palpation > 40 mm Hg than in arm (Hill).                      | $S_1$ often loud.   | Atrial fibrillation may be present.  |
| <b>Murmurs</b>                           |  |   |  |  |   |  |
| Location and transmission                | Localized at or near apex. Diastolic rumble best heard in left lateral position; may be accentuated by having patient do sit-ups. Rarely, short diastolic murmur along lower left sternal border (Graham Steell) in severe pulmonary hypertension. | Loudest over PMI; posteriorly directed jets (ie, anterior mitral prolapse) transmitted to left axilla, left infrascapular area; anteriorly directed jets (ie, posterior mitral prolapse) heard over anterior precordium. Murmur unchanged after premature beat. | Right second ICS parasternally or at apex, heard in carotid arteries and occasionally in upper interscapular area. May sound like MR at apex (Gallaverdin phenomenon), but murmur occurs after $S_1$ and stops before $S_2$ .                                  | Diastolic: louder along left sternal border in third to fourth interspace. Heard over aortic area and apex. May be associated with low-pitched mid-diastolic murmur at apex (Austin Flint) due to functional mitral stenosis. If due to an enlarged aorta, murmur may radiate to right sternal border. | Third to fifth ICS along left sternal border out to apex. Murmur increases with inspiration.  | Third to fifth ICS along left sternal border. Murmur hard to hear but increases with inspiration. Sit-ups can increase cardiac output and accentuate murmur. |

(continued)

**Table 10–1.** Differential diagnosis of valvular heart disease. (continued)

|  | Mitral Stenosis  | Mitral Regurgitation  | Aortic Stenosis  | Aortic Regurgitation   | Tricuspid Stenosis   | Tricuspid Regurgitation  |
|--|--|---|--|--|--|--|
| <b>Timing</b>                          | Relation of opening snap to $A_2$ important. The higher the LA pressure, the earlier the opening snap. Presystolic accentuation before $S_1$ if in sinus rhythm. Graham Steell begins with $P_2$ (early diastole) if associated pulmonary hypertension.                            | Pansystolic: begins with $S_1$ and ends at or after $A_2$ . May be late systolic in mitral valve prolapse.  | Begins after $S_1$ , ends before $A_2$ . The more severe the stenosis, the later the murmur peaks. | Begins immediately after aortic second sound and ends before first sound (blurring both); helps distinguish from MR. | Rumble often follows audible opening snap.   | At times, hard to hear. Begins with $S_1$ and fills systole. Increases with inspiration. |
| <b>Character</b>                       | Low-pitched, rumbling; presystolic murmur merges with loud $S_1$ .   | Blowing, high-pitched; occasionally harsh or musical.   | Harsh, rough.  | Blowing, often faint.  | As for mitral stenosis.  | Blowing, coarse, or musical.   |
| <b>Optimum auscultatory conditions</b> | After exercise, left lateral recumbency. Use stethoscope bell, lightly applied.  | After exercise; use stethoscope diaphragm. In prolapse, findings may be more evident while standing.  | Use stethoscope diaphragm. Patient resting, leaning forward, breath held in full expiration.       | Use stethoscope diaphragm. Patient leaning forward, breath held in expiration.                                       | Use stethoscope bell. Murmur usually louder and at peak during inspiration. Patient recumbent. | Use stethoscope diaphragm. Murmur usually becomes louder during inspiration.             |
| <b>Radiography</b>                     | Straight left heart border from enlarged LA appendage. Elevation of left mainstem bronchus. Large right ventricle and pulmonary artery if pulmonary hypertension is present. Calcification in mitral valve in rheumatic mitral stenosis or in annulus in calcific mitral stenosis. | Enlarged left ventricle and LA.   | Concentric left ventricular hypertrophy. Prominent ascending aorta. Calcified aortic valve common. | Moderate to severe left ventricular enlargement. Aortic root often dilated.  | Enlarged right atrium with prominent SVC and azygous shadow.                                   | Enlarged right atrium and right ventricle.   |
| <b>ECG</b>                             | Broad P waves in standard leads; broad negative phase of diphasic P in $V_1$ . If pulmonary hypertension is present, tall peaked P waves, right axis deviation, or right ventricular hypertrophy appears.  | Left axis deviation or frank left ventricular hypertrophy. P waves broad, tall, or notched in standard leads. Broad negative phase of diphasic P in $V_1$ . | Left ventricular hypertrophy.  | Left ventricular hypertrophy.  | Tall, peaked P waves. Possible right ventricular hypertrophy.                                  | Right axis usual.  |

| Echocardiography                          |  |  |  |  |  |   |
|---|--|--|--|--|--|---|
| Two-dimensional echocardiography          | Thickened, immobile mitral valve with anterior and posterior leaflets moving together. "Hockey stick" shape to opened anterior leaflet in rheumatic mitral stenosis. Annular calcium with thin leaflets in calcific mitral stenosis. LA enlargement, normal to small left ventricle. Orifice can be traced to approximate mitral valve orifice area. | Thickened mitral valve in rheumatic disease; mitral valve prolapse; flail leaflet or vegetations may be seen. Dilated left ventricle in volume overload. Operate for left ventricular end-systolic dimension < 4.5 cm. | Dense persistent echoes from the aortic valve with poor leaflet excursion. Left ventricular hypertrophy late in the disease. Bicuspid valve in younger patients. | Abnormal aortic valve or dilated aortic root. Diastolic vibrations of the anterior leaflet of the mitral valve and septum. In acute aortic regurgitation, premature closure of the mitral valve before the QRS. When severe, dilated left ventricle with normal or decreased contractility. Operate when left ventricular end-systolic dimension > 5.0 cm. | In rheumatic disease, tricuspid valve thickening, decreased early diastolic filling slope of the tricuspid valve. In carcinoid, leaflets fixed, but no significant thickening. | Enlarged right ventricle with paradoxical septal motion. Tricuspid valve often pulled open by displaced chordae.                                  |
| Continuous and color flow Doppler and TEE | Prolonged pressure half-time across mitral valve allows estimation of gradient. MVA estimated from pressure half-time. Indirect evidence of pulmonary hypertension by noting elevated right ventricular systolic pressure measured from the tricuspid regurgitation jet.   | Regurgitant flow mapped into LA. Use of PISA helps assess MR severity. TEE important in prosthetic mitral valve regurgitation.   | Increased transvalvular flow velocity; severe AS when peak jet > 4 m/sec (64 mm Hg). Valve area estimate using continuity equation is poorly reproducible.       | Demonstrates regurgitation and qualitatively estimates severity based on percentage of left ventricular outflow filled with jet and distance jet penetrates into left ventricle. TEE important in aortic valve endocarditis to exclude abscess. Mitral inflow pattern describes diastolic dysfunction.   | Prolonged pressure half-time across tricuspid valve can be used to estimate mean gradient. Severe tricuspid stenosis present when mean gradient > 5 mm Hg.                     | Regurgitant flow mapped into right atrium and venae cavae. Right ventricular systolic pressure estimated by tricuspid regurgitation jet velocity. |

A<sub>2</sub>, aortic second sound; AS, aortic stenosis; ICS, intercostal space; LA, left atrial; MCL, midclavicular line; MR, mitral regurgitation; MVA, measured valve area; P<sub>2</sub>, pulmonary second sound; PISA, proximal isovelocity surface area; PMI, point of maximal impulse; S<sub>1</sub>, first heart sound; S<sub>2</sub>, second heart sound; S<sub>4</sub>, fourth heart sound; SVC, superior vena cava; TEE, transesophageal echocardiography; V<sub>1</sub>, chest ECG lead 1.

**Table 10–2.** Effect of various interventions on systolic murmurs.

| Intervention                       | Hypertrophic Cardiomyopathy | Aortic Stenosis | Mitral Regurgitation | Mitral Prolapse |
|------------------------------------|-----------------------------|-----------------|----------------------|-----------------|
| Valsalva                           | ↑                           | ↓               | ↓ or ×               | ↑ or ↓          |
| Standing                           | ↑                           | ↑ or ×          | ↓ or ×               | ↑               |
| Handgrip or squatting              | ↓                           | ↓ or ×          | ↑                    | ↓               |
| Supine position with legs elevated | ↓                           | ↑ or ×          | ×                    | ↓               |
| Exercise                           | ↑                           | ↑ or ×          | ↓                    | ↑               |

↑, increased; ↓, decreased; ×, unchanged.

Modified, with permission, from Paraskos JA. Combined valvular disease. In: *Valvular Heart Disease*, 3e. Dalen JE, Alpert JS, Rahimtula SH (editors). Philadelphia: Lippincott Williams & Wilkins, 2000.

## MITRAL STENOSIS



### ESSENTIALS OF DIAGNOSIS

- ▶ Fatigue, exertional dyspnea, and orthopnea when the stenosis becomes severe.
- ▶ Symptoms often precipitated by onset of atrial fibrillation or pregnancy.
- ▶ Intervention indicated for symptoms, atrial fibrillation, or evidence of pulmonary hypertension. Most symptomatic patients have a mitral valve area of  $< 1.5 \text{ cm}^2$ .

### General Considerations

Most patients with native valve mitral stenosis are presumed to have had rheumatic heart disease, although a history of rheumatic fever is noted in only about one-third. (Also see section on Rheumatic Fever.) Rheumatic mitral stenosis results in thickening of the leaflets, fusion of the mitral commissures, retraction, thickening and fusion of the chordae, and calcium deposition in the valve. Mitral stenosis can also occur due to congenital disease with chordal fusion or papillary muscle malposition. The papillary muscles may be abnormally close together, sometimes so close that they merge into a single papillary muscle (the “parachute mitral valve”). In these patients, the chordae or valvular tissue (or both) may also be fused. In older patients and in those undergoing dialysis, mitral annular calcification may stiffen the mitral valve and reduce its motion to the point where a mitral gradient is present. Calcium in the mitral annulus virtually invades the mitral leaflet from the annulus inward as opposed to the calcium buildup in the leaflets and commissures as seen in rheumatic heart disease. Mitral valve obstruction may also develop in patients who have had mitral valve repair with a mitral annular ring that is too small, or in patients who have had a surgical valve replacement (prosthetic valve-patient mismatch or degeneration of the prosthetic valve over time).

### Clinical Findings

#### A. Symptoms and Signs

Two clinical syndromes classically occur in patients with mitral stenosis. In mild to moderate mitral stenosis, LA pressure and cardiac output may be essentially normal, and the patient is either asymptomatic or symptomatic only with extreme exertion. The measured valve area is usually between  $1.5 \text{ cm}^2$  and  $1.0 \text{ cm}^2$ . In severe mitral stenosis (valve area less than  $1.0 \text{ cm}^2$ ), severe pulmonary hypertension develops due to a “secondary stenosis” of the pulmonary vascular bed. In this condition, pulmonary edema is uncommon, but symptoms of low cardiac output and right heart failure predominate. Any measured valve area less than  $1.5 \text{ cm}^2$  should be considered significant.

A characteristic finding of rheumatic mitral stenosis is an **opening snap** following  $A_2$  due to the stiff mitral valve. The interval between the opening snap and aortic closure sound is long when the LA pressure is low but shortens as the LA pressure rises and approaches the aortic diastolic pressure. As mitral stenosis worsens, there is a localized low-pitched diastolic murmur whose duration increases with the severity of the stenosis as the mitral gradient continues throughout more of diastole. The diastolic murmur is best heard at the apex with the patient in the left lateral position (Table 10–1). Mitral regurgitation may be present as well.

Paroxysmal or chronic atrial fibrillation eventually develops in 50–80% of patients. Any increase in the heart rate reduces diastolic filling time and increases the mitral gradient. A sudden increase in heart rate may precipitate pulmonary edema. Therefore, heart rate control is important, with slow heart rates allowing for more diastolic filling of the LV.

#### B. Diagnostic Studies

Echocardiography is the most valuable technique for assessing mitral stenosis (Table 10–1). LA size can also be determined by echocardiography; increased size denotes an increased likelihood of atrial fibrillation and thrombus formation.

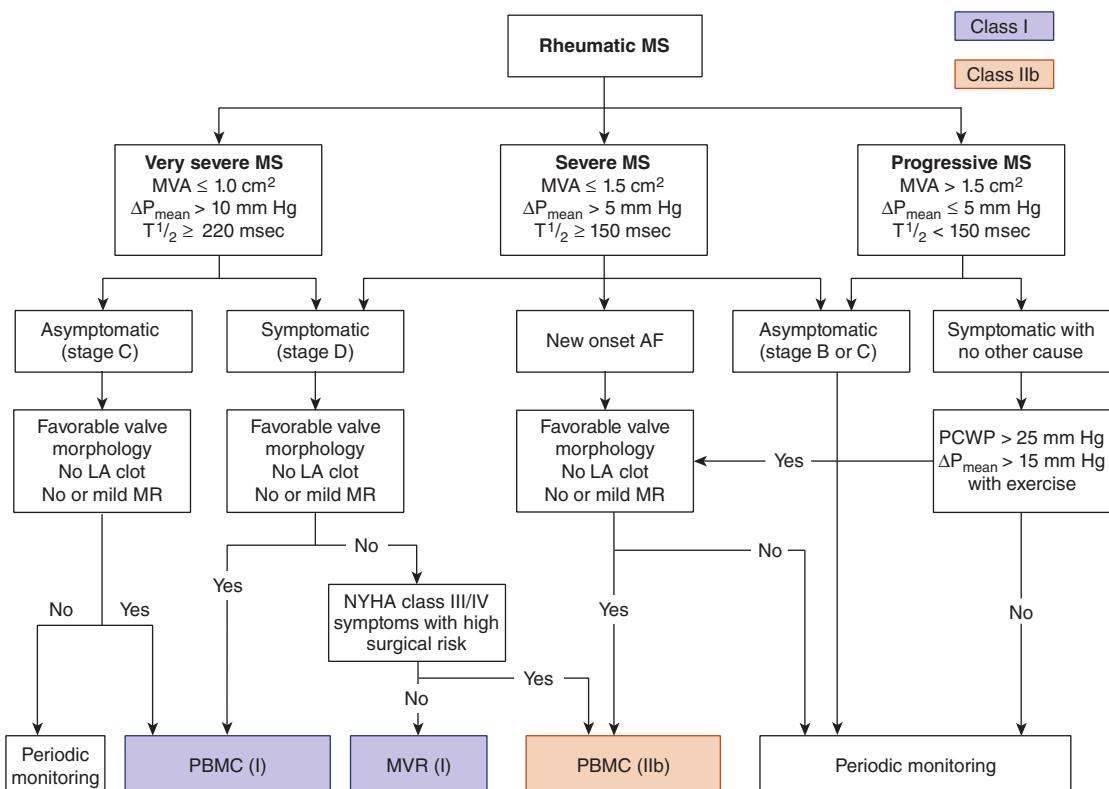
Because echocardiography and careful symptom evaluation provide most of the needed information, cardiac catheterization is used primarily to detect associated coronary or myocardial disease—usually after the decision to intervene has been made.

## Treatment & Prognosis

In most cases, there is a long asymptomatic phase after the initial rheumatic infection, followed by subtle limitation of activity. Pregnancy and its associated increase in stroke volume and heart rate result in an increased transmитral pressure gradient and may precipitate symptoms. In particular, toward the end of pregnancy, the cardiac output continues to be maintained by an increase in heart rate, increasing the mitral gradient by shortening diastolic time. Patients with moderate to severe mitral stenosis should have the condition corrected prior to becoming pregnant if possible (when the measured valve area is about  $2.0 \text{ cm}^2$ ). Pregnant patients who become symptomatic can undergo successful surgery, preferably in the third trimester, although balloon valvuloplasty is the treatment of choice if the echocardiography valve score is low enough.

The onset of atrial fibrillation often precipitates symptoms, which improve with control of the ventricular rate or restoration of sinus rhythm. Conversion to and subsequent maintenance of sinus rhythm are most commonly successful when the duration of atrial fibrillation is brief (less than 6–12 months) and the LA is not severely dilated (diameter less than 4.5 cm). Once atrial fibrillation occurs, the patient should receive warfarin even if sinus rhythm is restored, since atrial fibrillation often recurs even with antiarrhythmic therapy and 20–30% of these patients will have systemic embolization if untreated. Systemic embolization in the presence of only mild to moderate disease is not an indication for surgery but should be treated with warfarin. DOACs (dabigatran, apixaban, rivaroxaban, edoxaban) are *not* recommended by the most recent guidelines, since patients with atrial fibrillation were excluded from the approval trials.

Indications for intervention focus on symptoms such as an episode of pulmonary edema, a decline in exercise capacity, or any evidence of pulmonary hypertension (peak systolic pulmonary pressure greater than 50 mm Hg). Some experts believe that the presence of atrial fibrillation should also be a consideration for an intervention. Most interventions are not pursued until the patient is symptomatic (stage D) (Figure 10–1). In some patients, symptoms



**Figure 10–1.** The AHA/ACC guidelines for intervention in mitral stenosis. AF, atrial fibrillation; LA, left atrial; MR, mitral regurgitation; MS, mitral stenosis; MVA, mitral valve area; MVR, mitral valve replacement; NYHA, New York Heart Association; PBMC, percutaneous balloon mitral commissurotomy; PCWP, pulmonary capillary wedge pressure;  $\Delta P_{\text{mean}}$ , mean pressure gradient;  $T\frac{1}{2}$ , half-life. (Reproduced, with permission, from Nishimura RA et al. 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014;129:e521. © 2014 American Heart Association, Inc.)

develop with calculated mitral valve areas between  $1.5 \text{ cm}^2$  and  $1.0 \text{ cm}^2$ . Symptoms or evidence of pulmonary hypertension should drive the decision to intervene in these patients, not the estimated valve area.

Open mitral commissurotomy is now rarely performed and has been replaced by percutaneous balloon valvuloplasty. Ten-year follow-up data comparing surgery to balloon valvuloplasty suggest no real difference in outcome between the two modalities. Replacement of the valve is indicated when combined stenosis and regurgitation are present or when the mitral valve echo score is much greater than 8–10. To determine the valve score, numbers 1 to 4 are assigned to four valve characteristics: mobility, calcification, thickening, and submitral scar. Thus, a maximum score is 16. Percutaneous balloon valvuloplasty has a very low mortality rate (less than 0.5%) and a low morbidity rate (3–5%). Operative mortality rates are also low: 1–3% in most institutions. Repeat balloon valvuloplasty can be done if the morphology of the valve remains suitable. At surgery, a **Maze procedure** may be done at the same time to reduce recurrent atrial arrhythmias. It involves a number of endocardial incisions across the right and left atria to disrupt the electrical activity that sustains atrial arrhythmias. In many institutions, the LA appendage is sewn closed to help remove a potential future source for thrombosis.

Mechanical mitral prosthetic valves are more prone to thrombosis than mechanical aortic prosthetic valves. The recommended INR range is thus higher (INR 2.5–3.5 or average of 3.0). Low-dose aspirin should be used in conjunction with warfarin if the bleeding risk is low. DOACs are *not* recommended as an anticoagulant. It is a class IIa recommendation that warfarin be used for up to 6 months after implantation of a bioprosthetic mitral valve. Bioprosthetic valves tend to degenerate after about 10–15 years. Percutaneous balloon valvuloplasty is not effective when bioprosthetic valve stenosis occurs, but stented valve-in-valve procedures have been successful. However, valve-in-valve procedures are still uncommon due to the need for the technically challenging transseptal approach. Reported early outcomes have been positive in patients with bioprosthetic valves, ring annuloplasty, and even in some calcific mitral stenosis patients. Younger patients and those with end-stage renal disease are generally believed to do the poorest with bioprosthetic heart valves, although data have questioned the role of chronic kidney disease as a major risk factor. Endocarditis prophylaxis is indicated for patients with prosthetic heart valves but is not indicated in native valve disease (see Tables 33–3, 33–4, and 33–5). Mitral stenosis due to calcific encroachment of the leaflets from mitral annular calcium can progress to severe mitral stenosis at times (estimated to be about 1 in 6 over 10 years). It does not lend itself to percutaneous valvuloplasty, and there are only case reports of using a percutaneous mitral valve replacement option.

## ► When to Refer

- Patients with mitral stenosis should be monitored with yearly examinations, and echocardiograms should be performed more frequently as the severity of the obstruction increases.

- All patients should initially be seen by a cardiologist, who can then decide how often the patient needs cardiology follow-up and whether intervention is indicated.

Kim JY et al. Outcomes of direct oral anticoagulants in patients with mitral stenosis. *J Am Coll Cardiol.* 2019;73:1123. [PMID: 30871695]

Tsutsui RS et al. Natural history of mitral stenosis in patients with mitral annular calcium. *JACC Cardiovasc Imaging.* 2019;12:1105. [PMID: 30765312]

## MITRAL REGURGITATION



### ESSENTIALS OF DIAGNOSIS

- May be asymptomatic for years (or for life).
- Severe mitral regurgitation may cause left-sided heart failure and lead to pulmonary hypertension and right-sided heart failure.
- For chronic primary mitral regurgitation, surgery is indicated for symptoms or when the LV ejection fraction (LVEF) is < 60% or the echocardiographic LV end-systolic dimension is > 4.0 cm. Surgery also indicated in patients who have a progressive increase in LV size or decline in LVEF.
- In patients with mitral prolapse and severe mitral regurgitation, earlier surgery is indicated if mitral repair can be performed successfully with a high degree of certainty.
- Transcatheter edge-to-edge repair, if possible, can be done in symptomatic patients at higher surgical risk regardless of whether the mitral regurgitation is primary or secondary.
- Patients with functional chronic mitral regurgitation may improve with biventricular pacing and guideline-directed management and therapy.

## ► General Considerations

Mitral regurgitation results in a volume load on the heart (increases preload) and reduces afterload. The result is an enlarged LV with an increased ejection fraction (EF). Over time, the stress of the volume overload reduces myocardial contractile function; when this occurs, there is a drop in EF and a rise in end-systolic volume.

## ► Clinical Findings

### A. Symptoms and Signs

In acute mitral regurgitation, the LA size is not large, and LA pressure rises abruptly, leading to pulmonary edema if severe. When chronic, the LA enlarges progressively and the increased volume can be handled without a major rise in the LA pressure; the pressure in pulmonary veins and capillaries may rise only during exertion. Exertional dyspnea and fatigue progress gradually over many years.

Mitral regurgitation leads to chronic LA and LV enlargement and may result in subsequent atrial fibrillation and eventually LV dysfunction. Clinically, mitral regurgitation is characterized by a pansystolic murmur maximal at the apex, radiating to the axilla and occasionally to the base. The murmur does not change in intensity after a premature beat because the LV to LA gradient is unaffected. In addition, a hyperdynamic LV impulse and a brisk carotid upstroke may be present along with a prominent third heart sound due to the increased volume returning to the LV in early diastole (Tables 10–1 and 10–2). In acute mitral regurgitation, the murmur intensity may be modest due to little difference between the LA and LV systolic pressures during ventricular systole. The mitral regurgitation murmur due to mitral valve prolapse tends to radiate anteriorly in the presence of posterior leaflet prolapse and posteriorly when the prolapse is primarily of the anterior leaflet. Mitral regurgitation may not be pansystolic in these patients but occur only after the mitral click (until late in the disease process when it then becomes progressively more holosystolic).

### B. Diagnostic Studies

Echocardiographic information demonstrating the underlying pathologic process (rheumatic, calcific, prolapse, flail leaflet, endocarditis, cardiomyopathy), LV size and function, LA size, PA pressure, and RV function can be invaluable in planning treatment as well as in recognizing associated lesions. The valvular heart disease guidelines provide details of the classification and measures of severity for primary and secondary mitral valve regurgitation. Doppler techniques provide qualitative and semiquantitative estimates of the severity of mitral regurgitation. TEE may help reveal the cause of regurgitation and is especially useful in patients who have had mitral valve replacement, in suspected endocarditis, and in identifying candidates for valvular repair. Echocardiographic dimensions and measures of systolic function are critical in deciding the timing of surgery. Asymptomatic patients with severe mitral regurgitation (stage C1) but preserved LV dimensions should undergo at least yearly echocardiography. Exercise hemodynamics with either Doppler echocardiography or cardiac catheterization may be useful when the symptoms do not fit the anatomic severity of mitral regurgitation. B-type natriuretic peptide (BNP or NT-proBNP) is useful in the early identification of LV dysfunction in the presence of mitral regurgitation and asymptomatic patients, and values that trend upward over time appear to have prognostic importance.

Cardiac MRI is occasionally useful, especially if specific myocardial causes are being sought (such as amyloid or myocarditis) or if myocardial viability assessment is needed prior to deciding whether to add coronary artery bypass grafting to mitral valve surgery.

Cardiac catheterization provides a further assessment of regurgitation and its hemodynamic impact along with LV function, resting cardiac output, and PA pressure. **The guidelines recommend coronary angiography to determine the presence of incidental coronary artery disease (CAD) prior to valve surgery in all men over age 40 years and in menopausal women with coronary risk factors.**

In younger patients, no coronary angiography is needed unless there is a clinical suspicion of coronary disease. Cardiac multidetector coronary CT may be adequate to screen patients with valvular heart disease for asymptomatic CAD. A normal CT coronary angiogram has a high predictive value for patients with normal or insignificant disease.

## ► Treatment & Prognosis

### A. Primary Mitral Regurgitation

The degree of LV enlargement reflects the severity and chronicity of regurgitation. LV volume overload may ultimately lead to LV failure and reduced cardiac output. LA enlargement may be considerable in **chronic mitral regurgitation** and a large amount of mitral regurgitation regurgitant volume may be tolerated. Patients with chronic lesions may thus remain asymptomatic for many years. Surgery is necessary when symptoms develop or when there is evidence for LV dysfunction, since progressive and irreversible deterioration of LV function can occur prior to the onset of symptoms. Early surgery is indicated even in asymptomatic patients with a reduced EF (less than 60%) or marked LV dilation with reduced contractility (end-systolic dimension greater than 4.0 cm) (Figure 10–2).

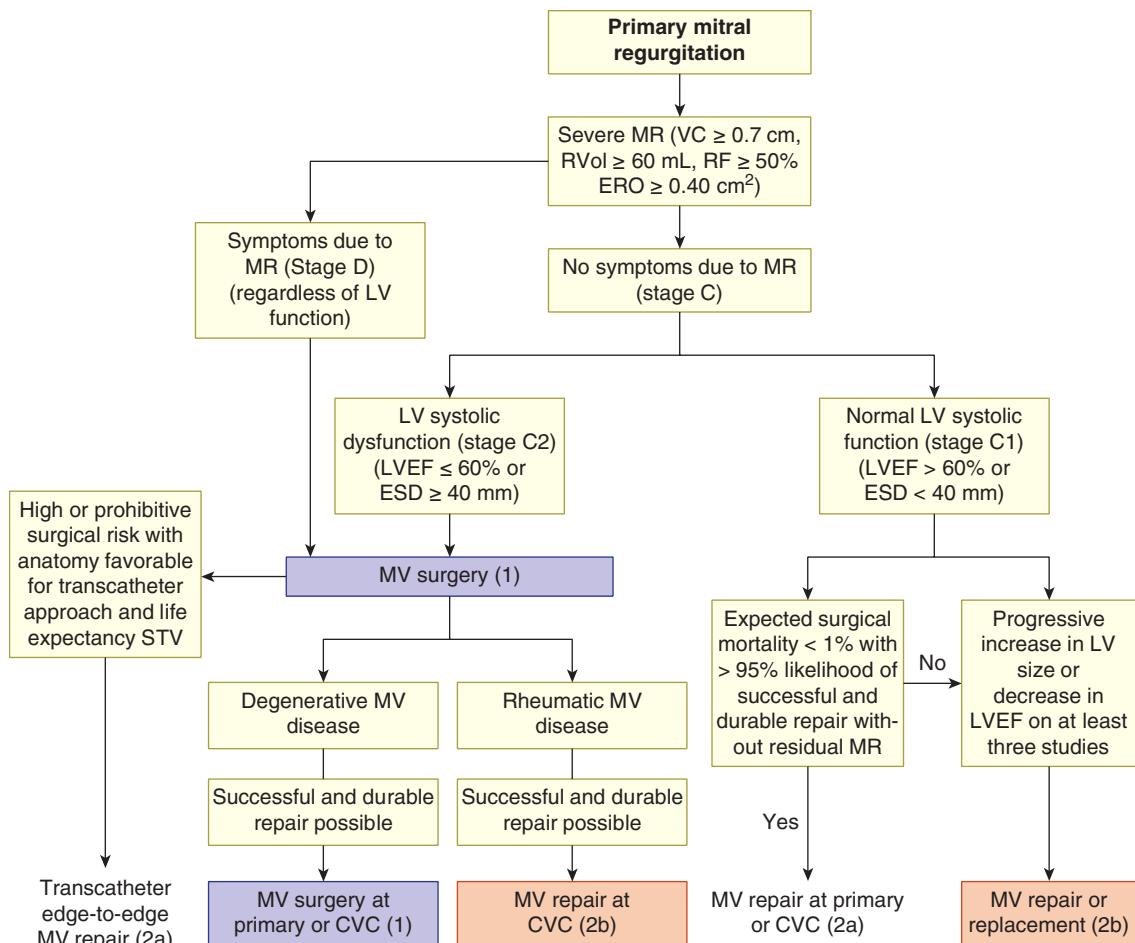
It is a class IIa indication for mitral valve surgery when the LVEF is greater than 60% and the LV end-systolic dimension is still less than 4.0 cm but serial imaging reveals a progressive increase in the LV end-systolic dimension or a serial decrease in the EF. Pulmonary hypertension development suggests the mitral regurgitation is severe and should prompt intervention.

**Acute mitral regurgitation** may develop abruptly, as with papillary muscle dysfunction following MI, valve perforation in infective endocarditis, in patients with hypertrophic cardiomyopathy (HCM), or when there are ruptured chordae tendineae in patients with mitral valve prolapse. Emergency surgery may be required.

Some patients may become hemodynamically unstable and require treatment with vasodilators or intra-aortic balloon counterpulsation that reduce the amount of retrograde regurgitant flow by lowering systemic vascular resistance and improving forward stroke volume. There is controversy regarding the role of afterload reduction in chronic mitral regurgitation, since the lesion inherently results in a reduction in afterload, and there are no data that chronic afterload reduction is effective in avoiding LV dysfunction or surgical intervention. A heightened sympathetic state has led some experts to suggest that beta-blockade be considered routinely, though this also remains speculative. The mitral regurgitation in patients with tachycardia-related cardiomyopathy may improve with normalization of the heart rate.

### B. Myocardial Disease and Mitral Regurgitation (Secondary Mitral Regurgitation)

When mitral regurgitation is due to cardiac dysfunction, it may subside as the infarction heals or LV dilation diminishes. The cause of the regurgitation in most of these situations is displacement of the papillary muscles and an enlarged mitral annulus rather than papillary muscle



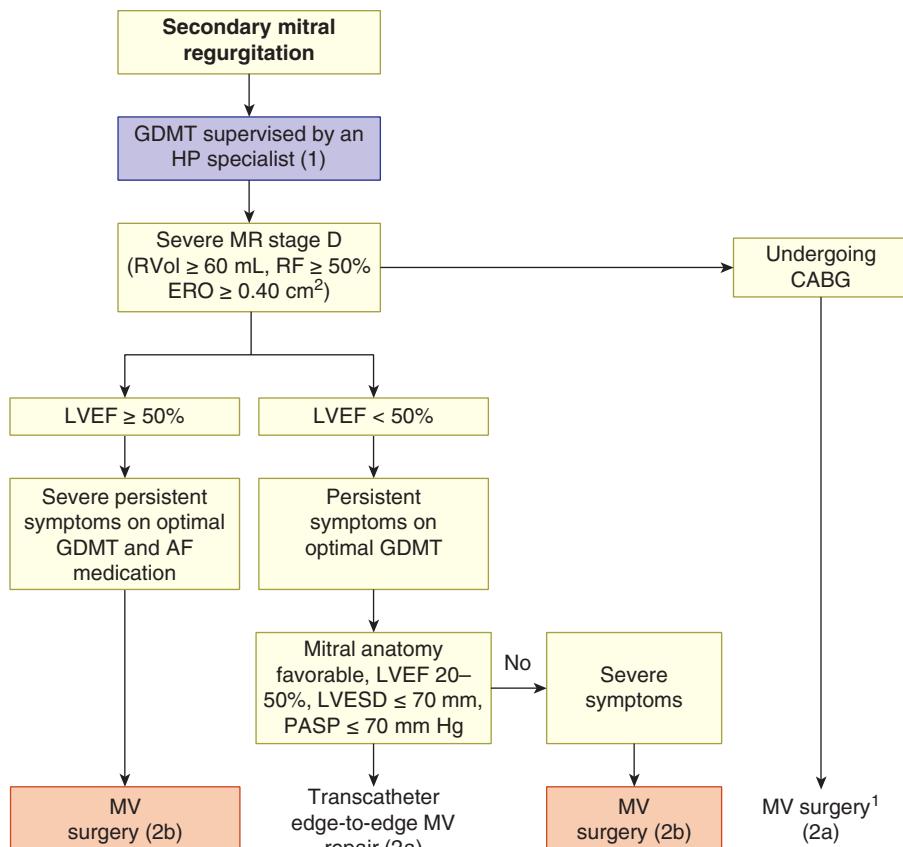
**Figure 10–2.** Algorithm for intervention in primary mitral regurgitation. CVC, Comprehensive Valve Center; ERO, effective regurgitant orifice; ESD, end-systolic dimension; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; MV, mitral valve; MVR, mitral valve replacement; RF, regurgitant fraction; RVol, regurgitant volume; VC, vena contracta. (Modified, with permission, from Otto CM et al. 2020 ACC/AHA guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2021;77:e25. © 2021 American College of Cardiology Foundation and the American Heart Association.)

ischemia. The fundamental problem is the lack of leaflet coaptation during systole (due to either leaflet prolapse or retraction). In acute MI, rupture of the papillary muscle may occur with catastrophic results. Transient—but sometimes severe—mitral regurgitation may occur during episodes of myocardial ischemia and contribute to flash pulmonary edema. Patients with dilated cardiomyopathies of any origin may have **secondary mitral regurgitation** due to the papillary muscle displacement or dilation of the mitral annulus, or both. If mitral valve replacement is performed, preservation of the chordae to the native valve helps prevent further ventricular dilation following surgery. Initially, several groups reported good results with mitral valve repair in patients with LVEF less than 30% and secondary mitral regurgitation. Current guidelines advise that mitral valve repair/replacement can be attempted in severe mitral regurgitation patients with an EF less than 30% or an LV end-systolic dimension greater than 5.5 cm,

or both, as long as repair and preservation of the chordae are possible. Figure 10–3 outlines the recommendations for intervention in secondary mitral regurgitation.

Mitral valve replacement with chordal preservation is preferred over mitral valve repair in patients with chronic ischemic cardiomyopathy. There may also be a role for cardiac resynchronization therapy with biventricular pacemaker insertion, which has been found to reduce mitral regurgitation related to cardiomyopathy in many patients. Guidelines recommend biventricular pacing prior to surgical repair in symptomatic patients who have functional mitral regurgitation as long as other criteria (eg, a QRS of greater than 150 msec or left bundle branch block or both) are present.

There are several ongoing trials of percutaneous approaches to reducing mitral regurgitation. These approaches include the use of a **mitral clip** (MitraClip) device to create a double orifice mitral valve, various



<sup>1</sup>Chordal-sparing MV replacement may be reasonable to choose over downsized annuloplasty repair.

**▲ Figure 10-3.** Algorithm for intervention in secondary mitral regurgitation. AF, atrial fibrillation; CABG, coronary artery bypass graft; ERO, effective regurgitant orifice; GDMT, guideline-directed management and therapy; HF, heart failure; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic dimension; MR, mitral regurgitation; MV, mitral valve; PASP, pulmonary artery systolic pressure; RF, regurgitant fraction; RVol, regurgitant volume. (Modified, with permission, from Otto CM et al. 2020 ACC/AHA guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. J Am Coll Cardiol. 2021;77:e25. © 2021 American College of Cardiology Foundation and the American Heart Association.)

coronary catheter devices to reduce the mitral annular area, and devices to reduce the septo-lateral ventricular size and consequent mitral orifice size. Of these devices, the most success has been noted with the edge-to-edge MitraClip. Two major trials have addressed the potential advantage of the percutaneous MitraClip. In the COAPT (Clinical Outcomes Assessment of MitraClip) trial among patients with heart failure and moderate-to-severe or severe secondary mitral regurgitation who remained symptomatic despite the use of maximum doses of guideline-directed medical therapy, transcatheter mitral-valve repair resulted in a lower rate of hospitalization for heart failure and lower all-cause mortality within 24 months of follow-up than medical therapy alone. The absolute risk reduction in all-cause mortality in patients receiving the MitraClip in the COAPT trial was 17%, which translated to a number needed to treat (NNT) of 6 to prevent 1 death over 2 years. This rather remarkably positive result, however, was tempered by another MitraClip randomized trial in a similar population that had a rather neutral result, the MITRA-FR

(Percutaneous Repair with MitraClip Device for Severe Functional/Secondary Mitral Regurgitation) study, in which the MitraClip therapy failed to show any survival benefit over medical therapy during the 1-year follow-up period. One suggestion to reconcile the differences in outcome has been suggested wherein the MitraClip is *ineffective* if the echocardiographic regurgitant orifice size is consistent with the size of the dilated LV, but the device is *effective* if the regurgitant orifice size is large compared to the size of the LV. This seemed to be verified by the results of the two trials. Current guidelines have accepted the use of the MitraClip in patients with secondary mitral regurgitation and high surgical risk. In addition, vascular plugging and occluder devices are being used in selected patients to occlude perivalvular leaks around prosthetic mitral valves. A transcatheter stented valve, which is used as a **transcatheter aortic valve replacement (TAVR)** device, can be used to open a degenerated mitral bioprosthetic valve in any position (aortic, mitral, tricuspid, or pulmonary). Transcatheter valve replacement has also been attempted in

small series to repair mitral regurgitation following mitral valve repair with mixed results. Finally, the first cases of a stented mitral valve prosthesis to replace the entire mitral valve have been reported. Abbott has initiated the SUMMIT trial, a US-based pivotal trial utilizing the Tendyne percutaneous mitral valve replacement device. The mitral valve and aortic valve share a common “annulus” and some of the early attempts at percutaneous valve replacement have failed due to obstruction of the aortic outflow.

### ► When to Refer

- All patients with more than mild mitral regurgitation should be referred to a cardiologist for an evaluation.
- Serial examinations and echocardiograms should be obtained and surgical referral made if there is an increase in the LV end-systolic dimensions, a fall in the LVEF to less than 60%, symptoms, evidence for pulmonary hypertension, or the new onset of atrial fibrillation.
- There is evidence that mitral valve repair should be done early in the course of the disease to improve mortality and morbidity.
- Treatment in severe mitral regurgitation in a patient with a dilated cardiomyopathy may be of benefit.

Ailawadi G et al; EVEREST II Investigators. One-year outcomes after MitraClip for functional mitral regurgitation. *Circulation*. 2019;139:37. [PMID: 30586701]

Grayburn PA et al. Proportionate and disproportionate functional mitral regurgitation: a new conceptual framework that reconciles the results of the MITRA-FR and COAPT trials. *JACC Cardiovasc Imaging*. 2019;12:353. [PMID: 30553663]

Obadia JF et al; MITRA-FR Investigators. Percutaneous repair or medical treatment for secondary mitral regurgitation. *N Engl J Med*. 2018;379:2297. [PMID: 30145927]

Otto CM et al. 2020 ACC/AHA guideline for the management of patients with valvular heart disease. *J Am Coll Cardiol*. 2021; 77:450. [PMID: 33342587]

Pibarot P et al. MITRA-FR versus COAPT: lessons from two trials with diametrically opposed results. *Eur Heart J Cardiovasc Imaging*. 2019;20:620. [PMID: 31115470]

Stone GW et al; COAPT Investigators. Transcatheter mitral-valve repair in patients with heart failure. *N Engl J Med*. 2018; 379:2307. [PMID: 30280640]

## AORTIC STENOSIS

### ESSENTIALS OF DIAGNOSIS

- ▶ Congenital bicuspid aortic valve (usually asymptomatic until middle or old age).
- ▶ “Degenerative” or calcific aortic stenosis; similar risk factors as atherosclerosis (symptoms usually in the elderly).
- ▶ Visual observation of immobile aortic valve plus a valve area of less than  $1.0 \text{ cm}^2$  define severe disease; low-gradient but severe aortic stenosis can thus be recognized when the stroke volume is reduced.
- ▶ Echocardiography/Doppler is diagnostic.

- ▶ Surgery typically indicated for symptoms. TAVR is approved for patients with calcific aortic stenosis.
- ▶ Intervention appropriate even in asymptomatic patients with super-severe aortic stenosis (mean gradient greater than 55 mm Hg) or when undergoing heart surgery for other reasons (eg, coronary artery bypass grafting [CABG]).
- ▶ BNP is a marker of early LV myocardial failure, and high levels (three times normal) suggest poor prognosis and can be an indication for intervention.

### ► General Considerations

There are two common clinical scenarios in which aortic stenosis is prevalent. The first is due to a congenitally abnormal **unicuspid** or **bicuspid valve**, rather than tricuspid. Symptoms can occur in young or adolescent individuals if the stenosis is severe, but more often emerge at age 50–65 years when calcification and degeneration of the valve become manifest. A dilated ascending aorta, due to an intrinsic defect in the aortic root media and the hemodynamic effects of the eccentric aortic jet, may accompany the bicuspid valve in about half of these patients. Coarctation of the aorta is also seen in a number of patients with congenital aortic stenosis. Offspring of patients with a bicuspid valve have a much higher incidence of the disease in either the valve, the aorta, or both (up to 30% in some series).

A second, more common pathologic process, **degenerative** or **calcific aortic stenosis**, is thought to be related to calcium deposition due to processes similar to those that occur in atherosclerotic vascular disease. Approximately 25% of patients over age 65 years and 35% of those over age 70 years have echocardiographic evidence of aortic valve thickening (sclerosis). About 10–20% of these will progress to hemodynamically significant aortic stenosis over a period of 10–15 years. Certain genetic markers are associated with aortic stenosis (most notably Notch 1), so a genetic component appears a likely contributor, at least in some patients. Other associated genetic markers have also been described.

Aortic stenosis has become the most common surgical valve lesion in developed countries, and many patients are elderly. The risk factors include hypertension, hypercholesterolemia, and smoking. HCM may also coexist with valvular aortic stenosis.

### ► Clinical Findings

#### A. Symptoms and Signs

Slightly narrowed, thickened, or roughened valves (**aortic sclerosis**) or aortic dilation may contribute to the typical ejection murmur of aortic stenosis. In mild or moderate cases where the valve is still pliable, an ejection click may precede the murmur and the closure of the valve ( $S_2$ ) is preserved. The characteristic systolic ejection murmur is heard at the aortic area and is usually transmitted to the neck and apex. In severe aortic stenosis, a palpable LV heave or thrill, a weak to absent aortic second sound, or

reversed splitting of the second sound is present (see Table 10-1). In some cases, only the high-pitched components of the murmur are heard at the apex, and the murmur may sound like mitral regurgitation (the so-called **Gallavardin phenomenon**). When the valve area is less than  $0.8\text{--}1.0 \text{ cm}^2$  (normal,  $3\text{--}4 \text{ cm}^2$ ), ventricular systole becomes prolonged and the typical carotid pulse pattern of delayed upstroke and low amplitude is present. A delayed upstroke, though, is an unreliable finding in older patients with extensive arteriosclerotic vascular disease and a stiff, noncompliant aorta. LVH increases progressively due to the pressure overload, eventually resulting in elevation of ventricular end-diastolic pressure. Cardiac output is maintained until the stenosis is severe. LV failure, angina pectoris, or syncope may be presenting symptoms of significant aortic stenosis; importantly, all symptoms tend to first occur with exertion.

### B. Redefining Severe Aortic Stenosis

There are four different anatomic syndromes that occur in patients with severe aortic stenosis. The common underlying measure of **severe aortic stenosis** is an aortic valve area of less than  $1.0 \text{ cm}^2$  and echocardiographic evidence of an immobile aortic valve. In patients with a normal LVEF and normal cardiac output, the threshold for intervention is a peak aortic gradient of greater than  $64 \text{ mm Hg}$  and mean aortic gradient of greater than  $40 \text{ mm Hg}$ . In the same situation, **super-severe aortic stenosis** is defined as a mean gradient of greater than  $55 \text{ mm Hg}$  or peak aortic velocity greater than  $5 \text{ m/sec}$  by Doppler.

In some patients with an aortic valve area of less than  $1.0 \text{ cm}^2$  with a low cardiac output and stroke volume, the mean gradient may be less than  $40 \text{ mm Hg}$ . This can occur when the LV systolic function is poor (**low-gradient severe aortic stenosis with low LVEF**) or when the LV systolic function is normal (**paradoxical low-flow severe aortic stenosis with a normal LVEF**). Low flow (low output) in these situations is defined by an echocardiographic stroke volume index of less than  $35 \text{ mL/min/m}^2$ . Prognosis in patients with low gradient, low valve area, low output, and a normal LVEF aortic stenosis may actually be worse than in patients with the traditional high gradient, low valve area, normal output, and normal LVEF aortic stenosis. If low-flow severe aortic stenosis is present in the face of a low LVEF, provocative testing with dobutamine or nitroprusside is sometimes warranted to increase the stroke volume to discover if a mean aortic valve gradient of at least  $40 \text{ mm Hg}$  can be demonstrated without increasing the aortic valve area. If the aortic valve area can be made to increase and a mean gradient of greater than  $40 \text{ mm Hg}$  cannot be demonstrated by inotropic challenge, the presumption is that the low gradient is due to an associated cardiomyopathy and not the aortic valve stenosis. In this latter situation intervention is not indicated. The guidelines acknowledge these four situations (Table 10-3). Intervention is indicated in super-severe aortic stenosis even without demonstrable symptoms (grade C) and in any of the other situations when symptoms are present: D1 defines the symptomatic high gradient patient; D2 the symptomatic low-flow, low-gradient patient with low

**Table 10-3.** Summary of AHA/ACC guideline definitions of symptomatic severe aortic stenosis.

| Category of Severe Aortic Stenosis <sup>1</sup> | Properties   |
|---|--|
| High Gradient                                   |  |
| High gradient                                   | > 4.0 m/sec Doppler jet velocity<br>> 40 mm Hg mean gradient |
| Super-severe                                    | > 5.0 m/sec Doppler jet velocity<br>> 55 mm Hg mean gradient |
| Low Gradient                                    |  |
| Low flow  | Reduced LVEF (< 50%)   |
| Low flow  | Paradoxical with normal LVEF (> 50%)                         |

<sup>1</sup>All categories of severe aortic stenosis have abnormal systolic opening of the aortic valve and an aortic valve area <  $1.0 \text{ cm}^2$ . LVEF, left ventricular ejection fraction.

LVEF; and D3 the symptomatic low-flow, low-gradient patient with normal LVEF.

Symptoms of LV failure may be sudden in onset or may progress gradually. Angina pectoris frequently occurs in aortic stenosis due to underperfusion of the endocardium. Of patients with calcific aortic stenosis and angina, half have significant associated CAD. Syncope, a late finding, occurs with exertion as the LV pressure rises, stimulating the LV baroreceptors to cause peripheral vasodilation. This vasodilation results in the need for an increase in stroke volume, which increases the LV systolic pressure again, creating a cycle of vasodilation and stimulation of the baroreceptors that eventually results in a drop in systemic BP, as the stenotic valve prevents further increase in stroke volume. Less commonly, syncope may be due to arrhythmias (usually ventricular tachycardia but sometimes AV block as calcific invasion of the conduction system from the aortic valve may occur).

### C. Diagnostic Studies

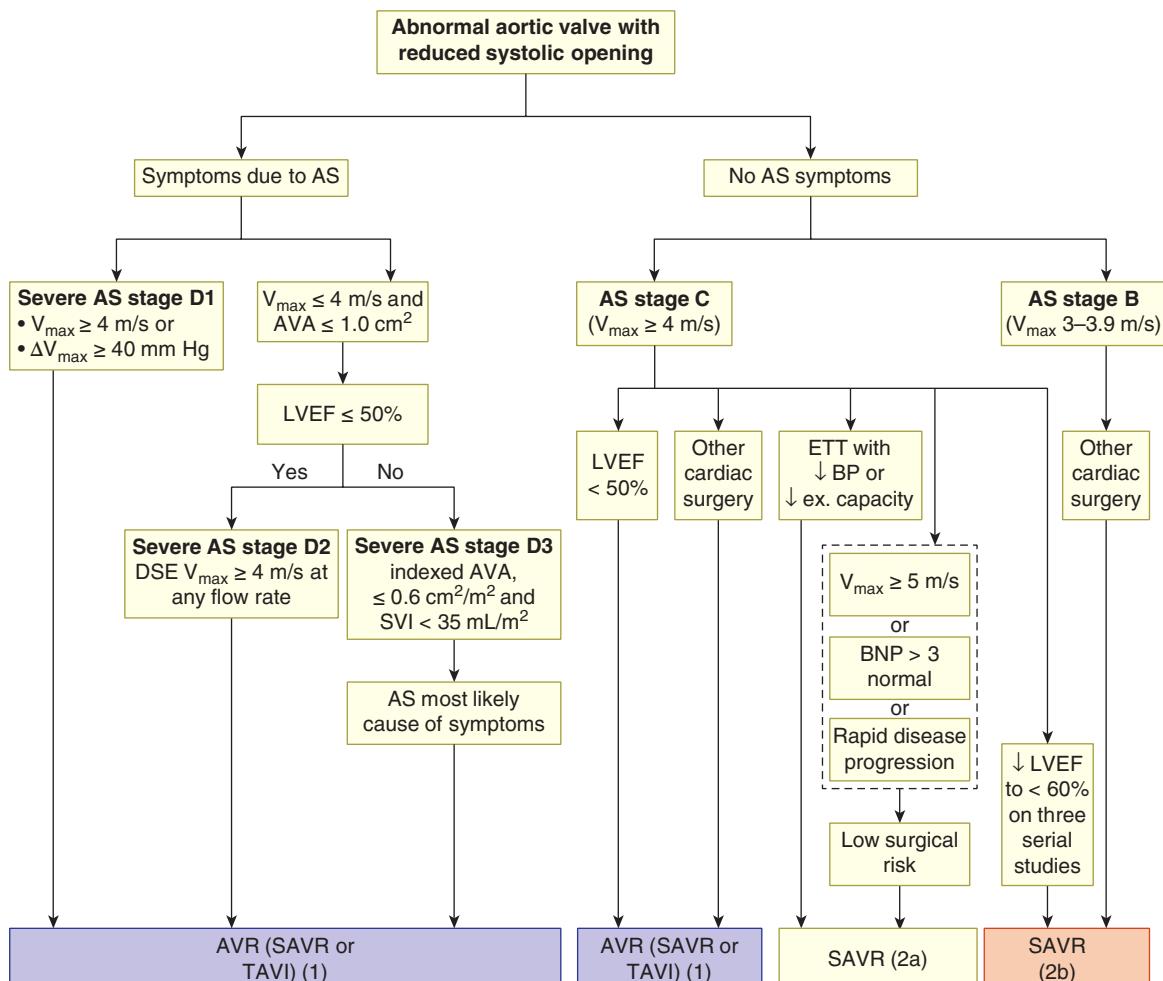
The ECG reveals LVH or secondary repolarization changes in most patients but can be normal in up to 10%. The chest radiograph may show (1) a normal or enlarged cardiac silhouette, (2) calcification of the aortic valve, and (3) dilation or calcification (or both) of the ascending aorta. The echocardiogram provides useful data about aortic valve calcification and leaflet opening, the severity of LV wall thickness, and overall ventricular function, while Doppler can provide an excellent estimate of the aortic valve gradient. Valve area estimation by echocardiography is a critical component of the diagnosis of aortic stenosis due to issues such as paradoxical low-flow aortic stenosis (low-gradient, low-flow, normal LVEF patients). Likewise, the echocardiography/Doppler can estimate the stroke volume index used to define the low-flow state when the valve area is small but the gradient is less than  $40 \text{ mm Hg}$ . Cardiac catheterization mostly provides an assessment of the hemodynamic consequence of the aortic stenosis, and the anatomy of the coronary arteries. Catheterization data can be

important when there is a discrepancy between symptoms and the echocardiography/Doppler information of aortic stenosis severity. In younger patients and in patients with high aortic gradients, the aortic valve need not be crossed at catheterization. Aortic regurgitation can be semiquantified by aortic root angiography. Either BNP or NT-proBNP may provide additional prognostic data in the setting of poor LV function and aortic stenosis. A BNP greater than 550 pg/mL has been associated with a poor outcome in these patients regardless of the results of dobutamine testing. Current guidelines suggest intervention when the NT-proBNP is three times normal (class IIa indication). Stress testing can be done cautiously in patients in whom the aortic stenosis severity does not match the reported symptoms in order to

confirm the reported clinical status. It should *not* be done in patients with super-severe aortic stenosis.

## ► Prognosis & Treatment

Valve intervention is warranted in all patients who have symptomatic severe aortic stenosis (Figure 10–4). There are also times when asymptomatic aortic stenosis should undergo intervention. Asymptomatic patients with severe aortic stenosis (aortic valve area less than  $1.0 \text{ cm}^2$ ) should generally undergo intervention according to the following guidelines: (1) they are undergoing other cardiac surgery (ie, CABG), (2) there is evidence for a reduced LVEF (less than 50%), (3) when the mean gradient exceeds 55 mm Hg



**Figure 10–4.** Algorithm for the timing of intervention in aortic valve stenosis. AS, aortic stenosis; AVA, aortic valve area; AVAi, aortic valve area index; AVR, aortic valve replacement; BNP, B-type natriuretic peptide; BP, blood pressure; DSE, dobutamine stress echocardiography; ETT, exercise treadmill test; LVEF, left ventricular ejection fraction;  $\Delta P_{\text{mean}}$ , mean systolic pressure gradient between LV and aorta; SAVR, surgical aortic valve replacement; SVI, stroke volume index; TAVI, transcatheter aortic valve implantation; TAVR, transcatheter aortic valve replacement;  $V_{\max}$ , maximum velocity. (Modified, with permission, from Otto CM et al. 2020 ACC/AHA guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2021;77:e25. © 2021 American College of Cardiology Foundation and the American Heart Association.)

(peak velocity greater than 5 m/sec), (4) when there is exercise intolerance or when the blood pressure falls more than 10 mm Hg with exercise, (5) when there is severe valvular calcium, (6) when there is evidence of a rapid increase in the peak aortic gradient (more than 0.3 m/sec/year), (7) when there has been a progressive decrease in the LVEF, or (8) when the NT-proBNP is three times normal. Following the onset of heart failure, angina, or syncope, the prognosis without surgery is poor (50% 3-year mortality rate). Medical treatment may stabilize patients in heart failure, but intervention is indicated for all symptomatic patients with evidence of significant aortic stenosis.

The surgical mortality rate for valve replacement is low, even in older adults, and ranges from 2% to 5%. This low risk is due to the dramatic hemodynamic improvement that occurs with relief of the increased afterload. Mortality rates are substantially higher when there is an associated ischemic cardiomyopathy. Severe coronary lesions are usually bypassed at the same time as aortic valve replacement (AVR), although there are few data to suggest this practice affects outcome. In some cases, a staged procedure with stenting of the coronaries prior to surgery may be considered, especially if a percutaneous AVR approach is being considered. Around one-third to one-half of all patients with aortic stenosis have significant CAD, so this is a common concern. With the success of **transcatheter aortic valve replacement (TAVR)** or **transcatheter aortic valve implantation (TAVI)**, the treatment options have greatly expanded for many patients with severe aortic stenosis. For this reason, a **Heart Valve Team** approach bringing together invasive and noninvasive cardiologists, radiologists, anesthesiologists, and cardiac surgeons is mandatory; clinical factors (such as frailty) and anatomic features (such as a calcified aorta, vascular access, etc) can affect the decision making.

Medical therapy to reduce the progression of disease has *not* been effective to date. Statins have been assessed in four major clinical trials. None revealed any benefit on the progression of aortic stenosis or on clinical outcomes despite the association of aortic stenosis with atherosclerosis. If patients with aortic stenosis have concomitant CAD, the guidelines for the use of statins should be followed. Efforts to reduce stenosis progression by blockage of the renin-angiotensin system have also been ineffective, though they are currently recommended for patients who have undergone TAVR. Control of systemic hypertension is an important adjunct, and inadequate systemic BP control is all too common due to unreasonable concerns about providing too much afterload reduction in patients with aortic stenosis. Normal systemic BP is important to maintain as the LV is affected by the total afterload (systemic BP plus the aortic valve gradient).

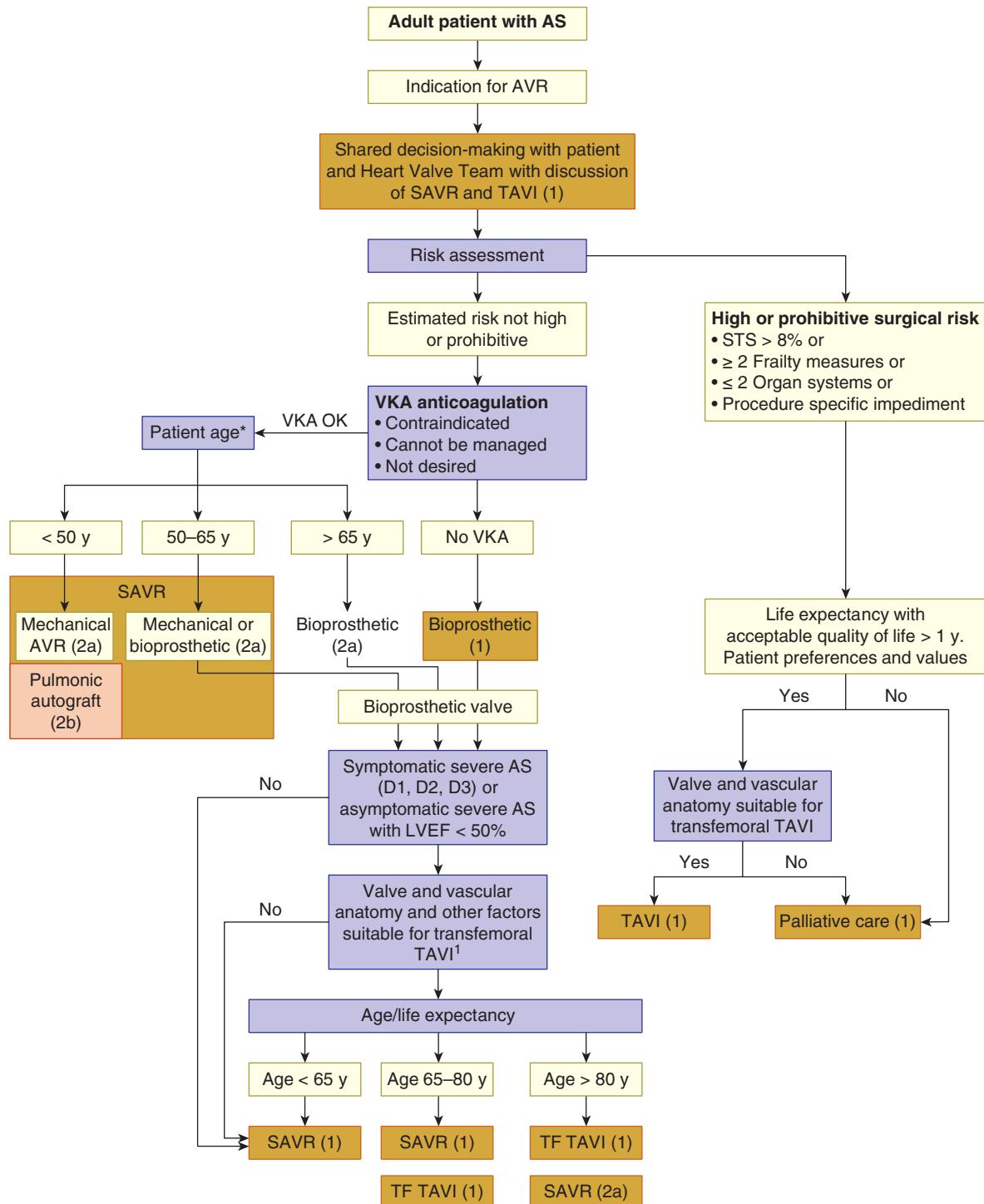
The interventional options in patients with aortic valve stenosis has expanded with the use of TAVR and depend on the patient's lifestyle and age. The algorithm to decide when an AVR is appropriate in various situations is outlined in Figure 10–5.

**TAVR has been shown to be equivalent to surgical AVR (SAVR) in all the randomized trials of symptomatic patients, including those at low risk for surgery**

(less than 4%). Surgery is recommended for patients younger than 65 years or with a life expectancy of more than 20 years. TAVR is recommended for all patients older than 80 years. Either SAVR or TAVR can be considered for all patients between 65 and 80 years. The decision about whether to perform SAVR or TAVR should be made by the Heart Team; anatomic issues (such as an enlarged aorta, a coronary that might be trapped by a leaflet when the valve is inserted, an annulus too large or too small, extensive LV outflow tract calcium, etc) are often the deciding factors whether TAVR can be done.

In young and adolescent patients, percutaneous balloon valvuloplasty still has a very small role. Balloon valvuloplasty is associated with early restenosis in the elderly population and, thus, is rarely used except as a temporizing measure prior to a more permanent SAVR or TAVR. Data suggest aortic balloon valvuloplasty in elderly people has an advantage only in those with preserved LV function, and such patients are usually excellent candidates for SAVR or TAVR.

The Ross procedure is generally still considered a viable option in younger patients with a bicuspid valve, and it is performed by moving the patient's own pulmonary valve and a portion of its root to the aortic position and replacing the pulmonary valve with a homograft (or rarely a bioprosthetic valve). The coronaries require reimplantation. However, dilation of the pulmonary valve autograft and consequent aortic regurgitation, plus early stenosis of the pulmonary homograft in the pulmonary position, has reduced the enthusiasm for this approach in most institutions. Current guidelines suggest the Ross procedure should only be considered in those younger than 50 years. Middle-aged and younger adults generally can tolerate the anticoagulation therapy necessary for the use of mechanical aortic valves, so patients younger than 50 years generally undergo AVR with a bileaflet mechanical valve. If the aortic root is severely dilated as well (greater than 4.5 cm), then the valve may be housed in a Dacron sheath (**Bentall procedure**) and the root replaced along with the aortic valve. Alternatively, a human homograft root and valve replacement can be used. In patients older than 50 years, bioprosthetic (either porcine or bovine pericardial) valves with a life expectancy of about 10–15 years are routinely used instead of mechanical valves to avoid need for anticoagulation. Data favor the bovine pericardial valve over the porcine aortic valve. Bioprosthetic valve degeneration in the larger valves can be potentially repaired by percutaneous valve-in-valve TAVR. If the aortic annulus is small, a bioprosthetic valve with a short sheath can be sewn to the aortic wall (the stentless AVR) rather than sewing the prosthetic annulus to the aortic annulus. (Annulus is a relative term when speaking of the aortic valve, since there is no true annulus.) Another popular surgical option when the aorta is enlarged is the use of the **Wheat procedure**; it involves aortic root replacement above the coronary arteries and replacement of the aortic valve below the coronary arteries. The coronary arteries thus remain attached to the native aorta between the new graft and prosthetic valve rather than being reimplanted onto an artificial sheath or homograft. Newer aortic valve replacements can be placed



**Figure 10–5.** Algorithm for the type of valvular intervention in aortic valve stenosis. AS, aortic stenosis; AVR, aortic valve replacement; LVEF, left ventricular ejection fraction; SAVR, surgical aortic valve replacement; STS, Society of Thoracic Surgeons; TAVI, transcatheter aortic valve implantation; TF, transfemoral; VKA, vitamin K antagonist. (Modified, with permission, from Otto CM et al. 2020 ACC/AHA guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. J Am Coll Cardiol. 2021;77:e25. © 2021 American College of Cardiology Foundation and the American Heart Association.)

quickly through a small incision and often require only three stitches to anchor (ie, the Perceval or Intuity valve replacements). These can shorten pump times at surgery.

In patients with a bicuspid aortic valve, there is an associated ascending aortic aneurysm in about half. If the maximal dimension of the aortic root is greater than 5.5 cm, it is recommended to proceed with root replacement regardless of the severity of the aortic valve disease. It is also appropriate to intervene when the maximal aortic root size is greater than 5.0 cm in diameter if there is a family history of aortic dissection or the aortic root size increases by more than 0.5 cm in 1 year. The aortic valve may be replaced at the same time if at least moderate aortic stenosis is present or may be either left alone or repaired (valve sparing operation). If there is an indication for AVR and the root is greater than 4.5 cm in diameter, root replacement is also recommended at the time of SAVR.

The use of mechanical versus bioprosthetic AVR has changed over time. A bioprosthetic valve is acceptable for patients at any age for whom anticoagulant therapy is contraindicated, not desired, or cannot be managed, and is preferred in patients over the age of 65. An aortic mechanical valve should be used in patients younger than 50 years of age who can take warfarin. **Anticoagulation** is required with the use of mechanical aortic valves, and the international normalized ratio (INR) should be maintained between 2.0 and 3.0 for bileaflet valves. In general, mechanical aortic valves are less subject to thrombosis than mechanical mitral valves and do not require bridging with enoxaparin unless there are other thromboembolic risk factors or it is an older generation AVR. Low-dose aspirin is recommended if there is a low bleeding risk. Some newer bileaflet mechanical valves (On-X) allow for a lower INR range from 1.5 to 2.0. Clopidogrel is recommended for the first 6 months after TAVR in combination with lifelong aspirin therapy. DOACs are *not* recommended for any mechanical valves but may be used in patients with a bioprosthetic AVR if treating atrial fibrillation or venous thrombosis.

The use of TAVR has grown dramatically. The Edwards SAPIEN valve is a balloon-expandable valvular stent, while the CoreValve is a valvular stent that self-expands when pushed out of the catheter sheath. Cost remains a major issue. The cost of TAVR is similar to SAVR, mostly due to the cost of the valve itself. All of the professional societies stress the importance of a Heart Valve Team when considering aortic stenosis intervention.

TAVR is also being used more frequently in “valve-in-valve” procedures to reduce the gradient in patients with prosthetic valve dysfunction (regardless of whether in the aortic, mitral, tricuspid, or pulmonary position). While the results of TAVR in patients with bicuspid aortic valves (as opposed to tricuspid) have been less impressive, newer modifications have improved the success rates in these anatomic situations as well.

## ► When to Refer

- All patients with echocardiographic evidence for mild-to-moderate aortic stenosis (estimated peak valve gradient greater than 30 mm Hg by echocardiography/

Doppler) should be referred to a cardiologist for evaluation and to determine the frequency of follow-up.

- Any patients with symptoms suggestive of aortic stenosis (ie, exertional symptoms of chest pressure, shortness of breath, or presyncope) should be seen by a cardiologist.

Mack MJ et al; PARTNER 3 Investigators. Transcatheter aortic-valve replacement with a balloon-expandable valve in low-risk patients. *N Engl J Med*. 2019;380:1695. [PMID: 30883058]  
Otto CM et al. 2020 ACC/AHA guideline for the management of patients with valvular heart disease. *J Am Coll Cardiol*. 2021;77:450. [PMID: 33342587]

Popma JJ et al; Evolut Low Risk Trial Investigators. Transcatheter aortic-valve replacement with a self-expanding valve in low-risk patients. *N Engl J Med*. 2019;380:1706. [PMID: 30883053]

## AORTIC REGURGITATION



- Usually asymptomatic until middle age; presents with left-sided failure or rarely chest pain.
- Echocardiography/Doppler is diagnostic.
- Surgery for symptoms, EF < 50%, LV end-systolic dimension > 50 mm, or LV end-diastolic dimension > 65 mm.

## ► General Considerations

Of all patients with isolated aortic valve disease, about 13% have predominately aortic regurgitation. Rheumatic aortic regurgitation has become much less common than in the preantibiotic era, and nonrheumatic causes now predominate. These include congenitally bicuspid valves, infective endocarditis, and hypertension. Many patients also have aortic regurgitation secondary to aortic root diseases, such as that associated with Marfan syndrome or aortic dissection. Rarely, inflammatory diseases, such as ankylosing spondylitis, may be implicated.

## ► Clinical Findings

### A. Symptoms and Signs

The clinical presentation is determined by the rapidity with which regurgitation develops. In **chronic aortic regurgitation**, the only sign for many years may be a soft aortic diastolic murmur. As the severity of the aortic regurgitation increases, diastolic BP falls, and the LV progressively enlarges. Most patients remain asymptomatic for long periods even at this point. LV failure is a late event and may be sudden in onset. Exertional dyspnea and fatigue are the most frequent symptoms, but paroxysmal nocturnal dyspnea and pulmonary edema may also occur. Angina pectoris or atypical chest pain may occasionally be present. Associated CAD and presyncope or syncope are less common than in aortic stenosis.

Hemodynamically, because of compensatory LV dilation, patients eject a large stroke volume, which is adequate to maintain forward cardiac output until late in the course of the disease. LV diastolic pressure may rise when heart failure occurs. Abnormal LV systolic function as manifested by reduced EF (less than 50%) and increasing end-systolic LV volume (greater than 5.0 cm) are signs that surgical intervention is warranted.

The major physical findings in chronic aortic regurgitation relate to the high stroke volume being ejected into the systemic vascular system with rapid runoff as the regurgitation takes place (see Table 10–1). This results in a **wide arterial pulse pressure**. The pulse has a rapid rise and fall (**water-hammer pulse** or **Corrigan pulse**), with an elevated systolic and low diastolic pressure. The large stroke volume and flow back into the heart are also responsible for characteristic findings, such as **Quincke pulses** (nailbed capillary pulsations), **Duroziez sign** (to-and-fro murmur over a partially compressed femoral peripheral artery), and **Musset sign** (head bob with each pulse). In younger patients, the increased stroke volume may summate with the pressure wave reflected from the periphery and create a higher than expected systolic pressure in the lower extremities compared with the central aorta. Since the peripheral bed is much larger in the leg than the arm, the BP in the leg may be over 40 mm Hg higher than in the arm (**Hill sign**) in severe aortic regurgitation. The apical impulse is prominent, laterally displaced, usually hyperdynamic, and may be sustained. A systolic flow murmur is usually present and may be quite soft and localized; the aortic diastolic murmur is usually high-pitched and decrescendo. A mid or late diastolic low-pitched mitral murmur (**Austin Flint murmur**) may be heard in advanced aortic regurgitation, owing to relative obstruction of mitral inflow produced by partial closure of the mitral valve by the rapidly rising LV diastolic pressure due to the aortic regurgitation.

In **acute aortic regurgitation** (usually from aortic dissection or infective endocarditis), LV failure is manifested primarily as pulmonary edema and may develop rapidly; surgery is urgently required in such cases. Patients with acute aortic regurgitation do not have the dilated LV of chronic aortic regurgitation and the extra LV volume is handled poorly. For the same reason, the diastolic murmur is shorter, may be minimal in intensity, and the pulse pressure may not be widened—making clinical diagnosis difficult. The mitral valve may close prematurely even before LV systole has been initiated (**preclosure**) due to the rapid rise in the LV diastolic pressure, and the first heart sound is thus diminished or inaudible. Preclosure of the mitral valve can be readily detected on echocardiography and is considered an indication for urgent surgical intervention.

## B. Diagnostic Studies

The ECG usually shows moderate to severe LVH. Radiographs show cardiomegaly with LV prominence and sometimes a dilated aorta.

Echocardiography demonstrates the major diagnostic features, including whether the lesion includes the proximal aortic root and what valvular pathology is present. Annual

assessments of LV size and function are critical in determining the timing for valve replacement when the aortic regurgitation is severe. The 2020 ACC/AHA valvular guideline provides criteria for assessing the severity of aortic regurgitation. Cardiac MRI and CT can estimate aortic root size, particularly when there is concern for an ascending aneurysm. MRI can provide a regurgitant fraction to help confirm severity. Cardiac catheterization may be unnecessary in younger patients, particularly those with acute aortic regurgitation, but can help define hemodynamics, aortic root abnormalities, and associated CAD preoperatively in older patients. Increasing data are emerging that serum BNP or NT-proBNP may be an early sign of LV dysfunction, and it is possible that these data will be added to recommendations for surgical intervention in the future.

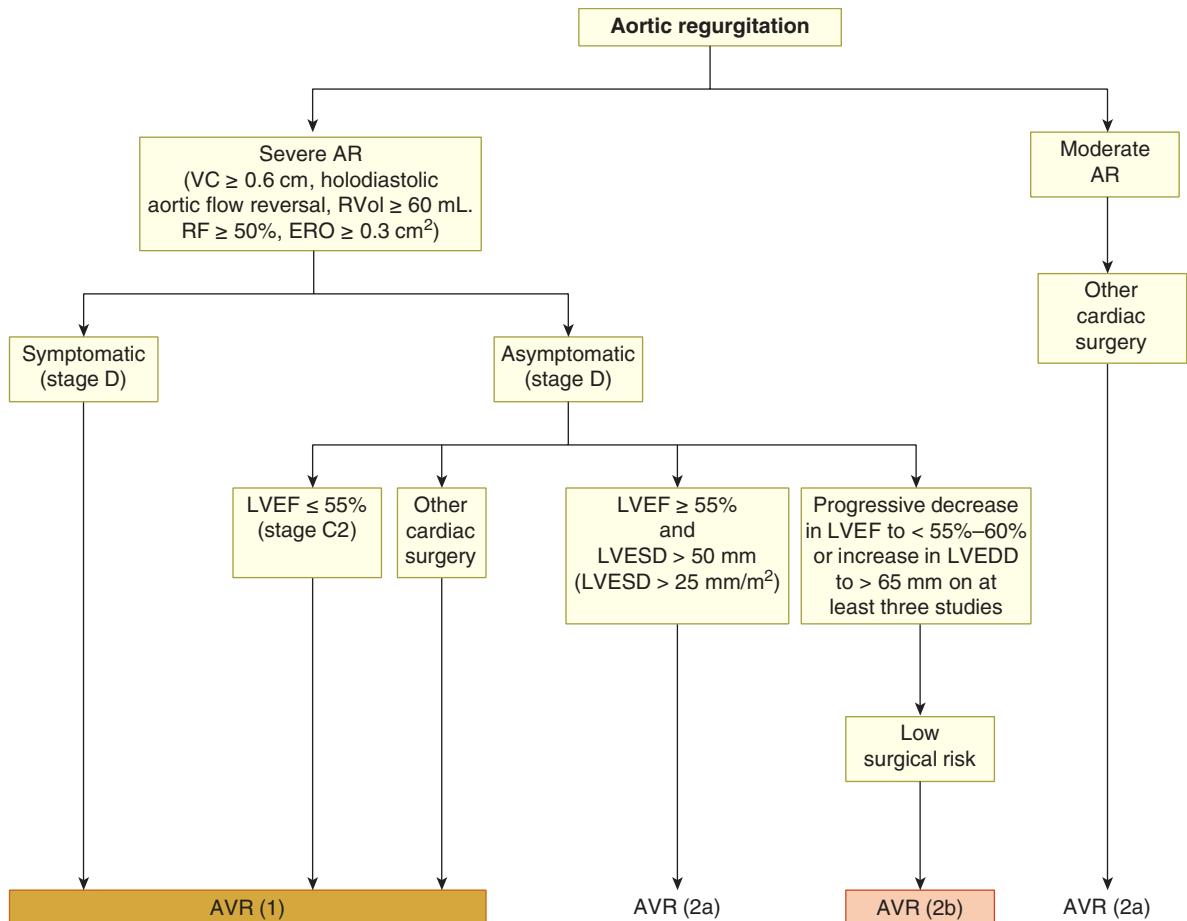
## ► Treatment & Prognosis

Aortic regurgitation that appears or worsens during or after an episode of infective endocarditis or aortic dissection may lead to acute severe LV failure or subacute progression over weeks or months. The former usually presents as pulmonary edema; surgical replacement of the valve is indicated even during active infection. These patients may be transiently improved or stabilized by vasodilators.

Chronic aortic regurgitation may be tolerated for many years, but the prognosis without surgery becomes poor when symptoms occur. Since aortic regurgitation places both a preload (volume) and afterload increase on the LV, medications that decrease afterload can reduce regurgitation severity, although there are no convincing data that afterload reduction alters mortality. **Recommendations advocate afterload reduction in aortic regurgitation only when there is associated systolic hypertension (systolic BP greater than 140 mm Hg).** Afterload reduction in normotensive patients does not appear warranted. Angiotensin receptor blockers (ARBs), rather than beta-blockers, are the preferred additions to the medical therapy in patients with an enlarged aorta, such as in Marfan syndrome, because of the theoretical ability of an ARB to reduce aortic stiffness (by blocking TGF-beta) and to slow the rate of aortic dilation. However, clinical trials evaluating the efficacy of ARBs to reduce aortic stiffness and slow the rate of aortic dilation have not yielded a positive outcome to support their use.

**Surgery is indicated once symptoms emerge or for any evidence of LV dysfunction** (as exhibited by a reduction in the LVEF to less than 55% or increase in the LV end-systolic diameter to greater than 50 mm by echocardiography). In addition, it is suggested that surgery should be considered even when the LV becomes excessively enlarged (LV end-diastolic diameter greater than 65 mm). Guidelines also suggest it be considered (class IIb) if serial imaging reveals a progressive increase in the size of the LV (Figure 10–6).

The issues with AVR covered in the above section concerning aortic stenosis pertain here. Early trials of TAVR had a high incidence of postprocedural residual aortic regurgitation (18.8% in one trial). Newer TAVR valves have greatly reduced residual aortic regurgitation when used in patients with pure native aortic regurgitation (4.2%). In



**Figure 10–6.** Algorithm for intervention in aortic regurgitation. AR, aortic regurgitation; AVR, aortic valve replacement; EDD, end-diastolic dimension; ERO, effective regurgitant orifice; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic dimension; RF, regurgitant fraction; RVol, regurgitant volume; VC, vena contracta. (Modified, with permission, from Otto CM et al. 2020 ACC/AHA guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol.* 2021;77:e25. © 2021 American College of Cardiology Foundation and the American Heart Association.)

multivariable analysis, postprocedural at least moderate aortic regurgitation was independently associated with 1-year all-cause mortality (hazard ratio: 2.85; 95% confidence interval: 1.52 to 5.35;  $P = 0.001$ ). Compared with the early-generation devices, TAVR using the new-generation devices was associated with improved procedural outcomes in treating patients with pure native aortic regurgitation. In patients with pure native aortic regurgitation, significant postprocedural aortic regurgitation was independently associated with increased mortality.

Aortic regurgitation due to a paravalvular prosthetic valve defect can occasionally be occluded with percutaneous occluder devices. The choice of prosthetic valve for AVR depends on the patient's age and compatibility with warfarin anticoagulation similar to the choices for AVR in aortic stenosis.

The operative mortality for AVR is usually in the 3–5% range. Aortic regurgitation due to aortic root disease

requires repair or replacement of the root as well as surgical treatment of the aortic valve. Though valve-sparing operations have improved recently, most patients with root replacement undergo valve replacement at the same time. Root replacement in association with valve replacement may require anastomosis of the coronary arteries, and thus the procedure is more complex than valve replacement alone. The Wheat procedure replaces the aortic root but spares the area where the coronaries attach to avoid the necessity for their reimplantation. Following any aortic valve surgery, LV size usually decreases and LV function generally improves even when the baseline EF is depressed.

Repair of the aortic root in patients with a bicuspid valve should be done once the root diameter exceeds 5.5 cm regardless of aortic valve disease severity. There are data that dissection is much more prevalent when the aortic root diameter exceeds 6.0 cm, and the general sense is not to let it approach that size. Patients with risk factors

(family history of dissection or an increase in the diameter of the root greater than 0.5 cm in 1 year) should have the aorta repaired when the maximal dimension exceeds 5.0 cm. The following classifications summarize when to operate on the aortic root in patients with a bicuspid aortic valve based on the guidelines:

**Class I** indication (LOE C): aortic root diameter at sinuses or ascending aorta greater than 5.5 cm (regardless of need for AVR).

**Class IIa** indication (LOE C): aortic root diameter at sinuses or ascending aorta greater than 5.0 cm when there are associated risk factors (family history of dissection or increase in size more than 0.5 cm in 1 year).

**Class IIa** indication (LOE C): aortic root diameter greater than 4.5 cm if patient undergoing AVR for valvular reasons.

be suspected when right heart failure appears in the course of mitral valve disease or in the postoperative period after tricuspid valve repair or replacement.

## ► Clinical Findings

### A. Symptoms and Signs

Tricuspid stenosis is characterized by right heart failure with hepatomegaly, ascites, and dependent edema. In sinus rhythm, a giant *a* wave is seen in the JVP, which is also elevated (see Table 10–1). The typical **diastolic rumble** along the lower left sternal border mimics mitral stenosis, though in tricuspid stenosis the rumble *increases with inspiration*. In sinus rhythm, a presystolic liver pulsation may be found. It should be considered when patients exhibit signs of carcinoid syndrome.

### B. Diagnostic Studies

In the absence of atrial fibrillation, the ECG reveals RA enlargement. The chest radiograph may show marked cardiomegaly with a normal PA size. A dilated superior vena cava and azygous vein may be evident.

The normal valve area of the tricuspid valve is  $10 \text{ cm}^2$ , so significant stenosis must be present to produce a gradient. Hemodynamically, a mean diastolic pressure gradient greater than 5 mm Hg is considered significant, although even a 2 mm Hg gradient can be considered abnormal. This can be demonstrated by echocardiography or cardiac catheterization. The 2017 update of the 2014 AHA/ACC guidelines suggests a tricuspid valve area of less than  $1.0 \text{ cm}^2$  and a pressure half-time longer than 190 msec should be defined as significant because the gradient may vary depending on the heart rate.

## ► Treatment & Prognosis

Tricuspid stenosis may be progressive, eventually causing severe right-sided heart failure. Initial therapy is directed at reducing the fluid congestion, with diuretics the mainstay (see Treatment, Heart Failure). When there is considerable bowel edema, torsemide or bumetanide may have an advantage over other loop diuretics, such as furosemide, because they are better absorbed from the gut. Aldosterone inhibitors also help, particularly if there is liver engorgement or ascites. Neither surgical nor percutaneous valvoplasty is particularly effective for relief of tricuspid stenosis, as residual tricuspid regurgitation is common. Tricuspid valve replacement is the preferred surgical approach. Mechanical tricuspid valve replacement is rarely done because the low flow predisposes to thrombosis and because the mechanical valve cannot be crossed should the need arise for right heart catheterization or pacemaker implantation. Therefore, bioprosthetic valves are almost always preferred. Often tricuspid valve replacement is performed in conjunction with mitral valve replacement for rheumatic mitral stenosis or regurgitation. Percutaneous transcatheter valve replacement (stented valve) has been used in degenerative tricuspid prosthetic valve stenosis and a percutaneous tricuspid valve replacement device is being

## ► When to Refer

- Patients with audible aortic regurgitation should be seen, at least initially, by a cardiologist who can determine whether the patient needs follow-up.
- Patients with a dilated aortic root should be monitored by a cardiologist, since imaging studies other than the chest radiograph or echocardiogram may be required to decide surgical timing.

O'Gara PT et al. Timing of valve interventions in patients with chronic aortic regurgitation: are we waiting too long? *J Am Coll Cardiol*. 2019;73:1753. [PMID: 30846337]

Otto CM et al. 2020 ACC/AHA guideline for the management of patients with valvular heart disease. *J Am Coll Cardiol*. 2021; 77:450. [PMID: 33342587]

## TRICUSPID STENOSIS



### ESSENTIALS OF DIAGNOSIS

- ▶ Female predominance.
- ▶ History of rheumatic heart disease most likely. Carcinoid disease and prosthetic valve degeneration are the most common etiologies in the United States.
- ▶ Echocardiography/Doppler is diagnostic.

## ► General Considerations

Tricuspid stenosis is rare, affecting less than 1% of the population in developed countries and less than 3% worldwide. Native valve tricuspid valve stenosis is usually rheumatic in origin. In the United States, tricuspid stenosis is more commonly due to prior tricuspid valve repair or replacement or to the carcinoid syndrome. The incidence of tricuspid stenosis after tricuspid valve replacement increases considerably after 8 years post surgery. Tricuspid regurgitation frequently accompanies the lesion. It should

investigated. The indications for valve replacement in severe tricuspid stenosis are straightforward:

**Class I** indication (LOE C): at time of operation for left-sided valve disease.

**Class I** indication (LOE C): if symptomatic.

**Class IIb** indication (LOE C): rarely percutaneous balloon commissurotomy for isolated tricuspid stenosis in high-risk patients with no significant tricuspid regurgitation.

## ► When to Refer

All patients with any evidence for tricuspid stenosis on an echocardiogram should be seen and monitored by a cardiologist to assess when intervention may be required.

Hirata K et al. Bioprosthetic tricuspid valve stenosis: a case series. Eur Heart J Case Rep. 2019;3:ytz110. [PMID: 31367735]

## TRICUSPID REGURGITATION



### ESSENTIALS OF DIAGNOSIS

- ▶ Frequently occurs in patients with pulmonary or cardiac disease with pressure or volume overload on the right ventricle.
- ▶ Tricuspid valve regurgitation from pacemaker lead placement is becoming more common.
- ▶ Echocardiography useful in determining cause (low- or high-pressure tricuspid regurgitation).

## ► General Considerations

Tricuspid valvular regurgitation often occurs whenever there is RV dilation from any cause. As tricuspid regurgitation increases, the RV size increases further pulling the valve open due to chordal and papillary muscle displacement. This, in turn, worsens the severity of the tricuspid regurgitation. In addition, the tricuspid annulus is shaped like a horse's saddle. With RV failure, the annulus flattens and becomes elliptical, further distorting the relationship between the leaflets and chordal attachments. In most cases, the cause of the tricuspid regurgitation is the RV geometry (functional) and not primary tricuspid valve disease. An enlarged, dilated RV may be present if there is RV systolic hypertension from valvular or subvalvular pulmonary valve stenosis, pulmonary hypertension for any reason, in severe pulmonary valve regurgitation, or in cardiomyopathy. The RV may also be injured from an MI or may be inherently dilated due to infiltrative diseases (RV dysplasia or sarcoidosis). RV dilation often occurs secondary to left heart failure. Inherent abnormalities of the tricuspid valve include **Ebstein anomaly** (displacement of the septal and posterior, but not the anterior, leaflets into the RV), tricuspid valve prolapse, carcinoid

plaque formation, collagen disease inflammation, valvular tumors, or tricuspid endocarditis. In addition, pacemaker lead valvular injury is an increasingly frequent iatrogenic cause.

