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study suggested that moxifloxacin (400 mg/d PO) is as effective and well tolerated as ampicillin-sulbactam. Notably, metronidazole is not effective as a single agent: it covers anaerobic organisms but not the microaerophilic streptococci that are often components of the mixed flora of primary lung abscesses.

In secondary lung abscesses, antibiotic coverage should be directed at the identified pathogen, and a prolonged course (until resolution of the abscess is documented) is often required. Treat ment regimens and courses vary widely, depending on the immune state of the host and the identified pathogen. Other interventions may be necessary as well, such as relief of an obstructing lesion or treatment directed at the underlying condition predisposing the patient to lung abscess. Similarly, if the condition of patients with presumed primary lung abscess fails to improve, additional studies to rule out an underlying predisposing cause for a secondary lung abscess are indicated. Although it can take as long as 7 days for patients receiving appropriate therapy to defervesce, as many as 10–20% of patients may not respond at all, with continued fevers and progression of the abscess cavity on imaging. An abscess >6–8 cm in diameter is less likely to respond to antibiotic therapy without additional interven tions. Options for patients who do not respond to antibiotics and whose additional diagnostic studies fail to identify a pathogen that can be treated include surgical resection and percutaneous drainage of the abscess, especially when the patient is a poor surgical candi date. Timing of surgical intervention can be challenging; the goal is to balance the morbidity/mortality risk of a procedure with the need for definitively clearing the abscess in the setting of persistent infection that is not responsive to nonsurgical approaches. Possible complications of percutaneous drainage include bacterial contami nation of the pleural space as well as pneumothorax and hemothorax. Traversing normal lung parenchyma might represent a risk factor for major complications from percutaneous abscess drainage. PART 5 Infectious Diseases ■ ■COMPLICATIONS Larger cavity size on presentation may correlate with the development of persistent cystic changes (pneumatoceles) or bronchiectasis. Addi tional possible complications include recurrence of abscesses despite appropriate therapy, extension to the pleural space with development of empyema, life-threatening hemoptysis, and massive aspiration of lung abscess contents. ■ ■PROGNOSIS AND PREVENTION Reported mortality rates for primary abscesses have been as low as 2%, while rates for secondary abscesses are generally higher—as high as 75% in some case series. Other poor prognostic factors include age

> 60, malignancy-related abscesses, the presence of aerobic bacteria, sepsis at presentation, symptom duration of >8 weeks, and abscess size 6 cm. Mitigation of underlying risk factors may be the best approach to prevention of lung abscesses, with attention directed toward airway protection, oral hygiene, and minimized sedation with elevation of the head of the bed for patients at risk for aspiration. Prophylaxis against certain pathogens in at-risk patients (e.g., recipients of bone marrow or solid organ transplants or patients whose immune systems are signifi cantly compromised by HIV infection) may be undertaken. APPROACH TO THE PATIENT Lung Abscess For patients with a lung abscess and a low likelihood of malignancy (e.g., smokers <45 years old) and with risk factors for aspiration, it is reasonable to administer empirical treatment and then to pursue further evaluation if therapy does not elicit a response. However, some clinicians may opt for up-front cultures, even in primary lung abscesses. In patients with risk factors for malignancy or other underlying conditions (especially immunocompromised hosts) or with an atypical presentation, earlier diagnostics should be

considered, such as bronchoscopy with biopsy or CT-guided needle aspiration. Bronchoscopy should be performed early in patients whose history, symptoms, or imaging findings are consistent with possible bronchial obstruction. In patients from areas endemic for tuberculosis or patients with other risk factors for tuberculosis (e.g., underlying HIV infection), induced sputum samples should be examined early in the workup to rule out this disease. ■ ■FURTHER READING Bartlett JG: How important are anaerobic bacteria in aspiration pneumonia: When should they be treated and what is optimal therapy. Infect Dis Clin North Am 27:149, 2013. Desai H, Agrawal A: Pulmonary emergencies: Pneumonia, acute respiratory distress syndrome, lung abscess, and empyema. Med Clin North Am 96:1127, 2012. Lee JH et al: Percutaneous transthoracic catheter drainage for lung abscess: A systematic review and meta-analysis. Eur Radiol 32:1184, 2022. Maitre T et al: Pyogenic lung abscess in an infectious disease unit: A 20-year retrospective study. Ther Adv Respir Dis 17534666211003012, 2021. Ott SR et al: Moxifloxacin vs ampicillin/sulbactam in aspiration pneu monia and primary lung abscess. Infection 36:23, 2008. Raymond D: Surgical intervention for thoracic infections. Surg Clin North Am 94:1283, 2014. Vaarst JK et al: Lung abscess: Clinical characteristics of 222 Danish patients diagnosed from 2016 to 2021. Respir Med 216: 107305, 2023. Sara E. Cosgrove, Michael T. Melia

Infective Endocarditis The prototypic lesion of infective endocarditis (IE), the vegetation (Fig. 133-1), is a mass of platelets, fibrin, microorganisms, and scant inflammatory cells. Infection most commonly involves heart valves but may also occur on the low-pressure side of a ventricular septal defect, on mural endocardium damaged by aberrant jets of blood or foreign bodies, or on intracardiac devices. The analogous process involving arteriovenous shunts, arterio-arterial shunts (patent ductus arteriosus), or a coarctation of the aorta is called infective endarteritis. FIGURE 133-1 Vegetations (arrows) due to viridans streptococci endocarditis involving the mitral valve.

IE can be classified according to the temporal evolution of disease, the site of infection, the cause of infection, or the predisposing risk factor (e.g., injection drug use, health care–associated). Acute IE is a hectically febrile illness that rapidly damages cardiac structures, seeds extracardiac sites,

and, if untreated, progresses to death within weeks. Subacute IE follows an indolent course; causes structural cardiac dam age only slowly, if at all; rarely metastasizes; and is gradually progressive unless complicated by a major embolic event or a ruptured mycotic aneurysm. In the United States and likely in other developed countries, the incidence of IE is estimated to be 15 cases per 100,000 population per year, with progressive increases during recent decades. While con genital heart diseases remain a constant predisposition, predisposing conditions in developed countries have shifted from chronic rheumatic heart disease (still common in developing countries) to injection drug use, degenerative valve disease, and intracardiac devices. Although the incidence of IE is increased among the elderly, recent data indicate age-adjusted mortality rates in people ≥55 years old have declined in the United States. Recently, however, there has been acceleration in mortality in people aged 25–44 years, likely associated with an increase in opioid use disorder (OUD) and injection drug use in this age group. In developed countries, 25–35% of cases of native-valve endocarditis (NVE) are health care–associated, and 16–30% of all cases are pros thetic-valve infections (PVE). The risk of PVE is greatest during the initial year after valve replacement; gradually declines to a low, stable rate thereafter; and is greater for bioprosthetic valves than mechanical valves. The incidence and rate of decline of transcatheter aortic valve replacement (TAVR)-PVE are similar to those for surgically implanted bioprosthetic aortic valves. IE involving cardiovascular implantable electronic devices (CIED-IE)—greater on implanted defibrillators and resynchronization devices than on permanent pacemakers—occurs in 0.5–1.14 cases per 1000 recipients. ■ ■ETIOLOGY Although many species of bacteria and fungi cause sporadic episodes of IE, a few bacterial species cause the majority of cases (Table 133-1). Recent large studies from developed areas identify Staphylococcus aureus as the most common bacterial species causing IE. The oral cavity, skin, and upper respiratory tract are the respective primary portals for viridans streptococci, staphylococci, and HACEK organ isms (Haemophilus species, Aggregatibacter species, Cardiobacterium TABLE 133-1 Organisms Causing Major Clinical Forms of Infective Endocarditis (IE)
NATIVE-VALVE IE COMMUNITY-

ACQUIRED (N = 1718) HEALTH CARE– ASSOCIATED (N = 1110) <2 (N = 144)

> “ 2-12 (N = 31) 12 (N = 194) (N = 295) (N = 337) ORGANISM(S) Streptococcib

Pneumococci

— Enterococcic

Staphylococcus aureus 28a 52d

Coagulase-negative staphylococci

Fastidious gram-negative coccobacilli (HACEK group)e

— — —

— — Gram-negative bacilli

Candida spp. <1

Polymicrobial/miscellaneous

Diphtheroids — <1

—

Culture-negative

aIncludes methicillin-susceptible and -resistant isolates. bIncludes viridans streptococci; Streptococcus gallolyticus; other non–group A, groupable streptococci; and Abiotrophia and Granulicatella spp. (nutritionally variant, pyridoxal-requiring streptococci). cPrimarily E. faecalis or nonspeciated isolates; occasionally E. faecium or other less likely species. dMethicillin resistance is common among these S. aureus strains. eIncludes Haemophilus spp., Aggregatibacter spp., Cardiobacterium hominis, Eikenella corrodens, and Kingella kingae. Abbreviations: CIED, cardiac implantable electronic device; TAVR, transcatheter aortic valve replacement. Note: Data are compiled from multiple studies.

hominis, Eikenella corrodens, and Kingella kingae). Streptococcus gal lolyticus subspecies gallolyticus (formerly S. bovis biotype 1) originates from the gastrointestinal tract and is associated with colonic polyps and tumors. Enterococci enter the bloodstream primarily from the genitourinary tract. Health care–associated IE, most commonly caused by S. aureus, coagulase-negative staphylococci (CoNS), and entero cocci, may have either a nosocomial onset (55%) or a community onset (45%). IE complicates 8–25% of episodes of catheter-associated S. aureus bacteremia; the higher rates are detected in high-risk patients studied by transesophageal echocardiography (TEE) (see “Cardiac Imaging,” below).

