Chapter 134: Bacteremia and Infective Endocarditis

Daniel B. Chastain

CHAPTER SUMMARY FROM THE PHARMACOTHERAPY HANDBOOK

For the Chapter in the Schwinghammer Handbook, please go to Chapter 38, Endocarditis.

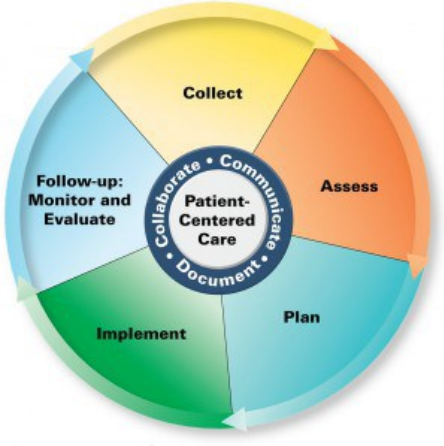
KEY CONCEPTS

KEY CONCEPTS

1. Bacteremia, defined as detection of bacteria in the bloodstream, is most often caused by a focal (primary) source of infection and may be complicated by the development of secondary (metastatic) foci, including infective endocarditis.
2. Infective endocarditis usually occurs secondary to a bloodstream infection in adult patients with specific risk factors (eg, injection drug use, heart failure, valvular disease, and healthcare exposure) and those with implanted cardiac material (eg, prosthetic heart valves).
3. A wide variety of pathogens may cause bacteremia, which is dependent on the patient population, primary source of infection, and geographic region.
4. Three groups of organisms cause most cases of infective endocarditis: staphylococci, streptococci, and enterococci.
5. The clinical presentation of bacteremia and infective endocarditis is highly variable and non-specific, but ranges from asymptomatic to hemodynamic instability and organ dysfunction.
6. Diagnosis of bacteremia and infective endocarditis requires the integration of clinical, laboratory, and diagnostic findings.
7. In patients with suspected or confirmed bacteremia, empirical antibacterial therapy should target the usual pathogens at the site(s) of suspected primary source(s) of infection and then be deescalated based on organism identification and susceptibility testing.
8. Treatment of infective endocarditis involves isolation of the infecting pathogen and determination of antimicrobial susceptibilities, followed by parenteral antimicrobial therapy (in most cases) for an extended period.
9. Source control which may include drainage, debridement, device removal, and definitive reconstructive manners is a critical component in managing patients with bacteremia.
10. Identification and susceptibility testing of the pathogen should guide definitive therapy in patients with bacteremia or infective endocarditis, but in most cases, β-lactams, such as penicillin G (or ceftriaxone), nafcillin (or an alternative antistaphylococcal or penicillinase-resistant penicillin), and ampicillin (with or without gentamicin or ceftriaxone), remain the drugs of choice for streptococcal, staphylococcal, and enterococcal bacteremia and endocarditis, respectively.

PATIENT CARE PROCESS

Patient Care Process for Bacteremia and Infective Endocarditis



Collect

- Patient characteristics (eg, age, sex, height, weight, pregnancy status, allergies)
- Patient history (eg, past medical, surgical, family)
- Social history (eg, ethanol/IV drug use, recent travel, home residence, exposure to animals) and dietary habits, including intake of unpasteurized dairy products
- Current medication use, including prescription, nonprescription, and other substances, with emphasis on previous inpatient and outpatient antimicrobial use
- Objective data
    - Temperature, blood pressure, respiratory rate, complete blood count (eg, white blood cell count, red blood cell count, hemoglobin, platelets), chemistry panel (eg, serum creatinine), urinalysis
    - Results from blood and/or valve tissue cultures and specialized testing (eg, serology, polymerase chain reaction)
    - Diagnostic testing (eg, electrocardiograph, chest radiograph, echocardiography)

Assess

- Identify risk factors (eg, immunocompromised status, recent dental procedure, central venous catheter, IV drug abuse, dietary habits) (see Tables 134-1 and 134-2)
- Assess signs and symptoms (eg, temperature >100.4°F [38°C], [see Clinical Presentation box], radiographic evidence, pathogen identification, physical examination findings)
- Determine potential infectious etiologies and likely primary (focal) source of infection based on patient history, current and previous antimicrobial use, risk factors, microbiologic data, and diagnostic testing (See Table 134-4)
- Interpret positive blood cultures to determine whether the organism(s) is of clinical significance or contamination (see Table 134-5)
- Determine the need for source control (eg, drainage, debridement, device removal, and definitive reconstructive manners) in patients with bacteremia and surgical intervention (eg, heart failure, persistent bacteremia, persistent vegetation) in patients with infective endocarditis
- Identify patients with underlying high-risk cardiac complications that would be candidates for antimicrobial prophylaxis

Plan*

- Determine the most appropriate empirical antimicrobial therapy, including dose, route, and frequency, based on patient characteristics, history, risk factors, and current and previous antimicrobial therapy
- Deescalate empirical therapy to an evidence-based regimen, including dose, route, frequency, and duration (see Tables 134-8 to 134-13), based on microbiologic and specialized testing results
- Develop monitoring parameters to assess efficacy and safety (eg, toxicities)
- Select evidence-based prophylaxis, including dose, route, and frequency (see Table 134-14)

Implement

- Provide patient education regarding all elements of treatment plan
- Initiate and deescalate antimicrobial therapy as appropriate
- Select an appropriate duration of therapy based on microbiologic and specialized testing results
- Develop an outpatient antimicrobial therapy (OPAT) plan at hospital discharge, including dose, route, frequency, and any necessary laboratory tests

Follow-up: Monitor and Evaluate

- Monitor for resolution of signs and symptoms of bacteremia and infective endocarditis
- Monitor results from blood and/or valve tissue cultures and specialized testing
- Monitor for the presence of antimicrobial related-adverse effects and toxicities
- Provide patient education regarding antimicrobial prophylaxis for infective endocarditis

**Collaborate with patient, caregivers, and other healthcare professionals.*

BEYOND THE BOOK

BEYOND THE BOOK

A 35-year-old man with a medical history of diabetes mellitus and injection drug use but no known drug allergies was admitted with diabetic ketoacidosis and left foot cellulitis associated with purulent drainage for which he was started on IV vancomycin and ampicillin/sulbactam. His cellulitis progressed over the next 3 days prompting magnetic resonance imaging (MRI) to be performed which revealed an abscess within the skin and subcutaneous fat, along the dorsum of the foot involving the metatarsals and phalanges consistent with osteomyelitis. He was taken to the operating room for debridement. Operating room cultures and blood cultures obtained on each day of hospitalization grew methicillin-susceptible *Staphylococcus aureus* (MSSA). Postoperatively, he has clinically improved and is anxious to be discharged.

Vital signs and laboratory values from today:

Na 142mEq/L, Cl 101mEq/L, BUN 14mg/dL, Glucose 90mg/dL, K 3.7mEq/L, BUN 22mEq/L, SCr 1.0mg/dL, WBC 20.1K/mm^3, Hgb 12.2g/dL, Hct 40%, Plt 307K/mm^3

1.9 m, 89.6 kg

96.9°F (36.1 °C), 95 beats/min, 17 breaths/min, 100% on room air, 110/53 mm Hg

Q1. Do you agree with this antibacterial regimen? If not, what alternative antibacterial regimen (drug/dose/route/duration) and monitoring plan do you recommend? Please explain rationale.

Q2. What was this patient's most likely primary source of infection? Does this patient need any additional diagnostic tests prior to developing a final plan? If so, please identify and explain rationale.

Q3. Does this patient meet criteria for uncomplicated or complicated *S. aureus* bacteremia? Please explain rationale.

Q4. Assuming the next set of blood cultures are sterile, what antibacterial regimen (drug/dose/route/duration) and monitoring plan do you recommend for outpatient treatment? Please explain rationale.

INTRODUCTION

1 Bacteremia reflects the presence of bacteria in the bloodstream, an otherwise sterile environment, which is identified based on the detection of any true-positive blood culture (Chapter e126, "Laboratory Tests to Direct Antimicrobial Pharmacotherapy").[1] Introduction of bacteria into blood is frequently caused by a focal (primary) source of infection, such as respiratory tract infections (Chapter 129, "Lower Respiratory Tract Infections"), intra-abdominal infections (Chapter 137, "Intra-abdominal Infections"), urinary tract infections (Chapter 139, "Urinary Tract Infections"), as well as bone and joint infections (Chapter 141, "Bone and Joint Infections"), but may also occur due to indwelling devices, medical procedures, or daily activities, such as oral hygiene. In select cases, a primary source cannot be identified. Bacteremia may be further complicated by the development of a systemic inflammatory response syndrome (SIRS) (Chapter 142, "Sepsis and Septic Shock"), or (metastatic) secondary foci, including infective endocarditis in 3% to 8% of cases.

Endocarditis is an inflammation of the endocardium, the membrane lining the chambers of the heart and covering the cusps of the heart valves.[2,3] More commonly, *infective endocarditis* refers to infection of the heart valves by various microorganisms after entry into the bloodstream. Although it typically affects native valves, it may also involve non-valvular areas or implanted material (eg, prosthetic heart valves, cardiac defibrillators, pacemakers, and vascular catheters). Bacteria primarily cause infective endocarditis, but fungi and a variety of other microorganisms can lead to the disease.[2,4] In most cases, infective endocarditis occurs secondary to a bloodstream infection, which originated from a primary source of infection (eg, bacterial endocarditis is secondary to a bacteremia originating from a primary source of infection).

Infective endocarditis is best classified based on the etiologic organism, anatomic site of infection, and pathogenic risk factors.[2,5,6] Infective endocarditis is often referred to as *acute* or *subacute* depending on the pace and severity of the clinical presentation. The acute, fulminating form is associated with high fevers and systemic toxicity. Virulent bacteria, such as *Staphylococcus aureus*, frequently cause this syndrome, and if untreated,

death may occur within days to weeks. On the other hand, subacute infective endocarditis is more indolent, caused by less virulent organisms, such as viridans group streptococci, and usually occurs in patients with preexisting valvular heart disease. Infection may also occur following surgical insertion of a prosthetic heart valve, resulting in prosthetic valve infective endocarditis (PVE), or insertion of a cardiac implantable electronic device, resulting in cardiac device infective endocarditis (CDIE).[7,8]

EPIDEMIOLOGY

In the United States, the incidence of bacteremia ranges from 113 to 204 per 100,000 persons and is associated with high rates of morbidity and mortality.[1,9] The epidemiology of bacteremia is difficult to characterize due to differences in study design, definitions used for community- and healthcare-associated bacteremia, as well as the overlap with numerous clinical syndromes.[10] However, patient population, geographic region, and infection prevention practices affect the etiology and rate of bacteremia. For example, in the United States, the annual incidence of *Staphylococcus aureus* bacteremia ranges from 38 to 46 per 100,000 person-years compared to 10 to 30 per 100,000 person-years elsewhere.[11,12]

Risk factors for developing bacteremia are generally non-specific, but some are more specific for individual pathogens or groups of pathogens than others (Table 134-1).[13,14] For example, persons who inject drugs (PWID) have a significantly increased risk for invasive methicillin resistant *S. aureus* (MRSA) bacteremia compared to others. Alternatively, patients who undergo urogenital surgeries are at increased risk for developing gram-negative bacteremia postoperatively.