## ► Clinical Findings

### A. Symptoms and Signs

The symptoms and signs of tricuspid regurgitation are identical to those resulting from RV failure due to any cause. As a generality, the diagnosis can be made by careful inspection of the JVP. The JVP waveform should decline during ventricular systole (the *x* descent). The timing of this decline can be observed by palpating the opposite carotid artery. As tricuspid regurgitation worsens, more and more of this *x* descent valley in the JVP is filled with the regurgitant wave until all of the *x* descent is obliterated and a positive systolic waveform will be noted in the JVP. An associated tricuspid regurgitation murmur may or may not be audible and can be distinguished from mitral regurgitation by the left parasternal location and an increase with inspiration (**Carvallo sign**). An *S<sub>3</sub>* may accompany the murmur and is related to the high flow returning to the RV from the RA. Cyanosis may be present if the increased RA pressure stretches the atrial septum and opens a PFO or there is a true ASD (eg, in about 50% of patients with Ebstein anomaly). Severe tricuspid regurgitation results in hepatomegaly, edema, and ascites.

### B. Diagnostic Studies

The ECG is usually nonspecific, though atrial flutter or atrial fibrillation is common. The chest radiograph may reveal evidence of an enlarged RA or dilated azygous vein and pleural effusion. The echocardiogram helps assess severity of tricuspid regurgitation (see the 2014 AHA/ACC valvular heart disease guidelines for definitions). In addition, echocardiography/Doppler provides RV systolic pressure as well as RV size and function. A paradoxically moving interventricular septum may be present due to the volume overload on the RV. Catheterization confirms the presence of the regurgitant wave in the RA and elevated RA pressures. If the PA or RV systolic pressure is less than 40 mm Hg, primary valvular tricuspid regurgitation should be suspected. In addition, in patients with severe tricuspid regurgitation and ascites, a hepatic wedge pressure can be performed at the time of the right heart catheterization. If there is a high gradient between the mean RA pressure and mean hepatic wedge, then cirrhosis is likely present. Normally, the gradient across the liver is less than 5 mm Hg. Mild cirrhosis is suspected if gradient is 5–10 mm Hg, moderate disease if 10–15 mm Hg, and significant cirrhosis if greater than 15 mm Hg.

## ► Treatment & Prognosis

Mild tricuspid regurgitation is common and generally can be well managed with diuretics. When severe tricuspid regurgitation is present, bowel edema may reduce the

effectiveness of diuretics, such as furosemide, and intravenous diuretics should be used initially. Torsemide or bumetanide is better absorbed in this situation when oral diuretics are added. Aldosterone antagonists have a role as well, particularly if ascites is present. At times, the efficacy of loop diuretics can be enhanced by adding a thiazide diuretic (see Treatment, Heart Failure).

Since most tricuspid regurgitation is secondary, definitive treatment usually requires elimination of the cause of the RV dysfunction. Surgical valve replacement in secondary (functional) tricuspid regurgitation is rarely if ever indicated until the cause of the RV dysfunction is resolved. If the problem is left heart disease, then treatment of the left heart issues may lower pulmonary pressures, reduce RV size, and resolve the tricuspid regurgitation. Treatment for primary and secondary causes of pulmonary hypertension will generally reduce the tricuspid regurgitation. Guidelines suggest that tricuspid valve surgery may be considered when the tricuspid annular dilation at end-diastole exceeds 4.0 cm and the patient is symptomatic. It is a class I recommendation that tricuspid annuloplasty be performed when significant tricuspid regurgitation is present and mitral valve replacement or repair is being performed for mitral regurgitation. Annuloplasty without insertion of a prosthetic ring (**DeVega annuloplasty**) may also be effective in reducing the tricuspid annular dilation. The valve leaflet itself can occasionally be primarily repaired in tricuspid valve endocarditis. If there is an inherent defect in the tricuspid valve apparatus that cannot be repaired, then replacement of the tricuspid valve is warranted. A bioprosthetic valve rather than a mechanical valve, is almost always used because the risk of mechanical valve thrombosis is increased if the INR is not stable. Anticoagulation is *not* required for bioprosthetic valves unless there is associated atrial fibrillation or flutter. Tricuspid regurgitation due to bioprosthetic degeneration has been shown to respond to transcatheter valve replacement. There are early reports of percutaneous tricuspid valve replacement for native valve tricuspid regurgitation being successful.

## ► When to Refer

- Anyone with moderate or severe tricuspid regurgitation should be seen at least once by a cardiologist to determine whether studies and intervention are needed.
- Severe tricuspid regurgitation requires regular follow-up by a cardiologist.

Asmarats L et al. Transcatheter tricuspid valve interventions: landscape, challenges, and future directions. *J Am Coll Cardiol.* 2018;71:2935. [PMID: 29929618]

Axtell AL et al. Surgery does not improve survival in patients with isolated severe tricuspid regurgitation. *J Am Coll Cardiol.* 2019;74:715. [PMID: 31071413]

Hahn RT et al. Anatomic relationship of the complex tricuspid valve, right ventricle, and pulmonary vasculature: a review. *JAMA Cardiol.* 2019;4:478. [PMID: 30994879]

## PULMONARY VALVE REGURGITATION



### ESSENTIALS OF DIAGNOSIS

- ▶ Most cases are due to pulmonary hypertension resulting in high-pressure pulmonary valve regurgitation.
- ▶ Echocardiogram is definitive in high-pressure but may be less definitive in low-pressure pulmonary valve regurgitation.
- ▶ Low-pressure pulmonary valve regurgitation is well tolerated.

## ► General Considerations

Pulmonary valve regurgitation can be divided into **high-pressure causes** (due to pulmonary hypertension) and **low-pressure causes** (usually due to a dilated pulmonary annulus, a congenitally abnormal [bicuspid or dysplastic] pulmonary valve, plaque from carcinoid disease, surgical pulmonary valve replacement, or the residual physiology following a surgical transannular patch used to reduce the outflow gradient in tetralogy of Fallot). Because the RV tolerates a volume load better than a pressure load, it tends to tolerate low-pressure pulmonary valve regurgitation for long periods of time without dysfunction.

## ► Clinical Findings

Most patients are asymptomatic. Those with marked pulmonary valve regurgitation may exhibit symptoms of right heart volume overload. On examination, a hyperdynamic RV can usually be palpated (RV lift). If the PA is enlarged, it also may be palpated along the left sternal border. P<sub>2</sub> will be palpable in pulmonary hypertension and both systolic and diastolic thrills are occasionally noted. On auscultation, the second heart sound may be widely split due to prolonged RV systole or an associated right bundle branch block. A pulmonary valve systolic click may be noted as well as a right-sided gallop. If pulmonic stenosis is also present, the ejection click may decline with inspiration, while any associated systolic pulmonary murmur will increase. In high-pressure pulmonary valve regurgitation, the pulmonary diastolic (**Graham Steell**) murmur is readily audible. It is often contributed to by a dilated pulmonary annulus. The murmur increases with inspiration and diminishes with the Valsalva maneuver. In low-pressure pulmonary valve regurgitation, the PA diastolic pressure may be only a few mm Hg higher than the RV diastolic pressure, and there is little diastolic gradient to produce a murmur or characteristic echocardiography/Doppler findings. At times, only contrast angiography or MRI of the main PA will show the free-flowing pulmonary valve regurgitation in low-pressure pulmonary valve regurgitation. This situation is common in patients following repair of tetralogy of Fallot where, despite little murmur, there

may effectively be no pulmonary valve present. This can be suspected by noting an enlarging right ventricle.

The ECG is generally of little value, although right bundle branch block is common, and there may be ECG criteria for RVH. The chest radiograph may show only the enlarged RV and PA. Echocardiography may demonstrate evidence of RV volume overload (paradoxical septal motion and an enlarged RV), and Doppler can determine peak systolic RV pressure and reveal any associated tricuspid regurgitation. The interventricular septum may appear flattened if there is pulmonary hypertension. The size of the main PA can be determined and color flow Doppler can demonstrate the pulmonary valve regurgitation, particularly in the high-pressure situation. Cardiac MRI and CT can be useful for assessing the size of the PA, for estimating regurgitant flow, for excluding other causes of pulmonary hypertension (eg, thromboembolic disease, peripheral PA stenosis), and for evaluating RV function. Cardiac catheterization is confirmatory only.

### Treatment & Prognosis

Pulmonary valve regurgitation rarely needs specific therapy other than treatment of the primary cause. In low-pressure pulmonary valve regurgitation due to surgical transannular patch repair of tetralogy of Fallot, pulmonary valve replacement may be indicated if RV enlargement or dysfunction is present. In tetralogy of Fallot, the QRS will widen as RV function declines (a QRS greater than 180 msec, among other features, suggests a higher risk for sudden death) and increasing RV volumes should trigger an evaluation for potential severe pulmonary valve regurgitation. In carcinoid heart disease, pulmonary valve replacement with a porcine bioprosthesis may be undertaken, though the plaque from this disorder eventually coats the prosthetic pulmonary valve, limiting the life span of these valves. In high-pressure pulmonary valve regurgitation, treatment to control the cause of the pulmonary hypertension is key. High-pressure pulmonary valve regurgitation is poorly tolerated and is a serious condition that needs a thorough evaluation for cause and choice of therapy. Pulmonary valve replacement requires a bioprosthetic valve in most cases. Pulmonary valve regurgitation due to an RV to PA conduit or due to a pulmonary autograft replacement as part of the Ross procedure can be repaired with a percutaneous pulmonary valve (Melody valve). Bioprosthetic pulmonary valve regurgitation has also been treated using a percutaneous valve (Edwards Sapien). When the pulmonary valve is replaced percutaneously, the PA is often stented open to provide a platform for the percutaneous valve.

### When to Refer

- Patients with pulmonary valve regurgitation that results in RV enlargement should be referred to a cardiologist regardless of the estimated pulmonary pressures.

Martin MH et al. Safety and feasibility of Melody transcatheter pulmonary valve replacement in the native right ventricular outflow tract: a multicenter pediatric heart network scholar study. JACC Cardiovasc Interv. 2018;11:1642. [PMID: 30077685]

## MANAGEMENT OF ANTICOAGULATION FOR PATIENTS WITH PROSTHETIC HEART VALVES

The risk of thromboembolism is much lower with bioprosthetic valves than mechanical prosthetic valves. Mechanical mitral valve prostheses also pose a greater risk for thrombosis than mechanical aortic valves. For that reason, **the INR should be kept between 2.5 and 3.5 for mechanical mitral prosthetic valves but can be kept between 2.0 and 2.5 for most mechanical aortic prosthetic valves**. If there are additional risk factors in patients with a mechanical AVR (atrial fibrillation, previous thromboembolism, LV dysfunction, hypercoagulable state, or presence of older valve such as a ball-in-cage), then the INR for a mechanical AVR should be similar to a mechanical mitral valve replacement. Guidelines currently suggest the following as well: (1) a recommendation (class IIa) to expand the use of vitamin K antagonists (VKAs), such as warfarin, for up to 6 months after initial bioprosthetic valve replacement; (2) a lower target INR of 1.5–2.0 for a mechanical AVR using the On-X valve (class IIb); and (3) a consideration of VKA use with an INR of 2.5 for at least 3 months after TAVR (class IIa). Data from 2018 suggest that antiplatelet medications are inferior to warfarin for the prevention of thrombus in patients with the On-X mechanical valve. Concern regarding thrombus formation on bioprosthetic valves (including TAVR valves) also led to a class I recommendation to use multimodality imaging to identify such thrombus (class I). The DOAC rivaroxaban has *not* been found to prevent stroke related to emboli from TAVR and it should not be used. It is acceptable, though, to use DOACs for the treatment of atrial fibrillation in patients with bioprosthetic valves. For patients with a TAVR valve, it is reasonable to use dual antiplatelet therapy (clopidogrel and aspirin) for 3–6 months after the procedure. After that, lifelong low-dose aspirin should be used. As noted earlier, using warfarin for at least 3 months after TAVR is reasonable (class IIb), although that practice is widely variable. Randomized trials have not shown a benefit with DOACs after TAVR.

The European Registry of Pregnancy and Cardiac Disease (ROPAC) reported on a registry that compared pregnant women who had undergone mechanical and bioprosthetic valve replacement to pregnant women who had not. Maternal mortality was similar between the mechanical and bioprosthetic valve patients (1.5% and 1.4%, respectively) but was much higher than those without an artificial valve (0.2%). When patients with either mechanical or bioprosthetic valves were further assessed, it was found that pregnant women with mechanical valves were more likely to suffer adverse events than women with bioprosthetic valves. Hemorrhagic events occurred in 23.1% versus 9.2%, miscarriage on warfarin occurred in 28.6% versus 9.2%, and late fetal death was noted in 7.1% versus 0.7%, respectively. These data suggest a **high risk for mortality and morbidity for pregnant patients with mechanical heart valves**, and in the WHO Classification of Maternal Cardiac Risk, the presence of a mechanical valve is considered a class III (out of IV) risk for pregnancy complications.

Stoppage of warfarin for noncardiac surgery is likewise dependent on which mechanical valve is involved, the patient-specific risk factors, and the procedure contemplated. The risk of thromboembolism is highest in the first few months after valve replacement. While the interruption of warfarin therapy is generally safe, most cases of valve thrombosis occur during periods of inadequate anticoagulation, so the time interval without coverage should be kept as short as possible. High-risk features include atrial fibrillation, a prior history of thromboembolism, heart failure or low LVEF, a hypercoagulable state, a mechanical valve in the mitral position, a known high-risk valve (ball-in-cage), or concomitant hypercoagulable state (such as with an associated cancer). The use of bridging VKAs, unfractionated heparin, low-molecular-weight heparin (LMWH), and antifibrinolytics in various clinical situations in patients with valvular heart disease is summarized in Table 10–4. In general, low-risk procedures (eg, pacemaker implantation, cataract removal, and routine dental work) require no stoppage of VKAs, while in other situations the warfarin can be stopped 3 days ahead of the procedure and resumed the night after the procedure (ie, in patients with bileaflet aortic valves) without any bridging unfractionated heparin or LMWH. It is reasonable to consider bridging based on the CHA2DS2-VASc score in patients with bioprosthetic heart valves or annuloplasty rings who take anticoagulants for atrial fibrillation. In high-risk patients, principally just those with a mechanical mitral valve, the warfarin should be stopped and *bridging with either unfractionated heparin or LMWH* begun once the INR falls below therapeutic levels. Fresh frozen plasma or prothrombin complex concentrate is reasonable in an emergency situation for acute reversal if serious bleeding occurs. Most patients with a mechanical valve should not have the warfarin reversed with vitamin K, if it can be avoided, because this can result in a transient hypercoagulable state, and it may take many days to reach a therapeutic INR again.

Warfarin causes fetal skeletal abnormalities in up to 2% of women who become pregnant while taking the medication, so every effort is made to defer mechanical valve replacement in women until after childbearing age. However, if a woman with a mechanical valve becomes pregnant while taking warfarin, the risk of stopping warfarin may be higher for the mother than the risk of continuing warfarin for the fetus. The risk of warfarin to the fetal skeleton is greatest during the first trimester and, remarkably, is more related to dose than to the INR level. Guidelines suggest it is reasonable to continue warfarin for the first trimester if the dose is 5 mg/day or less. If the dose is more than 5 mg/day, it is appropriate to consider either LMWH (as long as the anti-Xa is being monitored [range: 0.8 unit/mL to 1.2 units/mL 4–6 hours post-dose]) or continuous intravenous unfractionated heparin (if the activated partial thromboplastin time [aPTT] can be monitored and is at least two times control). Guidelines suggest warfarin and low-dose aspirin are safe during the second and third trimester, and then should be stopped upon anticipation of delivery. At time of vaginal delivery, unfractionated intravenous heparin with aPTT at least two times control is

desirable. DOACs (antithrombin or Xa inhibitors) should *not* be used in place of warfarin for mechanical prosthetic valves since there are no data that they are safe during pregnancy or safe for mechanical valves in general.

Management of suspected mechanical valve thrombosis depends on whether a left-sided or right-sided valve is involved, the size of the thrombus, and the patient's clinical condition. Simple fluoroscopy can help assess mechanical valve motion, although a TEE is indicated to assess thrombus size. **Therapeutic unfractionated heparin should be given to all patients with a thrombosed valve**, and this alone is generally effective. Fibrinolytic therapy is indicated if heparin therapy is ineffective and the clinical onset has been less than 2 weeks, the thrombus is smaller than 0.8 cm<sup>2</sup>, New York Heart Association (NYHA) class symptoms are mild (functional class I or II), or the valve is right-sided. Surgery is rarely indicated; it is reserved for those with left-sided mechanical valves in NYHA functional class III or IV heart failure or in whom TEE demonstrates a mobile thrombus larger than 0.8 cm<sup>2</sup>. The use of urgent initial therapy for a thrombosed mechanical valve should include low-dose, slow-infusion fibrinolytic therapy or urgent surgery if the patient is symptomatic.

Arya R. Pregnancy outcomes in women with mechanical prosthetic heart valves. Thromb Res. 2019;181:S37. [PMID: 31477226]

Puskas JD et al; PROACT Investigators. Anticoagulation and antiplatelet strategies after On-X mechanical aortic valve replacement. J Am Coll Cardiol. 2018;71:2717. [PMID: 29903344]

## CORONARY HEART DISEASE (Atherosclerotic CAD, Ischemic Heart Disease)

**Coronary heart disease (CHD), or atherosclerotic CAD, is the number one cause of death in the United States and worldwide.** Every minute in the United States, a person dies of CHD. About 37% of people who experience an acute coronary event, either angina or MI, will die of it in the same year. Death rates of CHD have declined every year since 1968, with about half of the decline from 1980 to 2000 due to treatments and half due to improved risk factors. CHD is still responsible for 23.5% of all deaths in the United States, totaling over 640,000 deaths annually. CHD afflicts nearly 16 million Americans and the prevalence rises steadily with age; thus, the aging of the US population promises to increase the overall burden of CHD.

### ► Risk Factors for CAD

Most patients with CHD have some identifiable risk factor. These include a **positive family history** (the younger the onset in a first-degree relative, the greater the risk), **male sex**, **blood lipid abnormalities**, **diabetes mellitus**, **hypertension**, **physical inactivity**, **abdominal obesity**, **cigarette smoking**, **psychosocial factors**, and consumption of **too few fruits and vegetables** and **too much alcohol**. Many of these risk factors are modifiable. **Smoking remains the**

**Table 10–4.** Recommendations for administering vitamin K antagonist (VKA) therapy in patients undergoing procedures or patients with certain clinical conditions.

| Procedures  | Recommendations   |
|---|---|
| General   | Stop VKA 5 days prior and resume 12–24 hours after procedure  |
| Bridging for mechanical heart valves  | Required only for those at high risk for thromboembolism (generally only those with a mechanical mitral [not aortic] valve)<br>Bridge with UFH or LMWH and stop UFH 4–6 hours before procedure or stop LMWH 24 hours before procedure<br>Resume 48–72 hours after the procedure   |
| Clinical Situations   | Recommendations   |
| Atrial fibrillation and moderate or severe mitral stenosis                          | VKA (target INR 2.0–3.0)<br>If patient refuses, aspirin (50–100 mg) plus clopidogrel (75 mg)  |
| Sinus rhythm and mitral stenosis  | If left atrial size > 5.5 cm, then consider VKA (target 2.0–3.0)  |
| Intermittent atrial fibrillation or history of systemic embolus and mitral stenosis | VKA (target INR 2.0–3.0)  |
| Endocarditis  | No anticoagulation recommended<br>Hold VKA until "safe to resume" (generally when mycotic aneurysm is ruled out or there is no need for urgent surgery)   |
| Aspirin use in patients with a bioprosthetic valve                                  | Aspirin (50–100 mg) indefinitely  |
| Bioprosthetic aortic or mitral valve replacement                                    | Aspirin (50–100 mg) indefinitely plus clopidogrel (75 mg) for first 6 months.   |
| Transcatheter valve replacement   | Reasonable to consider VKA to achieve INR 2.5 for first 3 months  |
| Mitral or aortic repair   | Aspirin (50–100 mg) indefinitely  |
| Long-term anticoagulation after valve replacement                                   | Aspirin (50–100 mg). Anticoagulation with a VKA to achieve an INR of 2.5 is reasonable for at least 3 months and up to 6 months after surgical MVR or AVR in patients at low risk for bleeding  |
| Bioprosthetic valve in normal sinus rhythm  |   |
| Mechanical valve replacement  | VKA (target INR 2.0–3.0 for mechanical aortic valve, target INR 1.5–2.5 for On-X aortic valve, target INR 2.5–3.5 for mechanical mitral valve) plus aspirin (50–100 mg)   |
| Prosthetic valve thrombosis   |   |
| Right-sided valve   | Slow infusion fibrinolytic therapy or intravenous heparin   |
| Left-sided valve  | Early surgery if thrombus large ( $> 0.8 \text{ cm}^2$ ), symptomatic from valvular obstruction, high surgical risk, or LA thrombus. Thrombolysis with heparin or slow-infusion fibrinolytic therapy may be tried initially if patient is stable<br>If thrombus evident on bioprosthetic valve creating increased gradient, use of VKA reasonable to assess whether obstructive gradient can be improved  |
| Pregnancy and a mechanical heart valve  | Add aspirin (50–100 mg) for high risk<br>VKA may be used during first trimester and throughout pregnancy if dose of warfarin is $\leq 5 \text{ mg/day}$<br>If VKA dosage normally $> 5 \text{ mg/day}$ , then adjusted dose LMWH twice daily throughout pregnancy (follow anti-Xa 4 hours after dose, with target of 0.8 units/mL to 1.2 units/mL) or LMWH may be used only during the first trimester, then resume VKA during second and third trimesters<br><i>or</i><br>Adjusted dose UFH every 12 hours throughout pregnancy (aPTT $> 2$ times control) or UFH may be used only during the first trimester, then resume VKA during second and third trimester<br>Discontinuation of VKA with initiation of UFH (2 times normal PTT) recommended before planned vaginal delivery |

aPTT, activated partial thromboplastin time; AVR, aortic valve replacement; INR, international normalized ratio; LMWH, low-molecular-weight heparin; MVR, mitral valve replacement; PTT, partial thromboplastin time. UFH, unfractionated heparin.

Adapted from Nishimura RA et al. 2014 AHA/ACC guidelines for the management of patients with valvular heart disease: executive summary. Circulation. 2014;129:2440–92; and Nishimura RA et al. 2017 AHA/ACC focused update of the 2014 AHA/ACC guideline for the management of patients with valvular heart disease. J Am Coll Cardiol. 2017;70:252–89.

**number one preventable cause of death and illness in the United States.** Although cigarette smoking rates have declined in the United States in recent decades, 18% of women and 21% of men still smoke. According to the World Health Organization, 1 year after quitting, the risk of CHD decreases by 50%. Various interventions have been shown to increase the likelihood of successful smoking cessation (see Chapter 1).

**Hypercholesterolemia** is an important modifiable risk factor for CHD. Risk increases progressively with higher levels of low-density lipoprotein (LDL) cholesterol and declines with higher levels of high-density lipoprotein (HDL) cholesterol. Composite risk scores, such as the Framingham score and the 10-year atherosclerotic cardiovascular disease risk calculator (<http://my.americanheart.org/cvriskcalculator>), provide estimates of the 10-year probability of development of CHD that can guide primary prevention strategies. The 2018 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults suggests statin therapy in four populations: patients with (1) clinical atherosclerotic disease, (2) LDL cholesterol 190 mg/dL or higher, (3) diabetes who are aged 40–75 years, and (4) an estimated 10-year atherosclerotic risk of 7.5% or more aged 40–75 years (Figure 10–7). Importantly, **the guidelines do not recommend treating to a target LDL cholesterol.** Patients in these categories should be treated with a moderate- or high-intensity statin, with high-intensity statin for the higher-risk populations (Table 10–5). The ACC/AHA atherosclerotic cardiovascular disease risk estimator allows clinicians to determine the 10-year CHD risk to determine treatment decisions (<http://tools.acc.org/ascvd-risk-estimator-plus/>).

The **metabolic syndrome** is defined as a constellation of three or more of the following: abdominal obesity, triglycerides 150 mg/dL or higher, HDL cholesterol less than 40 mg/dL for men or less than 50 mg/dL for women, fasting glucose 110 mg/dL or higher, and hypertension. This syndrome is increasing in prevalence at an alarming rate. Related to the metabolic syndrome, the epidemic of **obesity** in the United States is likewise a major factor contributing to CHD risk.

## ► Myocardial Hibernation & Stunning

Areas of myocardium that are persistently underperfused but still viable may develop sustained contractile dysfunction. This phenomenon, which is termed **myocardial hibernation**, appears to represent an adaptive response that may be associated with depressed LV function. It is important to recognize this phenomenon, since this form of dysfunction is reversible following coronary revascularization. Hibernating myocardium can be identified by radionuclide testing, positron emission tomography (PET), contrast-enhanced MRI, or its retained response to inotropic stimulation with dobutamine. A related phenomenon, termed **myocardial stunning**, is the occurrence of persistent contractile dysfunction following prolonged or repetitive episodes of myocardial ischemia. Clinically, myocardial stunning is often seen after reperfusion of acute MI and is defined with improvement following revascularization.

## ► Primary & Secondary Prevention of CHD

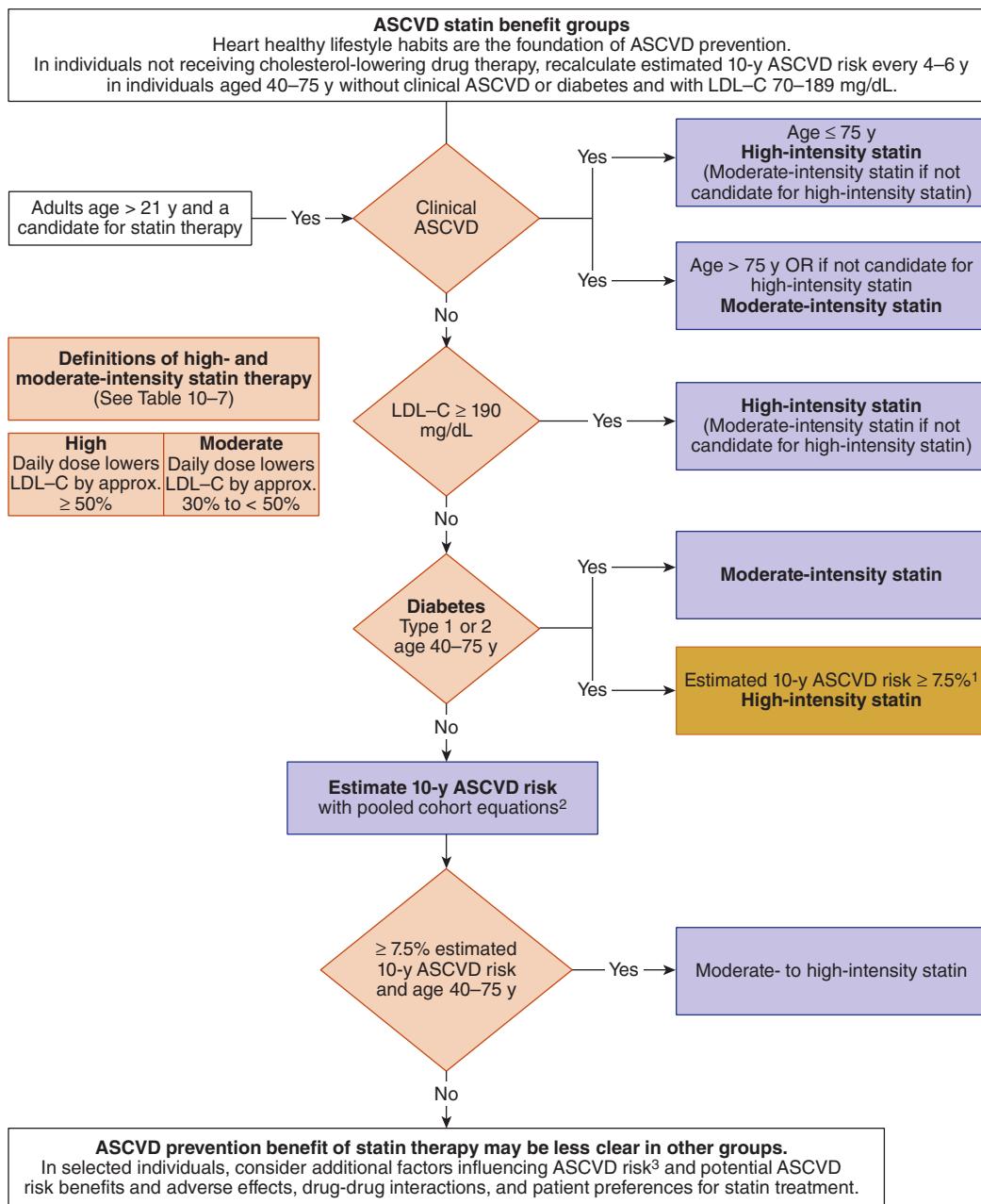
Although many risk factors for CHD are not modifiable, it is now clear that interventions, such as smoking cessation, treatment of dyslipidemia, and lowering of BP can both prevent coronary disease and delay its progression and complications after it is manifest.

Lowering LDL levels delays the progression of atherosclerosis and in some cases may produce regression. Even in the absence of regression, fewer new lesions develop, endothelial function may be restored, and coronary event rates are markedly reduced in patients with clinical evidence of vascular disease.

A series of clinical trials has demonstrated the efficacy of hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) in preventing death, coronary events, and strokes. Beneficial results have been found in patients who have already experienced coronary events (secondary prevention), those at particularly high risk for events (patients with diabetes and patients with peripheral artery disease), those with elevated cholesterol without multiple risk factors, and those without vascular disease or diabetes with elevated high-sensitivity C-reactive protein (hsCRP) with normal LDL levels. The benefits of statin therapy at moderate and high doses (Table 10–5) are recommended by the cholesterol treatment guidelines. The IMPROVE-IT study showed that ezetimibe, 10 mg daily, combined with simvastatin was modestly better than simvastatin alone in reducing the risk of MI and ischemic stroke, but not mortality, in stabilized patients following an acute coronary syndrome. This was associated with a reduction of LDL to 53.7 mg/dL compared to 69.7 mg/dL. With this data, ezetimibe can be used in combination with statin therapy in patients who are not at target cholesterol level for secondary prevention or cannot tolerate high-dose statin therapy.

Benefits occurred regardless of age, race, baseline cholesterol levels, or the presence of hypertension. It is clear that for patients with vascular disease, statins provide benefit for those with normal cholesterol levels, and that more aggressive statin use is associated with greater benefits. **All patients at significant risk for vascular events should receive a statin regardless of their cholesterol levels**, and many recommend that with those who have prior cardiovascular events should have their LDL lowered below 70 mg/dL.

Monoclonal antibodies that inhibit proprotein convertase subtilisin/kexin type 9 (PCSK9) reduce LDL cholesterol levels significantly beyond levels associated with traditional statin therapy. These therapies have been studied in randomized trials of patients with maximally tolerated statin therapy (and for patients with statin intolerance) and have lowered LDL with signals of improved cardiovascular outcomes. The FOURIER trial showed that the PCSK9 inhibitor evolocumab, on top of statin, reduced the composite of atherothrombotic outcomes by 20% but did not reduce mortality. The ODYSSEY Outcomes trial demonstrated alirocumab reduced cardiovascular events in patients with acute coronary syndromes. Alirocumab and evolocumab have been approved by the FDA for patients on maximally tolerated statin therapy with familial



<sup>1</sup>Percent reduction in LDL-C can be used as an indication of response and adherence to therapy but is not in itself a treatment goal.

<sup>2</sup>The Pooled Cohort Equations can be used to estimate 10-year ASCVD risk in individuals with and without diabetes. A downloadable spreadsheet enabling estimation of 10-year and lifetime risk for ASCVD and a web-based calculator are available at <http://my.americanheart.org/cvriskcalculator> and <http://www.cardiosource.org/science-and-quality/practice-guidelines-and-quality-standards/2013-prevention-guideline-tools.aspx>.

<sup>3</sup>Primary LDL-C  $\geq 160$  mg/dL or other evidence of genetic hyperlipidemias, family history of premature ASCVD with onset < 55 years of age in a first-degree male relative or < 65 years of age in a first-degree female relative, high-sensitivity C-reactive protein  $> 2$  mg/L, CAC score  $\geq 300$  Agatston units or  $\geq 75$  percentile for age, sex, and ethnicity, ankle-brachial index  $< 0.9$ , or elevated lifetime risk of ASCVD.

▲ **Figure 10-7.** Major recommendations for statin therapy for atherosclerotic cardiovascular disease prevention. ASCVD, atherosclerotic cardiovascular disease; CAC, coronary artery calcium; LDL-C, low-density lipoprotein cholesterol. (Adapted from Stone NJ et al. 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014;129:S1.)

**Table 10–5.** High-, moderate-, and low-intensity statin therapy.<sup>1,2,3</sup>

| High-Intensity Statin Therapy  | Moderate-Intensity Statin Therapy  | Low-Intensity Statin Therapy  |
|--|--|---|
| LDL-C lowering <sup>4</sup> ≥ 50%  | LDL-C lowering <sup>4</sup> 30% to 49%   | LDL-C lowering <sup>4</sup> < 30%   |
| <b>Atorvastatin (40 mg)<sup>5</sup> 80 mg</b><br><b>Rosuvastatin 20 mg (40 mg)</b> | <b>Atorvastatin 10 mg (20 mg)</b><br><b>Rosuvastatin (5 mg) 10 mg</b><br><b>Simvastatin 20–40 mg<sup>6</sup></b><br><b>Pravastatin 40 mg (80 mg)</b><br><b>Lovastatin 40 mg (80 mg)</b><br><b>Fluvastatin XL 80 mg</b><br><b>Fluvastatin 40 mg twice daily</b><br><b>Pitavastatin 1–4 mg</b> | <b>Simvastatin 10 mg</b><br><b>Pravastatin 10–20 mg</b><br><b>Lovastatin 20 mg</b><br><b>Fluvastatin 20–40 mg</b> |

<sup>1</sup>Percent LDL-C reductions with the primary statin medications used in clinical practice (atorvastatin, rosuvastatin, simvastatin) were estimated using the median reduction in LDL-C from the VOYAGER database.<sup>5,3,2,1–2</sup> Reductions in LDL-C for other statin medications (fluvastatin, lovastatin, pitavastatin, pravastatin) were identified according to FDA-approved product labeling in adults with hyperlipidemia, primary hypercholesterolemia, and mixed dyslipidemia.

<sup>2</sup>Boldface type indicates specific statins and doses that were evaluated in RCTs, and the Cholesterol Treatment Trialists' 2010 meta-analysis. All these RCTs demonstrated a reduction in major cardiovascular events.

<sup>3</sup>Percent reductions are estimates from data across large populations. Individual responses to statin therapy varied in the RCTs and should be expected to vary in clinical practice.

<sup>4</sup>LDL-C lowering that should occur with the dosage listed below.

<sup>5</sup>Evidence from one RCT only: down-titration if unable to tolerate atorvastatin 80 mg in IDEAL study.

<sup>6</sup>Although simvastatin 80 mg was evaluated in RCTs, initiation of simvastatin 80 mg or titration to 80 mg is not recommended by the FDA due to the increased risk of myopathy, including rhabdomyolysis.

FDA, Food and Drug Administration; IDEAL, Incremental Decrease through Aggressive Lipid Lowering study; LDL-C, low-density lipoprotein cholesterol; RCTs, randomized controlled trials.

Reproduced with permission, from Grundy SM et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APha/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2019 Jun 18;139 (25): e1082–e1143. © 2019 American Heart Association, Inc.

hypercholesterolemia and atherosclerotic vascular disease, or both, and who require additional lowering of LDL. These medications cost several thousand dollars per year in the United States. Alirocumab has also been approved by the FDA for secondary prevention of cardiovascular events. Inclisiran (a small interfering RNA that goes to the liver and prevents the production of PCSK9) has been studied as a twice yearly injection showing reduction in LDL. Outcomes trials are ongoing, and the therapy is not FDA approved as of early 2021.

While fish oil supplements have *not* been shown to provide benefit for reducing risk, icosapent ethyl, a concentrated eicosapentaenoic acid at a high dose, was shown to be beneficial in the REDUCE-IT trial. Patients with established cardiovascular disease or with diabetes and other risk factors, with fasting triglyceride level of 135–499 mg/dL, who were on statins were randomized to 2 g of icosapent ethyl twice daily or placebo. There was a 26% relative risk reduction in cardiovascular death, MI, and stroke, as well as a 20% relative risk reduction in cardiovascular death. Icosapent ethyl is approved by the FDA as an adjunct to maximally tolerated statin therapy to reduce the risk of MI, stroke, coronary revascularization, or unstable angina requiring hospitalization in patients with triglycerides of 150 mg/dL or more and either established cardiovascular disease or diabetes mellitus and two or more additional risk factors. The role of high-dose omega-3 fatty acids was studied compared to corn oil and not shown to reduce cardiovascular events, leading to increased interest in comparative studies.

**Treatment to raise HDL levels has failed to show benefit.** The AIM High trial found no benefit from the addition of niacin in patients with vascular disease and a serum LDL near 70 mg/dL who were receiving statin therapy. The HPS2-THRIVE trial found no benefit but rather substantial harm of extended-release niacin (2 g) plus laropiprant (an antiflushing agent) for preventing vascular events in a population of over 25,000 patients with vascular disease who were taking simvastatin.

**For primary prevention, aspirin has little overall benefit, including for patients with established diabetes, and is no longer recommended for most patients. Antiplatelet therapy is a very effective measure for secondary prevention and patients with established vascular disease should be treated with aspirin.** The exact dose of aspirin in chronic CAD (81 mg vs 325 mg) is being evaluated in a large ongoing pragmatic trial (ADAPTABLE). While clopidogrel was found to be effective at preventing vascular events for 9–12 months after acute coronary syndromes, and there are some benefits in prolonging dual antiplatelet therapy after coronary stenting, clopidogrel was *not* found to be effective at preventing vascular events in combination with aspirin with longer-term treatment in the CHARISMA trial. This trial included patients with clinically evident stable atherothrombosis or with multiple risk factors; all were treated with aspirin and observed for a median of 28 months.

In the COMPASS trial, rivaroxaban, a direct factor Xa inhibitor, at a dose of 2.5 mg twice daily in addition to 100 mg of aspirin, was shown to reduce cardiovascular death, MI, and

stroke by a relative risk reduction of 24% compared to 100 mg aspirin monotherapy in stable patients with CAD and peripheral artery disease. Bleeding was modestly increased. All-cause mortality was also reduced by 18%. This regimen is approved by the FDA and is used for long-term management of patients with CAD and peripheral artery disease.

The HOPE and the EUROPA trials demonstrated that angiotensin-converting enzyme (ACE) inhibitors (ramipril 10 mg/day and perindopril 8 mg/day, respectively) reduced fatal and nonfatal vascular events (cardiovascular deaths, nonfatal MIs, and nonfatal strokes) by 20–25% in patients at high risk, including patients with diabetes with additional risk factors or patients with clinical coronary, cerebral, or peripheral arterial atherosclerotic disease. An overview of these trials has demonstrated that while low-risk patients may *not* derive substantial benefits from ACE inhibitors, **most patients with vascular disease, even in the absence of heart failure or LV dysfunction, should be treated with an ACE inhibitor.**

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## CHRONIC STABLE ANGINA PECTORIS (Chronic Coronary Syndromes)



- ▶ Precordial chest pain, usually precipitated by stress or exertion, relieved rapidly by rest or nitrates.
- ▶ ECG or scintigraphic evidence of ischemia during pain or stress testing.
- ▶ Angiographic demonstration of significant obstruction of major coronary vessels.

## ► General Considerations

Angina pectoris is the manifestation of stable coronary artery disease or chronic coronary syndromes, and it is usually due to atherosclerotic heart disease. Coronary vasospasm may occur at the site of a lesion or, less frequently, in apparently normal vessels. Other unusual causes of coronary artery obstruction, such as congenital anomalies, emboli, arteritis, or dissection may cause ischemia or infarction. Angina may also occur in the absence of coronary artery obstruction as a result of severe myocardial hypertrophy, severe aortic stenosis or regurgitation, or in response to increased metabolic demands, as in hyperthyroidism, marked anemia, or paroxysmal tachycardias with rapid ventricular rates.

## ► Clinical Findings

### A. Symptoms

The diagnosis of angina pectoris principally depends on the history, which should specifically include the following information: circumstances that precipitate and relieve angina, characteristics of the discomfort, location and radiation, duration of attacks, and effect of nitroglycerin.

#### 1. Circumstances that precipitate and relieve angina—

Angina occurs most commonly during activity and is relieved by resting. Patients may prefer to remain upright rather than lie down, as increased preload in recumbency increases myocardial work. The amount of activity required to produce angina may be relatively consistent under comparable physical and emotional circumstances or may vary from day to day. The threshold for angina is usually lower after meals, during excitement, or on exposure to cold. It is often lower in the morning or after strong emotion; the latter can provoke attacks in the absence of exertion. In addition, discomfort may occur during sexual activity, at rest, or at night as a result of coronary spasm.

**2. Characteristics of the discomfort**—Patients often do not refer to angina as “pain” but as a sensation of tightness, squeezing, burning, pressing, choking, aching, bursting, “gas,” indigestion, or an ill-characterized discomfort. It is often characterized by clenching a fist over the mid chest. The distress of angina is rarely sharply localized and is not spasmodic.

**3. Location and radiation**—The distribution of the distress may vary widely in different patients but is usually the same for each patient unless unstable angina or MI supervenes. In most cases, the discomfort is felt behind or slightly to the left of the mid sternum. When it begins farther to the left or, uncommonly, on the right, it characteristically moves centrally substernally. Although angina may radiate to any dermatome from C8 to T4, it radiates most often to the left shoulder and upper arm, frequently moving down the inner volar aspect of the arm to the elbow, forearm, wrist, or fourth and fifth fingers. It may also radiate to the right shoulder or arm, the lower jaw, the neck, or even the back.

**4. Duration of attacks**—Angina is generally of short duration and subsides completely without residual discomfort. If the attack is precipitated by exertion and the patient

promptly stops to rest, it usually lasts under 3 minutes. Attacks following a heavy meal or brought on by anger often last 15–20 minutes. Attacks lasting more than 30 minutes are unusual and suggest the development of an acute coronary syndrome with unstable angina, MI, or an alternative diagnosis.

**5. Effect of nitroglycerin**—The diagnosis of angina pectoris is supported if sublingual nitroglycerin promptly and invariably shortens an attack and if prophylactic nitrates permit greater exertion or prevent angina entirely.

### B. Signs

Examination during angina frequently reveals a significant elevation in systolic and diastolic BP, although hypotension may also occur, and may reflect more severe ischemia or inferior ischemia (especially with bradycardia) due to a **Bezold-Jarisch reflex**. Occasionally, a gallop rhythm and an apical systolic murmur due to transient mitral regurgitation from papillary muscle dysfunction are present during pain only. Supraventricular or ventricular arrhythmias may be present, either as the precipitating factor or as a result of ischemia.

It is important to detect signs of diseases that may contribute to or accompany atherosclerotic heart disease, eg, diabetes mellitus (retinopathy or neuropathy), xanthelasma tendinous xanthomas, hypertension, thyrotoxicosis, myxedema, or peripheral artery disease. Aortic stenosis or regurgitation, HCM, and mitral valve prolapse should be sought, since they may produce angina or other forms of chest pain.

### C. Laboratory Findings

Other than standard laboratory tests to evaluate for acute coronary syndrome (troponin and CK-MB) and factors contributing to ischemia (such as anemia) and to screen for risk factors that may increase the probability of true CHD (such as hyperlipidemia and diabetes mellitus), blood tests are not helpful to diagnose chronic angina.

### D. ECG

The resting ECG is often normal in patients with angina. In the remainder, abnormalities include old MI, nonspecific ST-T changes, and changes of LVH. During anginal episodes, as well as during asymptomatic ischemia, the characteristic ECG change is **horizontal or downsloping ST-segment depression that reverses after the ischemia disappears**. T wave flattening or inversion may also occur. Less frequently, transient ST-segment elevation is observed; this finding suggests severe (transmural) ischemia from coronary occlusion, and it can occur with coronary spasm.

### E. Pretest Probability

The history as detailed above, the physical examination findings, and laboratory and ECG findings are used to develop a pretest probability of CAD as the cause of the clinical symptoms. Other important factors to include in calculating the pretest probability of CAD are patient age, sex, and clinical symptoms. Patients with low to

intermediate pretest probability for CAD should undergo noninvasive stress testing whereas patients with high pretest probability are generally referred for cardiac catheterization. National review of diagnostic cardiac catheterization findings in patients without known CAD undergoing angiography has shown that between 38% and 40% of patients do not have obstructive disease.

### F. Exercise ECG

Exercise ECG testing is the most commonly used noninvasive procedure for evaluating for inducible ischemia in the patient with angina. Exercise ECG testing is often combined with imaging studies (nuclear or echocardiography), but in low-risk patients without baseline ST-segment abnormalities or in whom anatomic localization is not necessary, the exercise ECG remains the recommended initial procedure because of considerations of cost, convenience, and longstanding prognostic data.

Exercise testing can be done on a motorized treadmill or with a bicycle ergometer. A variety of exercise protocols are utilized, the most common being the **Bruce protocol**, which increases the treadmill speed and elevation every 3 minutes until limited by symptoms. At least two ECG leads should be monitored continuously.

**1. Precautions and risks**—The risk of exercise testing is about one infarction or death per 1000 tests, but individuals who have pain at rest or minimal activity are at higher risk and should not be tested. **Many of the traditional exclusions, such as recent MI or heart failure, are no longer used if the patient is stable and ambulatory, but symptomatic aortic stenosis remains a relative contraindication.**

**2. Indications**—Exercise testing is used (1) to confirm the diagnosis of angina; (2) to determine the severity of limitation of activity due to angina; (3) to assess prognosis in patients with known coronary disease, including those recovering from MI, by detecting groups at high or low risk; and (4) to evaluate responses to therapy. Because false-positive tests often exceed true positives, leading to much patient anxiety and self-imposed or mandated disability, exercise testing of asymptomatic individuals should be done only for those whose occupations place them or others at special risk (eg, airline pilots).

**3. Interpretation**—The usual ECG criterion for a positive test is 1-mm (0.1-mV) horizontal or downsloping ST-segment depression (beyond baseline) measured 80 msec after the J point. By this criterion, 60–80% of patients with anatomically significant coronary disease will have a positive test, but 10–30% of those without significant disease will also be positive. False positives are uncommon when a 2-mm depression is present. Additional information is inferred from the time of onset and duration of the ECG changes, their magnitude and configuration, BP and heart rate changes, the duration of exercise, and the presence of associated symptoms. In general, patients exhibiting more severe ST-segment depression (more than 2 mm) at low workloads (less than 6 minutes on the Bruce protocol) or heart rates (less than 70% of age-predicted

maximum)—especially when the duration of exercise and rise in BP are limited or when hypotension occurs during the test—have more severe disease and a poorer prognosis. Depending on symptom status, age, and other factors, such patients should be referred for coronary arteriography and possible revascularization. On the other hand, less impressive positive tests in asymptomatic patients are often “false positives.” Therefore, exercise testing results that do not conform to the clinical suspicion should be confirmed by stress imaging.

### G. Myocardial Stress Imaging

Myocardial stress imaging (scintigraphy, echocardiography, or MRI) is indicated (1) when the resting ECG makes an exercise ECG difficult to interpret (eg, left bundle branch block, baseline ST-T changes, low voltage); (2) for confirmation of the results of the exercise ECG when they are contrary to the clinical impression (eg, a positive test in an asymptomatic patient); (3) to localize the region of ischemia; (4) to distinguish ischemic from infarcted myocardium; (5) to assess the completeness of revascularization following bypass surgery or coronary angioplasty; or (6) as a prognostic indicator in patients with known coronary disease. Published criteria summarize these indications for stress testing.

**1. Myocardial perfusion scintigraphy**—This test, also known as **radionuclide imaging**, provides images in which radionuclide uptake is proportionate to blood flow at the time of injection.

Stress imaging is positive in about 75–90% of patients with anatomically significant coronary disease and in 20–30% of those without it. Occasionally, other conditions, including infiltrative diseases (sarcoidosis, amyloidosis), left bundle branch block, and dilated cardiomyopathy, may produce resting or persistent perfusion defects. False-positive radionuclide tests may occur as a result of diaphragmatic attenuation or, in women, attenuation through breast tissue. Tomographic imaging (single-photon emission computed tomography, SPECT) can reduce the severity of artifacts.

**2. Radionuclide angiography**—This procedure, also known as **multi-gated acquisition scan**, or **MUGA scan**, uses radionuclide tracers to image the LV and measures its EF and wall motion. In coronary disease, resting abnormalities usually represent infarction, and those that occur only with exercise usually indicate stress-induced ischemia. Exercise radionuclide angiography has approximately the same sensitivity as myocardial perfusion scintigraphy, but it is less specific in older individuals and those with other forms of heart disease. In addition, because of the precision around LVEF, the test is also used for monitoring patients exposed to cardiotoxic therapies (such as chemotherapeutic agents).

**3. Stress echocardiography**—Echocardiograms performed during supine exercise or immediately following upright exercise may demonstrate exercise-induced segmental wall motion abnormalities as an indicator of ischemia. In experienced laboratories, the test accuracy is comparable to that obtained with scintigraphy—though a

higher proportion of tests is technically inadequate. While exercise is the preferred stress because of other information derived, pharmacologic stress with high-dose dobutamine (20–40 mcg/kg/min) can be used as an alternative to exercise.

### H. Other Imaging

**1. Positron emission tomography**—PET and SPECT scanning can accurately distinguish transiently dysfunctional (“stunned”) myocardium from scar tissue.

**2. CT and MRI scanning**—CT scanning can image the heart and, with contrast medium and multislice technology, the coronary arteries. **Multislice CT angiography** may be useful in evaluating patients with low likelihood of significant CAD to rule out disease. Its use has been associated with lower 5-year mortality compared to standard care in patients with stable chest pain. With lower radiation exposure than radionuclide SPECT imaging, CT angiography may also be useful for evaluating chest pain and suspected acute coronary syndrome. In the large randomized comparative effectiveness PROMISE trial, patients with stable chest pain undergoing anatomic imaging with CT angiography had similar outcomes to patients undergoing functional testing (stress ECG, stress radionuclide, or stress echocardiography). CT angiography with noninvasive functional assessment of coronary stenosis (fractional flow reserve), termed **CT-FFR**, has also been evaluated in patients with low-intermediate likelihood of CAD. CT-FFR has been shown to reduce the number of patients without coronary disease requiring invasive angiography. CT-FFR has been approved for clinical use and is being used in clinical practice in the United States and Europe.

**Electron beam CT (EBCT) (Coronary Calcium Score)** can quantify coronary artery calcification, which is highly correlated with atherosomatous plaque and has high sensitivity, but low specificity, for obstructive coronary disease. This test has not traditionally been used in symptomatic patients. According to the AHA, persons who are at low risk (less than 10% 10-year risk) or at high risk (greater than 20% 10-year risk) for obstructive coronary disease do not benefit from coronary calcium assessment (class III, level of evidence: B). However, in clinically selected, intermediate-risk patients (5–7.5% atherosclerotic cardiovascular disease), it may be reasonable to determine the atherosclerosis burden using EBCT in order to refine clinical risk prediction and to select patients for more aggressive target values for lipid-lowering therapies (class IIb, level of evidence: B).

**Cardiac MRI using gadolinium** provides high-resolution images of the heart and great vessels without radiation exposure or use of iodinated contrast media. Gadolinium has been associated with a rare but fatal complication in patients with severe kidney disease, called **necrotizing systemic fibrosis**. Gadolinium can demonstrate perfusion using dobutamine or adenosine to produce pharmacologic stress. Advances have been made in imaging the proximal coronary arteries. Perhaps the most clinically used indication of cardiac MRI is for identification of **myocardial fibrosis**, either from MI or infiltration, done with

gadolinium contrast. This allows high-resolution imaging of myocardial viability and infiltrative cardiomyopathies.

### I. Ambulatory ECG Monitoring

Ambulatory ECG recorders can monitor for ischemic ST-segment depression, but this modality is rarely used for ischemia detection. In patients with CAD, these episodes usually signify ischemia, even when asymptomatic (“silent”).

### J. Coronary Angiography

Selective coronary arteriography is the definitive diagnostic procedure for CAD. It can be performed with low mortality (about 0.1%) and morbidity (1–5%), but due to the invasive nature and cost, it is recommended only in patients with a high pretest probability of CAD.

Coronary arteriography should be performed in the following circumstances if percutaneous transluminal coronary angioplasty or bypass surgery is a consideration:

1. Life-limiting stable angina despite an adequate medical regimen.
2. Clinical presentation (unstable angina, postinfarction angina, etc) or noninvasive testing suggests high-risk disease (see Indications for Revascularization).
3. Concomitant aortic valve disease and angina pectoris, to determine whether the angina is due to accompanying coronary disease.
4. Asymptomatic older patients undergoing valve surgery so that concomitant bypass may be done if the anatomy is propitious.
5. Recurrence of symptoms after coronary revascularization to determine whether bypass grafts or native vessels are occluded.
6. Cardiac failure where a surgically correctable lesion, such as LV aneurysm, mitral regurgitation, or reversible ischemic dysfunction, is suspected.
7. Survivors of sudden death, symptomatic, or life-threatening arrhythmias when CAD may be a correctable cause.
8. Chest pain of uncertain cause or cardiomyopathy of unknown cause.
9. Emergently performed cardiac catheterization with intention to perform primary PCI in patients with suspected acute MI.

A narrowing of more than 50% of the luminal diameter is considered hemodynamically (and clinically) significant, although most lesions producing ischemia are associated with narrowing in excess of 70%. In those with strongly positive exercise ECGs or scintigraphic studies, three-vessel or left main disease may be present in 75–95% depending on the criteria used. **Intravascular ultrasound (IVUS)** is useful as an adjunct for assessing the results of angioplasty or stenting. In addition, IVUS is the invasive diagnostic method of choice for ostial left main lesions and coronary dissections. In **fractional flow reserve (FFR)**, a pressure wire is used to measure the relative change in pressure across a coronary lesion after adenosine-induced hyperemia. Revascularization based on abnormal FFR

improves clinical outcomes compared to revascularization of all angiographically stenotic lesions. FFR is an important invasive tool to aid with ischemia-driven revascularization and has become the standard tool to evaluate borderline lesions in cases in which the clinical team is evaluating the clinical and hemodynamic significance of a coronary stenosis. Additionally, pressures distally/pressures proximally during a wave-free period in diastole have been shown to demonstrate similar clinical outcomes to FFR, without the use of adenosine.

**LV angiography** is usually performed at the same time as coronary arteriography. Global and regional LV function are visualized, as well as mitral regurgitation if present. LV function is a major determinant of prognosis in CHD.

### ► Differential Diagnosis

When atypical features are present—such as prolonged duration (hours or days) or darting, or knifelike pains at the apex or over the precordium—ischemia is less likely.

**Anterior chest wall syndrome** is characterized by a sharply localized tenderness of the intercostal muscles. Inflammation of the chondrocostal junctions may result in diffuse chest pain that is also reproduced by local pressure (**Tietze syndrome**). Intercostal neuritis (due to herpes zoster or diabetes mellitus, for example) also mimics angina.

Cervical or thoracic spine disease involving the dorsal roots produces sudden sharp, severe chest pain suggesting angina in location and “radiation” but related to specific movements of the neck or spine, recumbency, and straining or lifting. Pain due to cervical or thoracic disk disease involves the outer or dorsal aspect of the arm and the thumb and index fingers rather than the ring and little fingers.

Reflux esophagitis, peptic ulcer, chronic cholecystitis, esophageal spasm, and functional gastrointestinal disease may produce pain suggestive of angina pectoris. The picture may be especially confusing because ischemic pain may also be associated with upper gastrointestinal symptoms, and esophageal motility disorders may be improved by nitrates and calcium channel blockers. Assessment of esophageal motility may be helpful.

Degenerative and inflammatory lesions of the left shoulder and thoracic outlet syndromes may cause chest pain due to nerve irritation or muscular compression; the symptoms are usually precipitated by movement of the arm and shoulder and are associated with paresthesias.

Pneumonia, pulmonary embolism, and spontaneous pneumothorax may cause chest pain as well as dyspnea. Dissection of the thoracic aorta can cause severe chest pain that is commonly felt in the back; it is sudden in onset, reaches maximum intensity immediately, and may be associated with changes in pulses. Other cardiac disorders, such as mitral valve prolapse, HCM, myocarditis, pericarditis, aortic valve disease, or RVH, may cause atypical chest pain or even myocardial ischemia.

### ► Treatment

Sublingual nitroglycerin is the medication of choice for acute management; it acts in about 1–2 minutes. As soon as the attack begins, one fresh tablet is placed under the

tongue. This may be repeated at 3- to 5-minute intervals, but if pain is not relieved or improving after 5 minutes, the patient should call 9-1-1; pain not responding to three tablets or lasting more than 20 minutes may represent evolving infarction. The dosage (0.3, 0.4, or 0.6 mg) and the number of tablets to be used before seeking further medical attention must be individualized. Nitroglycerin buccal spray is also available as a metered (0.4 mg) delivery system. It has the advantage of being more convenient for patients who have difficulty handling the pills and of being more stable.

## ► Prevention of Further Attacks

### A. Aggravating Factors

Angina may be aggravated by hypertension, LV failure, arrhythmia (usually tachycardias), strenuous activity, cold temperatures, and emotional states. These factors should be identified and treated when possible.

### B. Nitroglycerin

Nitroglycerin, 0.3–0.6 mg sublingually or 0.4–0.8 mg translingually by spray, should be taken 5 minutes before any activity likely to precipitate angina. Sublingual isosorbide dinitrate (2.5–5 mg) is only slightly longer-acting than sublingual nitroglycerin.

### C. Long-Acting Nitrates

Longer-acting nitrate preparations include isosorbide dinitrate, 10–40 mg orally three times daily; isosorbide mononitrate, 10–40 mg orally twice daily or 60–120 mg once daily in a sustained-release preparation; oral sustained-release nitroglycerin preparations, 6.25–12.5 mg two to four times daily; nitroglycerin ointment, 2% ointment, 0.5–2 inches (7.5–30 mg in the morning and 65 hours later); and transdermal nitroglycerin patches that deliver nitroglycerin at rates of 0.2, 0.4, and 0.6 mg/h rate (0.1–0.8 mg/h), and should be taken off after 12–14 hours of use for a 10–12 hour patch-free interval daily. The main limitation to long-term nitrate therapy is *tolerance*, which can be limited by using a regimen that includes a minimum 8- to 10-hour period per day without nitrates. Isosorbide dinitrate can be given three times daily, with the last dose after dinner, or longer-acting isosorbide mononitrate once daily. Transdermal nitrate preparations should be removed overnight in most patients.

Nitrate therapy is often limited by headache. Other side effects include nausea, light-headedness, and hypotension. Importantly, phosphodiesterase inhibitors used commonly for erectile dysfunction should not be taken within 24 hours of nitrate use.

### D. Beta-Blockers

Beta-blockers are the only antianginal agents that have been demonstrated to prolong life in patients with coronary disease (post-MI). Beta-blockers should be considered for first-line therapy in most patients with chronic angina and are recommended as such by the stable ischemic heart disease guidelines (Figure 10–8).

Beta-blockers with intrinsic sympathomimetic activity, such as pindolol, are less desirable because they may exacerbate angina in some individuals and have not been effective in secondary prevention trials. The pharmacology and side effects of the beta-blockers are discussed in Chapter 11 (see Table 11–9). The dosages of all these medications when given for angina are similar. The major contraindications are severe bronchospastic disease, bradyarrhythmias, and decompensated heart failure.

### E. Ranolazine

Ranolazine is indicated for chronic angina. Ranolazine has no effect on heart rate and BP, and it has been shown in clinical trials to prolong exercise duration and time to angina, both as monotherapy and when administered with conventional antianginal therapy. It is safe to use with erectile dysfunction medications. The usual dose is 500 mg orally twice a day. Because it can cause QT prolongation, it is contraindicated in patients with existing QT prolongation; in patients taking QT prolonging medications, such as class I or III antiarrhythmics (eg, quinidine, dofetilide, sotalol); and in those taking potent and moderate CYP450 3A inhibitors (eg, clarithromycin and rifampin). Of interest, in spite of the QT prolongation, there is a significantly lower rate of ventricular arrhythmias with its use following acute coronary syndromes, as shown in the MERLIN trial.

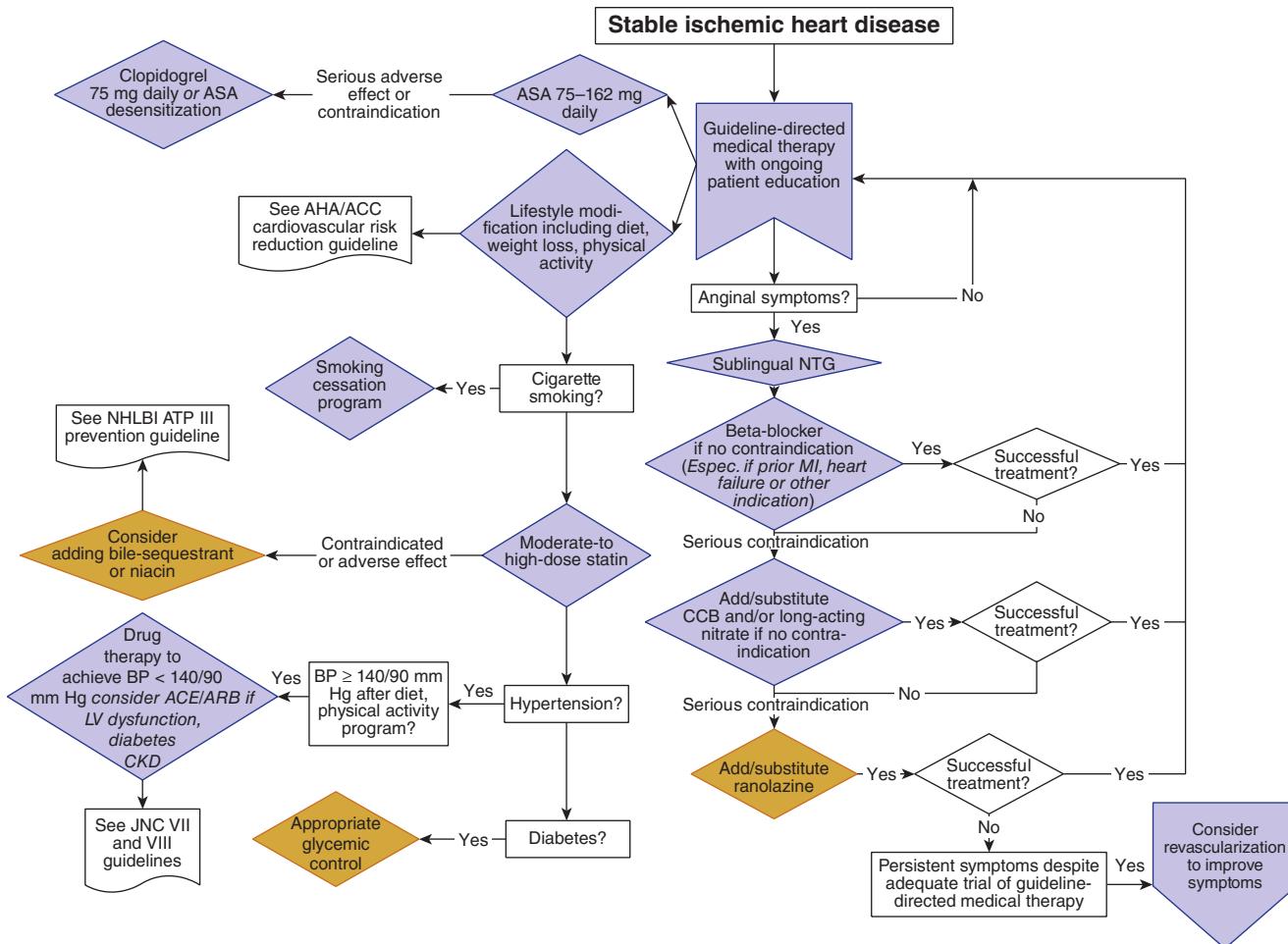
### F. Calcium Channel Blocking Agents

Unlike the beta-blockers, calcium channel blockers have *not* been shown to reduce mortality postinfarction and in some cases have increased ischemia and mortality rates. This appears to be the case with some dihydropyridines (eg, nifedipine) and with diltiazem and verapamil in patients with clinical heart failure or moderate to severe LV dysfunction. Meta-analyses have suggested that short-acting nifedipine in moderate to high doses causes an *increase* in mortality. It is uncertain whether these findings are relevant to longer-acting dihydropyridines. Nevertheless, considering the uncertainties and the lack of demonstrated favorable effect on outcomes, calcium channel blockers should be considered third-line anti-ischemic medications in the postinfarction patient. Similarly, these agents, with the exception of amlodipine (which proved safe in patients with heart failure in the PRAISE-2 trial), should be avoided in patients with heart failure or low EFs.

The pharmacologic effects and side effects of the calcium channel blockers are discussed in Chapter 11 and summarized in Table 11–7. Diltiazem, amlodipine, and verapamil are preferable because they produce less reflex tachycardia and because the former, at least, may cause fewer side effects. Nifedipine, nicardipine, and amlodipine are also approved agents for angina. Isradipine, felodipine, and nisoldipine are not approved for angina but probably are as effective as the other dihydropyridines.

### G. Ivabradine

Ivabradine selectively blocks the  $I_f$  current and specifically lowers heart rate. It has been shown to reduce angina in patients with chronic stable angina and is approved in



**Figure 10-8.** Algorithm for guideline-directed medical therapy for patients with stable ischemic heart disease. The use of bile acid sequestrant is relatively contraindicated when triglycerides are 200 mg/dL or higher and contraindicated when triglycerides are 500 mg/dL or higher. Dietary supplement niacin must not be used as a substitute for prescription niacin. ACE/ARB, angiotensin-converting enzyme/angiotensin receptor blocker; AHA/ACC, American Heart Association/American College of Cardiology; ASA, aspirin; BP, blood pressure; CCB, calcium channel blocker; CKD, chronic kidney disease; MI, myocardial infarction; NTG, nitroglycerin. (Reproduced, with permission, from Fihn SD et al; American College of Cardiology Foundation/American Heart Association Task Force. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease. Circulation. 2012;126:e354. © 2012 American Heart Association, Inc.)

Europe. However, the SIGNIFY trial found no overall difference in clinical outcomes in patients without heart failure and angina and that there may have been harm for patients with significant angina with regard to outcomes of cardiovascular death and MI.

## H. Alternative and Combination Therapies

Patients who do not respond to one class of antianginal medication often respond to another. It may, therefore, be worthwhile to use an alternative agent before progressing to combinations. The stable ischemic heart disease guidelines recommend starting with a beta-blocker as initial therapy, followed by calcium channel blockers, long-acting nitrates, or ranolazine. A few patients will have further response to a regimen including all four agents.

## I. Platelet-Inhibiting Agents

Several studies have demonstrated the benefit of antiplatelet medications for patients with stable and unstable vascular disease. Therefore, *unless contraindicated*, **aspirin** (81 mg orally daily) should be prescribed for all patients with angina. **Clopidogrel**, 75 mg orally daily, reduces vascular events in patients with stable vascular disease (as an alternative to aspirin) and in patients with acute coronary syndromes (in addition to aspirin). Thus, it is also a good alternative in aspirin-intolerant patients. Clopidogrel in addition to aspirin did not reduce MI, stroke, or cardiovascular death in the CHARISMA trial of patients with cardiovascular disease or multiple risk factors, with about a 50% increase in bleeding. However, it might be reasonable to use combination clopidogrel and aspirin for certain high-risk patients with established coronary disease, as tested in the DAPT trial. Specifically, **prolonged use of dual antiplatelet therapy with aspirin and clopidogrel may be beneficial in patients post-percutaneous stenting with drug-eluting stents who have a low bleeding risk.**

**Ticagrelor**, a P2Y<sub>12</sub> inhibitor, has been shown to reduce cardiovascular events in patients with acute coronary syndromes. Additionally, in patients with prior MI, long-term treatment with ticagrelor plus aspirin reduced cardiovascular events compared to aspirin alone. In patients with peripheral artery disease, ticagrelor monotherapy did not reduce cardiovascular events compared to clopidogrel.

**Vorapaxar** is an inhibitor of the protease-activated receptor-1. It was shown to reduce cardiovascular events for patients with stable atherosclerosis with a history of MI or peripheral artery disease in the TRA 2P trial. It is contraindicated for patients with a history of stroke or TIA due to increased risk of intracranial hemorrhage.

**Rivaroxaban**, a direct factor Xa inhibitor, when used at a dose of 2.5 mg twice daily in addition to low-dose aspirin, was found to reduce cardiovascular events including cardiovascular death, MI, or stroke when compared to aspirin monotherapy in patients with known CAD or peripheral artery disease. This agent is approved and provides another option for patients.

Current guidelines recommend **dual antiplatelet therapy (aspirin and P2Y<sub>12</sub> therapy) in patients with recent MI (within 1 year) or recent stenting (within 6 months) and for prolonged therapy (more than 1 year) in patients**

**at high ischemic risk (multivessel coronary disease or polyvascular disease) and low bleeding risk.**

## J. Risk Reduction

Patients with coronary disease should undergo aggressive **risk factor modification**. This approach, with a particular focus on statin treatment, treating hypertension, stopping smoking, and exercise and weight control (especially for patients with metabolic syndrome or at risk for diabetes), may markedly improve outcomes. For patients with diabetes and cardiovascular disease, there is uncertainty about the optimal target blood sugar control. The ADVANCE trial suggested some benefit for tight blood sugar control with target HbA<sub>1C</sub> of 6.5% or less, but the ACCORD trial found that routine aggressive targeting for blood sugar control to HbA<sub>1C</sub> to less than 6.0% in patients with diabetes and coronary disease was associated with *increased* mortality. Therefore, tight blood sugar control should be avoided particularly in patients with a history of severe hypoglycemia, long-standing diabetes, and advanced vascular disease. Aggressive BP control (target systolic BP less than 120 mm Hg) in the ACCORD trial was not associated with reduction in CHD events despite reducing stroke. In contrast, the SPRINT trial, which did not include diabetic patients, demonstrated a reduction in cardiovascular events in patients with a reduction in death from any cause and reduction in MI with a goal systolic BP of less than 120 mm Hg versus of goal of less than 140 mm Hg. Some increase in adverse events was noted. Based on this and the totality of results, **the AHA has recommended defining hypertension at the 130 mm Hg level.**

## K. Revascularization

**1. Indications**—There is general agreement that otherwise healthy patients in the following groups should undergo revascularization: (1) patients with unacceptable symptoms despite medical therapy to its tolerable limits; (2) patients with left main coronary artery stenosis greater than 50% with or without symptoms; (3) patients with three-vessel disease with LV dysfunction (EF less than 50% or previous transmural infarction); (4) patients with unstable angina who after symptom control by medical therapy continue to exhibit ischemia on exercise testing or monitoring; and (5) post-MI patients with continuing angina or severe ischemia on noninvasive testing. The use of revascularization for patients with acute coronary syndromes and acute ST-segment elevation MI (STEMI) is discussed below.

Data from the COURAGE trial have shown that for patients with chronic angina and disease suitable for PCI, PCI in addition to stringent guideline-directed medical therapy aimed at both risk reduction and anti-anginal care offers no mortality benefit beyond excellent medical therapy alone, and relatively moderate long-term symptomatic improvement. Therefore, **for patients with mild to moderate CAD and limited symptoms, revascularization may not provide significant functional status quality-of-life benefit**. For patients with moderate to significant coronary stenosis, such as those who have two-vessel disease associated with underlying LV dysfunction, anatomically critical lesions (greater than 90% proximal stenoses, especially of the proximal left anterior descending artery), or

physiologic evidence of severe ischemia (early positive exercise tests, large exercise-induced thallium scintigraphic defects, or frequent episodes of ischemia on ambulatory monitoring), a heart team consisting of revascularization physicians (interventional cardiologists and surgeons) may be required to review and provide patients with the best revascularization options.

The ISCHEMIA trial found that for patients with moderate to severe ischemia on stress testing, coronary angiography and revascularization did not reduce the risk of cardiovascular death, MI, hospitalization for unstable angina, heart failure, or resuscitated cardiac arrest. Thus, in the context of optimal medical therapy to prevent cardiovascular events, a higher threshold for whom to evaluate with stress tests and coronary angiography may be reasonable.

## 2. Type of procedure—

**A. PERCUTANEOUS CORONARY INTERVENTION INCLUDING STENTING**—PCI, including balloon angioplasty and coronary stenting, can effectively open stenotic coronary arteries. Coronary stenting, with either bare metal stents or drug-eluting stents, has substantially reduced restenosis. Stenting can also be used selectively for left main coronary stenosis, particularly when CABG is contraindicated or deemed high risk.

PCI is possible but often less successful in bypass graft stenoses. Experienced operators are able to successfully dilate more than 90% of lesions attempted. The major early complication is intimal dissection with vessel occlusion, although this is rare with coronary stenting. The use of intravenous platelet glycoprotein IIb/IIIa inhibitors (abciximab, eptifibatide, tirofiban) substantially reduces the rate of periprocedural MI, and placement of intracoronary stents markedly improves initial and long-term angiographic results, especially with complex and long lesions. After percutaneous coronary intervention, all patients should have CK-MB and troponin measured. The definition of a periprocedural infarction has been debated, with many experts advocating for a clinical definition that incorporates different enzyme cutpoints, angiographic findings, and electrocardiographic evidence. Acute thrombosis after stent placement can largely be prevented by aggressive antithrombotic therapy (long-term aspirin, 81–325 mg, plus clopidogrel, 300–600 mg loading dose followed by 75 mg daily, for between 30 days and 1 year, and with acute use of platelet glycoprotein IIb/IIIa inhibitors).

A major limitation with PCI has been **restenosis**, which occurs in the first 6 months in less than 10% of vessels treated with drug-eluting stents, 15–30% of vessels treated with bare metal stents, and 30–40% of vessels without stenting. Factors associated with higher restenosis rates include diabetes, small luminal diameter, longer and more complex lesions, and lesions at coronary ostia or in the left anterior descending coronary artery. Drug-eluting stents that elute antiproliferative agents, such as sirolimus, everolimus, zotarolimus, or paclitaxel, have substantially reduced restenosis. In-stent restenosis is often treated with restenting with drug-eluting stents, and rarely with brachytherapy. The nearly 2 million PCIs performed worldwide per year far exceed the number of CABG operations, but

the rationale for many of the procedures performed in patients with stable angina should be for angina symptom reduction. The COURAGE trial and the ORBITA sham-controlled trial have confirmed earlier studies in showing that, even for patients with moderate anginal symptoms and positive stress tests, PCI provides no benefit over medical therapy with respect to death or MI. PCI was more effective at relieving angina, although most patients in the medical group had improvement in symptoms. PCI was also not more effective than optimal medical therapy for exercise time in patients with one vessel coronary disease. Thus, **in patients with mild or moderate stable symptoms, aggressive lipid-lowering and antianginal therapy may be a preferable initial strategy, reserving PCI for patients with significant and refractory symptoms or for those who are unable to take the prescribed medicines.**

Several studies of PCI, including those with drug-eluting stents, versus CABG in patients with multivessel disease have been reported. The SYNTAX trial as well as previously performed trials with drug-eluting stent use in PCI patients show comparable mortality and infarction rates over follow-up periods of 1–3 years but a high rate (approximately 40%) of repeat procedures following PCI. Stroke rates are higher with CABG. As a result, the choice of revascularization procedure may depend on details of coronary anatomy and is often a matter of patient preference. However, it should be noted that less than 20% of patients with multivessel disease meet the entry criteria for the clinical trials, so these results cannot be generalized to all multivessel disease patients. Outcomes with percutaneous revascularization in patients with diabetes have generally been inferior to those with CABG. The FREEDOM trial demonstrated that **CABG surgery was superior to PCI with regard to death, MI, and stroke for patients with diabetes and multivessel coronary disease** at 5 years across all subgroups of SYNTAX score anatomy.

**B. CORONARY ARTERY BYPASS GRAFTING**—CABG can be accomplished with a very low mortality rate (1–3%) in otherwise healthy patients with preserved cardiac function. However, the mortality rate of this procedure rises to 4–8% in older individuals and in patients who have had a prior CABG.

Grafts using one or both internal mammary arteries (usually to the left anterior descending artery or its branches) provide the best long-term results in terms of patency and flow. Segments of the saphenous vein (or, less optimally, other veins) or the radial artery interposed between the aorta and the coronary arteries distal to the obstructions are also used. One to five distal anastomoses are commonly performed.

Minimally invasive surgical techniques may involve a limited sternotomy, lateral thoracotomy (MIDCAB), or thoracoscopy (port-access). They are more technically demanding, usually not suitable for more than two grafts, and do not have established durability. Bypass surgery can be performed both on circulatory support (on-pump) and without direct circulatory support (off-pump). Randomized trial data have not shown a benefit with off-pump bypass surgery, but minimally invasive surgical techniques allow earlier postoperative mobilization and discharge.

The operative mortality rate is increased in patients with poor LV function (LVEF less than 35%) or those requiring additional procedures (valve replacement or ventricular aneurysmectomy). Patients over 70 years of age, patients undergoing repeat procedures, or those with important noncardiac disease (especially chronic kidney disease and diabetes) or poor general health also have higher operative mortality and morbidity rates, and full recovery is slow. Thus, CABG should be reserved for more severely symptomatic patients in this group. Early (1–6 months) graft patency rates average 85–90% (higher for internal mammary grafts), and subsequent graft closure rates are about 4% annually. Early graft failure is common in vessels with poor distal flow, while late closure is more frequent in patients who continue smoking and those with untreated hyperlipidemia. Antiplatelet therapy with aspirin improves graft patency rates. Smoking cessation and vigorous treatment of blood lipid abnormalities (particularly with statins) are necessary. Repeat revascularization may be necessitated because of recurrent symptoms due to progressive native vessel disease and graft occlusions. Reoperation is technically demanding and less often fully successful than the initial operation. In addition, in patients with ischemic mitral regurgitation, mitral repair at the time of a CABG does not offer any clinical benefit.

### L. Mechanical Extracorporeal Counterpulsation

Extracorporeal counterpulsation entails repetitive inflation of a high-pressure chamber surrounding the lower half of the body during the diastolic phase of the cardiac cycle for daily 1-hour sessions over a period of 7 weeks. Randomized trials have shown that extracorporeal counterpulsation reduces angina, thus it may be considered for relief of refractory angina in patients with stable coronary disease.

### M. Neuromodulation

Spinal cord stimulation can be used to relieve chronic refractory angina. Spinal cord stimulators are subcutaneously implantable via a minimally invasive procedure under local anesthesia.

### ► Prognosis

The prognosis of angina pectoris has improved with development of therapies aimed at secondary prevention. Mortality rates vary depending on the number of vessels diseased, the severity of obstruction, the status of LV function, and the presence of complex arrhythmias. Mortality rates are progressively higher in patients with one-, two-, and three-vessel disease and those with left main coronary artery obstruction (ranging from 1% per year to 25% per year). The outlook in individual patients is unpredictable, and nearly half of the deaths are sudden. Therefore, risk stratification is attempted. Patients with accelerating symptoms have a poorer outlook. Among stable patients, those whose exercise tolerance is severely limited by ischemia (less than 6 minutes on the Bruce treadmill protocol) and those with extensive ischemia by exercise ECG or scintigraphy have more severe anatomic disease and a poorer prognosis. The **Duke Treadmill Score**, based on a standard

**Table 10–6.** Duke Treadmill Score: calculation and interpretation.

| Time in minutes on Bruce protocol   | = _____      |                  |
|---|--------------|------------------|
| -5 × amount of depression (in mm)   | = _____      |                  |
| -4 × angina index<br>0 = no angina on test<br>1 = angina, not limiting<br>2 = limiting angina | = _____      |                  |
| Total Summed Score  | Risk Group   | Annual Mortality |
| ≥ 5   | Low          | 0.25%            |
| -10 to 4  | Intermediate | 1.25%            |
| ≤ -11   | High         | 5.25%            |

Bruce protocol exercise treadmill test, provides an estimate of risk of death at 1 year. The score uses time on the treadmill, amount of ST-segment depression, and presence of angina (Table 10–6).

### ► When to Refer

All patients with new or worsening symptoms believed to represent progressive angina or a positive stress test for myocardial ischemia with continued angina despite medical therapy (or both) should be referred to a cardiologist.

### ► When to Admit

- Patients with elevated cardiac biomarkers, ischemic ECG findings, or hemodynamic instability.
- Patients with new or worsened symptoms, possibly thought to be ischemic, but who lack high-risk features can be observed with serial ECGs and biomarkers and discharged if stress testing shows low-risk findings.

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## CORONARY VASOSPASM & ANGINA OR MI WITH NORMAL CORONARY ARTERIOGRAMS



### ESSENTIALS OF DIAGNOSIS

- ▶ Precordial chest pain, often occurring at rest during stress or without known precipitant, relieved rapidly by nitrates.
- ▶ ECG evidence of ischemia during pain, sometimes with ST-segment elevation.
- ▶ Angiographic demonstration of:
  - No significant obstruction of major coronary vessels.
  - Coronary spasm that responds to intracoronary nitroglycerin or calcium channel blockers.

### General Considerations

Although most symptoms of myocardial ischemia result from fixed stenosis of the coronary arteries, intraplaque hemorrhage, or thrombosis at the site of lesions, some ischemic events may be precipitated or exacerbated by coronary vasoconstriction.

Spasm of the large coronary arteries with resulting decreased coronary blood flow may occur spontaneously or may be induced by exposure to cold, emotional stress, or vasoconstricting medications, such as ergot-derivative medications. Spasm may occur both in normal and in stenosed coronary arteries. Even MI may occur as a result of spasm in the absence of visible obstructive CHD, although most instances of such coronary spasm occur in the presence of coronary stenosis.

Cocaine can induce myocardial ischemia and infarction by causing coronary artery vasoconstriction or by increasing myocardial energy requirements. It also may contribute to accelerated atherosclerosis and thrombosis. The ischemia in **Prinzmetal (variant) angina** usually results from coronary vasoconstriction. It tends to involve the right coronary artery and there may be no fixed stenoses. Myocardial ischemia may also occur in patients with normal coronary arteries as a result of disease of the coronary microcirculation or abnormal vascular reactivity. MI without obstructive coronary disease is more frequent in women and has been shown to be due to atherosclerosis or ruptured plaques in 80% of cases. The 2020 ESC guidelines recommend cardiac MRI to aid in determining the cause of MI without obstructive coronary disease.

### Clinical Findings

Ischemia may be silent or result in angina pectoris.

Prinzmetal (variant) angina is a clinical syndrome in which chest pain occurs without the usual precipitating factors and is associated with ST-segment elevation rather than depression. It often affects women under 50 years of age. It characteristically occurs in the early morning, awakening patients from sleep, and is apt to be associated with arrhythmias or conduction defects. It may be diagnosed by

challenge with ergonovine (a vasoconstrictor), although the results of such provocation are not specific and it entails risk.

### Treatment

Patients with chest pain associated with ST-segment elevation should undergo coronary arteriography to determine whether fixed stenotic lesions are present. If they are, aggressive medical therapy or revascularization is indicated, since the presence of these lesions may represent an unstable phase of the disease. If significant lesions are not seen, there may still be endothelial disruption and plaque rupture. If spasm is suspected, avoidance of precipitants, such as cigarette smoking and cocaine, is the top priority. Episodes of coronary spasm generally respond well to nitrates, and both nitrates and calcium channel blockers (including long-acting nifedipine, diltiazem, or amlodipine [see Table 11-7]) are effective prophylactically. By allowing unopposed alpha-1-mediated vasoconstriction, beta-blockers have exacerbated coronary vasospasm, but they may have a role in management of patients in whom spasm is associated with fixed stenoses.

### When to Refer

All patients with persistent symptoms of chest pain that may represent spasm should be referred to a cardiologist.

## ACUTE CORONARY SYNDROMES WITHOUT ST-SEGMENT ELEVATION



### ESSENTIALS OF DIAGNOSIS

- ▶ Distinction in acute coronary syndrome between patients with and without ST-segment elevation at presentation is essential to determine need for reperfusion therapy.
- ▶ Fibrinolytic therapy is harmful in acute coronary syndrome without ST-segment elevation, unlike with ST-segment elevation, where acute reperfusion saves lives.
- ▶ Antiplatelet and anticoagulation therapies and coronary intervention are mainstays of treatment.

### General Considerations

**Acute coronary syndromes** comprise the spectrum of unstable cardiac ischemia from unstable angina to acute MI. Acute coronary syndromes are classified based on the presenting ECG as either **ST-segment elevation MI (STEMI)** or **non-ST-segment elevation MI (NSTEMI)**. This allows for immediate classification and guides determination of whether patients should be considered for acute reperfusion therapy. The evolution of cardiac biomarkers then allows determination of whether MI has occurred.

Acute coronary syndromes represent a dynamic state in which patients frequently shift from one category to another, as new ST elevation can develop after presentation and cardiac biomarkers can become abnormal with recurrent ischemic episodes.

## ► Clinical Findings

### A. Symptoms and Signs

Patients with acute coronary syndromes generally have symptoms and signs of myocardial ischemia either at rest or with minimal exertion. These symptoms and signs are similar to the chronic angina symptoms described above, consisting of substernal chest pain or discomfort that may radiate to the jaw, left shoulder or arm. Dyspnea, nausea, diaphoresis, or syncope may either accompany the chest discomfort or may be the only symptom of acute coronary syndrome. *About one-third of patients with MI have no chest pain per se*—these patients tend to be older, female, have diabetes, and be at higher risk for subsequent mortality. Patients with acute coronary syndromes have signs of heart failure in about 10% of cases, and this is also associated with higher risk of death.

Many hospitals have developed **chest pain observation units** to provide a systematic approach toward serial risk stratification to improve the triage process. In many cases, those who have not experienced new chest pain and have insignificant ECG changes and no cardiac biomarker elevation undergo treadmill exercise tests or imaging procedures to exclude ischemia at the end of an 8- to 24-hour period and are discharged directly from the emergency department if these tests are negative.

### B. Laboratory Findings

Depending on the time from symptom onset to presentation, initial laboratory findings may be normal. The markers of cardiac myocyte necrosis (**myoglobin**, **CK-MB**, and **troponin I and T**) may all be used to identify acute MI, although high-sensitivity troponin is now the recommended biomarker to diagnose acute MI (see Laboratory Findings, Acute Myocardial Infarction with ST-Segment Elevation). In patients with STEMI, these initial markers are often within normal limits as the patient is being rushed to immediate reperfusion. In patients without ST-segment elevation, it is the presence of abnormal CK-MB or troponin values that are associated with myocyte necrosis and the diagnosis of MI. High-sensitivity troponin assays allow rapid assessment of MI in emergency departments by using 1- or 2-hour rule out algorithms. The universal definition of MI is a rise of cardiac biomarkers with at least one value above the 99th percentile of the upper reference limit together with evidence of myocardial ischemia with at least one of the following: symptoms of ischemia, ECG changes of new ischemia, new Q waves, or imaging evidence of new loss of viable myocardium or new wall motion abnormality.