PVE arising within 2 months of valve surgery—i.e., early PVE—is generally nosocomial and is the result of intraoperative contamination of the prosthesis or a postoperative infection. This nosocomial origin is reflected in the microbial causes: S. aureus, CoNS, facultative gram-neg ative bacilli, diphtheroids, and fungi. The portals of entry and organisms causing PVE beginning >12 months after surgery—i.e., late PVE—are similar to those in community-acquired NVE. Regardless of the time of onset after surgery, the majority of CoNS strains that cause PVE are resistant to methicillin. The microbiology of TAVR-PVE, while generally similar to that of PVE, is notable for an increased frequency of entero cocci. Risk factors associated with TAVR-PVE include male sex, diabetes, renal failure, and moderate postimplantation aortic valve regurgitation. CIED-IE involves the device or the endothelium at points of device contact. Occasionally, there is concurrent valvular infection. One-third of cases of CIED-IE present within 3 months after device implantation or manipulation, one-third between 3 and 12 months, and one-third

> 1 year. S. aureus and CoNS cause the majority of cases. CHAPTER 133 IE in people who inject drugs (PWID), especially that involving the tricuspid valve, is commonly caused by S. aureus, which is often resis tant to methicillin. Left-sided valve infections in PWID have a more varied etiology. In addition to the usual causes of IE, infection due to Enterobacterales, Pseudomonas aeruginosa, Candida species, and spo radically by unusual organisms (Bacillus, Lactobacillus, Corynebacterium species) is encountered. Infective Endocarditis About 5–15% of patients with IE have negative blood cultures; in one-third to one-half of these cases, cultures are negative because of prior antibiotic exposure. The remainder are infected by fastidious organisms, such as some streptococci; nutritionally variant bacteria now designated Granulicatella, Gemella, and Abiotrophia species; Coxiella burnetii; and Bartonella species. Some fastidious organisms PROPORTION OF CASES PROSTHETIC-VALVE IE AT INDICATED TIME OF ONSET (MONTHS) AFTER VALVE SURGERY TAVR PVE CIED-IE

occur in characteristic geographic settings (e.g., C. burnetii and Barton ella species in Europe, Brucella species in the Middle East). Tropheryma whipplei causes an indolent, culture-negative form of IE. C. burnetii has a predilection for prosthetic valves. Corynebacterium species and Cuti bacterium acnes may involve intracardiac devices and be slow to grow in blood cultures. Mycobacterium chimaera, which may be difficult to recover from blood cultures unless special media is used, has caused a global outbreak of PVE and disseminated infection as a result of aero sols from contaminated heater-cooler machines used during cardiopul monary bypass. Lastly, atrial myxoma, marantic endocarditis, and the antiphospholipid antibody syndrome may mimic culture-negative IE.

■ ■PATHOGENESIS The undamaged endothelium is resistant to infection by most bacteria. Endothelial injury (e.g., at the site of impact of high-velocity blood jets or on the low-pressure side of a cardiac structural lesion) allows either direct infection by virulent organisms or the development of a platelet–fibrin thrombus—a condition called nonbacterial throm botic endocarditis (NBTE). This thrombus serves as a site of bacterial attachment during transient bacteremia. The cardiac conditions most commonly resulting in NBTE are mitral regurgitation, aortic stenosis, aortic regurgitation, ventricular septal defects, and complex congenital heart disease. NBTE also arises as a result of a hypercoagulable state; this phenomenon gives rise to marantic endocarditis (uninfected veg etations seen in patients with malignancy and chronic diseases) and to bland vegetations complicating systemic lupus erythematosus and antiphospholipid antibody syndrome. Organisms that cause IE enter the bloodstream from colonized body surfaces or sites of infection. S. aureus adherence to intact endothelium may be mediated by local inflammation inducing von Willebrand factor on endothelial cell surfaces with resulting adherence of both platelets and S. aureus. Alternatively, S. aureus adherence to injured endothelium may be mediated by local deposition of fibrin and cir culating von Willebrand factor on exposed subendothelial tissue to which in turn S. aureus adhere directly. Other microorganisms in the blood adhere to NBTE. The organisms that commonly cause IE have surface adhesin molecules, collectively called microbial surface com ponents recognizing adhesin matrix molecules (MSCRAMMs) that mediate adherence to NBTE sites or injured endothelium. Adherence is facilitated by fibronectin-binding proteins

present on many grampositive bacteria; by clumping factor (a fibrinogen- and fibrin-binding surface protein) on S. aureus; by fibrinogen-binding surface proteins (Fss2), collagen-binding surface protein (Ace), and Ebp pili (the latter mediating platelet adherence) on Enterococcus faecalis; and by glucans or FimA (a member of the family of oral mucosal adhesins) on strep tococci. Fibronectin-binding proteins are required for S. aureus inva sion of intact endothelium; thus, these surface proteins may facilitate infection of previously normal valves. If resistant to the bactericidal activity of serum and the microbicidal peptides released locally by platelets, adherent organisms proliferate to form dense microcolonies. Microorganisms also induce platelet deposition and a localized pro coagulant state by eliciting tissue factor from the endothelium and, in the case of S. aureus, from monocytes as well. Fibrin deposition combines with platelet aggregation and microorganism proliferation to generate an infected vegetation. Organisms deep in vegetations are metabolically inactive (nongrowing) and relatively resistant to killing by antimicrobial agents. Proliferating surface organisms are shed into the bloodstream continuously. PART 5 Infectious Diseases The clinical manifestations of IE—other than constitutional symp toms, which probably result from cytokine production—arise from damage to intracardiac structures; embolization of vegetation frag ments leading to infection or infarction of remote tissues; hematog enous infection of sites during bacteremia; and tissue injury due to the deposition of circulating immune complexes or immune responses to deposited bacterial antigens. ■ ■CLINICAL MANIFESTATIONS The highly variable clinical IE syndrome spans a continuum between acute and subacute presentations. Most forms of IE share clinical and

TABLE 133-2 Clinical and Laboratory Features of Infective Endocarditis FEATURE FREQUENCY, % Fever 80–90 Chills and sweats 40–75 Anorexia, weight loss, malaise 25–50 Myalgias, arthralgias 15–30 Back pain 7–15 Heart murmur 80–85 New/worsened regurgitant murmur 20–50 Arterial emboli 20–50 Splenomegaly 15–50 Clubbing 10–20 Neurologic manifestations 20–40 Peripheral manifestations (Osler’s nodes, subungual hemorrhages, Janeway lesions, Roth’s spots) 2–15 Petechiae 10–40 Laboratory manifestations Anemia 70–90 Leukocytosis 20–30 Microscopic hematuria 30–50 Elevated erythrocyte sedimentation rate 60–90 Elevated C-reactive protein level

> “ 90 Rheumatoid factor

Circulating immune complexes 65–100 Decreased serum complement 5–40 laboratory manifestations (Table 133-2). The causative microorganism is primarily responsible for the temporal course of IE. β-Hemolytic streptococci, S. aureus, and pneumococci typically result in an acute course, and IE caused by Staphylococcus lugdunensis (a coagulasenegative species) or by enterococci may present acutely. Subacute IE is typically caused by viridans streptococci, enterococci, CoNS, and the HACEK group. IE caused by Bartonella species, T. whipplei, C. burnetii, or M. chimaera is exceptionally indolent. In patients with subacute presentations, fever is typically low-grade, rarely exceeding 39.4°C (103°F); in contrast, temperatures of 39.4°– 40°C (103°–104°F) are often noted in acute IE. Fever may be blunted in patients who are elderly, are severely debilitated, or have renal failure. Cardiac Manifestations Although heart murmurs are usually indicative of the predisposing cardiac pathology rather than of IE, valvular damage and ruptured chordae may result in new regurgitant murmurs. In acute IE involving a normal valve, murmurs may be absent initially but ultimately are detected in 85% of cases. Congestive heart failure (CHF)

resulting from valve dysfunction or, occasion ally, intracardiac fistulae develop in 30–40% of patients. Extension of leaflet infection into adjacent annular or myocardial tissue results in paravalvular abscesses, which in turn may cause intracardiac fistulae with new murmurs. Aortic paravalvular infection may burrow into the upper ventricular septum and interrupt the conduction system, lead ing to varying degrees of heart block. Mitral paravalvular abscesses are more distant from the conduction system and rarely cause conduction abnormalities. Coronary artery emboli occur in 2% of patients and may result in myocardial infarction. Noncardiac Manifestations The classic nonsuppurative periph eral manifestations of subacute IE (e.g., Janeway lesions; Fig. 133-2A) are related to prolonged infection; with early diagnosis and treat ment, these have become infrequent. In contrast, septic embolization mimicking some of these lesions (subungual hemorrhage, Osler's nodes) is common in patients with acute S. aureus IE (Fig. 133-2B). Musculoskeletal pain usually remits promptly with treatment but

A B FIGURE 133-2 A. Janeway lesions on the toe (left) and plantar surface (right) of the foot in subacute Neisseria mucosa infective endocarditis (IE). (Images courtesy of Rachel Baden, MD.) B. Septic emboli with hemorrhage and infarction due to acute Staphylococcus aureus IE. must be distinguished from focal metastatic infections (e.g., spondy lodiscitis), which may complicate 10–15% of cases. Hematogenously seeded focal infection occurs most often in the skin, spleen, kidneys, skeletal system, and meninges. Arterial emboli, one-half of which precede the diagnosis of IE, are clinically apparent in up to 50% of patients. S. aureus IE, mobile vegetations >10 mm in diameter, and infection involving the mitral valve anterior leaflet are independently associated with an increased risk of embolization. Embolic arterial occlusion causes regional pain or ischemia-induced organ dysfunc tion (e.g., of the kidney, spleen, bowel, extremity). Cerebrovascular emboli presenting as strokes or occasionally as encephalopathy com plicate 15–35% of cases; however, evidence of clinically asymptomatic emboli is found on magnetic resonance imaging (MRI) in 30–65% of patients with left-sided IE. The frequency of stroke is 8 per 1000 patient-days during the week prior to diagnosis and decreases to 4.8 and 1.7 per 1000 patient-days during the first and second weeks of effective antimicrobial therapy, respectively. Only 3% of strokes occur after 1 week of effective therapy. Emboli occurring late during or after effective therapy do not in themselves constitute evidence of failed antimicrobial treatment. Other neurologic complications include aseptic or purulent menin gitis, intracranial hemorrhage due to hemorrhagic infarcts or ruptured mycotic aneurysms, and seizures. Mycotic aneurysms are focal dila tions of arteries occurring at points in the artery wall that have been weakened by infection in the vasa vasorum or where septic emboli have lodged. Microabscesses in the brain and meninges occur commonly in S. aureus IE; intracerebral abscesses requiring surgical drainage are infrequent. Immune complex deposition on the glomerular basement mem brane causes diffuse hypocomplementemic glomerulonephritis and renal dysfunction, which typically improve with effective antimicrobial therapy. Embolic renal infarcts cause flank pain and hematuria but rarely renal dysfunction. Splenic infarcts or abscess can manifest as left upper abdominal, pleuritic chest, or left shoulder pain. Manifestations with Specific Predisposing Conditions Among PWID, 35–60% of IE is limited to the tricuspid valve and presents with fever with faint or no murmur and without peripheral manifesta tions. Septic pulmonary emboli, which are common with tricuspid IE, cause cough, pleuritic chest pain, nodular pulmonary infiltrates, and occasionally empyema or pyopneumothorax. Infection of the aortic or mitral valve presents with the typical clinical features of IE, including peripheral manifestations. Health care–associated IE has typical manifestations unless associ ated with an intracardiac device or masked by the symptoms of concur rent illness. CIED-IE may be associated

with obvious (especially within 6 months of device manipulation) or cryptic generator pocket infection or arise through bacteremic seeding without pocket infection. Fever, sepsis, minimal murmur, and occasionally pulmonary symptoms due to septic emboli are seen. Late-onset PVE and TAVR-PVE present with typical clinical features. In early PVE, symptoms may be masked by recent surgery. In both early and late PVE, paravalvular infection is common and often results in partial valve dehiscence, regurgitant murmurs, CHF, or disruption of the conduction system.