TABLE 134-1

Risk Factors for Bacteremia

- Advanced age
- Chronic liver disease
- Diabetes mellitus
- End-stage renal disease on hemodialysis
- Functional or anatomic asplenia
- HIV infection
- Immunosuppressive medications
- Indwelling prostheses (eg, vascular catheters, surgically implanted materials, and orthopedic prostheses)
- Intravenous drug use
- Malignancies
- Malnutrition and hypoalbuminemia (less than 3 g/dL [30 g/L])
- Neutropenia
- Peripheral vascular disease
- Receipt of corticosteroids
- Recent procedures (eg, urogenital surgery, prostate biopsy, endoscopic retrograde cholangiopancreatography)
- Solid organ transplant
- Stem cell transplant
- Trauma or loss of skin integrity
- Urinary retention

Data from References 12–14

Though the overall incidence of infective endocarditis has remained stable in the United States, the prevalence of PWID has increased while the prevalence of patients with traditional risk factors has decreased.[15–17] Infective endocarditis is more common in men and primarily affects older patients likely due to an aging population with high rates of valvular disease and valve replacement surgery (increasing rates of healthcare-associated infective endocarditis). Most cases occur in individuals older than 60 years of age, and it is less common in children.[18–20] Native valve infective

endocarditis (NVE) occurs in 71% to 78% of cases, whereas PVE and CDIE account for 13% to 17% and 3% to 5% of cases, respectively.[6,16,21] PWID are also at high risk and account for 5% to 13% of cases. Other conditions associated with a higher incidence of infective endocarditis include diabetes mellitus, long-term hemodialysis, and poor dental hygiene.[6,20]

2 Most persons with infective endocarditis have risk factors, such as preexisting cardiac valvular abnormalities. Many types of structural heart disease result in turbulent blood flow that increases the risk for infective endocarditis. A predisposing risk factor, however, may be absent in up to 25% of cases (Table 134-2).[5,6,8,20,21]

TABLE 134-2

Risk Factors for Infective Endocarditis

- Presence of a prosthetic valve (highest risk)
- Previous infective endocarditis (highest risk)
- Healthcare-related exposure (high risk)
- Congenital heart disease (CHD)
- Advanced age
- Chronic IV access
- Diabetes mellitus
- Acquired valvular dysfunction (eg, rheumatic heart disease)
- Cardiac implantable device
- Chronic heart failure
- Mitral valve prolapse with regurgitation
- Intravenous drug use
- HIV infection
- Poor dentition and/or oral hygiene

Data from References 5,6,8,20,21.

Rheumatic heart disease was a prevalent risk factor for infective endocarditis, but the incidence of this disease continues to decline. The risk of infective endocarditis in persons with mitral valve prolapse and regurgitation is small; however, because the condition is prevalent, it is an important contributor to the overall number of infective endocarditis cases.[22] The risk of PVE is highest in the first 3 months after valve replacement and occurs in 1% to 3% of patients during the first postoperative year.[20,23]

ETIOLOGY

3 *Escherichia coli*, *Klebsiella* spp., *Pseudomonas aeruginosa*, *S. aureus*, *Enterococcus* spp., and *Streptococcus pneumoniae* are most often identified in patients with bacteremia from high income countries with the addition of *Salmonella* spp. in developing regions.[10] Historically, the etiology differed by whether the onset is community- or healthcare-acquired (eg, *S. pneumoniae* and *E. coli* are most often associated with community-acquired cases whereas *P. aeruginosa* is associated with healthcare-exposure) as well as the primary source of infection. However, a significant number of patients in the ambulatory care setting have frequent interaction with the healthcare system due to receipt of immunosuppressive medications, oftentimes necessitating vascular catheters, use of ambulatory surgery centers, and overall increasing age of the population. As a result, distinction between community- and healthcare-acquired has become less clear.[24] Alternatively, primary sources of infection differs, whereby urinary tract infections are more common in community-acquired cases while vascular catheters are more often implicated in patients who develop bacteremia in healthcare settings.[25]

4 Nearly every organism causing human disease may cause infective endocarditis, but three groups of organisms result in a majority of cases:

staphylococci, streptococci, and enterococci (Table 134-13).[4–6,26] The incidence of staphylococci, particularly *S. aureus*, continues to increase primarily due to healthcare exposure and intravenous drug use, surpassing viridans group streptococci as the leading cause of infective endocarditis.[5,21,26] Staphylococci (*S. aureus* and coagulase-negative staphylococci) are the most common cause of PVE within the first year after valve surgery. In general, streptococci cause infective endocarditis in patients with community-acquired disease and underlying cardiac abnormalities, such as mitral valve prolapse or rheumatic heart disease. Enterococcal endocarditis tends to follow genitourinary manipulations or obstetric procedures.[23] Although polymicrobial infective endocarditis is uncommon, it is encountered most often in PWID.[5] There are many exceptions to the preceding generalizations; thus, isolation of the causative pathogen and determination of its antimicrobial susceptibilities offer the best chance for successful therapy.

The mitral and aortic valves are affected most commonly in cases involving a single valve. Subacute endocarditis tends to involve the mitral valve, whereas acute disease often involves the aortic valve. Up to 35% of cases involve concomitant infections of both the aortic and the mitral valves. Infection of the tricuspid valve is less common, with most of these cases occurring in PWID. It is rare for the pulmonic valve to be infected.[23,26]

Although outcomes for infective endocarditis have improved with rapid diagnosis, appropriate treatment (eg, antimicrobial therapy, surgery, or both), and prompt recognition of complications should they arise, in-hospital mortality remains approximately 20%, while 6-month mortality is 30%.[19] Factors associated with increased mortality include heart failure, increasing age, endocarditis caused by resistant organisms, such as gram-negative bacteria, or fungi, left-sided endocarditis caused by *S. aureus*, paravalvular complications, healthcare-acquired infection, and PVE.[5,6,26] The presence of heart failure has the greatest negative impact on the short-term prognosis.[5] For left-sided NVE, mortality rates range from 15% to 45%; lower rates (4%-16%) occur with community-acquired disease that is most commonly caused by viridans group streptococci, while higher rates (25%-45%) occur with healthcare-associated disease that is more commonly caused by enterococci and staphylococci. Even higher mortality rates are seen with unusually encountered organisms (eg, mortality rates greater than 80% for fungi).[5,6] The mortality rate for right-sided infective endocarditis in PWID is generally low (eg, less than 10%).[5] For those who relapse after treatment for infective endocarditis, most will do so within the first 2 months after discontinuation of antimicrobials. Relapse rates for viridans group streptococcus are generally low (2%), whereas relapse is more likely in those with enterococcal infection (8%-20%) and PVE (10%-15%).[23] Despite appropriate treatment and recovery, the risk of morbidity and mortality following infective endocarditis persists for years, with a 5-year mortality rate of approximately 45%.[27] Morbidity remains elevated because of a greater likelihood of recurrent infective endocarditis, heart failure, and embolism or, if a valve is replaced, the risk of anticoagulation, valve thrombosis, or additional valve surgery.[28]

PATHOPHYSIOLOGY

The pathophysiology of bacteremia is multifactorial and may result from numerous causes such as daily oral hygiene, medical procedures, injection drug use, or seeding the bloodstream from focal (primary) source of infection, but the risk varies considerably between syndromes (Tables 134-3 and 134-4).[1,29,30] As a result, bacteremia is frequently considered a secondary infection originating from the focal source (eg, respiratory tract, intra-abdominal tract), but approximately 10% of cases are categorized as primary bacteremia in which bacteria are directly introduced into the bloodstream without an obvious primary source (eg, injection drug use, vascular catheter insertion).[31] Identification of the primary source is critical to making therapeutic decisions.

TABLE 134-3

Etiologic Organisms in Infective Endocarditis[a]

Agent	Percentage of Cases
Staphylococci	30-70
• *S. aureus* (coagulase positive)	20-68
• Coagulase negative	3-26
Streptococci	9-38
• Viridans group streptococci	10-28
• Other streptococci	3-14
Enterococci	5-18
Gram-negative aerobic bacilli	1.5-13
Fungi	1-9
Miscellaneous bacteria	less than 5
Polymicrobial infections	1-2
"Culture negative"	5-17

[a]Values encompass community-acquired, healthcare-associated, native valve, and prosthetic valve infective endocarditis.

Data from References 4,6,17,26.

TABLE 134-4

Probability of Bacteremia in Various Clinical Scenarios

High (greater than 50%)	• Discitis and vertebral osteomyelitis • Epidural abscesses • Acute, non-traumatic native septic arthritis • Meningitis • Septic shock • Catheter-related bloodstream infections • Endovascular infections (eg, infective endocarditis, septic thrombophlebitis, vascular graft infections)
Moderate (21%-50%)	• Severe sepsis • Acute pyelonephritis • Cholangitis • Community acquired pneumonia, severe • Pyogenic liver abscesses • Rigors/chills in a febrile patient • Non-vascular shunt (eg, ventriculoperitoneal shunt) infections
Low to moderate (10%-20%)	• Cellulitis in patients with comorbidities • Ventilator-associated pneumonia
Low (less than 10%)	• Uncomplicated cellulitis • Cystitis • Prostatitis • Community acquired pneumonia, non-severe • Hospital-acquired pneumonia
Very low (less than 5%)	• Fever within 48 hours postoperatively • Isolated fever in general medicine patients

Data from References 1,29,30.

Skin and mucosal membranes of the respiratory and gastrointestinal tract serve as the first barrier to defense against bacterial invasion into the bloodstream.[29] In some cases, the host immune response can eradicate bacteria that enter the bloodstream which results in a transient, benign condition. However, if bacteria are able to overcome the host immune response (patients with turbulent cardiac blood flow, foreign or prosthetic material, or when host defense mechanisms fail due to inherent or acquired immune deficits), bacteria can then disseminate throughout the body via hematogenous spread leading to a systemic infection and inducing an inflammatory response. Both transient and persistent bacteremia can lead to secondary metastatic infections involving the meninges, pericardium, kidneys, vertebrae, joints, as well as the heart valves resulting in infective endocarditis.

The development of infective endocarditis via hematogenous spread, the most common route, requires the sequential occurrence of several factors. These components are complex and not fully elucidated.[32,33] See figure 1 or reference 33 for a visual representation.

1. *The endothelial surface of the heart is damaged.* This injury occurs with turbulent blood flow associated with the valvular lesions previously described.

2. *Platelet and fibrin deposition occurs on the abnormal epithelial surface.* These platelet-fibrin deposits form a "sterile vegetation," which is referred to as *non-bacterial thrombotic endocarditis.*

3. *Bacteremia gives organisms access to the endocardial surface.* Transient bacteremia commonly follows certain dental, GI, urologic, and gynecologic procedures. Staphylococci, viridans group streptococci, and enterococci are most likely to adhere to non-bacterial thrombotic endocarditis, probably because of production of specific adherence factors such as adhesins for staphylococci and dextran by some oral streptococci. Gram-negative bacteria rarely adhere to heart valves and are uncommon causes of infective endocarditis.

4. *After colonization of the endothelial surface, a "vegetation" of fibrin, platelets, and bacteria forms.* As the vegetation matures, a protective cover of fibrin and platelets protects bacteria from host immune response. This allows unimpeded bacterial growth to concentrations as high as 10^9 to 10^{11} organisms per gram of tissue, in addition to biofilm formation.