Serum creatinine is an important determinant of risk, and estimated creatinine clearance is important to guide dosing of certain antithrombotics, including eptifibatide and enoxaparin.

### C. ECG

Many patients with acute coronary syndromes will exhibit ECG changes during pain—either ST-segment elevation, ST-segment depression, or T-wave flattening or inversion. Dynamic ST-segment shift is the most specific for acute

coronary syndrome. ST-segment elevation in lead AVR suggests left main or three-vessel disease.

## ► Treatment

### A. General Measures

Treatment of acute coronary syndromes without ST elevation should be multifaceted. Patients who are at medium or high risk should be hospitalized, maintained at bed rest or at very limited activity for the first 24 hours, monitored, and given supplemental oxygen. Sedation with a benzodiazepine agent may help if anxiety is present.

### B. Specific Measures

Figure 10–9 provides an algorithm for initial management of NSTEMI.

### C. Antiplatelet and Anticoagulation Therapy

Patients should receive a combination of antiplatelet and anticoagulant agents on presentation. Fibrinolytic therapy should be *avoided* in patients without ST-segment elevation since they generally do not have an acute coronary occlusion, and the risk of such therapy appears to outweigh the benefit.

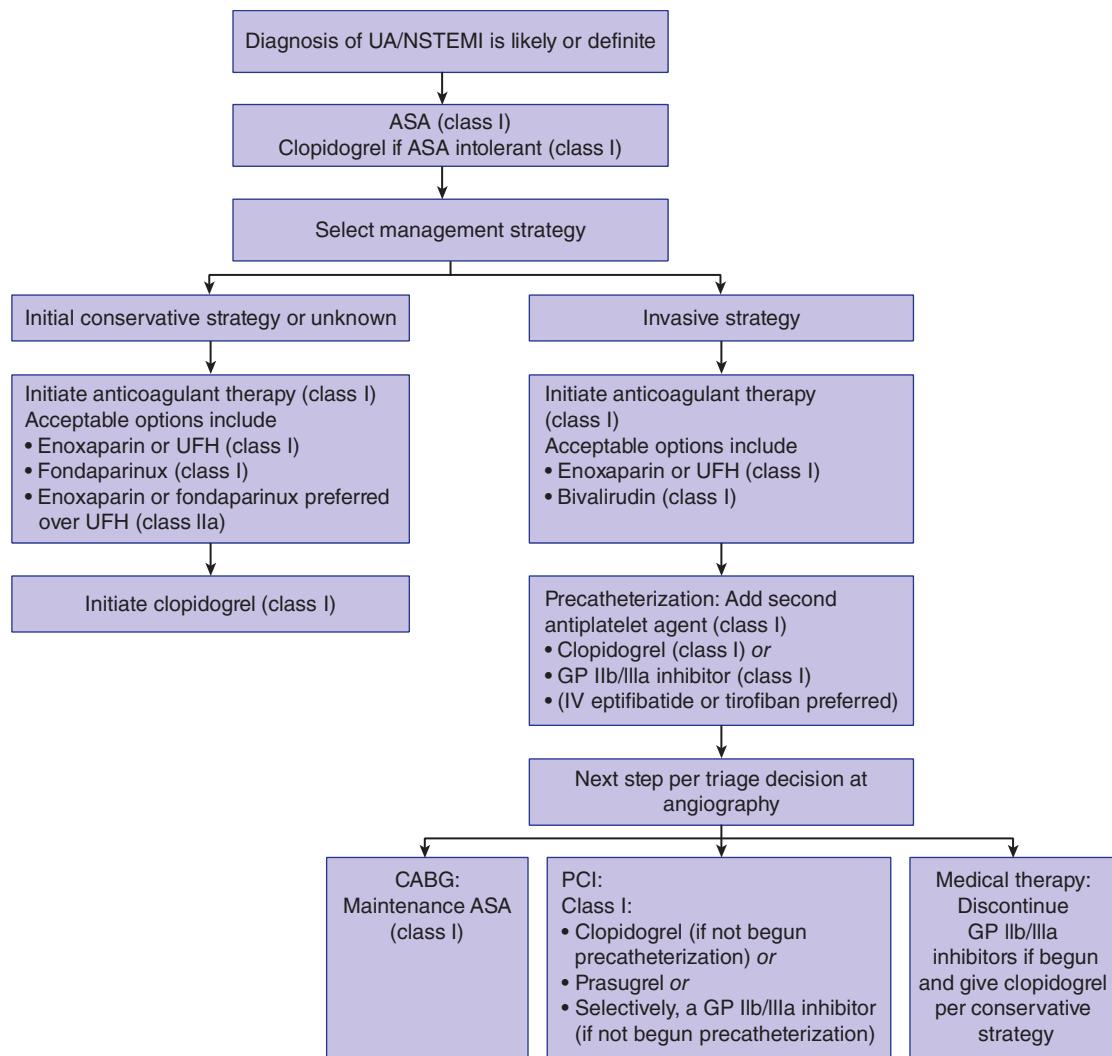
#### 1. Antiplatelet therapy—

**A. ASPIRIN**—Aspirin, 162–325 mg loading dose, then 81 mg daily, should be commenced immediately and continued for the first month. The 2020 ESC guidelines for longer-term aspirin treatment recommend aspirin 75–100 mg/day as preferable to higher doses with or without coronary stenting.

**B. P2Y<sub>12</sub> INHIBITORS**—ACC/AHA guidelines call for either a P2Y<sub>12</sub> inhibitor (clopidogrel, prasugrel [at the time of PCI], or ticagrelor) as a class I recommendation. The ESC guidelines provide a stronger recommendation for a P2Y<sub>12</sub> inhibitor up-front, as a class IA recommendation for all patients. Both sets of guidelines recommend postponing elective CABG surgery for at least 5 days after the last dose of clopidogrel or ticagrelor and at least 7 days after the last dose of prasugrel, due to risk of bleeding.

The Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial demonstrated a 20% reduction in the composite end point of cardiovascular death, MI, and stroke with the addition of clopidogrel (300-mg loading dose, 75 mg/day for 9–12 months) to aspirin in patients with non-ST-segment elevation acute coronary syndromes. The large CURRENT trial showed that “double-dose” clopidogrel (600-mg initial oral loading dose, followed by 150 mg orally daily) for 7 days reduced stent thrombosis with a modest increase in major (but not fatal) bleeding and, therefore, it is an option for patients with acute coronary syndrome undergoing PCI.

The ESC guidelines recommend ticagrelor for all patients at moderate to high risk for acute coronary syndrome (class I recommendation). Prasugrel is recommended for patients who have not yet received another P2Y<sub>12</sub> inhibitor, for whom a PCI is planned, and who are



**▲ Figure 10–9.** Flowchart for class I and class IIa recommendations for initial management of unstable angina/non-ST-segment elevation myocardial infarction (UA/NSTEMI). ASA, aspirin; CABG, coronary artery bypass grafting; GP IIb/IIIa, glycoprotein IIb/IIIa; LOE, level of evidence; UFH, unfractionated heparin. (Reproduced, with permission, from Wright RS et al. 2011 ACCF/AHA Focused Update of the Guidelines for the Management of Patients With Unstable Angina/Non-ST-Elevation Myocardial Infarction (Updating the 2007 Guideline): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2011;123:2222. © 2011 American Heart Association, Inc.)

not at high risk for life-threatening bleeding. Clopidogrel is reserved for patients who cannot receive either ticagrelor or prasugrel. Some studies have shown an association between assays of residual platelet function and thrombotic risk during P2Y<sub>12</sub> inhibitor therapy, and both the European and the US guidelines do not recommend routine platelet function testing to guide therapy (class IIb recommendation).

Prasugrel is both more potent and has a faster onset of action than clopidogrel. The TRITON trial compared prasugrel with clopidogrel in patients with STEMI or NSTEMI in whom PCI was planned; prasugrel resulted in a 19% relative reduction in death from cardiovascular causes, MI, or stroke, at the expense of an increase in serious bleeding

(including fatal bleeding). Stent thrombosis was reduced by half. Because patients with prior stroke or TIA had higher risk of intracranial hemorrhage, prasugrel is contraindicated in such patients. Bleeding was also higher in patients with low body weight (less than 60 kg) and age 75 years or older, and caution should be used in these populations. For patients with STEMI treated with PCI, prasugrel appears to be especially effective (compared to clopidogrel) without a substantial increase in bleeding. For patients who will not receive revascularization, prasugrel, when compared to clopidogrel, had no overall benefit in the TRILOGY trial (the dose of prasugrel was lowered for older adults). Prasugrel appears to be at least comparable to ticagrelor for

patients with STEMI regarding safety and efficacy based on the ISAR-REACT 5 trial.

Ticagrelor has a faster onset of action than clopidogrel and a more consistent and potent effect. The PLATO trial showed that when ticagrelor was started at the time of presentation in acute coronary syndrome patients (UA/NSTEMI and STEMI), it reduced cardiovascular death, MI, and stroke by 16% when compared with clopidogrel. In addition, there was a 22% relative risk reduction in mortality with ticagrelor. The overall rates of bleeding were similar between ticagrelor and clopidogrel, although non-CABG-related bleeding was modestly higher. The finding of a lesser treatment effect in the United States may have been related to use of higher-dose aspirin, and thus when using ticagrelor, low-dose aspirin (81 mg/day) is recommended.

**C. GLYCOPROTEIN IIb/IIIa INHIBITORS**—Small-molecule inhibitors of the platelet glycoprotein IIb/IIIa receptor are useful adjuncts in high-risk patients (usually defined by fluctuating ST-segment depression or positive biomarkers) with acute coronary syndromes, particularly when they are undergoing PCI. Tirofiban, 25 mcg/kg over 3 minutes, followed by 0.15 mcg/kg/min, and eptifibatide, 180 mcg/kg bolus followed by a continuous infusion of 2 mcg/kg/min, have both been shown to be effective. Downward dose adjustments of the infusions are required in patients with reduced kidney function. The bolus or loading dose remains unadjusted. For example, if the estimated creatinine clearance is below 50 mL/min, the eptifibatide infusion should be cut in half to 1 mcg/kg/min.

#### **2. Anticoagulant therapy—**

**A. HEPARIN**—Several trials have shown that LMWH (enoxaparin 1 mg/kg subcutaneously every 12 hours) is somewhat more effective than unfractionated heparin in preventing recurrent ischemic events in the setting of acute coronary syndromes. However, the SYNERGY trial showed that unfractionated heparin and enoxaparin had similar rates of death or (re)infarction in the setting of frequent early coronary intervention.

**B. FONDAPARINUX**—Fondaparinux, a specific factor Xa inhibitor given in a dose of 2.5 mg subcutaneously once a day, was found in the OASIS-5 trial to be equally effective as enoxaparin among 20,000 patients at preventing early death, MI, and refractory ischemia, and resulted in a 50% reduction in major bleeding. This reduction in major bleeding translated into a significant reduction in mortality (and in death or MI) at 30 days. While catheter-related thrombosis was more common during coronary intervention procedures with fondaparinux, the FUTURA trial found that it can be controlled by adding unfractionated heparin (in a dose of 85 units/kg without glycoprotein IIb/IIIa inhibitors, and 60 units/kg with glycoprotein IIb/IIIa inhibitors) during the procedure. Guidelines recommend fondaparinux, describing it as especially favorable for patients who are initially treated medically and who are at high risk for bleeding, such as elderly individuals.

**C. DIRECT THROMBIN INHIBITORS**—The ACUITY trial showed that bivalirudin appears to be a reasonable alternative to heparin (unfractionated heparin or enoxaparin) plus a

glycoprotein IIb/IIIa antagonist for many patients with acute coronary syndromes who are undergoing early coronary intervention. Bivalirudin (without routine glycoprotein IIb/IIIa inhibitor) is associated with substantially less bleeding than heparin plus glycoprotein IIb/IIIa inhibitor, although it may have numerically increased cardiovascular events. The ISAR REACT-4 trial showed that bivalirudin has similar efficacy compared to abciximab but better bleeding outcomes in NSTEMI patients. Bivalirudin does not currently have an FDA-approved indication for NSTEMI care.

#### **D. Temporary Discontinuation of Antiplatelet Therapy for Procedures**

Patients who have had recent coronary stents are at risk for thrombotic events, including stent thrombosis, if P2Y<sub>12</sub> inhibitors are discontinued for procedures (eg, dental procedures or colonoscopy). If possible, these procedures should be delayed until the end of the necessary treatment period with P2Y<sub>12</sub> inhibitors, which generally is at least 1 month with bare metal stents and 3–6 months with drug-eluting stents. With newer generation drug-eluting stents, elective stenting patients with bleeding risk may have P2Y<sub>12</sub> inhibitors stopped before 3 months. Before that time, if a procedure is necessary, risk and benefit of continuing the antiplatelet therapy through the time of the procedure should be assessed. Aspirin should generally be continued throughout the period of the procedure. Patients with polymer-free drug coated stents who are at high risk for bleeding and receiving a short course of dual antiplatelet therapy had fewer cardiovascular and bleeding events. A cardiologist should be consulted before temporary discontinuation of these agents.

#### **E. Nitroglycerin**

Nitrates are first-line therapy for patients with acute coronary syndromes presenting with chest pain. Nonparenteral therapy with sublingual or oral agents or nitroglycerin ointment is usually sufficient. If pain persists or recurs, intravenous nitroglycerin should be started. The usual initial dosage is 10 mcg/min. The dosage should be titrated upward by 10–20 mcg/min (to a maximum of 200 mcg/min) until angina disappears or mean arterial pressure drops by 10%. Careful—usually continuous—BP monitoring is required when intravenous nitroglycerin is used. Avoid hypotension (systolic BP less than 100 mm Hg). Tolerance to continuous nitrate infusion is common.

#### **F. Beta-Blockers**

Beta-blockers are an important part of the initial treatment of unstable angina unless otherwise contraindicated. The pharmacology of these agents is discussed in Chapter 11 and summarized in Table 11–9. Use of agents with intrinsic sympathomimetic activity should be avoided in this setting. Oral medication is adequate in most patients, but intravenous treatment with metoprolol, given as three 5-mg doses 5 minutes apart as tolerated and in the absence of heart failure, achieves a more rapid effect. Oral therapy should be titrated upward as BP permits.

## G. Calcium Channel Blockers

Calcium channel blockers have *not* been shown to favorably affect outcome in unstable angina, and they should be used primarily as third-line therapy in patients with continuing angina who are taking nitrates and beta-blockers or those who are not candidates for these medications. In the presence of nitrates and without accompanying beta-blockers, diltiazem or verapamil is preferred, since nifedipine and the other dihydropyridines are more likely to cause reflex tachycardia or hypotension. The initial dosage should be low, but upward titration should proceed steadily (see Table 11–7).

## H. Statins

The PROVE-IT trial provides evidence for starting a statin in the days immediately following an acute coronary syndrome. In this trial, more intensive therapy with atorvastatin 80 mg/day, regardless of total or LDL cholesterol level, improved outcome compared to pravastatin 40 mg/day, with the curves of death or major cardiovascular event separating as early as 3 months after starting therapy. **High-intensity statins are recommended for all patients with acute coronary syndromes** (see Table 10–5).

## ► Indications for Coronary Angiography

For patients with acute coronary syndrome, including NSTEMI, risk stratification is important for determining intensity of care. Several therapies, including glycoprotein IIb/IIIa inhibitors, LMWH heparin, and early invasive catheterization, have been shown to have the greatest benefit in higher-risk patients with acute coronary syndrome. As outlined in the ACC/AHA guidelines, patients with any high-risk feature (Table 10–7) generally warrant an early invasive strategy with catheterization and revascularization. For patients without these high-risk features, either an invasive or noninvasive approach, using exercise (or pharmacologic stress for patients unable to exercise) stress testing to identify patients who have residual ischemia and/or high risk, can be used. Moreover, based on the ICTUS trial, a strategy based on selective coronary angiography and revascularization for instability or inducible ischemia, or both, even for patients with positive troponin, is acceptable (ACC/AHA class IIb recommendation).

Two risk-stratification tools are available that can be used at the bedside, the **GRACE Risk Score** (<http://www.outcomes.umassmed.org/grace>) and the **TIMI Risk Score** (<http://www.timi.org>). The GRACE Risk Score, which applies to patients with or without ST elevation, was developed in a more generalizable registry population and has better discrimination of risk. It includes age (as a continuous variable), Killip class, BP, ST-segment deviation, cardiac arrest at presentation, serum creatinine, elevated creatine kinase (CK)-MB or troponin, and heart rate. The TIMI Risk Score includes seven variables: age 65 years or older, three or more cardiac risk factors, prior coronary stenosis of 50% or more, ST-segment deviation, two anginal events in prior 24 hours, aspirin in prior 7 days, and elevated cardiac markers.

**Table 10–7.** Indications for catheterization and percutaneous coronary intervention.<sup>1</sup>

| Acute coronary syndromes (unstable angina and non-ST elevation MI) |   |
|--|---|
| Class I  | Early invasive strategy for any of the following high-risk indicators:  |
|  | Recurrent angina/ischemia at rest or with low-level activity  |
|  | Elevated troponin   |
|  | ST-segment depression   |
|  | Recurrent ischemia with evidence of HF  |
|  | High-risk stress test result  |
|  | EF < 40%  |
|  | Hemodynamic instability   |
|  | Sustained ventricular tachycardia   |
|  | PCI within 6 months   |
|  | Prior CABG  |
|  | In the absence of these findings, either an early conservative or early invasive strategy   |
| Class IIa  | Early invasive strategy for patients with repeated presentations for ACS despite therapy  |
| Class III  | Extensive comorbidities in patients in whom benefits of revascularization are not likely to outweigh the risks<br>Acute chest pain with low likelihood of ACS |
| Acute MI after fibrinolytic therapy                                |   |
| Class I  | Cardiogenic shock or acute severe heart failure that develops after initial presentation  |
|  | Intermediate- or high-risk findings on predischarge noninvasive ischemia testing  |
|  | Spontaneous or easily provoked myocardial ischemia  |
| Class IIa  | Failed reperfusion or reocclusion after fibrinolytic therapy  |
|  | Stable <sup>2</sup> patients after successful fibrinolysis, before discharge and ideally between 3 and 24 hours   |

<sup>1</sup>Class I indicates treatment is useful and effective, IIa indicates weight of evidence is in favor of usefulness/efficacy, class IIb indicates weight of evidence is less well established, and class III indicates intervention is not useful/effective and may be harmful. Level of evidence A recommendations are derived from large-scale randomized trials, and B recommendations are derived from smaller randomized trials or carefully conducted observational analyses.

<sup>2</sup>Although individual circumstances will vary, clinical stability is defined by the absence of low output, hypotension, persistent tachycardia, apparent shock, high-grade ventricular or symptomatic supraventricular tachyarrhythmias, and spontaneous recurrent ischemia. ACCF/AHA, American College of Cardiology Foundation/American Heart Association; ACS, acute coronary syndrome; CABG, coronary artery bypass grafting; EF, ejection fraction; HF, heart failure; MI, myocardial infarction; PCI, percutaneous coronary intervention.

Data from O’Gara PT et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2013;127: e362–e425.

## ► When to Refer

- All patients with acute MI should be referred to a cardiologist.
- Patients who are taking a P2Y<sub>12</sub> inhibitor following coronary stenting should consult a cardiologist before discontinuing treatment for nonemergency procedures.

Collet JP et al. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Eur Heart J. 2021;42:1289. [PMID: 32860058]

Levine GN et al. 2016 ACC/AHA Guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines: An update of the 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention, 2011 ACCF/AHA guideline for coronary artery bypass graft surgery, 2012 ACC/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease, 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction, 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes, and 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery. Circulation. 2016;134:e123. [PMID: 27026020]

## ACUTE MYOCARDIAL INFARCTION WITH ST-SEGMENT ELEVATION



### ESSENTIALS OF DIAGNOSIS

- ▶ Sudden but not instantaneous development of prolonged (> 30 minutes) anterior chest discomfort (sometimes felt as "gas" or pressure).
- ▶ Sometimes painless, masquerading as acute heart failure, syncope, stroke, or shock.
- ▶ ECG: ST-segment elevation or left bundle branch block.
- ▶ Immediate reperfusion treatment is warranted.
- ▶ Primary PCI within 90 minutes of first medical contact is the goal and is superior to fibrinolytic therapy.
- ▶ Fibrinolytic therapy within 30 minutes of hospital presentation is the goal and reduces mortality if given within 12 hours of onset of symptoms.

## ► General Considerations

STEMI results, in most cases, from an occlusive coronary thrombus at the site of a preexisting (though not necessarily severe) atherosclerotic plaque. More rarely, infarction may result from prolonged vasospasm, inadequate myocardial blood flow (eg, hypotension), or excessive metabolic demand. Very rarely, MI may be caused by embolic occlusion, vasculitis, aortic root or coronary artery dissection, or

aortitis. Cocaine, a cause of infarction, should be considered in young individuals without risk factors. A condition that may mimic STEMI is stress cardiomyopathy (also referred to as **tako-tsubo** or **apical ballooning syndrome**). ST elevation connotes an acute coronary occlusion and warrants *immediate* reperfusion therapy with activation of emergency services.

## ► Clinical Findings

### A. Symptoms

**1. Premonitory pain**—There is usually a worsening in the pattern of angina preceding the onset of symptoms of MI; classically the onset of angina occurs with minimal exertion or at rest.

**2. Pain of infarction**—Unlike anginal episodes, most infarctions occur *at rest*, and more commonly in the early morning. The pain is similar to angina in location and radiation but it may be more severe, and it builds up rapidly or in waves to maximum intensity over a few minutes or longer. Nitroglycerin has little effect; even opioids may not relieve the pain.

**3. Associated symptoms**—Patients may break out in a cold sweat, feel weak and apprehensive, and move about, seeking a position of comfort. They prefer not to lie quietly. Light-headedness, syncope, dyspnea, orthopnea, cough, wheezing, nausea and vomiting, or abdominal bloating may be present singly or in any combination.

**4. Painless infarction**—One-third of patients with acute MI present *without* chest pain, and these patients tend to be undertreated and have poor outcomes. Older patients, women, and patients with diabetes mellitus are more likely to present without chest pain. As many as 25% of infarctions are detected on routine ECG without any recallable acute episode.

**5. Sudden death and early arrhythmias**—Of all deaths from MI, about half occur before the patients arrive at the hospital, with death presumably caused by ventricular fibrillation.

### B. Signs

**1. General**—Patients may appear anxious and sometimes are sweating profusely. The heart rate may range from marked bradycardia (most commonly in inferior infarction) to tachycardia, low cardiac output, or arrhythmia. The BP may be high, especially in former hypertensive patients, or low in patients with shock. Respiratory distress usually indicates heart failure. Fever, usually low grade, may appear after 12 hours and persist for several days.

**2. Chest**—The **Killip classification** is the standard way to classify heart failure in patients with acute MI and has powerful prognostic value. Killip class I is absence of rales and S<sub>3</sub>, class II is rales that do not clear with coughing over one-third or less of the lung fields or presence of an S<sub>3</sub>, class III is rales that do not clear with coughing over more than one-third of the lung fields, and class IV is cardiogenic shock (rales, hypotension, and signs of hypoperfusion).

**3. Heart**—The cardiac examination may be unimpressive or very abnormal. Jugular venous distention reflects RA hypertension, and a Kussmaul sign (failure of decrease of jugular venous pressure with inspiration) is suggestive of RV infarction. Soft heart sounds may indicate LV dysfunction. Atrial gallops ( $S_4$ ) are the rule, whereas ventricular gallops ( $S_3$ ) are less common and indicate significant LV dysfunction. Mitral regurgitation murmurs are not uncommon and may indicate papillary muscle dysfunction or, rarely, rupture. Pericardial friction rubs are uncommon in the first 24 hours but may appear later.

**4. Extremities**—Edema is usually not present. Cyanosis and cold temperature indicate low output. The peripheral pulses should be noted, since later shock or emboli may alter the examination.

### C. Laboratory Findings

Cardiac-specific markers of myocardial damage include quantitative determinations of CK-MB, highly sensitive and conventional troponin I, and troponin T. Each of these tests may become positive as early as 4–6 hours after the onset of an MI and should be abnormal by 8–12 hours. Troponins are more sensitive and specific than CK-MB. “Highly sensitive” or “fourth-generation” troponin assays were approved in 2017. They are the standard assays in most of Europe, with a 10- to 100-fold lower limit of detection, allowing MI to be detected earlier, using the change in value over 3 hours.

Circulating levels of troponins may remain elevated for 5–7 days or longer and therefore are generally not useful for evaluating suspected early reinfarction. Elevated CK-MB generally normalizes within 24 hours, thus being more helpful for evaluation of reinfarction. Low-level elevations of troponin in patients with severe chronic kidney disease may not be related to acute coronary disease but rather a function of the physiologic washout of the marker. While many conditions including chronic heart failure are associated with elevated levels of the high-sensitivity troponin assays, these assays may be especially useful when negative to exclude MI in patients reporting chest pain.

### D. ECG

The extent of the ECG abnormalities, especially the sum of the total amount of ST-segment deviation, is a good indicator of the extent of acute infarction and risk of subsequent adverse events. The classic evolution of changes is from peaked (“hyperacute”) T waves, to ST-segment elevation, to Q wave development, to T wave inversion. This may occur over a few hours to several days. The evolution of new Q waves (longer than 30 msec in duration and 25% of the R wave amplitude) is diagnostic, but Q waves do not occur in 30–50% of acute infarctions (**non-Q wave infarctions**). Left bundle branch block, especially when new (or not known to be old), in a patient with symptoms of an acute MI is considered to be a “**STEMI equivalent**”; reperfusion therapy is indicated for the affected patient. Concordant ST elevation (ie, ST elevation in leads with an overall positive QRS complex) with left bundle branch block is a specific finding indicating STEMI.

### E. Chest Radiography

The chest radiograph may demonstrate signs of heart failure, but these changes often lag behind the clinical findings. Signs of aortic dissection, including mediastinal widening, should be sought as a possible alternative diagnosis.

### F. Echocardiography

Echocardiography provides convenient bedside assessment of LV global and regional function. This can help with the diagnosis and management of infarction; echocardiography has been used successfully to make judgments about admission and management of patients with suspected infarction, including in patients with ST-segment elevation or left bundle branch block of uncertain significance, since normal wall motion makes an infarction unlikely. Doppler echocardiography is generally the most convenient procedure for diagnosing postinfarction mitral regurgitation or VSD.

### G. Other Noninvasive Studies

Diagnosis of MI and extent of MI can be assessed by various imaging studies in addition to echocardiography. **MRI with gadolinium contrast enhancement** is the most sensitive test to detect and quantitate extent of infarction, with the ability to detect as little as 2 g of MI. **Technetium-99m pyrophosphate scintigraphy**, when injected at least 18 hours postinfarction, complexes with calcium in necrotic myocardium to provide a “hot spot” image of the infarction. This test is insensitive to small infarcts, and false-positive studies occur, so its use is limited to patients in whom the diagnosis by ECG and enzymes is not possible—principally those who present several days after the event or have intraoperative infarcts. **Scintigraphy with thallium-201 or technetium-based perfusion tracers** will demonstrate “cold spots” in regions of diminished perfusion, which usually represent infarction when the radio-tracer is administered at rest, but abnormalities do not distinguish recent from old damage. All of these tests may be considered after the patient has had revascularization.

### H. Hemodynamic Measurements

These can be helpful in managing the patient with suspected cardiogenic shock. Use of PA catheters, however, has generally not been associated with better outcomes and should be limited to patients with severe hemodynamic compromise for whom the information would be anticipated to change management.

## ► Treatment

### A. Aspirin, P2Y<sub>12</sub> Inhibitors (Prasugrel, Ticagrelor, and Clopidogrel)

All patients with definite or suspected acute MI should receive aspirin at a dose of 162 mg or 325 mg at once regardless of whether fibrinolytic therapy is being considered or the patient has been taking aspirin. Chewable aspirin provides more rapid blood levels. Patients with a

definite aspirin allergy should be treated with a P2Y<sub>12</sub> inhibitor (clopidogrel, prasugrel, or ticagrelor).

P2Y<sub>12</sub> inhibitors, in combination with aspirin, have been shown to provide important benefits in patients with acute STEMI. Thus, guidelines call for a **P2Y<sub>12</sub> inhibitor to be added to aspirin for all patients with STEMI**, regardless of whether reperfusion is given, and continued for at least 14 days, and generally for 1 year. The preferred P2Y<sub>12</sub> inhibitors are prasugrel (60 mg orally on day 1, then 10 mg daily) or ticagrelor (180 mg orally on day 1, then 90 mg twice daily). Both of these medications demonstrated superior outcomes to clopidogrel in clinical studies of primary PCI. Clopidogrel should be administered as a loading dose of 300–600 mg orally for faster onset of action than the 75 mg maintenance dose. With fibrinolytic therapy, ticagrelor appears to be a reasonable alternative to clopidogrel, at least after an initial clopidogrel dose. Prasugrel is contraindicated in patients with history of stroke or who are older than 75 years.

### B. Reperfusion Therapy

Patients with STEMI who seek medical attention within 12 hours of the onset of symptoms should be treated with reperfusion therapy, either primary PCI or fibrinolytic therapy. Patients without ST-segment elevation (previously

labeled “non-Q wave” infarctions) do not benefit, and may derive harm, from thrombolysis.

#### 1. Primary percutaneous coronary intervention—

Immediate coronary angiography and primary PCI (including stenting) of the infarct-related artery have been shown to be *superior* to thrombolysis when done by experienced operators in high-volume centers with rapid time from first medical contact to intervention (“door-to-balloon”). US and European guidelines call for first medical contact or door-to-balloon times of 90 minutes or less. Several trials have shown that if efficient transfer systems are in place, transfer of patients with acute MI from hospitals without primary PCI capability to hospitals with primary PCI capability with first door-to-device times of 120 minutes or less can improve outcome compared with fibrinolytic therapy at the presenting hospital, although this requires sophisticated systems to ensure rapid identification, transfer, and expertise in PCI. Because PCI also carries a lower risk of hemorrhagic complications, including intracranial hemorrhage, it may be the preferred strategy in many older patients and others with contraindications to fibrinolytic therapy (see Table 10–8 for factors to consider in choosing fibrinolytic therapy or primary PCI).

**Table 10–8.** Fibrinolytic therapy for acute myocardial infarction.

|                                | Alteplase; Tissue Plasminogen Activator (t-PA)   | Reteplase   | Tenecteplase (TNK-t-PA)                 | Streptokinase  |
|--------------------------------|--|---|---|--|
| Source                         | Recombinant DNA  | Recombinant DNA   | Recombinant DNA                         | Group C <i>Streptococcus</i>   |
| Half-life                      | 5 minutes  | 15 minutes  | 20 minutes                              | 20 minutes   |
| Usual dose                     | 100 mg   | 20 units  | 40 mg                                   | 1.5 million units  |
| Administration                 | Initial bolus of 15 mg, followed by 50 mg infused over the next 30 minutes and 35 mg over the following 60 minutes                                       | 10 units as a bolus over 2 minutes, repeated after 30 minutes | Single weight-adjusted bolus, 0.5 mg/kg | 750,000 units over 20 minutes followed by 750,000 units over 40 minutes                                      |
| Anticoagulation after infusion | Aspirin, 325 mg daily; heparin, 5000 units as bolus, followed by 1000 units per hour infusion, subsequently adjusted to maintain PTT 1.5–2 times control | Aspirin, 325 mg; heparin as with t-PA                         | Aspirin, 325 mg daily                   | Aspirin, 325 mg daily; there is no evidence that adjunctive heparin improves outcome following streptokinase |
| Clot selectivity               | High   | High  | High                                    | Low  |
| Fibrinogenolysis               | +  | +   | +                                       | +++  |
| Bleeding                       | +  | +   | +                                       | +  |
| Hypotension                    | +  | +   | +                                       | +++  |
| Allergic reactions             | +  | +   | +                                       | ++   |
| Reocclusion                    | 10–30%   | —   | 5–20%                                   | 5–20%  |
| Approximate cost <sup>1</sup>  | \$10,560.43  | \$5964.98   | \$7462.63                               | Not available in the United States   |

<sup>1</sup>Average wholesale price (AWP, for AB-rated generic when available) for quantity listed.

PTT, partial thromboplastin time.

Source: IBM Micromedex, Red Book (electronic version). IBM Watson Health, Greenwood Village, CO, USA. Available at <https://www.micromedexsolutions.com> (accessed April 8, 2020). AWP may not accurately represent the actual pharmacy cost because wide contractual variations exist among institutions.

**A. STENTING—PCI with stenting is standard for patients with acute MI.** Although randomized trials have shown a benefit with regard to fewer repeat interventions for restenosis with the use of drug-eluting stents in STEMI patients, and current generation drug-eluting stents have similar or lower rates of stent thrombosis than bare metal stents, bare metal stents may still be used for selected patients without the ability to obtain and comply with P2Y<sub>12</sub> inhibitor therapy. In the subgroup of patients with cardiogenic shock, early catheterization and percutaneous or surgical revascularization are the preferred management and have been shown to reduce mortality.

“Facilitated” PCI, whereby a combination of medications (full- or reduced-dose fibrinolytic agents, with or without glycoprotein IIb/IIIa inhibitors) is given followed by immediate PCI, is *not* recommended. Patients should be treated either with primary PCI or with fibrinolytic agents (and immediate rescue PCI for reperfusion failure), if it can be done promptly as outlined in the ACC/AHA and European guidelines. Timely access to most appropriate reperfusion, including primary PCI, can be expanded with development of regional systems of care, including emergency medical systems and networks of hospitals. Patients treated with fibrinolytic therapy appear to have improved outcomes if transferred for routine coronary angiography and PCI within 24 hours. The AHA has a program called “Mission: Lifeline” to support the development of regional systems of care (<http://www.heart.org/missionlifeline>).

**B. ANTIPLATELET THERAPY AFTER DRUG-ELUTING OR BARE METAL STENTS**—In patients with an acute coronary syndrome, **dual antiplatelet therapy** is indicated for 1 year in all patients (including those with medical therapy and those patients undergoing revascularization irrespective of stent type). For patients undergoing elective or stable PCI, the duration of dual antiplatelet therapy is recommended for at least 1 month for patients receiving bare metal stents. For patients receiving drug-eluting stents for acute coronary syndromes, dual antiplatelet therapy is recommended for at least 1 year by the ACC/AHA and European guidelines. These recommendations are based both on the durations of therapies during the studies evaluating the stents, and the pathophysiological understanding of the timing of endothelialization following bare metal versus drug-eluting stent implantation. The DAPT (dual antiplatelet therapy) study showed fewer death, MI, and stroke events with longer (up to 30 months) dual antiplatelet therapy for patients who had received drug-eluting stents, but it also showed more bleeding and a tendency for higher mortality. Treatment with clopidogrel for longer than 1 year after drug-eluting stents, therefore, should be individualized based on thrombotic and bleeding risks.

## 2. Fibrinolytic therapy—

**A. BENEFIT**—Fibrinolytic therapy reduces mortality and limits infarct size in patients with STEMI (defined as 0.1 mV or more in two inferior or lateral leads or two contiguous precordial leads), or with left bundle branch block (not known to be old). The greatest benefit occurs if treatment is initiated within the first 3 hours after the onset of presentation, when up to a 50% reduction in mortality rate can be

achieved. The magnitude of benefit declines rapidly thereafter, but a 10% relative mortality reduction can be achieved up to 12 hours after the onset of chest pain. The survival benefit is greatest in patients with large—usually anterior—infarctions. Primary PCI (including stenting) of the infarct-related artery, however, is superior to thrombolysis when done by experienced operators with rapid time from first medical contact to intervention (“door-to-balloon”).

**B. CONTRAINDICATIONS**—Major bleeding complications occur in 0.5–5% of patients, the most serious of which is intracranial hemorrhage. The major risk factors for intracranial bleeding are age 75 years or older, hypertension at presentation (especially over 180/110 mm Hg), low body weight (less than 70 kg), and the use of fibrin-specific fibrinolytic agents (alteplase, reteplase, tenecteplase). Although patients over age 75 years have a much higher mortality rate with acute MI and therefore may derive greater benefit, the risk of severe bleeding is also higher, particularly among patients with risk factors for intracranial hemorrhage, such as severe hypertension or recent stroke. Patients presenting more than 12 hours after the onset of chest pain may also derive a small benefit, particularly if pain and ST-segment elevation persist, but rarely does this benefit outweigh the attendant risk.

Absolute contraindications to fibrinolytic therapy include previous hemorrhagic stroke, other strokes or cerebrovascular events within 1 year, known intracranial neoplasm, recent head trauma (including minor trauma), active internal bleeding (excluding menstruation), or suspected aortic dissection. Relative contraindications are BP greater than 180/110 mm Hg at presentation, other intracebral pathology not listed above as a contraindication, known bleeding diathesis, trauma within 2–4 weeks, major surgery within 3 weeks, prolonged (more than 10 minutes) or traumatic cardiopulmonary resuscitation, recent (within 2–4 weeks) internal bleeding, noncompressible vascular punctures, active diabetic retinopathy, pregnancy, active peptic ulcer disease, a history of severe hypertension, current use of anticoagulants (INR greater than 2.0–3.0), and (for streptokinase) prior allergic reaction or exposure to streptokinase or anistreplase within 2 years.

**C. FIBRINOLYTIC AGENTS**—The following fibrinolytic agents are available for acute MI and are characterized in Table 10–8.

**Alteplase** (recombinant tissue plasminogen activator; t-PA) results in about a 50% reduction in circulating fibrinogen. In the first GUSTO trial, which compared a 90-minute dosing of t-PA (with unfractionated heparin) with streptokinase, the 30-day mortality rate with t-PA was one absolute percentage point lower (one additional life saved per 100 patients treated), though there was also a small increase in the rate of intracranial hemorrhage. An angiographic sub-study confirmed a higher 90-minute patency rate and a higher rate of normal (TIMI grade 3) flow in patients.

**Reteplase** is a recombinant deletion mutant of t-PA that is slightly less fibrin specific. In comparative trials, it appeared to have efficacy similar to that of alteplase, but it has a longer duration of action and can be administered as two boluses 30 minutes apart.

**Tenecteplase** (TNK-t-PA) is a genetically engineered substitution mutant of native t-PA that has reduced plasma clearance, increased fibrin sensitivity, and increased resistance to plasminogen activator inhibitor-1. It can be given as a single weight-adjusted bolus. In the ASSENT 2 trial, this agent was equivalent to t-PA with regard to efficacy and resulted in significantly less noncerebral bleeding.

**Streptokinase**, commonly used outside of the United States, is somewhat less effective at opening occluded arteries and less effective at reducing mortality. It is non-fibrin-specific, causes depletion of circulating fibrinogen, and has a tendency to induce hypotension, particularly if infused rapidly. This can be managed by slowing or interrupting the infusion and administering fluids. There is controversy as to whether adjunctive heparin is beneficial in patients given streptokinase, unlike its administration with the more clot-specific agents. Allergic reactions, including anaphylaxis, occur in 1–2% of patients, and this agent should generally not be administered to patients with prior exposure.

(1) **Selection of a fibrinolytic agent**—In the United States, most patients are treated with alteplase, reteplase, or tenecteplase. The differences in efficacy between them are small compared with the potential benefit of treating a greater proportion of appropriate candidates in a more prompt manner. The principal objective should be to administer a thrombolytic agent within 30 minutes of presentation—or even during transport. The ability to administer tenecteplase as a single bolus is an attractive feature that may facilitate earlier treatment. The combination of a reduced-dose thrombolytic given with a platelet glycoprotein IIb/IIIa inhibitor does not reduce mortality but does cause a modest increase in bleeding complications.

(2) **Postfibrinolytic management**—After completion of the fibrinolytic infusion, aspirin (81–325 mg/day) and anti-coagulation should be continued until revascularization or for the duration of the hospital stay (or up to 8 days). Anti-coagulation with LMWH (enoxaparin or fondaparinux) is preferable to unfractionated heparin.

(A) **LOW-MOLECULAR-WEIGHT HEPARIN**—In the EXTRACT trial, enoxaparin significantly reduced death and MI at day 30 (compared with unfractionated heparin), at the expense of a modest increase in bleeding. In patients younger than age 75, enoxaparin was given as a 30-mg intravenous bolus and 1 mg/kg subcutaneously every 12 hours; in patients aged 75 years and older, it was given with no bolus and 0.75 mg/kg subcutaneously every 12 hours. This appeared to attenuate the risk of intracranial hemorrhage in older adults that had been seen with full-dose enoxaparin. Another antithrombotic option is fondaparinux, given at a dose of 2.5 mg subcutaneously once a day. There is no benefit of fondaparinux among patients undergoing primary PCI, and fondaparinux is not recommended as a sole anti-coagulant during PCI due to risk of catheter thrombosis.

(B) **UNFRACTIONATED HEPARIN**—Anticoagulation with intravenous heparin (initial dose of 60 units/kg bolus to a maximum of 4000 units, followed by an infusion of 12 units/kg/h to a maximum of 1000 units/hour, then adjusted to maintain an aPTT of 50–75 seconds beginning with an aPTT drawn 3 hours after thrombolytic) is continued for at

least 48 hours after alteplase, reteplase, or tenecteplase, and with continuation of an anticoagulant until revascularization (if performed) or until hospital discharge (or day 8).

The VALIDATE trial found no benefit to bivalirudin compared to unfractionated heparin regarding the outcome of death, MI, or major bleeding.

#### (C) PROPHYLACTIC THERAPY AGAINST GASTROINTES-

**TINAL BLEEDING**—For all patients with STEMI treated with intensive antithrombotic therapy, prophylactic treatment with proton pump inhibitors, or antacids and an H<sub>2</sub>-blocker, is advisable. However, certain proton pump inhibitors, such as omeprazole and esomeprazole, may decrease the clinical effect of clopidogrel; in such cases, pantoprazole may be a better proton pump inhibitor option.

#### 3. Assessment of myocardial reperfusion, recurrent isch-

**emic pain, reinfarction**—Myocardial reperfusion can be recognized clinically by the early cessation of pain and the resolution of ST-segment elevation. Although at least 50% resolution of ST-segment elevation by 90 minutes may occur without coronary reperfusion, ST resolution is a strong predictor of better outcome. Even with anticoagulation, 10–20% of reperfused vessels will reocclude during hospitalization, although reocclusion and reinfarction appear to be reduced following intervention. Reinfarction, indicated by recurrence of pain and ST-segment elevation, can be treated by readministration of a thrombolytic agent or immediate angiography and PCI.

### C. General Measures

Cardiac care unit monitoring should be instituted as soon as possible. Patients without complications can be transferred to a telemetry unit after 24 hours. Activity should initially be limited to bed rest but can be advanced within 24 hours. Progressive ambulation should be started after 24–72 hours if tolerated. For patients without complications, discharge by day 4 appears to be appropriate. Low-flow oxygen therapy (2–4 L/min) should be given if oxygen saturation is reduced, but there is no value to routine use of oxygen.

### D. Analgesia

An initial attempt should be made to relieve pain with sublingual nitroglycerin. However, if no response occurs after two or three tablets, intravenous opioids provide the most rapid and effective analgesia and may also reduce pulmonary congestion. Morphine sulfate, 4–8 mg, or meperidine, 50–75 mg, should be given. Subsequent small doses can be given every 15 minutes until pain abates.

Nonsteroidal anti-inflammatory agents, other than aspirin, should be avoided during hospitalization for STEMI due to increased risk of mortality, myocardial rupture, hypertension, heart failure, and kidney injury with their use.

### E. Beta-Adrenergic Blocking Agents

Trials have shown modest short-term benefit from beta-blockers started during the first 24 hours after acute MI if there are no contraindications (metoprolol 25–50 mg

orally twice daily). Aggressive beta-blockade can increase shock, with overall harm in patients with heart failure. Thus, early beta-blockade should be avoided in patients with any degree of heart failure, evidence of low output state, increased risk of cardiogenic shock, or other relative contraindications to beta-blockade. Carvedilol (beginning at 6.25 mg twice a day, titrated to 25 mg twice a day) was shown to be beneficial in the CAPRICORN trial following the acute phase of large MI.

#### F. Nitrates

Nitroglycerin is the agent of choice for continued or recurrent ischemic pain and is useful in lowering BP or relieving pulmonary congestion. However, routine nitrate administration is not recommended, since no improvement in outcome has been observed in the ISIS-4 or GISSI-3 trials. Nitrates should be avoided in patients who received phosphodiesterase inhibitors (sildenafil, vardenafil, and tadalafil) in the prior 24 hours.

#### G. Angiotensin-Converting Enzyme (ACE) Inhibitors

A series of trials (SAVE, AIRE, SMILE, TRACE, GISSI-III, and ISIS-4) have shown both short- and long-term improvement in survival with ACE inhibitor therapy. The benefits are greatest in patients with an EF of 40% or less, large infarctions, or clinical evidence of heart failure. Because substantial amounts of the survival benefit occur on the first day, ACE inhibitor treatment should be commenced early in patients without hypotension, especially patients with large or anterior MI. Given the benefits of ACE inhibitors for patients with vascular disease, it is reasonable to **use ACE inhibitors for all patients following STEMI who do not have contraindications**.

#### H. Angiotensin Receptor Blockers

Although there has been inconsistency in the effects of different ARBs on mortality for patients post-MI with heart failure and/or LV dysfunction, the VALIANT trial showed that valsartan 160 mg orally twice a day is *equivalent* to captopril in reducing mortality. Thus, valsartan should be used for all patients with ACE inhibitor intolerance, and is a reasonable, albeit more expensive, alternative to captopril. The combination of captopril and valsartan (at a reduced dose) was no better than either agent alone and resulted in more side effects.

#### I. Aldosterone Antagonists

The RALES trial showed that 25-mg spironolactone can reduce the mortality rate of patients with advanced heart failure, and the EPHESUS trial showed a 15% relative risk reduction in mortality with eplerenone 25 mg daily for patients post-MI with LV dysfunction (LVEF of 40% or less) and either clinical heart failure or diabetes. Kidney dysfunction or hyperkalemia are contraindications, and patients must be monitored carefully for development of hyperkalemia.

#### J. Calcium Channel Blockers

There are no studies to support the routine use of calcium channel blockers in most patients with acute MI—and indeed, they have the potential to exacerbate ischemia and cause death from reflex tachycardia or myocardial depression. Long-acting calcium channel blockers should generally be reserved for management of hypertension or ischemia as second- or third-line medications after beta-blockers and nitrates.

#### K. Long-Term Antithrombotic Therapy

Discharge on aspirin, 81–325 mg/day, since it is highly effective, inexpensive, and well tolerated, is a key quality indicator of MI care. Patients who received a coronary stent should also receive a P2Y<sub>12</sub> inhibitor (see Antiplatelet therapy after drug-eluting or bare metal stents, above).

Patients who have received a coronary stent and who require warfarin anticoagulation present a particular challenge, since “**triple therapy**” with aspirin, clopidogrel, and warfarin has a high risk of bleeding. Triple therapy should be (1) limited to patients with a clear indication for warfarin (such as CHADS<sub>2</sub> score of 2 or more or a mechanical prosthetic valve), (2) used for the shortest period of time (such as 1 month after placement of bare metal stent; drug-eluting stents that would require longer clopidogrel duration should be avoided if possible), (3) used with low-dose aspirin and with strategies to reduce risk of bleeding (eg, proton pump inhibitors for patients with a history of gastrointestinal bleeding), and (4) used with consideration of a lower target anticoagulation intensity (INR 2.0–2.5, at least for the indication of atrial fibrillation) during the period of concomitant treatment with aspirin and P2Y<sub>12</sub> therapy. The PIONEER trial studied three treatment regimens for patients with atrial fibrillation who had coronary stent placement with a primary outcome of bleeding: (1) rivaroxaban 2.5 mg twice daily plus clopidogrel, (2) rivaroxaban 15 mg once daily plus clopidogrel, and (3) warfarin plus aspirin plus clopidogrel. There was less bleeding in the patients who received rivaroxaban plus clopidogrel than in those who received “triple therapy,” although the trial was not powered to assess efficacy, and thus the low dose of rivaroxaban may be inadequate. Consensus statements recommend oral anticoagulation (with either warfarin or a DOAC) be combined with clopidogrel and with a relatively short duration of aspirin until hospital discharge up to 3 months for the typical patient with atrial fibrillation and coronary stents. Dabigatran, 110 mg and 150 mg, was also studied in patients with atrial fibrillation who underwent PCI. Dual therapy with dabigatran and clopidogrel was shown to be beneficial for bleeding compared to triple therapy, with similar rates of thrombotic cardiovascular events. However, there were too few thrombotic events to be certain about efficacy of discontinuing the aspirin, and there was a suggestion that MI and stent thrombosis occurred more often with the 110-mg dose of dabigatran than with clopidogrel alone. **Given the trial evidence to date, for a typical patient, it is reasonable to use a DOAC and clopidogrel and to discontinue aspirin at the time of**

**hospital discharge or at 7 days after stenting.** The AUGUSTUS trial, which tested apixaban versus warfarin and aspirin versus placebo in a factorial trial, found that apixaban resulted in 31% less major and clinically relevant non-major bleeding than warfarin for patients with atrial fibrillation and coronary stents or acute coronary syndromes or both. Avoiding aspirin, after an average of 6 days after the PCI, resulted in less bleeding and a nonsignificant increase in stent thrombosis. It is reasonable to stop aspirin at hospital discharge or at day 7 for patients with atrial fibrillation who are taking apixaban or warfarin at the time of discharge, although continuing aspirin for 1 month may reduce stent thrombosis.

## L. Coronary Angiography

For patients who do not reperfuse based on lack of at least 50% resolution of ST elevation, rescue angioplasty should be performed and has been shown to reduce the composite risk of death, reinfarction, stroke, or severe heart failure. Patients treated with coronary angiography and PCI 3–24 hours after fibrinolytic therapy showed improved outcomes. Patients with recurrent ischemic pain prior to discharge should undergo catheterization and, if indicated, revascularization. PCI of a totally occluded infarct-related artery more than 24 hours after STEMI should generally not be performed in asymptomatic patients with one or two vessel disease without evidence of severe ischemia.

## ► When to Refer

All patients with acute MI should be referred to a cardiologist.

Lopes RD et al; AUGUSTUS Investigators. Antithrombotic therapy after acute coronary syndrome or PCI in atrial fibrillation. *N Engl J Med.* 2019;380:1509. [PMID: 30883055]

## ► Complications

A variety of complications can occur after MI even when treatment is initiated promptly.

### A. Postinfarction Ischemia

In clinical trials of thrombolysis, recurrent ischemia occurred in about one-third of patients, was more common following NSTEMI than after STEMI, and had important short- and long-term prognostic implications. Vigorous medical therapy should be instituted, including nitrates and beta-blockers as well as aspirin 81–325 mg/day, anticoagulant therapy (unfractionated heparin, enoxaparin, or fondaparinux), and clopidogrel (75 mg orally daily). Most patients with postinfarction angina—and all who are refractory to medical therapy—should undergo early catheterization and revascularization by PCI or CABG.

### B. Arrhythmias

Abnormalities of rhythm and conduction are common.

**1. Sinus bradycardia**—This is most common in inferior infarctions or may be precipitated by medications.

Observation or withdrawal of the offending agent is usually sufficient. If accompanied by signs of low cardiac output, atropine intravenously is usually effective. Temporary pacing is rarely required.

**2. Supraventricular tachyarrhythmias**—Sinus tachycardia is common and may reflect either increased adrenergic stimulation or hemodynamic compromise due to hypovolemia or pump failure. In the latter, beta-blockade is contraindicated. Supraventricular premature beats are common and may be premonitory for atrial fibrillation. Electrolyte abnormalities and hypoxia should be corrected and causative agents (especially aminophylline) stopped. Atrial fibrillation should be rapidly controlled or converted to sinus rhythm. Intravenous beta-blockers, such as metoprolol (2.5–5 mg intravenously every 2–5 minutes, maximum 15 mg over 10 minutes) or short-acting esmolol (50–200 mcg/kg/min), are the agents of choice if cardiac function is adequate. Intravenous diltiazem (5–15 mg/h) may be used if beta-blockers are contraindicated or ineffective. Electrical cardioversion (commencing with 100 J) may be necessary if atrial fibrillation is complicated by hypotension, heart failure, or ischemia, but the arrhythmia often recurs. Amiodarone (150 mg intravenous bolus and then 15–30 mg/h intravenously, or rapid oral loading dose for cardioversion of 400 mg three times daily) may be helpful to restore or maintain sinus rhythm.

**3. Ventricular arrhythmias**—Ventricular arrhythmias are most common in the first few hours after infarction and are a marker of high risk. Ventricular premature beats may be premonitory for ventricular tachycardia or fibrillation, but generally should *not* be treated in the absence of frequent or sustained ventricular tachycardia. Lidocaine is *not* recommended as a prophylactic measure.

Sustained ventricular tachycardia should be treated with a 1 mg/kg bolus of lidocaine if the patient is stable or by electrical cardioversion (100–200 J) if not. If the arrhythmia cannot be suppressed with lidocaine, procainamide (100 mg boluses over 1–2 minutes every 5 minutes to a cumulative dose of 750–1000 mg) or intravenous amiodarone (150 mg over 10 minutes, which may be repeated as needed, followed by 360 mg over 6 hours and then 540 mg over 18 hours) should be initiated, followed by an infusion of 0.5 mg/min (720 mg/24 hours). Ventricular fibrillation is treated electrically (300–400 J). All patients taking antiarrhythmics should be monitored with telemetry or ECGs during initiation. Unresponsive ventricular fibrillation should be treated with additional amiodarone and repeat cardioversion while cardiopulmonary resuscitation (CPR) is administered.

Accelerated idioventricular rhythm is a regular, wide-complex rhythm at a rate of 60–120/min. It may occur with or without reperfusion and should not be treated with antiarrhythmics, which could cause asystole.

**4. Conduction disturbances**—All degrees of AV block may occur in the course of acute MI. Block at the level of the AV node is more common than infranodal block and occurs in approximately 20% of inferior MIs. First-degree block is

the most common and requires no treatment. Second-degree block is usually of the Mobitz type I form (Wenckebach), is often transient, and requires treatment only if associated with a heart rate slow enough to cause symptoms. Complete AV block occurs in up to 5% of acute inferior infarctions, usually is preceded by Mobitz I second-degree block, and generally resolves spontaneously, though it may persist for hours to several weeks. The escape rhythm originates in the distal AV node or AV junction and hence has a narrow QRS complex and is reliable, albeit often slow (30–50 beats/min). Treatment is often necessary because of resulting hypotension and low cardiac output. Intravenous atropine (1 mg) usually restores AV conduction temporarily, but if the escape complex is wide or if repeated atropine treatments are needed, temporary ventricular pacing is indicated. The prognosis for these patients is only slightly worse than for patients in whom AV block does not develop.

In anterior infarctions, the site of block is distal, below the AV node, and usually a result of extensive damage of the His-Purkinje system and bundle branches. New first-degree block (prolongation of the PR interval) is unusual in anterior infarction; Mobitz type II AV block or complete heart block may be preceded by intraventricular conduction defects or may occur abruptly. The escape rhythm, if present, is an unreliable wide-complex idioventricular rhythm. Urgent ventricular pacing is mandatory, but even with successful pacing, morbidity and mortality are high because of the extensive myocardial damage. New conduction abnormalities, such as right or left bundle branch block or fascicular blocks, may presage progression, often sudden, to second- or third-degree AV block. Temporary ventricular pacing is recommended for new-onset alternating bilateral bundle branch block, bifascicular block, or bundle branch block with worsening first-degree AV block. Patients with anterior infarction who progress to second- or third-degree block even transiently should be considered for insertion of a prophylactic permanent ventricular pacemaker before discharge.

### C. Myocardial Dysfunction

Persons with hypotension not responsive to fluid resuscitation or refractory heart failure or cardiogenic shock should be considered for urgent echocardiography to assess left and right ventricular function and for mechanical complications, right heart catheterization, and continuous measurements of arterial pressure. These measurements permit the accurate assessment of volume status and may facilitate decisions about volume resuscitation, selective use of vasoconstrictors and inotropes, and mechanical support.

**1. Acute LV failure**—Dyspnea, diffuse rales, and arterial hypoxemia usually indicate LV failure. General measures include supplemental oxygen to increase arterial saturation to above 95% and elevation of the trunk. Diuretics are usually the initial therapy unless RV infarction is present. Intravenous furosemide (10–40 mg) or bumetanide (0.5–1 mg) is preferred because of the reliably rapid onset and short duration of action of these medications. Higher dosages can be given if an inadequate response occurs. Morphine sulfate

(4 mg intravenously followed by increments of 2 mg) is valuable in acute pulmonary edema.

Diuretics are usually effective; however, because most patients with acute infarction are not volume overloaded, the hemodynamic response may be limited and may be associated with hypotension. In mild heart failure, sublingual isosorbide dinitrate (2.5–10 mg every 2 hours) or nitroglycerin ointment (6.25–25 mg every 4 hours) may be adequate to lower pulmonary capillary wedge pressure (PCWP). In more severe failure, especially if cardiac output is reduced and BP is normal or high, sodium nitroprusside may be the preferred agent. It should be initiated only with arterial pressure monitoring; the initial dosage should be low (0.25 mcg/kg/min) to avoid excessive hypotension, but the dosage can be increased by increments of 0.5 mcg/kg/min every 5–10 minutes up to 5–10 mcg/kg/min until the desired hemodynamic response is obtained. Excessive hypotension (mean BP less than 65–75 mm Hg) or tachycardia (greater than 10/min increase) should be avoided.

Intravenous nitroglycerin (starting at 10 mcg/min) also may be effective but may lower PCWP with less hypotension. Oral or transdermal vasodilator therapy with nitrates or ACE inhibitors is often necessary after the initial 24–48 hours.

Inotropic agents should be avoided if possible, because they often increase heart rate and myocardial oxygen requirements and worsen clinical outcomes. Dobutamine has the best hemodynamic profile, increasing cardiac output and modestly lowering PCWP, usually without excessive tachycardia, hypotension, or arrhythmias. The initial dosage is 2.5 mcg/kg/min, and it may be increased by similar increments up to 15–20 mcg/kg/min at intervals of 5–10 minutes. Dopamine is more useful in the presence of hypotension, since it produces peripheral vasoconstriction, but it has a less beneficial effect on PCWP. Digoxin has not been helpful in acute infarction except to control the ventricular response in atrial fibrillation, but it may be beneficial if chronic heart failure persists.

**2. Hypotension and shock**—Patients with hypotension (systolic BP less than 90 mm Hg, individualized depending on prior BP) and signs of diminished perfusion (low urinary output, confusion, cold extremities) that does not respond to fluid resuscitation should be presumed to have cardiogenic shock and should be considered for urgent catheterization and revascularization. Sparing use of **intracardiac balloon pump (IABP)** support and hemodynamic monitoring with a PA catheter can be considered, although these later measures have not been shown to improve outcome. Up to 20% will have findings indicative of intravascular hypovolemia (due to diaphoresis, vomiting, decreased venous tone, medications—such as diuretics, nitrates, morphine, beta-blockers, calcium channel blockers, and thrombolytic agents—and lack of oral intake). These should be treated with successive boluses of 100 mL of normal saline until PCWP reaches 15–18 mm Hg to determine whether cardiac output and BP respond. Pericardial tamponade due to hemorrhagic pericarditis (especially after thrombolytic therapy or cardiopulmonary resuscitation) or ventricular rupture should be considered and excluded by echocardiography if clinically indicated. RV infarction, characterized by

a normal PCWP but elevated RA pressure, can produce hypotension. This is discussed below.

Most patients with cardiogenic shock will have moderate to severe LV systolic dysfunction, with a mean EF of 30% in the SHOCK trial. If hypotension is only modest (systolic pressure higher than 90 mm Hg) and the PCWP is elevated, diuretics should be administered. If the BP falls, inotropic support will need to be added. A large randomized trial showed *no benefit* of IABP support in cardiogenic shock.

Norepinephrine (0.1–0.5 mcg/kg/min) is generally considered to be the most appropriate inotope/vasopressor for cardiogenic shock based on limited randomized clinical trial evidence suggesting less arrhythmias and improved outcomes compared with dopamine. Dopamine is nonetheless also an option and can be initiated at a rate of 2–4 mcg/kg/min and increased at 5-minute intervals to the appropriate hemodynamic end point. At dosages lower than 5 mcg/kg/min, it improves renal blood flow; at intermediate dosages (2.5–10 mcg/kg/min), it stimulates myocardial contractility; at higher dosages (greater than 8 mcg/kg/min), it is a potent alpha-1-adrenergic agonist. In general, BP and cardiac index rise, but PCWP does not fall. Dopamine may be combined with nitroprusside or dobutamine (see above for dosing), or the latter may be used in its place if hypotension is not severe.

Patients with cardiogenic shock not due to hypovolemia have a poor prognosis, with 30-day mortality rates of 40–80%. The IABP-SHOCK II trial found that the use of an IABP does not offer a mortality benefit at 30 days or 1 year, compared with routine care with rapid revascularization, and is likely not helpful. Surgically implanted (or percutaneous) ventricular assist devices may be used in refractory cases. Emergent cardiac catheterization and coronary angiography followed by percutaneous or surgical revascularization offer the best chance of survival. Additionally, revascularization in shock should be aimed at the culprit artery only, avoiding multivessel PCI.

#### D. RV Infarction

RV infarction is present in one-third of patients with inferior wall infarction but is clinically significant in less than 50% of these. It presents as hypotension with relatively preserved LV function and should be considered whenever patients with inferior infarction exhibit low BP, raised venous pressure, and clear lungs. Hypotension is often exacerbated by medications that decrease intravascular volume or produce venodilation, such as diuretics, nitrates, and opioids. RA pressure and JVP are high, while PCWP is normal or low and the lungs are clear. The diagnosis is suggested by ST-segment elevation in right-sided anterior chest leads, particularly RV<sub>4</sub>. The diagnosis can be confirmed by echocardiography or hemodynamic measurements. Treatment consists of fluid loading beginning with 500 mL of 0.9% saline over 2 hours to improve LV filling, and inotropic agents only if necessary.

#### E. Mechanical Defects

Partial or complete rupture of a papillary muscle or of the interventricular septum occurs in less than 1% of acute MIs and carries a poor prognosis. These complications occur in

both anterior and inferior infarctions, usually 3–7 days after the acute event. They are detected by the appearance of a new systolic murmur and clinical deterioration, often with pulmonary edema. The two lesions are distinguished by the location of the murmur (apical versus parasternal) and by Doppler echocardiography. Hemodynamic monitoring is essential for appropriate management and demonstrates an increase in oxygen saturation between the RA and PA in VSD and, often, a large *v* wave with mitral regurgitation. Treatment by nitroprusside and, preferably, **intra-aortic balloon counterpulsation (IABC)** reduces the regurgitation or shunt, but surgical correction is mandatory. In patients remaining hemodynamically unstable or requiring continuous parenteral pharmacologic treatment or counterpulsation, early surgery is recommended, though mortality rates are high (15% to nearly 100%, depending on residual ventricular function and clinical status). Patients who are stabilized medically can have delayed surgery with lower risks (10–25%), although this may be due to the death of sicker patients, some of whom may have been saved by earlier surgery.

#### F. Myocardial Rupture

Complete rupture of the LV free wall occurs in less than 1% of patients and usually results in immediate death. It occurs 2–7 days postinfarction, usually involves the anterior wall, and is more frequent in older women. Incomplete or gradual rupture may be sealed off by the pericardium, creating a pseudoaneurysm. This may be recognized by echocardiography, radionuclide angiography, or LV angiography, often as an incidental finding. It demonstrates a narrow-neck connection to the LV. Early surgical repair is indicated, since delayed rupture is common.

#### G. LV Aneurysm

An LV aneurysm, a sharply delineated area of scar that bulges paradoxically during systole, develops in 10–20% of patients surviving an acute infarction. This usually follows anterior ST-elevation infarctions. Aneurysms are recognized by persistent ST-segment elevation (beyond 4–8 weeks), and a wide neck from the LV can be demonstrated by echocardiography, scintigraphy, or contrast angiography. They rarely rupture but may be associated with arterial emboli, ventricular arrhythmias, and heart failure. Surgical resection may be performed for these indications if other measures fail. The best results (mortality rates of 10–20%) are obtained when the residual myocardium contracts well and when significant coronary lesions supplying adjacent regions are bypassed.

#### H. Pericarditis

The pericardium is involved in approximately 50% of infarctions, but pericarditis is often not clinically significant. Twenty percent of patients with ST-elevation infarctions will have an audible friction rub if examined repetitively. Pericardial pain occurs in approximately the same proportion after 2–7 days and is recognized by its variation with respiration and position (improved by sitting). Often, no treatment is required, but aspirin (650 mg

every 4–6 hours) will usually relieve the pain. Indomethacin and corticosteroids can cause impaired infarct healing and predispose to myocardial rupture, and therefore should generally be avoided in the early post-MI period. Likewise, anticoagulation should be used cautiously, since hemorrhagic pericarditis may result.

One week to 12 weeks after infarction, **Dressler syndrome** (post-MI syndrome) occurs in less than 5% of patients. This is an autoimmune phenomenon and presents as pericarditis with associated fever, leukocytosis, and, occasionally, pericardial or pleural effusion. It may recur over months. Treatment is the same as for other forms of pericarditis. A short course of nonsteroidal agents or corticosteroids may help relieve symptoms, but the use of nonsteroidal agents in the first several weeks after MI may impair infarct healing.

### I. Mural Thrombus

Mural thrombi are common in large anterior infarctions but not in infarctions at other locations. Arterial emboli occur in approximately 2% of patients with known infarction, usually within 6 weeks. Anticoagulation with heparin followed by short-term (3-month) warfarin therapy (or DOAC therapy based on limited case report experience) results in clot resolution and prevents most emboli and should be considered in all patients with large anterior infarctions and evidence of LV thrombi. Mural thrombi can be detected by echocardiography or cardiac MRI. If the thrombus is resolved at 3 months, then anticoagulation can be discontinued.

## ► Postinfarction Management

After the first 24 hours, the focus of patient management is to prevent recurrent ischemia, improve infarct healing and prevent remodeling, and prevent recurrent vascular events. Patients with hemodynamic compromise, who are at high risk for death, need careful monitoring and management of volume status.

### A. Risk Stratification

Risk stratification is important for the management of STEMI. GRACE and TIMI risk scores can be helpful tools. Patients with recurrent ischemia (spontaneous or provoked), hemodynamic instability, impaired LV function, heart failure, or serious ventricular arrhythmias should undergo cardiac catheterization (see Table 10–7). ACE inhibitor (or ARB) therapy is indicated in patients with clinical heart failure or LVEF of 40% or less. Aldosterone blockade is indicated for patients with an LVEF of 40% or less and either heart failure or diabetes mellitus.

For patients not undergoing cardiac catheterization, submaximal exercise (or pharmacologic stress testing for patients unable to exercise) before discharge or a maximal test after 3–6 weeks (the latter being more sensitive for ischemia) helps patients and clinicians plan the return to normal activity. Imaging in conjunction with stress testing adds additional sensitivity for ischemia and provides localizing information. Both exercise and pharmacologic stress imaging have successfully predicted subsequent outcome.

One of these tests should be used prior to discharge in patients who have received thrombolytic therapy as a means of selecting appropriate candidates for coronary angiography.

### B. Secondary Prevention

Postinfarction management should begin with identification and modification of risk factors. Treatment of hyperlipidemia and smoking cessation both prevent recurrent infarction and death. Statin therapy should be started before the patient is discharged from the hospital to reduce recurrent atherothrombotic events. BP control as well as cardiac rehabilitation and exercise are also recommended. They can be of considerable psychological benefit and appear to improve prognosis.

Beta-blockers improve survival rates, primarily by reducing the incidence of sudden death in high-risk subsets of patients, though their value may be less in patients without complications with small infarctions and normal exercise tests. While a variety of beta-blockers have been shown to be beneficial, for patients with LV dysfunction managed with contemporary treatment, carvedilol titrated to 25 mg orally twice a day has been shown to reduce mortality. Beta-blockers with intrinsic sympathomimetic activity have not proved beneficial in postinfarction patients.

Antiplatelet agents are beneficial; aspirin (75–100 mg daily, after the initial dose) and P2Y<sub>12</sub> inhibitor therapy for 1 year are recommended. Prasugrel provides further reduction in thrombotic outcomes compared with clopidogrel, at the cost of more bleeding, but is contraindicated for patients with prior stroke. Likewise, ticagrelor provides benefit over clopidogrel. Calcium channel blockers have not been shown to improve prognoses overall and should not be prescribed purely for secondary prevention. Antiarrhythmic therapy other than with beta-blockers has not been shown to be effective except in patients with symptomatic arrhythmias. Amiodarone has been studied in several trials of postinfarct patients with either LV dysfunction or frequent ventricular ectopy. Although survival was not improved, amiodarone was not harmful—unlike other agents in this setting. Therefore, it is the agent of choice for individuals with symptomatic postinfarction supraventricular arrhythmias. While implantable defibrillators improve survival for patients with postinfarction LV dysfunction and heart failure, the DINAMIT trial found no benefit to implantable defibrillators implanted in the 40 days following acute MI.

### C. ACE Inhibitors and ARBs in Patients With LV Dysfunction

Patients who sustain substantial myocardial damage often experience subsequent progressive LV dilation and dysfunction, leading to clinical heart failure and reduced long-term survival. In patients with EFs less than 40%, long-term ACE inhibitor (or ARB) therapy prevents LV dilation and the onset of heart failure and prolongs survival. The HOPE trial, as well as an overview of trials of ACE inhibitors for secondary prevention, also demonstrated a reduction of approximately 20% in mortality rates and the occurrence of

nonfatal MI and stroke with ramipril treatment of patients with coronary or peripheral vascular disease and without confirmed LV systolic dysfunction. Therefore, ACE inhibitor therapy should be strongly considered in this broader group of patients—and especially in patients with diabetes and those with even mild systolic hypertension, in whom the greatest benefit was observed (see Table 11–6).

### D. Revascularization

The indications for CABG are similar to those for patients with chronic coronary syndromes, including left main stenosis and multivessel disease (particularly with type 2 diabetes or LV dysfunction, or both). For patients who have undergone primary PCI and have residual left main or multivessel disease, CABG may be appropriate, but the timing needs to take into account high risk of stent thrombosis if P2Y<sub>12</sub> inhibitor therapy is interrupted. For patients with noninfarct-related coronary artery disease, stenting should generally be performed on these lesions prior to hospital discharge.

Ibanez B et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J. 2018;39:119. [PMID: 28886621]

## DISORDERS OF RATE & RHYTHM

Abnormalities of cardiac rhythm and conduction can be symptomatic (syncope, near syncope, dizziness, fatigue, or palpitations) or asymptomatic. In addition, they can be lethal (sudden cardiac death) or dangerous to the extent that they reduce cardiac output, so that perfusion of the brain and myocardium is impaired. Stable supraventricular tachycardia (SVT) is generally well tolerated in patients without underlying heart disease but may lead to myocardial ischemia or heart failure in patients with coronary disease, valvular abnormalities, and systolic or diastolic myocardial dysfunction. Ventricular tachycardia, if prolonged, often results in hemodynamic compromise and may deteriorate into ventricular fibrillation if left untreated.

Whether slow heart rates produce symptoms at rest or with exertion depends on whether cerebral and peripheral perfusion can be maintained, which is generally a function of whether the patient is upright or supine and whether LV function is adequate to maintain stroke volume. If the heart rate abruptly slows, as with the onset of complete heart block or sinus arrest, syncope or convulsions (or both) may result. Unless a clear, reversible cause is found, most symptomatic patients require implantation of a permanent pacemaker.

The diagnosis of an abnormal tachyarrhythmia often can be made via cardiac monitoring, including in-hospital and ambulatory ECG monitoring, event recorders, continuous mobile cardiac telemetry, or implantable loop recorders. Additionally, optic sensors on wearable devices, such as smartwatches, utilize a passive irregular pulse notification algorithm to identify possible arrhythmia, with a positive

predictive value for detection of atrial fibrillation of approximately 70%. Devices, such as certain Apple Watches and the AliveCor device, can record actual electrocardiograms of rhythm that can be transmitted to health care providers. More invasive testing, including catheter-based electrophysiologic studies (to assess sinus node function, AV conduction, and inducibility of arrhythmias), and tests of autonomic nervous system function (tilt-table testing) can also be performed.

Treatment of tachyarrhythmias varies and can include modalities such as antiarrhythmic medications and more invasive techniques such as catheter ablation.

### ► Antiarrhythmic Medications

Antiarrhythmic medications are frequently used to treat arrhythmias, but have variable efficacy and produce frequent side effects (Table 10–9). They are often divided into classes based on their electropharmacologic actions and many of these medications have multiple actions. The most frequently used classification scheme is the **Vaughan-Williams**, which consists of four classes.

**Class I** agents block membrane sodium channels. Three subclasses are further defined by the effect of the agents on the Purkinje fiber action potential. **Class Ia** medications (ie, quinidine, procainamide, disopyramide) slow the rate of rise of the action potential ( $V_{max}$ ) and prolong its duration, thus slowing conduction and increasing refractoriness (moderate depression of phase 0 upstroke of the action potential). **Class Ib** agents (ie, lidocaine, mexiletine) shorten action potential duration; they do not affect conduction or refractoriness (minimal depression of phase 0 upstroke of the action potential). **Class Ic** agents (ie, flecainide, propafenone) prolong  $V_{max}$  and slow repolarization, thus slowing conduction and prolonging refractoriness, but more so than class Ia medications (maximal depression of phase 0 upstroke of the action potential).

**Class II** agents are the beta-blockers, which decrease automaticity, prolong AV conduction, and prolong refractoriness.

**Class III** agents (ie, amiodarone, dronedarone, sotalol, dofetilide, ibutilide) block potassium channels and prolong repolarization, widening the QRS and prolonging the QT interval. They decrease automaticity and conduction and prolong refractoriness.

**Class IV** agents are the calcium channel blockers, which decrease automaticity and AV conduction.

There are some antiarrhythmic agents that do not fall into one of these categories. The most frequently used are digoxin and adenosine. Digoxin inhibits the Na<sup>+</sup>, K<sup>+</sup>-ATPase pump. Digoxin prolongs AV nodal conduction and the AV nodal refractory period, but it shortens the action potential and decreases the refractoriness of the ventricular myocardium and Purkinje fibers. Adenosine can block AV nodal conduction and shortens atrial refractoriness.

Although the in vitro electrophysiologic effects of most of these agents have been defined, their use remains largely empiric. **All can exacerbate arrhythmias (proarrhythmic effect), and many depress LV function.**

The risk of antiarrhythmic agents has been highlighted by many studies, most notably the Coronary Arrhythmia

**Table 10–9.** Antiarrhythmic medications (listed in alphabetical order within class).

| Agent  | Intravenous Dosage   | Oral Dosage   | Therapeutic Plasma Level                           | Route of Elimination | Side Effects  |
|--|--|---|--|----------------------|---|
| <b>Class Ia: Action: Sodium channel blockers: Depress phase 0 depolarization; slow conduction; prolong repolarization.</b>   |  |   |  |                      |   |
| <b>Indications:</b> Supraventricular tachycardia, ventricular tachycardia, symptomatic ventricular premature beats.  |  |   |  |                      |   |
| Disopyramide   |  | Immediate release:<br>100–200 mg every 6 h<br>Sustained release:<br>200–400 mg every 12 h | 2–8 mg/mL  | Renal                | Urinary retention, dry mouth, markedly ↓ LVF, QT prolongation   |
| Procainamide   | Loading: 10–17 mg/kg at 20–50 mg/min<br>Maintenance: 1–4 mg/min                                | 50 mg/kg/day in divided doses every 4 h (short-acting)                                    | 4–10 mg/mL; NAPA (active metabolite), 10–20 mcg/mL | Renal                |   |
| Quinidine  | 6–10 mg/kg (intramuscularly or intravenously) over 20 min (rarely used parenterally)           | 324–648 mg every 8 h  | 2–5 mg/mL  | Hepatic              | GI, ↓ LVF, ↑ Dig  |
| <b>Class Ib: Action: Shorten repolarization.</b>   |  |   |  |                      |   |
| <b>Indications:</b> Ventricular tachycardia, prevention of ventricular fibrillation, symptomatic ventricular premature beats.  |  |   |  |                      |   |
| Lidocaine  | Loading: 1 mg/kg<br>Maintenance: 1–4 mg/min  |   | 1–5 mg/mL  | Hepatic              | CNS, GI, ↓ LVF  |
| Mexiletine   |  | 100–300 mg every 8–12 h; maximum: 1200 mg/day   | 0.5–2 mg/mL  | Hepatic              | CNS, GI, leukopenia   |
| <b>Class Ic: Action: Depress phase 0 repolarization; slow conduction. (Propafenone is a weak calcium channel blocker and beta-blocker and prolongs action potential and refractoriness.)</b>   |  |   |  |                      |   |
| <b>Indications:</b> Ventricular tachycardia (in the absence of structural heart disease), refractory supraventricular tachycardia.   |  |   |  |                      |   |
| Flecainide   |  | 50–150 mg twice daily   | 0.2–1 mg/mL  | Hepatic              | CNS, GI, AFL with 1:1 conduction, ventricular pro-arrhythmia  |
| Propafenone  |  | 150–300 mg every 8–12 h   | Note: Active metabolites                           | Hepatic              | CNS, GI, AFL with 1:1 conduction, ventricular pro-arrhythmia  |
| <b>Class II: Action: Beta-blockers, slow AV conduction.</b>  |  |   |  |                      |   |
| <b>Indications:</b> Supraventricular tachycardia, ventricular tachycardia, symptomatic ventricular premature beats, long QT syndrome.  |  |   |  |                      |   |
| Esmolol  | Loading: 500 mcg/kg over 1–2 min<br>Maintenance: 50 mcg/kg/min                                 | Other beta-blockers may be used concomitantly   | Not established                                    | Hepatic              | ↓ LVF, bradycardia, AV block  |
| Metoprolol   | 5 mg every 5 min up to 3 doses   | 25–200 mg daily   | Not established                                    | Hepatic              | ↓ LVF, bradycardia, AV block, fatigue   |
| Propranolol  | 1–3 mg every 5 min up to total of 5 mg   | 40–320 mg in 1–4 doses daily (depending on preparation)                                   | Not established                                    | Hepatic              | ↓ LVF, bradycardia, AV block, bronchospasm  |
| <b>Class III: Action: Prolong action potential.</b>  |  |   |  |                      |   |
| <b>Indications:</b> Amiodarone: refractory ventricular tachycardia, supraventricular tachycardia, prevention of ventricular tachycardia, atrial fibrillation, ventricular fibrillation; Dofetilide: atrial fibrillation and flutter; Dronedarone: atrial fibrillation (not persistent); Ibutilide: conversion of atrial fibrillation and flutter; Sotalol: ventricular tachycardia, atrial fibrillation. |  |   |  |                      |   |
| Amiodarone   | 150–300 mg infused rapidly, followed by 1 mg/min infusion for 6 h and then 0.5 mg/min for 18 h | 800–1600 mg/day for 7–14 days; maintain at 100–400 mg/day                                 | 1–5 mg/mL  | Hepatic              | Pulmonary fibrosis, hypothyroidism, hyperthyroidism, photosensitivity, corneal and skin deposits, hepatitis, ↑ Dig, neurotoxicity, GI |

(continued)

**Table 10–9.** Antiarrhythmic medications (listed in alphabetical order within class). (continued)

| Agent       | Intravenous Dosage  | Oral Dosage                                 | Therapeutic Plasma Level | Route of Elimination  | Side Effects  |
|-------------|---|---|--------------------------|---|---|
| Dofetilide  |   | 125–500 mcg every 12 h                      |                          | Renal (dose must be reduced with kidney dysfunction)                              | Torsades de pointes in 3%; interaction with cytochrome P-450 inhibitors   |
| Dronedarone |   | 400 mg twice daily                          |                          | Hepatic (contraindicated in severe impairment)                                    | QTc prolongation, HF. Contraindicated in HF (NYHA class IV or recent decompensation), persistent AF                               |
| Ibutilide   | 1 mg over 10 min, followed by a second infusion of 0.5–1 mg over 10 min |   |                          | Hepatic and renal   | Torsades de pointes in up to 5% of patients within 3 h after administration; patients must be monitored with defibrillator nearby |
| Sotalol     | 75 mg every 12 h  | 80–160 mg every 12 h (maximum 320 mg daily) |                          | Renal (dosing interval should be extended if creatinine clearance is < 60 mL/min) | Early incidence of torsades de pointes, ↓ LVF, bradycardia, fatigue (and other side effects associated with beta-blockers)        |

**Class IV: Action: Slow calcium channel blockers.****Indications:** Supraventricular tachycardia, ventricular tachycardia (outflow tract, idiopathic).

|           |   |   |                |                                     |   |
|-----------|---|---|----------------|-------------------------------------|---|
| Diltiazem | 0.25 mg/kg over 2 min; second 0.35-mg/kg bolus after 15 min if response is inadequate; infusion rate, 5–15 mg/h         | 120–360 mg daily in 1–3 doses depending on preparation                          |                | Hepatic metabolism, renal excretion | Hypotension, ↓ LVF, bradycardia         |
| Verapamil | 2.5 mg bolus followed by additional boluses of 2.5–5 mg every 1–3 min; total 20 mg over 20 min; maintain at 5 mg/kg/min | 80–120 mg every 6–8 h; 240–480 mg once daily with sustained-release preparation | 0.1–0.15 mg/mL | Hepatic                             | Hypotension, ↓ LVF, constipation, ↑ Dig |

**Miscellaneous: Indications: Supraventricular tachycardia.**

|            |   |  |             |  |   |
|------------|---|--|-------------|--|---|
| Adenosine  | 6 mg rapidly followed by 12 mg after 1–2 min if needed; use half these doses if administered via central line |  |             | Adenosine receptor stimulation, metabolized in blood | Transient flushing, dyspnea, chest pain, AV block, sinus bradycardia; effect ↓ by theophylline, ↑ by dipyridamole |
| Digoxin    | 0.5 mg over 20 min followed by increment of 0.25 or 0.125 mg to 1–1.5 mg over 24 h                            | 1–1.5 mg over 24–36 h in 3 or 4 doses; maintenance, 0.125–0.5 mg/day | 0.7–2 mg/mL | Renal  | AV block, arrhythmias, GI, visual changes   |
| Ivabradine |   | 5–7.5 mg every 12 h  |             | Renal and fecal                                      | Bradycardia, phosphenes (visual brightness)   |

AF, atrial fibrillation; AV, atrioventricular; CNS, central nervous system; Dig, elevation of serum digoxin level; GI, gastrointestinal (nausea, vomiting, diarrhea); HF, heart failure; ↓LVF, reduced left ventricular function; NAPA, *N*-acetylprocainamide; NYHA, New York Heart Association; SLE, systemic lupus erythematosus.

Suppression Trial (CAST), in which two class Ic agents (flecainide, encainide) and a class Ia agent (moricizine) increased mortality rates in patients with asymptomatic ventricular ectopy after MI. Class Ic antiarrhythmic agents should therefore *not* be used in patients with prior MI or structural heart disease.

The use of antiarrhythmic agents for specific arrhythmias is discussed below.

## ► Catheter Ablation for Cardiac Arrhythmias

Catheter ablation has become the primary modality of therapy for many symptomatic supraventricular arrhythmias, including AV nodal reentrant tachycardia, tachycardias involving accessory pathways, paroxysmal atrial tachycardia, and atrial flutter. Catheter ablation of atrial fibrillation is more complex and usually involves complete electrical isolation of the pulmonary veins (which are often the sites of initiation of atrial fibrillation) or placing linear lesions within the atria to prevent propagation throughout the atrial chamber. This technique is considered a reasonable therapy for symptomatic patients with medication-refractory atrial fibrillation or as an alternative to long-term antiarrhythmic medication treatment. Catheter ablation of ventricular arrhythmias has proved more difficult, but experienced centers have demonstrated reasonable success with all types of ventricular tachycardias including bundle-branch reentry, tachycardia originating in the ventricular outflow tract or papillary muscles, tachycardias originating in the specialized conduction system (fascicular ventricular tachycardia), and ventricular tachycardias occurring in patients with ischemic or dilated cardiomyopathy. Ablation of many of these arrhythmias can be performed from the endocardial surface via endovascular catheter placement or on the epicardial surface of the heart via a percutaneous subxiphoid approach.

Catheter ablation has also been successfully performed for the treatment of ventricular fibrillation when a uniform premature ventricular contraction (PVC) can be identified. In addition, patients with symptomatic PVCs or PVCs occurring at a high enough burden to result in a cardiomyopathy (usually more than 10,000/day) are often referred for catheter ablation as well.

Catheter ablation procedures are generally safe, with an overall major complication rate ranging from 1% to 5%. Major vascular damage during catheter insertion occurs in less than 2% of patients. There is a low incidence of perforation of the myocardial wall resulting in pericardial tamponade. Sufficient damage to the AV node to require permanent cardiac pacing occurs in less than 1% of patients. When transseptal access through the interatrial septum or retrograde LV catheterization is required, additional potential complications include damage to the heart valves, damage to a coronary artery, or systemic emboli. A rare but potentially fatal complication after catheter ablation of atrial fibrillation is the development of an atrio-esophageal fistula resulting from ablation on the posterior wall of the LA just overlying the esophagus, estimated to occur in less than 0.1% of procedures.

Calkins H et al. 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation. *Europace*. 2018;20:e1. [PMID: 29016840]

## SINUS ARRHYTHMIA, BRADYCARDIA, & TACHYCARDIA



### ESSENTIALS OF DIAGNOSIS

- ▶ Wide variation in sinus rate is common in young, healthy individuals and generally not pathologic.
- ▶ Symptomatic bradycardia may require permanent pacemaker implantation, especially in the elderly or patients with underlying heart disease.
- ▶ Sinus tachycardia is usually secondary to another underlying process (ie, fever, pain, anemia, alcohol withdrawal).
- ▶ Sick sinus syndrome manifests as sinus bradycardia, pauses, or inadequate heart rate response to physiologic demands (chronotropic incompetence).

## ► General Considerations

**Sinus arrhythmia** is an irregularity of the normal heart rate defined as variation in the PP interval of more than 120 msec. This occurs commonly in young, healthy people due to changes in vagal influence on the sinus node during respiration (phasic) or independent of respiration (non-phasic). This is generally *not* a pathologic arrhythmia and requires no specific cardiac evaluation.

**Sinus bradycardia** is defined as a heart rate slower than 60 beats/min and may be due to increased vagal influence on the normal sinoatrial pacemaker or organic disease of the sinus node. In healthy individuals, and particularly in well-trained athletes, sinus bradycardia to rates of 50 beats/min or lower especially during sleep is a normal finding. However, in elderly patients and individuals with heart disease sinus bradycardia may be an indication of true sinus node pathology. When the sinus rate slows severely, the atrial-nodal junction or the nodal-His bundle junction may assume pacemaker activity for the heart, usually at a rate of 35–60 beats/min.