■ ■DIAGNOSIS Careful clinical, microbiologic, and echocardiographic evaluations should be pursued when febrile patients have IE predispositions, cardiac or noncardiac (e.g., stroke or splenic infarct) features of IE, or blood cultures yielding an IE-associated organism. Duke Criteria The diagnosis of IE is established with certainty only when vegetations are examined histologically and microbiologi cally. Nevertheless, a common clinical approach utilizes a diagnostic schema based on clinical, laboratory, and echocardiographic findings commonly encountered in patients with IE (Table 133-3). Now known as the Duke–International Society for Cardiovascular Infectious Dis eases (Duke-ISCVID) Criteria for IE, the criteria were updated in 2023 to encompass new epidemiologic data and microbiologic testing and imaging methodologies; these modifications have been validated in at least four bacteremia cohorts and show sensitivity in the 80–93% range. Clinical judgment must be exercised to use the criteria effectively. A clinical diagnosis of definite IE requires two major criteria, one major and three minor criteria, or five minor criteria. IE is rejected if an alternative diagnosis is established, if there is no recurrence despite therapy for <4 days, or if surgery or autopsy after <4 days of antimicro bial therapy yields no histologic evidence of IE. Cases not classified as definite or rejected are considered possible IE when either one major and one minor criterion or three minor criteria are fulfilled. Absent extenuating circumstances, patients with definite and possible IE are treated as having IE. CHAPTER 133 Infective Endocarditis Blood Cultures The Duke-ISCVID Criteria reiterate that multiple blood cultures are the gold standard for diagnosing IE. Collection of three cultures from separate venipuncture sites is still recommended but is no longer required. Further, the bacterial species considered “typical” for causing IE are defined as those whose recovery from blood has been strongly associated with IE; the pathogen list has been expanded to include all streptococcal species except S. pneumoniae and S. pyogenes, S. lugdunensis, E. faecalis regardless of the primary source, and “streptococcus-like bacteria” (e.g., Granulicatella spp., Abiotrophia spp., and Gemella spp.). To fulfill a major criterion, a typical organism that causes IE (e.g., those listed previously plus S. aureus and HACEK organisms) must be recovered in two or more blood culture sets; other organisms, considered “nontypical” must grow in three or more blood culture sets and the clinical presentation must be unexplained by an extracardiac focus of infection. In patients with intracardiac prosthetic material, CoNS, Corynebacterium striatum, Corynebacterium jeikeium, C. acnes, Serratia marcescens, Pseudomonas aeruginosa, nontubercu lous mycobacteria (e.g., M. chimaerae), and Candida species should be considered “typical.” Otherwise these organisms must be found in three or more blood culture sets to satisfy a major criterion. In patients with suspected NVE, PVE, TAVR-PVE, or CIED-IE who have not received antibiotics during the prior 2 weeks, three twobottle blood culture sets containing the appropriate volume of blood (10 mL per bottle) should be obtained, ideally from different venipunc ture sites. If the cultures remain negative after 48–72 h, two or three additional blood culture sets should be obtained, and the laboratory should be consulted for advice regarding optimal culture techniques.

TABLE 133-3 The Modified Duke Criteria for the Clinical Diagnosis of Infective Endocarditis (IE)a Major Criteria A. Microbiologic Criteria 1. Positive blood culture Microorganism that commonly cause IE in 2 or more separate blood culture sets (Typical—i.e., S. aureus, S. lugdunensis, E. faecalis, all streptococcal species except S. pneumoniae and S. pyogenes, Granulicatella spp., Abiotrophia spp., Gemella spp., HACEK group organisms and in the setting of intracardiac prosthetic material, CoNS, C. striatum, C. jeikeium, S. marcescens, P. aeruginosa, C. acnes, nontuberculosis mycobacteria, Candida spp.) or Microorganisms that occasionally or rarely cause IE isolated from 3 or more separate blood culture sets (Nontypical) 2. Positive laboratory tests Positive polymerase chain reaction (PCR) for Coxiella burnetti, Bartonella spp., or Tropheryma whipplei from blood or Single blood culture growing C. burnetti or phase I IgG Ab titer ≥ 1:800 or Indirect immunofluorescence assays (IFA) for IgM Ab and IgG Ab to

B. henselae or B. quintana with IgG Ab titer ≥ 1:800 B. Imaging Criteria 1. Echocardiography or cardiac CT showing vegetation, valvular/leaflet perforation/aneurysm, abscess, pseudoaneurysm or intracardiac fistula or New valvular regurgitation (new/worsening murmur is NOT sufficient; requires echocardiographic evidence) or New prosthetic valve dehiscence/insufficiency 2. FDG-PET/CT with abnormal metabolic activity involving a native or PART 5 Infectious Diseases prosthetic valve, ascending aortic graft, intracardiac device leads, or other prosthetic material C. Surgical Criteria Evidence of IE documented by direct inspection during heart surgery Minor Criteria A. Predisposition: previous history of IE, injection drug use, prosthetic valve, previous valve repair, congenital heart disease (e.g., bicuspid AV), CIED, more than mild regurgitation or stenosis, hypertrophic cardiomyopathy B. Fever: T > 38.0°C (100.4°F) C. Vascular phenomenon: arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhage, Janeway lesions, cerebral/splenic abscesses, purulent purpura D. Immunologic phenomena: glomerulonephritis, Osler nodes, Roth spots, positive rheumatoid factor E. Microbiologic evidence: positive blood cultures (not meeting above criteria) or Positive culture, PCR, or other nucleic acid-based test for an organism consistent with IE from a non-endovascular site or single finding of a skin bacterium by PCR on a valve or wire without additional clinical or microbiological supporting evidence F. Imaging criteria: abnormal metabolic activity on FDG-PET/CT within 3 months of implantation of a prosthetic valve, ascending aortic graft, intracardiac device lead G. Physical exam criteria: New valvular regurgitation on auscultation DIAGNOSIS Definite IE: 1. Pathologic criteria (microorganisms or active endocarditis identified in a vegetation/intra-cardiac abscess from cardiac tissue, prosthetic material, arterial embolus) 2. Clinical criteria (2 major or 1 major + 3 minor or 5 minor) Possible IE: 1 major + 1 minor or 3 minor Rejected IE: does not meet above criteria or firm alternative dx or lack of recurrence with <4 days of antibiotics or no evidence on autopsy Abbreviations: Ab, antibody; AV, aortic valve; CIED, cardiac implantable electronic device; CoNS, coagulase-negative staphylococci; CT, computed tomography; FDG, 18F-fluorodeoxyglucose; HACEK, Haemophilus species, Aggregatibacter species, Cardiobacterium hominis, Eikenella corrodens, and Kingella kingae; PET, positron emission tomography. Source: Reproduced with permission from VG Fowler Jr et al: The 2023 DukeInternational Society for Cardiovascular Infectious Diseases criteria for infective endocarditis: Updating the modified Duke criteria. Clin Infect Dis. 77:518, 2023, Table 2.

Pending culture results, empirical antimicrobial therapy should be withheld initially from hemodynamically and clinically stable patients with suspected subacute IE, especially those who have received antibiotics within the preceding 2 weeks. The delay allows blood for additional

cultures to be obtained without the confounding effect of empirical treatment. Patients with sepsis or deteriorating hemodynam ics who may require urgent surgery should receive empirical treatment immediately after the initial three sets of blood cultures are obtained. Non–Blood Culture Tests Non–blood culture laboratory criteria have been added to microbiologic major criteria in the Duke-ISCVID Criteria to implicate organisms that are difficult to recover by blood culture. These include polymerase chain reaction (PCR) or other nucleic acid–based techniques identifying C. burnetii, Bartonella spp., or T. whipplei from the blood and indirect immunofluorescence assays for IgM and IgG antibodies to Bartonella henselae or B. quintana with IgG titer ≥1:800. Next-generation (shotgun metagenomic) sequenc ing of pathogen DNA from serum has emerged as a novel nonculture technology capable of identifying a wide array of organisms in blood culture–negative IE. However, Duke-ISCVID Criteria recommend results from such testing that yield organisms other than C. burnetii, Bartonella spp., or T. whipplei be considered minor criteria at this time. In vegetations recovered at surgery or by embolectomy, pathogens can be identified by culture and histopathologic examination with spe cial stains. A sample of the vegetation should be collected using sterile technique and saved for molecular testing using PCR with organismspecific primers (e.g., C. burnetii, Bartonella, T. whipplei, C. acnes, Mycoplasma hominis) or broad-range PCR targeting 16S ribosomal RNA (or 28S rRNA, if fungi are suspected) followed by sequencing for organism identification. Histopathology may inform the selection of specific molecular tests. Molecular testing is a useful diagnostic tech nology when the histopathology of a vegetation is consistent with IE; however, it cannot be used to establish the viability of residual bacteria in vegetations. Additionally, molecular testing is only moderately sensi tive, and thus, a negative test cannot exclude IE. When tissue is limited, molecular testing should be prioritized over culture. Cardiac Imaging Echocardiography anatomically confirms and measures vegetations, detects intracardiac complications, and assesses cardiac function. Transthoracic echocardiography (TTE) is exception ally specific; however, in 20% of patients, the images are inadequate. TTE fails to detect vegetations in 20–35% of patients with definite clinical IE, missing vegetations <2 mm in diameter. It is not optimal for evaluating prosthetic valves, especially TAVR with large stents, or detecting intracardiac complications. TEE detects vegetations in >90% of patients with definite IE; nevertheless, initial studies may yield falsenegative results in 6–18% of IE patients, especially in TAVR-PVE. A negative TEE, when IE is likely, does not exclude the diagnosis but rather warrants repeating the study in 7–10 days. TEE is sometimes augmented by three-dimensional TEE, which can better visualize veg etations and perivalvular extension of infection. Other imaging should be pursued when anatomic confirmation of IE is unclear, when TEE is not confirmatory or is contraindicated, and in suspected PVE. Electrocardiographic-gated multislice cardiac CT angiogram (CTA), which is less sensitive than TEE in detection of vegetations, valvular perforation, and paravalvular leakage but superior in defining pseudoaneurysm or abscess, may be definitive. Further, it can be used in lieu of preoperative cardiac catheterization to assess coronary artery patency in patients at low to intermediate risk of coronary disease. 18F-Fluorodeoxyglucose positron emission tomog raphy (FDG-PET)/CT is less sensitive than TEE or CTA in detecting intracardiac pathology in NVE or CIED-IE but provides increased sensitivity in assessing suspected PVE, including TAVR-PVE, infection of ascending aorta grafts, extracardiac complications, left ventricular assist device (LVAD) infection, and CIED pocket and lead infection. As a whole-body image, findings may modify therapy in 25% of NVE and PVE patients. However, FDG-PET/CT is costly, requires preprocedure patient preparation, can have false-positive results in patients with recent valve surgery (<3 months), and requires experienced radiogra phers for interpretation. Of note, findings indicative of IE on CTA and