The pathogenesis of early PVE or CDIE differs from infective endocarditis acquired by the hematogenous route because surgery may directly inoculate prosthetic material with bacteria from the patient's skin or operating room personnel.[26,34] In the case of early PVE, a recently placed non-endothelialized valve is more susceptible to bacterial colonization than are native valves. Bacteria also may colonize the new valve from contaminated bypass pumps, cannulas, and pacemakers or from a nosocomial bacteremia subsequent to an intravascular catheter.[8,23,26] The mechanism of bacterial colonization and pathogenesis in late PVE is similar to NVE.[23]

One or more vegetations, varying in size from a few millimeters to centimeters, may be seen in a patient with infective endocarditis. Bacteria within the vegetation grow slowly and are protected from antimicrobials and host defenses. The adverse effects of infective endocarditis and the resulting lesions can be far-reaching and include the following: local perivalvular damage, embolization of septic fragments with potential hematogenous seeding of remote sites, and formation of antibody complexes.[23,32]

Formation of vegetations may destroy valvular tissue, and continued destruction can lead to acute heart failure in 50% to 60% of cases via perforation of the valve leaflet, rupture of the chordae tendineae or papillary muscle, or, for patients with PVE, valve dehiscence.[35,36] Occasionally, valvular stenosis may occur. Abscesses can develop in the valve ring or in myocardial tissue itself, potentially involving cardiac conduction tissue. Even with resolution of the process, fibrosis of tissue with some residual dysfunction is possible.

Vegetations may be friable, and fragments may be released downstream. These infected particles, termed *septic emboli*, can result in organ abscess or infarction. Septic emboli from right-sided endocarditis commonly lodge in the lungs, causing pulmonary abscesses. Emboli from left-sided vegetations commonly affect organs with high blood flow such as the kidneys, spleen, and brain.[5,32]

Circulating immune complexes consisting of antigen, antibody, and complement may deposit in organs, producing local inflammation, and damage them (eg, glomerulonephritis in the kidneys). Other potential pathologic changes that result from immune-complex deposition or septic emboli include the development of "mycotic" aneurysms (although the aneurysm is usually bacterial in origin, not fungal), cerebral infarction, splenic infarction and abscess, and skin manifestations such as petechiae, Osler's nodes, and Janeway lesions.[23,32]

CLINICAL PRESENTATION

Bacteremia

5 Clinical manifestations of bacteremia vary but may involve fever, chills, rigors, altered hemodynamics, shock, coagulation disorders, cutaneous findings (eg, ulcerations), and a documented or suspected primary source of infection.[1,25] Patients with bacteremia may be normothermic with a normal white blood cell count as neither leukocytosis nor fever (≥ 38°C) alone or in combination predict the presence of bacteremia.[30] However, rigors and shaking chills increased the likelihood of bacteremia. Symptoms may reflect the primary focus of infection and depend on whether other organs or organ systems are involved. Past medical and surgical history may also impact patient complaints upon presentation. In some cases, bacteremia may evoke an inflammatory response resulting in sepsis, but not all cases of bacteremia progress to sepsis.

Infective Endocarditis

The clinical presentation of infective endocarditis is highly variable and non-specific. Fever is the most common finding, in more than 90% of patients, and is often accompanied by other vague symptoms (Clinical Presentation).[35,36] Heart murmurs are found in the majority of patients (approximately 85%), most often preexisting, with some documented as new or changing. Infective endocarditis usually begins insidiously and worsens gradually. Patients may present with non-specific findings such as fever, chills, weakness, dyspnea, cough, night sweats, weight loss, or malaise. In contrast, patients with acute disease, such as PWID and those with *S. aureus* infective endocarditis, may appear with classic signs of sepsis.

Splenomegaly is an uncommon finding in acute infective endocarditis, due to improved diagnostics and antimicrobial therapy, but it occurs more frequently in patients with subacute infective endocarditis. Other important clinical signs may include the following peripheral manifestations ("stigmata") of endocarditis[19,26,32]:

1. Osler's nodes: 2 to 15 mm painful, tender, purplish or erythematous subcutaneous papules or nodules on the pads of the fingers and toes due to embolism, immunologic phenomena, or both occurring in less than 5% of cases.
2. Janeway lesions: Hemorrhagic, painless plaques on the palms of the hands or soles of the feet due to embolism occurring in less than 5% of cases.
3. Splinter hemorrhages: Thin, linear hemorrhages found under the nail beds of the fingers or toes.
4. Petechiae: 1 to 2 mm in diameter, erythematous, painless, non-blanching, hemorrhagic lesions most often visualized on the anterior trunk, buccal mucosa and palate, and conjunctivae that resolve after a few days.
5. Clubbing of the fingers: Proliferative changes in the soft tissues about the terminal phalanges observed in long-standing endocarditis.
6. Roth's spots: Retinal infarct with central pallor and surrounding hemorrhage.
7. Emboli: Embolic phenomena occur in up to one-third of cases and may result in significant complications. Right-sided endocarditis may result in pulmonary emboli, causing pleuritic pain with hemoptysis. Left-sided endocarditis can result in renal artery emboli causing flank pain with hematuria, splenic artery emboli causing abdominal pain, and cerebral emboli, which may result in hemiplegia or alteration in mental status.

Patients with infective endocarditis typically have laboratory abnormalities; however, none of these changes is specific for the disease. Anemia (normochromic, normocytic), thrombocytopenia, and leukocytosis may be present. The white blood cell count is often normal or only slightly elevated, sometimes with a mild left shift. Acute bacterial endocarditis, however, may present with an elevated white blood cell count, consistent with a fulminant infection. The erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) may be elevated in approximately 60% of patients. Often the urinalysis shows proteinuria and microscopic hematuria, which may occur in 50% to 65% and 30% to 60% of patients, respectively.[32]

CLINICAL PRESENTATION: Infective Endocarditis

General

The clinical presentation of infective endocarditis is highly variable and non-specific

Symptoms

The patient may complain of fever, chills, weakness, dyspnea, cough, night sweats, weight loss, and/or malaise

Signs

Fever is common, as is a heart murmur (sometimes new or changing). The patient may have congestive heart failure, cardiac conduction abnormalities, cerebral manifestations, embolic phenomenon, splenomegaly, or skin manifestations (eg, Osler's nodes, Janeway lesions)

Laboratory Tests

The patient's white blood cell count may be normal or only slightly elevated

Non-specific findings include anemia (normochromic, normocytic), thrombocytopenia, an elevated erythrocyte sedimentation rate or C-reactive protein, and altered urinalysis (proteinuria/microscopic hematuria)

Other Diagnostic Tests

An electrocardiogram, chest radiograph or computed tomography, and echocardiogram are commonly performed. Echocardiography to determine the presence of valvular vegetations plays a key role in the diagnosis of infective endocarditis; it should be performed in all suspected cases

Diagnosis

Bacteremia

Bacteremia is diagnosed by detection of organism(s) from blood cultures (Chapter e126). Ideally, at least two sets of blood cultures, where each set consists of one aerobic bottle and one anaerobic bottle is obtained prior to administration of antibacterial therapy to lessen the risk of false-negative results (3 sets are necessary in cases of infective endocarditis).[5,37] Each set of blood cultures should be collected by a trained phlebotomist from separate venipuncture sites that have been disinfected rather than vascular catheters due to a decreased risk of contamination from normal skin flora. Upper extremity vessels are preferred over lower extremity vessels or those affected by dermatologic diseases.[38]

Interpretation of positive blood cultures represents a challenging task to determine the clinical significance of the organism(s) identified, especially in the case of normal skin flora which can cause bacteremia in the right clinical setting (eg, intravascular catheter infections). Single blood culture sets should be avoided due to decreased sensitivity as the cumulative yield of true pathogens increases with the number of blood cultures[39]. In addition, collection of blood cultures after receipt of antibacterial therapy significantly decreases the sensitivity of blood cultures.[37]

When assessing significance of positive blood cultures, the number of positive cultures and the total number of cultures obtained, organism(s) isolated, site(s) of collection, and likelihood of bacteremia must be considered.[38,40] Detection of certain organisms (eg, *S. aureus*, *S. pneumoniae*, Enterobacterales, yeast) should always be considered clinically significant, whereas other organisms may represent clinically significant pathogens or contaminants depending on the clinical status of the patient (Table 134-5).

TABLE 134-5

Interpretation of Positive Blood Cultures

True pathogens	• β-Hemolytic streptococci • *Bacteroides* spp. • Enterobacterales • *Fusobacterium* spp. • *Haemophilus influenzae* • *Listeria monocytogenes* • *Neisseria meningitidis* • *Pseudomonas aeruginosa* • *Staphylococcus aureus* • *Streptococcus pneumoniae* • Yeast
Possible pathogens	• *Clostridium* spp. • *Enterococcus* spp. • Viridans group streptococci
Unlikely pathogens	• *Bacillus* spp. • Coagulase-negative staphylococci[a] • *Corynebacterium* spp. • *Cutibacterium acnes* • *Micrococcus* spp.

[a]Probability of being a true pathogen increases in the setting of a vascular catheter

Data from References 38,40

Infective Endocarditis

The signs and symptoms of infective endocarditis are not specific, and the diagnosis is often unclear. The identification of infective endocarditis requires the integration of clinical, laboratory, and echocardiographic findings. The Modified Duke Criteria include major and minor variables (Table 134-6).[41,42] Based on the number of major and minor criteria that are fulfilled, patients suspected of infective endocarditis are categorized into three separate groups: definite infective endocarditis, possible infective endocarditis, or rejected infective endocarditis.[42]

TABLE 134-6

Diagnosis of Infective Endocarditis According to the Modified Duke Criteria

Definite IE
Pathological criteria Microorganisms demonstrated by culture or histological examination of a vegetation, a vegetation that has embolized, or an intracardiac abscess specimen; or pathological lesions; vegetation or intracardiac abscess confirmed by histologic al examination showing active endocarditis
Clinical criteria

Two major criteria, or
One major criteria and three minor criteria, or
Five minor criteria

Possible IE

One major criterion and one minor criteria, or
Three minor criteria

Rejected IE

Firm alternative diagnosis explaining evidence of infective endocarditis, or
Resolution of infective endocarditis syndrome with antimicrobial therapy for four or fewer days, or
No pathological evidence of infective endocarditis at surgery or autopsy, with antimicrobial therapy for 4 or fewer days, or does not meet criteria for possible infective endocarditis, as above

Major Criteria

Blood culture positive for infective endocarditis
Typical microorganisms consistent with infective endocarditis from 2 separate blood cultures:
Viridans streptococci, *S. gallolyticus*, HACEK group, *S. aureus*; or
Community-acquired enterococci, in the absence of a primary focus; or
Microorganisms consistent with infective endocarditis from persistently positive blood cultures, defined as follows:
At least two positive blood cultures drawn greater than 12 hours apart;
or
Three or a majority of 4 or more separate blood cultures (with first and last sample drawn at least 1 hr apart)
Single positive blood culture for *Coxiella* burnetii or antiphase I immunoglobulin G antibody titer >1:800

Evidence of endocardial involvement
Echocardiogram positive for infective endocarditis (transesophageal echocardiography recommended for patients with prosth etic valves, rated at least “possible infective endocarditis” by clinical criteria, or complicated infective endocarditis [paravalvul ar abscess]; transthoracic echocardiography as first test for other patients), defined as follows:
Oscillating intracardiac mass on valve or supporting structures, in the path of regurgitant jets or on implanted material in the absence of an alternative anatomic explanation; or abscess; or
New partial dehiscence of prosthetic valve
New valvular regurgitation (worsening or changing of preexisting murmur not sufficient)

Minor Criteria

Predisposition, predisposing heart condition, or injection drug use

Fever, temperature >38°C (100.4°F)
Vascular phenomena, major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjuncti val hemorrhages, and Janeway lesions
Immunologic phenomena: glomerulonephritis, Osler’s nodes, Roth’s spots, and rheumatoid factor

Microbiologic evidence: positive blood culture but does not meet a major criterion as noted above or serologic evidence of active infection with organism consistent with infective endocarditis

Echocardiographic minor criteria eliminated

HACEK, Haemophilus species (*H. parainfluenzae, H. aphrophilus, H. paraphrophilus*), Aggregatibacter species, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella kingae*.