**Sinus tachycardia** is defined as a heart rate faster than 100 beats/min that is caused by rapid impulse formation from the sinoatrial node. It is a normal physiologic response to exercise or other conditions in which catecholamine release is increased. The rate infrequently exceeds 160 beats/min but may reach 180 beats/min in young persons. The onset and termination are usually gradual, in contrast to paroxysmal supraventricular tachycardia (PSVT) due to reentry. In rare instances, otherwise healthy individuals may present with “inappropriate” sinus tachycardia where persistently elevated basal heart rates are not in-line with physiologic demands. Long-term consequences of this disorder are few.

**Sick sinus syndrome** is a broad diagnosis applied to patients with sinus arrest, sinoatrial exit block (recognized

by a pause equal to a multiple of the underlying PP interval or progressive shortening of the PP interval prior to a pause), or persistent sinus bradycardia. A common presentation in elderly patients is of recurrent SVTs (often atrial fibrillation) accompanied by bradycardias (**“tachy-brady syndrome”**). The long pauses that often follow the termination of tachycardia cause the associated symptoms. Sick sinus syndrome may also manifest as **chronotropic incompetence**, defined as an inappropriate heart rate response to the physiologic demands of exercise or stress, and is an underrecognized cause of poor exercise tolerance.

## ► Clinical Findings

In most patients, sinus arrhythmia (bradycardia or tachycardia) does not cause symptoms in the absence of underlying cardiac disease or other comorbidities. When severe sinus bradycardia results in low cardiac output, however, patients may complain of weakness, confusion, or syncope if cerebral perfusion is impaired. Atrial, junctional, and ventricular ectopic rhythms are more apt to occur with slow sinus rates. Sinus bradycardia is often exacerbated by medications (digitalis, calcium channel blockers, beta-blockers, sympatholytic agents, antiarrhythmics), and non-essential agents that may be responsible should be withdrawn prior to making the diagnosis.

Sinus tachycardia is most often a *normal response* to conditions that require an increase in cardiac output, including fever, pain, anxiety, anemia, heart failure, hypovolemia, or thyrotoxicosis. Alcohol and alcohol withdrawal are common causes of sinus tachycardia and other supraventricular arrhythmias. In patients with underlying cardiac disease, sinus tachycardia may cause dyspnea or chest pain due to increased myocardial oxygen demand or reduced coronary artery blood flow.

Symptoms from sinus node dysfunction are nonspecific and may be due to other causes. It is therefore essential that symptoms be demonstrated to coincide temporally with arrhythmias. This may require prolonged ambulatory monitoring or the use of an event recorder.

## ► Treatment

Asymptomatic patients generally do *not* require treatment. For symptomatic patients with bradycardia or sick sinus syndrome, implantation of a permanent pacemaker is usually indicated. In patients without evidence of AV nodal or bundle branch conduction abnormality, a single chamber atrial pacemaker is reasonable. Based on the results of several randomized controlled trials, atrial-based pacing (single or dual chamber) is superior to ventricular only pacing for patients with sinus node dysfunction. When a dual-chamber pacemaker is implanted for sinus node dysfunction with intact AV conduction, unnecessary ventricular pacing should be avoided because it may exacerbate heart failure, especially in patients with preexisting LV dysfunction. In most situations, sinus tachycardia will improve or resolve with treatment of the underlying cause. Inappropriate sinus tachycardia in the presence of symptoms (palpitations, dizziness, exertional intolerance) can be treated with a trial of beta-blockers or calcium channel blockers

although treatment is often challenging. Ivabradine (5–7.5 mg twice daily), a selective inhibitor of the potassium funny channel ( $I_f$ ) specific to the sinus node, appears to be an effective treatment option.

## ► When to Refer

Patients with symptoms related to bradycardia or tachycardia when reversible etiologies have been excluded.

Kusumoto FM et al. 2018 ACC/AHA/HRS guideline on the evaluation and management of patients with bradycardia and cardiac conduction delay: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. *Heart Rhythm*. 2019;16:e128. [PMID: 30412778]

## AV BLOCK



### ESSENTIALS OF DIAGNOSIS

- ▶ Conduction disturbance between the atrium and ventricle that can be physiologic (due to enhanced vagal tone) or pathologic.
- ▶ Block occurs in the AV node (first-degree, second-degree Mobitz type I) or below the AV node (second-degree Mobitz type II, third-degree).
- ▶ Symptomatic AV block or block below the AV node in the absence of a reversible cause usually warrants permanent pacemaker implantation.

## ► General Considerations

AV block can be physiologic (due to increased vagal tone) or pathologic (due to underlying heart disease such as ischemia, myocarditis, fibrosis of the conduction system, or after cardiac surgery). AV block is categorized as **first-degree** (PR interval greater than 200 msec with all atrial impulses conducted), **second-degree** (intermittent blocked beats), or **third-degree** (complete heart block, in which no atrial impulses are conducted to the ventricles). Second-degree AV block is further subclassified into **Mobitz type I (Wenckebach)**, in which the AV conduction time (PR interval) progressively lengthens before the blocked beat, and **Mobitz type II**, in which there are intermittently non-conducted atrial beats not preceded by lengthening AV conduction. When only 2:1 AV block is present on the ECG, the differentiation between Mobitz type I or Mobitz type II is more difficult. If the baseline PR interval is prolonged (greater than 200 msec) or the width of the QRS complex is narrow (less than 120 msec), the block is usually nodal (Mobitz type I); if the QRS complex is wide (greater than or equal to 120 msec), the block is more likely infranodal (Mobitz type II).

**AV dissociation** occurs when an intrinsic ventricular pacemaker (accelerated idioventricular rhythm, ventricular premature beats, or ventricular tachycardia) is firing at

a rate faster than or close to the sinus rate, such that atrial impulses arriving at the AV node when it is refractory may not be conducted. This phenomenon does not necessarily indicate AV block. No treatment is required aside from management of the causative arrhythmia.

## ► Clinical Findings

The clinical presentation of first-degree and Mobitz type I block is typically benign and rarely produces symptoms. Normal, physiologic block of this type occurs in response to increases in parasympathetic output. This is commonly seen during sleep, with carotid sinus massage, or in well-trained athletes. It may also occur as a medication effect (calcium channel blockers, beta-blockers, digitalis, or antiarrhythmics). Pathologic causes, including myocardial ischemia or infarction (discussed earlier), inflammatory processes (ie, Lyme disease), fibrosis, calcification, or infiltration (ie, amyloidosis or sarcoidosis), should be excluded.

Mobitz type II block and complete (third-degree) heart block are almost always due to pathologic disease involving the infranodal conduction system, and symptoms including fatigue, dyspnea, presyncope or syncope are common. With complete heart block, where no atrial impulses reach the ventricle, the ventricular escape rate is usually slow (less than 50 beats/min) and severity of symptoms may vary depending on the rate and stability of the escape rhythm. As for lesser degrees of AV block, pathologic causes should be explored.

**Intraventricular conduction block** is relatively common and may be transient (ie, related to increases in heart rate) or permanent. Right bundle branch block is often seen in patients with structurally normal hearts. The left bundle is composed of two components (anterior and posterior fascicles) and left bundle branch block is more often a marker of underlying cardiac disease, including ischemic heart disease, inflammatory or infiltrative disease, cardiomyopathy, and valvular heart disease. In asymptomatic patients with bifascicular block (block in two of three infranodal components—right bundle, left anterior, and left posterior fascicle), the incidence of occult complete heart block or progression to it is low (1% annually).

## ► Treatment

Asymptomatic patients with first- or second-degree Mobitz type I AV block do not require any specific therapy. Patients should undergo treatment of any potentially reversible cause (ie, myocardial ischemia or medication effect). Symptomatic patients with any degree of heart block should be treated urgently with atropine (initial dose 0.5 mg given intravenously) or temporary pacing (transcutaneous or transvenous). The indications for permanent pacing are symptomatic bradycardia with any degree of AV block or asymptomatic high-degree AV block (second-degree Mobitz type II or third-degree heart block) not attributable to a reversible or physiologic cause. Patients with presumed cardiac syncope with normal heart rates and rhythm but bifascicular or trifascicular block on ECG should also be considered for permanent pacing.

A standardized nomenclature for pacemaker generators is used, usually consisting of four letters. The first letter refers to the chamber that is paced (A, atrium; V, ventricle; D, dual [for both]). The second letter refers to the chamber that is sensed (also A, V, or D). An additional option (O) indicates absence of sensing. The third letter refers to how the pacemaker responds to a sensed event (I, inhibition by a sensed impulse; T, triggering by a sensed impulse; D, dual modes of response; O, no response to sensed impulse). The fourth letter refers to the programmability or rate response capacity (R, rate modulation), a function that can increase the pacing rate in response to motion or respiratory rate when the intrinsic heart rate is inappropriately low.

A dual-chamber pacemaker that senses and paces in both chambers is the most physiologic approach to pacing patients who remain in sinus rhythm. **AV synchrony** is particularly important in patients in whom atrial contraction produces a substantial augmentation of stroke volume. For patients in permanent atrial fibrillation who require pacing for symptomatic bradycardia or pauses, catheter-based implantation of a leadless pacemaker directly to the RV endocardium may be considered. In patients with complete heart block with left ventricular systolic dysfunction, implantation of a pacemaker capable of direct capture of the native specialized conduction system (His bundle or left bundle) or simultaneous left and right ventricular pacing (CRT-P) may be indicated. Complications from pacemaker implantation include infection, hematoma, cardiac perforation, pneumothorax, and lead dislodgement.

## ► When to Refer

Patients with symptomatic AV block (any degree) or asymptomatic high-degree (second-degree Mobitz type II or third-degree) AV block after reversible causes have been excluded.

Upadhyay GA et al; His-SYNC Investigators. His corrective pacing or biventricular pacing for cardiac resynchronization in heart failure. J Am Coll Cardiol. 2019;74:157. [PMID: 31078637]

## PAROXYSMAL SUPRAVENTRICULAR TACHYCARDIA (PSVT)



### ESSENTIALS OF DIAGNOSIS

- Rapid, regular tachycardia most commonly seen in young adults and characterized by abrupt onset and offset.
- QRS duration narrow (< 120 msec) except in the presence of bundle branch block or accessory pathway.
- Often responsive to vagal maneuvers, AV nodal blockers, or adenosine. Cardioversion rarely required.

## ► General Considerations

PSVT is an intermittent arrhythmia that is characterized by a sudden onset and offset and a regular ventricular response. Episodes may last from a few seconds to several hours or longer. PSVT often occurs in patients without structural heart disease. The most common mechanism for PSVT is *reentry*, which may be initiated or terminated by a fortuitously timed atrial or ventricular premature beat. The reentrant circuit usually involves dual pathways (a slow and a fast pathway) within the AV node; this is referred to as **AV nodal reentrant tachycardia (AVNRT)** and accounts for 60% of cases of PSVT. Less commonly (30% of cases), reentry is due to an *accessory pathway* between the atria and ventricles, referred to as **atrioventricular reciprocating tachycardia (AVRT)**. The pathophysiology and management of arrhythmias due to accessory pathways differ in important ways and are discussed separately below.

## ► Clinical Findings

### A. Symptoms and Signs

Symptoms of PSVT can be quite variable depending on the degree of heart rate elevation, resultant hypotension, or presence of other comorbidities. Symptoms may include palpitations, diaphoresis, dyspnea, dizziness, and mild chest pain (even in the absence of associated CHD). Syncope is rare.

### B. ECG

Obtaining a 12-lead ECG when feasible is important to help determine the tachycardia mechanism. The QRS duration will be narrow (less than 120 ms) except in cases of PSVT with aberrant conduction (left bundle branch block, right bundle branch block, or antegrade conducting accessory pathway). The heart rate is regular and is usually 160–220 beats/min but may be greater than 250 beats/min. The P wave usually differs in contour from sinus beats and is often simultaneous with or just after the QRS complex.

## ► Treatment

In the absence of structural heart disease, serious effects are rare, and most episodes resolve spontaneously. Particular effort should be made to terminate the episode quickly if cardiac failure, syncope, or anginal pain develops or if there is underlying cardiac or (particularly) coronary disease. Because reentry is the most common mechanism for PSVT, effective therapy requires that conduction be interrupted at some point in the reentry circuit and the vast majority of these circuits involve the AV node.

### A. Mechanical Measures

A variety of maneuvers have been used to interrupt episodes, and patients may learn to perform these themselves. These maneuvers result in an acute increase in vagal tone and include the Valsalva maneuver, lowering the head between the knees, coughing, splashing cold water on the face, and breath holding. The **Valsalva maneuver** is performed with the patient semirecumbent (45 degrees), exerting around 40 mm Hg of intrathoracic pressure (by

blowing through a 10 mL syringe) for at least 15 seconds. Moving the patient supine immediately following the strain maneuver and passively raising their legs for an additional 15 seconds may increase effectiveness of the maneuver. **Carotid sinus massage** is an additional technique often performed by clinicians but should be avoided if the patient has a carotid bruit. Firm but gentle pressure and massage are applied first over the right carotid sinus for 10–20 seconds and, if unsuccessful, then over the left carotid sinus. Pressure should not be exerted on both sides at the same time. **Facial contact with cold water** may cause transient bradycardia and termination of PSVT, a phenomenon known as the diving reflex. When performed properly, these maneuvers result in abrupt termination of the arrhythmia in 20–50% of cases.

### B. Medication Therapy

If mechanical measures fail to terminate the arrhythmia, pharmacologic agents should be tried. **Intravenous adenosine** is recommended as the first-line agent due to its brief duration of action and minimal negative inotropic activity (Table 10–9). Because the half-life of adenosine is less than 10 seconds, the medication is given rapidly (in 1–2 seconds) as a 6 mg bolus followed by 20 mL of fluid. If this regimen is unsuccessful at terminating the arrhythmia, a second higher dose (12 mg) may be given. Adenosine causes block of electrical conduction through the AV node and results in termination of PSVT in approximately 90% of cases. Minor side effects are common and include transient flushing, chest discomfort, nausea, and headache. Adenosine may excite both atrial and ventricular tissue causing atrial fibrillation (in up to 12% of patients) or rarely ventricular arrhythmias and therefore administration should be performed with continuous cardiac monitoring and availability of an external defibrillator. Adenosine must also be used with caution in patients with reactive airways disease because it can promote bronchospasm.

When adenosine fails to terminate the arrhythmia or if a contraindication to its use is present, **intravenous calcium channel blockers**, including verapamil and diltiazem, may be used (Table 10–9). Verapamil in particular has been shown to be as effective at terminating PSVT in the acute setting (approximately 90%) as adenosine. Calcium channel blockers should be used with caution in patients with heart failure due to their negative inotropic effects. Their longer half-life compared to adenosine may result in prolonged hypotension despite restoration of normal rhythm.

**Intravenous beta-blockers** include esmolol (a very short-acting beta-blocker), propranolol, and metoprolol. While beta-blockers cause less myocardial depression than calcium channel blockers, the evidence of their effectiveness to terminate PSVT is limited. Although **intravenous amiodarone** is safe, it is usually not required and often ineffective for treatment of these arrhythmias.

### C. Cardioversion

If the patient is hemodynamically unstable or if adenosine, beta-blockers, and calcium channel blockers are

contraindicated or ineffective, synchronized electrical cardioversion (beginning at 100 J) should be performed.

## ► Prevention

### A. Catheter Ablation

Because of concerns about the safety and the intolerance of antiarrhythmic medications, **radiofrequency ablation is the preferred approach to patients with recurrent symptomatic reentrant PSVT**, whether it is due to dual pathways within the AV node or to accessory pathways.

### B. Medications

AV nodal blocking agents are the medications of choice as first-line medical therapy (Table 10–9). Beta-blockers or nondihydropyridine calcium channel blockers, such as diltiazem and verapamil, are typically used first. Patients who do not respond to agents that increase refractoriness of the AV node may be treated with antiarrhythmics. The class Ic agents (flecainide, propafenone) can be used in patients without underlying structural heart disease. In patients with evidence of structural heart disease, class III agents, such as sotalol or amiodarone, should be used because of the lower incidence of ventricular proarrhythmia during long-term therapy.

## ► When to Refer

All patients with sustained or symptomatic PSVT should be referred to a cardiologist or cardiac electrophysiologist for long-term treatment options (including observation, pharmacotherapy, or ablation).

Page RL et al. 2015 ACC/AHA/HRS guideline for the management of adult patients with supraventricular tachycardia: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol.* 2016;67:e27. [PMID: 26409259]

## PSVT DUE TO ACCESSORY AV PATHWAYS (Preexcitation Syndromes)



### ESSENTIALS OF DIAGNOSIS

- ▶ Two classic features of Wolff-Parkinson-White (WPW) pattern on ECG are short PR interval and wide, slurred QRS complex due to manifest preexcitation (delta wave).
- ▶ Most patients with WPW pattern do not have clinical history of arrhythmia but have a higher risk of sudden cardiac death due to rapidly conducted atrial fibrillation through the accessory pathway. Risk factors include age younger than 20, history of tachycardia, and rapid conduction properties at electrophysiologic testing.

## ► General Considerations

Accessory pathways or bypass tracts between the atrium and the ventricle bypass the compact AV node and can predispose to reentrant arrhythmias, such as AVRT and atrial fibrillation. When direct AV connections conduct antegrade (manifest preexcitation) they produce a classic **WPW pattern** on the baseline ECG consisting of a short PR interval and a wide, slurred QRS complex (**delta wave**) owing to early ventricular depolarization of the region adjacent to the pathway. Although the morphology and polarity of the delta wave can suggest the location of the pathway, mapping by intracardiac recordings is required for precise anatomic localization.

Accessory pathways occur in 0.1–0.3% of the population and facilitate reentrant arrhythmias owing to the disparity in refractory periods of the AV node and accessory pathway. **WPW syndrome** refers to a patient with baseline WPW pattern on ECG with associated SVT. Whether the tachycardia is associated with a narrow or wide QRS complex is frequently determined by whether antegrade conduction is through the node (narrow) or the bypass tract (wide). Some bypass tracts only conduct in a retrograde direction. In these cases, the bypass tract is termed “concealed” because it is not readily apparent on a baseline (sinus) ECG. **Orthodromic reentrant tachycardia** accounts for approximately 90% of AVRT episodes and is characterized by conduction antegrade down the AV node and retrograde up the accessory pathway, resulting in a narrow QRS complex (unless an underlying bundle branch block or interventricular conduction delay is present). **Antidromic reentrant tachycardia** conducts antegrade down the accessory pathway and retrograde through the AV node, resulting in a wide and often bizarre-appearing QRS complex that may be mistaken for ventricular tachycardia. Accessory pathways often have shorter refractory periods than specialized conduction tissue and thus tachycardias involving accessory pathways have the potential to be more rapid.

## ► Clinical Findings

Patients with WPW in whom arrhythmia develops often have palpitations, dizziness, or mild chest pain. Most patients that have a delta wave found incidentally on ECG (WPW pattern) do not have a clinical history of arrhythmia and are therefore asymptomatic. However, these patients are still at higher risk for sudden cardiac death than the general population. Atrial fibrillation with antegrade conduction down the accessory pathway and a rapid ventricular response will develop in up to 30% of patients with WPW. If this conduction is very rapid, it can potentially degenerate to ventricular fibrillation. The 10-year risk of sudden cardiac death in patients with WPW syndrome ranges from 0.15% to 0.24%. Risk factors include age younger than 20, a history of symptomatic tachycardia, and multiple accessory pathways.

Multiple risk stratification strategies have been proposed to identify asymptomatic patients with WPW pattern ECG who may be at higher risk for lethal cardiac arrhythmias. A sudden loss of preexcitation during exercise testing likely indicates an accessory pathway with poor conduction properties and therefore low risk for rapid

anterograde conduction. In the absence of this finding or other signs of weak anterograde properties (intermittent preexcitation on resting or ambulatory ECG monitoring), patients may be referred for invasive electrophysiology testing. During the study, patients found to have the shortest preexcited R-R interval during atrial fibrillation of 250 msec or less or inducible SVT are at increased risk for sudden cardiac death and should undergo catheter ablation.

## ► Treatment

### A. Pharmacotherapy

Initial treatment of narrow-complex reentrant rhythms involving a bypass tract (orthodromic AVRT) is similar to other forms of PSVT and includes vagal maneuvers, intravenous adenosine, or verapamil. Treatment of wide-complex tachycardia in the presence of an accessory pathway, be it reentrant-type (antidromic AVRT) or atrial fibrillation with antegrade conduction down the bypass tract, must be managed differently. Agents such as calcium channel blockers and beta-blockers may increase the refractoriness of the AV node with minimal or no effect on the accessory pathway, often leading to faster ventricular rates and increasing the risk of ventricular fibrillation. Therefore, these agents should be avoided. Intravenous class Ia (procainamide) and class III (ibutilide) antiarrhythmic agents will increase the refractoriness of the bypass tract and are the medications of choice for wide-complex tachycardias involving accessory pathways. If hemodynamic compromise is present, electrical cardioversion is warranted.

### B. Catheter Ablation

For long-term management, catheter ablation is the procedure of choice in patients with accessory pathways and recurrent symptoms or asymptomatic patients with WPW pattern on ECG and high-risk features at baseline or during electrophysiology study. Success rates for ablation of accessory pathways with radiofrequency catheters exceed 95% in appropriate patients. Major complications from catheter ablation are rare but include AV block, cardiac tamponade, and thromboembolic events. Minor complications, including hematoma at the catheter access site, occur in 1–2% of procedures. For patients not a candidate for catheter ablation, class Ic or class III antiarrhythmic medication may be considered.

## ► When to Refer

- Asymptomatic patients with an incidental finding of WPW pattern on ECG with high-risk features.
- Symptomatic patients with recurrent or prolonged episodes despite treatment with AV nodal blocking agents.
- Patients with preexcitation and a history of atrial fibrillation or syncope.

Al-Khatib SM et al. Risk stratification for arrhythmic events in patients with asymptomatic pre-excitation: a systematic review for the 2015 ACC/AHA/HRS guideline for the management of adult patients with supraventricular tachycardia. *Circulation*. 2016;133:e575. [PMID: 26399661]

## ATRIAL FIBRILLATION



### ESSENTIALS OF DIAGNOSIS

- Presents as an irregularly irregular heart rhythm on examination and ECG.
- Prevention of stroke should be considered in all patients with risk factors for stroke (eg, heart failure, hypertension, age 65 or older, diabetes mellitus, prior history of stroke or TIA, and vascular disease).
- Heart rate control with beta-blocker or calcium channel blockers generally required. Restoration of sinus rhythm with cardioversion, antiarrhythmic medications, or catheter ablation in symptomatic patients.

## ► General Considerations

Atrial fibrillation is the most common chronic arrhythmia, with an incidence and prevalence that rise with age, so that it affects approximately 9% of individuals over age 65 years. It occurs in rheumatic and other forms of valvular heart disease, dilated cardiomyopathy, ASD, hypertension, and CHD as well as in patients with no apparent cardiac disease; it may be the initial presenting sign in thyrotoxicosis, and this condition should be excluded with the initial episode. Atrial fibrillation often appears in a **paroxysmal** fashion before becoming the established rhythm. Pericarditis, chest trauma, thoracic or cardiac surgery, thyroid disorders, obstructive sleep apnea, or pulmonary disease (pneumonia, pulmonary embolism) as well as medications (beta-adrenergic agonists, inotropes, bisphosphonates, and certain chemotherapeutics) may cause attacks in patients with normal hearts. Acute alcohol excess and alcohol withdrawal (termed **holiday heart**) may precipitate atrial fibrillation. For regular, moderate drinkers, abstinence from alcohol reduces recurrences of atrial fibrillation by about 50%.

Atrial fibrillation, particularly when the ventricular rate is uncontrolled, can lead to LV dysfunction, heart failure, or myocardial ischemia (when underlying CAD is present). Perhaps the most serious consequence of atrial fibrillation is the propensity for thrombus formation due to stasis in the atria (particularly the left atrial appendage) and consequent embolization, most devastatingly to the cerebral circulation. **Untreated, the rate of stroke is approximately 5% per year.** However, patients with significant obstructive valvular disease, chronic heart failure or LV dysfunction, diabetes mellitus, hypertension, or age over 75 years and those with a history of prior stroke or other embolic events are at substantially higher risk (up to nearly 20% per year in patients with multiple risk factors). A substantial portion of the aging population with hypertension has **asymptomatic** or "**subclinical**" atrial fibrillation, which can be detected with monitoring devices and is also associated with increased risk of stroke, particularly if it lasts for 24 hours or longer. It is not clear whether, and for whom, oral anticoagulation should be used for subclinical atrial fibrillation, a question that is being addressed in ongoing clinical trials.

## ► Clinical Findings

### A. Symptoms and Signs

Atrial fibrillation itself is rarely life-threatening; however, it can have serious consequences if the ventricular rate is sufficiently rapid to precipitate hypotension, myocardial ischemia, or tachycardia-induced myocardial dysfunction. Moreover, particularly in patients with risk factors, atrial fibrillation is a major preventable cause of stroke. Although many patients—particularly older or inactive individuals—have relatively few symptoms if the rate is controlled, some patients are aware of the irregular rhythm and may find it very uncomfortable. Most patients will complain of fatigue whether they experience other symptoms or not. The heart rate may range from quite slow to extremely rapid, but is uniformly irregular unless underlying complete heart block with junctional escape rhythm or a permanent ventricular pacemaker is in place. **Atrial fibrillation is the only common arrhythmia in which the ventricular rate is rapid and the rhythm very irregular.**

### B. ECG

The surface ECG typically demonstrates erratic, disorganized atrial activity between discrete QRS complexes occurring in an irregular pattern. The atrial activity may be very fine and difficult to detect on the ECG, or quite coarse and often mistaken for atrial flutter.

### C. Echocardiography

Echocardiography provides assessment of chamber volumes, left ventricular size and function, or the presence of concomitant valvular heart disease and should be performed in all patients with a new diagnosis of atrial fibrillation. TEE is the most sensitive imaging modality to identify thrombi in the left atrium or left atrial appendage prior to any attempt at chemical or electrical cardioversion.

## ► Treatment

### A. Newly Diagnosed Atrial Fibrillation

#### 1. Initial management—

**A. HEMODYNAMICALLY UNSTABLE PATIENT**—If the patient is hemodynamically unstable, usually as a result of a rapid ventricular rate or associated cardiac or noncardiac conditions, hospitalization and immediate treatment of atrial fibrillation are required. Intravenous beta-blockers (esmolol, propranolol, and metoprolol) or calcium channel blockers (diltiazem and verapamil) are usually effective at rate control in the acute setting. Urgent electrical cardioversion is only indicated in patients with shock or severe hypotension, pulmonary edema, or ongoing MI or ischemia. There is a potential risk of thromboembolism in patients undergoing cardioversion who have not received anticoagulation therapy if atrial fibrillation has been *present for more than 48 hours or is of unknown duration*; however, in hemodynamically unstable patients the need for immediate rate control outweighs that risk. An initial shock with 100–200 J is administered in synchrony with the R wave. If sinus rhythm is not restored, an additional attempt with 360 J is

indicated. If this fails, cardioversion may be successful after loading with intravenous ibutilide (1 mg over 10 minutes, repeated in 10 minutes if necessary).

**B. HEMODYNAMICALLY STABLE PATIENT**—If the patient has no symptoms, hemodynamic instability, or evidence of important precipitating conditions (such as silent MI or ischemia, decompensated heart failure, pulmonary embolism, or hemodynamically significant valvular disease), hospitalization is usually not necessary. In most of these cases, atrial fibrillation is an unrecognized chronic or paroxysmal condition and should be managed accordingly (see Subsequent Management, below). For new-onset atrial fibrillation, thyroid function tests and echocardiography to assess for occult valvular or myocardial disease should be performed.

**In stable patients with atrial fibrillation, a strategy of rate control and anticoagulation is appropriate.** This is true whether the conditions that precipitated atrial fibrillation are likely to persist (such as following cardiac or non-cardiac surgery, with respiratory failure, or with pericarditis) or might resolve spontaneously over a period of hours to days (such as atrial fibrillation due to excessive alcohol intake or electrolyte imbalance). The choice of agent is guided by the hemodynamic status of the patient, associated conditions, and the urgency of achieving rate control. In the stable patient with atrial fibrillation, a beta-blocker or calcium channel blocker (orally or intravenously) is usually the first-line agent for ventricular rate control. In the setting of MI or ischemia, beta-blockers are the preferred agent. The most frequently used agents are either metoprolol (administered as a 5 mg intravenous bolus, repeated twice at intervals of 5 minutes and then given as needed by repeat boluses or orally at total daily doses of 25–200 mg) or, in unstable patients, esmolol (0.5 mg/kg intravenously, repeated once if necessary, followed by a titrated infusion of 0.05–0.2 mg/kg/min). If beta-blockers are contraindicated, calcium channel blockers are rapidly effective. Diltiazem (10–20 mg bolus, repeated after 15 minutes if necessary, followed by a maintenance infusion of 5–15 mg/h) is the preferred calcium blocker if hypotension or LV dysfunction is present. Otherwise, verapamil (5–10 mg intravenously over 2–3 minutes, repeated after 30 minutes if necessary) may be used. Rate control using digoxin is slow (onset of action more than 1 hour with peak effect at 6 hours) and may be inadequate and is rarely indicated for use in the acute setting. Similarly, amiodarone, even when administered intravenously, has a relatively slow onset and is most useful as an adjunct when rate control with the previously cited agents is incomplete or contraindicated or when cardioversion is planned in the near future. Care should be taken in patients with hypotension or heart failure because the rapid intravenous administration of amiodarone may worsen hemodynamics.

Up to two-thirds of patients experiencing acute onset (shorter than 36 hours) of atrial fibrillation will spontaneously revert to sinus rhythm without the need for cardioversion. If atrial fibrillation has been present for more than a week, spontaneous conversion is unlikely and cardioversion may be considered for symptomatic patients. Importantly, if the onset of atrial fibrillation was more than 48 hours prior to presentation (or unknown), a transesophageal

**echocardiogram should be performed prior to cardioversion to exclude left atrial thrombus.** If thrombus is present, the cardioversion is delayed until after a 4-week period of therapeutic anticoagulation. In either case, because atrial contractile activity may not recover for several weeks after restoration of sinus rhythm in patients who have been in atrial fibrillation for more than 48 hours, cardioversion should be followed by anticoagulation *for at least 1 month* unless there is a strong contraindication. Younger patients without heart failure, diabetes, hypertension, or other risk factors for stroke may not require long-term anticoagulation.

**2. Subsequent management**—If immediate cardioversion is not performed, adequate rate control can usually be achieved with beta-blockers or nondihydropyridine calcium channel blockers. Choice of the initial rate control medication is best based on the presence of accompanying conditions: Hypertensive patients can be given beta-blockers or calcium blockers (see Tables 11–9 and 11–7). Patients with CHD or heart failure should receive a beta-blocker preferentially, whereas beta-blockers should be avoided in patients with severe chronic obstructive pulmonary disease (COPD) or asthma. Long-term use of digoxin is associated with an *increase* in mortality in patients with chronic atrial fibrillation and is rarely indicated. In symptomatic patients, a resting heart rate of less than 80 beats/min is targeted. In asymptomatic patients without LV dysfunction, a more lenient resting heart rate of up to 100–110 beats/min is reasonable. Ambulatory monitoring to assess heart rate during exercise should be considered in all patients with a goal not to exceed maximum predicted heart rate (220 – age).

**A. ANTICOAGULATION**—For patients with atrial fibrillation, even when it is paroxysmal or occurs rarely, the need for oral anticoagulation should be evaluated and treatment initiated for those without strong contraindication. Patients with **lone atrial fibrillation** (eg, no evidence of associated heart disease, hypertension, atherosclerotic vascular disease, diabetes mellitus, or history of stroke or TIA) under age 65 years need no antithrombotic treatment. Patients with **transient atrial fibrillation**, such as in the setting of acute MI or pneumonia, but no prior history of arrhythmia, are at high risk for future development of atrial fibrillation and appropriate anticoagulation should be initiated based on risk factors. If the cause is reversible, such as after coronary artery bypass surgery or associated with hyperthyroidism, then long-term anticoagulation is not necessary.

In addition to the traditional five risk factors that comprise the **CHADS<sub>2</sub> score** (heart failure, hypertension, age 75 years or older, diabetes mellitus, and [2 points for] history of stroke or TIA), the European and American guidelines recommend that three additional factors included in the **CHA<sub>2</sub>DS<sub>2</sub>-VASc score** be considered: age 65–74 years, female sex, and presence of vascular disease (Table 10–10). The CHA<sub>2</sub>DS<sub>2</sub>-VASc score is especially relevant for patients who have a CHADS<sub>2</sub> score of 0 or 1; if the CHA<sub>2</sub>DS<sub>2</sub>-VASc score is greater than or equal to 2, oral anticoagulation is recommended, and if CHA<sub>2</sub>DS<sub>2</sub>-VASc score is 1, oral anticoagulation should be considered, taking into account risk, benefit, and patient preferences. Female sex is a relatively

**Table 10–10.** CHA<sub>2</sub>DS<sub>2</sub>-VASc Risk Score for assessing risk of stroke and for selecting antithrombotic therapy for patients with atrial fibrillation.

| CHA <sub>2</sub> DS <sub>2</sub> -VASc Risk Score  |                     |                               |
|--|---------------------|-------------------------------|
| Heart failure or LVEF ≤ 40%  | 1                   |                               |
| Hypertension   | 1                   |                               |
| Age ≥ 75 years   | 2                   |                               |
| Diabetes mellitus  | 1                   |                               |
| Stroke, transient ischemic attack, or thromboembolism  | 2                   |                               |
| Vascular disease (previous myocardial infarction, peripheral artery disease, or aortic plaque)   | 1                   |                               |
| Age 65–74 years  | 1                   |                               |
| Female sex (but not a risk factor if female sex is the only factor)  | 1                   |                               |
| Maximum score  | 9                   |                               |
| Adjusted stroke rate according to CHA <sub>2</sub> DS <sub>2</sub> -VASc score   |                     |                               |
| CHA <sub>2</sub> DS <sub>2</sub> -VASc Score   | Patients (n = 7329) | Adjusted stroke rate (%/year) |
| 0  | 1                   | 0%                            |
| 1  | 422                 | 1.3%                          |
| 2  | 1230                | 2.2%                          |
| 3  | 1730                | 3.2%                          |
| 4  | 1718                | 4.0%                          |
| 5  | 1159                | 6.7%                          |
| 6  | 679                 | 9.8%                          |
| 7  | 294                 | 9.6%                          |
| 8  | 82                  | 6.7 %                         |
| 9  | 14                  | 15.2%                         |
| CHA <sub>2</sub> DS <sub>2</sub> -VASc score = 0: recommend no antithrombotic therapy  |                     |                               |
| CHA <sub>2</sub> DS <sub>2</sub> -VASc score = 1: recommend antithrombotic therapy with oral anticoagulation or antiplatelet therapy but preferably oral anticoagulation |                     |                               |
| CHA <sub>2</sub> DS <sub>2</sub> -VASc score = 2: recommend oral anticoagulation   |                     |                               |

CHA<sub>2</sub>DS<sub>2</sub>-VASc, Cardiac failure, Hypertension, Age ≥ 75 years (doubled), Diabetes, Stroke (doubled), Vascular disease, Age 65–74, and Sex category (female); LVEF, left ventricular ejection fraction.

Data from Camm AJ et al. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation. Developed with the special contribution of the European Heart Rhythm Association. Eur Heart J. 2012 Nov;33(21):2719–47.

weak factor, however, and the European guidelines have removed it from their risk assessment, so that oral anticoagulation is indicated for men who are CHA<sub>2</sub>DS<sub>2</sub>-VASc of 2 and women who are CHA<sub>2</sub>DS<sub>2</sub>-VASc of 3. (The use of warfarin is discussed in the section on Selecting Appropriate Anticoagulant Therapy in Chapter 14.) Unfortunately,

studies show that *only about half* of patients with atrial fibrillation and an indication for oral anticoagulation are receiving it, and even when treated with warfarin, they are out of the target INR range nearly half the time. *One reason for undertreatment is the misperception that aspirin is useful for prevention of stroke due to atrial fibrillation.* In the European guidelines, aspirin is given a class III A recommendation, indicating that it should *not* be used because of harm (and with no good evidence of benefit). Cardioversion, if planned, should be performed after at least 3–4 weeks of anticoagulation at a therapeutic level (or after exclusion of left atrial appendage thrombus by transesophageal echocardiogram as discussed above). **Anticoagulation clinics** with systematic management of warfarin dosing and adjustment have been shown to result in better maintenance of target anticoagulation.

Four DOACs—dabigatran, rivaroxaban, apixaban, and edoxaban—have been shown to be at least as effective as warfarin for stroke prevention in patients with atrial fibrillation and have been approved by the FDA for this indication (Table 10–11). These medications have *not* been studied in patients with moderate or severe mitral stenosis, and they should *not* be used for patients with mechanical prosthetic valves. The term “nonvalvular atrial fibrillation” is no longer used in the American or European guidelines since most patients with other types of valvular heart disease have been included in trials of DOACs, which are equally effective in these patients.

**Dabigatran** (studied in the RE-LY trial) is superior to warfarin at preventing stroke at the 150 mg twice daily dose, and it is noninferior at the 110 mg twice daily dose, although this dose is not approved for treatment of atrial fibrillation in the United States. Both doses result in *less* intracranial hemorrhage than warfarin but also in *more* gastrointestinal bleeding than warfarin. Neither dabigatran nor any of the DOACs should be used in patients with mechanical prosthetic heart valves where the medications are less effective and riskier.

**Rivaroxaban** is noninferior to warfarin for stroke prevention in atrial fibrillation (in the ROCKET-AF trial). Rivaroxaban is dosed at 20 mg once daily, with a reduced dose (15 mg/day) for patients with creatinine clearances between 15 and 50 mL/min. It should be administered *with food*, since that results in a 40% higher drug absorption. Similar to dabigatran, there is substantially less intracranial hemorrhage with rivaroxaban than warfarin.

**Apixaban** is more effective than warfarin at stroke prevention while having a substantially lower risk of major bleeding (in the ARISTOTLE trial) and a lower risk of all-cause mortality. The apixaban dosage is 5 mg twice daily or 2.5 mg twice daily for patients with two of three high-risk criteria (age 80 years or older, body weight 60 kg or less, and serum creatinine of 1.5 mg/dL or more). Apixaban is associated with less intracranial hemorrhage and is well tolerated. Apixaban was also shown to be superior to aspirin (and better tolerated, with comparable rates of bleeding) in the AVERROES trial of patients deemed not suitable for warfarin. Apixaban has been studied in a small trial of patients receiving hemodialysis, in which the plasma concentrations were in an acceptable range using standard dosing criteria.

**Edoxaban**, 60 mg once a day, is noninferior to warfarin for stroke prevention with lower rates of major bleeding and lower rates of hemorrhagic stroke (studied in the ENGAGE-AF trial). Edoxaban carries a boxed warning in FDA labelling that it should *not* be used in patients whose creatinine clearance is more than 95 mL/min because it is less effective in this population. The dose is decreased to 30 mg/day for patients whose creatinine clearance is less than or equal to 50 mL/min.

**These four DOACs have important advantages over warfarin, and therefore, they are recommended preferentially over VKAs.** In practice, these medications are often underdosed. They should be used at the doses shown to be effective in the clinical trials as shown in Table 10–11. Even though labeled for “nonvalvular” atrial fibrillation, the DOACs are safe and effective for patients with moderate or

**Table 10–11.** Direct-acting oral anticoagulants for stroke prevention in patients with nonvalvular atrial fibrillation.

| Class                              | Dabigatran  | Rivaroxaban   | Apixaban   | Edoxaban  |
|------------------------------------|---|---|--|---|
| Class                              | Antithrombin  | Factor Xa inhibitor   | Factor Xa inhibitor  | Factor Xa inhibitor   |
| Bleeding risk compared to warfarin | Less intracranial bleeding<br>Higher incidence of gastrointestinal bleeding   | Less intracranial bleeding<br>Higher incidence of gastrointestinal bleeding | Substantially lower risk of major bleeding<br>Less intracranial bleeding   | Lower risk of major bleeding<br>Less intracranial bleeding  |
| Dosage                             | 110 mg twice daily<br>150 mg twice daily  | 20 mg once daily (give with food)   | 5 mg twice daily   | 60 mg once daily  |
| Dosage adjustments                 | 75 mg twice daily for creatinine clearance <sup>1</sup><br>15–30 mL/min (approved in the United States but not tested in clinical trials) | 15 mg once daily for creatinine clearance <sup>1</sup><br>< 50 mL/min       | 2.5 mg twice daily for patients with at least two of three risk factors:<br>1. Age ≥ 80 years<br>2. Body weight ≤ 60 kg<br>3. Serum creatinine ≥ 1.5 mg/dL | 30 mg once daily for creatinine clearance <sup>1</sup><br>≤ 50 mL/min<br>FDA recommends not to use if creatinine clearance <sup>1</sup> > 95 mL/min |

<sup>1</sup>Creatinine clearance calculated by Cockcroft-Gault equation.

Data from Nishimura RA et al. 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014 Jun 10;129(23):e521–643.

severe valvular abnormalities, with the exception of moderate or severe mitral stenosis. In part because of lower rates of intracerebral hemorrhage, DOACs have particular advantage over warfarin in the elderly and the frail, including patients with history of falls. For patients who fall, oral anticoagulation should generally be used, except for patients who are suffering head trauma with falls.

There are some patients with atrial fibrillation, however, who should be treated with VKAs. These patients include those who have mechanical prosthetic valves, advanced kidney disease (creatinine clearance less than 25 mL/min), or moderate or severe mitral stenosis, and those who cannot afford the newer medications. Apixaban may be a reasonable option for patients with creatinine clearance less than 25 mL/min, with one small randomized trial of patients receiving hemodialysis suggesting that it may be reasonable. Patients who have been stable while receiving warfarin for a long time, with a high time in target INR range, and who are at lower risk for intracranial hemorrhage will have relatively less benefit with a switch to a newer medication. It is important to note, however, that most patients who have intracranial hemorrhage while taking warfarin have had a recent INR below 3.0, so that good INR control does not ensure avoidance of intracranial bleeding. One way to reduce bleeding for patients taking oral anticoagulants is to avoid concurrent aspirin, unless the patient has a clear indication, like recent MI or coronary stent. Even then, use of oral anticoagulant plus clopidogrel without aspirin, or with only a brief period of “triple” therapy and then discontinuation of aspirin, may be a reasonable approach, as has been shown in clinical trials comparing rivaroxaban and dabigatran with warfarin.

There are some important practical issues with using the DOACs. It is important to monitor kidney function at baseline and at least once a year, or more often for those with impaired kidney function. Each of the medications interacts with other medications affecting the P-glycoprotein pathway, like oral ketoconazole, verapamil, dronedarone, and phenytoin. To transition patients from warfarin to a DOAC, wait until the INR decreases to about 2.0. Each of the medications has a half-life of about 10–12 hours for patients with normal kidney function. For elective procedures, stop the medications two to three half-lives (usually 24–48 hours) before procedures with low to moderate bleeding risk (ie, colonoscopy, dental extraction, cardiac catheterization), and five half-lives before procedures like major surgery. Discontinuation times should be extended in patients with impaired renal function, particularly with dabigatran. There are no practical tests to immediately measure the effect of the medications, although a normal aPTT suggests little effect with dabigatran, and a normal prothrombin suggests little effect with rivaroxaban. For rivaroxaban and apixaban, chromogenic Xa assays will measure the effect, but may not be readily available. For bleeding, standard measures (eg, diagnosing and controlling the source, stopping antithrombotic agents, and replacing blood products) should be taken. If the direct-acting medication was taken in the prior 2–4 hours, use activated oral charcoal to reduce absorption. If the patient is taking aspirin, consider platelet

transfusion. Antidotes should be considered for life-threatening bleeding or for patients with need for immediate surgery, or both. For cardioversion, the DOACs appear to have similar rates of subsequent stroke as warfarin, as long as patients have been taking the medications and adherent for at least several weeks. Like with warfarin, there appears to be a 1.5- to 2-fold increased rate of bleeding associated with the use of aspirin in combination with the DOACs. Even patients with atrial fibrillation and stable coronary disease taking a DOAC at least 1 year from most recent coronary stent or coronary bypass surgery appear to have substantially greater risk than benefit from the use of aspirin. Therefore, **aspirin should not be used with the DOACs unless there is a clear indication, such as coronary stents or acute coronary syndrome within the prior year.**

A patient with severe bleeding while taking dabigatran may be treated with the reversal agent **idarucizumab**, which is a humanized monoclonal antibody approved by the FDA for rapid reversal of the anticoagulation effects, for use in the event of severe bleeding or the need for an urgent procedure. This treatment is widely available in the United States. **Andexanet alfa**, an intravenous factor Xa decoy, is approved for reversal of factor Xa inhibitors. Four-factor prothrombin complex concentrate may partially reverse the effects of these agents. Due to the short half-life of the DOACs (10–12 hours with normal kidney function), supportive measures (local control, packed red blood cells, platelets) may suffice until the medication has cleared.

Each of the DOACs appears to be safe and effective around the time of electrical cardioversion. In each of these trials, and in one modest-sized prospective randomized trial of rivaroxaban that specifically addressed cardioversion, the rates of stroke were low (and similar to warfarin) with the DOACs when given for at least 3–4 weeks prior to cardioversion. An advantage of the DOACs is that when stable anticoagulation is desired before elective cardioversion, it is achieved faster than with warfarin.

Devices to exclude the left atrial appendage have been shown to protect against stroke, although they are not as effective as warfarin to prevent ischemic stroke; the most commonly used approved devices are the Watchman (United States and Europe) and Amulet (Europe), which are options for patients who are unsuitable for long-term anticoagulation.

**B. RATE CONTROL OR RHYTHM CONTROL**—After assessing stroke risk and initiating anticoagulation where appropriate, two main treatment strategies for long-term management of atrial fibrillation exist: rate control or rhythm control, although they are not mutually exclusive. Rate control should be considered background treatment in nearly all patients with atrial fibrillation, regardless of whether rhythm restoration is eventually pursued, and may be considered the primary treatment in patients with minimal to no symptoms related to long-standing atrial fibrillation. In patients with recent-onset atrial fibrillation (less than 1 year), the EAST-AFNET 4 trial found that rhythm control with antiarrhythmic medication or catheter ablation

is associated with a lower risk of death from cardiovascular causes, stroke, or hospitalization for heart failure.

The decision to pursue rhythm control is often individualized, based on symptoms, the type of atrial fibrillation (paroxysmal or persistent), comorbidities (such as heart failure), as well as general health status. As first treatment, elective cardioversion following an appropriate period of anticoagulation (minimum of 3 weeks) is generally recommended in patients in whom atrial fibrillation is thought to be of recent onset or when there is an identifiable precipitating factor. Similarly, cardioversion is appropriate in patients who remain symptomatic from the rhythm despite efforts to achieve rate control.

In cases in which elective cardioversion is required, it may be accomplished pharmacologically or electrically. Pharmacologic cardioversion with intravenous **ibutilide** (1 mg over 10 minutes, repeated in 10 minutes if necessary) or **procainamide** (15 mg/kg over 30 minutes) may be used in a setting in which the patient can undergo continuous ECG monitoring for at least 4–6 hours following administration. Pretreatment with intravenous magnesium (1–2 g) may prevent rare episodes of torsades de pointes associated with ibutilide administration. In patients in whom a decision has been made to continue antiarrhythmic therapy to maintain sinus rhythm (see next paragraph), cardioversion can be attempted with an agent that is being considered for long-term use. For instance, after therapeutic anticoagulation has been established, **amiodarone** can be initiated on an outpatient basis (400 mg twice daily for 2 weeks, followed by 200 mg twice daily for at least 2–4 weeks and then a maintenance dose of 200 mg daily). Because amiodarone increases the prothrombin time in patients taking warfarin and increases digoxin levels, careful monitoring of anticoagulation and medication levels is required.

Other antiarrhythmic medications that can be used for long-term maintenance therapy include propafenone, flecainide, dronedarone, dofetilide, and sotalol. **Dofetilide** (125–500 mcg twice daily orally) must be initiated in hospital due to the potential risk of torsades de pointes and the downward dose adjustment that is required for patients with renal impairment. **Propafenone** (150–300 mg orally every 8 hours) and flecainide (50–150 mg orally twice daily) should be avoided in patients with structural heart disease (CAD, systolic dysfunction, or significant LVH) and should be used in conjunction with an AV nodal blocking medication, especially if there is a history of atrial flutter. **Sotalol** (80–160 mg orally twice daily) should be initiated in the hospital in patients with structural heart disease due to a risk of torsades de pointes; it is not very effective for converting atrial fibrillation but can be used to maintain sinus rhythm following cardioversion. Dronedarone should not be used in patients with recent decompensated heart failure or when atrial fibrillation has become persistent.

In patients treated long-term with an antiarrhythmic agent, sinus rhythm will persist in 30–50%. Given this high rate of arrhythmia recurrence, the decision to maintain long-term anticoagulation should be based on risk factors ( $\text{CHA}_2\text{DS}_2\text{-VASC}$  score, Table 10–10) and not on the perceived presence or absence of atrial fibrillation, since future episodes may be asymptomatic.

## B. Recurrent and Refractory Atrial Fibrillation

**1. Recurrent paroxysmal atrial fibrillation**—For select patients with symptomatic but rare (a few times a year) episodes of atrial fibrillation, an effective treatment strategy is on-demand pharmacologic cardioversion, termed **pill-in-the-pocket treatment**. Patients without coronary or structural heart disease may be given flecainide (200–300 mg) or propafenone (450–600 mg) in addition to a beta-blocker or nondihydropyridine calcium channel blocker as a single dose at the onset of symptoms. It is recommended that the first such treatment take place in a monitored setting (eg, the emergency department or hospital) to evaluate safety and effectiveness. For more frequent, symptomatic arrhythmic episodes, daily antiarrhythmic agents are first-line therapy; however, they are not often successful in preventing all paroxysmal atrial fibrillation episodes and long-term tolerability is poor.

**2. Refractory atrial fibrillation**—Atrial fibrillation should generally be considered refractory if it causes persistent symptoms or limits activity despite attempts at rate or rhythm control. If antiarrhythmic or rate control medications fail to improve symptoms, catheter ablation of foci in and around the pulmonary veins that initiate and maintain atrial fibrillation (pulmonary vein isolation) may be considered. It is a reasonable therapy for individuals with symptomatic paroxysmal or persistent atrial fibrillation that is refractory to pharmacologic therapy and for select patients (younger than 65 years or with concurrent heart failure) as first-line therapy. The primary benefit of catheter ablation is an improvement in quality of life. In the CABANA trial, there was no difference in the primary endpoint of death, disabling stroke, serious bleeding, or cardiac arrest in patients randomized to catheter ablation versus medical therapy as first treatment for symptomatic atrial fibrillation. Ablation is successful about 50–70% of the time but repeat ablation may be required in up to 20% of patients. The procedure is routinely performed in the electrophysiology laboratory using a catheter-based approach and adverse event rates are low when performed by experienced operators. Surgical ablation can also be performed via a subxiphoid approach thoroscopically, via thoracotomy, or via median sternotomy in the operating room as a stand-alone or adjunct procedure. Finally, in symptomatic patients with poor rate control and deemed inappropriate for pulmonary vein isolation, radiofrequency ablation of the AV node and permanent pacing ensure rate control and may facilitate a more physiologic rate response to activity, but this is used only as a last resort.

### ► When to Refer

- Symptomatic atrial fibrillation with or without adequate rate control.
- Asymptomatic atrial fibrillation with poor rate control despite AV nodal blockers.
- Patients at risk for stroke who have not tolerated oral anticoagulants.

- Kirchhof P et al; EAST-AFNET 4 Trial Investigators. Early rhythm-control therapy in patients with atrial fibrillation. *N Engl J Med.* 2020;383:1305. [PMID: 32865375]
- Packer DL et al. Effect of catheter ablation vs antiarrhythmic drug therapy on mortality, stroke, bleeding, and cardiac arrest among patients with atrial fibrillation: the CABANA randomized clinical trial. *JAMA.* 2019;321:1261. [PMID: 30874766]
- Yasuda S et al; AFIRE Investigators. Antithrombotic therapy for atrial fibrillation with stable coronary disease. *N Engl J Med.* 2019;381:1103. [PMID: 31475793]

## ATRIAL FLUTTER



### ESSENTIALS OF DIAGNOSIS

- ▶ Rapid, regular tachycardia presenting classically with 2 to 1 block in the AV node and ventricular heart rate of 150 beats/min. ECG shows “sawtooth” pattern of atrial activity (rate 300 beats/min).
- ▶ Stroke risk should be considered equivalent to that with atrial fibrillation.
- ▶ Catheter ablation is highly successful and is considered the definitive treatment for typical atrial flutter.

### ► General Considerations

Atrial flutter is less common than fibrillation. It may occur in patients with structurally normal hearts but is more commonly seen in patients with COPD, valvular or structural heart disease, ASD, or surgically repaired congenital heart disease.

### ► Clinical Findings

Patients typically present with complaints of palpitations, fatigue, or mild dizziness. In situations where the arrhythmia is unrecognized for a prolonged period of time, patients may present with symptoms and signs of heart failure (dyspnea, exertional intolerance, edema) due to tachycardia-induced cardiomyopathy. The ECG typically demonstrates a “sawtooth” pattern of atrial activity in the inferior leads (II, III, and AVF). The reentrant circuit generates atrial rates of 250–350 beats/min, usually with transmission of every second, third, or fourth impulse through the AV node to the ventricles.

### ► Treatment

Ventricular rate control is accomplished using the same agents used in atrial fibrillation, but it is generally more difficult. Conversion of atrial flutter to sinus rhythm with class I antiarrhythmic agents is also difficult to achieve, and administration of these medications has been associated with slowing of the atrial flutter rate to the point at which 1:1 AV conduction can occur at rates in excess of 200 beats/min, with subsequent hemodynamic collapse. The intravenous class III antiarrhythmic agent ibutilide has been significantly more successful in converting atrial flutter (see

Table 10–9). About 50–70% of patients return to sinus rhythm within 60–90 minutes following the infusion of 1–2 mg of this agent. Electrical cardioversion is also very effective for atrial flutter, with approximately 90% of patients converting following synchronized shocks of as little as 25–50 J.

Although the organization of atrial contractile function in this arrhythmia may provide some protection against thrombus formation, **the risk of thromboembolism should be considered equivalent to that with atrial fibrillation** due to the common coexistence of these arrhythmias. Precadioversion anticoagulation is not necessary for atrial flutter of less than 48 hours duration except in the setting of mitral valve disease. As with atrial fibrillation, anticoagulation should be continued for at least 4 weeks after electrical or chemical cardioversion and chronically in patients with risk factors for thromboembolism.

Catheter ablation is the treatment of choice for long-term management of atrial flutter owing to the high success rate and safety of the procedure. The anatomy of the typical circuit is well defined and catheter ablation within the right atrium results in immediate and permanent elimination of atrial flutter in more than 90% of patients. Due to the frequent coexistence of atrial flutter with atrial fibrillation, however, some patients may require catheter ablation of both arrhythmias. If pharmacologic therapy is chosen, class III antiarrhythmics (amiodarone or dofetilide) are generally preferred (see Table 10–9).

### ► When to Refer

All patients with atrial flutter should be referred to a cardiologist or cardiac electrophysiologist for consideration of definitive treatment with catheter ablation.

## ATRIAL TACHYCARDIA



### ESSENTIALS OF DIAGNOSIS

- ▶ Characterized by bursts of rapid, regular tachycardia.
- ▶ Multifocal atrial tachycardia commonly seen with severe COPD and presents with three or more distinct P wave morphologies on ECG, often confused for atrial fibrillation. Treatment of the underlying lung disease is most effective therapy.

### ► General Considerations

**Atrial tachycardia** is an uncommon form of SVT characterized by paroxysms or bursts of rapid, regular arrhythmia due to focal atrial impulses originating outside of the normal sinus node. Common sites include the tricuspid annulus, the crista terminalis of the right atrium and the coronary sinus. **Multifocal atrial tachycardia** is a particular subtype seen in patients with severe COPD and characterized by varying P wave morphology (by definition, three or more foci) and markedly irregular PP intervals. The rate is usually between 100 beats/min and 140 beats/min, and it is often confused

for atrial fibrillation. **Solitary atrial premature beats** are benign and generally not associated with underlying cardiac disease. They occur when an ectopic focus in the atria fires before the next sinus node impulse. The contour of the P wave usually differs from the patient's normal complex, unless the ectopic focus is near the sinus node. Acceleration of the heart rate by any means usually abolishes most premature beats.

## ► Clinical Findings

Focal atrial tachycardias are usually intermittent and self-limiting although incessant forms do exist and may present with signs and symptoms of heart failure due to tachycardia-induced cardiomyopathy. Most patients report palpitations with an abrupt onset, similar to other forms of PSVT. Patients with underlying cardiac pathology (eg, CHD) can present with dyspnea or angina. Close inspection of the P wave on 12-lead ECG suggests a focus away from the sinus node, although certain locations (eg, high right atrial crista terminalis) may mimic sinus tachycardia. In this situation, the abrupt onset and offset of the arrhythmia is helpful in distinguishing atrial from sinus tachycardia, although electrophysiologic study is sometimes necessary.

## ► Treatment

Initial management of atrial tachycardia is similar to other types of PSVT; however, vagal maneuvers and intravenous adenosine are generally less effective. Intravenous beta-blockers or calcium channel blockers can be given in the hemodynamically stable patient with a transition to oral formulations for long-term management. Antiarrhythmic medications or catheter ablation should be considered in patients who continue to have symptomatic episodes. Long-term anticoagulation is not indicated in the absence of coexistent atrial fibrillation or atrial flutter.

For patients with multifocal atrial tachycardia, treatment of the underlying condition (eg, COPD) is paramount; verapamil, 240–480 mg orally daily in divided doses, may be effective in some patients.

## ► When to Refer

All patients with atrial tachycardia in whom initial medical management fails should be referred to a cardiologist or cardiac electrophysiologist.

## VENTRICULAR PREMATURE BEATS (Ventricular Extrasystoles)



### ESSENTIALS OF DIAGNOSIS

- Common but rarely symptomatic.
- Ambulatory ECG monitoring to quantify daily burden of PVCs. Asymptomatic patients with > 10% PVC burden should have periodic echocardiogram to exclude development of LV dysfunction.

## ► General Considerations

Ventricular premature beats, or **PVCs**, are isolated beats typically originating from the outflow tract or His-Purkinje regions of ventricular tissue. In most patients, the presence of PVCs is a benign finding; however, they rarely may trigger ventricular tachycardia or ventricular fibrillation, especially in patients with underlying heart disease.

## ► Clinical Findings

The patient may or may not sense the irregular beat, usually as a skipped beat. Exercise generally abolishes premature beats in normal hearts, and the rhythm becomes regular. PVCs are characterized by wide QRS complexes that differ in morphology from the patient's normal beats. They are usually not preceded by a P wave, although retrograde ventriculoatrial conduction may occur. **Bigeminy** and **trigeminy** are arrhythmias in which every second or third beat is premature; these patterns confirm a reentry mechanism for the ectopic beat. Ambulatory ECG monitoring may reveal more frequent and complex PVCs than occur in a single routine ECG. An increased frequency of PVCs during exercise is associated with a higher risk of cardiovascular mortality and should be investigated further.

## ► Treatment

If no associated cardiac disease is present and if the ectopic beats are asymptomatic, no therapy is indicated. Mild symptoms or anxiety from palpitations may be allayed with reassurance to the patient of the benign nature of this arrhythmia. If PVCs are frequent (bigeminal or trigeminal pattern), electrolyte abnormalities (especially hypokalemia or hyperkalemia and hypomagnesemia), hyperthyroidism, and occult heart disease should be excluded. In addition, an echocardiogram should be performed in patients in whom a burden of PVCs of greater than 10,000 per day has been documented by ambulatory ECG monitoring. Pharmacologic treatment is indicated only for patients who are symptomatic or who develop cardiomyopathy thought to be due to a high burden of PVCs (generally greater than 10% of daily heart beats). Beta-blockers or nondihydropyridine calcium channel blockers are appropriate as first-line therapy. The class I and III antiarrhythmic agents (see Table 10–9) may be effective in reducing PVCs but are often poorly tolerated and can be proarrhythmic in up to 5% of patients. Catheter ablation is a well-established therapy for symptomatic individuals who do not respond to medication or for those patients whose burden of ectopic beats has resulted in a cardiomyopathy.

## ► When to Refer

Patients with symptomatic PVCs who do not respond to initial medical management or asymptomatic patients with daily PVC burden greater than 10% on ambulatory ECG monitoring should be referred to a cardiologist or cardiac electrophysiologist.

## VENTRICULAR TACHYCARDIA



### ESSENTIALS OF DIAGNOSIS

- ▶ Fast, wide QRS complex on ECG.
- ▶ Associated with ischemic heart disease, particularly in older patients.
- ▶ In the absence of reversible cause, implantable cardioverter defibrillator (ICD) is recommended if meaningful life expectancy is > 1 year.

### ► General Considerations

Ventricular tachycardia is defined as three or more consecutive ventricular premature beats. It is classified as either **nonsustained** (lasting less than 30 seconds and terminating spontaneously) or **sustained** with a heart rate greater than 100 beats/min. In individuals without heart disease, nonsustained ventricular tachycardia is generally associated with a benign prognosis. In patients with structural heart disease, nonsustained ventricular tachycardia is associated with an increased risk of subsequent symptomatic ventricular tachycardia and sudden death, especially when seen more than 48 hours after MI.

Ventricular tachycardia is a frequent complication of acute MI and dilated cardiomyopathy but may occur in chronic coronary disease, HCM, myocarditis, and in most other forms of myocardial disease. It can also be a consequence of atypical forms of cardiomyopathies, such as arrhythmogenic RV cardiomyopathy. However, idiopathic ventricular tachycardia can also occur in patients with structurally normal hearts. **Accelerated idioventricular rhythm** is a regular wide complex rhythm with a rate of 60–120 beats/min, usually with a gradual onset. It occurs commonly in acute infarction and following reperfusion with thrombolytic medications. Treatment is not indicated unless there is hemodynamic compromise or more serious arrhythmias.

**Torsades de pointes**, a form of ventricular tachycardia in which QRS morphology twists around the baseline, may occur in the setting of severe hypokalemia, hypomagnesemia, or after administration of a medication that prolongs the QT interval. In nonacute settings, most patients with ventricular tachycardia have known or easily detectable cardiac disease, and the finding of ventricular tachycardia is an unfavorable prognostic sign.

### ► Clinical Findings

#### A. Symptoms and Signs

Patients commonly experience palpitations, dyspnea, or lightheadedness, but on rare occasion may be asymptomatic. Syncope or cardiac arrest can be presenting symptoms in patients with underlying cardiac disease or other severe comorbidities. Episodes may be triggered by exercise or emotional stress.

### B. Diagnostic Studies

Comprehensive blood laboratory work should be performed because ventricular tachycardia can occur in the setting of hypokalemia and hypomagnesemia. Cardiac markers may be elevated when ventricular tachycardia presents in the setting of acute MI or as a consequence of underlying CAD and demand ischemia. In patients with sustained, hemodynamically tolerated ventricular tachycardia, a 12-lead ECG during tachycardia should be obtained. Cardiac evaluation with echocardiography or cardiac MRI, ambulatory ECG monitoring, and exercise testing may be warranted depending on the clinical situation. In survivors of cardiac arrest or those with life-threatening ventricular arrhythmia, invasive coronary angiography is recommended to establish or exclude the presence of significant CAD.

There is generally no role for invasive electrophysiologic study in patients with sustained ventricular tachycardia who otherwise meet criteria for ICD. In patients with structural heart disease and syncope of unknown cause, or in situations in which the mechanism of wide-complex tachycardia is uncertain, electrophysiologic study may provide important information.

### C. Differentiation of Aberrantly Conducted Supraventricular Beats From Ventricular Beats

The distinction on 12-lead ECG of ventricular tachycardia from SVT with aberrant conduction may be difficult in patients with a wide-complex tachycardia; it is important because of the differing prognostic and therapeutic implications of each type. Findings favoring a **ventricular origin** include: (1) AV dissociation; (2) a QRS duration exceeding 0.14 second; (3) capture or fusion beats (infrequent); (4) left axis deviation with right bundle branch block morphology; (5) monophasic (R) or biphasic (qR, QR, or RS) complexes in V<sub>1</sub>; and (6) a qR or QS complex in V<sub>6</sub>. **Supraventricular origin** is favored by: (1) a triphasic QRS complex, especially if there was initial negativity in leads I and V<sub>6</sub>; (2) ventricular rates exceeding 170 beats/min; (3) QRS duration longer than 0.12 second but not longer than 0.14 second; and (4) the presence of preexcitation syndrome. Patients with a wide-complex tachycardia, especially those with known cardiac disease, should be presumed to have ventricular tachycardia if the diagnosis is unclear.

### ► Treatment

#### A. Initial Management

The treatment of acute ventricular tachycardia is determined by the degree of hemodynamic compromise and the duration of the arrhythmia. In patients with structurally normal hearts, the prognosis is generally benign and syncope is uncommon. The etiology is often triggered activity from the right or left ventricular outflow tract and immediate treatment with a short-acting intravenous beta-blocker or verapamil may terminate the episode.

In the presence of known or suspected structural heart disease, assessment of hemodynamic stability determines the need for urgent direct current cardioversion. When

ventricular tachycardia causes hypotension, heart failure, or myocardial ischemia, immediate synchronized direct current cardioversion with 100–360 J should be performed. If ventricular tachycardia recurs, intravenous amiodarone (150-mg bolus followed by 1 mg/min infusion for 6 hours and then 0.5 mg/min for 18 hours) should be administered to achieve a stable rhythm with further attempts at cardioversion as necessary. Significant hypotension can occur with rapid infusions of amiodarone. The management of ventricular tachycardia in the setting of acute MI is discussed in the Complications section of Acute Myocardial Infarction with ST-Segment Elevation.

In patients with sustained ventricular tachycardia who are hemodynamically stable, medical treatment with intravenous amiodarone, lidocaine, or procainamide can be used; however, direct current cardioversion should be performed if the ventricular tachycardia fails to terminate or symptoms worsen. Empiric magnesium replacement (1–2 g intravenously) may help, especially for polymorphic ventricular tachycardia. If polymorphic ventricular tachycardia recurs, increasing the heart rate with isoproterenol infusion (up to 20 mcg/min) or atrial pacing with a temporary pacemaker (at 90–120 beats/min) will effectively shorten the QT interval to prevent further episodes.

## B. Long-Term Management

Patients with symptomatic or sustained ventricular tachycardia in the absence of a reversible precipitating cause (acute MI or ischemia, electrolyte imbalance, medication toxicity, etc) are at high risk for recurrence. In patients with structurally normal hearts and ventricular tachycardia with typical outflow tract (left bundle branch block with inferior axis) or left posterior fascicle (right bundle branch block with superior axis) appearance on ECG, suppressive treatment with beta-blocker or a nondihydropyridine calcium channel blocker may be tried. Catheter ablation has a high success rate in these patients who fail initial medical treatment. In patients with significant LV dysfunction, subsequent sudden death is common and ICD implantation is recommended if meaningful survival is expected to be longer than 1 year. Beta-blockers are the mainstay for medical treatment of ventricular tachycardia in patients with structural heart disease. Antiarrhythmic medications have not been shown to lower mortality in these patients, but may decrease subsequent episodes and reduce the number of ICD shocks. Amiodarone is generally preferred in patients with structural heart disease but sotalol may be considered as well. Catheter ablation is an important treatment option for those patients with recurrent tachycardia who do not respond to or are intolerant of medical therapy; however, recurrence rates are high.

## ► When to Refer

Any patient with sustained ventricular tachycardia or syncope of unknown cause in the presence of underlying structural cardiac disease.

Al-Khatib SM et al. 2017 AHA/ACC/HRS guideline for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol.* 2018;72:e91. [PMID: 29097296]

## VENTRICULAR FIBRILLATION & SUDDEN DEATH



### ESSENTIALS OF DIAGNOSIS

- ▶ Most patients with sudden cardiac death have underlying CHD.
- ▶ In the absence of reversible cause, ICD is recommended.

## ► General Considerations

**Sudden cardiac death** is defined as unexpected nontraumatic death in clinically well or stable patients who die within 1 hour after onset of symptoms. The causative rhythm in most cases is ventricular fibrillation. **Sudden cardiac arrest** is a term reserved for the successful resuscitation of ventricular fibrillation, either spontaneously or via intervention (defibrillation).

## ► Clinical Findings

Approximately 70% of cases of sudden cardiac death are attributable to underlying CHD; in up to 40% of patients, sudden cardiac death may be the initial manifestation of CHD. In patients younger than 35, most sudden cardiac death (SCD) is caused by inherited heart disease (long QT syndrome, catecholaminergic polymorphic ventricular tachycardia, Brugada syndrome, HCM, arrhythmogenic RV cardiomyopathy, dilated cardiomyopathy). Over the age of 35, CHD is the most common cause of SCD, although inherited causes are common up until the age of 50. Noninherited forms of heart disease can also lead to SCD, including valvular heart disease (aortic stenosis, pulmonic stenosis), congenital heart disease, and myocarditis. Prompt evaluation to exclude reversible causes of sudden cardiac arrest should begin immediately following resuscitation. Laboratory testing should be performed to exclude severe electrolyte abnormalities (particularly hypokalemia and hypomagnesemia) and acidosis and to evaluate cardiac biomarkers. Caution should be taken in attributing cardiac arrest solely to an electrolyte disturbance, however, because laboratory abnormalities may be secondary to resuscitation and not causative of the event. A 12-lead ECG should be performed to evaluate for ongoing ischemia or conduction system disease. Ventricular function should be evaluated with echocardiography. Coronary arteriography should be performed to exclude coronary disease as the underlying cause, since revascularization may prevent recurrence. In the absence of coronary disease, contrast-enhanced cardiac MRI may be used to evaluate for the presence of

myocardial scar, which is a strong predictor of recurrent ventricular tachycardia/ventricular fibrillation in patients with nonischemic cardiomyopathy.

### ► Treatment

Unless ventricular fibrillation occurs shortly after MI, is associated with ischemia, or is seen with a correctable process (such as an electrolyte abnormality or medication toxicity), surviving patients require intervention since recurrences are frequent. Survivors of cardiac arrest appear to have improved long-term outcomes if a **targeted temperature management protocol** is rapidly initiated and continued for 24–36 hours after cardiac arrest.

Patients who survive sudden cardiac arrest have a high incidence of recurrence, so an **ICD** is generally indicated. Sudden cardiac arrest in the setting of acute ischemia or infarct should be managed with prompt coronary revascularization. However, implantation of a prophylactic ICD in patients immediately after MI is associated with a trend toward *worse* outcomes. These patients may be managed with a **wearable cardioverter defibrillator** until recovery of ventricular function can be assessed by echocardiogram at a later date (6–12 weeks following MI or coronary intervention). In patients in whom ventricular function remains low (EF less than or equal to 35%), a permanent subcutaneous ICD (when pacing is not required) or transvenous ICD should be implanted.

### ► When to Refer

All survivors of sudden cardiac arrest should be referred to a cardiologist or cardiac electrophysiologist.

## INHERITED ARRHYTHMIA SYNDROMES



### ESSENTIALS OF DIAGNOSIS

- ▶ Includes long QT syndrome, Brugada syndrome, arrhythmogenic RV cardiomyopathy, and catecholaminergic polymorphic ventricular tachycardia.
- ▶ Genetic testing for patients with suspected congenital long QT syndrome based on family history, ECG or exercise testing, or severely prolonged QT interval (> 500 msec) on serial ECGs.
- ▶ Patients with long QT syndrome or catecholaminergic polymorphic ventricular tachycardia should be treated long term with an oral beta-blocker (nadolol or propranolol). ICD is indicated for patients with ventricular arrhythmia or syncope despite medical treatment.

### ► General Considerations

Inherited arrhythmia syndromes may result in life-threatening ventricular arrhythmias due to gene mutations in cardiac channels resulting in abnormal electrolyte regulation across the cardiac cell membrane. **Congenital long**

**QT syndrome** is an uncommon disease (1 in 2500 live births) that is characterized by a long QT interval (usually greater than 470 msec) and ventricular arrhythmia, typically polymorphic ventricular tachycardia. **Acquired long QT syndrome** is usually secondary to use of antiarrhythmic agents (sotalol, dofetilide), methadone, antidepressant medications, or certain antibiotics; electrolyte abnormalities; myocardial ischemia; or significant bradycardia.

**Brugada syndrome** accounts for up to 20% of sudden cardiac death in the absence of structural heart disease and is most often due to a defect in a sodium channel gene.

**Arrhythmogenic RV cardiomyopathy** is an inherited cardiomyopathy that predominantly affects the right ventricle and is characterized by areas of myocardial replacement with fibrosis and adipose tissue that frequently causes ventricular arrhythmia. **Catecholaminergic polymorphic ventricular tachycardia** is a rare but important cause of sudden cardiac death associated with exercise.

### ► Clinical Findings

Patients with an inherited arrhythmia syndrome have a variable clinical presentation; they may be asymptomatic or have palpitations, sustained tachyarrhythmia, syncope, or sudden cardiac arrest. In young patients, syncopal episodes may be misdiagnosed as a primary seizure disorder. Personal and family history should be thoroughly reviewed in all patients. A 12-lead ECG should be performed with careful attention to any abnormality in the ST segment, T wave, and QT interval. A corrected QT interval longer than 500 msec on serial ECGs in the absence of a secondary cause (medication or electrolyte abnormality) identifies a high-risk subset of patients with long QT syndrome. Ambulatory ECG monitoring may be used to evaluate for ventricular arrhythmias as well as dynamic changes to the QT interval or T wave. Exercise ECG testing may be performed in patients with suspected long QT syndrome to assess for lack of appropriate QT interval shortening with higher heart rates. In cases where the cause of sudden cardiac arrest is suspected to be heritable, genetic testing under the guidance of a multidisciplinary genetics team is recommended to both determine the diagnosis and to facilitate the identification of first-degree family members at risk for developing the same disease.

### ► Treatment

The management of acute polymorphic ventricular tachycardia (*torsades de pointes*) differs from that of other forms of ventricular tachycardia. Class Ia, Ic, or III antiarrhythmics, which prolong the QT interval, should be avoided—or withdrawn immediately if being used in patients with long QT syndrome. Intravenous beta-blockers may be effective in treating electrical storm due to long QT syndrome or catecholaminergic polymorphic ventricular tachycardia. Increasing the heart rate, whether by infusion of beta-agonist (dopamine or isoproterenol) or temporary atrial or ventricular pacing, is an effective approach that can both break and prevent the rhythm.

Long-term treatment of patients with inherited arrhythmia syndromes depends on the presence of high-risk

features. Use of beta-blockers (particularly propranolol or nadolol) is the mainstay of treatment for patients with long QT syndrome or catecholaminergic polymorphic ventricular tachycardia. Surgical cervicothoracic sympathectomy should be considered for patients who do not respond to or are intolerant of beta-blockers. There is no reliable medication therapy for Brugada syndrome and prevention of arrhythmias focuses on prompt treatment of exacerbating triggers, particularly fever. Antiarrhythmic medications should be avoided in patients with inherited arrhythmia syndromes except for specific identified genetic abnormalities under the direction of a specialist. ICD implantation is recommended for patients with an inherited arrhythmia syndrome in whom sudden cardiac arrest is the initial presentation. An ICD should be considered in patients with recurrent sustained ventricular arrhythmias or syncope despite medical therapy.

## ► When to Refer

Any patient with known or suspected inherited arrhythmia syndrome or with severe corrected QT interval prolongation (greater than 500 msec on serial ECGs) should be referred to a cardiologist or cardiac electrophysiologist.

Stiles MK et al. 2020 APHRS/HRS expert consensus statement on the investigation of decedents with sudden unexplained death and patients with sudden cardiac arrest, and of their families. Heart Rhythm. 2021;18:e1. [PMID: 33091602]

## SYNCOPE



### ESSENTIALS OF DIAGNOSIS

- ▶ Transient loss of consciousness and postural tone from vasodepressor or cardiogenic causes with prompt recovery without resuscitative measures.
- ▶ High-risk features include history of structural heart disease, abnormal ECG, and age > 60 years.

## ► General Considerations

Syncope is a symptom defined as a transient, self-limited loss of consciousness, usually leading to a fall. Thirty percent of the adult population will experience at least one episode of syncope. It accounts for approximately 3% of emergency department visits. A specific cause of syncope is identified in about 50% of cases during the initial evaluation. The prognosis is relatively favorable except when accompanying cardiac disease is present. In many patients with recurrent syncope or near syncope, arrhythmias are not the cause. This is particularly true when the patient has no evidence of associated heart disease by history, examination, standard ECG, or noninvasive testing. The history is the most important component of the evaluation to identify the cause of syncope.

**Reflex (neurally mediated) syncope** may be due to excessive vagal tone or impaired reflex control of the

peripheral circulation. The most frequent type is **vasovagal syncope** or the “common faint,” which is often initiated by a stressful, painful, or claustrophobic experience, especially in young women. Enhanced vagal tone with resulting hypotension is the cause of syncope in **carotid sinus hypersensitivity** and **postmicturition syncope**; vagal-induced sinus bradycardia, sinus arrest, and AV block are common accompaniments and may themselves be the cause of syncope.

**Orthostatic (postural) hypotension** is another common cause of vasodepressor syncope, especially in elderly patients; in diabetic patients or others with autonomic neuropathy; in patients with blood loss or hypovolemia; and in patients taking vasodilators, diuretics, and adrenergic-blocking medications. In addition, a syndrome of **chronic idiopathic orthostatic hypotension** exists primarily in older men. In most of these conditions, the normal vasoconstrictive response to assuming upright posture, which compensates for the abrupt decrease in venous return, is impaired.

**Cardiogenic syncope** can occur on a mechanical or arrhythmic basis. There is usually no prodrome; thus, injury secondary to falling is common. Mechanical problems that can cause syncope include aortic stenosis (where syncope may occur from autonomic reflex abnormalities or ventricular tachycardia), pulmonary stenosis, HCM, congenital lesions associated with pulmonary hypertension or right-to-left shunting, and LA myxoma obstructing the mitral valve. Episodes are commonly exertional or postexertional. More commonly, cardiac syncope is due to disorders of automaticity (sick sinus syndrome), conduction disorders (AV block), or tachyarrhythmias (especially ventricular tachycardia and SVT with rapid ventricular rate).

## ► Clinical Findings

### A. Symptoms and Signs

Vasovagal syncope often has a prodrome of vasodepressor premonitory symptoms, such as nausea, diaphoresis, tachycardia, and pallor. Episodes can be aborted by lying down or removing the inciting stimulus. Cardiogenic syncope by contrast is characteristically abrupt in onset, often resulting in injury, transient (lasting for seconds to a few minutes), and followed by prompt recovery of full consciousness. In orthostatic (postural) hypotension, a greater than normal decline (20 mm Hg) in BP immediately upon arising from the supine to the standing position is observed, with or without tachycardia depending on the status of autonomic (baroreceptor) function.

### B. Diagnostic Tests

The evaluation for syncope depends on findings from the history and physical examination (especially orthostatic BP evaluation, auscultation of carotid arteries, and cardiac examination).

**1. ECG**—A resting ECG is recommended for all patients undergoing evaluation for syncope. High-risk findings on ECG include non-sinus rhythm, complete or partial left bundle branch block, and voltage criteria indicating left

ventricular hypertrophy. Patients with a normal initial evaluation, including unremarkable history and physical, absence of cardiac disease or significant comorbidities and normal baseline ECG may not need further testing. When initial evaluation suggests a possible cardiac arrhythmia, continuous ambulatory ECG monitoring, event recorder (for infrequent episodes), or an implantable cardiac monitor can be considered. Caution is required before attributing a patient's syncopal event to rhythm or conduction abnormalities observed during monitoring without concomitant symptoms. For instance, dizziness or syncope in older patients may be unrelated to incidentally observed bradycardia, sinus node abnormalities, or ventricular ectopy.

**2. Autonomic testing**—**Tilt-table testing** may be useful in patients with suspected vasovagal syncope where the diagnosis is unclear after initial evaluation, especially when syncope is recurrent. The hemodynamic response to tilting determines whether there is a *cardioinhibitory*, *vasodepressor*, or *mixed* response. The overall utility of the test is improved when there is a high pretest probability of neurally mediated syncope, since the sensitivity and specificity of the test in the general population is only moderate.

**3. Electrophysiologic studies**—Electrophysiologic study has limited role in the evaluation of syncope, particularly in patients without structural heart disease or when there is a low suspicion for arrhythmic etiology. In patients with ischemic heart disease, LV dysfunction, known conduction disease, or arrhythmia, electrophysiologic study may help elucidate the mechanism of syncope and guide treatment decisions. The diagnostic yield in patients with structural heart disease is approximately 50%.

## Treatment

In patients with vasovagal syncope, treatment consists largely of education on the benign nature of the condition and counseling to avoid predisposing situations. Counter-pressure maneuvers (squatting, leg-crossing, abdominal contraction) can be helpful in limiting or terminating episodes. Medical therapy is reserved for patients with symptoms despite these measures. Midodrine is an alpha-agonist that can increase the peripheral sympathetic neural outflow and decrease venous pooling during vasovagal episodes. Fludrocortisone and beta-blockers have also been used but generally provide minimal benefit. Selective serotonin reuptake inhibitors have shown some benefit in select patients. There is generally no role for permanent pacemaker implantation in patients with vasovagal syncope, with the possible exception of patients older than age 40 years with prolonged (longer than 3 seconds), symptomatic episodes of asystole documented on ambulatory monitoring. Pacemaker implantation based solely upon tilt-table–induced asystolic (cardioinhibitory) response is rarely indicated.

If symptomatic bradyarrhythmias or supraventricular tachyarrhythmias are detected and felt to be the cause of syncope, therapy can usually be initiated without additional diagnostic studies. Permanent pacing is indicated in patients with cardiogenic syncope and documented severe pauses (greater than 3 seconds), bradycardia, or

high-degree AV block (second-degree Mobitz type II or complete heart block) when symptoms are correlated to the arrhythmia.

An important consideration in patients who have experienced syncope, symptomatic ventricular tachycardia, or aborted sudden death is to provide recommendations concerning **automobile driving restrictions**. Patients with syncope thought to be due to temporary factors (acute MI, bradyarrhythmias subsequently treated with permanent pacing, medication effect, electrolyte imbalance) should be advised after recovery not to drive for at least 1 week. Other patients with symptomatic ventricular tachycardia or aborted sudden death, whether treated pharmacologically, with anti-achardia devices, or with ablation therapy, should not drive for at least 6 months. Longer restrictions are warranted in these patients if significant arrhythmias persist.

## When to Refer

- Patients with syncope and underlying structural heart disease, documented arrhythmia, or conduction disturbance.
- Unclear etiology of syncope with high-risk features (heart failure, abnormal ECG findings, advanced age, multiple unexplained episodes).

Brignole M et al; ESC Scientific Document Group. 2018 ESC guidelines for the diagnosis and management of syncope. Eur Heart J. 2018;39:1883. [PMID: 29562304]

## HEART FAILURE

### ESSENTIALS OF DIAGNOSIS

- 
- LV failure: Either due to systolic or diastolic dysfunction. Predominant symptoms are those of low cardiac output and congestion, including dyspnea.
  - RV failure: Symptoms of fluid overload predominate; usually RV failure is secondary to LV failure.
  - Assessment of LV function is a crucial part of diagnosis and management.
  - Optimal management of chronic heart failure includes combination medical therapies, such as ACE inhibitors, aldosterone antagonists, and beta-blockers.

## General Considerations

Heart failure is a common syndrome that is increasing in incidence and prevalence. Approximately 6.2 million patients in the United States have heart failure, with 8 million or more patients projected to have heart failure by 2030. Each year in the United States, 809,000 patients are discharged from the hospital with a diagnosis of heart failure. It is primarily a disease of aging, with over 75% of

existing and new cases occurring in individuals over 65 years of age. Seventy-five percent of heart failure patients have antecedent hypertension. The prevalence of heart failure rises from less than 1% in individuals below 60 years to nearly 10% in those over 80 years of age.

Heart failure may be right-sided or left-sided (or both). Patients with **left heart failure** may have symptoms of low cardiac output and elevated pulmonary venous pressure; dyspnea is the predominant feature. Signs of fluid retention predominate in **right heart failure**. Most patients exhibit symptoms or signs of both right- and left-sided failure, and LV dysfunction is the primary cause of RV failure. Approximately half of patients with heart failure have **preserved LV systolic function** and usually have some degree of **diastolic dysfunction**. Patients with reduced or preserved systolic function may have similar symptoms and it may be difficult to distinguish clinically between the two based on signs and symptoms. In developed countries, CAD with resulting MI and loss of functioning myocardium (**ischemic cardiomyopathy**) is the most common cause of systolic heart failure. Systemic hypertension remains an important cause of heart failure and, even more commonly in the United States, an exacerbating factor in patients with cardiac dysfunction due to other causes, such as CAD. Several processes may present with **dilated or congestive cardiomyopathy**, which is characterized by LV or biventricular dilation and generalized systolic dysfunction. These are discussed elsewhere in this chapter, but the most common are alcoholic cardiomyopathy, viral myocarditis (including infections by HIV; see also the COVID-19 section in Chapter 32), and dilated cardiomyopathies with no obvious underlying cause (idiopathic cardiomyopathy). Rare causes of dilated cardiomyopathy include infiltrative diseases (hemochromatosis, sarcoidosis, amyloidosis, etc), other infectious agents, metabolic disorders, cardiotoxins, and medication toxicity. Valvular heart diseases—particularly degenerative aortic stenosis and chronic aortic or mitral regurgitation—are not infrequent causes of heart failure. Persistent tachycardia, often related to atrial arrhythmias, can cause systolic dysfunction that may be reversible with controlling the rate. Diastolic cardiac dysfunction is associated with aging and related myocardial stiffening, as well as LVH, commonly resulting from hypertension. Conditions such as **hypertrophic or restrictive cardiomyopathy**, diabetes, and pericardial disease can produce the same clinical picture. Atrial fibrillation with or without rapid ventricular response may contribute to impaired left ventricular filling.

Heart failure is often preventable by early detection of patients at risk and by early intervention. The importance of these approaches is emphasized by US guidelines that have incorporated a classification of heart failure that includes four stages. **Stage A** includes patients at risk for developing heart failure (such as patients with hypertension). In the majority of these patients, development of heart failure can be prevented with interventions such as the aggressive treatment of hypertension, modification of coronary risk factors, and reduction of excessive alcohol intake. **Stage B** includes patients who have structural heart disease but no current or previously recognized symptoms

of heart failure. Examples include patients with previous MI, other causes of reduced systolic function, LVH, or asymptomatic valvular disease. Both ACE inhibitors and beta-blockers prevent heart failure in the first two of these conditions, and more aggressive treatment of hypertension and early surgical intervention are effective in the latter two. **Stages C** and **D** include patients with clinical heart failure and the relatively small group of patients who have become refractory to the usual therapies, respectively.