FDG-PET/CT are major criteria and considered equivalent to echocar diography in the Duke-ISCVID schema. In population-based studies and large series (using various diag nostic criteria), IE occurs frequently among patients who have mono microbial bacteremia due to those gram-positive organisms that are commonly associated with IE. For example, 12–17% of patients with blood cultures growing E. faecalis have IE; 7% of patients with blood cultures growing non-β-hemolytic streptococci have IE; and 8–14% of patients with blood cultures growing S. aureus have IE. Among patients with one or more positive monomicrobial blood culture, IE risk-prediction scoring systems have been developed to identify patients who are at sufficient risk of IE to justify echocardiographic assessment (Table 133-4). Because S. aureus bacteremia is associated with a high prevalence of IE and a resultant high risk for mortality, echocardiographic evaluation (high-quality TTE or preferably TEE) is recommended routinely. Prediction scores suggest that with S. aureus bacteremia, a patient with any of the features listed in Table 133-4 incurs at least a 6% risk of IE, with risk increasing when multiple features are present. Thus, when present, these findings are a strong indication for early TEE. In their absence, TTE should suffice unless other findings suggest IE. Among patients with either monomicrobial E. faecalis or non-β-hemolytic streptococcal bacteremia, any three of the respective listed features (Table 133-4) are associated with a significant frequency of IE. For these patients, the estimated number needed to test with TEE to detect IE is 2.4 and 3.6, respectively. While these predictive scoring systems need further evaluation and should be used with clinical judgment, they appear to have a high sensitivity and therefore a high negative predictive value, which allows identifica tion of patients at low risk of IE where echocardiography, particularly TEE, can be omitted. An approach to echocardiographic evaluation of patients with suspected IE is illustrated in Fig. 133-3. Other Studies Many studies that are not diagnostic—i.e., complete blood count, creatinine determination, liver function tests, chest radi ography, and electrocardiography—are important in the management of patients with IE. The erythrocyte sedimentation rate, C-reactive protein level, rheumatoid factor, and circulating immune complex titer are commonly increased in IE (Table 133-2). Brain MRI/magnetic TABLE 133-4 Features Guiding the Need for Echocardiographic Assessment in Patients with Selected Monomicrobial Bacteremia BLOOD CULTURE ISOLATE S. AUREUSa E. FAECALISb NON-a-HEMOLYTIC STREPTOCOCCIc Intracardiac device Symptoms ≥7 days Symptoms ≥7 days Preexisting valve disease (including prior endocarditis or valve prosthesis) Emboli

> 2 positive cultures Injection drug use ≥2 positive cultures One species: S. gallolyticus, S. sanguinis, S. mutans (not S. anginosus) Cerebral/peripheral emboli Unknown origin (no focus) Preexisting valve disease (including prior endocarditis or valve prosthesis) Meningitis Heart murmur Heart murmur Persistent bacteremia (≥72 h) Preexisting valve disease (including prior endocarditis or valve prosthesis) Community acquisition Vertebral osteomyelitis Community acquisition Nonnosocomial health care associated (including hemodialysis) Source: aS Tubiana et al: J Infect 72:544, 2016 and A Showler et al: JACC Cardiovasc Imaging 8:924, 2015. bA Berge et al: Infection 47:45, 2019. cT Sunnerhagen et al: Clin Infect Dis 66:693, 2018.

resonance angiography (MRA) should be obtained in patients with neurologic signs or symptoms, including unusual headache, to assess for emboli, hemorrhage, or mycotic aneurysms. The findings

can sup port the IE diagnosis as well as provide evidence requiring changes in planned surgical treatment. Patients with recalcitrant back pain or focal spine tenderness should undergo spine MRI targeted to the appropri ate level based on symptoms to assess for osteomyelitis and epidural abscess. Contrast-enhanced whole-body tomography to detect silent emboli in patients without localizing symptoms is not likely to enhance diagnostic accuracy and is associated with significant risk of kidney injury due to contrast media exposure; thus, it should not be per formed routinely.

TREATMENT Infective Endocarditis ANTIMICROBIAL THERAPY To cure IE, all bacteria in the vegetation must be killed. This is difficult because local host defenses are deficient and because the bacteria are largely nongrowing and metabolically inactive and thus are less easily killed by antibiotics. Consequently, therapy must be prolonged. Antibiotics are generally given parenterally to achieve serum concentrations that, through passive diffusion, result in effective concentrations in the depths of the vegetation. The deci sion to initiate treatment empirically must balance the need to establish a microbiologic diagnosis against the potential disease progression or the need to control infection prior to urgent surgery (see “Blood Cultures,” above). Infection at other sites (such as the meninges), allergies, end-organ dysfunction, interactions with con comitantly administered medications, and risks of adverse events must be considered in the selection of therapy. CHAPTER 133 The regimens recommended for the treatment of PVE (except that caused by staphylococci), although given for several weeks longer, are similar to those used to treat NVE (Table 133-5). Rec ommended antibiotic dosing and duration of therapy, which is measured from the time blood cultures become negative, should be followed unless alterations are required by end-organ dysfunction or adverse events. Infective Endocarditis Organism-Specific Therapies • Streptococci The recom mended therapies for streptococcal IE are based on the minimal inhibitory concentration (MIC) of penicillin for the causative isolate (Table 133-5). The 2-week penicillin/gentamicin and ceftri axone/gentamicin regimens should not be used to treat NVE com plicated by cardiac or extracardiac abscess or PVE. Caution should be exercised in considering aminoglycoside-containing regimens in patients at increased risk for aminoglycoside toxicity (renal or eighth cranial nerve). The regimens recommended for relatively penicillin-resistant streptococci are advocated for treatment of group B, C, or G streptococcal IE. Granulicatella, Abiotrophia, and Gemella species are treated with the regimens for moderately peni cillin-resistant streptococci, as is PVE caused by these organisms or by streptococci with a penicillin MIC of >0.1 μg/mL (Table 133-5). Enterococci Enterococci are resistant to oxacillin, nafcillin, and the cephalosporins and are only inhibited—not killed—by the cell wall–active agents penicillin, ampicillin, teicoplanin (not avail able in the United States), and vancomycin, with ampicillin and penicillin being preferred when susceptible. Enterococci are killed by the synergistic interaction of these cell wall–active antibiotics combined with gentamicin, unless the isolate exhibits high-level resistance to gentamicin, defined as growth of the isolate in the presence of gentamicin at ≥500 μg/mL. Bactericidal synergy with other aminoglycosides—tobramycin, netilmicin, kanamycin, and amikacin—is unpredictable even in the absence of high-level resis tance; thus, they are not used to treat enterococcal IE. Although the dose of gentamicin used to achieve bactericidal synergy in treating enterococcal IE is smaller than that used in stan dard therapy, nephrotoxicity is not uncommon during treatment

Low initial patient risk and low clinical suspicion Initial TTE Initial TEE – + + Increased suspicion during clinical course Low suspicion persists Rx High-risk echo features* No high-risk echo features TEE No TEE unless clinical status deteriorates TEE for detection of complications – Clinical judgment regarding treatment + Rx Look for other source FIGURE 133-3 The diagnostic use of

transesophageal and transthoracic echocardiography (TEE and TTE, respectively). †High initial patient risk for infective endocarditis (IE) or evidence of intracardiac complications (new regurgitant murmur, new electrocardiographic conduction changes, or congestive heart failure). *High-risk echocardiographic features include large vegetations, valve insufficiency, paravalvular infection, or ventricular dysfunction. Rx indicates initiation of antibiotic therapy. CTA, electrocardiogram-gated cardiac computed tomography (CT) angiogram; FDG-PET/CT, fluorodeoxyglucose-positron emission tomography CT. ^See text for discussion of these modalities. (Reproduced with permission from AS Bayer: Diagnosis and management of infective endocarditis and its complications. Circulation 98:2936, 1998, Figure 1.) PART 5 Infectious Diseases lasting 4–6 weeks. High concentrations of ampicillin plus ceftri axone or cefotaxime, by expanded binding of penicillin-binding proteins, also kill E. faecalis in vitro and in animal models of IE. Nonrandomized comparative studies suggest that high-dose regimens using ampicillin-ceftriaxone appear comparable and less nephrotoxic than penicillin or ampicillin plus gentamicin for treat ment of E. faecalis (but not E. faecium) IE and may also provide effective treatment when strains possess high-level gentamicin resistance. This regimen has been used increasingly to address not only high-level gentamicin-resistant strains but also to minimize nephrotoxicity. Alternatively, if there is a contraindication to an ampicillin-ceftriaxone regimen, shorter 2- to 3-week courses of synergistic gentamicin can be considered. The combinations of vancomycin (or teicoplanin) or gentamicin with ceftriaxone are not bactericidal for E. faecalis and are not recommended for treatment of enterococcal IE. If a combination regimen cannot be used due to resistance or toxicity, an 8- to 12-week course of a single cell wall–active agent can be considered, although the patient should be followed carefully for evidence of failure. Treatment of IE caused by E. faecium, which is generally more antibiotic resistant than E. faecalis and may be vancomycin resis tant, is not well established. Successful treatment of IE caused by vancomycin-resistant enterococci with high-dose daptomycin (10–12 mg/kg IV once daily), often in combination with ampicillin or other β-lactams, has been reported. If the isolate susceptibility allows treatment with penicillin or ampicillin plus gentamicin, this is preferred. These cases should be managed in conjunction with an infectious disease consultant. Staphylococci Management of S. aureus bacteremia and IE in conjunction with infectious disease consultants has been associ ated with improved outcomes and is recommended. Treatment of staphylococcal IE (Table 133-5) is based on the presence of a