Data from References 41,42.

The hallmark of infective endocarditis is a continuous bacteremia caused by bacteria shedding from the vegetation into the bloodstream; 90% to 95% of patients with infective endocarditis have positive blood cultures.[2,5,23,43] In most cases, three sets of blood cultures, should be collected prior to starting antimicrobial therapy, with the first and last set drawn at least 1 hour apart. This allows expedient initiation of empirical antimicrobial therapy and can help guide early decisions regarding other potential interventions. Most cases of infective endocarditis are caused by easily cultivable pathogens that can be isolated from routine blood cultures within a 5-day incubation period. However, prolonged incubation of blood cultures or specialized testing may need to be performed (see "'culture-negative' infective endocarditis" below). In patients who undergo valve surgery, excised valve tissue should be submitted for microbiologic testing. Additionally, histopathologic evaluation should be performed to identify the presence of microorganisms and characteristics of inflammatory changes. Specialized testing (eg, polymerase chain reaction [PCR]) may also be performed on valve tissue to improve the likelihood of identifying the infectious etiology.

"Culture-negative" infective endocarditis describes a patient in whom a clinical diagnosis of infective endocarditis is likely, but blood cultures do not yield a pathogen. This condition is often the consequence of previous antimicrobial therapy, improperly collected blood cultures, or unusual organisms.[5] When blood cultures from patients suspected of having infective endocarditis do not grow after 48 to 72 hours, cultures should be held for up to a month to detect growth of fastidious organisms.[5] Specialized testing, such as serology or PCR, may be required to identify less common pathogens (eg, *Coxiella burnetii*, *Bartonella* spp., *Brucella* spp.).

An electrocardiogram, chest radiograph or computed tomography, and echocardiogram are performed for patients suspected of endocarditis. The electrocardiogram rarely shows important diagnostic findings but may reveal heart block, suggesting extension of the infection. The chest radiograph or computed tomography may provide more diagnostic information, such as identification of septic pulmonary emboli in a patient with right-sided endocarditis. Septic pulmonary emboli may occur, leading to multiple lung foci.

Echocardiography plays an important role in the diagnosis and management of infective endocarditis and should be performed for all patients suspected of this infection.[5,6] In addition to helping in the diagnosis of infective endocarditis, the echocardiogram allows the clinician to evaluate hemodynamic stability and the need for urgent surgical intervention; it also provides a rough estimate of the likelihood of embolism.[5] Typically, transthoracic echocardiography (TTE) is performed first due to the rapidity (eg, fasting state unnecessary) and accessibility (eg, 24-hour service available in most institutions) followed by transesophageal echocardiography (TEE). TEE is more sensitive for detecting vegetations (90%-100%) as compared with TTE (40%-66%), and TEE maintains good specificity (90%-100%).[2,6,19] However, TTE may be the only evaluation needed for children or adults in whom the clinical suspicion of infective endocarditis is relatively low.[5,43] An initial or follow-up TEE is recommended in high-risk patients such as those with CHD, previous endocarditis, new murmur, heart failure, or other stigmata of endocarditis.[5,28] For those patients with suspected PVE or CDIE, TEE should be considered mandatory. The lack of vegetation on echocardiogram does not exclude infection even if the transesophageal approach is used. In these cases, there is an evolving role for advanced imaging modalities such as three dimensional TEE, 18-F fluorodeoxyglucose (FDG) positron emission tomographic/computed tomographic (PET/CT), and single-photon emission computed tomography.[5,6]

TREATMENT

Desired Outcomes

The desired outcomes for treatment of bacteremias are to:

1. Eradicate the causative organism with optimal therapy while minimizing therapeutic failure and potential for resistance

2. Identify and manage the focal (primary) source of infection as well as any secondary foci (metastatic) of infections
3. Relieve the signs and symptoms associated with the infection including the bacteremia, primary source of infection, and if present, secondary metastatic infections
4. Decrease morbidity and mortality associated with the bacteremia and primary source of infection
5. Provide cost-effective antimicrobial therapy determined by the likely or identified pathogen, drug susceptibilities, hepatic and renal function, drug allergies, and anticipated drug toxicities

The desired outcomes for treatment and prophylaxis of infective endocarditis are to:

1. Relieve the signs and symptoms of the disease
2. Decrease morbidity and mortality associated with the infection
3. Eradicate the causative organism with minimal drug exposure
4. Provide cost-effective antimicrobial therapy determined by the likely or identified pathogen, drug susceptibilities, hepatic and renal function, drug allergies, and anticipated drug toxicities
5. Prevent infective endocarditis from occurring or recurring in high-risk patients with appropriate prophylactic antimicrobials

General Approach to Treatment

Bacteremia

Urgent initiation of appropriate antibacterial therapy is necessary in patients with bacteremia as delays are associated with increased morbidity and mortality.[44] Empirical parenteral therapy should be based on the usual pathogens at the site(s) of presumptive primary source(s) of infection. In the case of an unknown primary source of infection or primary bacteremia (those without an obvious source), selection of empirical parenteral antibacterial therapy is more challenging but should provide a broad spectrum of activity while additional diagnostic testing is performed to determine the site(s) of infection. Source control (eg, drainage, debridement) may be required depending on the primary source(s) or secondary metastatic of infections (eg, intra-abdominal infections [Chapter 137], bone and joint infections [Chapter 141]). Additional (double) coverage is unnecessary if the empirical therapy is likely to have activity against the potential pathogens but may prove beneficial if patient-specific risk factors for antimicrobial resistance are present or local resistance rates are high based on antibiogram data (Chapter e126).

Once microbiologic data from blood cultures are available, findings should then be interpreted to differentiate contamination from true bacteremia (Table 134-5) in conjunction with the patient's clinical history, physical findings, risk factors (Table 134-1), and diagnostic testing. However, if the significance of blood culture findings or antimicrobial selection is uncertain, consultation with an infectious diseases specialist should be performed.[44] Antibacterial therapy should be deescalated to target that specific pathogen based on microbiologic data including Gram's stain results from rapid diagnostic testing and antimicrobial susceptibility testing data. Though no general guideline exists for bacteremia, management often depends on the specific organism(s) identified, as well as primary source(s) or secondary metastatic infections to determine the appropriate non-pharmacological and pharmacological treatments. In most cases, treatment is initiated in the hospital, but can often be completed in the outpatient setting (termed outpatient antimicrobial therapy [OPAT]) once source control has been achieved and the patient has clinically improved. Patients considered for OPAT must be hemodynamically stable, compliant with therapy, have careful medical monitoring, understand the potential complications of the disease, and have immediate access to medical care. Advances in technology allow for the outpatient administration of complex antimicrobial regimens that significantly reduce the cost of therapy. Simple regimens, such as single daily doses of ceftriaxone or continuous infusions of penicillin, may improve patient convenience and potentially compliance. Although bacteremia and infective endocarditis are common in PWID and home healthcare would substantially reduce the cost of treatment, many clinicians are hesitant with outpatient IV therapy because central venous access is required. However, there are no significant differences in rates of vascular access complications between those who do and do not inject drugs.[45] Parenteral antibacterial therapy has been considered the standard of care, but emerging data support the use of oral antibacterial therapy in

select patients.[46]

Infective Endocarditis

Empirical antimicrobial therapy should usually be initiated in most patients after presumptive or confirmed diagnosis of infective endocarditis.[5] However, in select patients, who are not acutely ill, empiric antimicrobial therapy can be withheld until the results of blood or tissue cultures or serologic tests are available. Due to the importance of identifying an infectious etiology, antimicrobial therapy should not be started until blood cultures have been obtained. Patient history, including past medical, surgical, social, and family, risk factors, and current and previous antimicrobial therapy should be considered when selecting empirical antimicrobial therapy (Table 134-2). Consultation with an infectious diseases specialist should occur to assist in selecting an optimal empirical therapy.

Specific treatment recommendations from the American Heart Association (AHA) and the European Society of Cardiology (ESC) provide guidance for the management of infective endocarditis.[5] Both provide important recommendations for the combination of early diagnosis, early antimicrobial therapy, and early surgery; but there are some subtle differences. The ESC guidelines recommend that an "endocarditis team," consisting of cardiologists, cardiac surgeons, and specialists in infectious diseases, manage patients with infective endocarditis. The AHA guidelines place more emphasis on a team-based approach when assessing the timing and need for surgical intervention.

The AHA and ESC guidelines use an evidence-based scoring system where recommendations are given a classification as well as level of evidence. Class I recommendations are conditions for which there is evidence, general agreement, or both that a given procedure or treatment is useful and effective. Class II recommendations are conditions for which there is conflicting evidence, a divergence of opinion, or both about the usefulness/efficacy of a procedure or treatment (IIa implies that the weight of evidence/opinion is in favor of usefulness/efficacy, whereas IIb implies that usefulness/efficacy is less well established by evidence/opinion). Class III recommendations are conditions for which there is evidence, general agreement, or both that the procedure/treatment is not useful/effective and in some cases may be harmful. Level of evidence is listed as A (data derived from multiple randomized clinical trials), B (data derived from a single randomized trial or non-randomized studies), and C (consensus opinion of experts).

8 The most important approach in the treatment of infective endocarditis is isolation of the infecting pathogen and determination of antimicrobial susceptibilities, followed by high-dose, antimicrobial therapy, most often administered via parenteral route, for an extended period.[5–7,32] Susceptibility testing is crucial given the increasing rate of antimicrobial resistance to commonly encountered pathogens. Treatment usually is started in the hospital, but for select patients it is often completed in the outpatient setting (OPAT). Large doses of parenteral antimicrobials, as opposed to oral antimicrobials, are recommended to achieve bactericidal concentrations within vegetations. An extended duration of therapy is required, even for susceptible pathogens, because microorganisms are enclosed within valvular vegetations and fibrin deposits. These barriers impair host defenses and protect microbes from phagocytic cells. In addition, high bacterial concentrations within vegetations may result in an inoculum effect that further resists killing (see Chapter e126 for additional discussion). Many bacteria are not actively dividing, further limiting the rate of bacterial death. For most patients, a minimum of 4 to 6 weeks of therapy is required.[5,6]

In the Partial Oral Treatment of Endocarditis (POET) trial, changing to oral antimicrobial therapy after at least 10 days of IV therapy was non-inferior to continuing IV antimicrobial therapy in patients with left-sided native or PVE caused by streptococci, *Enterococcus faecalis*, *S. aureus* (not MRSA), or coagulase-negative staphylococci.[47] All-cause mortality, unplanned cardiac surgery, embolic events, or relapse of bacteremia within 6 months, was similar between groups. Oral regimens included a combination of at least two of the following antimicrobials: moxifloxacin, amoxicillin, clindamycin, rifampicin, dicloxacillin, fusidic acid, and linezolid. Due to strict inclusion and exclusion criteria, frequent outpatient follow-up required, and use of oral antimicrobial agents that are unavailable or infrequently used in the United States, only a select group of patients with left-sided infective endocarditis with functioning GI tracts and a high likelihood for compliance may be candidates for combination oral antimicrobial therapy.