## Clinical Findings

### A. Symptoms

The most common symptom of patients with **left heart failure** is shortness of breath, chiefly exertional dyspnea at first and then progressing to orthopnea, paroxysmal nocturnal dyspnea, and rest dyspnea. Chronic nonproductive cough, which is often worse in the recumbent position, may occur. Nocturia due to excretion of fluid retained during the day and increased renal perfusion in the recumbent position is a common nonspecific symptom of heart failure, as is fatigue and exercise intolerance. These symptoms correlate poorly with the degree of cardiac dysfunction. Patients with **right heart failure** have predominate signs of fluid retention, with the patient exhibiting edema, hepatic congestion and, on occasion, loss of appetite and nausea due to edema of the gut or impaired gastrointestinal perfusion and ascites. Surprisingly, some individuals with severe LV dysfunction will display few signs of left heart failure and appear to have isolated right heart failure. Indeed, they may be clinically indistinguishable from patients with **cor pulmonale**, who have right heart failure secondary to pulmonary disease.

Patients with acute heart failure from MI, myocarditis, and acute valvular regurgitation due to endocarditis or other conditions usually present with pulmonary edema. Patients with episodic symptoms may be having LV dysfunction due to intermittent ischemia. Patients may also present with acute exacerbations of chronic, stable heart failure. Exacerbations may be caused by alterations in therapy (or patient noncompliance), excessive salt and fluid intake, arrhythmias, excessive activity, pulmonary emboli, intercurrent infection, or progression of the underlying disease.

Patients with heart failure are often categorized by the NYHA classification as **class I** (asymptomatic), **class II** (symptomatic with moderate activity), **class III** (symptomatic with mild activity), or **class IV** (symptomatic at rest). This classification is important since some of the treatments are indicated based on NYHA classification.

### B. Signs

Many patients with heart failure, including some with severe symptoms, appear comfortable at rest. Others will be dyspneic during conversation or minor activity, and those with long-standing severe heart failure may appear cachectic or cyanotic. The vital signs may be normal, but tachycardia, hypotension, and reduced pulse pressure may be present. Patients often show signs of increased sympathetic nervous system activity, including cold extremities

and diaphoresis. Important peripheral signs of heart failure can be detected by examination of the neck, the lungs, the abdomen, and the extremities. RA pressure may be estimated through the height of the pulsations in the jugular venous system. With the patient at 45 degrees, measure the height of the pulsation about the sternal angle, and add 5 cm to estimate the height above the left atrium, with a pressure greater than 8 cm being abnormal. In addition to the height of the venous pressure, abnormal pulsations, such as regurgitant *v* waves, should be sought. Examination of the carotid pulse may allow estimation of pulse pressure as well as detection of aortic stenosis. Thyroid examination may reveal occult hyperthyroidism or hypothyroidism, which are readily treatable causes of heart failure. Crackles at the lung bases reflect transudation of fluid into the alveoli. Pleural effusions may cause bibasilar dullness to percussion. Expiratory wheezing and rhonchi may be signs of heart failure. Patients with severe right heart failure may have hepatic enlargement—tender or nontender—due to passive congestion. Systolic pulsations may be felt in tricuspid regurgitation. Sustained moderate pressure on the liver may increase jugular venous pressure (a positive **hepatojugular reflux** is an increase of greater than 1 cm, which correlates with elevated PCWP). Ascites may also be present. Peripheral pitting edema is a common sign in patients with right heart failure and may extend into the thighs and abdominal wall.

Cardinal cardiac examination signs are a parasternal lift, indicating pulmonary hypertension; an enlarged and sustained LV impulse, indicating LV dilation and hypertrophy; a diminished first heart sound, suggesting impaired contractility; and an *S<sub>3</sub>* gallop originating in the LV and sometimes the RV. An *S<sub>4</sub>* is usually present in diastolic heart failure. Murmurs should be sought to exclude primary valvular disease; secondary mitral regurgitation and tricuspid regurgitation murmurs are common in patients with dilated ventricles. In chronic heart failure, many of the expected signs of heart failure may be absent despite markedly abnormal cardiac function and hemodynamic measurements.

### C. Laboratory Findings

A blood count may reveal anemia and a high red-cell distribution width (RDW), both of which are associated with poor prognosis in chronic heart failure through poorly understood mechanisms. Kidney function tests can determine whether cardiac failure is associated with impaired kidney function that may reflect poor kidney perfusion. Chronic kidney disease is another poor prognostic factor in heart failure and may limit certain treatment options. Serum electrolytes may disclose hypokalemia, which increases the risk of arrhythmias; hyperkalemia, which may limit the use of inhibitors of the renin–angiotensin system; or hyponatremia, an indicator of marked activation of the renin–angiotensin system and a poor prognostic sign. Thyroid function should be assessed to detect occult thyrotoxicosis or myxedema, and iron studies should be checked to test for hemochromatosis. In unexplained cases, appropriate biopsies may lead to a diagnosis of amyloidosis. Myocardial biopsy may exclude specific causes of dilated cardiomyopathy but rarely reveals specific reversible diagnoses.

Serum BNP is a powerful prognostic marker that adds to clinical assessment in differentiating dyspnea due to heart failure from noncardiac causes. Two markers—BNP and NT-proBNP—provide similar diagnostic and prognostic information. BNP is expressed primarily in the ventricles and is elevated when ventricular filling pressures are high. It is quite sensitive in patients with symptomatic heart failure—whether due to systolic or to diastolic dysfunction—but less specific in older patients, women, and patients with COPD. Studies have shown that BNP can help in emergency department triage in the diagnosis of acute decompensated heart failure, such that an NT-proBNP less than 300 pg/mL or BNP less than 100 pg/mL, combined with a normal ECG, makes heart failure unlikely. BNP is less sensitive and specific to diagnose heart failure in the chronic setting. BNP may be helpful in guiding the intensity of diuretic and a more consistent use of disease-modifying therapies, such as ACE inhibitors and beta-blockers, for the management of chronic heart failure. BNP, but not NT-proBNP, is increased by neprilysin inhibitors, since neprilysin degrades BNP. Thus, while NT-proBNP is still reliable, BNP should *not* be used to monitor degree of heart failure when patients are treated with sacubitril/valsartan. Worsening breathlessness or weight associated with a rising BNP (or both) might prompt increasing the dose of diuretics. However, there is no proven value in using serial natriuretic peptide measurements to guide therapy, as shown in the GUIDE-IT trial. Elevation of serum troponin, and especially of high-sensitivity troponin, is common in both chronic and acute heart failure, and it is associated with higher risk of adverse outcomes.

### D. ECG and Chest Radiography

ECG may indicate an underlying or secondary arrhythmia, MI, or nonspecific changes that often include low voltage, intraventricular conduction defects, LVH, and nonspecific repolarization changes. Chest radiographs provide information about the size and shape of the cardiac silhouette. Cardiomegaly is an important finding and is a poor prognostic sign. Evidence of pulmonary venous hypertension includes relative dilation of the upper lobe veins, perivascular edema (haziness of vessel outlines), interstitial edema, and alveolar fluid. In acute heart failure, these findings correlate moderately well with pulmonary venous pressure. However, patients with chronic heart failure may show relatively normal pulmonary vasculature despite markedly elevated pressures. Pleural effusions are common and tend to be bilateral or right-sided.

### E. Additional Studies

The clinical diagnosis of systolic myocardial dysfunction is often inaccurate. The primary confounding conditions are diastolic dysfunction of the heart with decreased relaxation and filling of the LV (particularly in hypertension and in hypertrophic states) and pulmonary disease.

**The most useful test is the echocardiogram because it can differentiate heart failure with and without preserved LV systolic function.** The echocardiogram can define the size and function of both ventricles and of the atria. LVEF is the most

commonly used measurement to define systolic function. RV function is assessed by contractility and other measures, such as tricuspid annular plane systolic excursion. Echocardiography will also allow detection of pericardial effusion, valvular abnormalities, intracardiac shunts, and segmental wall motion abnormalities suggestive of old MI as opposed to more generalized forms of dilated cardiomyopathy.

Radionuclide angiography as well as cardiac MRI also measure LVEF and permit analysis of regional wall motion. These tests are especially useful when echocardiography is technically suboptimal, such as in patients with severe pulmonary disease. MRI can assess for presence of scar tissue and of infiltrative disease. When myocardial ischemia is suspected as a cause of LV dysfunction, as it should be unless there is another clear cause, stress testing or coronary angiography should be performed.

## F. Cardiac Catheterization

In most patients with heart failure, clinical examination and noninvasive tests can determine LV size and function and valve function to support and refine the diagnosis. Left heart catheterization may be helpful to define the presence and extent of CAD, although CT angiography may also be appropriate, especially when the likelihood of coronary disease is low. Evaluation for coronary disease is particularly important when LV dysfunction may be partially reversible by revascularization. The combination of angina or noninvasive evidence of significant myocardial ischemia with symptomatic heart failure is often an indication for coronary angiography if the patient is a potential candidate for revascularization. Right heart catheterization may be useful to select and monitor therapy in patients refractory to standard therapy.

## Treatment: Heart Failure With Reduced LVEF

The treatment of heart failure is aimed at relieving symptoms, improving functional status, and preventing death and hospitalizations. Figure 10–10 outlines the role of the major pharmacologic and device therapies for heart failure with reduced LVEF (less than or equal to 40%). **The evidence of clinical benefit, including reducing death and hospitalization, as well as reducing sudden cardiac death, of most therapies is limited to patients with heart failure with reduced LVEF.** Treatment of heart failure with preserved LVEF is aimed at improving symptoms and treating comorbidities. Achieving target (or maximally tolerated up to target) dosing to obtain the benefits of these treatments that have been shown in clinical trials is important (Table 10–12).

## A. Correction of Reversible Causes

The major reversible causes of heart failure with reduced LVEF, also called chronic systolic heart failure, include valvular lesions, myocardial ischemia, uncontrolled hypertension, arrhythmias (especially persistent tachycardias), alcohol- or drug-induced myocardial depression, hypothyroidism, intracardiac shunts, and high-output states.

Calcium channel blockers with negative inotropy (specifically verapamil or diltiazem), antiarrhythmic medications, thiazolidinediones, and nonsteroidal anti-inflammatory agents may be important contributors to worsening heart failure. Some metabolic and infiltrative cardiomyopathies may be partially reversible, or their progression may be slowed; these include hemochromatosis, sarcoidosis, and amyloidosis. Once possible reversible components are being addressed, the measures outlined below are appropriate.

## B. Pharmacologic Treatment

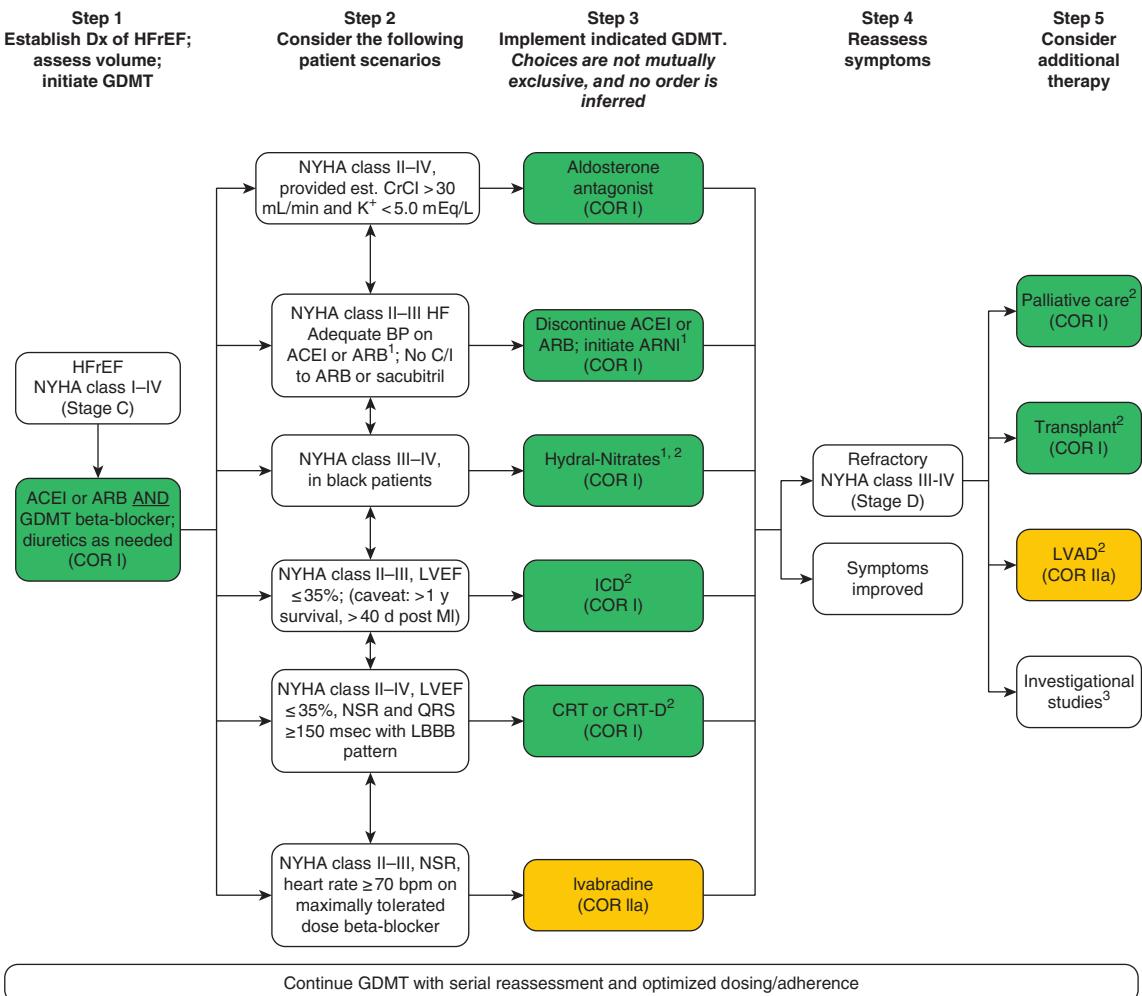
See also the following section Acute Heart Failure & Pulmonary Edema.

**1. Diuretic therapy**—Diuretics are the most effective means of providing symptomatic relief to patients with moderate to severe heart failure with dyspnea and fluid overload, for heart failure with either reduced or preserved LVEF. Few patients with symptoms or signs of fluid retention can be optimally managed without a diuretic. However, excessive diuresis can lead to electrolyte imbalance and neurohormonal activation. **A combination of a diuretic and an ACE inhibitor should be the initial treatment in most symptomatic patients with heart failure and reduced LVEF, with the early addition of a beta-blocker.**

When fluid retention is mild, **thiazide diuretics** or a similar type of agent (hydrochlorothiazide, 25–100 mg; metolazone, 2.5–5 mg; chlorthalidone, 25–50 mg; etc) may be sufficient. Thiazide or related diuretics often provide better control of hypertension than short-acting loop agents. The thiazides are generally *ineffective* when the glomerular filtration rate falls below 30–40 mL/min, a not infrequent occurrence in patients with severe heart failure. Metolazone maintains its efficacy down to a glomerular filtration rate of approximately 20–30 mL/min. Adverse reactions include hypokalemia and intravascular volume depletion with resulting prerenal azotemia, skin rashes, neutropenia and thrombocytopenia, hyperglycemia, hyperuricemia, and hepatic dysfunction.

Patients with more severe heart failure should be treated with one of the oral **loop diuretics**. These include furosemide (20–320 mg daily), bumetanide (1–8 mg daily), and torsemide (20–200 mg daily). These agents have a rapid onset and a relatively short duration of action. In patients with preserved kidney function, two or more daily doses are preferable to a single larger dose. In acute situations or when gastrointestinal absorption is in doubt, they should be given intravenously. Torsemide may be effective when furosemide is not, related to better absorption and a longer half life. Larger doses (up to 500 mg of furosemide or equivalent) may be required with severe renal impairment. The major adverse reactions include intravascular volume depletion, prerenal azotemia, and hypotension. Hypokalemia, particularly with accompanying digitalis therapy, is a major problem. Less common side effects include skin rashes, gastrointestinal distress, and ototoxicity (the latter more common with ethacrynic acid and possibly less common with bumetanide).

The **oral potassium-sparing agents** are often useful in combination with the loop diuretics and thiazides, with the



<sup>1</sup>The combination of ISDN/HYD with ARNI has not been robustly studied, BP response should be carefully monitored.

<sup>2</sup>See 2013 HF guidelines.

<sup>3</sup>Participation in investigational studies is also appropriate for stage C, NYHA class II and III HF.

**▲ Figure 10–10.** Major pharmacologic and device therapies for heart failure with reduced left ventricular ejection fraction. For all medical therapies, dosing should be optimized and serial assessment exercised. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; BP, blood pressure; bpm, beats per minute; C/I, contraindication; COR, Class of Recommendation; CrCl, creatinine clearance; CRT-D, cardiac resynchronization therapy-device; Dx, diagnosis; GDMT, guideline-directed management and therapy; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; ICD, implantable cardioverter-defibrillator; ISDN/HYD, isosorbide dinitrate hydral-nitrates; K+, potassium; LBBB, left bundle branch block; LVAD, left ventricular assist device; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NSR, normal sinus rhythm; NYHA, New York Heart Association. (Figure reproduced, with permission, from Yancy CW et al. 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. Circulation. 2017;136:e137. © 2017 American Heart Association, Inc.)

first choice being the aldosterone inhibitors spironolactone (12.5–100 mg daily) or eplerenone (25–100 mg daily). Aldosterone is often increased in heart failure. These medications spare loss of potassium, they have some diuretic effect (especially at higher doses), and they also improve clinical outcomes, including survival. Their onsets of action are slower than the other potassium-sparing agents, and spironolactone's side effects include gynecomastia and

hyperkalemia. Combinations of potassium supplements or ACE inhibitors and potassium-sparing medications can increase the risk of hyperkalemia but have been used with success in patients with persistent hypokalemia.

Patients with refractory edema may respond to combinations of a loop diuretic and thiazide-like agents. Metolazone, because of its maintained activity with chronic kidney disease, is the most useful agent for such a

**Table 10–12.** Evidence-based doses of disease-modifying medications in key randomized trials in HFrEF or after myocardial infarction (medications listed in alphabetical order within classes).

| Medications                          | Starting Dose             | Target Dose             |
|--------------------------------------|---------------------------|-------------------------|
| <b>ACE Inhibitors</b>                |                           |                         |
| Captopril                            | 6.25 mg three times daily | 50 mg three times daily |
| Enalapril                            | 2.5 mg twice daily        | 10–20 mg twice daily    |
| Lisinopril                           | 2.5–5.0 mg once daily     | 20–35 once daily        |
| Ramipril                             | 2.5 mg once daily         | 10 mg once daily        |
| Trandolapril                         | 0.5 mg once daily         | 4 mg once daily         |
| <b>Beta-Blockers</b>                 |                           |                         |
| Bisoprolol                           | 1.25 mg once daily        | 10 mg once daily        |
| Carvedilol                           | 3.125 mg twice daily      | 25 mg twice daily       |
| Metoprolol succinate (CR/XL)         | 12.5–25 mg once daily     | 200 mg once daily       |
| Nebivolol                            | 1.25 once daily           | 10 mg once daily        |
| <b>ARBs</b>                          |                           |                         |
| Candesartan                          | 4–8 mg once daily         | 32 mg once daily        |
| Losartan                             | 50 mg once daily          | 150 mg once daily       |
| Valsartan                            | 40 mg twice daily         | 160 mg twice daily      |
| <b>Aldosterone Antagonist</b>        |                           |                         |
| Eplerenone                           | 25 mg once daily          | 50 mg once daily        |
| Spironolactone                       | 25 mg once daily          | 50 mg once daily        |
| <b>ARNI</b>                          |                           |                         |
| Sacubitril/valsartan                 | 49/51 mg twice daily      | 97/103 mg twice daily   |
| <b>I<sub>f</sub> Channel Blocker</b> |                           |                         |
| Ivabradine                           | 5 mg twice daily          | 7.5 mg twice daily      |

ACE, angiotensin-converting enzyme; ARBs, angiotensin receptor blockers; ARNI, angiotensin receptor-neprilysin inhibitor; HFrEF, heart failure with reduced ejection fraction.

combination. Extreme caution must be observed with this approach, since massive diuresis and electrolyte imbalances often occur; 2.5 mg of metolazone orally should be added to the previous dosage of loop diuretic. In many cases this is necessary only once or twice a week, but dosages up to 10 mg daily have been used in some patients.

**2. Inhibitors of the renin–angiotensin–aldosterone system**—Inhibition of the renin–angiotensin–aldosterone system with ACE inhibitors should be part of the initial therapy of this syndrome based on their mortality benefits.

**A. ACE INHIBITORS**—At least seven ACE inhibitors have been shown to be effective for the treatment of heart failure or the related indication of postinfarction LV dysfunction

(see Table 11–6). ACE inhibitors reduce mortality by approximately 20% in patients with symptomatic heart failure and have also been shown to prevent hospitalizations, increase exercise tolerance, and reduce symptoms in these patients. As a result, ACE inhibitors generally should be part of first-line treatment of patients with symptomatic LV systolic dysfunction (EF less than 40%), usually in combination with a diuretic. They are also indicated for the management of patients with reduced EFs without symptoms because they prevent the progression to clinical heart failure.

Because ACE inhibitors may induce significant hypotension, particularly following the initial doses, they must be started with caution. Hypotension is most prominent in patients with already low BPs (systolic pressure less than 100 mm Hg), hypovolemia, prerenal azotemia (especially if it is diuretic induced), and hyponatremia (an indicator of activation of the renin–angiotensin system). These patients should generally be started at low dosages (captopril 6.25 mg orally three times daily, enalapril 2.5 mg orally daily, or the equivalent), but other patients may be started at twice these dosages. Within several days (for those with the markers of higher risk) or at most 2 weeks, patients should be questioned about symptoms of hypotension, and both kidney function and potassium levels should be monitored.

ACE inhibitors should be titrated to the dosages proved effective in clinical trials (captopril 50 mg three times daily, enalapril 10 mg twice daily, ramipril 10 mg daily, lisinopril 20 mg daily, or the equivalent) over a period of 1–3 months. Most patients will tolerate these doses. *Asymptomatic hypotension is not a contraindication to up-titrating or continuing ACE inhibitors.* Some patients exhibit increases in serum creatinine or potassium, but they do not require discontinuation if the levels stabilize—even at values as high as 3 mg/dL and 5.5 mEq/L, respectively. Kidney dysfunction is more frequent in patients with diabetes, older patients, and those with low systolic pressures, and these groups should be monitored more closely. The most common side effects of ACE inhibitors in heart failure patients are dizziness (often not related to the level of BP) and cough, though the latter is often due as much to heart failure or intercurrent pulmonary conditions as to the ACE inhibitor. ACE inhibitor-induced cough is more common in women than in men.

**B. ANGIOTENSIN II RECEPTOR BLOCKERS**—Another approach to inhibiting the renin–angiotensin–aldosterone system is the use of specific ARBs (see Table 11–6), which will decrease adverse effects of angiotensin II by blocking the AT<sub>1</sub> receptor. In addition, because there are alternative pathways of angiotensin II production in many tissues, the receptor blockers may provide more complete blockade of the AT<sub>1</sub> receptor.

However, these agents do *not* share the effects of ACE inhibitors on other potentially important pathways that produce increases in bradykinin, prostaglandins, and nitric oxide in the heart, blood vessels, and other tissues. ARBs, specifically candesartan or valsartan, provide important benefits as an alternative to ACE inhibitors in chronic heart failure with reduced LVEF. (A large trial of patients with

chronic heart failure and preserved LVEF found no benefit from the ARB irbesartan.) **While they have the same level of recommendation in the guidelines, generally ACE inhibitors are preferred over ARBs for patients who tolerate them.**

**C. SPIRONOLACTONE AND EPLERENONE**—Inhibiting aldosterone has become a mainstay of management of symptomatic heart failure with reduced LVEF. The RALES trial compared spironolactone 25 mg daily with placebo in patients with advanced heart failure (current or recent class IV) already receiving ACE inhibitors and diuretics and showed a 29% reduction in mortality as well as similar decreases in other clinical end points. Based on the EMPHASIS-HF trial, the efficacy and safety of aldosterone antagonism—in the form of eplerenone, 25–50 mg orally daily—is established for patients with mild or moderate heart failure. Hyperkalemia was uncommon in severe heart failure clinical trial patients who received high doses of diuretic as maintenance therapy; however, hyperkalemia in patients taking spironolactone appears to be common in general practice. Potassium levels must be monitored closely during initiation of spironolactone (after 1 and 4 weeks of therapy) and periodically thereafter, particularly for patients with even mild degrees of kidney injury, and in patients receiving ACE inhibitors.

**D. COMBINATION SACUBITRIL AND VALSARTAN**—The most recently approved medication to improve clinical outcome in patients with heart failure and reduced LVEF is the combination of valsartan and sacubitril, called an **angiotensin receptor-neprilysin inhibitor (ARNI)**. Compared to the ACE inhibitor enalapril, the ARNI was shown to reduce cardiovascular death and hospitalization for heart failure by 20% for patients with heart failure and reduced LVEF in a large randomized trial (PARADIGM-HF) of patients who had been taking an ACE inhibitor or ARB. Cardiovascular death itself was also reduced by 20%.

This has led to a class I recommendation by the ACC/AHA and the ESC guidelines for the use of **sacubitril/valsartan as a replacement for ACE inhibitors for patients with heart failure with reduced EF who remain symptomatic on an ACE inhibitor, beta-blocker, and mineralocorticoid inhibitor**. For some patients, cost will be a barrier to use, although analyses have shown that sacubitril/valsartan is cost effective. Patients with baseline systolic blood pressure less than 100 mmHg were not included in the PARADIGM trial, and symptomatic hypotension is more common with sacubitril/valsartan than ACE inhibitor. Sacubitril/valsartan can be safely started in the hospital for patients admitted with decompensated failure, once they are stable with systolic blood pressure of at least 100 mm Hg.

While there was some evidence of benefit, sacubatrill/valsartan did not result in significant improvement in the primary outcome of total heart failure hospitalizations and cardiovascular death in the PARAGON-HF trial studying a population of patients with heart failure and preserved LVEF (45% or greater). However, an FDA Advisory Panel has recommended approval for sacubitril/valsartan in this population, particularly for patients with mildly reduced or “mid-range” EF.

**3. Beta-blockers**—Beta-blockers are part of the foundation of care of chronic heart failure based on their life-saving benefits. The mechanism of this benefit remains unclear, but it is likely that chronic elevations of catecholamines and sympathetic nervous system activity cause progressive myocardial damage, leading to worsening LV function and dilation. The primary evidence for this hypothesis is that over a period of 3–6 months, beta-blockers produce consistent substantial rises in EF (averaging 10% absolute increase) and reductions in LV size and mass.

Three medications have strong evidence of reducing mortality: **carvedilol** (a nonselective beta-1- and beta-2-receptor blocker), the beta-1-selective **extended-release agent metoprolol succinate** (but not short-acting metoprolol tartrate), and **bisoprolol** (beta-1-selective agent).

This has led to a strong recommendation that **stable patients (defined as having no recent deterioration or evidence of volume overload) with mild, moderate, and even severe heart failure should be treated with a beta-blocker unless there is a noncardiac contraindication**. In the COPERNICUS trial, carvedilol was both well tolerated and highly effective in reducing both mortality and heart failure hospitalizations in a group of patients with severe (NYHA class III or IV) symptoms, but care was taken to ensure that they were free of fluid retention at the time of initiation. In this study, one death was prevented for every 13 patients treated for 1 year—as dramatic an effect as has been seen with a pharmacologic therapy in the history of cardiovascular medicine. One trial comparing carvedilol and (short-acting) metoprolol tartrate (COMET) found significant reductions in all-cause mortality and cardiovascular mortality with carvedilol. Thus, patients with chronic heart failure should be treated with extended-release metoprolol succinate, bisoprolol, or carvedilol but *not* short-acting metoprolol tartrate.

Because even apparently stable patients may deteriorate when beta-blockers are initiated, initiation must be done gradually and with great care. Carvedilol is initiated at a dosage of 3.125 mg orally twice daily and may be increased to 6.25, 12.5, and 25 mg twice daily at intervals of approximately 2 weeks. The protocols for sustained-release metoprolol use were started at 12.5 or 25 mg orally daily and doubled at intervals of 2 weeks to a target dose of 200 mg daily (using the Toprol XL sustained-release preparation). Bisoprolol was administered at a dosage of 1.25, 2.5, 3.75, 5, 7.5, and 10 mg orally daily, with increments at 1- to 4-week intervals. More gradual up-titration is often more convenient and may be better tolerated. The SENIORS trial of 2135 patients found that nebivolol was effective in elderly patients (70 years and older) with chronic heart failure, although the evidence of degree of benefit was not as strong as with the three proven beta-blockers carvedilol, metoprolol succinate, or bisoprolol.

**Patients should be instructed to monitor their weight at home as an indicator of fluid retention and to report any increase or change in symptoms immediately.** Before each dose increase, patients should be seen and examined to ensure that there has not been fluid retention or worsening of symptoms. If heart failure worsens, this can usually be managed by increasing diuretic doses and delaying

further increases in beta-blocker doses, though downward adjustments or discontinuation is sometimes required. Carvedilol, because of its beta-blocking activity, may cause dizziness or hypotension. This can usually be managed by reducing the doses of other vasodilators and by slowing the pace of dose increases.

**4. SGLT2 inhibitors**—Two large clinical trials of patients with type 2 diabetes have shown that inhibitors of sodium-glucose cotransporter 2 (SGLT2) substantially reduce the risk of cardiovascular death and hospitalization for heart failure for patients with reduced LVEF, with or without diabetes. Dapagliflozin also reduced all-cause mortality. Dapagliflozin has been approved for treating heart failure with reduced LVEF, and empagliflozin is under FDA review. While SGLT2 inhibitors also reduced kidney disease progression, patients with severe kidney impairment were not included in these trials.

**5. Digitalis glycosides**—The efficacy of digitalis glycosides in reducing the symptoms of heart failure has been established in at least four multicenter trials that have demonstrated that digoxin withdrawal is associated with worsening symptoms and signs of heart failure, more frequent hospitalizations for decompensation, and reduced exercise tolerance. Digoxin should be considered for patients who remain symptomatic when taking diuretics and ACE inhibitors as well as for patients with heart failure who are in atrial fibrillation and require rate control. However, there is uncertainty about the safety of digoxin in this population with atrial fibrillation, especially with higher digoxin concentrations.

Digoxin has a half-life of 24–36 hours and is eliminated almost entirely by the kidneys. The oral maintenance dose may range from 0.125 mg three times weekly to 0.5 mg daily. It is lower in patients with kidney dysfunction, in older patients, and in those with smaller lean body mass. Although an oral loading dose of 0.75–1.25 mg (depending primarily on lean body size) over 24–48 hours may be given if an early effect is desired, in most patients with chronic heart failure it is sufficient to begin with the expected maintenance dose (usually 0.125–0.25 mg daily). Amiodarone, quinidine, propafenone, and verapamil are among the medications that may increase digoxin levels up to 100%. It is prudent to measure a blood level after 7–14 days (and at least 6 hours after the last dose was administered). Optimum serum digoxin levels are 0.7–1.2 ng/mL. Digoxin may induce ventricular arrhythmias, especially when hypokalemia or myocardial ischemia is present. Digoxin toxicity is discussed in Chapter 38.

**6. Nitrates and hydralazine**—Although ACE inhibitors, which have vasodilating properties, improve prognosis, such a benefit is not established with the direct-acting vasodilators. The combination of hydralazine and isosorbide dinitrate has been shown to *improve outcomes in African Americans*, but the effect is less clear than the well-established benefits of ACE inhibitors. ARBs or ARNIs have largely supplanted the use of the hydralazine–isosorbide dinitrate combination in ACE-intolerant patients.

See section Acute Myocardial Infarction earlier in this chapter for a discussion on the intravenous vasodilating medications and their dosages.

**A. NITRATES**—Intravenous vasodilators (sodium nitroprusside or nitroglycerin) are used primarily for acute or severely decompensated chronic heart failure, especially when accompanied by hypertension or myocardial ischemia. If neither of the latter is present, therapy is best initiated and adjusted based on hemodynamic measurements. The starting dosage for nitroglycerin is generally about 10 mcg/min, which is titrated upward by 10–20 mcg/min (to a maximum of 200 mcg/min) until mean arterial pressure drops by 10%. Hypotension (BP less than 100 mm Hg systolic) should be avoided. For sodium nitroprusside, the starting dosage is 5–10 mcg/min, with upward titration to a maximum dose of 400 mcg/min.

Isosorbide dinitrate, 20–40 mg orally three times daily, and nitroglycerin ointment, 2%, 15–16 mg (1.4 inches; 1 inch = 15 mg) every 6–8 hours, appear to be equally effective, although the ointment is generally reserved for inpatient use only. The nitrates are moderately effective in relieving shortness of breath, especially in patients with mild to moderate symptoms, but less successful—probably because they have little effect on cardiac output—in advanced heart failure. Nitrate therapy is generally well tolerated, but headaches and hypotension may limit the dose of all agents. The development of tolerance to long-term nitrate therapy occurs. This is minimized by intermittent therapy, especially if a daily 8- to 12-hour nitrate-free interval is used, but probably develops to some extent in most patients receiving these agents. Transdermal nitroglycerin patches have no sustained effect in patients with heart failure and should *not* be used for this indication.

**B. HYDRALAZINE**—Oral hydralazine is a potent arteriolar dilator; when used as a single agent, it has not been shown to improve symptoms or exercise tolerance during long-term treatment. The combination of nitrates and oral hydralazine produces greater hemodynamic effects as well as clinical benefits.

**7. Ivabradine**—Ivabradine inhibits the  $I_f$  channel in the sinus node and has the specific effect of slowing sinus rate. Ivabradine is approved by the FDA for use in stable patients with heart failure and heart rate of 70 beats/min who are taking the maximally tolerated dose of beta-blockers or in patients in whom beta-blockers are contraindicated. It is approved by the European Medicines Agency for use in patients with a heart rate of 75 beats/min or more. Both the US and the European guidelines give it a class IIa recommendation for patients in sinus rhythm with a heart rate of 70 beats/min or more with an EF of 35% or less, and persisting symptoms despite treatment with an evidence-based dose of beta-blocker (or a maximum tolerated dose below that), ACE inhibitor (or ARB), and an aldosterone antagonist (or ARB). In a trial of patients with chronic angina, ivabradine did not reduce cardiovascular events, and there may have been more events with ivabradine (than placebo) in patients with symptomatic angina.

**8. Vericiguat (a soluble guanylate cyclase stimulator)**—In January 2021, the FDA approved vericiguat to reduce the risk of cardiovascular death and heart failure hospitalization following a hospitalization for heart failure in patients with chronic heart failure and LVEF less than 45%. The VICTORIA trial showed a modest but significant

reduction in cardiovascular death and heart failure hospitalization with vericiguat, on top of other effective therapies, in this high-risk population.

**9. Combination of medical therapies**—Optimal management of chronic heart failure involves using combinations of proven life-saving therapies. In addition to ACE inhibitors and beta-blockers, patients who remain symptomatic should be considered for mineralocorticoid (aldosterone) receptor antagonists and for sacubitril/valsartan. This combination, titrated to full tolerated doses, with careful monitoring of kidney function and potassium, will provide the greatest pharmacologic benefit to the majority of patients with heart failure with reduced LVEF.

**10. Treatments that may cause harm in heart failure with reduced LVEF**—Several therapies should be *avoided*, when possible, in patients with systolic heart failure. These include thiazolidinediones (glitazones) that cause worsening heart failure, most calcium channel blockers (with the exception of amlodipine and felodipine), nonsteroidal anti-inflammatory medications, and cyclooxygenase-2 inhibitors that cause sodium and water retention and renal impairment, and the combination of an ACE inhibitor, ARB, and aldosterone blocker that increases the risk of hyperkalemia.

**11. Anticoagulation**—Patients with LV failure and reduced EF are at somewhat increased risk for developing intracardiac thrombi and systemic arterial emboli. However, this risk appears to be primarily in patients who are in atrial fibrillation, who have had thromboemboli, or who have had a large recent anterior MI. In general, these patients should receive warfarin for 3 months following the MI. Other patients with heart failure have embolic rates of approximately two per 100 patient-years of follow-up, which approximates the rate of major bleeding, and routine anticoagulation is not warranted except in patients with prior embolic events or mobile LV thrombi. A clinical trial of low-dose rivaroxaban failed to show substantial benefit in patients with heart failure with reduced LVEF.

**12. Antiarrhythmic therapy**—Patients with moderate to severe heart failure have a high incidence of both symptomatic and asymptomatic arrhythmias. Although less than 10% of patients have syncope or presyncope resulting from ventricular tachycardia, ambulatory monitoring reveals that up to 70% of patients have asymptomatic episodes of nonsustained ventricular tachycardia. These arrhythmias indicate a poor prognosis independent of the severity of LV dysfunction, but many of the deaths are probably not arrhythmia related. Beta-blockers, because of their marked favorable effect on prognosis in general and on the incidence of sudden death specifically, should be initiated in these as well as all other patients with heart failure (see Beta-Blockers). Other evidence-based therapies for heart failure, including ACE inhibitors, ARBs, mineralocorticoid receptor antagonists, and ARNIs, have all been shown to reduce sudden cardiac death. Empiric antiarrhythmic therapy with amiodarone did not improve outcome in the SCD-HeFT trial, and most other agents are contraindicated because of their proarrhythmic effects in

this population and their adverse effect on cardiac function. For patients with systolic heart failure and atrial fibrillation, a rhythm control strategy has not been shown to improve outcome compared to a rate control strategy and thus should be reserved for patients with a reversible cause of atrial fibrillation or refractory symptoms. Then, amiodarone is the medication of choice.

**13. Statin therapy**—Even though vascular disease is present in many patients with chronic heart failure, the role of statins has not been well defined in the heart failure population. The CORONA and the GISSI-HF trials show no benefits of statins in the chronic heart failure population.

### C. Nonpharmacologic Treatment

**1. Implantable cardioverter defibrillators (ICDs)**—Indications for ICDs include not only patients with symptomatic or asymptomatic arrhythmias but also patients with chronic heart failure and LV systolic dysfunction who are receiving contemporary heart failure treatments, including beta-blockers. In the second Multicenter Automatic Defibrillator Implantation Trial (MADIT II), 1232 patients with prior MI and an EF less than 30%, were randomized to an ICD or a control group. Mortality was 31% lower in the ICD group, which translated into 9 lives saved for each 100 patients who received a device and were monitored for 3 years. The Centers for Medicare and Medicaid Services provides reimbursement coverage to include patients with chronic heart failure and ischemic or nonischemic cardiomyopathy with an EF of 35% or less.

**2. Biventricular pacing (resynchronization)**—Many patients with heart failure due to systolic dysfunction have abnormal intraventricular conduction that results in dysynchronous and hence inefficient contractions. Several studies have evaluated the efficacy of “multisite” pacing, using leads that stimulate the RV from the apex and the LV from the lateral wall via the coronary sinus. Patients with wide QRS complexes (generally 120 msec or more), reduced EFs, and moderate to severe symptoms have been evaluated. Results from trials with up to 2 years of follow-up have shown an increase in EF, improvement in symptoms and exercise tolerance, and reduction in death and hospitalization. The best responders to cardiac resynchronization therapy are patients with wider QRS, left bundle branch block, and nonischemic cardiomyopathy, and the lowest responders are those with narrow QRS and non-left bundle branch block pattern. Thus, as recommended in the 2013 European guidelines, resynchronization therapy is indicated for patients with class II, III, and ambulatory class IV heart failure, EF of 35% or less, and left bundle branch block pattern with QRS duration of 120 msec or more. Patients with non-left bundle branch block pattern and prolonged QRS duration may be considered for treatment.

**3. Case management, diet, and exercise training**—Thirty to 50 percent of heart failure patients who are hospitalized will be readmitted within 3–6 months. Strategies to prevent clinical deterioration, such as case management, home monitoring of weight and clinical status, and patient adjustment of diuretics, can prevent rehospitalizations and should be part of the treatment regimen of advanced heart failure.

Involvement of a multidisciplinary team (rather than a single physician) and in-person (rather than just telephonic) communication appear to be important features of successful programs.

Patients should routinely practice moderate salt restriction (2–2.5 g sodium or 5–6 g salt per day). More severe sodium restriction is usually difficult to achieve and unnecessary because of the availability of potent diuretic agents.

Exercise training improves activity tolerance in significant part by reversing the peripheral abnormalities associated with heart failure and deconditioning. In severe heart failure, restriction of activity may facilitate temporary recrudescence. A large trial showed no significant benefit (nor harm) from a structured exercise training program on death or hospitalization, although functional status and symptoms were improved. Thus, in stable patients, a prudent increase in activity or a regular exercise regimen can be encouraged. Indeed, a gradual exercise program is associated with diminished symptoms and substantial increases in exercise capacity.

**4. Coronary revascularization**—Since underlying CAD is the cause of heart failure in the majority of patients, coronary revascularization has been thought to be able to both improve symptoms and prevent progression. While the STITCH trial failed to show an overall survival benefit from CABG among patients with multivessel coronary disease who were candidates for CABG, but who also had heart failure and an LVEF of 35% or less, at 5 years, there was benefit at 10 years of follow-up. Thus, revascularization does appear warranted for some patients with heart failure, including those with more severe angina or left main coronary disease (excluded from the STITCH trial).

**5. Cardiac transplantation**—Because of the poor prognosis of patients with advanced heart failure, cardiac transplantation is widely used. Many centers have 1-year survival rates exceeding 80–90%, and 5-year survival rates above 70%. Infections, hypertension and kidney dysfunction caused by cyclosporine, rapidly progressive coronary atherosclerosis, and immunosuppressant-related cancers have been the major complications. The high cost and limited number of donor organs require careful patient selection early in the course.

**6. Other surgical treatment options**—Externally powered and implantable ventricular assist devices can be used in patients who require ventricular support either to allow the heart to recover or as a bridge to transplantation. The latest generation devices are small enough to allow patients unrestricted mobility and even discharge from the hospital. Continuous flow devices appear to be more effective than pulsatile flow devices. However, complications are frequent, including bleeding, thromboembolism, and infection, and the cost is very high, exceeding \$200,000 in the initial 1–3 months.

Although 1-year survival was improved in the REMATCH randomized trial, all 129 patients died by 26 months. Newer-generation continuous flow pump ventricular assist devices have been shown to result in better survival than the first-generation pulsatile flow device used in REMATCH.

**7. Palliative care**—Despite the technologic advances of recent years, it should be remembered that many patients with chronic heart failure are elderly and have multiple comorbidities. Many of them will not experience meaningful improvements in survival with aggressive therapy. The goal of management for these patients and all those with serious illness should include symptomatic improvement and palliative care as they approach the end of life (see Chapter 5).

## ► Treatment: Heart Failure With Preserved LVEF

Although half of all heart failure occurs among patients with normal LVEF, often with diastolic dysfunction, *no therapies have been shown to improve survival in this population*. The mainstay of management of patients with heart failure with preserved EF is to manage fluid overload with diuretic therapy and to treat comorbidities like hypertension, diabetes, and arrhythmias.

### A. Correction of Reversible Causes

Hypertension, pericardial disease, and atrial tachycardias are potentially reversible factors that can contribute to heart failure with preserved LVEF. Since tachycardia is associated with shorter overall diastolic filling time, controlling accelerated heart rate may be important. With effective treatment available for familial and wild-type transthyretin amyloid cardiomyopathy, this diagnosis should be considered for patients with unexplained heart failure with preserved EF.

### B. Pharmacologic Treatment

**1. Diuretic therapy**—Diuretics are important to control symptoms of fluid overload in patients with heart failure with preserved LVEF, similar to symptoms from systolic heart failure.

**2. Inhibitors of the renin-angiotensin-aldosterone system**—ACE inhibitors and ARBs have *not* been shown to improve outcome in patients with heart failure and preserved LVEF, despite being good therapies for the comorbidity of hypertension. Sacubatril/valsartan does *not* substantially improve outcome in patients with heart failure and preserved LVEF. Spironolactone has *not* been shown to improve outcome in a large trial of patients with heart failure and preserved LVEF, but there may have been some benefit in patients enrolled in the Americas who had more clearly defined heart failure. Spironolactone should remain a therapeutic option, especially for patients who also have hypertension.

### C. Nonpharmacologic Treatment

Unlike in patients with heart failure and reduced LVEF, ICD and resynchronization device treatments do *not* have a role in patients with preserved LVEF. Revascularization for patients with heart failure and preserved LVEF should be guided by the same considerations as for patients with heart failure with reduced LVEF.

## ► Prognosis

Once manifest, heart failure with reduced LVEF carries a poor prognosis. Even with appropriate treatment, the 5-year mortality is approximately 50%. Mortality rates vary from less than 5% per year in those with no or few symptoms to greater than 30% per year in those with severe and refractory symptoms. These figures emphasize the critical importance of early detection and intervention. Higher mortality is related to older age, lower LVEF, more severe symptoms, chronic kidney disease, and diabetes. The prognosis of heart failure has improved in the past two decades, probably at least in part because of the more widespread use of ACE inhibitors and beta-blockers, which markedly improve survival in those with heart failure with reduced LVEF.

## ► When to Refer

Patients with new symptoms of heart failure not explained by an obvious cause should be referred to a cardiologist. Patients with continued symptoms of heart failure and reduced LVEF (35% or less) should be referred to a cardiologist for consideration of placement of an ICD or cardiac resynchronization therapy (if QRS duration is 120 msec or more, especially with left bundle branch block pattern).

## ► When to Admit

- Patients with unexplained new or worsened symptoms or positive cardiac biomarkers concerning for acute myocardial necrosis.
- Patients with hypoxia, gross fluid overload, or pulmonary edema not readily resolved in an outpatient setting.

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Yancy CW et al. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *Circulation*. 2017;136:e137. [PMID: 28455343]

## ACUTE HEART FAILURE & PULMONARY EDEMA

### ESSENTIALS OF DIAGNOSIS

- Acute onset or worsening of dyspnea at rest.
- Tachycardia, diaphoresis, cyanosis.
- Pulmonary rales, rhonchi; expiratory wheezing.
- Radiograph shows interstitial and alveolar edema with or without cardiomegaly.
- Arterial hypoxemia.

## ► General Considerations

Typical causes of acute cardiogenic pulmonary edema include acute MI or severe ischemia, exacerbation of chronic heart failure, acute severe hypertension, acute kidney injury, acute volume overload of the LV (valvular regurgitation), and mitral stenosis. By far the most common presentation in developed countries is one of acute or subacute deterioration of chronic heart failure, precipitated by discontinuation of medications, excessive salt intake, myocardial ischemia, tachyarrhythmias (especially rapid atrial fibrillation), or intercurrent infection. Often in the latter group, there is preceding volume overload with worsening edema and progressive shortness of breath for which earlier intervention can usually avoid the need for hospital admission.

## ► Clinical Findings

Acute pulmonary edema presents with a characteristic clinical picture of severe dyspnea, the production of pink, frothy sputum, and diaphoresis and cyanosis. Rales are present in all lung fields, as are generalized wheezing and rhonchi. Pulmonary edema may appear acutely or subacutely in the setting of chronic heart failure or may be the first manifestation of cardiac disease, usually acute MI, which may be painful or silent. Less severe decompensations usually present with dyspnea at rest, rales, and other evidence of fluid retention but without severe hypoxia.

Noncardiac causes of pulmonary edema include intravenous opioids, increased intracerebral pressure, high altitude, sepsis, medications, inhaled toxins, transfusion reactions, shock, and disseminated intravascular coagulation. These are distinguished from cardiogenic pulmonary edema by the clinical setting, history, and physical examination. Conversely, in most patients with cardiogenic pulmonary edema, an underlying cardiac abnormality can usually be detected clinically or by ECG, chest radiograph, or echocardiogram.

The chest radiograph reveals signs of pulmonary vascular redistribution, blurriness of vascular outlines, increased

interstitial markings, and, characteristically, the butterfly pattern of distribution of alveolar edema. The heart may be enlarged or normal in size depending on whether heart failure was previously present. Assessment of cardiac function by echocardiography is important, since a substantial proportion of patients has normal EFs with elevated atrial pressures due to diastolic dysfunction. In cardiogenic pulmonary edema, BNP is elevated, and the PCWP is invariably elevated, usually over 25 mm Hg. In noncardiogenic pulmonary edema, the wedge pressure may be normal or even low.

## ► Treatment

In full-blown pulmonary edema, the patient should be placed in a sitting position with legs dangling over the side of the bed; this facilitates respiration and reduces venous return. **Oxygen** is delivered by mask to obtain an arterial  $\text{Po}_2$  greater than 60 mm Hg. Noninvasive pressure support ventilation may improve oxygenation and prevent severe  $\text{CO}_2$  retention while pharmacologic interventions take effect. However, if respiratory distress remains severe, endotracheal intubation and mechanical ventilation may be necessary.

**Morphine** is highly effective in pulmonary edema and may be helpful in less severe decompensations when the patient is uncomfortable. The initial dosage is 2–8 mg intravenously (subcutaneous administration is effective in milder cases) and may be repeated after 2–4 hours. Morphine increases venous capacitance, lowering LA pressure, and relieves anxiety, which can reduce the efficiency of ventilation. However, morphine may lead to  $\text{CO}_2$  retention by reducing the ventilatory drive. It should be avoided in patients with opioid-induced pulmonary edema, who may improve with opioid antagonists, and in those with neurogenic pulmonary edema.

**Intravenous diuretic therapy** (furosemide, 40 mg, or bumetanide, 1 mg—or higher doses if the patient has been receiving long-term diuretic therapy) is usually indicated even if the patient has not exhibited prior fluid retention. These agents produce venodilation prior to the onset of diuresis. The DOSE trial has shown that, for acute decompensated heart failure, bolus doses of furosemide are of similar efficacy as continuous intravenous infusion, and that higher-dose furosemide (2.5 times the prior daily dose) resulted in more rapid fluid removal without a substantially higher risk of kidney impairment.

**Nitrate therapy** accelerates clinical improvement by reducing both BP and LV filling pressures. Sublingual nitroglycerin or isosorbide dinitrate, topical nitroglycerin, or intravenous nitrates will ameliorate dyspnea rapidly prior to the onset of diuresis, and these agents are particularly valuable in patients with accompanying hypertension.

**Intravenous nesiritide**, a recombinant form of human BNP, is a potent vasodilator that reduces ventricular filling pressures and improves cardiac output. Its hemodynamic effects resemble those of intravenous nitroglycerin with a more predictable dose-response curve and a longer duration of action. In clinical studies, nesiritide (administered as 2 mcg/kg by intravenous bolus injection followed by an infusion of 0.01 mcg/kg/min, which may be up-titrated if needed) produced a rapid improvement in both dyspnea and hemodynamics. The primary adverse

effect is hypotension, which may be symptomatic and sustained. Because most patients with acute heart failure respond well to conventional therapy, the role of nesiritide may be primarily in patients who continue to be symptomatic after initial treatment with diuretics and nitrates.

A randomized placebo-controlled trial of 950 patients evaluating intravenous milrinone in patients admitted for decompensated heart failure who had no definite indications for inotropic therapy showed no benefit in increasing survival, decreasing length of admission, or preventing readmission. In addition, rates of sustained hypotension and atrial fibrillation were significantly increased. Thus, the role of positive inotropic agents appears to be limited to patients with refractory symptoms and signs of low cardiac output, particularly if life-threatening vital organ hypoperfusion (such as deteriorating kidney function) is present. In some cases, dobutamine or milrinone may help maintain patients who are awaiting cardiac transplantation.

Bronchospasm may occur in response to pulmonary edema and may itself exacerbate hypoxemia and dyspnea. Treatment with inhaled beta-adrenergic agonists or intravenous aminophylline may be helpful, but both may also provoke tachycardia and supraventricular arrhythmias.

In most cases, pulmonary edema responds rapidly to therapy. When the patient has improved, the cause or precipitating factor should be ascertained. In patients without prior heart failure, evaluation should include echocardiography and, in many cases, cardiac catheterization and coronary angiography. Patients with acute decompensation of chronic heart failure should be treated to achieve a euvolemic state and have their medical regimen optimized. Generally, an oral diuretic and an ACE inhibitor should be initiated, with efficacy and tolerability confirmed prior to discharge. In selected patients, early but careful initiation of beta-blockers in low doses should be considered.

## MYOCARDITIS & THE CARDIOMYOPATHIES

### INFECTIOUS MYOCARDITIS



#### ESSENTIALS OF DIAGNOSIS

- ▶ Often follows an upper respiratory infection.
- ▶ May present with chest pain (pleuritic or nonspecific) or signs of heart failure.
- ▶ Echocardiogram documents cardiomegaly and contractile dysfunction. Initial heart size is generally normal with thickened walls.
- ▶ Myocardial biopsy, though not sensitive, may reveal a characteristic inflammatory pattern. MRI has a role in diagnosis.
- ▶ COVID-19 myocarditis impacts between 3% and 58% of people with COVID-19 based on underlying myocardial risk and imaging.

## ► General Considerations

Cardiac dysfunction due to primary myocarditis is presumably caused by either an acute viral infection or a post viral immune response. Secondary myocarditis is the result of inflammation caused by nonviral pathogens, medications, chemicals, physical agents, or inflammatory diseases (such as systemic lupus erythematosus). The list of both infectious and noninfectious causes of myocarditis is extensive (Table 10–13).

Myopericarditis due to the coronavirus has been of particular concern during the COVID-19 pandemic. Much

**Table 10–13.** Causes of myocarditis.

### 1. INFECTIOUS CAUSES

**RNA viruses:** Picornaviruses (coxsackie A and B, echovirus, poliovirus, hepatitis virus), orthomyxovirus (influenza), paramyxoviruses (respiratory syncytial virus, mumps), togaviruses (rubella), flaviviruses (dengue fever, yellow fever), SARS-CoV-2

**DNA viruses:** Adenovirus (A1, 2, 3, and 5), erythrovirus (B19 and 2), herpesviruses (human herpes virus 6 A and B, cytomegalovirus, Epstein-Barr virus, varicella-zoster), retrovirus (HIV)

**Bacteria:** Chlamydia (*Chlamydophila pneumoniae*, *C psittaci*), *Haemophilus influenzae*, *Legionella*, *Pneumophilia*, *Brucella*, *Clostridium*, *Francisella tularensis*, *Neisseria meningitidis*, *Mycobacterium* (tuberculosis), *Salmonella*, *Staphylococcus*, *streptococcus A*, *Streptococcus pneumoniae*, tularemia, tetanus, syphilis, *Vibrio cholera*

**Spirocheta:** *Borrelia recurrentis*, leptospira, *Treponema pallidum*

**Rickettsia:** *Coxiella burnetii*, *R rickettsii*, *R prowazekii*

**Fungi:** *Actinomycetes*, *Aspergillus*, *Candida*, *Cryptococcus*, *Histoplasma*, *Noxardia*

**Protozoa:** *Entamoeba histolytica*, *Plasmodium falciparum*, *Trypanosoma cruzi*, *T burchi*, *T gondii*, *Leishmania*

**Helminthic:** *Ascaris*, *Echinococcus granulosus*, *Schistosoma*, *Trichinella spiralis*, *Wuchereria bancrofti*

### 2. NONINFECTIOUS CAUSES

**Autoimmune diseases:** Dermatomyositis, inflammatory bowel disease, rheumatoid arthritis, Sjögren syndrome, systemic lupus erythematosus, granulomatosis with polyangiitis, giant cell myocarditis

**Medications:** Aminophylline, amphetamine, anthracycline, catecholamines, chloramphenicol, cocaine, cyclophosphamide, doxorubicin, 5-FU, mesylate, methysergide, phenytoin, trastuzumab, zidovudine

**Hypersensitivity reactions due to medications:** Azithromycin, benzodiazepines, clozapine, cephalosporins, dapsone, dobutamine, lithium, diuretics, thiazide, methylldopa, mexiletine, streptomycin, sulfonamides, nonsteroidal anti-inflammatory drugs, tetanus toxoid, tetracycline, tricyclic antidepressants

**Hypersensitivity reactions due to venoms:** Bee, wasp, black widow spider, scorpion, snake

**Systemic diseases:** Eosinophilic granulomatosis with polyangiitis (formerly known as Churg-Strauss syndrome), collagen diseases, sarcoidosis, Kawasaki disease, systemic sclerosis

**Other:** Heat stroke, hypothermia, transplant rejection, radiation injury

remains unknown. There is speculation that the SARS-CoV-2 spike protein may be able to bind to the ACE-2 membrane receptor on cardiomyocytes creating direct cellular injury and T-lymphocyte-mediated cytotoxicity augmented by a cytokine storm. This process activates more T cells and furthers a cycle of T-cell activation and further release of cytokines.

The currently accepted definition of myocarditis is biopsy dependent and includes the observation of 14 or more lymphocytes/mcL including up to 4 monocytes/mcL with the presence of 7 or more CD3-positive T lymphocytes/mcL. Injury can be **fulminant**, **subclinical**, or **chronic**. Both cellular and humoral inflammatory processes contribute to the progression to chronic injury, and there are subgroups that appear to benefit from immunosuppression.

Genetic predisposition is a likely factor in at least a few cases. Autoimmune myocarditis (eg, giant cell myocarditis) may occur with no identifiable viral infection. The heterogeneity of the clinical syndromes and the incomplete understanding of the immunopathology hinder a more complete understanding of the mechanisms involved.

With COVID-19, myocarditis appears to affect ethnic groups disproportionately with death rates highest among Blacks likely due to both an increase in comorbidities and health care disparities. The true incidence of myocarditis is unclear. In a German study of 100 patients who had recovered from COVID-19, cardiac MRI revealed some degree of abnormality in 78 patients, with inflammation noted in 60, independent of severity of the illness.

## ► Clinical Findings

### A. Symptoms and Signs

Patients may present several days to a few weeks after the onset of an acute febrile illness or a respiratory infection or they may present with heart failure without antecedent symptoms. The onset of heart failure may be gradual or may be abrupt and fulminant. In acute fulminant myocarditis, low output and shock may be present with severely depressed LV systolic function. The LV chamber size is typically not very enlarged. A pericardial friction rub may be present. In the European Study of Epidemiology and Treatment of Inflammatory Heart Disease, 72% of participants had dyspnea, 32% had chest pain, and 18% had arrhythmias. Pulmonary and systemic emboli may occur. Pleural-pericardial chest pain is common. Examination reveals tachycardia, a gallop rhythm, and other evidence of heart failure or conduction defects. At times, the presentation may mimic an acute MI with ST changes, positive cardiac markers, and regional wall motion abnormalities despite normal coronaries. Microaneurysms may also occur and may be associated with serious ventricular arrhythmias. It has been estimated that approximately 10% of all dilated cardiomyopathy patients have viral myocarditis as the cause.

### B. ECG and Chest Radiography

ECG may show sinus tachycardia, other arrhythmias, non-specific repolarization changes, and intraventricular conduction abnormalities. The presence of Q waves or left

bundle branch block portends a higher rate of death or cardiac transplantation. Ventricular ectopy may be the initial and only clinical finding. The chest radiograph is nonspecific, but cardiomegaly is frequent, though not universal. Evidence for pulmonary venous hypertension is common and frank pulmonary edema may be present.

### C. Diagnostic Studies

There is no specific laboratory finding that is consistently present, though the white blood cell count is usually elevated and the sedimentation rate and CRP usually are increased. Troponin I or T levels are elevated in about one-third of patients, but CK-MB is elevated in only 10%. Other biomarkers, such as BNP and NT-proBNP, are usually elevated. Echocardiography provides the most convenient way of evaluating cardiac function and can exclude many other processes. MRI with gadolinium enhancement reveals spotty areas of injury throughout the myocardium, but both T2- and T1-weighted images are needed to achieve optimal results; correlation with endomyocardial biopsy results is poor.

### D. Endomyocardial Biopsy

**Confirmation of myocarditis still requires histologic evidence.** The AHA/ACC/ESC class I recommendations for biopsy are (1) in patients with heart failure, a normalized or dilated LV less than 2 weeks after onset of symptoms, and hemodynamic compromise; or (2) in patients with a dilated LV 2 weeks to 3 months after onset of symptoms, new ventricular arrhythmias or AV nodal block (Mobitz II or complete heart block) or who do not respond to usual care after 1–2 weeks. In some cases, the identification of inflammation without viral genomes by polymerase chain reaction (PCR) suggests that immunosuppression might be useful. Because the cardiac involvement is often patchy, the diagnosis even with biopsy can be missed in up to one-half of cases.

## ► Treatment & Prognosis

Patients with fulminant myocarditis may present with acute cardiogenic shock. Acute myocarditis has been implicated as a cause of sudden death in 5–22% of such cases in athletes younger than 35 years. The ventricles are usually not dilated but thickened (possibly due to myxedema). There is a high death rate. Traditionally, there has been a paradox noted, wherein patients with fulminant myocarditis were thought to more likely fully recover after the event. Several recent observations have challenged this concept. Patients with subacute disease have a dilated cardiomyopathy and generally make an incomplete recovery. Those who present with chronic disease tend to have only mild dilation of the LV and eventually present with a more restrictive cardiomyopathy. Treatment is directed toward the clinical scenario with ACE inhibitors and beta-blockers if LVEF is less than 40%. Nonsteroidal anti-inflammatory medications should be used if myopericarditis-related chest pain occurs. Colchicine has been suggested if pericarditis predominates. Arrhythmias should be suppressed.

For COVID-19 related myocarditis, treatment is generally supportive. A 2020 review noted that of the attempted therapies, such as remdesivir, glucocorticoids, IL-6 inhibitors (tocilizumab), intravenous immunoglobulin (IVIG), and colchicine, only corticosteroids appeared to have any favorable effect on outcomes. The data are still incomplete, however, as of early 2021.

Specific antimicrobial therapy is indicated when an infecting agent is identified. Exercise should be limited during the recovery phase. Some experts believe digoxin should be avoided, and it likely has little value in this setting anyway. Controlled trials of immunosuppressive therapy with corticosteroids and IVIG have not suggested a benefit, though some recommend IVIG given at 2 g/kg over 24 hours in proven cases. Uncontrolled trials suggest that interferon might have a supportive role. Similarly, antiviral medication (such as pleconaril for enteroviruses) has been tried empirically. Studies are lacking as to when to discontinue the chosen therapy if the patient improves. Patients with fulminant myocarditis require aggressive short-term support, including an IABP or an LV assist device. If severe pulmonary infiltrates accompany the fulminant myocarditis, extracorporeal membrane oxygenation (ECMO) support may be temporarily required and has had notable success.

The question of what to do with the athlete in whom evidence of COVID-19 myocarditis has developed has led to a series of national discussions, some prompted by the cardiac MRI findings in young adults with minimal symptoms. The higher troponin levels associated with poorer outcomes have generally occurred only in hospitalized patients. The findings of an abnormal cardiac MRI have not consistently proven to result in any long-term cardiac injury. Table 10–14 outlines the suggested guidelines by a recent Task Force from the American College of Cardiology Sports and Exercise Section.

**Table 10–14.** American College of Cardiology Sports and Exercise Section Guidelines for athletes with COVID-19 myocarditis.

#### Myocarditis diagnosis if both of the following are present

- A clinical syndrome of < 3 months, duration
- Otherwise, unexplained increase in serum troponin levels, ECG changes, arrhythmias, high-grade AV block, regional wall motion abnormalities, or pericardial effusion. MRI findings suggesting myocarditis including T1- or T2-weighted imaging or late gadolinium enhancement.

#### Sports eligibility after myocarditis

- Must obtain a resting echocardiogram, 24-hour ambulatory ECG monitoring, and an exercise ECG no earlier than 3–6 months after the illness (class I, LOE C)
- Can resume exercise training if ALL of the following are met (class IIa, LOE C)
  - Normal ventricular function
  - Serum markers of myocardial injury, heart failure, and inflammation have returned to normal
  - Clinically relevant arrhythmias on ambulatory ECG monitoring or exercise ECG are absent.

AV, atrioventricular; ECG, electrocardiogram; LOE, level of evidence; MRI, magnetic resonance imaging.

## ► When to Refer

Patients in whom myocarditis is suspected should be seen by a cardiologist at a tertiary care center where facilities are available for diagnosis and therapies available should a fulminant course ensue. The facility should have ventricular support devices and transplantation options available.

- Kim JH et al. Coronavirus disease 2019 and the athletic heart: emerging perspectives on pathology, risks, and return to play. *JAMA Cardiol.* 2021;6:219. [PMID: 33104154]
- Moslehi JJ et al. Fulminant myocarditis: evolving diagnosis, evolving biology, evolving prognosis. *J Am Coll Cardiol.* 2019;74:312. [PMID: 31319913]
- Puntmann VO et al. Outcomes of cardiovascular magnetic resonance imaging in patients recently recovered from coronavirus disease 2019 (COVID-19). *JAMA Cardiol.* 2020;5:1265. [PMID: 32730619]
- Sawalha K et al. Systematic review of COVID-19 related myocarditis: insights on management and outcome. *Cardiovasc Revasc Med.* 2021;23:107. [PMID: 32847728]
- Sharma AN et al. Fulminant myocarditis: epidemiology, pathogenesis, diagnosis, and management. *Am J Cardiol.* 2019;124:1954. [PMID: 31679645]
- Siripanthong B et al. Recognizing COVID-19-related myocarditis: the possible pathophysiology and proposed guideline for diagnosis and management. *Heart Rhythm.* 2020;17:1463. [PMID: 32387246]

## NONINFECTIOUS MYOCARDITIS

A variety of medications, illicit drugs, and toxic substances can produce acute or chronic myocardial injury; the clinical presentation varies widely. The phenothiazines, lithium, chloroquine, disopyramide, antimony-containing compounds, and arsenicals can also cause ECG changes, arrhythmias, or heart failure. Hypersensitivity reactions to sulfonamides, penicillins, and aminosalicylic acid as well as other medications can result in cardiac dysfunction. Radiation can cause an acute inflammatory reaction as well as a chronic fibrosis of heart muscle, usually in conjunction with pericarditis.

Cardiotoxicity from cocaine may occur from coronary artery spasm, MI, arrhythmias, and myocarditis. A cocaine cardiomyopathy has also been described. Because many of these processes are believed to be mediated by cocaine's inhibitory effect on norepinephrine reuptake by sympathetic nerves, beta-blockers have been used in patients with fixed stenosis. In documented coronary spasm, calcium channel blockers and nitrates may be effective. Usual therapy for heart failure or conduction system disease is warranted when symptoms occur. Other recreational drug use has been associated with myocarditis in various case reports.

Systemic disorders are also associated with myocarditis. These include giant cell myocarditis, eosinophilic myocarditis, celiac disease, granulomatosis with polyangiitis, and sarcoidosis. A benefit from immunosuppressive therapy, especially in giant cell myocarditis has been suggested in a number of observational studies, including those directed primarily at T cells (ie, using muromonab-CD3). Treatment of eosinophilic myocarditis includes the use of high-dose corticosteroids and removal of the offending medication or underlying trigger, if known. Most studies

suggest that HIV is only indirectly responsible for HIV cardiomyopathy, and other factors, gp 120 protein, adverse reaction to antiretroviral therapy, and opportunistic infections have been implicated more often. Epstein-Barr and herpes simplex viruses have been identified in some patients' myocardium.

The problem of cardiovascular side effects from cancer chemotherapy agents is an ever growing one and has spawned a new clinical area in cardiology called **cardio-oncology**. Anthracyclines (doxorubicin, daunorubicin, idarubicin, epirubicin, and mitoxantrone) remain the cornerstone of treatment of many malignancies but may result in cardiomyopathy. Heart failure can be expected in 5% of patients treated with a cumulative dose of 400–450 mg/m<sup>2</sup>, and this rate is doubled if the patient is over age 65. While symptoms and evidence for myocardial dysfunction usually appear within 1 year of starting therapy, late onset manifestation of heart failure may appear up to a decade later. The major mechanism of cardiotoxicity is thought to be due to oxidative stress inducing both apoptosis and necrosis of myocytes. There is also disruption of the sarcomere. This pathologic understanding is the rationale behind the superoxide dismutase mimetic and iron-chelating agent, dexrazoxane, to protect from the injury. The use of trastuzumab in combination with anthracyclines increases the risk of cardiac dysfunction up to 28%; this has been an issue since combined use of these agents is particularly effective in *HER2*-positive breast cancer. Other risk factors for patients receiving anthracyclines include the use of paclitaxel, concurrent radiation, and preexisting cardiovascular disease (including hypertension, peripheral vascular disease, CAD, and diabetes). A summary of cardiotoxic cancer therapeutic agents and their role may be found in the 2019 AHA statement on cardio-oncology.

In patients receiving chemotherapy, it is important to look for subtle signs of cardiovascular compromise. Serial echocardiography, cardiac MR, or both can provide concrete data regarding LV function. Echo/Doppler myocardial global strain abnormalities may be the first abnormality observed (even prior to a drop in the LVEF) and assessment of the T2 signal from cardiac MRI may also provide early detection of cardiotoxicity. Biomarkers such as BNP or NT-proBNP may be of some value when serial measures are obtained. Other biomarkers may appear early in the course of myocardial injury (especially troponin and myeloperoxidase) and may allow for early detection of cardiotoxicity before other signs become evident. There is some evidence that beta-blocker therapy may reduce the negative effects on myocardial function. There are anecdotal data from animal models that nonsteroidal anti-inflammatory drugs may be harmful in patients with myocarditis. They should be avoided along with alcohol and strenuous physical exercise.

## ► When to Refer

Many patients with myocardial injury from toxic agents can be monitored safely if ventricular function remains relatively preserved (EF greater than 40%) and no heart failure symptoms occur. Diastolic dysfunction may be subtle.

Once heart failure or a reduced LVEF becomes evident or significant conduction system disease becomes manifest, the patient should be evaluated and monitored by a cardiologist in case myocardial dysfunction worsens and further intervention becomes warranted.

Campia U et al. Cardio-oncology: vascular and metabolic perspectives: a scientific statement from the American Heart Association. Circulation. 2019;139:e579. [PMID: 30786722]

Ye L et al. Myocardial strain imaging by echocardiography for the prediction of cardiotoxicity of chemotherapy treated patients: a meta-analysis. JACC Cardiovasc Imaging. 2020;13:881. [PMID: 31734206]

Yu AF et al. Cardiac magnetic resonance and cardio-oncology: does T(2) signal the end of anthracycline cardiotoxicity? J Am Coll Cardiol. 2019;73:792. [PMID: 30784672]

deficiency of thiamine, selenium, and carnitine have also been documented. Dilated cardiomyopathy may also be caused by prolonged tachycardia either from supraventricular arrhythmias, from very frequent PVCs (more than 15% of heart beats), or from frequent RV pacing. Dilated cardiomyopathy is also associated with HIV, Chagas disease, rheumatologic disorders, iron overload, sleep apnea, amyloidosis, sarcoidosis, chronic alcohol usage, end-stage kidney disease, or cobalt exposure (“Quebec beer-drinkers cardiomyopathy”). Peripartum cardiomyopathy and stress-induced disease (tako-tsubo) are discussed separately.

## ► Clinical Findings

### A. Symptoms and Signs

In most patients, symptoms of heart failure develop gradually. It is important to seek out a history of familial dilated cardiomyopathy and to identify behaviors that might predispose patients to the disease. The physical examination reveals rales, an elevated JVP, cardiomegaly, S<sub>3</sub> gallop rhythm, often the murmurs of functional mitral or tricuspid regurgitation, peripheral edema, or ascites. In severe heart failure, Cheyne-Stokes breathing, pulsus alternans, pallor, and cyanosis may be present.

### B. ECG and Chest Radiography

The major findings are listed in Table 10–15. Sinus tachycardia is common. Other common abnormalities include left bundle branch block and ventricular or atrial arrhythmias. The chest radiograph reveals cardiomegaly, evidence for left and/or right heart failure, and pleural effusions (right more frequently than left).

### C. Diagnostic Studies

In the 2017 AHA/ACCF heart failure guideline focused update, patients with dyspnea should have a BNP or NT-proBNP measured to help establish prognosis and disease severity (class I, level of evidence [LOE] A).

An echocardiogram is indicated to exclude unsuspected valvular or other lesions and confirm the presence of ventricular dilatation, reduced LV systolic function and associated RV systolic dysfunction, or pulmonary hypertension. Mitral Doppler inflow patterns also help in the diagnosis of concomitant diastolic dysfunction. Color flow Doppler can reveal tricuspid or mitral regurgitation, and continuous Doppler can estimate PA pressures. Intracavitary thrombosis is occasionally seen. Exercise or pharmacologic stress myocardial perfusion imaging may uncover underlying coronary disease. Radionuclide ventriculography provides a noninvasive measure of the EF and both RV and LV wall motion, though its use has been supplanted by cardiac MRI in most institutions. Cardiac MRI is particularly helpful in inflammatory or infiltrative processes, such as sarcoidosis or hemochromatosis, and is the diagnostic study of choice for RV dysplasia. MRI can also help define an ischemic etiology by noting gadolinium hyperenhancement consistent with myocardial scar from infarction or prior myocarditis. Cardiac catheterization is seldom of specific value unless myocardial ischemia is suspected, although right

## DILATED CARDIOMYOPATHY



### ESSENTIALS OF DIAGNOSIS

- ▶ Symptoms and signs of heart failure.
- ▶ Echocardiogram confirms LV dilation, thinning, and global dysfunction.
- ▶ Severity of RV dysfunction critical in long-term prognosis.

## ► General Considerations

Heart failure definitions have changed over the years and patients with a dilated cardiomyopathy are generally placed into the category of heart failure with reduced EF where the LVEF is defined as less than or equal to 40%. *In about half of the patients in this category, there is LV enlargement and it is this group that defines dilated cardiomyopathy.* This is a large group of heterogeneous myocardial disorders characterized by reduced myocardial contractility in the absence of abnormal loading conditions such as with hypertension or valvular disease. The prevalence averages 36 cases/100,000 in the United States and accounts for approximately 10,000 deaths annually. Blacks are afflicted three times as often as Whites. The prognosis is poor with 50% mortality at 5 years once symptoms emerge.

The causes are multiple and diverse. Up to 20–35% have a familial etiology. It is common for hereditary causes to first present with conduction system disease prior to a reduced LVEF. A 2020 report of 2538 patients with a dilated cardiomyopathy in whom genetics were available suggested a clear association with at least 12 differing genes. Recent attention has focused particularly on the lamin A/C genotype. While a large proportion of dilated cardiomyopathy causes are listed as idiopathic, it is likely that genetic variants may be responsible for many of these. Endocrine, inflammatory, and metabolic causes include obesity, diabetes, thyroid disease, celiac disease, systemic lupus erythematosus, acromegaly, and growth hormone deficiency. Toxic, drug-induced, and inflammatory causes are listed in the prior section. Nutritional diseases such as

**Table 10–15.** Classification of the cardiomyopathies.

|   | Dilated  | Hypertrophic   | Restrictive   |
|---|--|--|---|
| Frequent causes                               | Idiopathic, alcoholic, major catecholamine discharge, myocarditis, postpartum, chemotherapy, endocrinopathies, genetic diseases, burnt out HOCM, CAD, tachycardia-induced, cocaine | Hereditary syndrome, possibly chronic hypertension in older adults   | Amyloidosis, post-radiation, post-open heart surgery, diabetes, endomyocardial fibrosis, Fabry disease, sarcoidosis           |
| Symptoms                                      | Left or biventricular heart failure  | Dyspnea, chest pain, syncope   | Dyspnea, fatigue, right heart failure > left heart failure  |
| Physical examination                          | Cardiomegaly, $S_3$ , elevated jugular venous pressure, rales  | Sustained point of maximal impulse, $S_4$ , variable systolic murmur, bisferiens carotid pulse   | Elevated jugular venous pressure  |
| Electrocardiogram                             | ST-T changes, conduction abnormalities, ventricular ectopy   | Left ventricular hypertrophy, exaggerated septal Q waves   | ST-T changes, conduction abnormalities, low voltage   |
| Chest radiograph                              | Enlarged heart, pulmonary congestion   | Mild cardiomegaly  | Mild to moderate cardiomegaly   |
| Echocardiogram, nuclear studies, MRI, PET, CT | Left ventricular dilation and dysfunction  | Left ventricular hypertrophy, asymmetric septal or other myocardial wall thickness > 15 mm, small left ventricular size, normal or supranormal function, systolic anterior mitral motion, diastolic dysfunction. May be nonobstructive or apical | Small or normal left ventricular size, normal or mildly reduced left ventricular function. Gadolinium hyperenhancement on MRI |
| Cardiac catheterization                       | Left ventricular dilation and dysfunction, high diastolic pressures, low cardiac output. Coronary angiography important to exclude ischemic cause                                  | Small, hypercontractile left ventricle, dynamic outflow gradient, diastolic dysfunction  | High diastolic pressure, "square root" sign, normal or mildly reduced left ventricular function                               |

CAD, coronary artery disease; CT, computed tomography; HOCM, hypertrophic obstructive cardiomyopathy; MRI, magnetic resonance imaging; PET, positron emission tomography.

heart catheterization should be considered to help guide therapy when the clinical syndrome is not clear cut (class I indication, LOE C). Myocardial biopsy is rarely useful in establishing the diagnosis, although occasionally the underlying cause (eg, sarcoidosis, hemochromatosis) can be discerned. Its use is considered a class IIa indication with LOE of C. It should not be used routinely. Biopsy is most useful in transplant rejection.

## ► Treatment

The management of heart failure is outlined in the section on heart failure. Standard therapy includes control of BP and of contributing factors such as obesity, smoking, diabetes or potentially cardiotoxic agents. All patients with a remote history of MI or acute coronary syndrome and reduced LVEF should be given ACE inhibitors, ARBs, or sacubitril/valsartan. Beta-blockers should be included in this population as well. **All patients with dilated cardiomyopathy regardless of etiology should be treated with beta-blockers and ACE inhibitors. If still symptomatic, aldosterone antagonists should be added, and ARNI used instead of an ACE inhibitor or ARB.** The use of the combination of all three of ACE inhibition, ARB, and aldosterone antagonists can create harm, though, and is

discouraged due to concerns for hyperkalemia. Calcium channel blockers should be avoided except as necessary to control ventricular response in atrial fibrillation or flutter. If congestive symptoms are present, diuretics and an aldosterone antagonist should be added. In patients with class II–IV heart failure symptoms, an aldosterone receptor antagonist should be added when the LVEF is less than 35% (unless contraindicated). Care in the use of mineralocorticoid receptor antagonists is warranted when the glomerular filtration rate is less than 30 mL/min/1.73 m<sup>2</sup> or when the potassium is elevated. All patients with diabetes should be taking mineralocorticoid antagonists if the LVEF is less than or equal to 40%. Systemic BP control is extremely important. Use of the angiotensin receptor-neprilysin inhibitor, sacubitril/valsartan, has been approved for NYHA Heart Failure of Functional class II–IV. If the resting heart rate is greater than 70 beats per minute, the LVEF is less than 35%, and the patient has chronic stable heart failure, the use of ivabradine to slow the heart rate has also been approved. Ivabradine should not replace other beta-blockers, however. Digoxin is a second-line medication but remains favored as an adjunct by some clinicians; digoxin may be beneficial to reduce recurrent hospitalizations and to control the ventricular response in atrial fibrillation in sedentary patients. Given the question of abnormal

nitric oxide utilization in Blacks, the use of hydralazine-nitrate combination therapy is recommended in this population. Sodium restriction is helpful, especially in acute heart failure. Continuous positive airway pressure can improve LV function in patients with sleep apnea.

When atrial fibrillation is present, heart rate control is important if sinus rhythm cannot be established or maintained. There are few data, however, to suggest an advantage of sinus rhythm over atrial fibrillation on long-term outcomes. Many patients may be candidates for cardiac synchronization therapy with biventricular pacing if there is significant mitral regurgitation and the QRS width is greater than 150 msec.

To help prevent sudden death, an ICD is reasonable (class IIa, LOE B) in asymptomatic ischemic cardiomyopathy patients with an LVEF of less than 30% on appropriate medical therapy (at least 3 months post-MI). Cardiac rehabilitation and exercise training have consistently been found to improve clinical status.

Few cases of cardiomyopathy are amenable to specific therapy for the underlying cause. Alcohol use should be discontinued, since there is often marked recovery of cardiac function following a period of abstinence in alcoholic cardiomyopathy. Endocrine causes (hyperthyroidism or hypothyroidism, acromegaly, and pheochromocytoma) should be treated. Immunosuppressive therapy is not indicated in chronic dilated cardiomyopathy. There are some patients who may benefit from implantable LV assist devices either as a bridge to transplantation or as a temporary measure until cardiac function returns. LV assist devices can be considered as *destination therapy* in patients who are not candidates for cardiac transplantation. Arterial and pulmonary emboli are more common in dilated cardiomyopathy than in ischemic cardiomyopathy, and suitable candidates may benefit from long-term anticoagulation. All patients with atrial fibrillation should be so treated. DOACs are preferred over warfarin unless there is associated mitral stenosis. Either warfarin or a DOAC should be considered when a mobile LV thrombus is observed on the echocardiogram.

## ► Prognosis

The prognosis of dilated cardiomyopathy without clinical heart failure is variable, with some patients remaining stable, some deteriorating gradually, and others declining rapidly. Once heart failure is manifest, the natural history is similar to that of other causes of heart failure, with an annual mortality rate of around 11–13%. The underlying cause of heart failure has prognostic value in patients with unexplained cardiomyopathy. Patients with peripartum cardiomyopathy or stress-induced cardiomyopathy appear to have a better prognosis than those with other forms of cardiomyopathy. Patients with cardiomyopathy due to infiltrative myocardial diseases, HIV infection, or doxorubicin therapy have an especially poor prognosis.

## ► When to Refer

Patients with new or worsening symptoms of heart failure with dilated cardiomyopathy should be referred to a

cardiologist. Patients with continued symptoms of heart failure and reduced LVEF (35% or less) should be referred for consideration of placement of an ICD or cardiac resynchronization therapy (if QRS duration is 150 msec or more, especially with a left bundle branch block pattern). Patients with advanced refractory symptoms should be referred for consideration of heart transplant or LV assist device therapy.

## ► When to Admit

Patients with hypoxia, fluid overload, or pulmonary edema not readily resolved in an outpatient setting should be admitted.

Mazzarotto F et al. Reevaluating the genetic contribution of monogenetic dilated cardiomyopathy. *Circulation*. 2020; 141:387. [PMID: 31983221]

Rosenbaum AN et al. Genetics of dilated cardiomyopathy: practical implications for heart failure management. *Nat Rev Cardiol*. 2020;17:286. [PMID: 31605094]

Yancy CW et al. 2016 ACC/AHA/HFSA focused update on new pharmacological therapy for heart failure: an update of the 2013 ACCF/AHA guideline for the management of heart failure. *J Am Coll Cardiol*. 2016;68:1476. [PMID: 27216111]

Yancy CW et al. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *Circulation*. 2017;136:e137. [PMID: 28455343]

## STRESS CARDIOMYOPATHY



### ESSENTIALS OF DIAGNOSIS

- ▶ Occurs after a major catecholamine discharge.
- ▶ Acute chest pain or shortness of breath.
- ▶ Predominately affects postmenopausal women.
- ▶ Presents as an acute anterior MI, but coronaries normal at cardiac catheterization.
- ▶ Imaging reveals apical left ventricular ballooning due to anteroapical stunning of the myocardium.
- ▶ Most patients recover completely, although there are complications similar to MI.

## ► General Considerations

Stress cardiomyopathy (**tako-tsubo syndrome**) generally follows a high catecholamine surge. The resulting shape of the LV acutely suggests a rounded ampulla form similar to a Japanese octopus pot (tako-tsubo pot). Mid-ventricular ballooning has also been described. The key feature is that the myocardial stunning that occurs does *not* follow the pattern suggestive of coronary ischemia (even though about 15% of patients will have coexisting CAD, and some may have concomitant plaque rupture MI). Over two-thirds of patients report a prior stressful event, either emotional or physical, including hypoglycemia, lightning

strikes, earthquakes, postventricular tachycardia, during alcohol withdrawal, following surgery, during hyperthyroidism, after stroke, and following emotional stress (“broken-heart syndrome”). Virtually any event that triggers excess catecholamines has been implicated in a wide number of case reports. Pericarditis and even tamponade have been described in isolated cases. Recurrences have also been described. In Western countries it predominantly affects women (up to 90%), primarily postmenopausal. Among patients with stress cardiomyopathy, compared to patients with acute coronary syndrome, there are more neurologic and psychiatric disorders. Patients with COPD, migraines, or affective disorders who take beta-agonists may have an increased risk of a poor outcome. The prognosis was initially thought to be benign, but subsequent studies have demonstrated that both short-term mortality and long-term mortality are higher than thought. Indeed, mortality reported during the acute phase in hospitalized patients is approximately 4–5%, a figure comparable to that of STEMI in the era of primary percutaneous coronary interventions. Approximately 10% of patients will have cardiac and neurologic adverse outcomes over the next year.

The structures that mediate the stress response are in both the central and autonomic nervous systems. Acute stressors induce brain activation, increasing bioavailability of cortisol and catecholamine. Both circulating epinephrine and norepinephrine released from adrenal medullary chromaffin cells and norepinephrine released locally from sympathetic nerve terminals are significantly increased. This catecholamine surge leads to myocardial damage through multiple mechanisms, including, direct catecholamine toxicity, adrenoceptor-mediated damage, epicardial and microvascular coronary vasoconstriction and/or spasm, and increased cardiac workload. The relative preponderance among postmenopausal women suggests that estrogen deprivation may be facilitating, possibly via endothelial dysfunction.

## Clinical Findings

### A. Symptoms and Signs

The symptoms are similar to any acute coronary syndrome. Typical angina and dyspnea are usually present. Syncope is rare, although arrhythmias are not uncommon.

### B. ECG and Chest Radiography

The ECG reveals ST-segment elevation as well as deep anterior T-wave inversion. The chest radiograph is either normal or reveals pulmonary congestion. The dramatic T-wave inversions gradually resolve over time.

### C. Diagnostic Studies

The echocardiogram reveals LV apical dyskinesia usually not consistent with any particular coronary distribution. The urgent cardiac catheterization reveals the LV apical ballooning in association with normal coronaries. Initial cardiac enzymes are positive but often taper quickly. In almost all cases, MRI hyperenhancement studies reveal no long-term scarring.

## Treatment

Immediate therapy is similar to any acute MI. Initiation of long-term therapy depends on whether LV dysfunction persists. Most patients receive aspirin, beta-blockers, and ACE inhibitors until the LV fully recovers. Despite the presumed association with high catecholamines, the use of ACE inhibitors or ARBs, but not beta-blockers, has been associated with improved long-term survival. See Treatment of Heart Failure With Reduced LVEF.

## Prognosis

In a 2015 registry of 1759 patients, the rate of severe in-hospital complications, including shock and death, were similar between those with an acute coronary syndrome and tako-tsubo. Overall, prognosis is good unless there is a serious complication (such as mitral regurgitation, ventricular rupture, or ventricular tachycardia). Recovery of the LVEF is expected in most cases after a period of days to weeks.