High initial patient risk†; moderate to high clinical suspicion or difficult imaging candidate IE suspected – Look for other source of symptoms High suspicion persists Rx + – Repeat TEE Alternative diagnosis established – + Consider CTA or FDG-PET/CT^ Rx – + Follow-up TEE or TTE to reassess vegetations, complications, or Rx response as clinically indicated prosthetic valve or foreign device, the native valve(s) involved (right vs left side), and the antibiotic susceptibility of the isolate. Penicillin resistance and, except in specific countries, methicillin resistance are widespread among staphylococci. Thus, empirical therapy for possible staphylococcal IE should use a regimen effective against methicillin-resistant organisms. Therapy should be revised to an antistaphylococcal penicillin if the isolate is susceptible to methicil lin. Cefazolin is generally considered an alternative β-lactam agent for the treatment of methicillin-susceptible S. aureus (MSSA) IE. Ease of administration and reduced adverse events compared to treatment with an antistaphylococcal penicillin have prompted use of cefazolin as a primary agent in this setting. Concerns, however, have been raised about inactivation of cefazolin by type A and C staphylococcal β-lactamases (these do not hydrolyze antistaphylo coccal penicillins), resulting in treatment failure in high-inoculum infections. Initiating treatment with an antistaphylococcal

penicil lin until there is source control and a reduced inoculum and then transitioning to cefazolin should be considered. The addition of gentamicin to a β-lactam antibiotic or vancomycin to enhance therapy for left-sided NVE has not improved survival rates and is associated with nephrotoxicity. Guidelines do not recommend the routine addition of gentamicin, fusidic acid, rifampin, or daptomy cin to regimens for MSSA NVE. For treatment of NVE due to methicillin-resistant S. aureus (MRSA), vancomycin, dosed to achieve trough concentrations of 15 μg/mL (or an area under the time-concentration curve/broth microdilution MIC ratio [AUC:MIC] >400 achieved with the assis tance of a pharmacist), is recommended, with the caveat that high vancomycin trough concentrations may be associated with nephro toxicity. Although resistance to vancomycin among staphylococci is rare, reduced vancomycin susceptibility among MRSA strains is increasingly encountered. Isolates with a vancomycin MIC of 4–8 μg/mL have intermediate susceptibility and are referred to as

TABLE 133-5 Antibiotic Treatment for Infective Endocarditis Caused by Common Organismsa ORGANISM(S) DRUG (DOSE, DURATION) COMMENTS Streptococci For PVE 6-week regimens are preferred. Penicillin-susceptible streptococci, S. gallolyticus (MIC ≤0.12 μg/mL) • Penicillin G (2–3 mU IV q4h for 4 weeks) Can use ampicillin or amoxicillin (2 g IV q4h) if penicillin is unavailable. • Ceftriaxone (2 g once daily for 4 weeks) Can use ceftriaxone in patients with nonimmediate penicillin allergy. • Vancomycinb (15 mg/kg IV q12h for 4 weeks) Use vancomycin for patients with immediate (urticarial) or severe penicillin allergy. Obtain allergy consultation for further evaluation including role of β-lactam desensitization. • Penicillin G (2–3 mU IV q4h) or ceftriaxone

(2 g IV once daily) for 2 weeks plus Gentamicinc (3 mg/kg daily IV or IM, as a single dosed for 2 weeks) Relatively penicillin-resistant streptococci, S. gallolyticus (MIC >0.12 μg/mL and

<0.5 μg/mLe) • Penicillin G (4 mU IV q4h) or ceftriaxone

(2 g IV daily) for 4 weeks plus Gentamicinc (3 mg/kg daily IV or IM, as a single dosed for 2 weeks) • Vancomycinb as noted above for 4 weeks Use vancomycin for patients with immediate (urticarial) or severe penicillin allergy. Obtain allergy consultation for further evaluation including role of β-lactam desensitization. Ceftriaxone alone or with gentamicin can be used in patients with nonimmediate β-lactam allergy. Moderately penicillin-resistant streptococci (MIC, ≥0.5 μg/mL and <8 μg/mL); Granulicatella, Abiotrophia, or Gemella spp. • Penicillin G (4–5 mU IV q4h) or ceftriaxone (2 g IV daily) for 6 weeks plus Gentamicinc (3 mg/kg daily IV or IM in 2–3 equally divided doses for 6 weeks) • Vancomycinb as noted above for 6 weeks Regimen is preferred by some. Enterococcie For PVE, 6-week regimens are preferred. • Ampicillin (2 g IV q4h) plus ceftriaxone (2 g IV q12h), both for 6 weeks • Penicillin G (4–5 mU IV q4h) for 4–6 weeks plus gentamicinc (3 mg/kg daily IV or 1 mg/kg IV q8h) for 2–6 weeks • Ampicillin (2 g IV q4h) for 4–6 weeks plus gentamicinc (3 mg/kg daily IV or 1 mg/kg IV q8h) for 2–6 weeks • Vancomycinb (15 mg/kg IV q12h) for 6 weeks plus gentamicinc (3 mg/kg daily IV or 1 mg/kg IV q8h) for 2–6 weeks Staphylococci (S. aureus and coagulase-negative) MSSA infecting native valves (no foreign devices) including complicated right-sided and left-sided endocarditis. • Nafcillin, oxacillin, or flucloxacillin (2 g IV q4h for 4–6 weeks) • Cefazolin (2 g IV q8h for 4–6 weeks) Can use cefazolin regimen for patients with nonimmediate penicillin allergy; see text regarding cefazolin vs antistaphylococcal penicillin as primary therapy. Addition of gentamicin not recommended. • Vancomycinb (15 mg/kg IV q12h for 4–6 weeks) MRSA infecting native valves (no foreign devices) • Vancomycinb (15

mg/kg IV q8–12h) or daptomycin (8–10 mg/kg daily) for 4–6 weeks MSSA infecting prosthetic valves • Nafcillin, oxacillin, or flucloxacillin (2 g IV q4h for 6–8 weeks) plus Gentamicinc (1 mg/kg IM or IV q8h for 2 weeks) plus • Rifampinf (300 mg PO q8h for 6–8 weeks) MRSA infecting prosthetic valves • Vancomycinb (15 mg/kg IV q12h for 6–8 weeks) plus Gentamicinc (1 mg/kg IM or IV q8h for 2 weeks) plus • Rifampinf (300 mg PO q8h for 6–8 weeks)

Can use ampicillin or amoxicillin (2 g IV q4h) if penicillin is unavailable. Avoid 2-week regimen when risk of aminoglycoside toxicity is increased and in prosthetic-valve or complicated endocarditis. Penicillin G at a dose of 4 mU IV q4h or ceftriaxone 2 g once daily for 6 weeks both with or without gentamicin during the initial 2 weeks preferred for PVE caused by streptococci with penicillin MICs ≤0.12 μg/mL. Can use ampicillin or amoxicillin (2 g IV q4h) if penicillin is unavailable. Penicillin G at a dose of 4 mU IV q4h or ceftriaxone 2 g once daily for 6 weeks both with gentamicin during the initial 2 weeks preferred for PVE caused by streptococci with penicillin MICs >0.12 μg/mL. Can use ampicillin or amoxicillin (2 g IV q4h) if penicillin is unavailable. CHAPTER 133 Use for E. faecalis isolates with or without high-level resistance to gentamicin or for patients at risk for aminoglycoside nephrotoxicity. Infective Endocarditis Can treat NVE for 4 weeks if symptoms last <3 months. Treat NVE for 6 weeks if

> 3 months of symptoms. Can abbreviate gentamicin course in some patients (see text). Can use IV amoxicillin in lieu of ampicillin (same dose). Can abbreviate gentamicin course in some patients (see text). Use vancomycin plus gentamicin only for penicillin-allergic patients (preferable to desensitize to penicillin if immediate [urticarial] allergy; consult allergy) and for isolates resistant to penicillin/ampicillin. Addition of gentamicin is not recommended. For uncomplicated right-sided endocarditis, a 2-week course may be effective (see text). Only use vancomycin for patients with immediate (urticarial) or severe penicillin allergy until allergy consultation can be obtained for β-lactam desensitization evaluation; addition of gentamicin not recommended. No role for routine use of rifampin (see text). For daptomycin treatment, see text. Use gentamicin during initial 2 weeks; determine gentamicin susceptibility and await blood culture clearance before initiating rifampin (see text); if patient is highly allergic to penicillin, use regimen for MRSA and obtain allergy consultation; if β-lactam allergy is of the minor nonimmediate type, cefazolin can be substituted for oxacillin, nafcillin, or flucloxacillin. Use gentamicin during initial 2 weeks; determine gentamicin susceptibility and await blood culture clearance before initiating rifampin (see text). Daptomycin (8–10 mg/kg daily) is an alternative to vancomycin. (Continued)

TABLE 133-5 Antibiotic Treatment for Infective Endocarditis Caused by Common Organismsa ORGANISM(S) DRUG (DOSE, DURATION) COMMENTS HACEK organisms For PVE, 6-week regimens are preferred. • Ceftriaxone (2 g once daily IV for 4 weeks) • Ampicillin/sulbactam (3 g IV q6h for 4 weeks) Use ampicillin alone (2 g IV q4h) only if β-lactamase production can be excluded. If the isolate is susceptible, ciprofloxacin (500 mg by mouth q12h or 400 mg IV q12h) can be used. Coxiella burnetii • Doxycycline (100 mg PO q12h) plus hydroxychloroquine (200 mg PO q8h), both