Non-pharmacologic Therapy

Bacteremia

1 Management of bacteremia requires identification and resolution of primary source(s) of infection via source control which is defined as a physical intervention aimed at removing or eliminating a focus of invasive infection (Table 134-7) and most often performed by a surgeon.[48] Source control may include one or more of the following: drainage, debridement, device removal, and definitive reconstructive manners. The ability to successfully

complete source control depends on whether an anatomic diagnosis can be established and if the patient is stable enough to undergo the procedure(s).

TABLE 134-7

Sources for Common Causes of Bacteremia

Enterobacterales (eg, *E. coli*, *Klebsiella* spp., *Enterobacter* spp., *Serratia* spp., *Citrobacter* spp.)	• Genitourinary tract • Gastrointestinal tract • Respiratory tract (in hospitalized patients) • Translocation from the gastrointestinal or genitourinary tract due to disruption or procedure • Vascular catheter-related (if applicable)
Pseudomonas aeruginosa	• Respiratory tract (in hospitalized patients) • Vascular catheter- or prostheses-related (if applicable) • Genitourinary tract • Wounds
Staphylococcus aureus	• Wounds • Vascular catheter- or prostheses-related (if applicable) • Post-surgical • Injection drug use
Coagulase negative staphylococci	• Vascular catheter- or prostheses-related (if applicable) • Post-surgical
Enterococcus spp.	• Translocation from the gastrointestinal tract due to disruption or procedure • Genitourinary tract (eg, UTI, prostatitis) • Vascular catheter- or prostheses-related (if applicable)
Viridans group streptococci	• Oral mucosa
Anaerobes	• Oral mucosa • Gastrointestinal tract • Genitourinary tract

Data from References 48

In addition, echocardiography, a component of the Modified Duke Criteria, is frequently performed in patients with bacteremia, especially in those with suspected infective endocarditis. Though less clear for other causes of bacteremia, echocardiography should be performed in all patients with *S. aureus* bacteremia as the prevalence of infective endocarditis is approximately 25%.[49] However, significant variation exists as to which patients should undergo TEE following an unremarkable TTE. While TEE is preferred due to increased sensitivity, TTE may be sufficient in select patients without specific risk factors for infective endocarditis, such as those with nosocomial acquisition without intracardiac devices or dependence on hemodialysis.

Due to the high morbidity and mortality associated with bacteremia, evidence-based practices that include appropriate selection and duration of antimicrobial therapy, in addition to diagnostic testing to identify the primary source(s) or secondary metastatic infection(s), as well as infective endocarditis, are crucial. Unfortunately, these recommendations do not always translate into clinical practice. Consultation with infectious diseases providers to ensure adherence to these evidence-based practices, especially in patients with *S. aureus* or *Enterococcus* spp. bacteremia, has been associated with decreased risk of recurrence, fewer readmissions, and lower mortality rates.[50–53] Since consultation with infectious diseases providers may not be feasible in all healthcare settings, automated pharmacist and/or antimicrobial stewardship program interventions have been developed to increase adherence to evidence-based practices.[54]

Infective Endocarditis

Surgical intervention to remove the infectious foci and repair valves and/or valvular structures is an important adjunct in the management of both NVE and PVE and is now performed in up to 50% of patients.[21] In most surgical cases, valvectomy and valve replacement are performed to remove infected tissue and to restore hemodynamic function. Indications for surgery include heart failure, persistent bacteremia, persistent vegetation, an increase in vegetation size, or recurrent emboli despite prolonged antimicrobial treatment, valve dysfunction, paravalvular extension (eg, abscess), or endocarditis caused by difficult to treat or resistant organisms (eg, fungi or gram-negative bacteria).[5–7] More controversial is the appropriate timing of surgery as well as duration of antimicrobial therapy postoperatively. Additionally, studies evaluating postsurgical outcomes and associated mortality are limited such that a specific risk prediction system has not been established.[55–59] Early surgery (eg, within 48 hr) may be appropriate in patients with severe heart failure and large vegetations, whereas patients with septic shock, advanced age, or neurologic complications of infective endocarditis may have more detrimental outcomes.[55,57,60,61] The multiple factors that need to be considered in evaluating the need for and timing of surgery is why a multidisciplinary management approach (eg, “endocarditis team”) is critical.[5,6,32]

Pharmacologic Therapy

Bacteremia

Gram-Negative Bacilli

Detection of gram-negative bacilli from blood cultures should always be considered significant and prompt initiation of empirical parenteral therapy based on the patient’s history, comorbidities, previous microbiologic results, as well as whether the infection is community- or healthcare-acquired and local resistance patterns. Ceftriaxone, cefepime, or piperacillin/tazobactam should be added in cases where *P. aeruginosa* is an unlikely pathogen. While an anti-pseudomonal carbapenem (eg, meropenem) should be active, these broad-spectrum antibacterial agents are typically reserved for patients with a history of drug-resistant gram-negative organisms. The risks for *P. aeruginosa* bacteremia include hospital-onset gram-negative bacteremia, as well as healthcare exposures, hemodialysis, residence in a long-term care facility, recent antibacterial or chemotherapy treatment, or immunodeficiency. If *P. aeruginosa* is a concern (eg, hospital-onset gram-negative bacteremia), a single agent consisting of an anti-pseudomonal cephalosporin, anti-pseudomonal β-lactam/β-lactamase inhibitor (eg, piperacillin/tazobactam), or anti-pseudomonal carbapenem (eg, meropenem), is appropriate where less than 10% to 20% of *P. aeruginosa* isolates are resistant to the empiric therapy. Alternatively, double coverage consisting of an anti-pseudomonal cephalosporin (eg, ceftazidime, cefepime), anti-pseudomonal β-lactam/β-lactamase inhibitor (eg, piperacillin/tazobactam), or anti-pseudomonal carbapenem (eg, meropenem) combined with an aminoglycoside or anti-pseudomonal fluoroquinolone should be considered in patients with immunodeficiencies or risk factors for drug-resistant *P. aeruginosa* hospitalized at a facility where more than 10% to 20% of *P. aeruginosa* isolates are resistant to the empiric therapy.[62] Empiric antibacterial therapy against multidrug-resistant organisms (eg, extended spectrum β-lactamase [ESBL]- or carbapenem resistant) is warranted in patients with a history of infection(s) caused multidrug-resistant organisms, areas with high local prevalence of multidrug-resistant organisms, and cases of breakthrough bacteremia in patients receiving antibacterial therapy for gram-negative organisms.

Once identification and susceptibility results are available, antibacterial therapy should be deescalated to the most narrow spectrum agent to target the specific pathogen(s) isolated and avoid unnecessary adverse events and inducing resistance.[62] Parenteral therapy has been considered the standard of care for gram-negative bacilli bacteremia. Many oral antimicrobial agents are highly bioavailable and provide therapeutic concentrations within the bloodstream and at the primary source of infection, which may achieve similar outcomes to patients treated exclusively with parenteral antimicrobial therapy, especially in patients with uncomplicated gram-negative bacteremia defined as no evidence of central nervous system,

cardiovascular, osteoarticular, or other deep-seated infection.[63]

Similar 30-day mortality was observed in patients with uncomplicated Enterobacterales bacteremia from a urinary, intra-abdominal, vascular catheter, pulmonary, or skin and soft tissue source who switched to an oral antibacterial agent after a median 3 days of parenteral therapy compared to those who continued parenteral therapy for the entire duration.[46] The majority of patients in the oral therapy group were changed to a fluoroquinolone or trimethoprim/sulfamethoxazole, while the remainder received oral β-lactams. Oral β-lactams have not been frequently used for patients with uncomplicated Enterobacterales bacteremia due to limited bioavailability and variable bloodstream concentrations.[63] However, 30-day recurrent bacteremia and 30-day mortality were not significantly different with oral β-lactams compared with oral fluoroquinolones or trimethoprim/sulfamethoxazole among patients with *E. coli*, *Klebsiella* spp., or *Proteus* spp. bacteremia from a urinary source.[64] Patients were transitioned to oral fluoroquinolones or trimethoprim/sulfamethoxazole after a median 5 days of parenteral therapy compared to 4 days for those receiving oral β-lactams, which consisted of amoxicillin/clavulanate, cephalexin, and cefpodoxime proxetil. In most cases, patients with uncomplicated Enterobacterales bacteremia may be safely transitioned to oral antibacterial therapy after approximately 3 days of parenteral therapy. Selection of oral antibacterial therapy with high bioavailability and optimal dosing are necessary to ensure therapeutic concentrations within the bloodstream and at the primary source of infection.[65] However, parenteral therapy should be administered for the entire duration in cases where those criteria cannot be satisfied.

Traditionally, patients with uncomplicated gram-negative bacteremia received 14 days of parenteral antibacterial therapy, but treatment durations can be shortened to 7 days in most patients. A randomized trial comparing 7 to 14 days of antibacterial therapy in patients with uncomplicated gram-negative bacteremia found no significant differences in 14- or 28-day mortality between groups.[66] Additionally, a 9-day duration of antimicrobial therapy and a 16-day duration for uncomplicated *P. aeruginosa* bacteremia resulted in similar rates of recurrent infection or mortality within 30 days of antimicrobial cessation.[30]

Gram Positive

Staphylococcus aureus

Empirical therapy in patients with suspected *S. aureus* bacteremia, prior to susceptibility results, should include activity against MRSA with either vancomycin or daptomycin in the majority of cases due to the increased rate of MRSA identified in hospital- and community-acquired bacteremias.[49] If the isolate is later identified as MSSA, therapy should be deescalated to an antistaphylococcal or penicillinase-resistant penicillin (eg, nafcillin, oxacillin) or cephalosporin (eg, cefazolin) as vancomycin is less effective than β-lactams against MSSA.[67] Though cefazolin may be considered in patients who report a hypersensitivity to penicillin not associated with anaphylactic features, treatment should be dictated by allergy history or skin testing. Alternatively, vancomycin or daptomycin (a respiratory source of bacteremia should be ruled out prior to starting daptomycin) should be administered to those unable to tolerate β-lactams. Vancomycin and daptomycin are considered first-line treatment of MRSA bacteremia. Though time to blood culture sterilization may be decreased with combination therapy compared to single-drug therapy, rates of morbidity and mortality remain unchanged.