## When to Refer

All patients with an acute coronary syndrome should be urgently seen by a cardiologist for further evaluation and monitored until resolution of the ventricular dysfunction.

## HYPERTROPHIC CARDIOMYOPATHY



### ESSENTIALS OF DIAGNOSIS

- May present with dyspnea, chest pain, syncope.
- Though LV outflow gradient is classic, symptoms are primarily related to diastolic dysfunction.
- Echocardiogram is diagnostic. Any area of LV wall thickness > 1.5 cm defines the disease.
- Increased risk of sudden death.

## General Considerations

In 2020, an ACC/AHA joint committee on clinical practice guidelines issued updated guidelines for the diagnosis and treatment of HCM. The guidelines address many clinical scenarios and provide a host of clinically relevant suggestions. HCM is noted when there is LVH unrelated to any pressure or volume overload. The definition has evolved over time; while it traditionally was defined by LV outflow obstruction due to septal hypertrophy, currently it is considered present any time that *any portion of LV wall is measured at more than 1.5 cm thick on an echocardiogram*. This allows for many forms to be considered that do not create LV outflow obstruction. The increased wall thickness reduces LV systolic stress, increases the EF, and can result in an “empty ventricle” at end-systole. The interventricular septum may be disproportionately involved (**asymmetric septal hypertrophy**), but in some cases the hypertrophy is localized to the mid-ventricle or to the apex.

In a normal heart, the LV apex may be paper thin; in HCM, the LV obstruction may trap blood just above the apex and the LV pressure may be very high there. This can result in the apex becoming aneurysmal. The LV outflow tract is usually narrowed during systole due to the hypertrophied septum and systolic anterior motion of the mitral valve occurs as the anterior mitral valve leaflet is pulled into the LV outflow. The obstruction is worsened by factors that increase myocardial contractility (sympathetic stimulation, digoxin, and postextrasystolic beat) or that decrease LV filling (Valsalva maneuver, peripheral vasodilators). The amount of obstruction is preload and afterload dependent and can vary from day to day. The consequence of the hypertrophy is *elevated LV diastolic pressures* rather than systolic dysfunction. Rarely, systolic dysfunction develops late in the course of the disease. The LV is usually more involved than the RV, and the atria are frequently significantly enlarged.

HCM is inherited as an autosomal-dominant trait with variable penetrance and is caused by mutations of one of a large number of genes, most of which code for myosin heavy chains or proteins regulating calcium handling. The prognosis is related to the specific gene mutation. Patients usually present in early adulthood. Elite athletes may demonstrate considerable hypertrophy that can be confused with HCM, but generally diastolic dysfunction is not present in the athlete and this finding helps separate pathologic disease from **athletic hypertrophy**. The apical variety is particularly common in those of Asian descent. A **HCM in older adults** (usually in association with hypertension) has also been defined as a distinct entity (often a sigmoid interventricular septum is noted with a knob of cardiac muscle below the aortic valve). Mitral annular calcification is often present. Mitral regurgitation is variable and often dynamic, depending on the degree of outflow tract obstruction.

## ► Clinical Findings

### A. Symptoms and Signs

The most frequent symptoms are dyspnea and chest pain. Syncope is also common and is typically postexertional, when diastolic filling diminishes due to fluid loss and tachycardia increasing LV outflow tract obstruction. Residual circulating catecholamines accentuate the changes. Arrhythmias are an important problem. Atrial fibrillation is a long-term consequence of chronically elevated LA pressures and is a poor prognostic sign. Ventricular arrhythmias are also common, and sudden death may occur, often after extraordinary exertion.

Features on physical examination include a bisferiens carotid pulse, triple apical impulse (due to the prominent atrial filling wave and early and late systolic impulses), and a loud S<sub>4</sub>. The JVP may reveal a prominent *a* wave due to reduced RV compliance. In cases with LV outflow obstruction, a loud systolic murmur is present along the left sternal border that increases with upright posture or Valsalva maneuver and decreases with squatting. These maneuvers help differentiate the murmur of HCM from that of aortic stenosis. In HCM, reducing the LV volume *increases* the

outflow obstruction and the murmur intensity; whereas in valvular aortic stenosis, reducing the stroke volume across the valve *decreases* the murmur. Mitral regurgitation is frequently present as well.

### B. ECG and Chest Radiography

LHV is nearly universal in symptomatic patients, though entirely normal ECGs are present in up to 25%, usually in those with localized hypertrophy. Exaggerated septal Q waves inferolaterally may mimic MI. The chest radiograph is often unimpressive. Unlike with aortic stenosis, the ascending aorta is not dilated.

### C. Diagnostic Studies

The echocardiogram is diagnostic, revealing LHV (involving the septum more commonly than the posterior walls), systolic anterior motion of the mitral valve, early closing followed by reopening of the aortic valve, a small and hypercontractile LV, and delayed relaxation and filling of the LV during diastole. The septum is usually 1.3–1.5 times the thickness of the posterior wall. Septal motion tends to be reduced. Doppler ultrasound reveals turbulent flow and a dynamic gradient in the LV outflow tract and, commonly, mitral regurgitation. Abnormalities in the diastolic filling pattern are present in 80% of patients.

Echocardiography can usually differentiate the disease from ventricular noncompaction, a congenital myocardial disease pattern with marked trabeculation that partially fills the LV cavity. Myocardial perfusion imaging may suggest septal ischemia in the presence of normal coronary arteries. Cardiac MRI confirms the hypertrophy and contrast enhancement frequently reveals evidence of scar at the junction of the RV attachment to the interventricular septum. Cardiac catheterization confirms the diagnosis and defines the presence or absence of CAD. Frequently, coronary arterial bridging (squeezing of the coronary in systole) occurs, especially in the septal arteries. Exercise studies are recommended to assess for ventricular arrhythmias and to document the BP response. Loop monitoring is recommended for determination of ventricular ectopy.

## ► Treatment

**Beta-blockers should be the initial medication in symptomatic individuals**, especially when dynamic outflow obstruction is noted on the echocardiogram. The resulting slower heart rates assist with diastolic filling of the stiff LV. Dyspnea, angina, and arrhythmias respond in about 50% of patients. Calcium channel blockers, especially verapamil, have also been effective in symptomatic patients. Verapamil or nondihydropyridine calcium channel blockers, such as diltiazem, are class I recommendations. Their effect is due primarily to improved diastolic function; however, their vasodilating actions can also increase outflow obstruction and cause hypotension. Verapamil should not be used if there is hypotension or a resting gradient of over 100 mm Hg. Disopyramide is also effective because of its negative inotropic effects; it is usually used as an

addition to the medical regimen rather than as primary therapy or to help control atrial arrhythmias. Oral diuretics are frequently necessary due to the high LV diastolic pressure and elevated LA pressures but should be used with caution to avoid dehydration that would increase obstruction. Digoxin is relatively contraindicated, except rarely for rate control in atrial fibrillation. For acute hypotension that does not respond to fluids, phenylephrine may be considered. In HCM patients without outflow obstruction, similar treatment should be used only if symptomatic and the use of oral diuretics is safer. In a very small number of these patients, apical myomectomy may be considered.

Patients do best in sinus rhythm, and atrial fibrillation should be aggressively treated with antiarrhythmics or radiofrequency ablation. DOACs are preferred over warfarin if atrial fibrillation occurs. Patients with HCM should be treated regardless of their CHA<sub>2</sub>DS<sub>2</sub>-VASc score.

The 2020 AHA/ACC guidelines recommend a preventive ICD for HCM patients with documented cardiac arrest or sustained ventricular tachycardia (class I). It is a class IIa recommendation for an ICD if there are one or more of the following risk factors: (1) sudden death in one or more first-degree or close relative 50 years of age or younger, (2) any LV wall greater than or equal to 30 mm, (3) any recent syncope likely to have been arrhythmogenic, (4) LV apical aneurysm, or (5) LV systolic dysfunction (EF less than 50%). It is a class IIb recommendation for an ICD if there is significant (greater than 15%) late gadolinium enhancement on cardiac MRI. In those who receive an ICD, antitachycardia pacing should be programmed to minimize shocks. The use of an ICD is contraindicated, though, if the purpose is simply to allow for the patient to play competitive sports.

Excision of part of the outflow myocardial septum (myotomy–myomectomy) by experienced surgeons is successful in patients with symptoms unresponsive to medical therapy. A few surgeons advocate mitral valve replacement, since this results in resolution of the gradient and prevents associated mitral regurgitation. In some cases, myomectomy has been combined with an Alfieri stitch on the mitral valve (a stitch that binds the midportion of the anterior and posterior mitral valve leaflets together). Rare cases of progression to LV dilation or patients with intractable symptoms can be considered for cardiac transplantation. Nonsurgical septal ablation can be performed by injection of alcohol into septal branches of the left coronary artery to create a controlled myocardial infarct in the regions of greatest wall thickness. It is now considered first-line therapy, if feasible, for those with LV outflow tract obstruction greater than 50 mm Hg who do not respond to medical therapy or who are not deemed surgical candidates. In “burnt out” HCM, the medical therapy is similar to that of dilated cardiomyopathy. In those with refractory arrhythmias or heart failure, cardiac transplantation is an option.

Pregnancy results in an increased risk in patients with symptoms or outflow tract gradients of greater than 50 mm Hg. Genetic counseling is indicated before planned conception. In pregnant patients with HCM, continuation of beta-blocker therapy is recommended. For more details on the impact of HCM on sport, activity, and occupation

(such as driving commercially or piloting an aircraft), the reader is referred to the discussions in the 2020 AHA/ACC guidelines.

### ► When to Refer

Patients should be referred to a cardiologist to establish care, consider genetic testing, review the presence of any high-risk features, and discuss medications or the need for any intervention. This is particularly important if any symptoms are present.

Ommen SR. 2020 AHA/ACC guidelines for the diagnosis and treatment of patients with hypertrophic cardiomyopathy: executive summary. *Circulation*. 2020;142:e533. [PMID: 33215938]

## RESTRICTIVE CARDIOMYOPATHY



### ESSENTIALS OF DIAGNOSIS

- ▶ Right heart failure tends to dominate over left heart failure.
- ▶ Pulmonary hypertension is present.
- ▶ Amyloidosis is the most common cause.
- ▶ Echocardiography is key to diagnosis.
- ▶ Radionuclide imaging or myocardial biopsy can confirm amyloid.

### ► General Considerations

Restrictive cardiomyopathy is characterized by *impaired diastolic filling with reasonably preserved LV chamber size*. The condition is relatively uncommon, with the most frequent cause being amyloidosis. The diagnosis of **cardiac amyloidosis** has dramatically increased in the last few years since diagnostic testing has improved and there is an awareness of its prevalence. The prevalence of AL amyloid is approximately 12 cases per million, the prevalence of variant or hereditary ATTR amyloid is about 0.3 cases per million, and the prevalence of wild type ATTR amyloid is 155–191 cases per million. Many experts believe the actual prevalence of wild type ATTR is much higher. While light-chain amyloid proteins can be toxic to cardiomyocytes, they may also internalize into many cell types and this may explain some of the cardiac dysfunction observed. ATTR refers to transthyretin, a protein normally found in the liver that helps transport thyroid hormones and vitamin A. Wild type (normal) occurs more commonly in the elderly and in men, and previously was referred to as “senile systemic amyloidosis.” Hereditary or variant ATTR is genetically transmitted, deposition occurs at an earlier age, and it has associated neurologic impact. TTR is a tetramer that can dissociate into four monomers and aggregate as amyloid fibrils. The differential diagnosis of a restrictive cardiomyopathy includes infiltrative disorders beside amyloidosis,

such as sarcoidosis, Gaucher disease, and Hurler syndrome. Storage diseases such as hemochromatosis, Fabry disease, and glycogen storage diseases can also produce the picture. Noninfiltrative diseases, such as familial cardiomyopathy and pseudoxanthoma elasticum, can be implicated rarely, and other secondary causes include diabetes, systemic sclerosis (scleroderma), radiation, chemotherapy, CAD, and longstanding hypertension.

## ► Clinical Findings

### A. Symptoms and Signs

Restrictive cardiomyopathy must be distinguished from constrictive pericarditis (see Table 10–15). The key feature is that *ventricular interaction is accentuated with respiration in constrictive pericarditis* and that interaction is absent in restrictive cardiomyopathy. In addition, the pulmonary arterial pressure is invariably elevated in restrictive cardiomyopathy due to the high PCWP and is normal in uncomplicated constrictive pericarditis. Symptoms may include angina, syncope, stroke, and peripheral neuropathy. Periorbital purpura, a thickened tongue, and hepatomegaly are all suggestive physical findings of amyloidosis.

### B. Diagnostic Studies

Conduction disturbances are frequently present. Low voltage on the ECG combined with ventricular hypertrophy on the echocardiogram is suggestive of disease. Technetium pyrophosphate imaging (bone scan imaging) can also identify amyloid deposition in the myocardium, and it has become the noninvasive imaging modality of choice for diagnosing transthyretin amyloidosis. With typical scintigraphic findings in patients without a monoclonal gammopathy, biopsy is no longer necessary for diagnosis. Cardiac MRI presents a distinctive pattern of diffuse hyperenhancement of the gadolinium image in amyloidosis and is a useful screening test. Late gadolinium hyperenhancement of a high degree suggests more extensive cardiac involvement. The echocardiogram reveals a small, thickened LV with bright myocardium (speckled), rapid early diastolic filling revealed by the mitral inflow Doppler, and batrial enlargement. Characteristic longitudinal strain patterns may help identify cardiac amyloidosis. The LV chamber size is usually normal with a reduced LVEF. Atrial septal thickening may be evident and an amyloid variant that primarily affects the atria has been described. Rectal, abdominal fat, or gingival biopsies can confirm systemic involvement, but myocardial involvement may still be present if these are negative and requires endomyocardial biopsy for the confirmation that cardiac amyloid is present. Demonstration of tissue infiltration on biopsy specimens using special stains followed by immunohistochemical studies and genetic testing are essential to define which specific protein is involved. TTR gene sequencing in patients in whom the TTR wild type or TTR mutant variant is suspected and mass spectroscopy on all tissue in question are recommended highly. BNP and NT-proBNP are traditionally elevated and have been used to help

distinguish constrictive pericarditis from a restrictive cardiomyopathy.

## ► Treatment

Treatment for AL amyloidosis includes alkylator-based chemotherapy or high-dose melphalan followed by autologous stem cell transplantation. In immunoglobulin light chain amyloidosis, standard- or high-dose chemotherapy with stem cell rescue is often pursued. Treatment of ATTR amyloid is undergoing an evolution. Tafamidis helps prevent the misfolding of the TTR tetramer and is now approved for treatment. Patisiran is also available, and it inhibits both variant and wild type TTR production. For the variant TTR polyneuropathy, subcutaneous inotuzumab is available (it binds to TTR mRNA preventing transcription).

In acute heart failure, diuretics can help, but excessive diuresis can produce worsening kidney dysfunction. As with most patients with severe right heart failure, loop diuretics, thiazides, and aldosterone antagonists are all useful. Atrial thrombi are not uncommon, although the role of anticoagulation in amyloidosis remains ill defined. Digoxin may precipitate arrhythmias and should not be used. Beta-blockers help slow heart rates and improve filling by increasing diastolic time. Verapamil presumably works by improving myocardial relaxation and increasing diastolic filling time. Slow heart rates are desired to allow for increased diastolic filling time. ACE inhibition or angiotensin II receptor blockade may improve diastolic relaxation and filling at times and can be tried with caution if the systemic blood pressure is adequate. Corticosteroids may be helpful in sarcoidosis, but they are more effective for conduction abnormalities in this disease than in heart failure.

## ► When to Refer

All patients with the diagnosis of a restrictive cardiomyopathy should be referred to a cardiologist to decide etiology and plan appropriate treatment. Unexplained LVH with relatively preserved LVEF and symptoms of heart failure should raise the question of cardiac amyloid, particularly now that there is effective treatment available.

- Kitaoka H et al; Japanese Circulation Society Joint Working Group. JCS 2020 guideline on diagnosis and treatment of cardiac amyloidosis. Circ J. 2020;84:1610. [PMID: 32830187]
- Marques N et al. Specific therapy for transthyretin cardiac amyloidosis: a systematic literature review and evidence-based recommendations. J Am Heart Assoc. 2020;9:e016614. [PMID: 32969287]
- Maurer MS et al; ATTR-ACT Study Investigators. Tafamidis treatment for patients with transthyretin amyloid cardiomyopathy. N Engl J Med. 2018;379:1007. [PMID: 30145929]
- Pereira NL et al. Spectrum of restrictive and infiltrative cardiomyopathies: part 1 of a 2-part series. J Am Coll Cardiol. 2018;71:1130. [PMID: 29519355]
- Pereira NL et al. Spectrum of restrictive and infiltrative cardiomyopathies: part 2 of a 2-part series. J Am Coll Cardiol. 2018;71:1149. [PMID: 29519356]

## RHEUMATIC FEVER



### ESSENTIALS OF DIAGNOSIS

- ▶ More common in developing countries (100 cases/100,000 population) than in the United States (~2 cases/100,000 population).
- ▶ Peak incidence between ages 5 and 15 years.
- ▶ Revision of Jones criteria in 2015 includes echocardiographic findings.
- ▶ May involve mitral and other valves acutely, rarely leading to heart failure.

### General Considerations

Rheumatic fever is a systemic immune process that is a sequela of a beta-hemolytic streptococcal infection of the pharynx. It is a major scourge in developing countries and responsible for 320,000 deaths in young people worldwide each year. Over 15 million people have evidence for rheumatic heart disease. Signs of **acute rheumatic fever** usually commence 2–3 weeks after infection but may appear as early as 1 week or as late as 5 weeks. The disease has become quite uncommon in the United States, except in immigrants. The peak incidence is between ages 5 and 15 years; rheumatic fever is rare before age 4 years or after age 40 years. Rheumatic carditis and valvulitis may be self-limited or may lead to slowly progressive valvular deformity. The characteristic lesion is a perivasculär granulomatous reaction with valvulitis. The mitral valve is acutely attacked in 75–80% of cases, the aortic valve in 30% (but rarely as the sole valve involved), and the tricuspid and pulmonary valves in under 5% of cases.

The clinical profile of the infection includes carditis in 50–70% and arthritis in 35–66%, followed by chorea (10–30%, predominantly in girls) then subcutaneous nodules (0–10%) and erythema marginatum (in less than 6%). Echocardiography has been found to be superior to auscultation, and the 2015 guidelines introduced **subclinical carditis** to the Jones criteria to represent abnormal echocardiographic findings when auscultatory findings were either not present or not recognized.

**Chronic rheumatic heart disease** results from single or repeated attacks of rheumatic fever that produce rigidity and deformity of valve cusps, fusion of the commissures, or shortening and fusion of the chordae tendineae. Valvular stenosis or regurgitation results, and the two often coexist. In chronic rheumatic heart disease, the mitral valve alone is abnormal in 50–60% of cases; combined lesions of the aortic and mitral valves occur in 20%; pure aortic lesions are less common. Tricuspid involvement occurs in about 10% of cases, but only in association with mitral or aortic disease and is thought to be more common when recurrent infections have occurred. The pulmonary valve is rarely affected long term. A history of rheumatic fever is obtainable in only 60% of patients with rheumatic heart disease. While there has been progress against this disease, it remains a major cardiovascular problem in the poorest regions of the world.

### Clinical Findings

**The presence of two major criteria—or one major and two minor criteria—establishes the diagnosis.** While India, New Zealand, and Australia have all published revised guidelines since 2001, the 2015 recommendations have revised the Jones criteria (Table 10–16) in a scientific

**Table 10–16.** The 2015 revised Jones criteria.<sup>1</sup>

| Population             | Criteria   |  |
|------------------------|--|--|
|                        | Major  | Minor  |
| Low risk               | Carditis (clinical or subclinical)                       | Polyarthralgia   |
|                        | Arthritis (polyarthritis only)                           | Fever ( $\geq 38.5^{\circ}\text{C}$ )                                |
|                        | Chorea   | ESR $\geq 60 \text{ mm/h}$ or CRP $\geq 3.0 \text{ mg/dL}$ (or both) |
|                        | Erythema marginatum                                      | Prolonged PR interval (unless carditis is major criterion)           |
|                        | Subcutaneous nodules                                     |  |
| Moderate and high risk | Carditis (clinical or subclinical)                       | Monoarthralgia   |
|                        | Arthritis (monoarthritis, polyarthritis, polyarthralgia) | Fever ( $\geq 38^{\circ}\text{C}$ )                                  |
|                        | Chorea   | ESR $\geq 30 \text{ mm/h}$ or CRP $\geq 3.0 \text{ mg/dL}$ (or both) |
|                        | Erythema marginatum                                      | Prolonged PR interval (unless carditis is a major criterion)         |
|                        | Subcutaneous nodules                                     |  |

<sup>1</sup>For all patients with evidence of preceding group A streptococcal pharyngitis: initial acute rheumatic fever can be diagnosed when 2 major criteria or 1 major plus 2 minor criteria are met. Recurrent acute rheumatic fever can be diagnosed when 2 major or 1 major plus 2 minor or 3 minor criteria are met.

ESR, erythrocyte sedimentation rate; CRP, C-reactive protein.

Modified, with permission, from Gewitz MH et al; American Heart Association Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease of the Council on Cardiovascular Disease in the Young. Revision of the Jones criteria for the diagnosis of acute rheumatic fever in the era of Doppler echocardiography. A scientific statement from the American Heart Association. Circulation. 2015 May 19;131(20):1806–18. © 2015 American Heart Association, Inc.

statement from the AHA where subclinical carditis is now recognized with the advent of echocardiography. The revised criteria also recognize that a lower threshold should be used to diagnosis acute rheumatic fever in high-risk populations.

### A. Major Criteria

**1. Carditis**—Carditis is most likely to be evident in children and adolescents. Any of the following suggests the presence of carditis: (1) pericarditis; (2) cardiomegaly, detected by physical signs, radiography, or echocardiography; (3) heart failure, right- or left-sided—the former perhaps more prominent in children, with painful liver engorgement due to tricuspid regurgitation; and (4) mitral or aortic regurgitation murmurs, indicative of dilation of a valve ring with or without associated valvulitis or morphologic findings on echocardiography of rheumatic valvulitis. The Carey-Coombs short mid-diastolic mitral murmur may be present due to inflammation of the mitral valve. It is a class I (LOE B) indication to perform echocardiography/Doppler studies on all cases of suspected or confirmed acute rheumatic fever.

**2. Erythema marginatum and subcutaneous nodules**—

Erythema marginatum begins as rapidly enlarging macules that may be less notable on black skin and that assume the shape of rings or crescents with clear centers. They may be raised, confluent, and either transient or persistent and usually on the trunk or proximal extremities. Subcutaneous nodules are uncommon except in children. They are small (2 cm or less in diameter), firm, and nontender and are attached to fascia or tendon sheaths over bony prominences. They persist for days or weeks, are recurrent, and are indistinguishable from rheumatoid nodules. Neither the rash nor nodules ever occur as the sole manifestation of acute rheumatic fever.

**3. Sydenham chorea**—This is the most definitive manifestation of acute rheumatic fever. Defined as involuntary choreoathetoid movements primarily of the face, tongue, and upper extremities, Sydenham chorea may be the sole manifestation of rheumatic fever. Girls are more frequently affected than boys, and occurrence in adults is rare.

**4. Polyarthritis**—This is a migratory polyarthritis that involves the large joints sequentially. In adults and in certain moderate- to high-risk populations, only a single joint may be affected. The arthritis lasts 1–5 weeks and subsides without residual deformity. Prompt response of arthritis to therapeutic doses of salicylates or nonsteroidal agents is characteristic.

### B. Minor Criteria

These include fever, polyarthralgia, reversible prolongation of the PR interval, and an elevated erythrocyte sedimentation rate or CRP. A lower threshold is set for patients at high risk (Table 10–16). The 2015 guidelines stipulate that evidence for a preceding streptococcal infection can be defined by an increase or rising anti-streptolysin O titer or streptococcal antibodies (anti-DNAase B), a positive throat

culture for group A beta-hemolytic streptococcal or a positive rapid group A streptococcal carbohydrate antigen test in a child with a high pretest probability of streptococcal pharyngitis.

## ► Treatment

### A. General Measures

The patient should be kept at strict bed rest until the temperature returns to normal (without the use of antipyretic medications) and the sedimentation rate, plus the resting pulse rate, and the ECG have all returned to baseline.

### B. Medical Measures

**1. Salicylates**—The salicylates markedly reduce fever and relieve joint pain and swelling. They have no effect on the natural course of the disease. Adults may require large doses of aspirin, 0.6–0.9 g every 4 hours; children are treated with lower doses.

**2. Penicillin**—Penicillin (benzathine penicillin, 1.2 million units intramuscularly once, or procaine penicillin, 600,000 units intramuscularly daily for 10 days) is used to eradicate streptococcal infection if present. Erythromycin may be substituted (40 mg/kg/day).

**3. Corticosteroids**—There is no proof that cardiac damage is prevented or minimized by corticosteroids. A short course of corticosteroids (prednisone, 40–60 mg orally daily, with tapering over 2 weeks) usually causes rapid improvement of the joint symptoms and is indicated when response to salicylates has been inadequate.

## ► Prevention of Recurrent Rheumatic Fever

Improvements in socioeconomic conditions and public health are critical to reducing bouts of rheumatic fever. The initial episode of rheumatic fever can usually be prevented by early treatment of streptococcal pharyngitis with penicillin (see Chapter 33). Prevention of recurrent episodes of rheumatic fever is critical. Recurrences of rheumatic fever are most common in patients who have had carditis during their initial episode and in children, 20% of whom will have a second episode within 5 years. The preferred method of prophylaxis is with benzathine penicillin G, 1.2 million units intramuscularly every 4 weeks. Oral penicillin (250 mg twice daily) is less reliable.

If the patient is allergic to penicillin, sulfadiazine (or sulfisoxazole), 1 g daily, or erythromycin, 250 mg orally twice daily, may be substituted. The macrolide azithromycin is similarly effective against group A streptococcal infection. If the patient has not had an immediate hypersensitivity (anaphylactic-type) reaction to penicillin, then cephalosporin may also be used.

Recurrences are uncommon after 5 years following the first episode and in patients over 21 years of age. Prophylaxis is usually discontinued after these times except in groups with a high risk of streptococcal infection—parents or teachers of young children, nurses, military recruits, etc. Secondary prevention of rheumatic fever depends on whether carditis has occurred. Current guidelines suggest

that if there is no evidence for carditis, preventive therapy can be stopped at age 21 years. If carditis has occurred but there is no residual valvular disease, it can be stopped at 10 years after the acute rheumatic fever episode. If carditis has occurred with residual valvular involvement, it should be continued for 10 years after the last episode or until age 40 years if the patient is in a situation in which reexposure would be expected.

## ► Prognosis

Initial episodes of rheumatic fever may last months in children and weeks in adults. The immediate mortality rate is 1–2%. Persistent rheumatic carditis with cardiomegaly, heart failure, and pericarditis implies a poor prognosis; 30% of children thus affected die within 10 years after the initial attack. After 10 years, two-thirds of patients will have detectable valvular abnormalities (usually thickened valves with limited mobility), but significant symptomatic valvular heart disease or persistent cardiomyopathy occurs in less than 10% of patients with a single episode. In developing countries, acute rheumatic fever occurs earlier in life and recurs more frequently; thus, the evolution to chronic valvular disease is both accelerated and more severe.

Gewitz MH et al; American Heart Association Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease of the Council on Cardiovascular Disease in the Young. Revision of the Jones criteria for the diagnosis of acute rheumatic fever in the era of Doppler echocardiography. A scientific statement from the American Heart Association. Circulation. 2015;131:1806. [PMID: 25908771]

Dooley LM et al. Rheumatic heart disease: a review of the current status of global research activity. Autoimmun Rev. 2021;20:102740. [PMID: 33333234]

diseases (autoimmune syndromes, uremia), neoplasm, radiation, drug toxicity, hemopericardium, postcardiac surgery, or contiguous inflammatory processes in the myocardium or lung. In many of these conditions, the pathologic process involves both the pericardium and the myocardium. Overall pericarditis accounts for 0.2% of hospital admissions and about 5% of patients with non-ischemic chest pain seen in the emergency department. The ESC in 2015 proposed four categories of pericarditis and elucidated diagnostic criteria for each (Table 10–17).

**Viral infections** (especially infections with coxsackieviruses and echoviruses but also influenza, Epstein-Barr, varicella, hepatitis, mumps, and HIV viruses) are the most common cause of acute pericarditis and probably are responsible for many cases classified as idiopathic. COVID-19 has been associated with both acute pericarditis and even cardiac tamponade. Males—usually under age 50 years—are most commonly affected. The differential diagnosis primarily requires exclusion of acute MI. **Tuberculous pericarditis** is rare in developed countries but remains common in certain areas of the world. It results from direct lymphatic or hematogenous spread; clinical pulmonary involvement may be absent or minor, although associated pleural effusions are common. **Bacterial pericarditis** is equally rare and usually results from direct extension from pulmonary infections. Pneumococci, though, can cause a primary pericardial infection. *Borrelia burgdorferi*, the organism responsible for Lyme disease, can also cause myopericarditis (and occasionally

**Table 10–17.** Definitions and diagnostic criteria for pericarditis.

| Pericarditis     | Definition and Diagnosis  |
|------------------|---|
| <b>Acute</b>     | At least two of the following four listed findings:<br>1. Pericardial chest pain<br>2. Pericardial rub<br>3. New widespread ST-elevation or PR depression<br>4. Pericardial effusion (new or worsening) |
|                  | Additional supportive findings:<br>1. Elevated inflammatory markers (CRP, ESR, WBC)<br>2. Evidence for pericardial inflammation (CT or MRI)   |
| <b>Incessant</b> | Pericarditis lasting longer than 4–6 weeks but less than 3 months without remission   |
| <b>Recurrent</b> | Recurrence after a documented first episode and a symptom-free interval of 4–6 weeks or longer  |
| <b>Chronic</b>   | Pericarditis lasting longer than 3 months   |

CRP, C-reactive protein; CT, computed tomography; ESR, erythrocyte sedimentation rate; MRI, magnetic resonance imaging; WBC, white blood cell count.

Modified, with permission, from Adler Y et al. 2015 ESC guidelines for the diagnosis and management of pericardial diseases: the Task Force for the Diagnosis and Management of Pericardial Diseases of the European Society of Cardiology (ESC) endorsed by: the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J. 2015 Nov 7;36(42):2921–64. By permission of Oxford University Press and the European Society of Cardiology. © The European Society of Cardiology 2015. All rights reserved.

## DISEASES OF THE PERICARDIUM

### ACUTE INFLAMMATORY PERICARDITIS



#### ESSENTIALS OF DIAGNOSIS

- Anterior pleuritic chest pain that is worse supine than upright.
- Pericardial rub.
- Fever common.
- Erythrocyte sedimentation rate or inflammatory CRP usually elevated.
- ECG reveals diffuse ST-segment elevation with associated PR depression.

## ► General Considerations

Acute (less than 2 weeks) inflammation of the pericardium may be infectious in origin or may be due to systemic

heart block). **Uremic pericarditis** is a common complication of chronic kidney disease. The pathogenesis is uncertain; it occurs both with untreated uremia and in otherwise stable dialysis patients. Spread of adjacent lung cancer as well as invasion by breast cancer, renal cell carcinoma, Hodgkin disease, and lymphomas are the most common **neoplastic processes** involving the pericardium and have become the most frequent causes of pericardial tamponade in many countries. Pericarditis may occur 2–5 days after infarction due to an inflammatory reaction to transmural myocardial necrosis (**post-MI or postcardiotomy pericarditis [Dressler syndrome]**). **Radiation** can initiate a fibrinous and fibrotic process in the pericardium, presenting as subacute pericarditis or constriction. Radiation pericarditis usually follows treatments of more than 4000 cGy delivered to ports including more than 30% of the heart.

Other causes of pericarditis include **connective tissue diseases**, such as lupus erythematosus and rheumatoid arthritis, **drug-induced pericarditis** (minoxidil, penicillins, clozapine), and **myxedema**. In addition, pericarditis may result from **pericardial injury** from invasive cardiac procedures (such as cardiac pacemaker and defibrillator perforation and intracardiac ablation, especially atrial fibrillation ablation), and the implantation of intracardiac devices (such as ASD occluder devices).

Pericarditis and myocarditis may coexist in 20–30% of patients. Myocarditis is often suspected when there is an elevation of serum troponins, although there are no data that suggest troponin elevations are associated with a poor prognosis.

## Clinical Findings

### A. Symptoms and Signs

The presentation and course of inflammatory pericarditis depend on its cause, but most syndromes have associated chest pain, which is usually pleuritic and postural (relieved by sitting). The pain is substernal but may radiate to the neck, shoulders, back, or epigastrium. Dyspnea may also be present and the patient is often febrile. A pericardial **friction rub** is characteristic, with or without evidence of fluid accumulation or constriction. The presentation of tuberculous pericarditis tends to be subacute, but nonspecific symptoms (fever, night sweats, fatigue) may be present for days to months. Pericardial involvement develops in 1–8% of patients with pulmonary tuberculosis. Symptoms and signs of bacterial pericarditis are similar to those of other types of inflammatory pericarditis, but patients appear toxic and are often critically ill. Uremic pericarditis can present with or without symptoms; fever is absent. Often neoplastic pericarditis is painless, and the presenting symptoms relate to hemodynamic compromise or the primary disease. At times the pericardial effusion is very large, consistent with its chronic nature. Post-MI or postcardiotomy pericarditis (Dressler syndrome) usually presents as a recurrence of pain with pleural-pericardial features. A rub is often audible, and repolarization changes on the ECG may be confused with ischemia. Large effusions are uncommon, and spontaneous resolution usually occurs in

a few days. Dressler syndrome occurs days to weeks to several months after MI or open heart surgery, may be recurrent, and probably represents an autoimmune syndrome. Patients present with typical pain, fever, malaise, and leukocytosis. Rarely, other symptoms of an autoimmune disorder, such as joint pain and fever, may occur. Tamponade is rare with Dressler syndrome after MI but not when it occurs postoperatively. The clinical onset of radiation pericarditis is usually within the first year but may be delayed for many years; often a full decade or more may pass before constriction becomes evident.

### B. Laboratory Findings and Diagnostic Studies

The diagnosis of viral pericarditis is usually clinical, and leukocytosis is often present. Rising viral titers in paired sera may be obtained for confirmation but are rarely done. Cardiac enzymes may be slightly elevated, reflecting an epicardial myocarditis component. The echocardiogram is often normal or reveals only a trivial amount of extra fluid during the acute inflammatory process. The diagnosis of tuberculous pericarditis can be inferred if acid-fast bacilli are found elsewhere. The tuberculous pericardial effusions are usually small or moderate but may be large when chronic. The yield of mycobacterial organisms by pericardiocentesis is low; pericardial biopsy has a higher yield but may also be negative, and pericardectomy may be required. If bacterial pericarditis is suspected on clinical grounds, diagnostic pericardiocentesis can be confirmatory. In uremic patients not on dialysis, the incidence of pericarditis correlates roughly with the level of blood urea nitrogen (BUN) and creatinine. The pericardium is characteristically “shaggy” in uremic pericarditis, and the effusion is hemorrhagic and exudative. The diagnosis of neoplastic pericarditis can occasionally be made by cytologic examination of the effusion or by pericardial biopsy, but it may be difficult to establish clinically if the patient has received mediastinal radiation within the previous year. Neoplastic pericardial effusions develop over a long period of time and may become quite huge (more than 2 L). The sedimentation rate is high in post-MI or postcardiotomy pericarditis and can help confirm the diagnosis. Large pericardial effusions and accompanying pleural effusions are frequent. Myxedema pericardial effusions due to hypothyroidism usually are characterized by the presence of cholesterol crystals within the fluid.

### C. Other Studies

The ECG usually shows generalized ST and T wave changes and may manifest a characteristic progression beginning with diffuse ST elevation, followed by a return to baseline and then to T-wave inversion. Atrial injury is often present and manifested by PR depression, especially in the limb leads. The chest radiograph is frequently normal but may show cardiac enlargement (if pericardial fluid is present), as well as signs of related pulmonary disease. Mass lesions and enlarged lymph nodes may suggest a neoplastic process. About 60% of patients have a pericardial effusion (usually mild) detectable by echocardiography. MRI and CT scan can visualize neighboring tumor in

neoplastic pericarditis. A screening chest CT or MRI is often recommended to ensure there are no extracardiac diseases contiguous to the pericardium. A consensus statement from the American Society of Echocardiography proposes adding an elevated CRP and late gadolinium enhancement of the pericardium to confirmatory criteria for the diagnosis of pericarditis. There are data that the degree of quantitative delayed enhancement of the pericardium is associated with a higher rate of recurrent pericarditis. PET scanning can also be used to help define pericardial inflammation.

## ► Treatment

For acute pericarditis, experts suggest a restriction in activity until symptom resolution. For athletes, the duration of exercise restriction should be until resolution of symptoms and normalization of all laboratory tests (generally 3 months). The 2015 ESC guidelines recommend aspirin 750–1000 mg every 8 hours for 1–2 weeks with a taper by decreasing the dose 250–500 mg every 1–2 weeks or ibuprofen 600 mg every 8 hours for 1–2 weeks with a taper by decreasing the dose by 200–400 mg every 1–2 weeks. Gastroprotection should be included. Studies support initial treatment of the acute episode with colchicine to prevent recurrences. Colchicine should be added to the nonsteroidal anti-inflammatory medication at 0.5–0.6 mg once (for patients less than 70 kg) or twice (for patients more than 70 kg) daily and continued for at least 3 months. Tapering of colchicine is not mandatory; however, in the last week of treatment, the dosage can be reduced every other day for patients less than 70 kg or once a day for those more than 70 kg. Aspirin and colchicine should be used instead of nonsteroidal anti-inflammatory medications in post-MI pericarditis (Dressler syndrome), since nonsteroidal anti-inflammatory medications and corticosteroids may have an adverse effect on myocardial healing. Aspirin in doses of 750–1000 mg three times daily for 1–2 weeks plus 3 months of colchicine is the recommended treatment for Dressler syndrome. Despite initial treatment, recurrence has been reported in about 30%.

Colchicine should be used for at least 6 months as therapy in all refractory cases and in recurrent pericarditis. At times a longer duration of therapy is required. The CRP is used to assess the effectiveness of treatment, and once it is normalized, tapering is initiated. Indomethacin in doses of 25–50 mg every 8 hours can also be considered in recurrent pericarditis in place of ibuprofen. Systemic corticosteroids can be added in patients with severe symptoms, in refractory cases, or in patients with immune-mediated etiologies, but such therapy may entail a higher risk of recurrence and may actually prolong the illness. Colchicine is recommended in addition to corticosteroids, again for at least 3 months, to help prevent recurrences. Prednisone in doses of 0.25–0.5 mg/kg/day orally is generally suggested with tapering over a 4- to 6-week period. Recent studies have confirmed the advantage of adding anakinra, an interleukin-1 receptor antagonist, for the treatment of recurrent pericarditis, especially for corticosteroid-dependent and colchicine-resistant pericarditis.

As a rule, symptoms subside in several days to weeks. The major early complication is **tamponade**, which occurs in less than 5% of patients. There may be recurrences in the first few weeks or months. Rarely, when colchicine therapy alone fails or cannot be tolerated (usually due to gastrointestinal symptoms), the pericarditis may require more significant immunosuppression, such as cyclophosphamide, azathioprine, intravenous human immunoglobulins, interleukin-1 receptor antagonists (anakinra), or methotrexate. If colchicine plus more significant immunosuppression fails, surgical pericardial stripping may be considered in recurrent cases even without clinical evidence for constrictive pericarditis.

Standard antituberculous medication therapy is usually successful for tuberculous pericarditis (see Chapter 9), but constrictive pericarditis can occur. Uremic pericarditis usually resolves with the institution of—or with more aggressive—dialysis. Tamponade is fairly common, and partial pericardectomy (**pericardial window**) may be necessary. Whereas anti-inflammatory agents may relieve the pain and fever associated with uremic pericarditis, indomethacin and systemic corticosteroids do not affect its natural history. The prognosis with neoplastic effusion is poor, with only a small minority surviving 1 year. If it is compromising the clinical comfort of the patient, the effusion is initially drained percutaneously. Attempts at balloon pericardiectomy have been abandoned because outcomes were not more effective than simple drainage. A pericardial window, either by a subxiphoid approach or via video-assisted thoracic surgery, allows for partial pericardectomy. Installation of chemotherapeutic agents or tetracycline may be used to reduce the recurrence rate. Symptomatic therapy is the initial approach to radiation pericarditis, but recurrent effusions and constriction often require surgery.

## ► Prognosis

There are data that patients with acute pericarditis and any of the following criteria have the poorest prognosis: fever higher than 38°C, subacute onset, large effusion with or without tamponade, lack of response to anti-inflammatory medication after 1 week, myopericarditis, traumatic pericarditis, and those on oral anticoagulation. About 15% of patients have at least one of these high-risk findings.

## ► When to Refer

Patients who do not respond initially to conservative management, who have recurrences, or who appear to be developing constrictive pericarditis should be referred to a cardiologist for further assessment.

Adler Y et al. 2015 ESC guidelines for the diagnosis and management of pericardial diseases: The Task Force for the Diagnosis and Management of Pericardial Diseases of the European Society of Cardiology (ESC) endorsed by: the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J. 2015;36:2921. [PMID: 26320112]

Imazio M et al. Anakinra for corticosteroid-dependent and colchicine-resistant pericarditis. The IRAP (International Registry of Anakinra for Pericarditis) study. Eur J Prev Cardiol. 2020;27:956. [PMID: 31610707]

## PERICARDIAL EFFUSION & TAMPOONADE



### ESSENTIALS OF DIAGNOSIS

#### Pericardial effusion

- ▶ Clinical impact determined by the speed of accumulation.
- ▶ May or may not cause pain.

#### Tamponade

- ▶ Tachycardia with an elevated JVP and either hypotension or a paradoxical pulse.
- ▶ Low voltage or electrical alternans on ECG.
- ▶ Echocardiography is diagnostic.

Pericardial effusion can develop during any of the acute pericarditis processes. Because the pericardium covers the ascending aorta and arch, aortic dissection and/or rupture can lead to tamponade as well. The *speed of accumulation* determines the physiologic importance of the effusion. Because of pericardial stretch, effusions larger than 1000 mL that develop slowly may produce no hemodynamic effects. Conversely, smaller effusions that appear rapidly can cause tamponade due to the curvilinear relationship between the volume of fluid and the intrapericardial pressure. Tamponade is characterized by elevated intrapericardial pressure (greater than 15 mm Hg), which restricts venous return and ventricular filling. As a result, the stroke volume and arterial pulse pressure fall, and the heart rate and venous pressure rise. Shock and death may result.

## ► Clinical Findings

### A. Symptoms and Signs

Pericardial effusions may be associated with pain if they occur as part of an acute inflammatory process or may be painless, as is often the case with neoplastic or uremic effusion. Dyspnea and cough are common, especially with tamponade. Cardiac tamponade can be a life-threatening syndrome evidenced by tachycardia, hypotension, pulsus paradoxicus, raised JVP, muffled heart sounds, and decreased ECG voltage or electrical alternans. Other symptoms may result from the primary disease. The prognosis is a function of the cause. Large idiopathic chronic effusions (over 3 months) have a 30–35% risk of progression to cardiac tamponade.

A pericardial friction rub may be present even with large effusions. In cardiac tamponade, tachycardia, tachypnea, a narrow pulse pressure, and a relatively preserved systolic pressure are characteristic. **Pulsus paradoxus** is defined as a decline of greater than 10 mm Hg in systolic pressure during inspiration. Since the RV and LV share the same pericardium, when there is significant pericardial effusion, as the RV enlarges with inspiratory filling, septal motion toward the LV chamber reduces LV filling and results in an accentuated drop in the stroke volume and systemic BP with inspiration (the paradoxical pulse). Central venous

pressure is elevated and, since the intrapericardial, and thus intracardiac, pressures are high even at the initiation of diastole, there is no evident *y* descent in the RA, RV, or LV hemodynamic tracings because the pericardial pressure prevents early ventricular filling. This differs from constriction where most of the initial filling of the RV and LV occurs during early diastole (rapid *y* descent), and it is only in mid to late diastole that the ventricles can no longer fill. In tamponade, ventricular filling is inhibited throughout diastole. Edema or ascites are rarely present in tamponade; these signs favor a more chronic process.

### B. Laboratory Findings

Laboratory tests tend to reflect the underlying processes (see causes of pericarditis under General Considerations above).

### C. Diagnostic Studies

Chest radiograph can suggest chronic effusion by an enlarged cardiac silhouette with a globular configuration but may appear normal in acute situations. The ECG often reveals nonspecific T wave changes and reduced QRS voltage. **Electrical alternans** is present only occasionally but is pathognomonic and is believed to be due to the heart swinging within the large effusion. Echocardiography is the primary method for demonstrating pericardial effusion and is quite sensitive. If tamponade is present, the high intrapericardial pressure may collapse lower pressure cardiac structures, such as the RA and RV. Cardiac CT and MRI also demonstrate pericardial fluid, pericardial thickening, and any associated contiguous lesions within the chest. Diagnostic pericardiocentesis or biopsy may be indicated for microbiologic and cytologic studies; a pericardial biopsy may be performed relatively simply through a small subxiphoid incision or by use of a video-assisted thoracoscopic surgical procedure. Unfortunately, the quality of the pericardial fluid itself rarely leads to a diagnosis, and any type of fluid (serous, serosanguinous, bloody, etc) can be seen in most diseases. Pericardial fluid analysis is most useful in excluding a bacterial cause and is occasionally helpful in malignancies. Effusions due to hypothyroidism or lymphatic obstruction may contain cholesterol or be chylous in nature, respectively.

## ► Treatment

Small effusions can be followed clinically by careful observations of the JVP and by testing for a change in the paradoxical pulse. The most common cause of a paradoxical pulse is severe pulmonary disease, especially asthma, where marked changes in intrapleural pressures occur with inspiration and expiration. Serial echocardiograms are indicated if no intervention is immediately contemplated. Vasodilators and diuretics should be avoided. **When tamponade is present, urgent pericardiocentesis or cardiac surgery is required.** Because the pressure-volume relationship in the pericardial fluid is curvilinear and upsloping, removal of even a small amount of fluid often produces a dramatic fall in the intrapericardial pressure and immediate hemodynamic benefit; but complete drainage with a

catheter is preferable. Continued or repeat drainage may be indicated, especially in malignant effusions. Pericardial windows via video-assisted thoracoscopy have been particularly effective in preventing recurrences when the underlying cause of the effusion continues to be present and are more effective than needle pericardiocentesis, subxiphoid surgical windows, or percutaneous balloon pericardiotomy. Effusions related to recurrent inflammatory pericarditis can be treated as noted above (see Acute Inflammatory Pericarditis). The presence of pericardial fluid in patients with pulmonary hypertension is a poor prognostic sign.

## ► When to Refer

- Any unexplained pericardial effusion should be referred to a cardiologist.
- Trivial pericardial effusions are common, especially in heart failure, and need not be referred unless symptoms of pericarditis are evident.
- Hypotension or a paradoxical pulse suggesting the pericardial effusion is hemodynamically compromising the patient is a medical emergency and requires immediate drainage.
- Any echocardiographic signs of tamponade.

## CONSTRICITIVE PERICARDITIS



### ESSENTIALS OF DIAGNOSIS

- ▶ Clinical evidence of right heart failure.
- ▶ No fall or an elevation of the JVP with inspiration (Kussmaul sign).
- ▶ Echocardiographic evidence for septal bounce and reduced mitral inflow velocities with inspiration.
- ▶ At times may be difficult to differentiate from restrictive cardiomyopathy.
- ▶ Cardiac catheterization may be necessary when clinical and echocardiographic features are equivocal.

## ► General Considerations

Pericardial inflammation can lead to a thickened, fibrotic, adherent pericardium that restricts diastolic filling and produces chronically elevated venous pressures. In the past, tuberculosis was the most common cause of constrictive pericarditis, but while it remains so in underdeveloped countries, it is rare now in the rest of the world. Constrictive pericarditis rarely occurs following recurrent pericarditis. The risk of constrictive pericarditis due to viral or idiopathic pericarditis is less than 1%. Its occurrence increases following immune-mediated or neoplastic pericarditis (2–5%) and is highest after purulent bacterial pericarditis (20–30%). Other causes include post cardiac surgery, radiation therapy, and connective tissue disorders. A small number of cases are drug-induced or secondary to

trauma, asbestos, sarcoidosis, or uremia. At times, both pericardial tamponade and constrictive pericarditis may coexist, a condition referred to as **effusive-constrictive pericarditis**. The only definitive way to diagnose this condition is to reveal the underlying constrictive physiology once the pericardial fluid is drained. The differentiation of constrictive pericarditis from a restrictive cardiomyopathy may require cardiac catheterization and the utilization of all available noninvasive imaging methods.

## ► Clinical Findings

### A. Symptoms and Signs

The principal symptoms are slowly progressive dyspnea, fatigue, and weakness. Chronic edema, hepatic congestion, and ascites are usually present. Ascites often seems out of proportion to the degree of peripheral edema. The examination reveals these signs and a characteristically elevated jugular venous pressure with a rapid *y* descent. This can be detected at bedside by careful observation of the jugular pulse and noting an apparent increased pulse wave at the end of ventricular systole (due to the relative accentuation of the *v* wave by the rapid *y* descent). **Kussmaul sign**—a failure of the JVP to fall with inspiration—is also a frequent finding. The apex may actually retract with systole and a pericardial “knock” may be heard in early diastole. Pulsus paradoxus is unusual. Atrial fibrillation is common.

### B. Diagnostic Studies

At times, constrictive pericarditis is extremely difficult to differentiate from restrictive cardiomyopathy and the two may coexist. When unclear, the use of both noninvasive testing and cardiac catheterization is required to sort out the difference.

**1. Radiographic findings**—The chest radiograph may show normal heart size or cardiomegaly. Pericardial calcification is best seen on the lateral view and is uncommon. It rarely involves the LV apex, and finding of calcification at the LV apex is more consistent with LV aneurysm.

**2. Echocardiography**—Echocardiography rarely demonstrates a thickened pericardium. A **septal “bounce”** reflecting the rapid early filling is common, though. RV/LV interaction may be demonstrated by an inspiratory reduction in the mitral inflow Doppler pattern of greater than 25%, much as in tamponade. Usually the initial mitral inflow into the LV is very rapid, and this can be demonstrated as well by the Doppler inflow (*E* wave) pattern. Other echocardiographic features, such as the ratio of the medial and lateral mitral annular motion (*e'* velocity), the respiration-related septal shift, and hepatic vein expiratory diastolic reversal ratio, also suggest constrictive physiology.

**3. Cardiac CT and MRI**—These imaging tests are only occasionally helpful. Pericardial thickening of more than 4 mm must be present to establish the diagnosis, but no pericardial thickening is demonstrable in 20–25% of patients with constrictive pericarditis. Some MRI techniques demonstrate the septal bounce and can provide further evidence for ventricular interaction.

**4. Cardiac catheterization**—This procedure is often confirmatory or can be diagnostic in difficult cases where the echocardiographic features are unclear or mixed. As a generality, the pulmonary pressure is low in constriction (as opposed to restrictive cardiomyopathy). In constrictive pericarditis, because of the need to demonstrate RV/LV interaction, cardiac catheterization should include simultaneous measurement of both the LV and RV pressure tracings with inspiration and expiration. This interaction can be demonstrated by cardiac MRI. Hemodynamically, patients with constriction have equalization of end-diastolic pressures throughout their cardiac chambers, there is rapid early filling then an abrupt increase in diastolic pressure (“square-root” sign), the RV end-diastolic pressure is more than one-third the systolic pressure, simultaneous measurements of RV and LV systolic pressure reveal a discordance with inspiration (the RV rises as the LV falls), and there is usually a Kussmaul sign (failure of the RA pressure to fall with inspiration). In restrictive cardiomyopathy, there is concordance of RV and LV systolic pressures with inspiration.

## ► Treatment

Therapy should be aimed at the specific etiology initially. If there is laboratory evidence of ongoing inflammation, then anti-inflammatory medications may have a role. Once the hemodynamics are evident, the mainstay of treatment is diuresis. As in other disorders of right heart failure, the diuresis should be aggressive, using loop diuretics (oral torsemide or bumetanide if bowel edema is suspected or intravenous furosemide), thiazides, and aldosterone antagonists (especially in the presence of ascites and liver congestion). Surgical pericardectomy should be recommended when diuretics are unable to control symptoms. Pericardectomy removes only the pericardium between the phrenic nerve pathways, however, and most patients still require diuretics after the procedure, though symptoms are usually dramatically improved. Morbidity and mortality after pericardectomy are high (up to 15%) and are greatest in those with the most disability prior to the procedure. Poor prognostic predictors include prior radiation, kidney dysfunction, higher pulmonary systolic pressures, abnormal LV systolic function, a lower serum sodium level, liver dysfunction, and older age. Pericardial calcium has no impact on survival.

## ► When to Refer

If the diagnosis of constrictive pericarditis is unclear or the symptoms of fluid retention resist medical therapy, then referral to a cardiologist is warranted to both establish the diagnosis and recommend therapy.

Anasari-Gilani K et al. Multimodality approach to the diagnosis and management of constrictive pericarditis. *Echocardiography*. 2020;30:632. [PMID: 32240548]  
 Goldstein JA et al. Hemodynamics of constrictive pericarditis and restrictive cardiomyopathy. *Catheter Cardiovasc Interv*. 2020;95:1240. [PMID: 31904891]

## PULMONARY HYPERTENSION



### ESSENTIALS OF DIAGNOSIS

- ▶ Mean PA pressure  $\geq$  25 mm Hg.
- ▶ Dyspnea and often cyanosis.
- ▶ Enlarged pulmonary arteries on chest radiograph.
- ▶ Elevated JVP and RV heave.
- ▶ Echocardiography is often diagnostic.

## ► General Considerations

The normal pulmonary bed offers about one-tenth as much resistance to blood flow as the systemic arterial system. Based on the 2019 Sixth World Symposium on Pulmonary Hypertension, the definition of pulmonary hypertension was changed. It was defined by a mean PA pressure of 20 mm Hg with a pulmonary vascular resistance of greater than or equal to 3 Wood units. Three categories were then defined:

1. Precapillary pulmonary hypertension: mean pulmonary artery pressure greater than 20 mm Hg, PVR greater than or equal to 3.0 Wood units, PCWP less than or equal to 15 mm Hg
2. Isolated post-capillary pulmonary hypertension: mean pulmonary artery pressure greater than 20 mm Hg, PVR less than 3.0 Wood units, PCWP greater than 15 mm Hg
3. Combined pre- and post-pulmonary hypertension: mean pulmonary artery pressure greater than 20 mm Hg, PVR greater than or equal to 3.0 Wood units, PCWP greater than 15 mm Hg

The clinical classification of pulmonary hypertension by the Sixth World Symposium on Pulmonary Hypertension is outlined in Table 10–18.

**Group I** includes **pulmonary arterial hypertension (PAH)** related to an underlying pulmonary vasculopathy. It includes the former “primary pulmonary hypertension” under the term “idiopathic pulmonary hypertension” and is defined as pulmonary hypertension and elevated PVR in the absence of other disease of the lungs or heart. Its cause is unknown. About 6–10% have heritable PAH. Drug and toxic pulmonary hypertension have been described as associated with the use of anorexigenic agents that increase serotonin release and block its uptake. These include amphetamine, fenfluramine, and dexfenfluramine. In some cases, there is epidemiologic linkage to ingestion of rapeseed oil or L-tryptophan and use of recreational drugs, such as amphetamines and cocaine. Pulmonary hypertension associated with connective tissue disease includes cases associated with systemic sclerosis—up to 8–12% of patients with systemic sclerosis may be affected. Pulmonary hypertension has also been associated with HIV infection, portal hypertension, congenital heart disease (Eisenmenger syndrome), schistosomiasis, and chronic hemolytic anemia.

**Table 10–18.** Updated classification of pulmonary hypertension (PH).

| Pulmonary arterial hypertension (PAH)  |
|--|
| Idiopathic PAH   |
| Heritable PAH  |
| Drug- and toxin-induced PAH  |
| PAH associated with connective tissue disease, HIV infection, portal hypertension, congenital heart disease, schistosomiasis |
| PAH long-term responders to calcium channel blockers   |
| PAH with overt features of venous/capillaries (PVOD/PCH) involvement   |
| Persistent PH of the newborn syndrome  |
| PH due to left heart disease   |
| Due to heart failure with preserved LVEF   |
| Due to heart failure with reduced LVEF   |
| Valvular heart disease   |
| Congenital/acquired cardiovascular conditions leading to post-capillary pulmonary hypertension                               |
| PH due to lung diseases or hypoxia (or both)   |
| Obstructive lung disease   |
| Restrictive lung disease   |
| Other lung disease with mixed obstructive/restrictive pattern  |
| Hypoxia without lung disease   |
| Developmental lung disorders   |
| PH due to pulmonary artery obstructions  |
| Chronic thromboembolic pulmonary hypertension  |
| Other pulmonary artery obstructions  |
| PH with unclear or multifactorial mechanisms   |
| Hematologic disorders  |
| Systemic and metabolic disorders   |
| Others   |
| Complex congenital heart disease   |

LVEF, left ventricular ejection fraction; PVOD/PCH, pulmonary veno-occlusive disease/ pulmonary capillary hemangiomatosis.

Modified, with permission, from Simonneau G et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. Eur Respir J. 2019;53:1801913. © ERS 2021.

(eg, sickle cell anemia). In rare instances, obstruction of the pulmonary venous circulation may occur (pulmonary veno-occlusive disease and capillary hemangiomatosis).

**Group II** includes all cases related to left heart disease. **Group III** includes cases due to parenchymal lung disease, impaired control of breathing, or living at high altitude. This group encompasses those with idiopathic pulmonary fibrosis and COPD. **Group IV** represents patients with chronic thromboembolic disease or other pulmonary artery obstruction. **Group V** includes multifactorial causes such as hematologic, systemic, and metabolic disorders.

## ► Clinical Findings

### A. Symptoms and Signs

Common to all is exertional dyspnea, chest pain, fatigue, and lightheadedness as early symptoms; later symptoms include syncope, abdominal distention, ascites, and peripheral edema as RV function worsens. Chronic lung disease, especially sleep apnea, often is overlooked as a cause for pulmonary hypertension as is chronic thromboembolic disease.

Patients with idiopathic pulmonary hypertension are characteristically young women who have evidence of right heart failure that is usually progressive, leading to death in 2–8 years without therapy. This is a decidedly different prognosis than patients with Eisenmenger physiology due to a left-to-right shunt; 40% of patients with Eisenmenger physiology are alive 25 years after the diagnosis has been made. Patients have manifestations of low cardiac output, with weakness and fatigue, as well as edema and ascites as right heart failure advances. Peripheral cyanosis is present, and syncope on effort may occur.

### B. Diagnostic Studies

The ESC and European Respiratory Society updated guidelines for the diagnosis and treatment of pulmonary hypertension in 2019. All patients with a high risk for PAH should undergo *confirmatory right heart catheterization*.

The laboratory evaluation of idiopathic pulmonary hypertension must exclude a secondary cause. A hypercoagulable state should be sought by measuring protein C and S levels, the presence of a lupus anticoagulant, the level of factor V Leiden, prothrombin gene mutations, and D-dimer. Chronic pulmonary emboli must be excluded (usually by ventilation-perfusion lung scan or contrast spiral CT); the ventilation-perfusion scan is the more sensitive test but not specific. If it is normal, then chronic thromboembolic pulmonary hypertension is very unlikely. The chest radiograph helps exclude a primary pulmonary etiology—evidence for patchy pulmonary edema may raise the suspicion of pulmonary veno-occlusive disease due to localized obstruction in pulmonary venous drainage. A sleep study may be warranted if sleep apnea is suspected. The ECG is generally consistent with RVH and RA enlargement. Echocardiography with Doppler helps exclude an intracardiac shunt and usually demonstrates an enlarged RV and RA—at times they may be huge and hypocontractile. Severe pulmonic or tricuspid valve regurgitation may be present. Interventricular septal flattening seen on the echocardiogram is consistent with pulmonary hypertension. Doppler interrogation of the tricuspid regurgitation jet provides an estimate of RV systolic pressure. Pulmonary function tests help exclude other disorders, though primary pulmonary hypertension may present with only a reduced carbon monoxide diffusing capacity of the lung ( $DL_{CO}$ ) or severe desaturation (particularly if a PFO has been stretched open and a right-to-left shunt is present). A declining  $DL_{CO}$  may precede the development of pulmonary hypertension in a patient with systemic sclerosis. Chest CT demonstrates enlarged pulmonary arteries and excludes other causes (such as emphysema or interstitial lung disease). Pulmonary angiography (or magnetic resonance angiography or CT angiography) reveals loss of the smaller acinar pulmonary vessels and tapering of the larger ones. Catheterization allows measurement of pulmonary pressures and testing for vasoreactivity using a variety of agents, but **nitric oxide** is the preferred testing agent due to its ease of use and short half-life. A positive response is defined as one that decreases the pulmonary mean pressure by greater than 10 mm Hg, with the final mean PA pressure less than 40 mm Hg. Abdominal ultrasound is

recommended to exclude portal hypertension. A lung biopsy is no longer suggested as relevant for the diagnosis.

## Treatment & Prognosis

The treatment of PAH continues to evolve and depends on the etiology. For group I patients with a normal PCWP, treatment is related to the response to nitric oxide challenge with those responsive being initially treated with calcium channel blockers. The vast majority of patients, unfortunately, do not respond to the acute vasoreactivity testing. Specific PAH therapy is therefore recommended in this situation. This begins with monotherapy but expands to the use of sequential medication therapy when pulmonary pressures are not improved. In critically ill hypotensive patients inotropic support may be required and eventually lung transplantation considered. Balloon atrial septostomy is considered a IIb recommendation (on the notion that increased right-to-left shunting will improve cardiac output), but it is very rarely utilized.

Medication monotherapy varies in effectiveness depending on the etiologic classification. Only those in class I who respond to nitric oxide should get calcium channel blockers. The current medication therapies include endothelin-receptor blockers (ambrisentan, bosentan, macitentan), phosphodiesterase type-5 inhibitors (sildenafil, tadalafil, and vardenafil), a guanylate cyclase stimulator (riociguat), prostaglandins (epoprostenol, iloprost, treprostil, and beraprost), and an IP-receptor agonist (selexipag). Various medication combinations have been approved and, when ineffective, sequential medication therapies may be used. Many medications interfere with HIV treatment, and this needs to be assessed if relevant. Due to inherent lung disease or left heart disease, there are no therapies that are specific to PAH. Bosentan, an endothelin receptor blocker, has received a class I indication for patients with Eisenmenger syndrome. Anticoagulation is often recommended and is required lifelong in chronic thromboembolic pulmonary hypertension. The number of patients with inoperable chronic thromboembolic pulmonary hypertension being treated with balloon pulmonary angioplasty has increased dramatically since favorable results have been reported. Riociguat remains the only approved medical therapy for chronic thromboembolic pulmonary hypertension patients in this latter group.

Counseling and patient education are also important. Aerobic exercise is recommended but no heavy physical exertion or isometric exercise. Routine immunizations are advised. Pregnancy should be strongly discouraged and preventive measures taken to ensure it does not occur. Maternal mortality in severe PAH may be up to 50%.

Warfarin anticoagulation is recommended in all patients with idiopathic PAH and no contraindication. Diuretics are useful for the management of right-sided heart failure; clinical experience suggests loop diuretics (torsemide or bumetanide, which are absorbed even if bowel edema is present) plus spironolactone are preferable. Oxygen should be used to maintain oxygen saturation greater than 90%. Acute vasodilator testing (generally with nitric oxide) should be performed in all patients with idiopathic PAH who may be potential candidates for long-term

therapy with calcium channel blockers. Patients with PAH caused by conditions other than idiopathic PAH respond poorly to oral calcium channel blockers, and there is little value of acute vasodilator testing in these patients.

## When to Refer

All patients with suspected pulmonary hypertension should be referred to either a cardiologist or pulmonologist who specializes in pulmonary hypertension.

- Frost A et al. Diagnosis of pulmonary hypertension. *Eur Respir J.* 2019;53:1801904. [PMID: 30545972]
- Galiè N et al. An overview of the 6th World Symposium on Pulmonary Hypertension. *Eur Respir J.* 2019;53:1802148. [PMID: 30552088]
- Kataoka M et al. Balloon pulmonary angioplasty (percutaneous transluminal pulmonary angioplasty) for chronic thromboembolic pulmonary hypertension: a Japanese perspective. *JACC Cardiovasc Interv.* 2019;12:1382. [PMID: 31103538]
- Mahmud E et al. Chronic thromboembolic pulmonary hypertension: evolving therapeutic approaches for operable and inoperable disease. *J Am Coll Cardiol.* 2018;71:2468. [PMID: 29793636]
- Simonneau G et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. *Eur Respir J.* 2019;53:1801913. [PMID: 30545968]
- Thenappan T et al. Pulmonary arterial hypertension: pathogenesis and clinical management. *BMJ.* 2018;360:j5492. [PMID: 29540357]

## NEOPLASTIC DISEASES OF THE HEART

### PRIMARY CARDIAC TUMORS

Primary cardiac tumors are rare and constitute only a small fraction of all tumors that involve the heart or pericardium. The most common primary tumor is **atrial myxoma**; it comprises about 50% of all tumors in adult case series. It is generally attached to the atrial septum and is more likely to grow on the LA side of the septum rather than the RA. Patients with myxoma can rarely present with the characteristics of a systemic illness, with obstruction of blood flow at the mitral valve level, or with signs of peripheral embolization. The syndrome includes fever, malaise, weight loss, leukocytosis, elevated sedimentation rate, and emboli (peripheral or pulmonary, depending on the location of the tumor). This is sometimes confused with infective endocarditis, lymphoma, other cancers, or autoimmune diseases. In most cases, the tumor may grow to considerable size and produce symptoms by simply obstructing mitral inflow. Episodic pulmonary edema (classically occurring when an upright posture is assumed) and signs of low output may result. Physical examination may reveal a diastolic sound related to motion of the tumor ("tumor plop") or a diastolic murmur similar to that of mitral stenosis. Right-sided myxomas may cause symptoms of right-sided failure. Familial myxomas occur as part of the Carney complex, which consists of myxomas, pigmented skin lesions, and endocrine neoplasia.

The diagnosis of atrial myxoma is established by echocardiography or by pathologic study of embolic material. Cardiac MRI is useful as an adjunct. Contrast angiography

is frequently unnecessary, although it may demonstrate a “tumor blush” when the mass is vascular. Surgical excision is usually curative, though recurrences do occur and serial echocardiographic follow-up is recommended.

The second most common primary cardiac tumors are **valvular papillary fibroelastomas** and **atrial septal lipomas**. These tend to be benign and usually require no therapy. Papillary fibroelastomas are usually on the pulmonary or aortic valves, may embolize or cause valvular dysfunction, and should be removed if large and mobile. Other primary cardiac tumors include rhabdomyomas (that often appear multiple in both the RV and LV), fibrous histiocytomas, hemangiomas, and a variety of unusual sarcomas. Some sarcomas may be of considerable size before discovery. Primary pericardial tumors, such as mesotheliomas related to asbestos exposure, may also occur. The diagnosis may be supported by an abnormal cardiac contour on radiograph. Echocardiography is usually helpful but may miss tumors infiltrating the ventricular wall. Cardiac MRI is the diagnostic procedure of choice along with gated CT imaging for all cardiac tumors.

## SECONDARY CARDIAC TUMORS

Metastases from malignant tumors can also affect the heart. Most often this occurs in malignant melanoma, but other tumors that are known to metastasize to the heart include bronchogenic carcinoma; carcinoma of the breast; lymphoma; renal cell carcinoma; sarcomas; and, in patients with AIDS, Kaposi sarcoma. These are often clinically silent but may lead to pericardial tamponade, arrhythmias and conduction disturbances, heart failure, and peripheral emboli. The ECG may reveal regional Q waves. The diagnosis is often made by echocardiography, but cardiac MRI and CT scanning can often better delineate the extent of involvement. Metastatic tumors, especially lung or breast, may invade the pericardium and result in very large pericardial effusions as they result in slow accumulation of fluid. The prognosis is poor for all secondary cardiac tumors and treatment is generally palliative. On occasion, surgical resection for debulking or removal and chemotherapy may be effective in relieving symptoms.

### Treatment

Many primary tumors may be resectable. Atrial myxomas should be removed surgically due to the high incidence of embolization from these friable tumors. Recurrences require lifelong monitoring with echocardiography. Papillary fibroelastomas are usually benign but they should be removed if they appear mobile and are larger than 10 mm in size or if there is evidence of embolization at the time of discovery. Large pericardial effusions from metastatic tumors may be drained for comfort, but the fluid invariably recurs. Rhabdomyomas may be surgically cured if the tumor is accessible and can be removed while still leaving enough functioning myocardium intact.

### When to Refer

All patients with suspected cardiac tumors should be referred to a cardiologist or cardiac surgeon for evaluation and possible therapy.

Lichtenberger JP 3rd et al. MR imaging of cardiac masses. *Top Magn Reson Imaging*. 2018;27:103. [PMID: 29613965]  
Rahouma M et al. Cardiac tumors prevalence and mortality: a systematic review and meta-analysis. *Int J Surg*. 2020;76:178. [PMID: 32169566]

Taguchi S. Comprehensive review of the epidemiology and treatments for malignant adult cardiac tumors. *Gen Thorac Cardiovasc Surg*. 2018;66:257. [PMID: 29594875]

## TRAUMATIC HEART DISEASE

Trauma is the leading cause of death in patients aged 1–44 years; cardiac and vascular trauma is second only to neurologic injury as the reason for these deaths. Penetrating wounds to the heart are often lethal unless immediately surgically repaired. In a 20-year review of penetrating trauma at a single institution, it was found that gunshot wounds were fatal 13 times more often than stab wounds and that factors such as hypotension, Glasgow Coma Score less than 8, Revised Trauma Score less than 7.84, associated injuries, and the more severe the injuries (Injury Severity Score greater than 25) all added to the mortality and morbidity risk.

Blunt trauma is a more frequent cause of cardiac injuries. This type of injury is common in motor vehicle accidents and may occur with any form of chest trauma, including CPR efforts. The most common injuries are myocardial contusions or hematomas. The RV is particularly prone to contusion as it sits directly under the sternum. Other forms of nonischemic cardiac injury include metabolic injury due to burns, electrical current, or sepsis. These may be asymptomatic (particularly in the setting of more severe injuries) or may present with chest pain of a nonspecific nature or, not uncommonly, with a pericardial component. Elevations of cardiac enzymes are frequent, and can be quite high, but the levels do not correlate with prognosis. There are some data that the presence of certain other cardiac biomarkers, such as NT-proBNP, correlate better with significant myocardial injury. Echocardiography may reveal an akinetic myocardial segment or pericardial effusion. Cardiac MRI may also suggest acute injury. Coronary CT angiography or angiography can reveal a coronary dissection or acute occlusion if that is a concern. Pericardiocentesis is warranted if tamponade is evident. As noted above, tako-tsubo transient segmental myocardial dysfunction can occur due to the accompanying stress.

Severe trauma may also cause myocardial or valvular rupture. Cardiac rupture can involve any chamber, but survival is most likely if injury is to one of the atria or the RV. Hemopericardium or pericardial tamponade is the usual clinical presentation, and surgery is almost always necessary. Mitral and aortic valve rupture may occur during severe blunt trauma—the former presumably if the impact occurs during systole and the latter if during diastole. Patients reach the hospital in shock or severe heart failure. Immediate surgical repair is essential. The same types of injuries may result in transection of the aorta, either at the level of the arch or distal to the takeoff of the left subclavian artery at the ligamentum arteriosum. Transthoracic echocardiography and TEE are the most helpful and immediately available diagnostic techniques. CT and MRI may also be required to better define the injury before surgical intervention.

Blunt trauma may also result in damage to the coronary arteries. Acute or subacute coronary thrombosis is the most common presentation. The clinical syndrome is one of acute MI with attendant ECG, enzymatic, and contractile abnormalities. Emergent revascularization is sometimes feasible, either by the percutaneous route or by coronary artery bypass surgery. LV aneurysms are common outcomes of traumatic coronary occlusions, likely due to sudden occlusion with no collateral vascular support. Coronary artery dissection or rupture may also occur in the setting of blunt cardiac trauma.

As expected, patients with severe preexisting conditions fare the least well after cardiac trauma. Data from ReCONNECT, a trauma consortium, reveal that mortality is linked to volume of cases seen at various centers, preexisting coronary disease or heart failure, intubation, age, and a severity scoring index.

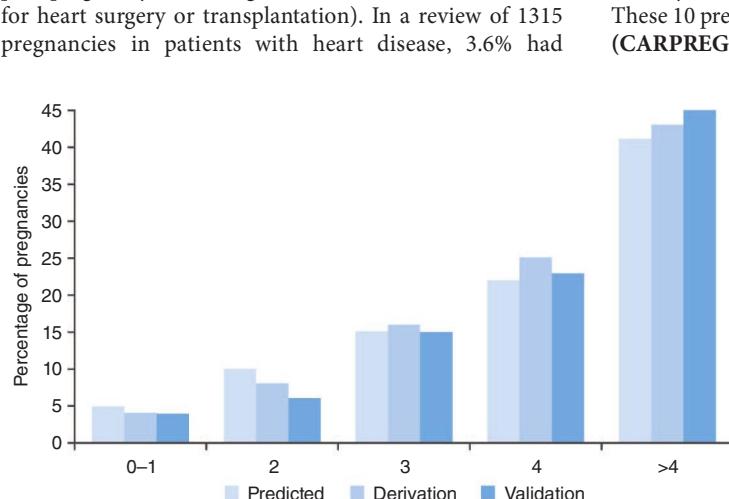
Huis In't Veld MA et al. Blunt cardiac trauma review. *Cardiol Clin*. 2018;36:183. [PMID: 29173678]

Qamar SR et al. State of the art imaging review of blunt and penetrating cardiac trauma. *Can Assoc Radiol J*. 2020;71:301. [PMID: 32066272]

Schellenberg M et al. Critical decisions in the management of thoracic trauma. *Emerg Med Clin North Am*. 2018;36:135. [PMID: 29132573]

serious cardiovascular complications and half were found to be preventable. Two-thirds of the complications occurred in the antepartum period. Adverse fetal and neonatal events, as expected, were much more common in those pregnancies with cardiovascular events.

The **Cardiac Disease in Pregnancy Investigation (CARPREG I)** scoring system for risk from cardiac events for women with heart disease noted four major risk factors: (1) NYHA FC III or IV heart failure, (2) prior cardiac events, (3) mitral or aortic obstruction, and (4) LVEF less than 40%. One point is assigned to each. Patients with no points had a 5% risk, those with 1 point had a complication rate of 27%, while for those with 2 or more points, the risk was 74%. Other reviews have suggested that the major risk for adverse outcomes or death to either the mother or fetus include pulmonary hypertension (with pulmonary pressure greater than three-quarters of systemic pressure), maternal cyanosis, systemic ventricular dysfunction, poor maternal functional class, severe left-sided valvular obstruction, aortic coarctation, significantly dilated aortic root, significant unrepaired heart defects, and warfarin therapy in patients with mechanical valves. In 2018, this group reported the results from a follow-up study (CARPREG II). Cardiac complications occurred in 16% of pregnancies and were primarily related to arrhythmias and heart failure. Although the overall rates of cardiac complications during pregnancy did not change over the years, the frequency of pulmonary edema decreased (8% from 1994 to 2001 vs. 4% from 2001 to 2014). Ten predictors of maternal cardiac complications were identified: five general predictors (prior cardiac events or arrhythmias, poor functional class or cyanosis, high-risk valve disease/LV outflow tract obstruction, systemic ventricular dysfunction, no prior cardiac interventions); four lesion-specific predictors (mechanical valves, high-risk aortopathies, pulmonary hypertension, CAD); and one delivery of care predictor (late pregnancy assessment). These 10 predictors were incorporated into a new risk index (CARPREG II) shown in Figure 10–11.



**▲ Figure 10–11.** Risk index for material cardiac complications in pregnancy (CARPREG II). The risk index is divided into five categories based on the sum of the points for a given pregnancy: 0 to 1 point; 2 points; 3 points; 4 points; and > 4 points. The predicted risks for primary cardiac events stratified according to point score were 0 to 1 point (5%), 2 points (10%), 3 points (15%), 4 points (22%), and > 4 points (41%). (Modified, with permission, from Silversides CK et al. Pregnancy outcomes in women with heart disease: the CARPREG II Study. *J Am Coll Cardiol*. 2018;71:2419. Copyright © 2018 by the American College of Cardiology Foundation. Published by Elsevier.)

In 2011, the World Health Organization outlined guidelines for the management of pregnancy in patients with congenital heart disease. This guideline also outlines risks to the fetus. Table 10–19 summarizes the observations and recommendations. Medication usage during pregnancy is always a difficult decision since *most have not been studied*. ACE inhibitors and amiodarone are contraindicated. Beta-blockers (including labetalol, metoprolol, and sotalol), digoxin, and calcium channel blockers are generally well

tolerated (especially nifedipine, amlodipine, or verapamil, although there is controversy with diltiazem). There are concerns about the use of atenolol and premature birth, and it should not be used. Labetalol has been found to be particularly useful for treating hypertension as has methyldopa (though this is rarely used). Diuretics can generally be given safely. Pregnancy is a hypercoagulable state; the use of warfarin is discussed above under valvular disease and congenital heart disease, but fundamentally the risk is

**Table 10–19.** Management strategies for women with valve disease, complex congenital heart disease, pulmonary hypertension, aortopathy, and dilated cardiomyopathy.

| High-Risk Heart Disease in Pregnancy |   |   |  |
|--------------------------------------|---|---|--|
| Disease                              | Management Strategy   |   |  |
|                                      | Pregnancy Not Advised   | Pregnancy Management  | Delivery   |
| Valve disease                        | <ul style="list-style-type: none"> <li>Severe mitral and aortic valve disease</li> <li>Mechanical prosthetic valves if effective anticoagulation not possible</li> </ul>  | <ul style="list-style-type: none"> <li>Close follow-up</li> <li>Medication therapy for heart failure or arrhythmias</li> <li>Balloon valvuloplasty or surgical valve replacement in refractory cases</li> </ul>   | <ul style="list-style-type: none"> <li>Vaginal delivery preferred</li> <li>C-section in case of fetal or maternal instability</li> <li>Early delivery for clinical and hemodynamic deterioration</li> <li>Consider hemodynamic monitoring during labor and delivery</li> </ul>   |
| Complex congenital heart disease     | <ul style="list-style-type: none"> <li>Significant ventricular dysfunction</li> <li>Severe AV valve dysfunction</li> <li>Falling Fontan circulation</li> <li>Oxygen saturation &lt; 85%</li> </ul>  | <ul style="list-style-type: none"> <li>Close follow-up</li> </ul>   | <ul style="list-style-type: none"> <li>Vaginal delivery preferred</li> <li>C-section in case of fetal or maternal instability</li> <li>Consider hemodynamic monitoring during labor and delivery</li> </ul>  |
| Pulmonary hypertension               | <ul style="list-style-type: none"> <li>Established pulmonary arterial hypertension</li> </ul>   | <ul style="list-style-type: none"> <li>Close follow-up</li> <li>Early institution of pulmonary vasodilators</li> </ul>  | <ul style="list-style-type: none"> <li>Vaginal delivery preferred</li> <li>C-section in case of fetal or maternal instability</li> <li>Timing of delivery depends on clinical and RV function</li> <li>Early delivery advisable</li> <li>Diuresis after delivery to prevent RV volume overload</li> <li>Extended hospital stay after delivery</li> </ul> |
| Aortopathy                           | <p><b>For some women—</b></p> <ul style="list-style-type: none"> <li>Marfan syndrome</li> <li>Bicuspid aortic valve</li> <li>Turner syndrome</li> <li>Rapid growth of aortic diameter or family history of premature aortic dissection</li> </ul> | <ul style="list-style-type: none"> <li>Treat hypertension</li> <li>Beta-blockers to reduce heart rate</li> <li>Frequent echocardiographic assessment</li> <li>Surgery during pregnancy or after C-section if large increase in aortic diameter</li> </ul> | <ul style="list-style-type: none"> <li>C-section in cases of significant aortic dilation</li> <li>– Marfan syndrome &gt; 40 mm</li> <li>– Bicuspid aortic valve &gt; 45 mm</li> <li>– Turner syndrome: aortic size index &gt; 20 mm/m<sup>2</sup></li> </ul>   |
| Dilated cardiomyopathy               | <ul style="list-style-type: none"> <li>LVEF &lt; 40%</li> <li>History of peripartum cardiomyopathy</li> </ul>   | <ul style="list-style-type: none"> <li>Close follow-up</li> <li>Beta-blockers</li> <li>Diuretic agents for volume overload</li> <li>Vasodilators for hemodynamic and symptomatic improvement</li> </ul>   | <ul style="list-style-type: none"> <li>Vaginal delivery preferred</li> <li>C-section in case of fetal or maternal instability</li> <li>Consider hemodynamic monitoring during labor and delivery</li> <li>Early delivery for clinical and hemodynamic deterioration</li> </ul>   |

AV, atrioventricular; C-section, cesarean section; LV, left ventricular; LVEF, left ventricular ejection fraction; RV, right ventricular.

Modified, with permission, from Elkayam U et al. High-risk cardiac disease in pregnancy: Part I. J Am Coll Cardiol. 2016 Jul 26;68(4):396–410. © 2016 by the American College of Cardiology Foundation.

dose related (not INR related) and warfarin can be used during the first trimester if the dose is 5 mg or less. For many patients, the most common potential complication is an atrial arrhythmia or systemic hypertension (systemic blood pressure greater than 140/90 mm Hg). Patients should be hospitalized if blood pressure exceeds 170/110 mm Hg.

Patients with adult congenital heart disease are at risk not only for cardiovascular events, but for obstetric events such as hypertension, preeclampsia, placenta previa or abruption, and early delivery.

Pfaller B et al. Preventing complications in pregnant women with cardiac disease. *J Am Coll Cardiol.* 2020;75:1443. [PMID: 32216913]

Schluchting LE et al. Maternal comorbidities and complications of delivery in pregnant women with congenital heart disease. *J Am Coll Cardiol.* 2019;73:2181. [PMID: 31047006]

Silversides CK et al. Pregnancy outcomes in women with heart disease: the CARPREG II study. *J Am Coll Cardiol.* 2018;71:2419. [PMID: 29793631]

## CARDIOVASCULAR COMPLICATIONS OF PREGNANCY

Pregnancy-related hypertension (eclampsia and pre-eclampsia) is discussed in Chapter 19.

### 1. Cardiomyopathy of Pregnancy (Peripartum Cardiomyopathy)

In approximately 1 in 3000 to 4000 live births, dilated cardiomyopathy develops in the mother in the final month of pregnancy or within 6 months after delivery. Risk factors include preeclampsia, twin pregnancies, and African ethnicity. The cause is slowly being elucidated. The vasculo-hormonal hypothesis requires two events. One is genetic, a reduction in a STAT3 transcription factor that results in cleavage of prolactin from the pituitary by cathepsin D. This results in a 16-kd fragment that increases microRNA 146a that results in myocardial apoptosis. The second is from the placenta, soluble tyrosine kinase that blocks VEGF (vascular endothelial growth factor). It appears both components may be necessary to effectively result in peripartum cardiomyopathy. The course of the disease is variable; most cases improve or resolve completely over several months, but others progress to refractory heart failure. About 60% of patients make a complete recovery. Serum BNP levels are routinely elevated in pregnancy, but serial values may be useful in predicting who may be at increased risk for a worse outcome. Beta-blockers have been administered judiciously to these patients, with at least anecdotal success. Diuretics, hydralazine, and nitrates help treat the heart failure with minimal risk to the fetus. Sotalol is acceptable for ventricular or atrial arrhythmias if other beta-blockers are ineffective. Some experts advocate anticoagulation because of an increased risk of thrombotic events, and both warfarin and heparin have their proponents. In severe cases, transient use of extracorporeal membrane oxygenation (ECMO) has been lifesaving. Recurrence in

subsequent pregnancies is common, particularly if cardiac function has not completely recovered, and subsequent pregnancies are to be discouraged if the EF remains less than 55%. The risk of recurrent heart failure in a subsequent pregnancy has been estimated to be 21%. Delivery of the baby is important, though the peak incidence of the problem is in the first week after delivery and a few cases appear up to 5 weeks after delivery. Since the antiangiogenic cleaved prolactin fragment is considered causal for peripartum cardiomyopathy, bromocriptine (a prolactin release inhibitor) has been reported to be beneficial. A multicenter trial in Europe found LVEF improved to a greater extent in patients with peripartum cardiomyopathy who were given bromocriptine than those who were not given bromocriptine. In addition, bromocriptine treatment was associated with high rate of full LV recovery and low morbidity and mortality in peripartum cardiomyopathy patients compared with other peripartum cardiomyopathy cohorts not treated with bromocriptine.

For a complete review of the current issues surrounding peripartum cardiomyopathy, the reader is referred to the state-of-art article noted below.

Davis MB et al. Peripartum cardiomyopathy: JACC State-of-the-Art Review. *J Am Coll Cardiol.* 2020;75:207. [PMID: 31948651]

Honigberg MC et al. Peripartum cardiomyopathy. *BMJ.* 2019;364:k5287. [PMID: 30700415]

### 2. Coronary Artery & Aortic Vascular Abnormalities During Pregnancy

An acute coronary syndrome occurs in 2.8–8.1 per 1,000,000 pregnancies. Many are women over 35 years. It is known that pregnancy predisposes to dissection of the aorta and other arteries, perhaps because of the accompanying connective tissue changes. The risks are particularly high in patients with Marfan, Ehlers-Danlos, or Loey-Dietz syndromes. The risk is highest in the third trimester, and coronary dissection, thrombosis, and atherosclerosis have about equal prevalence. The most frequent cause in one study was coronary dissection, and it has a peak incidence in the early postpartum period. Paradoxical emboli through a PFO to the coronary arteries have been implicated in a few instances. Clinical management is essentially similar to that of other patients with acute infarction, unless there is a connective tissue disorder. If nonatherosclerotic dissection is present, coronary intervention may be risky, as further dissection can be aggravated. In most instances, conservative management is warranted. At times, extensive aortic dissection requires surgical intervention. Marfan patients are particularly susceptible to further aortic expansion during pregnancy when the aortic diameter is more than 4.5 cm (greater or equal to 27 mm/m<sup>2</sup>) and pregnancy be discouraged in these situations. Some data, however, suggest that there is an increased risk of dissection during pregnancy even when the elective repair is reasonable (ie, when the aortic root is greater than 4.0 cm in women with Marfan syndrome contemplating pregnancy). Acute infarction during

pregnancy is associated with an 8% maternal mortality and 56% incidence of premature delivery. If PCI is required, it is now recommended that a drug-eluting stent be considered rather than a bare metal stent. Medications that appear to be safe during pregnancy include aspirin, beta-blockers, clopidogrel, heparin or enoxaparin, and nitrates. Medications that are not safe include aldosterone inhibitors, ACE inhibitors or ARBs, DOACs, and statins. If need be, fibrinolytics, GP IIb/IIIa inhibitors, bivalirudin, and calcium channel blockers can be used.