for at least 18 (native valve) or 24 (prosthetic valve) months Bartonella spp. • Doxycycline (100 mg q12h PO) for 6 weeks plus Gentamicin (1 mg/kg IV q8h for 2 weeks) aRegimens adapted from the guidelines of the American Heart Association and the European Society of Cardiology (ESC). Doses of gentamicin, vancomycin, and daptomycin must be adjusted for reduced renal function. Ideal body weight is used to calculate doses of gentamicin and daptomycin per kilogram (men = 50 kg + 2.3 kg per inch over 5 feet; women = 45.5 kg + 2.3 kg per inch over 5 feet). bVancomycin dose is based on actual body weight. Adjust for trough level of 10–15 μg/mL for streptococcal and enterococcal infections and 15–20 μg/mL for staphylococcal infections (see text). cTarget peak and trough serum concentrations of divided-dose gentamicin 1 h after a 20- to 30-min infusion or IM injection are ~3.5 μg/mL and ≤1 μg/mL, respectively. dNetilmicin (4 mg/kg qd, as a single dose) can be used in lieu of gentamicin for streptococcal infection only. eAntimicrobial susceptibility must be evaluated; see text. fRifampin increases warfarin and dicumarol requirements for anticoagulation. Abbreviations: HACEK, Haemophilus species, Aggregatibacter species, Cardiobacterium hominis, Eikenella corrodens, and Kingella kingae; MIC, minimal inhibitory concentration; MRSA, methicillin-resistant S. aureus; MSSA, methicillin-susceptible S. aureus; NVE, native-valve endocarditis; PVE, prosthetic-valve endocarditis. vancomycin-intermediate S. aureus (VISA). Isolates with a vanco mycin MIC of 2 μg/mL may harbor subpopulations with higher MICs. These isolates, called heteroresistant VISA (hVISA), are not detectable by routine susceptibility testing and yet may impair van comycin effectiveness. PART 5 Infectious Diseases Daptomycin has provided effective alternative treatment for left-sided NVE caused by documented daptomycin-susceptible MRSA and is associated with less nephrotoxicity than vancomycin (although it is associated with myositis and, rarely, eosinophilic pneumonitis). Although it is U.S. Food and Drug Administration (FDA) approved only for right-sided IE at a dose of 6 mg/kg daily, most recommend doses of 8–10 mg/kg daily for treatment of leftsided IE. Because receipt of vancomycin has been associated with emergence of daptomycin nonsusceptibility, caution should be exercised when switching from vancomycin to daptomycin mono therapy in a patient who has received vancomycin without clearing blood cultures. Daptomycin activity against MRSA—even against some daptomycin-nonsusceptible isolates—is enhanced when given in combination with nafcillin or ceftaroline. Case series suggest that high-dose daptomycin combined with nafcillin or ceftaroline, ceftaroline combined with trimethoprim/sulfamethoxazole, or cef taroline alone (600 mg IV q8h) may be effective salvage treatment for vancomycin-unresponsive MRSA IE and should be considered in patients with sepsis, in those with multifocal sites of infection, or when bacteremia persists for 4 or more days. Eradicable sources of bacteremia should always be addressed; failure of source control is a very common reason for persistent MRSA bacteremia. MSSA IE that is uncomplicated and limited to the tricuspid or pulmonic valve can often be treated with 2 weeks of oxacillin or nafcillin (but not vancomycin). Prolonged fever (≥5 days) during therapy or multiple septic pulmonary emboli mandate standardduration therapy. Right-sided MRSA IE is treated for at least 4 weeks with vancomycin or daptomycin (6 mg/kg daily); 2-week courses of therapy are suboptimal. Left-sided staphylococcal IE is treated with a minimum of 6 weeks of therapy. Staphylococcal PVE is treated with a multidrug regimen for 6–8 weeks (Table 133-5). To achieve long-term bacterial eradica tion, rifampin, which kills staphylococci embedded in biofilm adherent to foreign material, is considered an essential component of this regimen. Rifampin resistance can emerge during therapy. To prevent emergence of resistance, administration of rifampin should be delayed until initial therapy with two agents (gentamicin plus an

(Continued) Follow serology to monitor response during treatment (antiphase I IgG and IgA decreased fourfold and IgM antiphase II negative) and thereafter for relapse. If doxycycline is not tolerated, use azithromycin (500 mg PO daily). Some experts recommend that doxycycline be continued for 3–6 months unless all infection is resected surgically. antistaphylococcal penicillin or vancomycin selected on the basis of susceptibility testing) has eradicated bacteremia (reduced the inoc ulum). The isolate's susceptibility to gentamicin or an alternative agent as well as to rifampin should be established before rifampin treatment is begun. The impact of adding rifampin and gentamicin on survival of patients with staphylococcal PVE has not been dem onstrated convincingly; thus, it is reasonable to discontinue these agents if patients are experiencing toxicity or drug interactions. Other Organisms In the absence of meningitis, IE caused by Streptococcus pneumoniae isolates with a penicillin MIC of ≤4 μg/ mL can be treated with IV penicillin (4 million units IV every 4 h), ceftriaxone (2 g once daily), or vancomycin. Ceftriaxone or vanco mycin is preferred for pneumococcal strains with a penicillin MIC of ≥2 μg/mL. If meningitis is suspected, treatment with vancomycin plus ceftriaxone—at the doses advised for meningitis—should be initiated until susceptibility results are known. Definitive therapy should then be selected on the basis of meningitis breakpoints (penicillin MIC, 0.06 μg/mL; ceftriaxone MIC, 0.5 μg/mL). Pneu mococcal NVE is treated for 4 weeks and pneumococcal PVE for 6 weeks. P. aeruginosa IE is treated with an antipseudomonal cephalosporin and traditionally high doses of tobramycin, and IE caused by Enterobacterales is treated with a β-lactam antibiotic, also traditionally, plus an aminoglycoside, although data substantiating a need for combination therapy for these organisms are limited. Therapy for Candida IE consists of a lipid formulation of ampho tericin B (5 mg/kg IV daily) with or without flucytosine (25 mg/kg PO q6h) (if using flucytosine, monitor renal function, flucytosine levels, and bone marrow function). Alternatively, a high-dose echi nocandin regimen can be used. If there is valve dysfunction or PVE, early surgery is advised, as is long-term (if not indefinite) oral azole suppression. Absent valve dysfunction, medical treatment with long-term oral azole suppression may achieve results comparable to surgical treatment. Empirical Therapy and Treatment for Culture-Negative IE In designing therapy to be administered before culture results are known or when cultures are truly negative, clinical clues to etiol ogy (e.g., acute vs subacute presentation, NVE, early or late PVE, the patient's predispositions) as well as epidemiologic clues (e.g., region of residence, animal exposure) must be considered. Thus, empirical therapy for acute IE should cover MRSA and in a PWID or for health care–associated NVE potentially antibiotic-resistant

gram-negative bacilli. Treatment with vancomycin plus gentamicin or cefepime, initiated immediately after blood cultures are obtained, covers these organisms as well as many others. For empirical treat ment of NVE with a subacute presentation, vancomycin plus ceftri axone is reasonable. For blood culture–pending PVE, vancomycin, gentamicin, and cefepime should be used if the prosthetic valve has been in place for ≤1 year. Empirical therapy for late PVE (valve in place for >1 year) is similar to that for culture-negative NVE. Therapy is revised once a pathogen has been identified. In the treatment of blood culture–negative episodes, marantic endocarditis and the antiphospholipid antibody syndrome must be considered. In the absence of prior antibiotic therapy, it is unlikely that infection due to S. aureus, CoNS, enterococci, or Enterobacterales will present with negative blood cultures; thus, recommended empirical therapy targets fastidious streptococci, Abiotrophia, Gemella, Granulicatella, the HACEK group, and Bar tonella species. Pending the availability of diagnostic data, blood culture–negative subacute NVE is treated with vancomycin plus ampicillin-sulbactam (12 g every 24 h) or ceftriaxone; doxycycline (100 mg twice daily) is

added for enhanced Bartonella coverage. If cultures are negative because of prior antibiotic administration, pathogens likely to be inhibited by the specific prior therapy should be considered. TAVR-PVE The vast majority of these patients are treated medi cally with classic PVE antibiotic regimens for the given pathogen. Selection of empirical therapy pending blood culture results simi larly parallels that for classic PVE but with recognition that entero coccal infection occurs with increased frequency. CIED-IE Antimicrobial therapy for CIED-IE (as well as for gen erator pocket and lead infection) is adjunctive to complete removal of the device. The antimicrobial selected is based on the causative organism and should be used as recommended for NVE (Table 1335). Bacteremic CIED infection may be complicated by coincident left-sided NVE, PVE, or remote-site infection (e.g., osteomyelitis), which may require modification of antimicrobial therapy. A 4- to 6-week course of IE-targeted therapy is recommended for patients with CIED-IE and for those with bacteremia that continues after device removal. Generator pocket infection without bacteremia is treated with a 10- to 14-day course, some of which can be given orally. In the absence of another source, S. aureus bacteremia (and persistent CoNS bacteremia) is likely indicative of CIED-IE or valvular IE and should be investigated and managed accordingly. However, not all bloodstream infections in these patients indicate IE. If evidence suggesting CIED-IE is lacking, bloodstream infec tion due to gram-negative bacilli, streptococci, and enterococci species may not indicate CIED-IE and can be treated with anti microbial therapy for the alternative diagnosis. However, in these patients, relapse after antimicrobial therapy increases the likelihood of CIED-IE and warrants treatment as such. Attempted salvage of an infected CIED with antibiotics alone and long-term suppressive therapy is usually unsuccessful and should be reserved for patients whose devices cannot be removed or who decline removal. Careful follow-up is required. Partial Oral Antibiotic Treatment of IE Recent studies have examined the use of oral antibiotics to complete therapy in patients who have received an initial course of intravenous treatment (with or without cardiac surgery). A noninferiority, multicenter, randomized study found mortality among patients with left-sided IE caused by streptococci, enterococci, and staphy lococci who received partial oral treatment comparable to that of patients who were treated intravenously for the full course of therapy (6.5% and 7.5%, respectively). Four hundred clini cally stable patients (20% of the population screened) who had received at least 10 days of parenteral therapy (or at least 7 days after surgery) were enrolled. IE was caused by streptococci (49%), enterococci (24%), and MSSA (22%); no patients had MRSA. Of note, the median duration of intravenous treatment before the

switch to oral agents was 16 days (interquartile range, 13–23 days); thus, some patients may have been effectively cured by intrave nous therapy with or without surgery prior to transition to oral therapy. The results in this highly selected and monitored cohort with relatively small numbers of patients with enterococcal and S. aureus IE may not be generalizable to most patients with IE. If oral therapy is considered in patients who meet the criteria in the studied population, the decision on agents and duration should be made in consultation with infectious diseases.