Management of some patients with MRSA bacteremia may be complicated by persistent bacteremia, defined as inability to sterilize blood cultures after 3 to 7 days of active therapy.[68,69] Persistent *S. aureus* bacteremia is associated with higher rates of secondary metastatic infections and death and may warrant the use of salvage therapy consisting of daptomycin 8 to 10 mg/kg combined with a β-lactam such as ceftaroline.[70]

Establishing a duration of therapy requires differentiation of patients with uncomplicated or low-risk and complicated or high-risk *S. aureus* bacteremia.[49,68] To meet criteria for uncomplicated or low-risk *S. aureus* bacteremia, all of the following criteria must be met: 1) sterile repeat blood cultures 48 to 96 hours after the initial positive culture, 2) defervescence within 72 hr after initiation of active therapy, 3) exclusion of infective endocarditis/secondary metastatic infection, 4) no implanted prostheses (eg, prosthetic valves, cardiac devices, or arthroplasties), 5) not dependent on hemodialysis. Patients with uncomplicated *S. aureus* bacteremia require treatment for 2 weeks, whereas those with complicated *S. aureus* bacteremia should be treated for 4 to 6 weeks from the first negative blood culture or source control. Differentiating uncomplicated *S. aureus* bacteremia from complicated *S. aureus* bacteremia is challenging as almost 33% of patients initially classified as having uncomplicated *S. aureus* bacteremia were eventually diagnosed with complicated *S. aureus* bacteremia.[71] As a result, the majority of patients should receive 4 to 6 weeks of treatment. Parenteral therapy is considered standard of care in patients with uncomplicated and complicated *S. aureus* bacteremia, but successful use

of oral therapies has been reported in patients with or uncomplicated *S. aureus* bacteremia.[72]

Coagulase negative Staphylococcus spp.

IV vancomycin should be started empirically in patients with suspected coagulase negative *Staphylococcus* spp. bacteremia due to high rates of methicillin resistance.[73] As with management of *S. aureus* bacteremia, an antistaphylococcal or penicillinase-resistant penicillin (eg, nafcillin, oxacillin) or cephalosporin (eg, cefazolin) should be administered if the isolate is methicillin susceptible, whereas vancomycin or daptomycin should be reserved for those infected with methicillin-resistant strains. Treatment duration varies, depending on catheter removal, from 5 to 7 days in patients with negative follow-up blood cultures, no evidence of secondary metastatic infection, and no intravascular prostheses to 7 to 14 days in patients with at least two positive blood cultures obtained more than 24 hours apart or intravascular prostheses.[74] However, treatment of *S. lugdunensis* bacteremia should be managed in a similar manner to that of *S. aureus* bacteremia due to similarities in virulence.

Streptococcus spp.

β-Lactams remain first-line therapy for streptococcal bacteremias. However, combination empirical therapy with IV vancomycin and ceftriaxone should administered in patients with suspected *S. pneumoniae* bacteremia, pending susceptibilities, until central nervous system involvement can be ruled out. For empirical treatment of Group A streptococcal (*S. pyogenes*) bacteremia, IV penicillin should be combined with IV clindamycin to suppress toxin production, as well as decrease the risk of treatment failure and death.[75] IV clindamycin can be discontinued after 48 hr in patients without shock, organ failure, or necrotizing fasciitis. In most cases of streptococcal bacteremia, monotherapy with IV penicillin or ceftriaxone is appropriate once susceptibility results are available, although it is unclear if parenteral therapy is required for the entire duration of treatment.[76] Antibacterial therapy is typically administered for 14 days, but limited data are available evaluating optimal treatment duration.

Enterococcus spp.

Enterococcus spp. are usually of low virulence but inherently resistant to many classes of antibacterial agents.[5] *E. faecalis* is the most common clinical isolate (approximately 97%) of the two species.[74,77] Penicillins and glycopeptides are most active despite their inability to consistently kill these organisms. Ampicillin has greater in vitro activity than penicillin, although there are no clinical data to document differences in efficacy. IV ampicillin should be administered when the isolate is susceptible in non-critically ill patients with no evidence of infective endocarditis. Alternatively, IV vancomycin can be administered in patients who report hypersensitivity to penicillin and are unable to be desensitizied. Ampicillin-resistant, vancomycin-susceptible isolates can be treated with IV vancomycin or daptomycin. The incidence of vancomycin-resistant enterococci (VRE), primarily with *E. faecium*, is increasing. Vancomycin resistance occurs when the bacterium replaces the normal vancomycin target with a peptidoglycan precursor that does not bind vancomycin.[78] In cases of ampicillin-resistant enterococci and VRE, at least 10 mg/kg of daptomycin or linezolid should be administered.[79] Combination therapy, consisting of a β-lactam plus an aminoglycoside (IV ampicillin or IV penicillin plus gentamicin) or β-lactam combination (IV ampicillin plus ceftriaxone) should be used in critically ill patients or those with suspected infective endocarditis.[77] IV ampicillin plus ceftriaxone is preferred if the isolate displays high-level aminoglycoside resistance or to avoid potential aminoglycoside toxicities. Because the aminoglycoside cannot penetrate the bacterial cell in the absence of the penicillin, enterococci is resistant to aminoglycosides by routine susceptibility testing (low-level resistance). However, in the presence of an agent that disrupts the cell wall such as penicillin, the aminoglycoside can gain entry, attach to bacterial ribosomes, and cause rapid cell death. A combination of vancomycin plus gentamicin is also synergistic against enterococci and is an appropriate therapy for the penicillin-allergic patient.[78,80,81] Other aminoglycosides, such as tobramycin and amikacin, cannot be substituted routinely due to resistance. Use of two β-lactam antimicrobials results in saturation of the cell membrane penicillin-binding proteins producing synergistic bactericidal activity.[77] Though the optimal duration of treatment remains undefined, the majority of cases can be treated with 5 to 7 days of therapy.[74]

Anaerobes

In most situations, treatment of anaerobic bacteremia is usually empiric based on historical susceptibility patterns due to difficulties associated with isolating an organism and performing susceptibility tests.[82] Limited data are available describing treatment of anaerobic bacteremia as management depends on resolution of the primary source.

Infective endocarditis

In most cases, vancomycin should be included in the empirical regimen to cover the most common causes of infective endocarditis, staphylococci, streptococci, and enterococci. Ceftriaxone should be added to cover aerobic gram-negative bacilli in patients with acute presentations. In patients with subacute presentations, ampicillin/sulbactam should be included in the empirical regimen to provide coverage against *S. aureus*, viridans group streptococci, enterococci, and HACEK organisms. Once causative bacteria is identified from blood or tissue cultures or serologic tests, antimicrobial therapy should be deescalated to target that specific pathogen.

β-Lactam antimicrobials, such as penicillin G (or ceftriaxone), nafcillin (or oxacillin), and ampicillin, remain the drugs of choice for streptococcal, staphylococcal, and enterococcal infective endocarditis, respectively. Tables 134-8 to 134-11 summarize these recommendations, which are discussed in more detail in the following sections. Tables 134-12 and 134-13 list drug dosing and monitoring recommendations for adult and pediatric patients, respectively. Because these guidelines focus on common causes of infective endocarditis, readers are referred to other references for more in-depth discussion of unusually encountered organisms.[5,6,83,84]

TABLE 134-8

Treatment options for native valve endocarditis caused by Streptococcus spp. and Staphylococcus spp.'

Agent[a]	Duration	Strength of Recommendation	Comments
Highly Penicillin-Susceptible (MIC ≤ 0.12 µg/mL [mg/L]) Viridans Group Streptococci and *S. gallolyticus*			
Aqueous crystalline penicillin G sodium[b]	4 weeks	IIaB	2-week regimens are not intended for the following patients: ○ Most patients >65 years of age ○ Children ○ Impairment of the eighth cranial nerve function ○ Renal function with a creatinine clearance <20 mL/min (<0.33 mL/s) ○ Known cardiac or extracardiac abscess ○ Infection with *Abiotrophia, Granulicatella*, or *Gemalla* species
Ceftriaxone	4 weeks	IIaB	
Aqueous crystalline penicillin G sodium[b] plus gentamicin	2 weeks	IIaB	
Ceftriaxone plus gentamicin	2 weeks	IIaB	
Vancomycin	4 weeks	IIaB	Recommended only for patients unable to tolerate penicillin or ceftriaxone
Viridans Group Streptococci and *S. gallolyticus* Relatively Resistant to Penicillin (MIC >0.12 to ≤0.5 µg/mL [mg/L])			
Aqueous crystalline penicillin G sodium[b]	4 weeks	IIaB	
plus gentamicin	2 weeks		
Ceftriaxone	4 weeks	IIbC	
plus gentamicin	2 weeks		
Vancomycin	4 weeks	IIaB	Recommended only for patients unable to tolerate penicillin or ceftriaxone
Oxacillin-Susceptible Staphylococci[c]			

Nafcillin or oxacillin	6 weeks	IC	
Cefazolin	6 weeks	IB	For use in patients with non-anaphylactoid-type penicillin allergies; patients with an unclear history of immediate-type hypersensitivity to penicillin should be considered for skin testing
Vancomycin	6 weeks	IB	For use in patients with anaphylactoid-type hypersensitivity to penicillin and/or cephalosporins
Daptomycin	6 weeks	IIaB	For use in patients with immediate-type hypersensitivity reactions to penicillin
Oxacillin-Resistant Staphylococci			
Vancomycin	6 weeks	IC	
Daptomycin	6 weeks	IIbB	

[a]See Tables 134-9 and 134-10 for appropriate dosing, administration, and monitoring information.

[b]May use ampicillin in the event of a penicillin shortage.

[c]Regimens indicate treatment for left-sided endocarditis or complicated right-sided endocarditis; uncomplicated right-sided endocarditis may be treated for shorter durations and is described in the text. Please refer Table 134-7 for treatment of NVE caused by enterococci.

Data from References 5,6.

TABLE 134-9

Treatment options for prosthetic valve endocarditis (PVE) caused by Streptococcus spp. and Staphylococcus spp.'

Agent[a]	Duration	Strength of Recommendation	Comments
Highly Penicillin-Susceptible (MIC ≤ 0.12 µg/mL [mg/L]) Viridans Group Streptococci and *S. gallolyticus*			
Aqueous crystalline penicillin G sodium[b]	6 weeks	IIaB	Combination therapy with gentamicin has not demonstrated superior cure rates compared with monotherapy with a penicillin or cephalosporin and should be avoided in patients with CrCl <30 mL/min (<0.50 mL/s)
plus gentamicin	2 weeks		
Ceftriaxone	6 weeks	IIaB	
plus gentamicin	2 weeks		
Vancomycin	6 weeks	IIaB	Recommended only for patients unable to tolerate penicillin or ceftriaxone
Relatively Resistant or Fully Resistant (MIC > 0.12 µg/mL [mg/L]) Viridans Group Streptococci and *S. gallolyticus*			
Aqueous crystalline	6 weeks	IIaB	

penicillin G sodium[b] plus gentamicin			
Ceftriaxone plus gentamicin	6 weeks	IIaB	
Vancomycin[c]	6 weeks	IIaB	Recommended only for patients unable to tolerate penicillin or ceftriaxone
Oxacillin-Susceptible Staphylococci			
Nafcillin or oxacillin	≥6 weeks	IB	Cefazolin may be substituted for nafcillin or oxacillin in patients with non-immediate-type hypersensitivity
plus rifampin	≥6 weeks		
plus gentamicin	2 weeks		
Vancomycin	≥6 weeks	IB	Recommended only for patients with anaphylactoid-type hypersensitivity to penicillin and/or cephalosporins
plus rifampin	≥6 weeks		
plus gentamicin	2 weeks		
Oxacillin-Resistant Staphylococci			
Vancomycin	≥6 weeks	IB	
plus rifampin	≥6 weeks		
plus gentamicin	2 weeks		

[a]See Tables 134-9 and 134-10 for appropriate dosing, administration, and monitoring information.