Honigberg MC et al. Pregnancy-associated myocardial infarction. *Curr Treat Options Cardiovasc Med.* 2018;20:58. [PMID: 29923127]

Tweet MS et al. Pregnancy-associated myocardial infarction: prevalence, causes, and interventional management. *Circ Cardiovasc Interv.* 2020. [Epub ahead of print] [PMID: 32862672]

### 3. Management of Labor

Although vaginal delivery is usually well tolerated, unstable patients (including patients with severe hypertension and worsening heart failure) should have planned cesarean section. Spinal anesthesia results in a large drop in the systemic vascular resistance and can worsen right-to-left shunting. An increased risk of aortic rupture has been noted during delivery in patients with coarctation of the aorta and severe aortic root dilation with Marfan syndrome, and vaginal delivery should be avoided in these patients. For most patients, even those with complex congenital heart disease, vaginal delivery is the preferred method, however. Immediately following delivery, there are numerous fluid shifts that occur with the initial blood loss, reducing preload and accompanied by the loss of afterload reduction that had been provided by the placenta. Quickly, however, venous return increases as the uterus is no longer compressing the inferior vena cava and there is an infusion of fluid into the vascular system as the uterus quickly shrinks back toward its normal size. The sudden increase in preload and loss of afterload following delivery can result in heart failure during the first 48–72 hours after the delivery and that remains the high-risk time for susceptible patients.

## CARDIOVASCULAR SCREENING OF ATHLETES

The **sudden death** of a competitive athlete inevitably becomes an occasion for local, if not national, publicity. On each occasion, the public and the medical community ask whether such events could be prevented by more careful or complete screening. Although each event is tragic, it must be appreciated that there are approximately 5 million competitive athletes at the high school level or above in any given year in the United States. The number of cardiac deaths occurring during athletic participation is unknown but estimates at the high school level range from one in 100,000 to one in 300,000 participants. Death rates among more mature athletes increase as the prevalence of CAD

rises. These numbers highlight the problem of how best to screen individual participants. Even an inexpensive test such as an ECG would generate an enormous cost if required of all athletes, and it is likely that only a few at-risk individuals would be detected. Echocardiography, either as a routine test or as a follow-up examination for abnormal ECGs, would be prohibitively expensive except for the elite professional athlete. Thus, the most feasible approach is that of a careful medical history and cardiac examination performed by personnel aware of the conditions responsible for most sudden deaths in competitive athletes.

It is important to point out that sudden death is much more common in the older than the younger athlete. Older athletes will generally seek advice regarding their fitness for participation. These individuals should recognize that strenuous exercise is associated with an increase in risk of sudden cardiac death and that appropriate training substantially reduces this risk. Preparticipation screening for risk of sudden death in the older athlete is a complex issue and at present is largely focused on identifying inducible ischemia due to significant coronary disease.

In a series of 158 athletic deaths in the United States between 1985 and 1995, hypertrophic cardiomyopathy (36%) and coronary anomalies (19%) were by far the most frequent underlying conditions. LVH was present in another 10%, ruptured aorta (presumably due to Marfan syndrome or cystic medial necrosis) in 6%, myocarditis or dilated cardiomyopathy in 6%, aortic stenosis in 4%, and arrhythmogenic RV dysplasia in 3%. In addition, commotio cordis, or sudden death due to direct myocardial injury, may occur. More common in children, ventricular tachycardia or ventricular fibrillation may occur even after a minor direct blow to the heart; it is thought to be due to the precipitation of a PVC just prior to the peak of the T wave on ECG.

A careful family and medical history and cardiovascular examination will identify most individuals at risk. An update in 2014 recommends that **all middle school and higher athletes undergo a medical screen questionnaire and examination.** The 12 elements in the examination are outlined in Table 10–20.

A family history of premature sudden death or cardiovascular disease, or of any of these predisposing conditions should mandate further workup, including an ECG and echocardiogram. Symptoms of unexplained fatigue or dyspnea, exertional chest pain, syncope, or near syncope also warrant further evaluation. A Marfan-like appearance, significant elevation of BP, abnormalities of heart rate or rhythm, and pathologic heart murmurs or heart sounds should also be investigated before clearance for athletic participation is given. Such an evaluation is recommended before participation at the high school and college levels and every 2 years during athletic competition.

Stress-induced syncope or chest pressure may be the first clue to an anomalous origin of a coronary artery. Anatomically, this lesion occurs most often when the left

**Table 10–20.** 12-element AHA recommendations for preparticipation cardiovascular screening of competitive athletes.

| Medical History  |
|--|
| <b>Personal History</b>  |
| 1. Exertional chest pain/discomfort  |
| 2. Unexplained syncope/near-syncope  |
| 3. Excessive exertional and unexplained dyspnea/fatigue  |
| 4. Prior recognition of a heart murmur   |
| 5. Elevated systemic blood pressure  |
| <b>Family History</b>  |
| 6. Premature death (sudden and unexpected, or otherwise) before age of 50 years due to heart disease in one or more relatives  |
| 7. Disability from heart disease in a close relative before age of 50 years  |
| 8. Specific knowledge of certain cardiac conditions in family members: hypertrophic cardiomyopathy, dilated cardiomyopathy, long QT syndrome or other ion channelopathies, Marfan syndrome, or other important arrhythmias |
| <b>Physical Examination</b>  |
| 9. Heart murmur  |
| 10. Diminished femoral pulse (to exclude coarctation)  |
| 11. Phenotype of Marfan syndrome   |
| 12. Brachial artery blood pressure (sitting position)  |

Reproduced, with permission, from Lawless CE et al. Protecting the heart of the American athlete: proceedings of the American College of Cardiology Sports and Exercise Cardiology Think Tank, October 18, 2012, Washington, DC. J Am Coll Cardiol. 2014 Nov 18–25;64(20):2146–71. Copyright © Elsevier.

anterior descending artery or left main coronary arises from the right coronary cusp and traverses between the aorta and pulmonary trunks. The “slit-like” orifice that results from the angulation at the vessel origin is thought to cause ischemia when the aorta and pulmonary arteries enlarge during vigorous exercise and tension is placed on the coronary.

The toughest distinction may be in sorting out the healthy athlete with LVH from the athlete with hypertrophic cardiomyopathy. In general, the healthy athlete's heart is less likely to have an unusual pattern of LVH (such as asymmetric septal hypertrophy), or to have LA enlargement, an abnormal ECG, an LV cavity less than 45 mm in diameter at end-diastole, an abnormal diastolic filling pattern, or a family history of hypertrophic cardiomyopathy. The athlete is more likely to be male than the individual with hypertrophic cardiomyopathy, where women are equally at risk. Cardiac MRI is emerging as a useful means to separate the athlete's heart from hypertrophic obstructive cardiomyopathy. Increased risk is also evident in patients with the WPW syndrome, a prolonged QTc interval, or those who demonstrate the abnormal ST changes in leads V1 and V2 consistent with the Brugada syndrome.

Selective use of routine ECG and stress testing is recommended in men above age 40 years and women above age 50 years who continue to participate in vigorous exercise and at earlier ages when there is a positive family history for premature CAD, hypertrophic cardiomyopathy, or multiple risk factors. Because at least some of the risk features (long QT,

LVH, Brugada syndrome, WPW syndrome) may be evident on routine ECG screening, several cost-effectiveness studies have been done. Most suggest that preparticipation ECGs are of potential value, though what to do when the QTc is mildly increased is unclear. Many experts feel the high incidence of false-positive ECG studies makes it very ineffective as a screening tool. With the low prevalence of cardiac anomalies in the general public, it has been estimated that 200,000 individual athletes would need to be screened to identify the single individual who would die suddenly. A report from Canada reviewing 74 sudden cardiac arrests during sports activity noted that the vast majority occurred during noncompetitive sports. The incidence during competitive sports was 0.76 per 100,000 athlete-years, and there was not a clear association with structural heart disease in most. Genetic testing of all athletes that demonstrate T wave inversions on their ECG also has been shown to be ineffective; the genetic testing contributed an additional diagnosis in only 2.5% of subjects over that obtained by routine clinical means.

*The issue of routine screening, therefore, remains controversial.* A report from the United Kingdom in 2018, screening adolescent soccer players from 1996 to 2016 (that included ECG and echocardiography), identified diseases associated with sudden death in only 0.38% of the 11,168 athletes screened for a total of 118,351 person-years. The incidence of sudden death was about 7 per 100,000 athletes and most were related to cardiomyopathies that had not been detected on the screening procedures.

In 2017, a position paper from a number of European societies presented arguments regarding the use of a number of preparticipation screening options. The manuscript also provided input from a number of international sports organizations. They concluded that there were data to support obtaining the clinical history, performing a physical examination, and performing a 12-lead ECG on all participants. They did not recommend echocardiography as a screening tool.

In 2017, a consensus statement from the American Medical Society for Sports Medicine was published summarizing the current recommendations for the appropriate screening options in the various clinical scenarios. Once a high-risk individual has been identified, guidelines from the Bethesda conference and the ESC can be used to help determine whether the athlete may continue to participate in sporting events. Table 10–21 summarizes these recommendations.

Screening for return to play after myocardial/pericardial involvement with COVID-19 is currently an important issue (see also Infectious Myocarditis above). An expert consensus statement from the ACC suggests the following:

1. In the athlete who has had COVID-19, the ECG and high-sensitivity troponin should be normal. If any clinical concerns remain, then a transthoracic echocardiogram should be obtained.
2. Point of care echocardiography is not recommended, as the most common echocardiogram abnormalities may be missed by point of care echocardiography. These include RV dysfunction, diastolic LV abnormalities, and

**Table 10–21.** Recommendations for competitive sports participation among athletes with potential causes of SCD.

| Condition                               | 36th Bethesda Conference  | European Society of Cardiology  |
|---|---|---|
| <b>Structural Cardiac Abnormalities</b> |   |   |
| HCM                                     | Exclude athletes with a probable or definitive clinical diagnosis from all competitive sports.<br>Genotype-positive/phenotype-negative athletes may still compete.  | Exclude athletes with a probable or definitive clinical diagnosis from all competitive sports.<br>Exclude genotype-positive/phenotype-negative individuals from competitive sports.   |
| ARVC                                    | Exclude athletes with a probable or definitive diagnosis from competitive sports.   | Exclude athletes with a probable or definitive diagnosis from competitive sports.   |
| CCAA                                    | Exclude from competitive sports.<br>Participation in all sports 3 months after successful surgery would be permitted for an athlete with ischemia, ventricular arrhythmia or tachyarrhythmia, or LV dysfunction during maximal exercise testing.  | Not applicable.   |
| <b>Electrical Cardiac Abnormalities</b> |   |   |
| WPW                                     | Athletes without structural heart disease, without a history of palpitations, or without tachycardia can participate in all competitive sports.<br>In athletes with symptoms, electrophysiological study and ablation are recommended. Return to competitive sports is allowed after corrective ablation, provided that the ECG has normalized. | Athletes without structural heart disease, without a history of palpitations, or without tachycardia can participate in all competitive sports.<br>In athletes with symptoms, electrophysiological study and ablation are recommended. Return to competitive sports is allowed after corrective ablation, provided that the ECG has normalized. |
| LQTS                                    | Exclude any athlete with a previous cardiac arrest or syncopeal episode from competitive sports.<br>Asymptomatic patients restricted to competitive low-intensity sports.<br>Genotype-positive/phenotype-negative athletes may still compete.   | Exclude any athlete with a clinical or genotype diagnosis from competitive sports.  |
| BrS                                     | Exclude from all competitive sports except those of low intensity.  | Exclude from all competitive sports.  |
| CPVT                                    | Exclude all patients with a clinical diagnosis from competitive sports.<br>Genotype-positive/phenotype-negative patients may still compete in low-intensity sports.   | Exclude all patients with a clinical diagnosis from competitive sports.<br>Genotype-positive/phenotype-negative patients are also excluded.   |
| <b>Acquired Cardiac Abnormalities</b>   |   |   |
| Commotio cordis                         | Eligibility for returning to competitive sport in survivors is a matter of individual clinical judgment. Survivors must undergo a thorough cardiovascular workup including 12-lead electrocardiography, ambulatory ECG monitoring, and echocardiography.  | Not applicable.   |
| Myocarditis                             | Exclude from all competitive sports.<br>Convalescent period of 6 months.<br>Athletes may return to competition when test results normalize.   | Exclude from all competitive sports.<br>Convalescent period of 6 months.<br>Athletes may return to competition when test results normalize.   |

ARVC, arrhythmicogenic right ventricular cardiomyopathy; BrS, Brugada syndrome; CCAA, congenital coronary artery anomalies; CPVT, catecholaminergic polymorphic ventricular tachycardia; ECG, electrocardiogram; HCM, hypertrophic cardiomyopathy; LQTS, long QT syndrome; LV, left ventricular; SCD, sudden cardiac death; WPW, Wolff-Parkinson-White syndrome.

Reproduced, with permission, from Chandra N et al. Sudden cardiac death in young athletes: practical challenges and diagnostic dilemmas. J Am Coll Cardiol. 2013 Mar 12;61(10):1027–40. Copyright © Elsevier.

- early signs of LV dysfunction (including abnormal global longitudinal strain). These are “red flags.”
- If any “red flags” from echocardiogram are present, then cardiac MRI should be obtained. MRI provides better assessment of RV function and abnormalities of myocardial edema (T2 imaging), intracellular and extracellular

- signaling (T1 imaging), and late gadolinium enhancement. The long-term significance of these findings is unknown.
- Other imaging modalities can include coronary CT, chest CTA (looking for PE, given the hypercoagulable state COVID-19 creates), and rarely PET imaging.

5. Cardiopulmonary exercise testing is to be avoided during the acute phase but is valuable at 3–6 months after the illness if symptoms persist and as part of return to play guidelines.

Lampert R. ECG screening in athletes: differing views from two sides of the Atlantic. *Heart*. 2018;104:1037. [PMID: 29101265]

Malhotra A et al. Outcomes of cardiac screening in adolescent soccer players. *N Engl J Med*. 2018;379:524. [PMID: 30089062]

Mont L et al. Pre-participation cardiovascular evaluation for athletic participants to prevent sudden death: position paper from the EHRA and the EACPR, branches of the ESC. Endorsed by APHRS, HRS, and SOLAECE. *Eur J Prev Cardiol*. 2017;24:41. [PMID: 27815537]

Phelan D et al. Screening of potential cardiac involvement in competitive athletes recovering from COVID-19: an expert consensus statement. *JACC Cardiovasc Imaging*. 2020;13:2635. [PMID: 33303102]

Sheikh N et al. Diagnostic yield of genetic testing in young athletes with T-wave inversion. *Circulation*. 2018;138:1184. [PMID: 29764897]

# Systemic Hypertension

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11

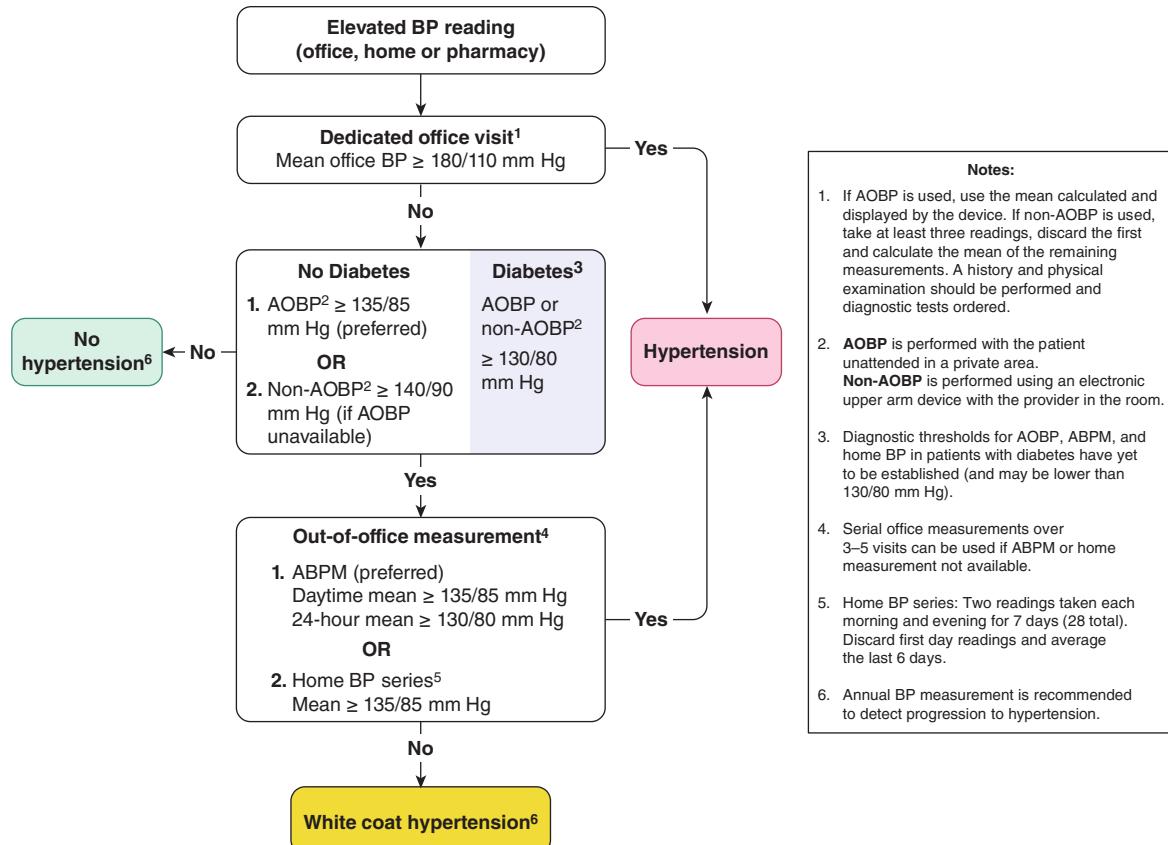
Based on the National Health and Nutrition Survey through 2016, about 45% of adults in the United States have a blood pressure greater than 140/90 mm Hg or are being treated for hypertension. About 80% of people with hypertension are aware of the diagnosis and 75% are receiving treatment, but hypertension is controlled in only 52% of those affected. Cardiovascular morbidity and mortality increase as both systolic and diastolic blood pressures rise, but in individuals over age 50 years, the systolic pressure and pulse pressure are better predictors of complications than diastolic pressure. The prevalence of hypertension increases with age, and it is more common in Blacks than in Whites. Adequate blood pressure control reduces the incidence of acute coronary syndrome by 20–25%, stroke by 30–35%, and heart failure by 50%.

## HOW IS BLOOD PRESSURE MEASURED & HYPERTENSION DIAGNOSED?

Blood pressure should be measured with a well-calibrated sphygmomanometer. The bladder width within the cuff should encircle at least 80% of the arm circumference. Readings should be taken after the patient has been resting comfortably, back supported in the sitting or supine position, for at least 5 minutes and at least 30 minutes after smoking or coffee ingestion. Automated office blood pressure readings, made with office-based devices that permit multiple automated measurements after a pre-programmed rest period, produce data that are independent of digit preference bias (tendency to favor numbers that end with zero or five) and avoid the “white coat” phenomenon (where blood pressure is elevated in the clinic but normal at home). Blood pressure measurements taken outside the office environment, either by intermittent self-monitoring (home blood pressure) or with an automated device programmed to take measurements at regular intervals (ambulatory blood pressure) are more powerful predictors of outcomes and are advocated in clinical guidelines. Home measurements are also helpful in differentiating white coat hypertension from hypertension that is resistant to treatment, and in diagnosis of “masked hypertension” (where blood pressure is normal in the clinic but elevated at home). The cardiovascular risk associated with masked hypertension is similar to that observed in sustained hypertension.

A single elevated blood pressure reading is not sufficient to establish the diagnosis of hypertension. The major exceptions to this rule are hypertension presenting with unequivocal evidence of life-threatening end-organ damage, as seen in hypertensive emergency, or hypertensive urgency where blood pressure is greater than 220/125 mm Hg but life-threatening end-organ damage is absent. In less severe cases, the diagnosis of hypertension depends on a series of measurements of blood pressure, since readings can vary and tend to regress toward the mean with time. Patients whose initial blood pressure is in the hypertensive range exhibit the greatest fall toward the normal range between the first and second encounters. However, the concern for diagnostic precision needs to be balanced by an appreciation of the importance of establishing the diagnosis of hypertension as quickly as possible, since a 3-month delay in treatment of hypertension in high-risk patients is associated with a twofold increase in cardiovascular morbidity and mortality. Based on epidemiological data, the conventional 140/90 mm Hg threshold for the diagnosis of hypertension has been revised, and the stages of hypertension have been redefined. The 2017 guidelines from the American College of Cardiology and American Heart Association (ACC/AHA) (based on conventional office-based measurements) define **normal blood pressure** as less than 120/80 mm Hg, **elevated blood pressure** as 120–129/less than 80 mm Hg, **stage 1 hypertension** as 130–139/80–89 mm Hg, and **stage 2 hypertension** as greater than or equal to 140/90 mm Hg. As exemplified by Hypertension Canada's 2017 guidelines (Figure 11–1), automated and home blood pressure measurements have assumed greater prominence in the diagnostic algorithms published by many national hypertension workgroups. Equivalent blood pressures for these different modes of measurement are described in Table 11–1.

Blood pressure is normally lowest at night and the loss of this nocturnal dip is a dominant predictor of cardiovascular risk, particularly risk of thrombotic stroke. An accentuation of the normal morning increase in blood pressure is associated with increased likelihood of cerebral hemorrhage. Furthermore, variability of systolic blood pressure predicts cardiovascular events independently of mean systolic blood pressure.



**Figure 11–1.** According to these recommendations, if AOBP measurements are not available, blood pressures recorded manually in the office may be substituted if taken as the mean of the last two readings of three consecutive readings. Note that the blood pressure threshold for diagnosing hypertension is higher if recorded manually in these guidelines. If home blood pressure monitoring is unavailable, office measurements recorded over three to five separate visits can be substituted. ABPM, ambulatory blood pressure measurement; AOBP, automated office blood pressure; BP, blood pressure. (Reproduced, with permission, from Leung AA et al; Hypertension Canada. Hypertension Canada's 2017 guidelines for diagnosis, risk assessment, prevention, and treatment of hypertension in adults. Can J Cardiol. 2017;33:557. Copyright © 2017 Canadian Cardiovascular Society. Published by Elsevier Inc. All rights reserved.)

**Table 11–1.** Corresponding blood pressure values across a range of blood pressure measurement methods.

| Manual Measurement<br>in Clinic <sup>1</sup> | Home Blood Pressure<br>Measurement | Ambulatory Blood<br>Pressure Measurement<br>(Daytime) | Ambulatory Blood<br>Pressure Measurement<br>(Nighttime) | Ambulatory Blood<br>Pressure Measurement<br>(24-Hour) |
|--|------------------------------------|---|---|---|
| 120/80 mm Hg                                 | 120/80 mm Hg                       | 120/80 mm Hg  | 100/65 mm Hg  | 115/75 mm Hg  |
| 130/80 mm Hg                                 | 130/80 mm Hg                       | 130/80 mm Hg  | 110/65 mm Hg  | 125/75 mm Hg  |
| 140/90 mm Hg                                 | 135/85 mm Hg                       | 135/85 mm Hg  | 120/70 mm Hg  | 130/80 mm Hg  |
| 160/100 mm Hg                                | 145/90 mm Hg                       | 145/90 mm Hg  | 140/85 mm Hg  | 145/90 mm Hg  |

<sup>1</sup>Clinic manual blood pressures are critically dependent on technique. The use of automated devices in an unattended setting typically result in systolic blood pressures 9–13 mm Hg lower than clinic manual pressures.

Data abstracted from Greenland P et al. The New 2017 ACC/AHA Guidelines “up the pressure” on diagnosis and treatment of hypertension. JAMA. 2017;318:2083.

It is important to recognize that the diagnosis of hypertension does not automatically entail drug treatment; this decision depends on the clinical setting and evaluation of cardiovascular risk, as discussed below.

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## APPROACH TO HYPERTENSION

### Etiology & Classification

#### A. Primary Essential Hypertension

“Essential hypertension” is the term applied to the 95% of hypertensive patients in which elevated blood pressure results from complex interactions between multiple genetic and environmental factors. Blood pressure elevation above 140/90 mm Hg occurs in 10–15% of White adults and 20–30% of Black adults in the United States. The onset is usually between ages 25 and 50 years; it is uncommon before age 20 years. The best understood pathways underlying hypertension include overactivation of the sympathetic nervous and renin-angiotensin-aldosterone systems (RAAS), blunting of the pressure-natriuresis relationship, variation in cardiovascular and renal development, and elevated intracellular sodium and calcium levels.

**Exacerbating factors** include obesity, sleep apnea, increased salt intake, excessive alcohol use, cigarette smoking, polycythemia, nonsteroidal anti-inflammatory drug (NSAID) therapy, and low potassium intake. Obesity is associated with an increase in intravascular volume, elevated cardiac output, activation of the renin-angiotensin system, and, probably, increased sympathetic outflow. Lifestyle-driven weight reduction lowers blood pressure modestly, but the dramatic weight reduction following bariatric surgery results in improved blood pressure in most patients, and actual remission of hypertension in 20–40% of cases. In patients with sleep apnea, treatment with continuous positive airway pressure (CPAP) has been associated with improvements in blood pressure. Increased salt intake probably elevates blood pressure in some individuals so dietary salt restriction is recommended in patients with hypertension. Excessive use of alcohol also raises blood pressure, perhaps by increasing plasma catecholamines. Hypertension can be difficult to control in patients who consume more than 40 g of ethanol (two drinks) daily or drink in “binges.” Cigarette smoking raises blood pressure by increasing plasma norepinephrine. Although the long-term effect of smoking on blood pressure is less clear, the synergistic effects of smoking and high blood pressure on

cardiovascular risk are well documented. The relationship of exercise to hypertension is variable. Aerobic exercise lowers blood pressure in previously sedentary individuals, but increasingly strenuous exercise in already active subjects has less effect. The relationship between stress and hypertension is not established. Polycythemia, whether primary, drug-induced, or due to diminished plasma volume, increases blood viscosity and may raise blood pressure. NSAIDs produce increases in blood pressure averaging 5 mm Hg and are best avoided in patients with borderline or elevated blood pressures. Low potassium intake is associated with higher blood pressure in some patients; an intake of 90 mmol/day is recommended.

The complex of abnormalities termed the “**metabolic syndrome**” (upper body obesity, insulin resistance, and hypertriglyceridemia) is associated with both the development of hypertension and an increased risk of adverse cardiovascular outcomes. Affected patients usually also have low high-density lipoprotein (HDL) cholesterol levels and elevated catecholamines and inflammatory markers such as C-reactive protein.

#### B. Secondary Hypertension

Approximately 5% of patients have hypertension secondary to identifiable specific causes (Table 11–2). Secondary hypertension should be suspected in patients in whom hypertension develops at an early age or after the age of 50 years, and in those previously well controlled who become refractory to treatment. Hypertension resistant to maximum doses of three medications is another clue, although multiple medications are usually required to control hypertension in persons with diabetes.

**1. Genetic causes**—Hypertension can be caused by mutations in single genes, inherited on a Mendelian basis. Although rare, these conditions provide important insight into blood pressure regulation and possibly the genetic basis of essential hypertension. Glucocorticoid remediable aldosteronism is an autosomal dominant cause of early-onset hypertension with normal or high aldosterone and low renin levels. The syndrome of hypertension exacerbated in pregnancy is inherited as an autosomal dominant trait. In these patients, a mutation in the mineralocorticoid receptor makes it abnormally responsive to progesterone and, paradoxically, to spironolactone.

**2. Kidney disease**—Renal parenchymal disease is the most common cause of secondary hypertension, which results from increased intravascular volume and increased activity of the RAAS. Increased sympathetic nerve activity may also contribute.

**3. Renal vascular hypertension**—Renal artery stenosis is present in 1–2% of hypertensive patients. The most common cause is atherosclerosis, but fibromuscular dysplasia should be suspected in women under 50 years of age. Excessive renin release occurs due to reduction in renal perfusion pressure, while attenuation of pressure natriuresis contributes to hypertension in patients with a single kidney or bilateral lesions. Activation of the renal sympathetic nerves may also be important.

**Table 11–2.** Causes of secondary hypertension.

| Endocrine  |
|--|
| Conn syndrome (hyperaldosteronism)                 |
| Licorice   |
| Cushing syndrome (hypercortisolism)                |
| Thyroid disease                                    |
| Pheochromocytoma                                   |
| Acromegaly   |
| Mutations in steroid gene regulatory domains       |
| Hypercalcemia                                      |
| Renal  |
| Parenchymal kidney disease                         |
| Polycystic kidney disease                          |
| Systemic sclerosis (scleroderma)                   |
| Page kidney  |
| Mutations in genes encoding ion transport proteins |
| Vascular   |
| Renal artery stenosis                              |
| Coarctation  |
| Autonomic  |
| Stress   |
| Neurogenic   |
| Medications  |
| Nonsteroidal anti-inflammatory drugs               |
| Corticosteroids                                    |
| Calcineurin inhibitors                             |
| Stimulants   |
| Decongestants                                      |
| Angiogenesis inhibitors                            |
| Tyrosine kinase inhibitors                         |
| Estrogen   |
| Erythropoietin                                     |
| Alcohol, cocaine                                   |
| Gemcitabine  |
| Atypical antipsychotics                            |
| Monoamine oxidase inhibitors                       |
| Other  |
| Obstructive sleep apnea                            |
| Pregnancy  |

Renal vascular hypertension should be suspected in the following circumstances: (1) the documented onset is before age 20 or after age 50 years, (2) the hypertension is resistant to three or more drugs, (3) there are epigastric or renal artery bruits, (4) there is atherosclerotic disease of the aorta or peripheral arteries (15–25% of patients with symptomatic lower limb atherosclerotic vascular disease have renal artery stenosis), (5) there is an abrupt increase (more than 25%) in the level of serum creatinine after administration of angiotensin-converting enzyme (ACE) inhibitors, or (6) episodes of pulmonary edema are associated with abrupt surges in blood pressure. (See Renal Artery Stenosis, Chapter 22.)

**4. Primary hyperaldosteronism**—Hyperaldosteronism should be considered in people with resistant hypertension, blood pressures consistently greater than 150/100 mm Hg, hypokalemia (although this is often absent), or adrenal incidentaloma, and in those with a family history of hyperaldosteronism. Mild hypernatremia and metabolic alkalosis may also occur. Hypersecretion of aldosterone is estimated to be present in 5–10% of hypertensive patients

and, besides noncompliance, is the most common cause of resistant hypertension. The initial screening step is the simultaneous measurement of aldosterone and renin in blood in a morning sample collected after 30 minutes quietly seated. Hyperaldosteronism is suggested when the plasma aldosterone concentration is elevated (normal: 1–16 ng/dL) in association with suppression of plasma renin activity (normal: 1–2.5 ng/mL/h). However, the plasma aldosterone/renin ratio (normal less than 30) is not highly specific as a screening test. This is because renin levels may approach zero, which leads to exponential increases in the plasma aldosterone/renin ratio even when aldosterone levels are normal. Hence, an elevated plasma aldosterone/renin ratio should probably not be taken as evidence of hyperaldosteronism unless the aldosterone level is actually elevated.

During the workup for hyperaldosteronism, an initial plasma aldosterone/renin ratio can be measured while the patient continues taking usual medications. If under these circumstances the ratio proves normal or equivocal, medications that alter renin and aldosterone levels, including ACE inhibitors, angiotensin receptor blockers (ARBs), diuretics, beta-blockers, and clonidine, should be discontinued for 2 weeks before repeating the plasma aldosterone/renin ratio; spironolactone and eplerenone should be held for 4 weeks. Slow-release verapamil and alpha-receptor blockers can be used to control blood pressure during this drug washout period. Patients with a plasma aldosterone level greater than 16 ng/dL and an aldosterone/renin ratio of 30 or more might require further evaluation for primary hyperaldosteronism.

The lesion responsible for hyperaldosteronism is an adrenal adenoma or bilateral adrenal hyperplasia.

**5. Cushing syndrome**—Hypertension occurs in about 80% of patients with spontaneous Cushing syndrome. Excess glucocorticoid may act through salt and water retention (via mineralocorticoid effects), increased angiotensinogen levels, or permissive effects in the regulation of vascular tone.

Diagnosis and treatment of Cushing syndrome are discussed in Chapter 26.

**6. Pheochromocytoma**—Pheochromocytomas are uncommon; they are probably found in less than 0.1% of all patients with hypertension and in approximately two individuals per million population. Chronic vasoconstriction of the arterial and venous beds leads to a reduction in plasma volume and predisposes to postural hypotension. Glucose intolerance develops in some patients. Hypertensive crisis in pheochromocytoma may be precipitated by a variety of drugs, including tricyclic antidepressants, antidopaminergic agents, metoclopramide, and naloxone. The diagnosis and treatment of pheochromocytoma are discussed in Chapter 26.

**7. Coarctation of the aorta**—This uncommon cause of hypertension is discussed in Chapter 10. Evidence of radial-femoral delay should be sought in all younger patients with hypertension.

**8. Hypertension associated with pregnancy**—Hypertension occurring de novo or worsening during pregnancy, including preeclampsia and eclampsia, is one of the most common

causes of maternal and fetal morbidity and mortality (see Chapter 19). Autoantibodies with the potential to activate the angiotensin II type 1 receptor have been causally implicated in preeclampsia, in resistant hypertension, and in progressive systemic sclerosis.

**9. Estrogen use**—A small increase in blood pressure occurs in most women taking oral contraceptives. A more significant increase of 8/6 mm Hg systolic/diastolic is noted in about 5% of women, mostly in obese individuals older than age 35 who have been treated for more than 5 years. This is caused by increased hepatic synthesis of angiotensinogen. The lower dose of postmenopausal estrogen does not generally cause hypertension but rather maintains endothelium-mediated vasodilation.

**10. Other causes of secondary hypertension**—Hypertension has been associated with hypercalcemia, acromegaly, hyperthyroidism, hypothyroidism, baroreceptor denervation, compression of the rostral ventrolateral medulla, and increased intracranial pressure. Certain medications may cause or exacerbate hypertension—most importantly cyclosporine, tacrolimus, angiogenesis inhibitors, and erythrocyte-stimulating agents (such as erythropoietin). Decongestants, NSAIDs, cocaine, and alcohol should also be considered. Over-the-counter products should not be overlooked, eg, a dietary supplement marketed to enhance libido was found to contain yohimbine, an alpha-2-antagonist, which can produce severe rebound hypertension in patients taking clonidine.

## ► When to Refer

Referral to a hypertension specialist should be considered in cases of severe, resistant or early-/late-onset hypertension or when secondary hypertension is suggested by screening.

- Byrd JB et al. Primary aldosteronism. *Circulation*. 2018;138:823. [PMID: 30359120]  
Herrmann SM et al. Renovascular hypertension. *Endocrinol Metab Clin North Am*. 2019;48:765. [PMID: 31655775]

## ► Complications of Untreated Hypertension

Most of the adverse outcomes in hypertension are associated with thrombosis rather than bleeding, possibly because increased vascular shear stress converts the normally anticoagulant endothelium to a prothrombotic state. The excess morbidity and mortality related to hypertension approximately doubles for each 6 mm Hg increase in diastolic blood pressure. However, target-organ damage varies markedly between individuals with similar levels of office hypertension; home and ambulatory pressures are superior to office readings in the prediction of end-organ damage (Table 11–1).

### A. Hypertensive Cardiovascular Disease

Cardiac complications are the major causes of morbidity and mortality in primary (essential) hypertension. For any level of blood pressure, left ventricular hypertrophy is associated with incremental cardiovascular risk in association with heart failure (through systolic or diastolic dysfunction), ventricular arrhythmias, myocardial ischemia, and sudden death.

The occurrence of heart failure is reduced by 50% with antihypertensive therapy. Hypertensive left ventricular hypertrophy regresses with therapy and is most closely related to the degree of systolic blood pressure reduction. Diuretics have produced equal or greater reductions of left ventricular mass when compared with other drug classes. Conventional beta-blockers are less effective in reducing left ventricular hypertrophy but play a specific role in patients with established coronary artery disease or impaired left ventricular function.

### B. Hypertensive Cerebrovascular Disease and Dementia

Hypertension is the major predisposing cause of hemorrhagic and ischemic stroke. Cerebrovascular complications are more closely correlated with systolic than diastolic blood pressure. The incidence of these complications is markedly reduced by antihypertensive therapy. Preceding hypertension is associated with a higher incidence of subsequent dementia of both vascular and Alzheimer types. Home and ambulatory blood pressure may be a better predictor of cognitive decline than office readings in older people. Effective blood pressure control reduces the risk of cognitive dysfunction developing later in life.

### C. Hypertensive Kidney Disease

Chronic hypertension is associated with injury to vascular, glomerular, and tubulointerstitial compartments within the kidney, accounting for about 25% of end-stage kidney disease. Nephrosclerosis is particularly prevalent in Blacks, in whom susceptibility is linked to *APOL1* mutations and hypertension results from kidney disease rather than causing it.

### D. Aortic Dissection

Hypertension is a contributing factor in many patients with dissection of the aorta. Its diagnosis and treatment are discussed in Chapter 12.

### E. Atherosclerotic Complications

Most Americans with hypertension die of complications of atherosclerosis, but antihypertensive therapy seems to have a lesser impact on atherosclerotic complications compared with heart failure, stroke, and kidney disease. Prevention of cardiovascular outcomes related to atherosclerosis probably requires control of multiple risk factors, of which hypertension is only one.

- Seccia TM et al. Hypertensive nephropathy. Moving from classic to emerging pathogenetic mechanisms. *J Hypertens*. 2017;35:205. [PMID: 27782909]

- Supiano MA et al. New guidelines and SPRINT results: implications for geriatric hypertension. *Circulation*. 2019;140:976. [PMID: 31525101]

## ► Clinical Findings

The clinical and laboratory findings are mainly referable to involvement of the target organs: heart, brain, kidneys, eyes, and peripheral arteries.

## A. Symptoms

Mild to moderate primary (essential) hypertension is largely asymptomatic for many years. The most frequent symptom, headache, is also nonspecific. Accelerated hypertension is associated with somnolence, confusion, visual disturbances, and nausea and vomiting (hypertensive encephalopathy).

Hypertension in patients with pheochromocytomas that secrete predominantly norepinephrine is usually sustained but may be episodic. The typical attack lasts from minutes to hours and is associated with headache, anxiety, palpitation, profuse perspiration, pallor, tremor, and nausea and vomiting. Blood pressure is markedly elevated, and angina or acute pulmonary edema may occur. In primary aldosteronism, patients may have muscular weakness, polyuria, and nocturia due to hypokalemia; hypertensive emergency is rare. Chronic hypertension often leads to left ventricular hypertrophy and diastolic dysfunction, which can present with exertional and paroxysmal nocturnal dyspnea. Cerebral involvement causes stroke due to thrombosis or hemorrhage from microaneurysms of small penetrating intracranial arteries. Hypertensive encephalopathy is probably caused by acute capillary congestion and exudation with cerebral edema and may present as posterior reversible encephalopathy syndrome, comprising headache, visual disturbances, altered mental state, and seizures. These symptoms usually improve rapidly with control of hypertension.

## B. Signs

Like symptoms, physical findings depend on the cause of hypertension, its duration and severity, and the degree of effect on target organs.

**1. Blood pressure**—Blood pressure is taken in both arms and, if lower extremity pulses are diminished or delayed, in the legs to exclude coarctation of the aorta. If blood pressure differs between right and left arms, the higher reading should be recorded as the actual blood pressure and subclavian stenosis suspected in the other arm. An orthostatic drop of at least 20/10 mm Hg is often present in pheochromocytoma. Older patients may have falsely elevated readings by sphygmomanometry because of noncompressible vessels. This may be suspected in the presence of Osler sign—a palpable brachial or radial artery when the cuff is inflated above systolic pressure. Occasionally, it may be necessary to make direct measurements of intra-arterial pressure, especially in patients with apparent severe hypertension who do not tolerate therapy.

**2. Retinas**—Narrowing of arterial diameter to less than 50% of venous diameter, copper or silver wire appearance, exudates, hemorrhages, and hypertensive retinopathy are associated with a worse prognosis. The typical changes of severe hypertensive retinopathy are shown in Figure 11–2 (see Chapter 7).

**3. Heart**—A left ventricular heave indicates severe hypertrophy. Aortic regurgitation may be auscultated in up to 5% of patients, and hemodynamically insignificant aortic regurgitation can be detected by Doppler echocardiography in 10–20%. A presystolic ( $S_4$ ) gallop due to decreased



▲ **Figure 11–2.** Severe, chronic hypertensive retinopathy with hard exudates, increased vessel light reflexes, and sausage-shaped veins. (Used, with permission, from Richard E. Wyszynski, MD, in Knoop KJ, Stack LB, Storrow AB, Thurman RJ. *The Atlas of Emergency Medicine*, 4th ed. McGraw-Hill, 2016.)

compliance of the left ventricle is quite common in patients in sinus rhythm.

**4. Pulses**—Radial-femoral delay suggests coarctation of the aorta; loss of peripheral pulses occurs due to atherosclerosis, less commonly aortic dissection, and rarely Takayasu arteritis, all of which can involve the renal arteries.

## C. Laboratory Findings

Recommended testing includes hemoglobin; serum electrolytes and serum creatinine; fasting blood sugar level (hypertension is a risk factor for the development of diabetes, and hyperglycemia can be a presenting feature of pheochromocytoma); plasma lipids (necessary to calculate cardiovascular risk and as a modifiable risk factor); serum uric acid (hyperuricemia is a relative contraindication to diuretic therapy); and urinalysis.

## D. Electrocardiography and Chest Radiographs

Electrocardiographic criteria are highly specific but not very sensitive for left ventricular hypertrophy. The “strain” pattern of ST-T wave changes is a sign of more advanced disease and is associated with a poor prognosis. A chest radiograph is not necessary in the workup for uncomplicated hypertension.

## E. Echocardiography

The primary role of echocardiography should be to evaluate patients with clinical symptoms or signs of cardiac disease.

## F. Diagnostic Studies

Additional diagnostic studies are indicated only if the clinical presentation or routine tests suggest secondary or complicated hypertension. These may include 24-hour urine free cortisol, urine or plasma metanephrenes, and plasma

aldosterone and renin concentrations to screen for endocrine causes of hypertension. Renal ultrasound will detect structural changes (such as polycystic kidneys, asymmetry, and hydronephrosis); echogenicity and reduced cortical volume are reliable indicators of advanced chronic kidney disease. Evaluation for renal artery stenosis should be undertaken in concert with subspecialist consultation.

### G. Summary

Since most hypertension is essential or primary, few studies are necessary beyond those listed above. If conventional therapy is unsuccessful or if secondary hypertension is suspected, further studies and perhaps referral to a hypertension specialist are indicated.

## ► Nonpharmacologic Therapy

Lifestyle modification is recommended in all patients with elevated blood pressure. A diet rich in fruits, vegetables, and low-fat dairy foods and low in saturated and total fats (DASH diet) has been shown to lower blood pressure. Increased dietary fiber lowers blood pressure. For every 7 g of dietary fiber ingested, cardiovascular risk could be lowered by 9%. The effect of diet on blood pressure may be mediated by shifts in the microbial species in the gut, the intestinal microbiota. Hand squeezing exercises three times a week can lower systolic blood pressure by 6 mm Hg. The protocol comprises four repeats of 2 minutes at 30% of maximum force (using a handheld dynamometer) with 1- to 3-minute rest intervals between squeezes. The acute increase in systolic blood pressure during vigorous exercise, known as the exercise pressor response, is around 50 mm Hg in normal individuals. In hypertensive persons, the exercise pressor response is elevated to about 75 mm Hg above resting systolic blood pressure. This exaggerated response is not reduced by antihypertensive medications, even in those with otherwise controlled hypertension, and is exacerbated by increased dietary sodium intake.

Additional lifestyle changes, listed in Table 11–3, can prevent or mitigate hypertension or its cardiovascular consequences.

Fu J et al. Nonpharmacologic interventions for reducing blood pressure in adults with prehypertension to established hypertension. *J Am Heart Assoc.* 2020;9:e016804. [PMID: 32975166]

Smart NA et al. An evidence-based analysis of managing hypertension with isometric resistance exercise—are the guidelines current? *Hypertens Res.* 2020;43:249. [PMID: 31758166]

**Table 11–3.** The impact of lifestyle modifications.

| Modifica-tion  | Intervention  | Resulting Decrease in Blood Pressure |
|----------------|---|--------------------------------------|
| Weight loss    | Target BMI 18.5–24.9  | 5–20 mm Hg/<br>10-kg loss            |
| DASH diet      | Fruit, vegetables, low fat dairy  | 8–14 mm Hg                           |
| Sodium intake  | < 100 mmol/day<br>(< 6 g salt)  | 2–8 mm Hg                            |
| Alcohol intake | Male ≤ 2 drinks/day<br>Female ≤ 1 drink/day   | 4 mm Hg                              |
| Exercise       | Aerobic 30 min/day<br>Dynamic 90–150 min/week<br>Isometric (hand grip 4 repetitions 3 times/week) | 5–10 mm Hg                           |
| Mindfulness    | Meditation and breathing control  | 5 mm Hg                              |

BMI, body mass index; DASH, Dietary Approaches to Stop Hypertension.

(ESH/ESC) have developed independent guidelines for the evaluation and management of hypertension. There is broad agreement that drug treatment is necessary in those with office-based blood pressures exceeding 160/100 mm Hg, irrespective of cardiac risk. Similarly, the American, Canadian, and European guidelines agree that treatment thresholds should be lower in the presence of elevated cardiovascular risk. American guidelines stand apart in recommending initiation of antihypertensive pharmacotherapy in those with blood pressure of 140–159/90–99 mm Hg, even if cardiovascular risk is not elevated. By contrast, the Canadian guidelines suggest lifestyle modifications in this low-cardiovascular-risk group, while the European guidelines recommend initiation of pharmacotherapy only if elevated pressure in this low-risk population persists after lifestyle modification. There is no outcomes evidence that mortality or risk of cardiovascular events can be reduced by treating mild hypertension (140/90–160/100 mm Hg) in low-risk individuals. Table 11–4 compares these three sets of guidelines. Since evaluation of total cardiovascular risk (Table 11–5) is important in deciding who to treat with antihypertensive medications, risk calculators are essential clinical tools. The ACC has an online toolkit relevant to primary prevention (<https://tools.acc.org/ascvd-risk-estimator-plus/#!/calculate/estimate/>), and an associated app called ASCVD Risk Estimator Plus (downloadable at <https://www.acc.org/ASCVDAp>).

## ► Who Should Be Treated With Medications?

Treatment should be offered to all persons in whom blood pressure reduction, irrespective of initial blood pressure levels, will reduce cardiovascular risk with an acceptably low rate of medication-associated adverse effects. The American College of Cardiology and the American Heart Association (ACC/AHA), Hypertension Canada (HC), and the European Society of Hypertension and European Society of Cardiology

## ► Goals of Treatment

Traditionally, the most widely accepted goal for blood pressure management has been less than 140/90 mm Hg. However, observational studies suggest that there does not seem to be a blood pressure level below which decrements in cardiovascular risk taper off, and a number of randomized controlled trials have suggested that treatment to blood

**Table 11–4.** Comparison of blood pressure treatment thresholds from the 2017 ACC/AHA guidelines, the 2018 Hypertension Canada guidelines, and the 2018 ESH/ESC guidelines.

| Guidelines <sup>1</sup>          | Cardiovascular Risk      | Threshold for Pharmacotherapy (mm Hg) | Target (mm Hg)                         |
|----------------------------------|--------------------------|---------------------------------------|--|
| ACC/AHA                          | Not increased            | > 140/90                              | < 130/80 (reasonable)                  |
| Hypertension Canada              | Not increased            | > 160/100                             | < 140/90 (< 130/80 for diabetes)       |
| ESH/ESC                          | Not increased            | > 140/90 <sup>2</sup>                 | All < 140/90, most < 130/80, not < 120 |
| ACC/AHA                          | Increased                | < 130/80                              | < 130/80 (recommended)                 |
| Hypertension Canada              | Increased                | > 140 systolic <sup>3</sup>           | < 120 systolic                         |
| ESH/ESC                          | Increased                | > 130/80 <sup>3</sup>                 | 120–130/< 80                           |
| ACC/AHA > 65 yr                  | Risk due to advanced age | > 130/80                              | < 130 systolic                         |
| Hypertension Canada <sup>4</sup> | Increased                | Not specified <sup>4</sup>            | Not specified <sup>4</sup>             |
| ESH/ESC > 65 yr                  | Not increased            | > 140/90 <sup>5</sup>                 | 130–140/> 80 <sup>6</sup>              |

<sup>1</sup>In all three sets of guidelines, blood pressure values are based upon nonautomated office blood pressure readings.

<sup>2</sup>Consider drug treatment if lifestyle changes fail to control blood pressure.

<sup>3</sup>Consider drug treatment if very high risk, eg, established cardiovascular disease, especially coronary disease. **Note:** The > 130/80 mm Hg threshold for treatment of high-risk patients in the Canadian guidelines refers to automated blood pressure readings, which are lower than nonautomated readings.

<sup>4</sup>Recommendations for persons > 75 years are not explicitly stated in the Hypertension Canada guidelines. They removed separate goals for the elderly but consider age > 75 years to be a risk signifier triggering an approach that many would view as overly aggressive in the extremely old.

<sup>5</sup>The European guidelines indicate a slightly more conservative treatment threshold of > 160/90 mm Hg for those > 80 years.

<sup>6</sup>This target range is also suggested in the European guidelines for patients > 80 years.

ACC, American College of Cardiology; AHA, American Heart Association; ESC, European Society of Cardiology; ESH, European Society of Hypertension.

**Table 11–5.** Cardiovascular risk factors.

| Major risk factors   |
|--|
| Hypertension <sup>1</sup>  |
| Cigarette smoking  |
| Obesity (BMI ≥ 30) <sup>1</sup>  |
| Physical inactivity  |
| Dyslipidemia <sup>1</sup>  |
| Diabetes mellitus <sup>1</sup>   |
| Microalbuminuria or estimated GFR < 60 mL/min/1.73 m <sup>2</sup>                                |
| Age (> 55 years for men, > 65 years for women)   |
| Family history of premature cardiovascular disease<br>(< 55 years for men, < 65 years for women) |
| Target-organ damage  |
| Heart  |
| Left ventricular hypertrophy   |
| Angina or prior myocardial infarction  |
| Prior coronary revascularization   |
| Heart failure  |
| Brain  |
| Stroke or transient ischemic attack  |
| Chronic kidney disease   |
| Peripheral arterial disease  |
| Retinopathy  |

<sup>1</sup>Components of the metabolic syndrome.

BMI, body mass index; GFR, glomerular filtration rate.

Data from Chobanian AV et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA*. 2003 May 21;289(19):2560–72.

pressure targets considerably below 140 mm Hg may benefit certain patient groups.

The SPRINT study suggests that outcomes improve in nondiabetic patients with considerably elevated cardiovascular risk when treatment lowers systolic pressure to less than 120 mm Hg compared to less than 140 mm Hg. On the other hand, in the HOPE3 study of largely nondiabetic patients at somewhat lower risk than those in SPRINT, reducing blood pressure by an average of 6/3 mm Hg systolic/diastolic from a baseline of 138/82 mm Hg provided no significant outcomes benefits. Therefore, it appears that blood pressure targets should be lower in people at greater estimated cardiovascular risk. In response to the SPRINT study, the 2018 Hypertension Canada guidelines urge prescribers to consider a blood pressure goal of less than 120/80 mm Hg in patients considered at elevated risk for cardiovascular events. The 2017 ACC/AHA guidelines take a different approach by defining a 130/80 mm Hg goal as “reasonable” in nonelevated risk patients, strengthening this to “recommended” in elevated risk hypertensive patients. The 2018 ESH/ESC guidelines specify a target of less than 140 mm Hg systolic for all, and less than 130 mm Hg for most if tolerated. There is a trend toward recommending similar treatment targets in the elderly; this topic is discussed in greater detail below. Some experts note that manual office measurements of around 130/80 mm Hg are likely to approximate the lower blood pressure targets specified in the SPRINT study, which used automated office blood pressure measuring devices that have been demonstrated to read as much as 16/7 mm Hg lower

than manual office readings. The 2018 Canadian guidelines acknowledge this disparity in measurement methods by specifying that automated office devices should be used in the monitoring of patients selected for the aggressive blood pressure goal of less than 120/80 mm Hg. Table 11–4 compares the treatment threshold and target recommendations laid out in the American, Canadian, and European guidelines.

Treatment to blood pressures less than 130 mm Hg systolic seems especially important in stroke prevention. The ACCORD study examined the effect of treatment of systolic pressures to below 130–135 mm Hg in patients with diabetes; the study's two by two factorial design addressed glycemic control as well as blood pressure control. In the original analysis, the lower blood pressure treatment goal significantly increased the risk of serious adverse effects (with no additional gain in terms of heart, kidney, or retinal disease). There was, however, significant additional reduction in the risk of stroke, indicating that lower blood pressure targets might be justified in diabetic patients at high risk for cerebrovascular events. Post hoc analysis of the ACCORD study after 9 years of follow-up suggested that a beneficial effect of lower blood pressure in older high-risk persons (mostly on nonfatal myocardial infarctions) could be detected in the standard glycemic control group. Similarly, in the SPS3 trial in patients who have had a lacunar stroke, treating the systolic blood pressure to less than 130 mm Hg (mean systolic blood pressure of 127 mm Hg among treated versus mean systolic blood pressure 138 mm Hg among untreated patients) probably reduced the risk of recurrent stroke (and with an acceptably low rate of adverse effects from treatment). Blood pressure management in acute stroke is discussed below.

### ► How Low To Go?

Although observational studies indicate that the blood pressure–risk relationship holds up at levels considerably below 120 mm Hg, there is uncertainty about whether this is true for treated blood pressure. This question was addressed in a secondary analysis of data from the ONTARGET and TRANSCEND studies in which participants with elevated cardiovascular risk but no history of stroke were treated with telmisartan (plus or minus ramipril) or placebo. The risk of the composite cardiovascular endpoint was lowest at a treated systolic blood pressure range between 120 mm Hg and 140 mm Hg. Increased risk was observed at blood pressures below and above this range. The risk of stroke was the only exception, with incremental benefit observed below a treated systolic of 120 mm Hg. With respect to diastolic blood pressure on treatment, composite risk began to increase at levels below 70 mm Hg. This suggests that the blood pressure–cardiovascular risk relationship evident in observational studies of untreated hypertension may not hold in the case of treated blood pressure and that there are grounds for a degree of caution in treating below a systolic pressure of 120 mm Hg.

In seeking to simplify decision making in the treatment of hypertension, some authors have suggested that a systolic blood pressure goal in the 120–130 mm Hg range would be safe and effective in high-risk patients, and a systolic blood pressure of around 130 mm Hg would be

reasonable in lower-risk patients, irrespective of diastolic pressures. Diastolic blood pressure will track with systolic blood pressure; the main concern about diastolic blood pressure is that treatment will lower it too much in patients who have wider pulse pressures. However, it seems that a lower diastolic blood pressure as a consequence of treatment does not negate the benefits of systolic blood pressure control, even though wider pulse pressures at baseline are associated with cardiovascular mortality.

### ► Treatment of Other Cardiovascular Risk Factors

Data from multiple studies indicate that statins should be part of the strategy to reduce overall cardiovascular risk. The HOPE3 study of persons at intermediate cardiovascular risk showed that 10 mg of rosuvastatin reduced average low-density lipoprotein (LDL) cholesterol from 130 mg/dL to 90 mg/dL (3.36–2.33 mmol/L), and significantly reduced the risk of multiple cardiovascular events, including myocardial infarction and coronary revascularization. Low-dose aspirin (81 mg/day) is likely to be beneficial in patients older than age 50 with either target-organ damage or elevated total cardiovascular risk (greater than 20–30%). Care should be taken to ensure that blood pressure is controlled to the recommended levels before starting aspirin to minimize the risk of intracranial hemorrhage. Data do not support the routine use of aspirin for prophylaxis in low-risk patients, including those over 65 years of age.

Böhm M et al. Achieved blood pressure and cardiovascular outcomes in high-risk patients: results from ONTARGET and TRANSCEND trials. *Lancet*. 2017;389:2226. [PMID: 28390695]

Ruiz-Hurtado G et al. Has the SPRINT trial introduced a new blood-pressure goal in hypertension? *Nat Rev Cardiol*. 2017;14:560. [PMID: 28492286]

Sheppard JP et al. Benefits and harms of antihypertensive treatment in low-risk patients with mild hypertension. *JAMA Intern Med*. 2018;178:1626. [PMID: 30383082]

Sobieraj P et al. Low on-treatment diastolic blood pressure and cardiovascular outcome: a post-hoc analysis using NHLBI SPRINT research materials. *Sci Rep*. 2019;9:13070. [PMID: 31506550]

Williams B et al. 2018 Practice guidelines for the management of arterial hypertension of the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC). *Blood Press*. 2018;27:314. [PMID: 30380928]

## DRUG THERAPY: CURRENT ANTIHYPERTENSIVE AGENTS

There are many classes of antihypertensive drugs of which six (ACE inhibitors, ARBs, renin inhibitors, calcium channel blockers, diuretics, and beta-blockers) are suitable for initial therapy based on efficacy and tolerability. The specific classes of antihypertensive medications are discussed below, and guidelines for the choice of initial medications are offered.

### A. Angiotensin-Converting Enzyme Inhibitors

ACE inhibitors are commonly used as the initial medication in mild to moderate hypertension (Table 11–6).

**Table 11–6.** Antihypertensive drugs: renin and ACE inhibitors and angiotensin II receptor blockers.

| Drug                      | Proprietary Name       | Initial Oral Dosage       | Dosage Range                           | Cost per Unit         | Cost of 30 Days of Treatment (Average Dosage) <sup>1</sup> | Adverse Effects  | Comments   |
|---------------------------|------------------------|---------------------------|--|-----------------------|--|--|--|
| <b>Renin Inhibitors</b>   |                        |                           |  |                       |  |  |  |
| Aliskiren                 | Tekturna               | 150 mg once daily         | 150–300 mg once daily                  | \$7.48/150 mg         | \$224.41   | Angioedema, hypotension, hyperkalemia. Contraindicated in pregnancy.   | Probably metabolized by CYP3A4. Absorption is inhibited by high-fat meal.  |
| Aliskiren and HCTZ        | Tekturna HCT           | 150 mg/12.5 mg once daily | 150 mg/12.5 mg–300 mg/25 mg once daily | \$9.78/150 mg/12.5 mg | \$293.54   |  |  |
| <b>ACE Inhibitors</b>     |                        |                           |  |                       |  |  |  |
| Benazepril                | Lotensin               | 10 mg once daily          | 5–40 mg in 1 or 2 doses                | \$0.95/20 mg          | \$28.50  | Cough, hypotension, dizziness, hyperkalemia, kidney dysfunction, angioedema; taste alteration and rash (may be more frequent with captopril); rarely, proteinuria, blood dyscrasias. Contraindicated in pregnancy. | More fosinopril is excreted by the liver in patients with kidney dysfunction (dose reduction may or may not be necessary). Captopril and lisinopril are active without metabolism. Captopril, enalapril, lisinopril, and quinapril are approved for heart failure. |
| Benazepril and HCTZ       | Lotensin HCT           | 5 mg/6.25 mg once daily   | 5 mg/6.25 mg–20 mg/25 mg               | \$1.07/any dose       | \$32.21  |  |  |
| Benazepril and amlodipine | Lotrel                 | 10 mg/2.5 mg once daily   | 10 mg/2.5 mg–40 mg/10 mg               | \$3.32/20 mg/10 mg    | \$99.60  |  |  |
| Captopril                 | Capoten                | 25 mg twice daily         | 50–450 mg in 2 or 3 doses              | \$0.65/25 mg          | \$19.50  |  |  |
| Captopril and HCTZ        | Capozide               | 25 mg/15 mg twice daily   | 25 mg/15 mg–50 mg/25 mg                | \$2.85/25 mg/15 mg    | \$171.00   |  |  |
| Enalapril                 | Vasotec                | 5 mg once daily           | 5–40 mg in 1 or 2 doses                | \$0.95/20 mg          | \$28.50  |  |  |
| Enalapril and HCTZ        | Vaseretic              | 5 mg/12.5 mg once daily   | 5 mg/12.5 mg–10 mg/25 mg               | \$1.19/10 mg/25 mg    | \$35.70  |  |  |
| Fosinopril                | Monopril               | 10 mg once daily          | 10–80 mg in 1 or 2 doses               | \$0.29/20 mg          | \$8.70   |  |  |
| Fosinopril and HCTZ       | Monopril-HCT           | 10 mg/12.5 mg once daily  | 10 mg/12.5 mg–20 mg/12.5 mg            | \$1.48/any dose       | \$44.40  |  |  |
| Lisinopril                | Prinivil, Zestril      | 5–10 mg once daily        | 5–40 mg once daily                     | \$0.08/20 mg          | \$2.45   |  |  |
| Lisinopril and HCTZ       | Prinzide or Zestoretic | 10 mg/12.5 mg once daily  | 10 mg/12.5 mg–20 mg/12.5 mg            | \$0.14/20 mg/12.5 mg  | \$4.20   |  |  |
| Moexipril                 | Univasc                | 7.5 mg once daily         | 7.5–30 mg in 1 or 2 doses              | \$1.39/7.5 mg         | \$41.70  |  |  |
| Moexipril and HCTZ        | Uniretic               | 7.5 mg/12.5 mg once daily | 7.5 mg/12.5 mg–15 mg/25 mg             | \$1.70/15 mg/12.5 mg  | \$51.00  |  |  |

|   |             |                               |   |                             |          |   |  |
|---|-------------|-------------------------------|---|-----------------------------|----------|---|--|
| Perindopril                             | Aceon       | 4 mg once daily               | 4–16 mg in 1 or 2 doses                         | \$2.80/8 mg                 | \$84.00  |   |  |
| Perindopril and amlodipine              | Prestalia   | 3.5 mg/2.5 mg once daily      | 3.5 mg/2.5–14 mg/10 mg once daily               | \$6.81/7 mg/5 mg            | \$204.30 |   |  |
| Quinapril                               | Accupril    | 10 mg once daily              | 10–80 mg in 1 or 2 doses                        | \$1.22/20 mg                | \$36.60  |   |  |
| Quinapril and HCTZ                      | Accuretic   | 10 mg/12.5 mg once daily      | 10 mg/12.5 mg–20 mg/25 mg                       | \$1.22/20 mg/12.5 mg        | \$36.60  |   |  |
| Ramipril                                | Altace      | 2.5 mg once daily             | 2.5–20 mg in 1 or 2 doses                       | \$1.80/5 mg                 | \$54.00  |   |  |
| Trandolapril                            | Mavik       | 1 mg once daily               | 1–8 mg once daily                               | \$1.21/4 mg                 | \$36.30  |   |  |
| Trandolapril and verapamil              | Tarka       | 2 mg/180 mg ER once daily     | 2 mg/180 mg ER–8 mg/480 mg ER                   | \$5.29/any dose             | \$158.70 |   |  |
| <b>Angiotensin II Receptor Blockers</b> |             |                               |   |                             |          |   |  |
| Azilsartan                              | Edarbi      | 40 mg once daily              | 40–80 mg once daily                             | \$8.80/80 mg                | \$264.00 | Hyperkalemia, kidney dysfunction, rare angioedema. Combinations have additional side effects. Contraindicated in pregnancy. | Losartan has a flat dose-response curve. Valsartan and irbesartan have wider dose-response ranges and longer durations of action. Addition of low-dose diuretic (separately or as combination pills) increases the response. |
| Azilsartan and chlorthalidone           | Edarbychlor | 40 mg/12.5 mg once daily      | 40 mg/12.5–40 mg/25 mg once daily               | \$8.30/any dose             | \$249.14 |   |  |
| Candesartan cilextil                    | Atacand     | 16 mg once daily              | 8–32 mg once daily                              | \$3.06/16 mg                | \$91.80  |   |  |
| Candesartan cilextil and HCTZ           | Atacand HCT | 16 mg/12.5 mg once daily      | 32 mg/12.5 mg once daily                        | \$4.72/16 mg/12.5 mg        | \$141.60 |   |  |
| Eprosartan                              | Teveten     | 600 mg once daily             | 400–800 mg in 1–2 doses                         | \$3.43/600 mg               | \$102.90 |   |  |
| Irbesartan                              | Avapro      | 150 mg once daily             | 150–300 mg once daily                           | \$0.46/150 mg               | \$13.80  |   |  |
| Irbesartan and HCTZ                     | Avalide     | 150 mg/12.5 mg once daily     | 150–300 mg irbesartan once daily                | \$0.67/150 mg/12.5 mg       | \$20.10  |   |  |
| Losartan and HCTZ                       | Hyzaar      | 50 mg/12.5 mg once daily      | 50 mg/12.5 mg–100 mg/25 mg tablets once daily   | \$2.47/50 mg/12.5 mg/tablet | \$74.10  |   |  |
| Olmesartan                              | Benicar     | 20 mg once daily              | 20–40 mg once daily                             | \$6.28/20 mg                | \$188.40 |   |  |
| Olmesartan and HCTZ                     | Benicar HCT | 20 mg/12.5 mg once daily      | 20 mg/12.5 mg–40 mg/25 mg once daily            | \$6.28/20 mg/12.5 mg        | \$188.40 |   |  |
| Olmesartan and amlodipine               | Azor        | 20 mg/5 mg once daily         | 20 mg/5 mg–40 mg/10 mg                          | \$3.03/20 mg/5 mg           | \$90.90  |   |  |
| Olmesartan and amlodipine and HCTZ      | Tribenzor   | 20 mg/5 mg/12.5 mg once daily | 20 mg/5 mg/12.5 mg–40 mg/10 mg/25 mg once daily | \$4.54/20 mg/5 mg/12.5 mg   | \$136.20 |   |  |
| Telmisartan                             | Micardis    | 40 mg once daily              | 20–80 mg once daily                             | \$4.34/40 mg                | \$130.20 |   |  |

(continued)

**Table 11–6.** Antihypertensive drugs: renin and ACE inhibitors and angiotensin II receptor blockers. (continued)

| Drug  | Proprietary Name | Initial Oral Dosage            | Dosage Range                         | Cost per Unit           | Cost of 30 Days of Treatment (Average Dosage) <sup>1</sup> | Adverse Effects | Comments |
|---|------------------|--------------------------------|--------------------------------------|-------------------------|--|-----------------|----------|
| <b>Angiotensin II Receptor Blockers (cont.)</b> |                  |                                |                                      |                         |  |                 |          |
| Telmisartan and HCTZ                            | Micardis HCT     | 40 mg/12.5 mg once daily       | 40 mg/12.5 mg–80 mg/25 mg once daily | \$4.83/40 mg/12.5 mg    | \$144.90   |                 |          |
| Telmisartan and amlodipine                      | Twynsta          | 40 mg/5 mg once daily          | 40 mg/5 mg–80 mg/10 mg once daily    | \$5.20/any dose         | \$156.00   |                 |          |
| Valsartan                                       | Diovan           | 80 mg once daily               | 80–320 mg once daily                 | \$2.09/160 mg           | \$62.70  |                 |          |
| Valsartan and HCTZ                              | Diovan HCT       | 80 mg/12.5 mg once daily       | 80–320 mg valsartan once daily       | \$4.27/160 mg/12.5 mg   | \$128.10   |                 |          |
| Valsartan and amlodipine                        | Exforge          | 160 mg/5 mg once daily         | 160 mg/5 mg–320 mg/10 mg once daily  | \$1.71/160 mg/10 mg     | \$51.30  |                 |          |
| <b>Other Combination Products</b>               |                  |                                |                                      |                         |  |                 |          |
| Amlodipine and valsartan and HCTZ               | Exforge HCT      | 5 mg/160 mg/12.5 mg once daily | 10 mg/320 mg/25 mg up to once daily  | \$5.70/160 mg valsartan | \$171.00   |                 |          |

<sup>1</sup>Average wholesale price (AWP, for AB-rated generic when available) for quantity listed.

Source: IBM Micromedex Red Book (electronic version) IBM Watson Health. Greenwood Village, CO, USA. Available at <https://www.micromedexsolutions.com>, accessed March 27, 2021. AWP may not accurately represent the actual pharmacy cost because wide contractual variations exist among institutions.

ACE, angiotensin-converting enzyme; ER, extended release; HCTZ, hydrochlorothiazide.

Their primary mode of action is inhibition of the RAAS, but they also inhibit bradykinin degradation, stimulate the synthesis of vasodilating prostaglandins, and can reduce sympathetic nervous system activity. ACE inhibitors appear to be more effective in younger White patients. They are relatively less effective in Blacks and older persons and in predominantly systolic hypertension. Although as single therapy they achieve adequate antihypertensive control in only about 40–50% of patients, the combination of an ACE inhibitor and a diuretic or calcium channel blocker is potent.

ACE inhibitors are the agents of choice in persons with type 1 diabetes with frank proteinuria or evidence of kidney dysfunction because they delay the progression to end-stage renal disease. Many authorities have expanded this indication to include persons with type 1 and type 2 diabetes mellitus with microalbuminuria who do not meet the usual criteria for antihypertensive therapy. ACE inhibitors may also delay the progression of nondiabetic kidney disease. The Heart Outcomes Prevention Evaluation (HOPE) trial demonstrated that the ACE inhibitor ramipril reduced the number of cardiovascular deaths, nonfatal myocardial infarctions, and nonfatal strokes and also reduced the incidence of new-onset heart failure, kidney dysfunction, and new-onset diabetes in a population of patients at high risk for vascular events. Although this was not specifically a hypertensive population, the benefits were associated with a modest reduction in blood pressure, and the results inferentially support the use of ACE inhibitors in similar hypertensive patients. ACE inhibitors are a drug of choice (usually in conjunction with a diuretic and a beta-blocker) in patients with heart failure with reduced ejection fraction and are indicated also in asymptomatic patients with reduced ejection fraction.

**How to initiate therapy**—A baseline metabolic panel should be drawn prior to starting medications that interfere with the RAAS, repeated 1–2 weeks after initiation of therapy to evaluate changes in creatinine and potassium. Minor dose adjustments of these medications rarely trigger significant shifts in these values.

**Side effects**—An advantage of the ACE inhibitors is their relative freedom from troublesome side effects (Table 11–6). Severe hypotension can occur in patients with bilateral renal artery stenosis; significant increases in creatinine may ensue but are usually reversible with the discontinuation of the ACE inhibitor. Hyperkalemia may develop in patients with kidney disease and type IV renal tubular acidosis (commonly seen in patients with diabetes) and in older adults. A chronic dry cough is common, seen in 10% of patients or more, and may require stopping the drug. Skin rashes are observed with any ACE inhibitor. Angioedema is an uncommon but potentially dangerous side effect of all agents of this class because of their inhibition of kininase. Exposure of the fetus to ACE inhibitors during the second and third trimesters of pregnancy has been associated with a variety of defects due to hypotension and reduced renal blood flow.

### B. Angiotensin II Receptor Blockers

ARBs can improve cardiovascular outcomes in patients with hypertension as well as in patients with related conditions, such as heart failure and type 2 diabetes with nephropathy.

ARBs have not been compared with ACE inhibitors in randomized controlled trials in patients with hypertension, but two trials comparing losartan with captopril in heart failure and post-myocardial infarction left ventricular dysfunction showed trends toward worse outcomes in the losartan group. By contrast, valsartan seems as effective as ACE inhibitors in these settings. Within group heterogeneity of antihypertensive potency and duration of action might explain such observations. The Losartan Intervention for Endpoints (LIFE) trial in nearly 9000 hypertensive patients with electrocardiographic evidence of left ventricular hypertrophy—comparing losartan with the beta-blocker atenolol as initial therapy—demonstrated a significant reduction in stroke with losartan. Of note is that in diabetic patients, death and myocardial infarction were also reduced, and there was a lower occurrence of new-onset diabetes. In a subgroup analysis from the LIFE trial, atenolol appeared to be superior to losartan in Blacks, while the opposite was the case in non-Blacks. A similar lack of efficacy of lisinopril compared to diuretics and calcium channel blockers was observed in Blacks in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), suggesting that ACE inhibitors and ARBs may not be the preferred agents in Black patients. In the treatment of hypertension, combination therapy with an ACE inhibitor and an ARB is not advised because it generally offers no advantage over monotherapy at maximum dose with addition of a complementary class where necessary.

**Side effects**—Unlike ACE inhibitors, the ARBs rarely cause cough and are less likely to be associated with skin rashes or angioedema (Table 11–6). However, as seen with ACE inhibitors, hyperkalemia can be a problem, and patients with bilateral renal artery stenosis may exhibit hypotension and worsened kidney function. Olmesartan has been linked to a sprue-like syndrome, presenting with abdominal pain, weight loss, and nausea, which subsides upon drug discontinuation. There is evidence from an observational study suggesting that ARBs and ACE inhibitors are less likely to be associated with depression than calcium channel blockers and beta-blockers.

### C. Renin Inhibitors

Since renin cleavage of angiotensinogen is the rate-limiting step in the renin-angiotensin cascade, the most efficient inactivation of this system would be expected with renin inhibition. Conventional ACE inhibitors and ARBs probably offer incomplete blockade, even in combination. Aliskiren, a renin inhibitor, binds the proteolytic site of renin, thereby preventing cleavage of angiotensinogen. Aliskiren effectively lowers blood pressure, reduces albuminuria, and limits left ventricular hypertrophy, but it has yet to be established as a first-line drug based on outcomes data. The combination of aliskiren with ACE inhibitors or ARBs in persons with type 2 diabetes mellitus offers no advantage and might even increase the risk of adverse cardiac or renal consequences.

### D. Calcium Channel Blocking Agents

These agents act by causing peripheral vasodilation but with less reflex tachycardia and fluid retention than other

vasodilators. They are effective as single-drug therapy in approximately 60% of patients in all demographic groups and all grades of hypertension (Table 11–7). For these reasons, they may be preferable to beta-blockers and ACE inhibitors in Blacks and older persons. Verapamil and diltiazem should be combined cautiously with beta-blockers because of their potential for depressing atrioventricular (AV) conduction and sinus node automaticity as well as contractility.

Calcium channel blockers are equivalent to ACE inhibitors and thiazide diuretics in prevention of coronary heart disease, major cardiovascular events, cardiovascular death, and total mortality. A protective effect against stroke with calcium channel blockers is well established, and in two trials (ALLHAT and the Systolic Hypertension in Europe trial), these agents appeared to be more effective than diuretic-based therapy.

**Side effects**—The most common side effects of calcium channel blockers are headache, peripheral edema, bradycardia, and constipation (especially with verapamil in older adults) (Table 11–7). The dihydropyridine agents—nifedipine, nicardipine, isradipine, felodipine, nisoldipine, and amlodipine—are more likely to produce symptoms of vasodilation, such as headache, flushing, palpitations, and peripheral edema. Edema is minimized by coadministration of an ACE inhibitor or ARB. Calcium channel blockers have negative inotropic effects and should be used cautiously in patients with cardiac dysfunction. Amlodipine is the only calcium channel blocker with established safety in patients with severe heart failure.

## E. Diuretics

Thiazide diuretics (Table 11–8) are the antihypertensives that have been most extensively studied and most consistently effective in clinical trials. They lower blood pressure initially by decreasing plasma volume, but during long-term therapy, their major hemodynamic effect is reduction of peripheral vascular resistance. Most of the antihypertensive effect of these agents is achieved at lower dosages (typically, 12.5 mg of hydrochlorothiazide or equivalent), but their biochemical and metabolic effects are dose related. Chlorthalidone has the advantage of better 24-hour blood pressure control than hydrochlorothiazide in clinical trials. Thiazides may be used at higher doses if plasma potassium is above 4.5 mmol/L. The loop diuretics (such as furosemide) may lead to electrolyte and volume depletion more readily than the thiazides and have short durations of action. Because of these adverse effects, loop diuretics should be reserved for use in patients with kidney dysfunction (serum creatinine greater than 2.5 mg/dL [208.3 μmol/L]; estimated glomerular filtration rate [eGFR] less than 30 mL/min/1.73 m<sup>2</sup>) in which case they are more effective than thiazides. Relative to beta-blockers and ACE inhibitors, diuretics are more potent in Blacks, older individuals, the obese, and other subgroups with increased plasma volume or low plasma renin activity (or both). They are relatively more effective in smokers than in nonsmokers. Long-term thiazide administration also mitigates the loss of bone mineral content in older women at risk for osteoporosis.

Overall, diuretics administered alone control blood pressure in 50% of patients with mild to moderate hypertension and can be used effectively in combination with all other agents. They are also useful for lowering isolated or predominantly systolic hypertension.

**Side effects**—The adverse effects of diuretics relate primarily to the metabolic changes listed in Table 11–8. Erectile dysfunction, skin rashes, and photosensitivity are less frequent. Hypokalemia has been a concern but is uncommon at the recommended dosages. The risk can be minimized by limiting dietary salt or increasing dietary potassium; potassium replacement is not usually required to maintain serum K<sup>+</sup> at greater than 3.5 mmol/L. Higher serum K<sup>+</sup> levels are prudent in patients at special risk from intracellular potassium depletion, such as those taking digoxin or with a history of ventricular arrhythmias in which case a potassium-sparing agent could be used. Compared with ACE inhibitors and ARBs, diuretic therapy is associated with a slightly higher incidence of mild new-onset diabetes. Diuretics also increase serum uric acid and may precipitate gout. Increases in blood glucose, triglycerides, and LDL cholesterol may occur but are relatively minor during long-term low-dose therapy. The potential for worsening of diabetes is outweighed by the advantages of blood pressure control, and diuretics should not be withheld from diabetic patients.

## F. Aldosterone Receptor Antagonists

Spironolactone and eplerenone are natriuretic in sodium-retaining states, such as heart failure and cirrhosis, but only very weakly so in hypertension. These drugs have reemerged in the treatment of hypertension, particularly in resistant patients and are helpful additions to most other antihypertensive medications. Consistent with the increasingly appreciated importance of aldosterone in essential hypertension, the aldosterone receptor blockers are effective at lowering blood pressure in all hypertensive patients regardless of renin level and are also effective in Blacks. Aldosterone plays a central role in target-organ damage, including the development of ventricular and vascular hypertrophy and renal fibrosis. Aldosterone receptor antagonists ameliorate these consequences of hypertension, to some extent independently of effects on blood pressure.

**Side effects**—Spironolactone can cause breast pain and gynecomastia in men through activity at the progesterone receptor, an effect not seen with the more specific eplerenone. Hyperkalemia is a problem with both drugs, chiefly in patients with chronic kidney disease. Hyperkalemia is more likely if the pretreatment plasma potassium exceeds 4.5 mmol/L.

## G. Beta-Adrenergic Blocking Agents

These drugs are effective in hypertension because they decrease the heart rate and cardiac output. The beta-blockers also decrease renin release and are more efficacious in populations with elevated plasma renin activity, such as younger White patients. They neutralize the reflex tachycardia caused by vasodilators and are especially useful in patients with associated conditions that benefit from the cardioprotective effects of these agents.

**Table 11–7.** Antihypertensive drugs: calcium channel blocking agents.

| Drug                             | Proprietary Name | Initial Oral Dosage         | Dosage Range                  | Cost of 30 Days of Treatment (Average Dosage) <sup>1</sup> | Special Properties      |                                     | Contractility | Adverse Effects   | Comments                                  |
|----------------------------------|------------------|-----------------------------|-------------------------------|--|-------------------------|-------------------------------------|---------------|---|---|
|                                  |                  |                             |                               |  | Peripheral Vasodilation | Cardiac Automaticity and Conduction |               |   |   |
| <b>Nondihydropyridine Agents</b> |                  |                             |                               |  |                         |                                     |               |   |   |
| Diltiazem                        | Cardizem SR      | 90 mg twice daily           | 180–360 mg in 2 doses         | \$283.20 (120 mg twice daily)                              | ++                      | ↓↓                                  | ↓↓            | Edema, headache, bradycardia, bloating and constipation, dizziness, AV block, heart failure, urinary frequency. | Also approved for angina.                 |
|                                  | Cardizem CD      | 180 mg ER once daily        | 180–360 mg ER once daily      | \$46.80 (240 mg once daily)                                |                         |                                     |               |   |   |
|                                  | Cartia XT        | 180 or 240 mg ER once daily | 180–480 mg ER once daily      | \$46.80 (240 mg once daily)                                |                         |                                     |               |   |   |
|                                  | Dilacor XR       | 180 or 240 mg ER once daily | 180–540 mg ER once daily      | \$39.00 (240 mg once daily)                                |                         |                                     |               |   |   |
|                                  | Dilt-CD          | 180 or 240 mg ER once daily | 180–480 mg ER once daily      | \$46.80 (240 mg once daily)                                |                         |                                     |               |   |   |
|                                  | Diltia XT        | 180 or 240 mg ER once daily | 180–540 mg ER once daily      | \$46.80 (240 mg once daily)                                |                         |                                     |               |   |   |
|                                  | Taztia XT        | 120 or 180 mg ER once daily | 120–540 mg ER once daily      | \$53.40 (240 mg once daily)                                |                         |                                     |               |   |   |
|                                  | Tiazac           | 120 or 240 mg ER once daily | 120–540 mg ER once daily      | \$53.40 (240 mg once daily)                                |                         |                                     |               |   |   |
| Verapamil                        | Calan            | 80 mg three times daily     | 80–480 mg in 3 divided doses  | \$35.10 (80 mg three times daily)                          | ++                      | ↓↓↓                                 | ↓↓↓           | Same as diltiazem but more likely to cause constipation and heart failure.                                      | Also approved for angina and arrhythmias. |
|                                  | Calan SR         | 180 mg ER once daily        | 180–480 mg ER in 1 or 2 doses | \$36.60 (240 mg once daily)                                |                         |                                     |               |   |   |
|                                  | Verelan          | 120 or 240 mg ER once daily | 240–480 mg ER once daily      | \$68.70 (240 mg once daily)                                |                         |                                     |               |   |   |
|                                  | Verelan PM       | 100 or 200 mg ER once daily | 100–400 mg ER once daily      | \$75.90 (200 mg once daily)                                |                         |                                     |               |   |   |

(continued)

**Table 11–7.** Antihypertensive drugs: calcium channel blocking agents. (continued)

| Drug                        | Proprietary Name | Initial Oral Dosage       | Dosage Range               | Cost of 30 Days of Treatment (Average Dosage) <sup>1</sup> | Special Properties      |                                     | Contractility | Adverse Effects   | Comments  |
|-----------------------------|------------------|---------------------------|----------------------------|--|-------------------------|-------------------------------------|---------------|---|---|
|                             |                  |                           |                            |  | Peripheral Vasodilation | Cardiac Automaticity and Conduction |               |   |   |
| <b>Dihydropyridines</b>     |                  |                           |                            |  |                         |                                     |               |   |   |
| Amlodipine                  | Norvasc          | 2.5 mg once daily         | 2.5–10 mg once daily       | \$3.00 (10 mg once daily)                                  | +++                     | ↓/0                                 | ↓/0           | Edema, dizziness, palpitations, flushing, headache, hypotension, tachycardia, bloating and constipation, urinary frequency. | Amlodipine, nicardipine, and nifedipine also approved for angina. |
| Amlodipine and atorvastatin | Caduet           | 2.5 mg/10 mg once daily   | 10 mg/80 mg once daily     | \$281.10 (10 mg/40 mg daily)                               | +++                     | ↓/0                                 | ↓/0           | Edema (amlodipine), myopathy and hepatotoxicity (atorvastatin).   |   |
| Felodipine                  | Plendil          | 5 mg ER once daily        | 5–10 mg ER once daily      | \$81.60 (10 mg ER daily)                                   | +++                     | ↓/0                                 | ↓/0           |   |   |
| Isradipine                  | DynaCirc         | 2.5 mg twice daily        | 2.5–5 mg twice daily       | \$120.00 (5 mg twice daily)                                | +++                     | ↓/0                                 | ↓             |   |   |
| Nicardipine                 | Cardene          | 20 mg three times daily   | 20–40 mg three times daily | \$52.20 (20 mg three times daily)                          | +++                     | ↓/0                                 | ↓             |   |   |
| Nifedipine                  | Adalat CC        | 30 mg ER once daily       | 30–90 mg ER once daily     | \$67.50/60 mg daily  | +++                     | ↓                                   | ↓↓            |   |   |
|                             | Procardia XL     | 30 or 60 mg ER once daily | 30–120 mg ER once daily    | \$60.30/60 mg daily  |                         |                                     |               |   |   |
| Nisoldipine                 | Sular            | 17 mg daily               | 17–34 mg daily             | \$251.70 (34 mg once daily)                                | +++                     | ↓/0                                 | ↓             |   |   |

<sup>1</sup>Average wholesale price (AWP, for AB-rated generic when available) for quantity listed.Source: IBM Micromedex Red Book (electronic version) IBM Watson Health. Greenwood Village, CO, USA. Available at <https://www.micromedexsolutions.com>, accessed March 27, 2021. AWP may not accurately represent the actual pharmacy cost because wide contractual variations exist among institutions.

AV, atrioventricular; ER, extended release; GI, gastrointestinal.