Use of Long-Acting Lipoglycopeptide Agents Dalbavancin, a lipoglycopeptide with a long half-life allowing for infrequent dos ing, is FDA approved for treatment of skin and soft tissue infections. Only limited data are available supporting its use in the treatment of IE, particularly due to S. aureus, with most being case series of patients who received dalbavancin upon discharge from the hospi tal after having received several weeks of active intravenous therapy. Consideration can be given to using this agent in patients who are clinically stable with negative blood cultures and in patients with complicated IE who are not candidates to continue hospitalization or to transition to

outpatient parenteral therapy, in consultation with infectious diseases. Outpatient Parenteral Antimicrobial Therapy Fully compliant, clinically stable patients who are no longer bacteremic, are not febrile, and have no clinical or echocardiographic findings that suggest an impending complication may complete IV therapy as outpatients. Careful follow-up and a stable residential setting are necessary, as are predictable IV access and use of antimicrobial agents that are stable in solution and less frequently associated with severe adverse effects. Recommended regimens should not be com promised to accommodate outpatient therapy. CHAPTER 133 Monitoring Antimicrobial Therapy Antibiotic-related adverse events occur in 25–40% of IE patients and commonly arise after several weeks of therapy. Blood tests to detect renal, hepatic, and hematologic toxicity should be performed periodically. Serum concentrations of aminoglycosides and vancomycin should be monitored and doses adjusted to optimize treatment and minimize toxicity. Infective Endocarditis Control of peripheral sites of infection—source control—should be addressed promptly. Blood cultures should be repeated daily until sterile in patients with IE due to S. aureus or difficult-totreat organisms and rechecked if there is recrudescent fever. Blood cultures become sterile after 2 days of appropriate therapy when infection is caused by viridans streptococci, E. faecalis, or HACEK organisms. In MSSA IE, β-lactam therapy results in sterile cultures in 3–5 days, whereas in MRSA IE, the duration of bacteremia is often longer with vancomycin or daptomycin treatment. MRSA bacteremia persisting despite an appropriate dosage of vancomycin or daptomycin may indicate emergence of reduced susceptibility in the infecting strain and point to a need for alternative therapy. When fever persists for 7 days despite appropriate antibiotic ther apy, patients should be evaluated further for paravalvular abscess, extracardiac abscesses (spleen, kidney), or complications (embolic events). Recrudescent fever raises the possibility of these complica tions but also of drug reactions or complications of hospitaliza tion. It is advisable to obtain follow-up echocardiography after the completion of therapy to assess valvular function. Of note, veg etations become smaller with effective therapy; however, 3 months after cure, 50% are unchanged, and 25% each are slightly larger or smaller. Antithrombotic Therapy Because patients with IE are at risk for hemorrhagic transformation of embolic strokes and for intracere bral hemorrhage from septic arteritis or ruptured mycotic aneu rysms, initiation of antithrombotic (anticoagulant or antiplatelet) therapy requires careful consideration of the risks and benefits. Antithrombotic therapy can render such bleeding catastrophic. Neither anticoagulant nor antiplatelet therapy reduces the risk of emboli in patients with NVE, and thus, such treatment is not

TABLE 133-6 Indications for Cardiac Surgical Treatment in Patients with Endocarditis Surgery Required for Optimal Outcome Native-valve or prosthetic-valve endocarditis Moderate or severe congestive heart failure or shock due to valve dysfunction Paravalvular extension of infection with abscess, fistula, or heart block Persistent bacteremia without an extracardiac cause despite 7–10 days of optimal antimicrobial therapy Lack of effective antimicrobial therapy (e.g., fungal [see text regarding Candida spp.], Brucella, multidrug-resistant gram-negative bacillary endocarditis) Prosthetic-valve endocarditis Partially dehisced unstable prosthetic valve Surgery to Be Strongly Considered for Improved Outcomea Prosthetic-valve endocarditis S. aureus infection with intracardiac complications Relapse after optimal antimicrobial therapy Native-valve endocarditis Large (>10-mm) hypermobile vegetation, particularly with prior systemic embolus and significant valve dysfunctionb Very large (>30-mm) vegetation Persistent unexplained fever (≥10 days) in blood culture–negative endocarditis Poorly responsive or relapsed endocarditis due to highly antibiotic-resistant enterococci or gram-negative bacilli aCarefully consider surgery. Multiple

findings are often combined to justify surgery. bIn the group with an estimated low cardiac-surgery mortality risk (see text). PART 5 Infectious Diseases indicated for that purpose. However, patients with IE may have coexisting conditions wherein anticoagulation is indicated. Thus, in the absence of a contraindication (i.e., no clinical or imaging evidence of a recent large embolic stroke, intracerebral hemor rhage, or mycotic aneurysm), anticoagulant therapy is given to patients who have a mechanical prosthetic valve, atrial fibrilla tion with either mitral stenosis or a CHA2DS2-VASc score ≥2, or deep-vein thrombophlebitis. Most experts use unfractionated or low-molecular-weight heparin for ease of reversal. Anticoagulant TABLE 133-7 Timing of Cardiac Surgical Intervention in Patients with Endocarditis INDICATION FOR SURGICAL INTERVENTION TIMING STRONG SUPPORTING EVIDENCE Emergent (same day) Valve dysfunction with pulmonary edema or cardiogenic shock Acute aortic regurgitation plus preclosure of mitral valve Sinus of Valsalva abscess ruptured into right heart Rupture into pericardial sac Urgent (within 1–2 days) Valve obstruction by vegetation Unstable (dehisced) prosthesis Acute aortic or mitral regurgitation with heart failure (New York Heart Association class III or IV) Septal perforation Mobile vegetation >30 mm Paravalvular extension of infection with or without new electrocardiographic conduction system changes Lack of effective antibiotic therapy Elective (earlier usually preferred) Progressive paravalvular prosthetic regurgitation Valve dysfunction plus persisting infection after ≥7–10 days of antimicrobial therapy Fungal (mold) endocarditis Antibiotic-resistant organisms aSupported by a single-institution randomized trial showing benefit from early surgery. Implementation requires clinical judgment. If surgery is elected, it must be done early (see text). Source: Reproduced with permission from L Olaison, G Pettersson: Current best practices and guidelines: Indications for surgical intervention in infective endocarditis. Infect Dis Clin North Am 16:453, 2002.

therapy should be reversed, at least temporarily, in most patients who have had an acute ischemic stroke or an intracerebral hemorrhage. SURGICAL TREATMENT The indications for cardiac surgical treatment of IE (Table 133-6) have been derived from observational studies and expert opinion. The strength of specific indications varies; thus, the risks and benefits as well as the timing of surgery must be individualized (Table 133-7). These are best weighed by a team that includes cardiologists, cardiac surgeons, infectious disease physicians, and neurologists if there have been neurologic complications. Between 25% and 40% of patients with left-sided IE undergo cardiac surgery during active infection, with slightly higher surgery rates for PVE than NVE. The benefit of surgery has been assessed primarily in retrospective studies comparing populations of medically and sur gically treated patients matched for the necessity of surgery, with adjustments for predictors of death (comorbidities) and the timing of surgical intervention (a correction for survival bias). Although study results vary, surgery for NVE based on current indications appears to convey a significant survival benefit (27–55%), which is greatest among those with the most pressing indications. The survival benefit becomes more apparent after ≥6 months. The effect of surgery for PVE is more nuanced, with survival ben efits accruing largely to those with intracardiac complications. Of note, surgery itself carries mortality risks that may offset survival benefits in patients with lesser indications. Among patients with TAVR-PVE, 50–80% are reported to have an indication for surgical intervention—yet because of high pre-TAVR estimated operative mortality, <15% undergo surgery. Some patients with significant aortic regurgitation after medical cure of infection have undergone valve-in-valve redo-TAVR. Indications • Congestive Heart Failure Moderate to severe refractory CHF caused by new or worsening valve dysfunction or intracardiac fistulae is the major indication for cardiac surgery. Surgery can relieve functional stenosis due to

large vegetations or restore competence to damaged regurgitant valves by repair or replacement. At 6–12 months of follow-up of patients with left-sided NVE or PVE and moderate to severe CHF due to valve CONFLICTING EVIDENCE, BUT MAJORITY OF OPINIONS FAVOR SURGERY Vegetation diameter >10 mm plus severe but not urgent aortic or mitral valve dysfunctiona Major embolus plus persisting large vegetation (>10 mm) Staphylococcal prosthetic-valve endocarditis with intracardiac complications Early prosthetic-valve endocarditis (≤2 months after valve surgery) Candida spp. endocarditis (see text)

dysfunction, survival is significantly improved among those treated surgically compared with those treated medically. The survival ben efit with surgery is inversely related to the severity of preoperative CHF; thus, surgery should not be delayed in the face of deteriorat ing hemodynamics. Paravalvular Infection This complication, which is most com mon with aortic valve infection, occurs in 10–15% of patients with NVE and in 45–60% of those with PVE. It is suggested clinically by persistent unexplained fever during appropriate therapy, new electrocardiographic conduction disturbances, or pericarditis. TEE with color Doppler is the test of choice to detect paravalvular abscesses (sensitivity, ≥85%). Occasionally, three-dimensional TEE, ECG-gated CTA, or FDG-PET/CT demonstrates paravalvular infection not detected by TEE. For optimal outcome, paravalvular infection requires surgery, especially when fever persists, fistulae develop, prostheses are dehisced and unstable, or infection relapses after appropriate treatment. Cardiac rhythm must be monitored since high-grade heart block may require insertion of a pacemaker. Uncontrolled Infection Continued positive blood cultures or otherwise unexplained persistent fevers despite optimal antibiotic therapy may reflect uncontrolled infection that warrants surgery. Surgical treatment is also advised for IE caused by organisms against which effective antimicrobial therapy is lacking (e.g., yeasts, molds, P. aeruginosa, other highly antibiotic-resistant bacteria, Brucella species). S. aureus IE The mortality rate for S. aureus PVE exceeds 50% with medical treatment and may be reduced with surgical treat ment. Nevertheless, surgery is not routinely advised for uncom plicated S. aureus PVE. Rather, survival benefits are most likely in those with paravalvular infection, dysfunctional valves, and CHF. Surgical treatment of S. aureus NVE should be guided by the stan dard indications. Isolated tricuspid-valve S. aureus IE, even with persistent fever, rarely requires surgery. Prevention of Systemic Emboli Persisting morbidity and/or death may result from cerebral or coronary artery emboli. Anti thrombotic therapy does not prevent systemic emboli in NVE. The frequency of embolization decreases rapidly with effective antimi crobial therapy. Thus, if emboli are to be prevented through surgical intervention, surgery must occur very early. Vegetation characteris tics defined echocardiographically can identify patients at high risk of embolization but do not identify those patients in whom surgery to prevent emboli will increase survival. In a small randomized trial in patients who were at low risk of surgery-related mortality and had large vegetations (>10 mm) and significant valve dysfunction, emboli were prevented by early surgery (≤48 h after diagnosis), but there was no survival benefit. Rarely is prevention of emboli the sole indication for surgery; more often, this may be an additional benefit of early surgery for other indications. Valve repair, with the consequent avoidance of a prosthesis, improves the benefit-to-risk ratio of surgery performed to eliminate vegetations. CIED-IE Removal of all hardware is recommended for patients with established CIED-IE as well as for pocket or intracardiac lead infection. Percutaneous lead extraction is preferred; if hard ware remains after attempted percutaneous extraction, surgical removal should be considered. With lead vegetations >2 cm, there is a risk of a pulmonary embolism; nevertheless, the need for CIED removal surgically is unclear. Removal of the infected CIED during the initial hospitalization is associated with increased

30-day and 1-year survival rates over those attained with anti biotic therapy and device retention. The CIED, if needed, can be reimplanted at a new site after at least 10–14 days of effective antimicrobial therapy. CIEDs should be replaced when patients undergo surgery for IE. Timing of Cardiac Surgery With life-threatening indications for surgery (valve dysfunction and severe CHF, perivalvular abscess, major prosthesis dehiscence), surgery during the initial days of

therapy is associated with greater survival than later surgery. With less compelling indications, surgery may reasonably be delayed to allow further treatment as well as improvement in overall health (Table 133-7). Recrudescent IE on a newly implanted prosthetic valve follows surgery for active NVE and PVE in 2% and 6–15% of patients, respectively. These frequencies do not justify the increased mortality risk associated with delaying surgery in patients with severe heart failure, valve dysfunction, and uncontrolled infections. Delay is justified when infection and CHF are controlled with medi cal therapy.