[b]May use ampicillin in the event of a penicillin shortage.

[c]The ESC 2015 guidelines recommend gentamicin (3 mg/kg/day) be administered with vancomycin for the initial 2 weeks of therapy in patients with relatively resistant strains to penicillin.

PVE, prosthetic valve endocarditis; MIC, minimum inhibitory concentration.

Please refer Table 134-3 for treatment of PVE caused by enterococci.

Data from References 5,6.

TABLE 134-10

Treatment Options for Native or Prosthetic Valve Endocarditis Caused by Enterococci

Agent[a]	Duration[b]	Strength of Recommendation	Comments
Ampicillin-, Penicillin-, and Vancomycin-Susceptible Strains			
Ampicillin plus gentamicin	4-6 weeks	IIaB	Native valve plus symptoms present for <3 months: use 4-week regimen
Aqueous crystalline penicillin G sodium plus gentamicin	4-6 weeks	IIaB	Prosthetic valve or native valve plus symptoms present for >3 months: use 6-week regimen
Ampicillin plus ceftriaxone	6 weeks	IIaB	Recommended regimen if creatinine clearance is <50 mL/min (<0.83 mL/s; at baseline or due to therapy with a gentamicin-containing regimen)
Vancomycin plus gentamicin	6 weeks	IIaB	Recommended only for patients unable to tolerate penicillin or ampicillin
Gentamicin-Resistant Strains			
If susceptible, use streptomycin in the place of gentamicin in the regimens listed above if creatinine clearance is >50 mL/min (>0.83 mL/s), cranial nerve VIII function is intact and there is laboratory capability for rapid streptomycin serum concentrations.			
Penicillin-Resistant Strains			
Ampicillin–sulbactam plus gentamicin (β-lactamase–producing strain)	6 weeks	IIbC	
Vancomycin plus gentamicin (intrinsic penicillin resistance[c])	6 weeks	IIbC	May also be used in patients with β-lactamase–producing strains who have known intolerance to ampicillin–sulbactam
***Enterococcus Faecium* Strains Resistant to Penicillin, Aminoglycosides, and Vancomycin[d]**			
Linezolid	>6 weeks	IIbC	Antimicrobial cure rates may be <50%; bacteriologic cure may only be achieved with cardiac valve replacement
Daptomycin	>6 weeks	IIbC	

[a]See Tables 134-9 and 134-10 for appropriate dosing, administration, and monitoring information.

[b]All patients with prosthetic valves should be treated for at least 6 weeks.

[c]Infectious diseases consult highly recommended.

[d]Patients should be managed by a multidisciplinary team that includes specialists in cardiology, cardiovascular surgery, infectious diseases, and clinical pharmacy.

Data from Reference 5.

TABLE 134-11

Treatment Options for Culture-Negative Endocarditis and Endocarditis Caused by Gram-Negative Organisms[a]

Agent[b]	Duration[c]	Strength of Recommendation	Comments
HACEK[d] Microorganisms			
Ceftriaxone	4 weeks	IIaB	Other third- or fourth-generation cephalosporins may be used as an alternative
Ampicillin or Ampicillin–sulbactam	4 weeks	IIaB	Should only use if growth is adequate for in vitro susceptibility testing; otherwise, consider organism to be resistant
Ciprofloxacin	4 weeks	IIbC	Recommended for patients with known intolerance to cephalosporins or ampicillin; other fluoroquinolones may be used as an alternative
Culture-Negative Endocarditis, Native Valve[e]			
Vancomycin plus cefepime	4-6 weeks	IIaC	Recommended when onset is acute (days); *S. aureus*, β-hemolytic streptococci, and aerobic gram-negative bacilli should be covered
Vancomycin plus ampicillin–sulbactam	4-6 weeks	IIaC	Recommended when onset is subacute (weeks); *S. aureus*, viridans group streptococci, HACEK, and enterococci should be covered
Culture-Negative Endocarditis, Early (<1 Year) Prosthetic Valve[e]			
Vancomycin plus cefepime plus rifampin plus gentamicin	6 weeks	IIaC	Staphylococci, enterococci, and aerobic gram-negative bacilli should be covered
Culture-Negative Endocarditis, Late (>1 Year) Prosthetic Valve[e]			
Vancomycin plus ceftriaxone	6 weeks	IIaC	Staphylococci, viridans group streptococci, and enterococci should be covered
Suspected *Bartonella*, Culture-Negative			
Ceftriaxone	6 weeks	IIaB	
plus gentamicin	2 weeks		
with or without doxycycline	6 weeks		
Culture-Positive *Bartonella*			
Doxycycline plus gentamicin	6 weeks 2 weeks	IIaB	Rifampin is recommended as an alternative in patient who cannot be given gentamicin

[a]Infectious disease consult highly recommended.

[b]See Tables 134-9 and 134-10 for appropriate dosing, administration, and monitoring.

[c]All patients with prosthetic valves should be treated for 6 weeks.

[d]*Haemophilus* species (*H. parainfluenzae, H. aphrophilus*, and *H. paraphrophilus*), *Aggregatibacter* species, *Cardiobacterium hominis, Eikenella corrodens*, and *Kingella kingae.*

[e]Duration of therapy for culture-negative endocarditis may be variable and should be based on clinical course and recommendations from infectious diseases consult.

Data from References 5,6.

TABLE 134-12

Drug Dosing Table for Treatment of Infective Endocarditis[a]

Drug	Brand Name	Recommended Dose	Pediatric (Ped) Dose[b]	Additional Information
Ampicillin	NA	2 g IV every 4 hr	50 mg/kg every 4 hr or 75 mg/kg every 6 hr	24-hr total dose may be administered as a continuous infusion: 12 g IV every 24 hr
Ampicillin–sulbactam	Unasyn®	3 g IV every 6 hr	50 mg/kg every 4 hr or 75 mg/kg every 6 hr	
Aqueous crystalline penicillin G sodium	NA			
• MIC <0.12 µg/mL (mg/L) (native valve only)		3 million units IV every 4 hr or every 6 hr	50,000 units/kg IV every 6 hr	24-hr total dose may be administered as a continuous infusion: 12-18 million units IV every 24 hr (Ped: 200,000 units/kg IV/24 hours)
• All other indications		4 million units IV every 4 hr or 6 million units IV every 6 hr	50,000 units/kg IV every 4 hr or 75,000 units/kg IV every 6 hr	24 million units IV every 24 hr (Ped: 300,000 units/kg IV every 24 hr)
Cefazolin	N/A	2 g IV every 8 hr	33 mg/kg IV every 8 hr	
Cefepime	Maxipime®	2 g IV every 8 hr	50 mg/kg IV every 8 hr	
Ceftriaxone sodium	N/A	2 g IV or IM every 24 hr	100 mg/kg IV or IM every 24 hr	

		2 g IV or IM every 12 hr		
Ciprofloxacin	Cipro®	400 mg IV every 12 hr or 500 mg po every 12 hr	20-30 mg/kg IV or po every 12 hr	Avoid use if possible in patients <18 years of age
Daptomycin	Cubicin®	≥8 mg/kg IV every 24 hr	6 mg/kg IV every 24 hr	Doses as high as 10-12 mg/kg IV every 24 hr have been used in adults with enterococcus resistant to penicillin, aminoglycosides and vancomycin; doses should be calculated using actual body weight
Doxycycline	Vibramycin®	100 mg IV or po every 12 hr	1-2 mg/kg IV or po every 12 hr	
Gentamicin sulfate	NA	3 mg/kg IV or IM every 24 hr or 1 mg/kg IV or IM every 8 hr[c]	1 mg/kg IV or IM every 8 hr	Once-daily dosing is only recommended for treatment of streptococcal infections.
Linezolid	Zyvox®	600 mg IV or po every 12 hr	10 mg/kg IV every 8 hr	
Nafcillin or oxacillin	NA	2 g IV every 4 hr	50 mg/kg IV every 6 hr	24-hr total dose may be administered as a continuous infusion: 12 g IV every 24 hr
Rifampin	Rifadin®	300 mg IV or po every 8 hr	5-7 mg/kg IV or po every 8 hr	
Streptomycin	NA	7.5 mg/kg IV or IM every 12 hr		
Vancomycin	Vancocin®	15-20 mg/kg IV every 8 hours or every 12 hr	15 mg/kg IV every 6 hr	A loading dose of 25-30 mg/kg may be administered in adults; doses should be calculated using actual body weight; single doses should not exceed 2 g

[a]All doses assume normal renal function.

[b]Should not exceed adult dosage.

[c]Actual body weight should be used when the full aminoglycoside dose is administered once daily; when administered in three divided doses, use ideal body weight or adjusted body weight when actual body weight is >120% ideal body weight.

TABLE 134-13

Drug Monitoring of Select Agents

Drug	Major Adverse Drug Reactions	Monitoring Parameters	Comments
Daptomycin	Myopathy, rhabdomyolysis	CPK at least weekly; monitor for signs and symptoms of muscle pain	More frequent monitoring may be warranted in patients with renal dysfunction or receiving concomitant therapy with HMG-CoA reductase inhibitors; discontinue if symptomatic and CPK >5 times ULN or if CPK ≥10 times ULN
Gentamicin	Nephrotoxicity, ototoxicity, neuromuscular blockade	When dosed three times daily: ○ Target peak serum concentrations of 3-4 µg/mL (mg/L; 6.3-8.4 µmol/L) and trough serum concentrations of <1 µg/mL (mg/L; <2.1 µmol/L)	Avoid concomitant use of other nephrotoxic agents such as diuretics, non-steroidal antiinflammatory drugs, and radiocontrast media. Avoid rapid IV administration
Linezolid	Thrombocytopenia, optic, or peripheral neuropathy	Platelet counts at baseline and weekly, visual changes	More common with prolonged therapy (≥2 weeks for thrombocytopenia, >28 days for visual symptoms); avoid concomitant myelosuppressive agents
Rifampin	Hepatotoxicity	Baseline liver function tests, and then at least every 2-4 weeks during therapy	Avoid concomitant medications that cause hepatotoxicity; may cause red or orange discoloration of bodily secretions (urine, sweat, tears)
Vancomycin	Nephrotoxicity, vancomycin infusion reaction	AUC-guided or trough-guided serum concentration monitoring	Vancomycin infusion reaction may be managed by prolonging the infusion time from 1 to 2 hr; administration of an antihistamine prior to loading or maintenance doses may also be considered

CPK, creatinine phosphokinase; ULN, upper limit of normal; AUC, area under the curve.

For some pathogens, such as enterococci, the use of synergistic antimicrobial combinations (including an aminoglycoside) is essential to obtain a bactericidal effect. Combination antimicrobials may also decrease the emergence of resistant organisms during treatment (eg, PVE caused by coagulase-negative staphylococci) and hasten the pace of clinical and microbiologic response (eg, some streptococcal and staphylococcal infections). Occasionally, combination treatment will result in a shorter treatment course.