**Table 11–8.** Antihypertensive drugs: diuretics (in descending order of preference).

| Drugs                                  | Proprietary Names  | Initial Oral Doses        | Dosage Range                  | Cost per Unit | Cost of 30 Days of Treatment <sup>1</sup> (Average Dosage) | Adverse Effects  | Comments  |
|--|--------------------|---------------------------|-------------------------------|---------------|--|--|---|
| <b>Thiazides and Related Diuretics</b> |                    |                           |                               |               |  |  |   |
| Hydrochlorothiazide (HCTZ)             | Esidrix, Microzide | 12.5 or 25 mg once daily  | 12.5–50 mg once daily         | \$0.08/25 mg  | \$2.40   | ↓K <sup>+</sup> , ↓Mg <sup>2+</sup> , ↑Ca <sup>2+</sup> , ↓Na <sup>+</sup> , ↑uric acid, ↑glucose, ↑LDL cholesterol, ↑triglycerides; rash, erectile dysfunction. | Low dosages effective in many patients without associated metabolic abnormalities   |
| Chlorthalidone                         | Thalitone          | 12.5 or 25 mg once daily  | 12.5–50 mg once daily         | \$1.21/25 mg  | \$36.30  |  | Better 24-hour blood pressure control than HCTZ because of longer half-life   |
| Metolazone                             | Zaroxolyn          | 1.25 or 2.5 mg once daily | 1.25–5 mg once daily          | \$1.51/5 mg   | \$45.30  |  | More effective with concurrent kidney disease   |
| Indapamide                             | Lozol              | 2.5 mg once daily         | 2.5–5 mg once daily           | \$0.83/2.5 mg | \$24.90  |  | Does not alter serum lipid levels   |
| Bendroflumethiazide                    | Aprinox Neo-Naclex | 2.5 mg once daily         | —                             | —             | —  |  | Not available in United States  |
| <b>Loop Diuretics</b>                  |                    |                           |                               |               |  |  |   |
| Furosemide                             | Lasix              | 20 mg twice daily         | 40–320 mg in 2 or 3 doses     | \$0.16/40 mg  | \$9.60   | Same as thiazides, but with higher risk of excessive diuresis and electrolyte imbalance. Increases calcium excretion.  | Short duration of action a disadvantage; should be reserved for patients with kidney disease or fluid retention. Poor antihypertensive. |
| Ethacrynic acid                        | Edecrin            | 50 mg once daily          | 50–100 mg once or twice daily | \$23.95/25 mg | \$1437.00  |  |   |
| Bumetanide                             | (generic)          | 0.25 mg twice daily       | 0.5–10 mg in 2 or 3 doses     | \$0.54/1 mg   | \$32.40  |  |   |
| Torsemide                              | Demadex            | 5 mg once daily           | 5–10 mg once daily            | \$0.70/10 mg  | \$21.00  |  | Effective blood pressure medication at low dosage.  |

(continued)

**Table 11–8.** Antihypertensive drugs: diuretics (in descending order of preference). (continued)

| Drugs                                | Proprietary Names                | Initial Oral Doses          | Dosage Range           | Cost per Unit      | Cost of 30 Days of Treatment <sup>1</sup> (Average Dosage) | Adverse Effects   | Comments  |
|--------------------------------------|----------------------------------|-----------------------------|------------------------|--------------------|--|---|---|
| <b>Aldosterone Receptor Blockers</b> |                                  |                             |                        |                    |  |   |   |
| Spironolactone                       | Aldactone                        | 12.5 or 25 mg once daily    | 12.5–100 mg once daily | \$0.19/25 mg       | \$5.70   | Hyperkalemia, metabolic acidosis, gynecomastia.   | Can be useful add-on therapy in patients with refractory hypertension.                  |
| Amiloride                            | (generic)                        | 5 mg once daily             | 5–10 mg once daily     | \$1.25/5 mg        | \$37.50  |   |   |
| Eplerenone                           | Inspra                           | 25 mg once daily            | 25–100 mg once daily   | \$4.10/25 mg       | \$123.00   |   |   |
| <b>Combination Products</b>          |                                  |                             |                        |                    |  |   |   |
| HCTZ and triamterene                 | Dyazide, Maxzide-25 (25/37.5 mg) | 1 tab once daily            | 1 or 2 tabs once daily | \$0.27             | \$8.10   | Same as thiazides plus GI disturbances, hyperkalemia rather than hypokalemia, headache; triamterene can cause kidney stones and kidney dysfunction; spironolactone causes gynecomastia. Hyperkalemia can occur if this combination is used in patients with advanced kidney disease or those taking ACE inhibitors. | Use should be limited to patients with demonstrable need for a potassium-sparing agent. |
| HCTZ and amiloride                   | (generic) (50/5 mg)              | ½ tab once daily            | 1 or 2 tabs once daily | \$1.16             | \$34.80  |   |   |
| HCTZ and spironolactone              | Aldactazide (25/25 mg; 50/50 mg) | 1 tab (25/25 mg) once daily | 1–4 tabs once daily    | \$1.24/ (25/25 mg) | \$37.20  |   |   |

<sup>1</sup>Average wholesale price (AWP; for AB-rated generic when available) for quantity listed.

Source: IBM Micromedex Red Book (electronic version) IBM Watson Health. Greenwood Village, CO, USA. Available at <https://www.micromedexsolutions.com>, accessed March 27, 2021. AWP may not accurately represent the actual pharmacy cost because wide contractual variations exist among institutions.

ACE, angiotensin-converting enzyme; GI, gastrointestinal; LDL, low-density lipoprotein.

These include individuals with angina pectoris, previous myocardial infarction, and stable heart failure as well as those with migraine headaches and somatic manifestations of anxiety.

Although all beta-blockers appear to be similar in antihypertensive potency, they differ in a number of pharmacologic properties (these differences are summarized in Table 11–9), including specificity to the cardiac beta-1-receptors (cardioselectivity) and whether they also block the beta-2-receptors in the bronchi and vasculature; *at higher dosages, however, all agents are nonselective.* The beta-blockers also differ in their pharmacokinetics, lipid solubility—which determines whether they cross the blood-brain barrier predisposing to central nervous system side effects—and route of metabolism. Metoprolol reduces mortality and morbidity in patients with chronic stable heart failure with reduced ejection fraction (see Chapter 10). Carvedilol and nebivolol maintain cardiac output and are beneficial in patients with left ventricular systolic dysfunction. Carvedilol and nebivolol may reduce peripheral vascular resistance by concomitant alpha-blockade (carvedilol) and increased nitric oxide release (nebivolol). Because of the lack of efficacy in primary prevention of myocardial infarction and inferiority compared with other drugs in prevention of stroke and left ventricular hypertrophy, traditional beta-blockers should not be used as first-line agents in the treatment of hypertension without specific compelling indications (such as active coronary artery disease). Vasodilating beta-blockers may emerge as alternative first-line antihypertensives, but this possibility has yet to be rigorously tested in outcome studies.

**Side effects**—The side effects of beta-blockers include inducing or exacerbating bronchospasm in predisposed patients; sinus node dysfunction and AV conduction depression (resulting in bradycardia or AV block); nasal congestion; Raynaud phenomenon; and central nervous system symptoms with nightmares, excitement, depression, and confusion. Fatigue, lethargy, and erectile dysfunction may occur. The traditional beta-blockers (but not the vasodilator beta-blockers carvedilol and nebivolol) have an adverse effect on lipids and glucose metabolism. Beta-blockers are used cautiously in patients with type 1 diabetes, since they can mask the symptoms of hypoglycemia and prolong these episodes by inhibiting gluconeogenesis. These drugs should also be used with caution in patients with advanced peripheral vascular disease associated with rest pain or nonhealing ulcers, but they are generally well tolerated in patients with mild claudication. Nebivolol can be safely used in patients with stage II claudication (claudication at 200 m).

*In treatment of pheochromocytoma, beta-blockers should not be administered until alpha-blockade (eg, phentolamine) has been established.* Otherwise, blockade of vasodilatory beta-2-adrenergic receptors will allow unopposed vasoconstrictor alpha-adrenergic receptor activation with worsening of hypertension. *For the same reason, beta-blockers should not be used to treat hypertension arising from cocaine use.*

Great care should be exercised if the decision is made, in the absence of compelling indications, to remove beta-blockers from the treatment regimen because abrupt withdrawal can precipitate acute coronary events and severe increases in blood pressure.

## H. Alpha-Adrenoceptor Antagonists

Prazosin, terazosin, and doxazosin (Table 11–10) block postsynaptic alpha-receptors, relax smooth muscle, and reduce blood pressure by lowering peripheral vascular resistance. These agents are effective as single-drug therapy in some individuals, but tachyphylaxis may appear during long-term therapy. Unlike beta-blockers and diuretics, alpha-blockers have no adverse effect on serum lipid levels. In fact, alpha-blockers increase HDL cholesterol while reducing total cholesterol; whether this is beneficial in the long term has not been established.

**Side effects**—Side effects are relatively common (Table 11–10). These include marked hypotension after the first dose which, therefore, should be small and given at bedtime. Post-dosing palpitations, headache, and nervousness may continue to occur during long-term therapy; these symptoms may be less frequent or severe with doxazosin because of its more gradual onset of action. In ALLHAT, persons receiving doxazosin as initial therapy had a significant increase in heart failure hospitalizations and a higher incidence of stroke relative to those receiving diuretics, prompting discontinuation of this arm of the study. Cataractectomy in patients exposed to alpha-blockers can be complicated by the floppy iris syndrome, even after discontinuation of the drug, so the ophthalmologist should be alerted that the patient has been taking the drug prior to surgery.

To summarize, alpha-blockers should generally not be used as initial agents to treat hypertension—except perhaps in men with symptomatic prostatism or nightmares linked to posttraumatic stress disorder.

## I. Drugs With Central Sympatholytic Action

Methyldopa, clonidine, guanabenz, and guanfacine (Table 11–10) lower blood pressure by stimulating alpha-adrenergic receptors in the central nervous system, thus reducing efferent peripheral sympathetic outflow. There is considerable experience with methyldopa in pregnant women, and it is still used for this population. Clonidine is available in patches, which may have particular value in noncompliant patients. All of these central sympatholytic agents are effective as single therapy in some patients, but they are usually used as second- or third-line agents because of the high frequency of drug intolerance.

**Side effects**—Side effects include sedation, fatigue, dry mouth, postural hypotension, and erectile dysfunction. An important concern is rebound hypertension following withdrawal. Methyldopa also causes hepatitis and hemolytic anemia and should be restricted to individuals who have already tolerated long-term therapy.

## J. Peripheral Sympathetic Inhibitors

These agents are usually used only in refractory hypertension. Reserpine remains a cost-effective antihypertensive agent (Table 11–10). Its reputation for inducing mental depression and its other side effects—sedation, nasal stuffiness, sleep disturbances, and peptic ulcers—has made it unpopular, though these problems are uncommon at low dosages.

**Table 11–9.** Antihypertensive drugs: beta-adrenergic blocking agents.

| Drug                     | Proprietary Name  | Initial Oral Dosage                        | Dosage Range                                    | Cost per Unit                     | Cost of 30 Days of Treatment (Based on Average Dosage) <sup>1</sup> | Special Properties              |                  |                  |                  |                              | Comments <sup>5</sup>   |
|--------------------------|-------------------|--|---|-----------------------------------|---|---------------------------------|------------------|------------------|------------------|------------------------------|---|
|                          |                   |  |   |                                   |   | Beta-1 Selectivity <sup>2</sup> | ISA <sup>3</sup> | MSA <sup>4</sup> | Lipid Solubility | Renal vs Hepatic Elimination |   |
| Acebutolol               | Sectral           | 400 mg once daily                          | 200–1200 mg in 1 or 2 doses                     | \$1.34/400 mg                     | \$40.20   | +                               | +                | +                | +                | H > R                        | Positive ANA; rare LE syndrome; also indicated for arrhythmias. Doses > 800 mg have beta-1 and beta-2 effects.                                  |
| Atenolol                 | Tenormin          | 25 mg once daily                           | 25–100 mg once daily                            | \$0.79/50 mg                      | \$23.70   | +                               | 0                | 0                | 0                | R                            | Also indicated for angina and post-MI. Doses > 100 mg have beta-1 and beta-2 effects.   |
| Atenolol/ chlorthalidone | Tenoretic         | 50 mg/25 mg once daily                     | 50 mg/25 mg–100 mg/25 mg once daily             | \$1.88/50 mg/25 mg                | \$56.40   | +                               | 0                | 0                | 0                | R                            |   |
| Betaxolol                | Kerlone           | 10 mg once daily                           | 10–40 mg once daily                             | \$0.78/10 mg                      | \$23.40   | +                               | 0                | 0                | +                | H > R                        |   |
| Bisoprolol               | Zebeta            | 5 mg once daily                            | 5–20 mg once daily                              | \$1.22/10 mg                      | \$36.60   | +                               | 0                | 0                | 0                | R = H                        | Also effective for heart failure.   |
| Bisoprolol and HCTZ      | Ziac              | 2.5 mg/6.25 mg once daily                  | 2.5 mg/6.25 mg–10 mg/6.25 mg once daily         | \$1.14/2.5/6.25 mg                | \$34.20   | +                               | 0                | 0                | 0                | R = H                        | Low-dose combination approved for initial therapy.  |
| Carvedilol               | Coreg<br>Coreg CR | 6.25 mg twice daily<br>20 mg ER once daily | 12.5–50 mg in 2 doses<br>20–80 mg ER once daily | \$0.09/25 mg<br>\$9.91/any tablet | \$5.40 (25 mg twice a day)<br>\$297.30                              | 0                               | 0                | 0                | +++              | H > R                        | Alpha:beta blocking activity 1:9; may cause orthostatic symptoms; effective for heart failure. Nitric oxide potentiating vasodilatory activity. |
| Labetalol                | Trandate          | 100 mg twice daily                         | 200–2400 mg in 2 doses                          | \$0.39/200 mg                     | \$23.40   | 0                               | 0/+              | 0                | ++               | H                            | Alpha:beta blocking activity 1:3; more orthostatic hypotension, fever, hepatotoxicity.  |

|                                 |                                      |                                       |   |                               |                   |   |    |    |     |       |   |
|---------------------------------|--------------------------------------|---------------------------------------|---|-------------------------------|-------------------|---|----|----|-----|-------|---|
| Metoprolol                      | Lopressor Toprol-XL (SR preparation) | 50 mg twice daily<br>25 mg once daily | 50–200 mg twice daily<br>25–400 mg once daily | \$0.03/50 mg<br>\$1.50/100 mg | \$1.80<br>\$45.00 | + | 0  | +  | +++ | H     | Also indicated for angina and post-MI. Approved for heart failure. Doses > 100 mg have beta-1 and beta-2 effects. |
| Metoprolol and HCTZ             | Lopressor HCT                        | 50 mg/<br>12.5 mg twice daily         | 50 mg/25 mg–<br>200 mg/50 mg                  | \$1.77/100 mg/<br>25 mg       | \$106.20          | + | 0  | +  | +++ | H     |   |
| Nadolol                         | Corgard                              | 20 mg once daily                      | 20–320 mg once daily                          | \$3.96/40 mg                  | \$118.80          | 0 | 0  | 0  | 0   | R     |   |
| Nadolol and bendroflumethiazide | Corzide                              | 40 mg/5 mg once daily                 | 40 mg/5 mg–<br>80 mg/5 mg once daily          | 6.14/80 mg/<br>5 mg           | \$184.20          |   |    |    |     |       |   |
| Nebivolol                       | Bystolic                             | 5 mg once daily                       | 40 mg once daily                              | \$6.32/5 mg                   | \$189.60          | + | 0  | 0  | ++  | H     | Nitric oxide potentiating vasodilatory activity.  |
| Pindolol                        | Visken                               | 5 mg twice daily                      | 10–60 mg in 2 doses                           | \$1.10/5 mg                   | \$66.00           | 0 | ++ | +  | +   | H > R | In adults, 35% renal clearance.   |
| Propranolol                     | Inderal                              | 20 mg twice daily                     | 40–640 mg in 2 doses                          | \$0.41/40 mg                  | \$24.60           | 0 | 0  | ++ | +++ | H     | Also indicated for angina and post-MI.  |
|                                 | Inderal LA                           | 80 mg ER once daily                   | 120–640 mg ER once daily                      | \$2.98/120 mg                 | \$89.40           |   |    |    |     |       |   |
|                                 | InnoPran XL                          | 80 mg ER once nightly                 | 80–120 mg ER once nightly                     | \$30.20/<br>120 mg            | \$906.00          |   |    |    |     |       |   |
| Propranolol and HCTZ            | (generic)                            | 40 mg/25 mg twice daily               | 80 mg/25 mg twice daily                       | \$1.41/80 mg/<br>25 mg        | \$84.60           | 0 | 0  | ++ | +++ | H     |   |
| Timolol                         | (generic)                            | 5 mg twice daily                      | 10–60 mg in 2 doses                           | \$1.70/10 mg                  | \$102.00          | 0 | 0  | 0  | ++  | H > R | Also indicated for post-MI; 80% hepatic clearance.  |

<sup>1</sup>Average wholesale price (AWP, for AB-rated generic when available) for quantity listed.

Source: IBM Micromedex Red Book (electronic version) IBM Watson Health. Greenwood Village, CO, USA. Available at <https://www.micromedexsolutions.com>, accessed March 27, 2021. AWP may not accurately represent the actual pharmacy cost because wide contractual variations exist among institutions.

<sup>2</sup>Agents with beta-1 selectivity are less likely to precipitate bronchospasm and decrease peripheral blood flow in low doses, but selectivity is only relative.

<sup>3</sup>Agents with ISA cause less resting bradycardia and lipid changes.

<sup>4</sup>MSA generally occurs at concentrations greater than those necessary for beta-adrenergic blockade. The clinical importance of MSA by beta-blockers has not been defined.

<sup>5</sup>Adverse effects of all beta-blockers: bronchospasm, fatigue, sleep disturbance and nightmares, bradycardia and atrioventricular block, worsening of heart failure, cold extremities, gastrointestinal disturbances, erectile dysfunction, ↑ triglycerides, ↓ high-density lipoprotein cholesterol, rare blood dyscrasias.

ANA, antinuclear antibody; ER, extended release; HCTZ, hydrochlorothiazide; ISA, intrinsic sympathomimetic activity; LE, lupus erythematosus; MI, myocardial infarction; MSA, membrane-stabilizing activity; SR, sustained release; 0, no effect; +, some effect; ++, moderate effect; +++, most effect.

**Table 11–10.** Alpha-adrenoceptor blocking agents, sympatholytics, and vasodilators.

| Drug                               | Proprietary Names                | Initial Dosage                        | Dosage Range                | Cost per Unit         | Cost of 30 Days of Treatment (Average Dosage) <sup>1</sup> | Adverse Effects   | Comments   |
|------------------------------------|----------------------------------|---------------------------------------|-----------------------------|-----------------------|--|---|--|
| <b>Alpha-Adrenoceptor Blockers</b> |                                  |                                       |                             |                       |  |   |  |
| Doxazosin                          | Cardura                          | 1 mg at bedtime                       | 1–16 mg once daily          | \$0.29/4 mg           | \$8.70 (4 mg once daily)                                   | Syncope with first dose; postural hypotension, dizziness, palpitations, headache, weakness, drowsiness, sexual dysfunction, anticholinergic effects, urinary incontinence; first-dose effects may be less with doxazosin. | May ↑ HDL and ↓ LDL cholesterol. May provide short-term relief of obstructive prostatic symptoms. Less effective in preventing cardiovascular events than diuretics. |
|                                    | Cardura XL                       | 4 mg ER once daily                    | 4–8 mg ER once daily        | \$7.07/4 mg ER        | \$212.10 (4 mg ER once daily)                              |   |  |
| Prazosin                           | Minipress                        | 1 mg at bedtime                       | 2–20 mg in 2 or 3 doses     | \$0.95/5 mg           | \$57.00 (5 mg twice daily)                                 |   |  |
| Terazosin                          | Hytrin                           | 1 mg at bedtime                       | 1–20 mg in 1 or 2 doses     | \$1.60/1, 2, 5, 10 mg | \$48.00 (5 mg once daily)                                  |   |  |
| <b>Central Sympatholytics</b>      |                                  |                                       |                             |                       |  |   |  |
| Clonidine                          | Catapres                         | 0.1 mg twice daily                    | 0.2–0.6 mg in 2 doses       | \$0.21/0.1 mg         | \$12.60 (0.1 mg twice daily)                               | Sedation, dry mouth, sexual dysfunction, headache, bradycardia; side effects may be less with guanfacine. Contact dermatitis with clonidine patch.  | "Rebound" hypertension may occur even after gradual withdrawal.  |
|                                    | Catapres TTS (transdermal patch) | 0.1 mg/day patch weekly               | 0.1–0.3 mg/day patch weekly | \$55.77/0.2 mg patch  | \$223.08 (0.2 mg weekly)                                   |   |  |
| Clonidine and chlorthalidone       | Clorpres                         | 0.1 mg/15 mg one to three times daily | 0.1 mg/15 mg–0.3 mg/15 mg   | \$2.77/0.1 mg/15 mg   | \$166.20/0.1 mg/15 mg twice daily                          |   |  |
| Guanfacine                         | Tenex                            | 1 mg once daily                       | 1–3 mg once daily           | \$0.87/1 mg           | \$26.10 (1 mg once daily)                                  |   |  |
| Methyldopa                         | Aldochlor                        | 250 mg twice daily                    | 500–2000 mg in 2 doses      | \$0.66/500 mg         | \$39.60 (500 mg twice daily)                               | Hepatitis, hemolytic anemia, fever.   | Avoid in favor of safer agents.  |

| Peripheral Neuronal Antagonists |            |                    |                         |               |                             |  |   |
|---------------------------------|------------|--------------------|-------------------------|---------------|-----------------------------|--|---|
| Reserpine                       | (generic)  | 0.05 mg once daily | 0.05–0.25 mg once daily | \$1.19/0.1 mg | \$35.70 (0.1 mg once daily) | Depression (less likely at low dosages, ie, < 0.25 mg), night terrors, nasal stuffiness, drowsiness, peptic disease, GI disturbances, bradycardia. |   |
| Direct Vasodilators             |            |                    |                         |               |                             |  |   |
| Hydralazine                     | Apresoline | 25 mg twice daily  | 50–300 mg in 2–4 doses  | \$0.15/25 mg  | \$9.00 (25 mg twice daily)  | GI disturbances, tachycardia, headache, nasal congestion, rash, LE-like syndrome.  | May worsen or precipitate angina.                             |
| Minoxidil                       | (generic)  | 5 mg once daily    | 10–40 mg once daily     | \$1.28/10 mg  | \$38.40 (10 mg once daily)  | Tachycardia, fluid retention, headache, hirsutism, pericardial effusion, thrombocytopenia.   | Should be used in combination with beta-blocker and diuretic. |

<sup>1</sup>Average wholesale price (AWP, for AB-rated generic when available) for quantity listed.

Source: IBM Micromedex Red Book (electronic version) IBM Watson Health. Greenwood Village, CO, USA. Available at <https://www.micromedexsolutions.com>, accessed March 27, 2021. AWP may not accurately represent the actual pharmacy cost because wide contractual variations exist among institutions.

ER, extended release; GI, gastrointestinal; LE, lupus erythematosus.

Guanethidine and guanadrel inhibit catecholamine release from peripheral neurons but frequently cause orthostatic hypotension (especially in the morning or after exercise), diarrhea, and fluid retention.

### K. Arteriolar Dilators

Hydralazine and minoxidil (Table 11–10) relax vascular smooth muscle and produce peripheral vasodilation. When given alone, they stimulate reflex tachycardia; increase myocardial contractility; and cause headache, palpitations, and fluid retention. To counteract these effects, the agents are usually given in combination with diuretics and beta-blockers in resistant patients. Hydralazine produces frequent gastrointestinal disturbances and may induce a lupus-like syndrome. Minoxidil causes hirsutism and marked fluid retention; this very potent agent is reserved for the most refractory of cases.

## ► Antihypertensive Medications & the Risk of Cancer

A number of observational studies have examined the association between long-term exposure to antihypertensive medications and cancer. Weak associations have been suggested by some of these studies, but results have been very mixed. In the absence of large-scale prospective studies with cancer as a prespecified outcome measure, the effect of antihypertensive drugs on the risk of cancer remains uncertain. By contrast, the beneficial effect of these drugs on cardiovascular outcomes has been clearly established. Concern about increased risk of cancer should not be minimized, but at present there are no compelling data to prompt a change in prescribing patterns.

Hicks BM et al. Angiotensin converting enzyme inhibitors and risk of lung cancer: population based cohort study. *BMJ*. 2018;363:k4209. [PMID: 30355745]

Su KA et al. Photosensitizing antihypertensive drug use and risk of cutaneous squamous cell carcinoma. *Br J Dermatol*. 2018;179:1088. [PMID: 29723931]

Wright CM et al. Calcium channel blockers and breast cancer incidence: an updated systematic review and meta-analysis of the evidence. *Cancer Epidemiol*. 2017;50:113. [PMID: 28866282]

accepted in general clinical practice, it seems probable that renal sympathetic nerve ablation will emerge as an alternative or adjunctive modality in the treatment of hypertension and may become useful in the management of resistant hypertension and drug intolerance.

Böhm M et al; SPYRAL HTN-OFF MED Pivotal Investigators.

Efficacy of catheter-based renal denervation in the absence of antihypertensive medications (SPYRAL HTN-OFF MED Pivotal): a multicentre, randomised, sham-controlled trial. *Lancet*. 2020;395:1444. [PMID: 32234534]

Hermida RC et al; Hygia Project Investigators. Bedtime hypertension treatment improves cardiovascular risk reduction: the Hygia Chronotherapy Trial. *Eur Heart J*. 2020;41:4565. [PMID: 31641769]

## ► Developing an Antihypertensive Regimen

Historically, data from large placebo-controlled trials supported the overall conclusion that antihypertensive therapy with diuretics and beta-blockers had a major beneficial effect on a broad spectrum of cardiovascular outcomes, reducing the incidence of stroke by 30–50% and of heart failure by 40–50%, and halting progression to accelerated hypertension syndromes. The decreases in fatal and nonfatal coronary heart disease and cardiovascular and total mortality were less dramatic, ranging from 10% to 15%. Similar placebo-controlled data pertaining to the newer agents are generally lacking, except for stroke reduction with the calcium channel blocker nitrrendipine in the Systolic Hypertension in Europe trial. However, there is substantial evidence that ACE inhibitors, and to a lesser extent ARBs, reduce adverse cardiovascular outcomes in other related populations (eg, patients with diabetic nephropathy, heart failure, or postmyocardial infarction and individuals at high risk for cardiovascular events). Most large clinical trials that have compared outcomes in relatively unselected patients have failed to show a difference between newer agents—such as ACE inhibitors, calcium channel blockers, and ARBs—and the older diuretic-based regimens with regard to survival, myocardial infarction, and stroke. Where differences have been observed, they have mostly been attributable to subtle asymmetries in blood pressure control rather than to any inherent advantages of one agent over another. Recommendations for initial treatment identify ACE inhibitors, ARBs, and calcium channel blockers as valid choices. Because of their adverse metabolic profile, initial therapy with thiazides might best be restricted to older patients. Thiazides are acceptable as first-line therapy in Blacks because of specific efficacy in this group.

As discussed above, beta-blockers are not ideal first-line drugs in the treatment of hypertension without compelling indications for their use (such as active coronary artery disease and heart failure). Vasodilator beta-blockers (such as carvedilol and nebivolol) may produce better outcomes than traditional beta-blockers; however, this possibility remains a theoretical consideration.

The American Diabetes Association has advocated evening dosing of one or more antihypertensive medications to restore nocturnal blood pressure dipping. The HYGIA

## ► Procedures That Modulate the Activity of the Autonomic Nervous System

Before the advent of antihypertensive medications, lumbar sympathectomy was used to lower blood pressure. In a more specific and less invasive approach, the renal sympathetic nerves can be ablated using radiofrequency energy applied to the luminal surface of the renal arteries. However, the Symplicity HTN-3 study of renal sympathetic denervation did not show any difference in blood pressure reduction compared to a sham procedure group. Subsequently, the SPYRAL HTN-OFF MED study, using a more intensive and closely controlled ablation strategy, demonstrated clinically meaningful blood pressure reductions compared to the sham control group. Although not yet

trial compared the effect of nighttime dosing of at least one antihypertensive medication with morning dosing of all antihypertensive medications in 19,000 participants with median follow-up 6.3 years, and demonstrated improved ambulatory blood pressure and nocturnal dipping, and a significant decline in major cardiovascular events in the nighttime dosing group. Participants were monitored via ambulatory blood pressure measurement, and the incidence of nocturnal hypotension in the HYGIA trial was very low. However, profound nocturnal hypotension might not be detected in the absence of ambulatory blood pressure monitoring, and ischemic optic neuropathy or other low perfusion complications would be a concern.

Drugs that interrupt the renin-angiotensin cascade are more effective in young, White persons, in whom renin tends to be higher. Calcium channel blockers and diuretics are more effective in older or Black persons, in whom renin levels are generally lower. Many patients require two or more medications and even then a substantial proportion fail to achieve the goal blood pressure. A stepped care approach to the drug treatment of hypertension is outlined in Table 11–11. In diabetic patients, three or four drugs are usually required to reduce systolic blood pressure to goal. In many patients, blood pressure cannot be adequately controlled with any combination. As a result, debating the appropriate first-line agent is less relevant than determining the most appropriate combinations of agents.

The mnemonic ABCD can be used to remember four classes of antihypertensive medications. These four classes can be divided into two categories: AB and CD. AB refers to drugs that block the RAAS (ACE/ARB and beta-blockers). CD refers to those that work in other pathways (calcium channel blockers and diuretics). Combinations of drugs between the two categories are more potent than combinations from within a category. Many experts recommend the use of fixed-dose combination (between two categories) antihypertensive agents as first-line therapy in patients

with substantially elevated systolic pressures (greater than 160/100 mm Hg) or difficult-to-control hypertension (which is often associated with diabetes or kidney dysfunction). In light of unwanted metabolic effects, calcium channel blockers might be preferable to thiazides in the younger hypertensive patient requiring a second antihypertensive drug following initiation of therapy with an ACE inhibitor or ARB. Furthermore, based on the results from the ACCOMPLISH trial, a combination of ACE inhibitor and calcium channel blocker may also prove optimal for patients at high risk for cardiovascular events. The initial use of low-dose combinations allows faster blood pressure reduction without substantially higher intolerance rates and is likely to be better accepted by patients. Data from the ALTITUDE study (in patients with type 2 diabetes and chronic kidney disease or cardiovascular disease or both) indicate that the addition of aliskiren to either ARB or ACE inhibitor was associated with worse outcomes and cannot be recommended, at least in this population. A suggested approach to treatment, tailored to patient demographics, is outlined in Table 11–12.

In sum, as a prelude to treatment, the patient should be informed of common side effects and the need for diligent compliance. In patients with blood pressure less than 160/90 mm Hg in whom pharmacotherapy is indicated, treatment should start with a single agent or two-drug combination at a low dose. Follow-up visits usually should be at 4- to 6-week intervals to allow for full medication effects to be established (especially with diuretics) before further titration or adjustment. If, after titration to usual doses, the patient has shown a discernible but incomplete response and a good tolerance of the initial drug, another medication should be added. See Goals of Treatment, above. As a rule of thumb, a blood pressure reduction of 10 mm Hg can be expected for each antihypertensive agent added to the regimen and titrated to the optimum dose. In those with more severe hypertension, or with comorbidities (such as diabetes) that are likely to render them

**Table 11–11.** A step care approach to the initiation and titration of antihypertension medications.<sup>1,2</sup>

|        |   |
|--------|---|
| Step 1 | ACE inhibitor/ARB <b>or</b> <sup>3</sup><br>Calcium channel blocker <b>or</b><br>Thiazide diuretic <sup>4</sup>             |
| Step 2 | ACE inhibitor/ARB <b>plus</b><br>Calcium channel blocker <b>or</b> thiazide diuretic <sup>5</sup>                           |
| Step 3 | ACE inhibitor/ARB <b>plus</b> calcium channel blocker <b>plus</b> thiazide diuretic   |
| Step 4 | ACE inhibitor/ARB <b>plus</b> calcium channel blocker <b>plus</b> thiazide diuretic <b>plus</b> spironolactone <sup>6</sup> |

<sup>1</sup>Allow 2 weeks to reach full effect of each drug. Proceed through steps until target blood pressure is attained.

<sup>2</sup>Beta-blockers can be used at any stage if specifically indicated, eg, heart failure or angina.

<sup>3</sup>The European guidelines recommend starting with low-dose combination of two antihypertensive drugs in all but low-risk grade 1 hypertension (140–159/90–99 mm Hg). American guidelines suggest initiation with dual therapy for stage 2 hypertension (> 140/90 mm Hg).

<sup>4</sup>Thiazide or calcium channel blocker is more effective initial therapy in older people and Blacks.

<sup>5</sup>If required, add a calcium channel blocker rather than diuretic in younger patients to avoid long-term exposure to metabolic side effects of diuretics.

<sup>6</sup>Alternatives to spironolactone include eplerenone, amiloride, or triamterene. Watch for hyperkalemia, especially if also receiving ACE inhibitor/ARB. Avoid potassium-sparing diuretics in advanced CKD. If more than three drugs are required at maximum dose, consider specialist referral. ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CKD, chronic kidney disease.

**Table 11–12.** Choice of antihypertensive agent based on demographic considerations.<sup>1,2</sup>

|                               | <b>Black, All Ages</b>   | <b>All Others, Age &lt; 55 Years</b>                                       | <b>All Others, Age &gt; 55 Years</b>  |
|-------------------------------|--|--|---|
| <b>First-line</b>             | CCB or diuretic  | ACE inhibitor or ARB <sup>3</sup> or CCB or diuretic <sup>4</sup>          | CCB or diuretic <sup>5</sup>  |
| <b>Second-line</b>            | ARB <sup>3</sup> or ACE inhibitor <sup>6</sup> or vasodilating beta-blocker <sup>6</sup> | Vasodilating beta-blocker  | ACE inhibitor or ARB <sup>3</sup> or vasodilating beta-blocker <sup>7</sup> |
| <b>Resistant hypertension</b> | Aldosterone receptor blocker   | Aldosterone receptor blocker   | Aldosterone receptor blocker  |
| <b>Additional options</b>     | Centrally acting alpha-agonist or peripheral alpha-antagonist <sup>8</sup>               | Centrally acting alpha-agonist or peripheral alpha-antagonist <sup>8</sup> | Centrally acting alpha-agonist or peripheral alpha-antagonist <sup>8</sup>  |

<sup>1</sup>Compelling indications may alter the selection of an antihypertensive drug.

<sup>2</sup>Start with full dose of one agent, or lower doses of combination therapy. In more severe hypertension ( $\geq 140/90$  mm Hg), consider initiating therapy with a fixed dose combination.

<sup>3</sup>Women of childbearing age should avoid ACE inhibitors and ARBs or discontinue as soon as pregnancy is diagnosed.

<sup>4</sup>The adverse metabolic effects of thiazide diuretics and beta-blockers should be considered in younger patients but may be less important in the older patient.

<sup>5</sup>For patients with significant kidney dysfunction, use loop diuretic instead of thiazide.

<sup>6</sup>Despite the elevated risk of angioedema and cough in Blacks, ACE inhibitors are generally well tolerated and are a useful adjunct.

<sup>7</sup>There are theoretical advantages in the use of vasodilating beta-blockers such as carvedilol and nebivolol.

<sup>8</sup>Alpha-antagonists may precipitate or exacerbate orthostatic hypotension in older adults.

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CCB, calcium channel blocker.

resistant to treatment, initiation with combination therapy is advised and more frequent follow-up is indicated.

Patients who are compliant with their medications and who do not respond to conventional combination regimens should usually be evaluated for secondary hypertension before proceeding to more complex regimens.

### ► Medication Nonadherence

Adherence to antihypertensive treatment is alarmingly poor. In one European study of antihypertensive medication compliance, there was a 40% discontinuation rate at 1 year after initiation. Collaborative care, using clinicians, pharmacists, social workers, and nurses to encourage compliance, has had a variable and often rather modest effect on blood pressure control. Adherence is enhanced by patient education and by use of home blood pressure measurement. The choice of antihypertensive medication is important. Better compliance has been reported for patients whose medications could be taken once daily or as combination pills. Adherence is best with ACE inhibitors and ARBs, and worse with beta-blockers and diuretics.

### ► Consideration of Gender in Hypertension

Because of the preponderance of male recruitment into large-scale clinical trials, the impact of gender on the evaluation and management of hypertension remains uncertain. The limited data that exist suggest a steeper relationship in women between 24-hour ambulatory and night time systolic blood pressure and the risk of cardiovascular events. There are many gender-specific effects on the mechanisms and end organ impact of hypertension. In younger adults, men are more likely to be hypertensive than women, a relationship that reverses in later life.

Regression of left ventricular hypertrophy in response to ACE inhibitors is less pronounced in women. Women are more likely to have isolated systolic hypertension, probably because they develop more active left ventricular systolic function and greater vascular stiffness than men. Fibromuscular dysplasia of the renal artery is much more common in women than men. The side effects of many antihypertensive drugs are more pronounced in women than men, including ACE inhibitor-associated cough and hyponatremia and hypokalemia in response to diuretics. Conversely, thiazides can help preserve bone density. Dependent edema due to amlodipine is more likely in women, and women are more sensitive to beta-blockers. There are no data to support a different blood pressure target in women, but this question has not been examined in dedicated clinical trials.

### ► Treatment of Hypertension in Diabetes

Hypertensive patients with diabetes are at particularly high risk for cardiovascular events. Data from the ACCORD study of diabetic patients demonstrated that most of the benefits of blood pressure lowering were seen with a systolic target of less than 140 mm Hg. Although there was a reduction in stroke risk at a systolic target below 120/70 mm Hg, treatment to this lower target was associated with an increased risk of serious adverse effects. US and Canadian guidelines recommend a blood pressure goal of less than 130/80 mm Hg in diabetic patients. Because of the beneficial effects of ACE inhibitors in diabetic nephropathy, they should be part of the initial treatment regimen. ARBs or perhaps renin inhibitors may be substituted in those intolerant of ACE inhibitors. While the ONTARGET study showed that combinations of ACE inhibitors and ARBs in persons with atherosclerosis or type 2 diabetes with

end-organ damage appeared to minimize proteinuria, this strategy slightly increased the risks of progression to dialysis and of death; thus, it is not recommended. Most diabetic patients require combinations of three to five agents to achieve target blood pressure, usually including a diuretic and a calcium channel blocker or beta-blocker. Canagliflozin improves glycemic control through inhibition of the sodium-glucose co-transporter 2 (SGLT2) and, in addition, generally lowers blood pressure by 3–4 mm Hg. This drug was associated with improved renal outcomes and reduced cardiovascular risk in the CREDENCE trial of patients with diabetic nephropathy and can be considered when additional blood pressure control is needed in patients with type 2 diabetes. In addition to rigorous blood pressure control, treatment of persons with diabetes should include aggressive treatment of other risk factors.

### ► Treatment of Hypertension in Chronic Kidney Disease

Hypertension is present in 40% of patients with a GFR of 60–90 mL/min/1.73 m<sup>2</sup>, and 75% of patients with a GFR less than 30 mL/min/1.73 m<sup>2</sup>. The rate of progression of chronic kidney disease is markedly slowed by treatment of hypertension. In the SPRINT trial, the reduction in cardiovascular risk associated with lower blood pressure targets was also observed in the subgroup with a GFR of less than 60 mL/min/1.73 m<sup>2</sup>. However, an effect of *lower* blood pressure targets on the slowing of chronic kidney disease progression appears to be restricted to those with pronounced proteinuria. In the SPRINT trial, the lower blood pressure goal was associated with increased risk of acute kidney injury, but this was generally reversible and not associated with elevated biomarkers for ischemic injury. Most experts recommend a blood pressure target of less than 130/80 mm Hg in patients with chronic kidney disease, with consideration of more intensive lowering if proteinuria greater than 1 g per 24 hours is present. Medications that interrupt the renin-angiotensin cascade can slow the progression of kidney disease and are preferred for initial therapy, especially in those with albuminuria of greater than 300 mg/g creatinine. Transition from thiazide to loop diuretic is often necessary to control volume expansion as the eGFR falls below 30 mL/min/1.73 m<sup>2</sup>. ACE inhibitors remain protective and safe in kidney disease associated with significant proteinuria and serum creatinine as high as 5 mg/dL (380 μmol/L). However, the use of drugs blocking the RAAS cascade in patients with advanced chronic kidney disease should be supervised by a nephrologist. Kidney function and electrolytes should be measured 1 week after initiating treatment and subsequently monitored carefully in patients with kidney disease. An increase in creatinine of 20–30% is acceptable and expected; more exaggerated responses suggest the possibility of renal artery stenosis or volume contraction. Although lower blood pressure levels are associated with acute decreases in GFR, this appears not to translate into an increased risk of developing end-stage renal disease in the long term. Persistence with ACE inhibitor or ARB therapy as the serum potassium level exceeds 5.5 mEq/L is probably not

warranted, since other antihypertensive medications are renoprotective as long as goal blood pressures are maintained. However, diuretics can often be helpful in controlling mild hyperkalemia, and there are novel cation exchange polymers (such as patiromer) that sequester potassium in the gut and are more effective and better tolerated than sodium polystyrene sulfonate.

### ► Treatment of Hypertension in Blacks

Substantial evidence indicates that Blacks in the United States are not only more likely to become hypertensive and more susceptible to the cardiovascular and renal complications of hypertension—they also respond differently to many antihypertensive medications. The REGARDS study illustrates these differences. At systolic blood pressures less than 120 mm Hg, Black and White participants between 45 and 64 years of age had equal risk of stroke. For a 10 mm Hg increase in systolic blood pressure, the risk of stroke was threefold higher in Black participants. At levels above 140–159/90–99 mm Hg, the hazard ratio for stroke in Black compared to White participants between 45 and 64 years of age was 2.35. This increased susceptibility may reflect genetic differences in the cause of hypertension or the subsequent responses to it, differences in occurrence of comorbid conditions such as diabetes or obesity, or environmental factors such as diet, activity, stress, or access to health care services. In any case, as in all persons with hypertension, a multifaceted program of education and lifestyle modification is warranted. Early introduction of combination therapy has been advocated, but there are no clinical trial data to support a lower than usual blood pressure goal in Blacks. Because it appears that ACE inhibitors and ARBs—in the absence of concomitant diuretics—are less effective in Blacks than in Whites, initial therapy should generally be a diuretic or a diuretic in combination with a calcium channel blocker. However, inhibitors of the RAAS do lower blood pressure in Black patients, are useful adjuncts to the recommended diuretic and calcium channel blockers, and should be used in patients with hypertension and compelling indications such as heart failure and kidney disease (especially in the presence of proteinuria) (Table 11–13). *Black patients have an elevated risk of ACE inhibitor-associated angioedema and cough, so ARBs would be the preferred choice.*

### ► Treating Hypertension in Older Adults

Several studies in persons over 60 years of age have confirmed that antihypertensive therapy prevents fatal and nonfatal myocardial infarction and reduces overall cardiovascular mortality. The HYVET study indicated that a reasonable ultimate blood pressure goal is 150/80 mm Hg. Updated guidelines suggest that blood pressure goals should not generally be influenced by age alone. An exploratory subgroup analysis of the SPRINT study found that people older than age 75 years showed benefit at the 120 mm Hg systolic treatment target. Importantly, these benefits were also evident in patients classified as frail. This more aggressive approach was, however, associated with greater risk of falls and worsening kidney function,

**Table 11–13.** Recommended antihypertensive medications for coexisting indications.

| Indication                  | Antihypertensive Medication |              |               |     |                         |                        |
|-----------------------------|-----------------------------|--------------|---------------|-----|-------------------------|------------------------|
|                             | Diuretic                    | Beta-Blocker | ACE Inhibitor | ARB | Calcium Channel Blocker | Aldosterone Antagonist |
| Heart failure               | ✓                           | ✓            | ✓             | ✓   |                         | ✓                      |
| Following MI                |                             | ✓            | ✓             |     |                         | ✓                      |
| High coronary disease risk  | ✓                           | ✓            | ✓             |     | ✓                       |                        |
| Diabetes                    | ✓                           | ✓            | ✓             | ✓   | ✓                       |                        |
| Chronic kidney disease      |                             |              | ✓             | ✓   |                         |                        |
| Recurrent stroke prevention | ✓                           |              | ✓             |     |                         |                        |

ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; MI, myocardial infarction.

indicating that close monitoring is required in elderly patients treated to lower blood pressure goals. It is also important to note the exclusion criteria of the SPRINT study, which included diabetes mellitus, stroke, and orthostatic hypotension.

Blood pressure treatment goals should be individualized in the very elderly. In the SPRINT MIND study, the lower systolic blood pressure target of 120 mm Hg was associated with a 15% reduction in the incidence of mild cognitive impairment and probable all cause dementia compared to the 140 mm Hg in the target group. Based upon this data, aggressive control of hypertension in high-risk individuals would have a significant impact on the prevalence of dementia. As discussed above, it is important to note that blood pressure measurements in the SPRINT study were made by automated devices, which are known to read lower than conventional office measurements.

**How to initiate antihypertensive therapy in older patients**—The same medications are used in older patients but at 50% lower doses. Pressure should be reduced more gradually with a safe intermediate systolic blood pressure goal of 160 mm Hg. As treatment is initiated, older patients should be carefully monitored for orthostasis, altered cognition, and electrolyte disturbances. The elderly are especially susceptible to problems associated with polypharmacy, including drug interactions and dosing errors.

### ► Management of Supine Hypertension in Patients With Orthostatic Hypotension

Supine hypertension is common in patients with orthostatic hypotension and is associated with increased cardiovascular risk. Treatment of orthostasis can exacerbate supine hypertension and vice versa. Life expectancy is often reduced in patients with profound autonomic nervous system dysfunction. In those whose life expectancy is at least several years, though, treatment of nocturnal hypertension might be considered with the use of shorter acting agents (eg, captopril, hydralazine, losartan, or quick-release nifedipine). In patients with supine hypertension, medications used to increase blood pressure during the day should not be given within 5 hours of bedtime.

### ► Follow-Up of Patients Receiving Hypertension Therapy

Once blood pressure is controlled on a well-tolerated regimen, follow-up visits can be infrequent and laboratory testing limited to those appropriate for the patient and the medications used. Yearly monitoring of blood lipids is recommended, and an electrocardiogram could be repeated at 2- to 4-year intervals depending on whether initial abnormalities are present and on the presence of coronary risk factors. Patients who have had excellent blood pressure control for several years, especially if they have lost weight and initiated favorable lifestyle modifications, might be considered for a trial of reduced antihypertensive medications.

Carnethon MR et al; American Heart Association Council on Epidemiology and Prevention; Council on Cardiovascular Disease in the Young; Council on Cardiovascular and Stroke Nursing; Council on Clinical Cardiology; Council on Functional Genomics and Translational Biology; and Stroke Council. Cardiovascular health in African Americans: a scientific statement from the American Heart Association. Circulation. 2017;136:e393. [PMID: 29061565]

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Wenger NK et al. Hypertension across a woman's life cycle. J Am Coll Cardiol. 2018;71:1797. [PMID: 29673470]

### RESISTANT HYPERTENSION

Resistant hypertension is defined as the failure to reach blood pressure control in patients who are adherent to full doses of an appropriate three-drug regimen (including a diuretic). In the approach to resistant hypertension, the clinician should first confirm compliance and rule out “white coat hypertension,” ideally using ambulatory or home-based measurement of blood pressure. Exacerbating factors should be considered (as outlined above). Finally, identifiable causes of resistant hypertension should be sought (Table 11–14). The clinician should pay particular

**Table 11–14.** Causes of resistant hypertension.

|  |
|--|
| Improper blood pressure measurement  |
| Nonadherence   |
| Volume overload and pseudotolerance  |
| Excess sodium intake   |
| Volume retention from kidney disease   |
| Inadequate diuretic therapy  |
| Drug-induced or other causes   |
| Inadequate doses   |
| Inappropriate combinations   |
| Nonsteroidal anti-inflammatory drugs; cyclooxygenase-2 inhibitors                                  |
| Cocaine, amphetamines, other illicit drugs   |
| Sympathomimetics (decongestants, anorectics)   |
| Oral contraceptives  |
| Adrenal steroids   |
| Cyclosporine and tacrolimus  |
| Erythropoietin   |
| Licorice (including some chewing tobacco)  |
| Selected over-the-counter dietary supplements and medicines (eg, ephedra, ma huang, bitter orange) |
| Associated conditions  |
| Obesity  |
| Excess alcohol intake  |
| Identifiable causes of hypertension (see Table 11–2)   |

Data from Chobanian AV et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA*. 2003;289:2560.

attention to the type of diuretic being used in relation to the patient's kidney function. Aldosterone may play an important role in resistant hypertension and aldosterone receptor blockers can be very useful. If goal blood pressure cannot be achieved following completion of these steps, consultation with a hypertension specialist should be considered. Renal sympathetic nerve ablation is a consideration for these patients in the absence of other options, but further trials are needed before this procedure can be routinely integrated into clinical practice.

Wei FF et al. Diagnosis and management of resistant hypertension: state of the art. *Nat Rev Nephrol*. 2018;14:428. [PMID: 29700488]

## HYPERTENSIVE URGENCIES & EMERGENCIES

**Hypertensive urgencies** are situations in which blood pressure must be reduced within a few hours. These include patients with asymptomatic severe hypertension (systolic blood pressure greater than 220 mm Hg or diastolic pressure greater than 125 mm Hg that persists after a period of observation) and those with optic disk edema, progressive target-organ complications, and severe perioperative hypertension. Elevated blood pressure levels alone—in the absence of symptoms of new or progressive target-organ damage—rarely require emergency therapy. Parenteral drug therapy is not usually required; partial reduction of blood pressure with relief of symptoms is the

goal. Effective oral agents are clonidine, captopril, and slow-release nifedipine.

**Hypertensive emergencies** require substantial reduction of blood pressure within 1 hour to avoid the risk of serious morbidity or death. Although blood pressure is usually strikingly elevated (diastolic pressure greater than 130 mm Hg), the correlation between pressure and end-organ damage is often poor. *It is the presence of critical multiple end-organ injury that determines the seriousness of the emergency and the approach to treatment.* Emergencies include hypertensive encephalopathy (headache, irritability, confusion, and altered mental status due to cerebrovascular spasm), hypertensive nephropathy (hematuria, proteinuria, and acute kidney injury due to arteriolar necrosis and intimal hyperplasia of the interlobular arteries), intracranial hemorrhage, aortic dissection, preeclampsia-eclampsia, pulmonary edema, unstable angina, or myocardial infarction. Encephalopathy or nephropathy accompanying hypertensive retinopathy has historically been called malignant hypertension, but the therapeutic approach is identical to that used in other hypertensive emergencies.

Parenteral therapy is indicated in most hypertensive emergencies, especially if encephalopathy is present. The initial goal in hypertensive emergencies is to reduce the pressure by no more than 25% (within minutes to 1 or 2 hours) and then toward a level of 160/100 mm Hg within 2–6 hours. Excessive reductions in pressure may precipitate coronary, cerebral, or renal ischemia. To avoid such declines, the use of agents that have a predictable, dose-dependent, transient, and progressive antihypertensive effect is preferable (Table 11–15). *In that regard, the use of sublingual or oral fast-acting nifedipine preparations is best avoided.*

**Acute ischemic stroke** is often associated with marked elevation of blood pressure, which will usually fall spontaneously. In such cases, antihypertensives should only be used if the systolic blood pressure exceeds 180–200 mm Hg, and blood pressure should be reduced cautiously by 10–15% (Table 11–15). If thrombolytics are to be given, blood pressure should be maintained at less than 185/110 mm Hg during treatment and for 24 hours following treatment.

In **intracerebral hemorrhage**, the aim is to minimize bleeding by reducing the systolic blood pressure in most patients to 130–140 mm Hg within the first 6 hours. In acute subarachnoid hemorrhage, as long as the bleeding source remains uncorrected, a compromise must be struck between preventing further bleeding and maintaining cerebral perfusion in the face of cerebral vasospasm. In this situation, blood pressure goals depend on the patient's usual blood pressure. In previously normotensive patients, the target should be a systolic blood pressure of 110–120 mm Hg; in hypertensive patients, blood pressure should be treated to 20% below baseline pressure. In the treatment of hypertensive emergencies complicated by (or precipitated by) central nervous system injury, labetalol or nicardipine are good choices, since they are nonsedating and do not appear to cause significant increases in cerebral blood flow or intracranial pressure. Patients with subarachnoid hemorrhage should receive nimodipine for 3 weeks following presentation to minimize cerebral vasospasm. *In hypertensive emergencies arising from catecholaminergic mechanisms,*

**Table 11–15.** Treatment of hypertensive emergency depending on primary site of end-organ damage.  
See Table 11–16 for dosages.

| Type of Hypertensive Emergency                                     | Recommended Drug Options and Combinations  | Drugs to Avoid                                      |
|--|--|---|
| Myocardial ischemia and infarction                                 | Nicardipine plus esmolol <sup>1</sup><br>Nitroglycerin plus labetalol<br>Nitroglycerin plus esmolol <sup>1</sup>                     | Hydralazine, diazoxide, minoxidil, nitroprusside    |
| Acute kidney injury  | Fenoldopam<br>Nicardipine<br>Clevidipine   |   |
| Aortic dissection  | Esmolol plus nicardipine<br>Esmolol plus clevidipine<br>Labetalol<br>Esmolol plus nitroprusside                                      | Hydralazine, diazoxide, minoxidil                   |
| Acute pulmonary edema, LV systolic dysfunction                     | Nicardipine plus nitroglycerin <sup>2</sup> plus a loop diuretic<br>Clevidipine plus nitroglycerin <sup>2</sup> plus a loop diuretic | Hydralazine, diazoxide, beta-blockers               |
| Acute pulmonary edema, diastolic dysfunction                       | Esmolol plus low-dose nitroglycerin plus a loop diuretic<br>Labetalol plus low-dose nitroglycerin plus a loop diuretic               |   |
| Ischemic stroke (systolic blood pressure > 180–200 mm Hg)          | Nicardipine<br>Clevidipine<br>Labetalol  | Nitroprusside, methyldopa, clonidine, nitroglycerin |
| Intracerebral hemorrhage (systolic blood pressure > 140–160 mm Hg) | Nicardipine<br>Clevidipine<br>Labetalol  | Nitroprusside, methyldopa, clonidine, nitroglycerin |
| Hyperadrenergic states, including cocaine use                      | Nicardipine plus a benzodiazepine<br>Clevidipine plus a benzodiazepine<br>Phentolamine<br>Labetalol                                  | Beta-blockers                                       |
| Preeclampsia, eclampsia  | Labetalol<br>Nicardipine   | Diuretics, ACE inhibitors                           |

<sup>1</sup>Avoid if there is LV systolic dysfunction.

<sup>2</sup>Drug of choice if LV systolic dysfunction is associated with ischemia.

ACE, angiotensin-converting enzyme; LV, left ventricular.

such as pheochromocytoma or cocaine use, beta-blockers can worsen the hypertension because of unopposed peripheral vasoconstriction; nicardipine, clevidipine, or phentolamine is preferred. Labetalol is useful in these patients if the heart rate must be controlled. Table 11–15 provides guidelines for the choice of antihypertensive agent based on the site of end-organ damage. ACE inhibitors are specifically indicated for hypertensive crisis from systemic sclerosis (scleroderma).

In acute aortic dissection, systolic blood pressure and heart rate should be reduced within 30 minutes to below 120 mm Hg and less than 60 beats per minute, using a combination of vasodilation and beta-blockade.

## ► Pharmacologic Management

### A. Parenteral Agents

Sodium nitroprusside is no longer the treatment of choice for acute hypertensive problems; in most situations, appropriate

control of blood pressure is best achieved using combinations of nicardipine or clevidipine plus labetalol or esmolol. (Table 11–16 lists drugs, dosages, and adverse effects.)

**1. Nicardipine**—Intravenous nicardipine is the most potent and the longest acting of the parenteral calcium channel blockers. As a primarily arterial vasodilator, it has the potential to precipitate reflex tachycardia, and for that reason it should not be used without a beta-blocker in patients with coronary artery disease.

**2. Clevidipine**—Intravenous clevidipine is an L-type calcium channel blocker with a 1-minute half-life, which facilitates swift and tight control of severe hypertension. It acts on arterial resistance vessels and is devoid of venodilatory or cardiodepressant effects.

**3. Labetalol**—This combined beta- and alpha-blocking agent is the most potent adrenergic blocker for rapid blood

**Table 11–16.** Drugs for hypertensive emergencies and urgencies (in descending order of preference).

| Agent                           | Action                    | Dosage   | Onset         | Duration        | Adverse Effects   | Comments   |
|---------------------------------|---------------------------|--|---------------|-----------------|---|--|
| <b>Hypertensive Emergencies</b> |                           |  |               |                 |   |  |
| Nicardipine (Cardene)           | Calcium channel blocker   | 5 mg/h intravenously; may increase by 1–2.5 mg/h every 15 minutes to 15 mg/h   | 1–5 minutes   | 3–6 hours       | Hypotension, tachycardia, headache.   | May precipitate myocardial ischemia.   |
| Clevidipine (Cleviprex)         | Calcium channel blocker   | 1–2 mg/h intravenously initially; double rate every 90 seconds until near goal, then by smaller amounts every 5–10 minutes to a maximum of 32 mg/h | 2–4 minutes   | 5–15 minutes    | Headache, nausea, vomiting.   | Lipid emulsion: contraindicated in patients with allergy to soy or egg.        |
| Labetalol (Trandate)            | Beta- and alpha-blocker   | 20–40 mg intravenously every 10 minutes to 300 mg; 2 mg/min infusion   | 5–10 minutes  | 3–6 hours       | Nausea, hypotension, bronchospasm, bradycardia, heart block.  | Avoid in acute LV systolic dysfunction, asthma. May be continued orally.       |
| Esmolol (Brevibloc)             | Beta-blocker              | Loading dose 500 mcg/kg intravenously over 1 minute; maintenance, 25–200 mcg/kg/min  | 1–2 minutes   | 10–30 minutes   | Bradycardia, nausea.  | Avoid in acute LV systolic dysfunction, asthma. Weak antihypertensive.         |
| Fenoldopam (Corlopam)           | Dopamine receptor agonist | 0.1–1.6 mcg/kg/min intravenously   | 4–5 minutes   | < 10 minutes    | Reflex tachycardia, hypotension, increased intraocular pressure.  | May protect kidney function.   |
| Enalaprilat (Vasotec)           | ACE inhibitor             | 1.25 mg intravenously every 6 hours  | 15 minutes    | 6 hours or more | Excessive hypotension.  | Additive with diuretics; may be continued orally.                              |
| Furosemide (Lasix)              | Diuretic                  | 10–80 mg orally or intravenously   | 15 minutes    | 4 hours         | Hypokalemia, hypotension.   | Adjunct to vasodilator.  |
| Hydralazine (Apresoline)        | Vasodilator               | 5–20 mg intravenously; may repeat after 20 minutes   | 10–30 minutes | 2–6 hours       | Tachycardia, headache, vomiting, diarrhea   | Avoid in coronary artery disease, dissection. Rarely used except in pregnancy. |
| Nitroglycerin                   | Vasodilator               | 0.25–5 mcg/kg/min intravenously  | 2–5 minutes   | 3–5 minutes     | Headache, nausea, hypotension, bradycardia.   | Tolerance may develop. Useful primarily with myocardial ischemia.              |
| Nitroprusside (Nitropress)      | Vasodilator               | 0.25–10 mcg/kg/min intravenously   | Seconds       | 3–5 minutes     | Anxiety, increased intracranial pressure, vomiting, bowel obstruction; thiocyanate and cyanide toxicity, especially with kidney and liver dysfunction; hypotension. Coronary steal, decreased cerebral blood flow, increased intracranial pressure. | No longer the first-line agent.  |
| <b>Hypertensive Urgencies</b>   |                           |  |               |                 |   |  |
| Clonidine (Catapres)            | Central sympatholytic     | 0.1–0.2 mg orally initially; then 0.1 mg every hour to 0.8 mg orally   | 30–60 minutes | 6–8 hours       | Sedation.   | Rebound may occur.   |
| Captopril (Capoten)             | ACE inhibitor             | 12.5–25 mg orally  | 15–30 minutes | 4–6 hours       | Excessive hypotension.  |  |
| Nifedipine (Adalat, Procardia)  | Calcium channel blocker   | 10 mg orally initially; may be repeated after 30 minutes   | 15 minutes    | 2–6 hours       | Excessive hypotension, tachycardia, headache, angina, myocardial infarction, stroke.  | Response unpredictable.  |

ACE, angiotensin-converting enzyme; CNS, central nervous system; GI, gastrointestinal; LV, left ventricular.

pressure reduction. Other beta-blockers are far less potent. Excessive blood pressure drops are unusual. Experience with this agent in hypertensive syndromes associated with pregnancy has been favorable.

**4. Esmolol**—This rapidly acting beta-blocker is approved only for treatment of supraventricular tachycardia, but is often used for lowering blood pressure. It is less potent than labetalol and should be reserved for patients in whom there is particular concern about serious adverse events related to beta-blockers.

**5. Fenoldopam**—Fenoldopam is a peripheral dopamine-1 (DA<sub>1</sub>) receptor agonist that causes a dose-dependent reduction in arterial pressure without evidence of tolerance, rebound, withdrawal, or deterioration of kidney function. In higher dosage ranges, tachycardia may occur. This drug is natriuretic, which may simplify volume management in acute kidney injury.

**6. Enalaprilat**—This is the active form of the oral ACE inhibitor enalapril. The onset of action is usually within 15 minutes, but the peak effect may be delayed for up to 6 hours. Thus, enalaprilat is used primarily as an adjunctive agent.

**7. Diuretics**—Intravenous loop diuretics can be very helpful when the patient has signs of heart failure or fluid retention, but the onset of their hypotensive response is slow, making them an adjunct rather than a primary agent for hypertensive emergencies. Low dosages should be used initially (furosemide, 20 mg, or bumetanide, 0.5 mg). They facilitate the response to vasodilators, which often stimulate fluid retention.

**8. Hydralazine**—Hydralazine can be given intravenously or intramuscularly, but its effect is less predictable than that of other drugs in this group. It produces reflex tachycardia and should not be given without beta-blockers in patients with possible coronary disease or aortic dissection. Hydralazine is used primarily in pregnancy and in children, but even in these situations, it is not a first-line drug.

**9. Nitroglycerin, intravenous**—This agent should be reserved for patients with accompanying acute coronary ischemic syndromes.

**10. Nitroprusside sodium**—This agent is given by controlled intravenous infusion gradually titrated to the

desired effect. It lowers the blood pressure within seconds by direct arteriolar and venous dilation. Monitoring with an intra-arterial line avoids hypotension. Nitroprusside—in combination with a beta-blocker—is useful in patients with aortic dissection.

## B. Oral Agents

Patients with less severe acute hypertensive syndromes can often be treated with oral therapy. Suitable drugs will reduce the blood pressure over a period of hours. In those presenting as a consequence of noncompliance, it is usually sufficient to restore the patient's previously established oral regimen.

**1. Clonidine**—Clonidine, 0.2 mg orally initially, followed by 0.1 mg every hour to a total of 0.8 mg, will usually lower blood pressure over a period of several hours. Sedation is frequent, and rebound hypertension may occur if the drug is stopped.

**2. Captopril**—Captopril, 12.5–25 mg orally, will also lower blood pressure in 15–30 minutes. The response is variable and may be excessive. Captopril is the drug of choice in the management of systemic sclerosis hypertensive crisis.

**3. Nifedipine**—The effect of fast-acting nifedipine capsules is unpredictable and may be excessive, resulting in hypotension and reflex tachycardia. Because myocardial infarction and stroke have been reported in this setting, the use of sublingual nifedipine is not advised. Nifedipine retard, 20 mg orally, appears to be safe and effective.

## C. Subsequent Therapy

When the blood pressure has been brought under control, combinations of oral antihypertensive agents can be added as parenteral drugs are tapered off over a period of 2–3 days.

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# Blood Vessel & Lymphatic Disorders

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# 12

## ATHEROSCLEROTIC PERIPHERAL VASCULAR DISEASE

### OCCLUSIVE DISEASE: AORTA & ILIAC ARTERIES



#### ESSENTIALS OF DIAGNOSIS

- ▶ Claudication: cramping pain or tiredness in the calf, thigh, or hip while walking.
- ▶ Diminished femoral pulses.
- ▶ Tissue loss (ulceration, gangrene) or rest pain.

#### ► General Considerations

Occlusive atherosclerotic lesions developing in the extremities, or peripheral artery disease (PAD), is evidence of a systemic atherosclerotic process. The prevalence of PAD is 30% in patients who are 70 years old without other risk factors, or 50 years old with risk factors such as diabetes mellitus or tobacco use. Pathologic changes of atherosclerosis may be diffuse, but flow-limiting stenoses occur segmentally. In the lower extremities, stenoses classically occur in three anatomic segments: the aortoiliac segment, femoral-popliteal segment, and the infrapopliteal or tibial segment of the arterial tree. Lesions in the distal aorta and proximal common iliac arteries classically occur in White male smokers aged 50–60 years. Disease progression may lead to complete occlusion of one or both common iliac arteries, which can precipitate occlusion of the entire abdominal aorta to the level of the renal arteries.

#### ► Clinical Findings

##### A. Symptoms and Signs

Approximately two-thirds of patients with PAD are either asymptomatic or do not have classic symptoms. Intermittent claudication, which is pain with ambulation that occurs from insufficient blood flow relative to demand, is typically

described as severe and cramping and primarily in the calf muscles. The pain from aortoiliac lesions may extend into the thigh and buttocks and erectile dysfunction may occur from bilateral common iliac disease. Rarely, patients complain only of weakness in the legs when walking, or simply extreme limb fatigue. The symptoms are relieved with rest and are reproducible when the patient walks again. Femoral pulses and distal pulses are absent or very weak. Bruits may be heard over the aorta, iliac, and femoral arteries.

#### B. Doppler and Vascular Findings

The ratio of systolic blood pressure detected by Doppler examination at the ankle compared with the brachial artery (referred to as the ankle-brachial index [ABI]) is reduced to below 0.9 (normal ratio is 0.9–1.2); this difference is exaggerated by exercise. Both the dorsalis pedis and the posterior tibial arteries are measured and the higher of the two artery pressures is used for calculation. Segmental waveforms or pulse volume recordings obtained by strain gauge technology through blood pressure cuffs demonstrate blunting of the arterial inflow throughout the lower extremity.

#### C. Imaging

CT angiography (CTA) and magnetic resonance angiography (MRA) can identify the anatomic location of disease. Due to overlying bowel, duplex ultrasound has a limited role in imaging the aortoiliac segment. Imaging is required only when symptoms necessitate intervention, since a history and physical examination with vascular testing should appropriately identify the involved levels of the arterial tree.

#### ► Treatment

##### A. Medical and Exercise Therapy

The cornerstones of PAD treatment are cardiovascular risk factor reduction and a supervised or structured exercise program. Essential elements include smoking cessation, antiplatelet therapy, lipid and blood pressure management, and weight loss. Nicotine replacement therapy, bupropion, and varenicline have established benefits in smoking cessation (see Chapter 1). Antiplatelet agents (aspirin, 81 mg orally daily, or clopidogrel, 75 mg orally daily) reduce overall

cardiovascular morbidity. Low-dose rivaroxaban (2.5 mg orally twice daily) with aspirin 100 mg orally daily reduces both major cardiovascular and limb-related adverse events in symptomatic patients. All patients with PAD should receive high-dose statin (eg, atorvastatin 80 mg daily if tolerated) to treat hypercholesterolemia and inflammation. A trial of cilostazol 100 mg orally twice a day, may improve walking distance in approximately two-thirds of patients.

Supervised exercise programs for PAD provide significant improvements in pain, walking distance, and quality of life and may be more effective than an endovascular treatment alone. A minimum training goal is a walking session of 30–45 minutes at least 3 days per week for a minimum of 12 weeks. Structured community or home-based exercise programs as well as alternative exercises (cycling, upper-body ergometry) may also be effective.

### B. Endovascular Therapy

When the atherosclerotic lesions are focal, they can be effectively treated with angioplasty and stenting. This approach matches the results of surgery for single stenoses but both effectiveness and durability decrease with longer or multiple stenoses.

### C. Surgical Intervention

A prosthetic aorto-femoral bypass graft that bypasses the diseased artery segments is a highly effective and durable treatment for this disease. Patients may also be treated with a graft from the axillary artery to the femoral arteries (axillo-femoral bypass graft) or with a graft from the contralateral femoral artery (femoral-femoral bypass) when iliac disease is limited to one side. The operative risk of axillo-femoral and femoral-to-femoral bypass grafts is lower because the abdominal cavity is not entered and the aorta is not cross-clamped, but the grafts are less durable.

### ► Complications

The complications of the aorto-femoral bypass are those of any major abdominal surgery in a patient population with a high prevalence of cardiovascular disease. Mortality is low (2–3%), but morbidity is higher and includes a 5–10% rate of myocardial infarction. While endovascular approaches are safer and the complication rate is 1–3%, they are less durable with extensive disease.

### ► Prognosis

Patients with isolated aortoiliac disease may have a further reduction in walking distance without intervention, but symptoms rarely progress to rest pain or threatened limb loss. Life expectancy is limited by their attendant cardiovascular disease with a mortality rate of 25–40% at 5 years.

Symptomatic relief is generally excellent with supervised exercise or after intervention. After aorto-femoral bypass, a patency rate of 90% at 5 years is common. Endovascular patency rates and symptom relief for patients with short stenoses are also good with 80% symptom free at 3 years. Recurrence rates following endovascular treatment of extensive disease are 30–50%.

### ► When to Refer

Patients with progressive reduction in walking distance in spite of risk factor modification and supervised exercise programs and those with limitations that interfere with their activities of daily living should be referred for consultation to a vascular surgeon.

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## OCCLUSIVE DISEASE: FEMORAL & POPLITEAL ARTERIES



### ESSENTIALS OF DIAGNOSIS

- ▶ Cramping pain or tiredness in the calf with exercise.
- ▶ Reduced popliteal and pedal pulses.
- ▶ Foot pain at rest, relieved by dependency.
- ▶ Foot gangrene or ischemic ulcers.

### ► General Considerations

The superficial femoral artery is the peripheral artery most commonly occluded by atherosclerosis. Atherosclerosis of the femoral-popliteal segment usually occurs about a decade after the development of aortoiliac disease, has an even gender distribution, and commonly affects Black and Hispanic patients. The disease frequently occurs where the superficial femoral artery passes through the abductor magnus tendon in the distal thigh (Hunter canal). The common femoral artery and the popliteal artery are less often diseased but lesions in these vessels are debilitating, resulting in short-distance claudication.

### ► Clinical Findings

#### A. Symptoms and Signs

Symptoms of intermittent claudication caused by lesions of the common femoral artery, superficial femoral artery, and popliteal artery are confined to the calf. Claudication occurs at 2–4 blocks when there is occlusion or stenosis of the superficial femoral artery at the adductor canal, provided good collateral vessels from the profunda femoris are maintained. However, with concomitant disease of the profunda femoris or the popliteal artery, much shorter distances may trigger symptoms. With short-distance claudication, dependent rubor of the foot with blanching on elevation may be present. Chronic low blood flow states will also cause atrophic changes in the lower leg and foot.

with loss of hair, thinning of the skin and subcutaneous tissues, and disuse atrophy of the muscles. With segmental occlusive disease of the superficial femoral artery, the common femoral pulsation is normal, but the popliteal and pedal pulses are reduced.

### B. Doppler and Vascular Findings

ABI values less than 0.9 are diagnostic of PAD and levels below 0.4 suggest chronic limb-threatening ischemia (formerly critical limb ischemia). ABI readings depend on arterial compression. Since the vessels may be calcified in diabetes mellitus, chronic kidney disease, and in older adults, ABIs can be misleading. In such patients, the toe-brachial index is usually reliable with a value less than 0.7 considered diagnostic of PAD. Pulse volume recordings with cuffs placed at the high thigh, mid-thigh, calf, and ankle will delineate the levels of obstruction with reduced pressures and blunted waveforms.

### C. Imaging

Duplex ultrasonography, CTA, and MRA all adequately show the anatomic location of the obstructive lesions and are done only if revascularization is planned.

## Treatment

### A. Medical and Exercise Therapy

As with aortoiliac disease, risk factor reduction, medical optimization with a high-dose statin, and exercise treatment are the cornerstone of therapy. Cilostazol, 100 mg orally twice a day, may improve intermittent claudication symptoms.

### B. Surgical Intervention

Intervention is indicated if claudication is progressive, incapacitating, or interferes significantly with essential daily activities or employment. Intervention is mandatory if there is ischemic rest pain or ischemic ulcers threaten the foot.

**1. Bypass surgery**—The most effective and durable treatment for lesions of the superficial femoral artery is a femoral-popliteal bypass with autologous saphenous vein. Synthetic material, usually polytetrafluoroethylene (PTFE), can be used, but these grafts do not have the durability of vein bypass.

**2. Endovascular surgery**—Endovascular techniques, such as angioplasty and stenting, are often used for lesions of the superficial femoral artery. These techniques have lower morbidity than bypass surgery but also have lower rates of durability.

Endovascular therapy is most effective in patients undergoing aggressive risk factor modification in whom lesions measure less than 10 cm long. Paclitaxel-eluting stents or paclitaxel-coated balloons offer modest improvement over bare metal stents and noncoated balloons, but the effect is not as robust as in the coronary arteries. The 1-year patency rate is 50% for balloon angioplasty, 70% for drug-coated balloons, and 80% for stents. However, by 3 years, the patency rates are significantly worse for all three techniques and reintervention for restenosis is common.

After a meta-analysis of clinical trial data showed increased mortality at 3–5 years after treatment with paclitaxel-coated devices, the US FDA performed an independent review and recommends judicious use of the devices. Ongoing trials, such as SWEDEPAD, are expected to provide additional data on the risks and benefits of paclitaxel devices.

**3. Thromboendarterectomy**—Removal of the atherosclerotic plaque is limited to the lesions of the common femoral and the profunda femoris arteries where bypass grafts and endovascular techniques have a more limited role.

## Complications

Open surgical procedures of the lower extremities, particularly long bypasses with vein harvest, have a risk of wound infection that is higher than in other areas of the body. Wound infection or seroma can occur in as many as 10–15% of cases. Myocardial infarction rates after open surgery are 5–10%, with a 1–4% mortality rate. Complication rates of endovascular surgery are 1–5%, making these therapies attractive despite their lower durability.

## Prognosis

The prognosis for motivated patients with isolated superficial femoral artery disease is excellent, and surgery is not recommended for mild or moderate claudication in these patients. However, when claudication significantly limits daily activity undermining quality of life and cardiovascular health, intervention may be warranted. All interventions require close postprocedure follow-up with repeated ultrasound surveillance so that recurrent narrowing can be treated promptly with angioplasty or bypass to prevent complete occlusion. The reported patency rate of bypass grafts of the femoral artery, superficial femoral artery, and popliteal artery is 65–70% at 3 years, whereas the patency of angioplasty is less than 50% at 3 years.

Because of the extensive atherosclerotic disease, including associated coronary lesions, 5-year survival with lower extremity PAD is 70% and decreases to 50% when there is involvement of the tibial arteries. However, with aggressive risk factor modification, substantial improvement in longevity has been reported.

## When to Refer

Patients with progressive symptoms, short-distance claudication, rest pain, or any ulceration should be referred to a peripheral vascular specialist.

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## OCCLUSIVE DISEASE: TIBIAL & PEDAL ARTERIES



### ESSENTIALS OF DIAGNOSIS

- ▶ Severe pain of the forefoot that is relieved by dependency (ischemic rest pain).
- ▶ Pain or numbness of the foot with walking.
- ▶ Ulcer or gangrene, and not claudication, is a frequent initial manifestation.
- ▶ Pallor when the foot is elevated.

### ► General Considerations

Occlusive processes of the tibial arteries of the lower leg and pedal arteries in the foot occur primarily in patients with diabetes. There often is extensive calcification of the artery wall.

### ► Clinical Findings

#### A. Symptoms and Signs

Unless there are concomitant lesions in the aortoiliac or femoral/superficial femoral artery segments, the first manifestation of leg ischemia due to tibial artery disease is frequently an ischemic ulcer or foot gangrene, rather than claudication. The presence of ischemic rest pain or ulcers is termed **chronic limb-threatening ischemia** and is associated with the highest rate of amputation. Classically, ischemic rest pain is confined to the dorsum of the foot and is relieved with dependency: the pain does not occur with standing, sitting, or dangling the leg over the edge of the bed. It is severe and burning in character, and because it is present only when recumbent, it may awaken the patient from sleep.

On examination, femoral and popliteal pulses may or may not be present depending on disease extent, but palpable pedal pulses will be absent. Dependent rubor may be prominent with pallor on elevation. The skin of the foot is generally cool, atrophic, and hairless.

#### B. Doppler and Vascular Findings

The ABI is often below 0.4; however, the ABI may be falsely elevated due to calcification of the arterial media layer (Mönckeberg medial calcific sclerosis) and may not be compressible. Toe-brachial indexes are preferred for assessing perfusion and predicting wound healing.

#### C. Imaging

Digital subtraction angiography is the gold standard method to delineate the anatomy of the tibial-popliteal

segment. MRA or CTA is less helpful for detection of lesions in this location due to the small vasculature and other technical issues related to image resolution.

### ► Differential Diagnosis

Because of the high incidence of neuropathy in these patients, it is important to differentiate rest pain from diabetic neuropathic dysesthesia. Leg night cramps cause pain in the leg rather than the foot and should not be confused with ischemic rest pain. Dependent rubor in the presence of a toe wound can often be mistaken for cellulitis; pallor on elevation helps confirm the diagnosis of rubor.

### ► Treatment

Good foot care may prevent ulcers, and most diabetic patients will do well with a conservative regimen. However, if ulcerations appear and there is no significant healing within 2–3 weeks, blood flow studies (ankle-brachial index/toe-brachial index) are indicated. Poor blood flow and a foot ulcer or nightly ischemic rest pain requires expeditious revascularization to avoid a major amputation.

#### A. Bypass and Endovascular Techniques

Bypass with vein to the distal tibial or pedal arteries is an effective therapy to treat rest pain and heal ischemic ulcers of the foot. Because the foot often has relative sparing of vascular disease, these bypasses have had adequate patency rates (70% at 3 years). Fortunately, in nearly all series, limb preservation rates are much higher than patency rates.

Endovascular treatment with plain balloon angioplasty is effective for short segment lesions. The technical failure and reocclusion rates increase drastically with long segment disease in multiple tibial arteries. Stents and drug-coated balloons have not been successful in the tibial vessels to date.

#### B. Amputation

Patients with ischemic rest pain or ulcers have a 30–40% 1-year risk for major amputation that increases if revascularization cannot be done. Patients with diabetes and PAD have a 4-fold risk of chronic limb-threatening ischemia compared with nondiabetic patients with PAD and have a risk of amputation up to 20-fold when compared to an age-matched population. Many patients who have below-the-knee or above-the-knee amputations due to vascular insufficiency never regain independent ambulatory status and often need assisted-living facilities. These factors combine to demand revascularization whenever possible to preserve the limb.

### ► Complications

The complications of intervention are similar to those listed for superficial femoral artery disease with evidence that the overall cardiovascular risk of intervention increases with decreasing ABI. Patients with chronic limb-threatening ischemia require aggressive risk factor modification. Wound infection rates after bypass are higher if there is an open wound in the foot.

## ► Prognosis

Patients with tibial atherosclerosis have extensive atherosclerotic burden and a high prevalence of diabetes. Their prognosis without intervention is poor and complicated by the risk of amputation.

## ► When to Refer

Patients with diabetes and foot ulcers should be referred for a formal vascular evaluation. Intervention may not be necessary but the severity of the disease will be quantified, which has implications for future symptom development. Any patient with an ulcer and a diabetic foot infection should be evaluated for an emergent operative incision and drainage. Broad-spectrum intravenous antibiotics should be given empirically; for example, vancomycin should be given to cover methicillin-resistant *Staphylococcus aureus* (MRSA) and ertapenem or piperacillin/tazobactam should be given to cover gram-negative and anaerobic organisms. Centers that have a multidisciplinary limb preservation center staffed with vascular surgeons, podiatrists, plastic and orthopedic surgeons, prosthetics and orthotic specialists, and diabetes specialists should be sought.

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## ACUTE ARTERIAL OCCLUSION OF A LIMB

### ESSENTIALS OF DIAGNOSIS

- ▶ Sudden pain in a limb with absent limb pulses.
- ▶ Usually some neurologic dysfunction with numbness, weakness, or complete paralysis.
- ▶ Loss of light touch sensation requires revascularization within 3 hours for limb viability.

## ► General Considerations

Acute occlusion may be due to an embolus or to thrombosis of a diseased atherosclerotic segment. Emboli large enough to occlude proximal arteries in the lower extremities are almost always from the heart and are related to atrial fibrillation. Over 50% of the emboli from the heart go to the lower extremities, 20% to the cerebrovascular circulation, and the remainder to the upper extremities and mesenteric and renal circulation. Atrial fibrillation is the most common cause of cardiac thrombus formation; other causes are valvular disease or thrombus formation on the ventricular surface of a large anterior myocardial infarct.

Emboli from arterial sources such as arterial ulcerations or calcified excrescences are usually small and go to the distal arterial tree (toes).

The typical patient with primary thrombosis has had a history of claudication and now has an acute occlusion. If the stenosis is chronic, collateral blood vessels will develop, and the resulting occlusion may cause only minimal increase in symptoms.

## ► Clinical Findings

### A. Symptoms and Signs

The sudden onset of extremity pain, with loss or reduction in pulses, is diagnostic of acute arterial occlusion. This often will be accompanied by neurologic dysfunction, such as numbness or paralysis in extreme cases. With popliteal occlusion, symptoms may affect only the foot. With proximal occlusions, the whole leg may be affected. Signs of severe arterial ischemia include pallor, coolness of the extremity, and mottling. Impaired neurologic function progressing to anesthesia with paralysis indicates irreversible injury requiring amputation.

### B. Doppler and Laboratory Findings

There will be little or no flow found with Doppler examination of the distal vessels. Imaging, if done, may show an abrupt cutoff of contrast with embolic occlusion. Blood work may show myoglobinemia and metabolic acidosis.

### C. Imaging

Whenever possible, imaging should be done in the operating room because obtaining angiography, MRA, or CTA may delay revascularization and jeopardize the viability of the extremity. However, in cases with only modest symptoms and where light touch of the extremity is maintained, imaging may be helpful in planning the revascularization procedure.

## ► Treatment

Immediate revascularization is required in all cases of symptomatic acute arterial thrombosis. *Evidence of neurologic injury, including loss of light touch sensation, indicates that collateral flow is inadequate to maintain limb viability and revascularization should be accomplished within 3 hours.* Longer delays carry a significant risk of irreversible tissue damage. This risk approaches 100% at 6 hours.

### A. Heparin

As soon as the diagnosis is made, unfractionated heparin should be administered (5000–10,000 units) intravenously, followed by a heparin infusion to maintain the activated partial thromboplastin time (aPTT) in the therapeutic range (60–85 seconds) (12–18 units/kg/h). This helps prevent clot propagation and may also help relieve associated vessel spasm. Anticoagulation may improve symptoms, but revascularization will still be required.

### B. Endovascular Techniques

Pharmacomechanical thrombectomy catheters can achieve rapid revascularization and are most effective for the smaller arteries of the lower leg. Catheter-directed chemical thrombolysis into the clot with tissue plasminogen activator (TPA) may be done but often requires 24 hours or

longer to fully lyse the thrombus. This approach can be taken only in patients with an intact neurologic examination without absolute contraindications, such as bleeding diathesis, gastrointestinal bleeding, intracranial trauma, or neurosurgery within the past 3 months. Heparin is administered systemically to prevent thrombus formation around the sheath. Frequent vascular and access site examinations are required during the thrombolytic procedure to guard against the development of a hematoma.

### C. Surgical Intervention

General anesthesia is usually indicated; local anesthesia may be used in extremely high-risk patients if the exploration is to be limited to the common femoral artery. In extreme cases, it may be necessary to perform thromboembolectomy from the femoral, popliteal, and even the pedal vessels to revascularize the limb. The combined use of devices that pulverize and aspirate clot and intraoperative thrombolysis with TPA improves outcomes.

### ► Complications

Complications of revascularization of an acutely ischemic limb can include severe metabolic acidosis, hyperkalemia, acute kidney injury, and cardiac arrest. In cases where several hours have elapsed but recovery of viable tissue may still be possible, significant levels of lactic acid, potassium, and other harmful agents such as myoglobin may be released into the circulation during revascularization. Administering sodium bicarbonate (150 mEq NaHCO<sub>3</sub> in 1 L of dextrose 5% in water) prior to reestablishing arterial flow is required. Surgery in the presence of thrombolytic agents and heparin carries a high risk of postoperative wound hematoma.

### ► Prognosis

There is a 10–25% risk of amputation with an acute arterial embolic occlusion, and a 25% or higher in-hospital mortality rate. Prognosis for acute thrombotic occlusion of an atherosclerotic segment is generally better because the collateral flow can maintain extremity viability. The longer-term survival reflects the overall condition of the patient. In high-risk patients, an acute arterial occlusion is associated with a dismal prognosis.

## OCCLUSIVE CEREBROVASCULAR DISEASE



### ESSENTIALS OF DIAGNOSIS

- ▶ Sudden onset of weakness and numbness of an extremity or the face, aphasia, dysarthria, or unilateral blindness (amaurosis fugax).
- ▶ Bruit heard loudest in the mid neck.

### ► General Considerations

Unlike the other vascular territories, symptoms of ischemic cerebrovascular disease are predominantly due to emboli. The ischemia is reversible (transient ischemic attacks

[TIAs]) when collateral flow reestablishes perfusion, but is a sign that the risk of additional emboli and a stroke is high. Most ischemic strokes are due to emboli from the heart. One-quarter of all ischemic strokes may be due to emboli from an arterial source; approximately 90% of these emboli originate from the proximal internal carotid artery, an area uniquely prone to the development of atherosclerosis. Intracranial atherosclerotic lesions are uncommon in western populations but are the most frequent location of cerebrovascular disease in Asian populations.

### ► Clinical Findings

#### A. Symptoms and Signs

Generally, the symptoms of a TIA last only a few seconds to minutes (but may continue up to 24 hours) while a stroke is defined as persistent symptoms beyond 24 hours. The most common lesions associated with carotid disease involve the anterior circulation in the cortex with both motor and sensory involvement. Emboli to the retinal artery cause unilateral blindness; transient monocular blindness is termed “amaurosis fugax.” Posterior circulation symptoms referable to the brainstem, cerebellum, and visual regions of the brain may be due to atherosclerosis of the vertebral basilar systems and are much less common.

Signs of cerebrovascular disease may include carotid artery bruits. However, there is poor correlation between the degree of stenosis and the presence of the bruit. Furthermore, the presence of a bruit does not correlate with stroke risk. Nonfocal symptoms, such as dizziness and unsteadiness, seldom are related to cerebrovascular atherosclerosis.

#### B. Imaging

Duplex ultrasonography is the imaging modality of choice with high specificity and sensitivity for detecting and grading the degree of stenosis at the carotid bifurcation (see Chapter 24).

Excellent depiction of the full anatomy of the cerebrovascular circulation from aortic arch to cranium can be obtained with either MRA or CTA. Each of the modalities may have false-positive or false-negative findings. Since the decision to intervene in cases of carotid stenosis depends on an accurate assessment of the degree of stenosis, it is recommended that at least two modalities be used to confirm the degree of stenosis. Diagnostic cerebral angiography is reserved for cases where carotid artery stenting (CAS) is to be done.

### ► Treatment

See Chapter 24 for a discussion of the medical management of occlusive cerebrovascular disease.

#### A. Asymptomatic Patients

Large studies have shown a 5-year reduction in stroke rate from 11.5% to 5.0% with surgical treatment of asymptomatic carotid stenosis that is greater than 60%; patients with asymptomatic carotid stenosis may benefit from carotid intervention if their risk from intervention is low and their expected survival is longer than 5 years. Aggressive risk