Neurologic complications of IE may be exacerbated during car diac surgery. The risk of neurologic deterioration is related to the type and severity of the preoperative neurologic complication and the interval between the complication and surgery. In a nonob tunded patient with an ischemic stroke and hemorrhage excluded by imaging, cardiac surgery, if urgent, should be performed early because risk of hemorrhagic conversion or other neurologic side effects is low. In patients with intracranial hemorrhage and need for urgent surgery, early surgery should be pursued as long as the patient is expected to have meaningful recovery. Similar rates of postoperative intracranial hemorrhage and no difference in mortal ity have been observed in patients with and without preoperative intracranial hemorrhage. Nonurgent cardiac surgery should be delayed for 2–3 weeks after a large nonhemorrhagic embolic infarc tion and for 4 weeks after a significant cerebral hemorrhage. A rup tured mycotic aneurysm should be treated before cardiac surgery. Antibiotic Therapy after Cardiac Surgery Organisms have been detected on Gram stain—or their DNA has been detected by PCR— in excised valves from 45% of patients who have completed the recommended therapy for IE. However, organisms, most of which are unusual or antibiotic resistant, are rarely cultured from these valves. Detection of organisms or their DNA does not necessarily indicate antibiotic failure; in fact, relapse after surgery for active IE is uncommon. Thus, in uncomplicated NVE caused by susceptible organisms, the duration of preoperative plus postoperative treat ment should equal the total duration of recommended therapy. For IE complicated by perivalvular abscess, partially treated PVE, or valves culture-positive for the original organism, a full course of therapy should be given postoperatively. CHAPTER 133 Infective Endocarditis Treatment of IE in PWID PWID should be treated according to the standard guidelines for antibiotic selection and surgical inter vention. Additionally, OUD must be recognized as an ongoing predisposition for IE and treated; this includes medication-assisted therapy that is initiated during hospitalization and continued with out delay upon discharge. Addressing OUD significantly increases completion of antibiotic therapy, decreases resumption of injection drug use, and decreases recurrent IE and requirement for cardiac surgery. Extracardiac Complications Splenic abscess develops in 3–5% of patients with IE. Effective therapy requires either image-guided percutaneous drainage or splenectomy. Mycotic aneurysms occur in 2–15% of IE patients; one-half of these cases involve the cere bral arteries and present as headaches, focal neurologic symp toms, or hemorrhage. Cerebral aneurysms should be monitored by angiography. Some will resolve with effective antimicrobial therapy, but those that have leaked or persist or enlarge should be treated surgically, if possible. Extracerebral aneurysms present as local pain, a mass, local

ischemia, or bleeding; these are treated surgically. ■ ■OUTCOME IE is a heterogeneous disease that occurs in extremely heterogeneous patient populations. Adverse outcomes are associated with older age, severe comorbid conditions and diabetes, delayed diagnosis, involve ment of prosthetic valves or the aortic valve, an invasive (S. aureus) or antibiotic-resistant (P. aeruginosa, yeast) pathogen, intracardiac and major neurologic complications, and health care–associated infection.

TABLE 133-8 Antibiotic Regimens for Prophylaxis of Endocarditis in Adults with High-Risk Cardiac Lesionsa,b A. Standard oral regimen Amoxicillin: 2 g PO 1 h before procedure B. Inability to take oral medication Ampicillin: 2 g IV or IM within 1 h before procedure C. Penicillin allergy 1. Cephalexinc: 2 g PO 1 h before procedure 2. Clarithromycin or azithromycin: 500 mg PO 1 h before procedure 3. Doxycycline: 100 mg PO 1 h before procedure D. Penicillin allergy, inability to take oral medication Cefazolinc or ceftriaxonec: 1 g IV or IM 30 min before procedure aDosing for children: for amoxicillin, ampicillin, cephalexin, or cefadroxil, use 50 mg/kg PO; cefazolin, 25 mg/kg IV; clindamycin, 20 mg/kg PO or 25 mg/kg IV; clarithromycin, 15 mg/kg PO; and vancomycin, 20 mg/kg IV. bFor high-risk lesions, see Table 133-9. Prophylaxis is not advised for other lesions. cDo not use cephalosporins in patients with immediate hypersensitivity (urticaria, angioedema, anaphylaxis) to penicillin. Source: Table created using the guidelines published by the American Heart Association and the European Society of Cardiology (W Wilson et al: Circulation 116:1736, 2007; W Wilson et al: Circulation 143:e963, 2021; and G Habib et al: Eur Heart J 30:2369, 2009). Death or poor outcome often is related not to failure of antibiotic therapy but rather to the interactions of comorbidities and IE-related end-organ complications. In developed countries, overall survival rates are 80–85%; however, rates vary considerably among subpopula tions of IE patients. The outcome for a given patient depends on that individual’s infection, the complexity of required therapy, and preex isting comorbidities. About 85–90% of patients with NVE caused by viridans streptococci, HACEK organisms, or enterococci (susceptible to synergistic therapy) survive. For S. aureus NVE in patients who do not inject drugs, survival rates are 55–70%; rates are 85–90% among PWID. However, 1-year mortality rises to 20–30% among PWID if substance use disorder is not successfully addressed. PVE beginning within 2 months after valve replacement results in mortality rates of 40–50%, whereas rates are only 10–20% in late-onset cases. In the elderly population with TAVR-PVE the in-hospital mortality is 35–50% and increases to 60–75% at 1 year. Crude survival rates after successful treatment of IE generally are 80–90% and 70–80% at 1 and 2 years, respectively. PART 5 Infectious Diseases ■ ■PREVENTION Prevention of IE has been a goal of clinical practice; however, the evi dence establishing benefit from antibiotic prophylaxis for IE is insuffi cient to recommend it as a widespread standard of care. The American Heart Association and the European Society of Cardiology recommend limiting prophylactic antibiotics (Table 133-8) to only patients at high est risk for severe morbidity or death from IE (Table 133-9). TABLE 133-9 High-Risk Cardiac Lesions for Which Endocarditis Prophylaxis Is Advised Before Dental Procedures Prosthetic heart valves or material Left ventricular assist devices or implantable heart Prior endocarditis Unrepaired cyanotic congenital heart disease, including palliative shunts or conduits Completely repaired congenital heart defects during the 6 months after repair Repaired congenital heart disease with residual defects adjacent to prosthetic material Surgical or transcatheter pulmonary artery valve or conduit placement Valvulopathy developing after cardiac transplantation Source: Table created using the guidelines published by the American Heart Association and the European Society of Cardiology (W Wilson et al: Circulation 116:1736, 2007; W Wilson et al: Circulation 143:e963, 2021; and G Habib et al: Eur Heart J 30:2369, 2009).

In at-risk patients, maintaining good dental hygiene is recom mended, and antibiotic prophylaxis is recommended only when there is manipulation of gingival tissue or the periapical region of the teeth or perforation of the oral mucosa (including with respiratory tract surgery). Recent studies suggest that severe adverse events related to amoxicillin prophylaxis are exceedingly rare; however, clindamycin prophylaxis has been associated with low but significant rates of fatal and nonfatal adverse reactions with Clostridioides difficile infection. Consequently, the American Heart Association now recommends against the use of clindamycin for prophylaxis. Although prophylaxis is not advised for patients undergoing gastrointestinal or genitourinary tract procedures, genitourinary tract infections (or skin infection) should be treated before or when these sites undergo procedures. In patients with aortic or mitral valve regurgitation or a prosthetic valve, treatment of acute Q fever for 12 months with doxycycline plus hydroxychloroquine (see Table 133-4) is highly effective in preventing C. burnetii IE. Acknowledgment The authors would like to acknowledge the important contributions of Adolf W. Karchmer, MD, to this chapter in prior editions. ■ ■FURTHER READING Baddour LM et al: Infective endocarditis in adults: Diagnosis, anti microbial therapy, and management of complications: A scientific statement for healthcare professionals from the American Heart Association. Circulation 132:1435, 2015. Baddour LM et al: Update on cardiovascular implantable electronic device infections and their prevention, diagnosis, and management: A scientific statement from the American Heart Association. Circula tion 149:e201, 2024. Baddour LM et al: Management of infective endocarditis in people who inject drugs: A scientific statement from the American Heart Association. Circulation 146:e187, 2022. Bourque JM et al: 18F-FDG PET/CT and radiolabeled leukocyte SPECT/CT imaging for the evaluation of cardiovascular infection in the multimodality context: ASNC Imaging Indications (ASNC I2) Series Expert Consensus Recommendations from ASNC, AATS, ACC, AHA, ASE, EANM, HRS, IDSA, SCCT, SNMMI, and STS. Clin Infect Dis 2024. Corrected and republished in Heart Rhythm 21:e1, 2024. Chirouze C et al: Impact of early valve surgery on outcome of Staphy lococcus aureus prosthetic valve infective endocarditis: Analysis in the International Collaboration of Endocarditis–Prospective Cohort Study. Clin Infect Dis 60:741, 2015. Chobufo MD et al: Trends in infective endocarditis mortality in the United States: 1999 to 2020: A cause for alarm. J Am Heart Assoc 12:e031589, 2023. Delgado V et al: 2023 ESC guidelines for the management of endo carditis. Eur Heart J 44:3948, 2023. Duval X et al: Impact of systematic whole-body 18F-fluorodeoxyglu cose PET/CT on the management of patients suspected of infective endocarditis: The prospective multicenter TEPvENDO study. Clin Infect Dis 73:393, 2021. Fowler VG Jr et al: The 2023 Duke-International Society for Car diovascular Infectious Diseases criteria for infective endocarditis: Updating the modified Duke criteria. Clin Infect Dis 77:518, 2023. Liesman RM et al: Laboratory diagnosis of infective endocarditis. J Clin Microbiol 55:2599, 2017. Regueiro A et al: Association between transcatheter aortic valve replacement and subsequent infective endocarditis and in-hospital death. JAMA 316:1083, 2016. Wilson W et al: Prevention of viridans group streptococcal infective endocarditis: A scientific statement from the American Heart Asso ciation. Circulation 143:e963, 2021.

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