Streptococcal Endocarditis

Streptococci are a common cause of infective endocarditis, with most isolates being viridans group streptococci. Viridans group streptococci refers to many different species, such as *Streptococcus sanguinis, Streptococcus oralis, Streptococcus salivarius, Streptococcus mutans*, and *Gemella morbillorum*.[5] These bacteria are common inhabitants of the human mouth and gingiva, and they are especially common causes of NVE.[5,42] During dental surgery, and even when brushing the teeth, these organisms can cause a transient bacteremia. In susceptible individuals, this may result in infective endocarditis. Streptococcal endocarditis is usually subacute, and the response to medical treatment is very good. *Streptococcus gallolyticus* (formerly known as *Streptococcus bovis*) is not a viridans group streptococcus, but it is included in this treatment group because it is penicillin-susceptible and requires the same treatment. *S. gallolyticus* is a non-enterococcal group D streptococci that resides in the GI tract. Infective endocarditis caused by this organism is often associated with a GI pathology, especially colon carcinoma. Endocarditis caused by *Streptococcus pneumoniae, Streptococcus pyogenes*, and group B, C, and G streptococci are uncommon, and their treatment is not well defined.[5,6]

Antibacterial regimens for viridans group streptococci are well studied, and in uncomplicated cases, the cure rate is expected to be more than 95%.[5,6] Viridans group streptococci are penicillin-susceptible, although some are more susceptible than others. Most are highly susceptible to penicillin G and have minimum inhibitory concentrations (MICs) of less than 0.12 µg/mL (mg/L).[45]

Approximately 10% to 20% are moderately susceptible (MIC 0.12-0.5 µg/mL [mg/L]). This different in vitro susceptibility led to recommendations that the MIC be determined for all viridans group streptococci to guide therapy. Some streptococci are deemed tolerant to the killing effects of penicillin, where the minimum bactericidal concentration (MBC) exceeds the MIC by 32 times. A tolerant organism is inhibited but not killed by an antimicrobial normally considered bactericidal.[5] Bactericidal activity is preferred for successful treatment of infective endocarditis; therefore, infections with a tolerant organism may relapse after treatment. Tolerant strains do not respond as readily to β-lactam therapy as non-tolerant ones, this phenomenon is primarily a laboratory finding with little clinical significance. Treatment for tolerant strains is identical to that for non-tolerant organisms, and measurement of the MBC is not recommended.

An assortment of regimens can be used to treat uncomplicated NVE caused by fully susceptible viridans group streptococci (see Table 134-5). Shorter-course antimicrobial regimens are advocated when possible. With susceptible streptococcal endocarditis (MIC ≤0.12 µg/mL [mg/L]), a 2-week regimen of high-dose parenteral penicillin G or ceftriaxone in combination with an aminoglycoside is as effective as 4 weeks of penicillin alone.[5]

Two single-drug regimens consist of high-dose parenteral penicillin G or ceftriaxone for 4 weeks. If short- term, 2-week therapy is desired, the guidelines suggest either high-dose parenteral penicillin G or ceftriaxone in combination with an aminoglycoside.[5] When used in select patients, this combination is as effective as 4 weeks of penicillin alone. Although streptomycin was listed in previous guidelines, gentamicin is the preferred aminoglycoside because serum drug concentrations are obtained easily, clinicians are more familiar with its use, and the few strains of streptococci resistant to the effects of streptomycin–penicillin remain susceptible to gentamicin–penicillin. Other aminoglycosides are not recommended. Whether extended-interval aminoglycoside dosing has a role in infective endocarditis continues to be debated. The combination of ceftriaxone (2 g daily) with gentamicin (3 mg/kg daily) for 2 weeks was compared with ceftriaxone (2 g daily) alone for 4 weeks for penicillin-susceptible streptococci and both regimens were safe and effective with similar clinical cure rates at 3 months following treatment.[85] Data support extended-interval dosing for the treatment of streptococcal infective endocarditis, and as compared with three-times- daily dosing this approach may have greater efficacy.[5]

The rationale for combination therapy against penicillin-susceptible viridans group streptococci is that enhanced activity against these organisms is usually observed in vitro when cell-wall-active agents are combined with aminoglycosides.[86] Combined treatment results in quicker sterilization of vegetations in animal models of endocarditis and probably explains the high response rates observed for patients treated for a total of 2 weeks.[5,85] The combined treatment, however, is not superior to penicillin alone.

The decision of which regimen to use depends on the perceived risk versus benefit. For example, a 2-week course of gentamicin in an elderly patient with renal impairment may be associated with ototoxicity, nephrotoxicity, or both. Furthermore, the 2-week regimen is not recommended for patients with known extracardiac infection. On the other hand, a 4-week course of penicillin alone generally entails greater expense, especially if the patient remains in the hospital. Monotherapy with once-daily ceftriaxone offers ease of administration, facilitates home healthcare treatment, and may be cost-effective.[5,6]

9 When a patient has a history of hypersensitivity with anaphylactic features to penicillin, vancomycin should be chosen for infective endocarditis caused by viridans group streptococci. When vancomycin is used, the addition of gentamicin is not recommended.[5] The published experience with penicillin is more extensive than with alternative regimens; consequently, a thorough allergy history and skin test, if available, must be obtained before a second-line therapy is administered.

For patients with complicated infections (eg, extracardiac foci) or when the streptococcus has an MIC of 0.12 to less than or equal to 0.5 µg/mL (mg/L), combination therapy with an aminoglycoside for the first 2 weeks and penicillin (higher dose) or ceftriaxone is recommended, followed by penicillin or ceftriaxone alone for an additional 2 weeks (see Table 134-9).[5] Some viridans group streptococci, previously referred to as nutritionally variant streptococci, have biologic characteristics that complicate diagnosis and treatment. For patients infected with nutritionally variant streptococci or when the *Streptococcus* spp. has an MIC of more than 0.5 µg/mL (mg/L), treatment should follow the enterococcal endocarditis treatment guidelines.

For patients with endocarditis of prosthetic valves or other prosthetic material caused by viridans group streptococci and *S. gallolyticus*, choices of

treatment are similar to those without prosthetic material (eg, penicillin or ceftriaxone); however, treatment courses are extended to 6 weeks (see Table 134-9). For penicillin-susceptible isolates with an MIC of 0.12 µg/mL (mg/L) or less, high-dose parenteral penicillin G or ceftriaxone should be administered for 6 weeks with or without an aminoglycoside for the first 2 weeks. On the contrary, for isolates with an MIC greater than 0.12 µg/mL (mg/L), high-dose parenteral penicillin G or ceftriaxone combined with an aminoglycoside should be administered for the entire 6 weeks.

Staphylococcal Endocarditis

Endocarditis is most commonly caused by staphylococci, in particular *S. aureus*, mainly because of increased rates of injection drug use, more frequent use of vascular catheters, and increased frequency of valve replacement surgery.[19] Coagulase-negative staphylococci (usually *Staphylococcus epidermidis*) and *S. aureus* are prominent causes of PVE.

Staphylococcal endocarditis is not a homogeneous disease; appropriate management requires consideration of several questions: Is the organism methicillin resistant? Should combination therapy be used? Is the infection on a native or prosthetic valve? Does the patient have a history of injection drug use? Is the infection on the left or right side of the heart? Another consideration in staphylococcal endocarditis is that some organisms may exhibit tolerance to antimicrobials. Similar to streptococci, however, the concern for tolerance among staphylococci should not affect antimicrobial selection.[5]

The recommended therapy for patients with left-sided, native valve infective endocarditis caused by MSSA is 6 weeks of nafcillin or oxacillin; a longer duration of therapy may be needed for complicated infections (eg, presence of perivalvular abscess or septic metastases). From in vitro studies, the combination of an aminoglycoside and penicillinase-resistant penicillin or vancomycin enhances the activity of these drugs for MSSA. In animal models of endocarditis, combinations of penicillin with an aminoglycoside eradicate organisms from vegetations more rapidly than penicillins alone.[5,49] In most human studies, the addition of an aminoglycoside to nafcillin hastens the resolution of fever and bacteremia, but it does not affect survival or relapse rates and can increase nephrotoxicity.[49] As a result, the AHA and ESC guidelines no longer recommend the addition of gentamicin because clinical benefit has not been demonstrated and there is an increased risk of toxicity (see Table 134-5).

If a patient has a mild, delayed hypersensitivity to penicillin, cefazolin may be an effective alternative, but should be avoided for patients who report anaphylactic-type reactions to penicillins (see Table 134-8). The potential for a true immediate-type hypersensitivity should be assessed through a careful history or skin test, if available (Chapter e108). Vancomycin is an option for a patient with a positive skin test or a history of hypersensitivity with anaphylactic features to penicillin.

Vancomycin, however, kills *S. aureus* slowly and is inferior to antistaphylococcal or penicillinase-resistant penicillins (eg, nafcillin, oxacillin) or cephalosporins (eg, cefazolin).[5] Alternatively, patients with hypersensitivity to penicillin can be considered for penicillin desensitization or daptomycin, a lipopeptide antimicrobial approved for right-sided infective endocarditis and *S. aureus* bacteremia.[5,6] Unfortunately, left-sided infective endocarditis caused by *S. aureus* continues to have a poor prognosis, with a mortality rate between 25% and 40%.[5] For reasons discussed in the following section, those with infective endocarditis associated with injection drug use have a more favorable response to therapy.

During the past decade, staphylococci more commonly have become resistant to antistaphylococcal or penicillinase- resistant penicillins (eg, MRSA). Although vancomycin is still the most commonly selected antimicrobial in these cases (see Table 134-8), susceptibility reports with an MIC greater than 2 µg/mL (mg/L) and reports of vancomycin-resistant *S. aureus* strains are increasing.[68] Success with daptomycin or linezolid has been demonstrated for these patients.[87–89] Use of daptomycin in clinical practice may extend beyond the FDA-approved indication of right-sided NVE, and higher doses of daptomycin (greater than or equal to 8 mg/kg/day) should be used. Additionally, higher doses may be preferred by some experts due to favorable drug tolerability and potential for decreased treatment-emergent resistance, although prospective, randomized clinical trials are lacking.[90–92] To date, linezolid has not been approved by the FDA for use in endocarditis as most available data are based on case reports, and there is concern regarding use of a bacteriostatic agent for this condition.[68,87] The presence or lack of a prosthetic heart valve in patients with a methicillin-resistant organism guides therapy and determines whether vancomycin should be used alone or, if a prosthetic valve is present, combination therapy is necessary (Table 134-6).[5]

Staphylococcus Endocarditis: PWID

Infective endocarditis in PWID is frequently (60%-70%) caused by *S. aureus*, although other organisms may be common in certain geographic locations.[6,19] In this setting, the tricuspid valve is frequently infected, resulting in right-sided infective endocarditis. Most patients have no history of valve abnormalities, are usually otherwise healthy, and have a good response to medical treatment. Nonetheless, surgery may be required.

As previously mentioned, an uncomplicated, left-sided MSSA endocarditis may be treated sufficiently with 6 weeks of monotherapy with an antistaphylococcal or penicillinase-resistant penicillin.[5] However, the clinical response with right- sided MSSA endocarditis in PWID is usually excellent and may be treated effectively (clinical and microbiologic cure exceeding 85%) with a 2-week course of nafcillin, oxacillin, or daptomycin.[5] Short 2-week courses of vancomycin for endocarditis in PWID are not recommended because of limited bactericidal activity, poor penetration into vegetations, and increased drug clearance in this population resulting in high rates of failure. If vancomycin is selected, the standard 6-week regimen should be used. Selection of a 2-week treatment duration may be appropriate for patients with MSSA right-sided endocarditis if they do not have signs of renal failure, extrapulmonary septic emboli, aortic or mitral valve involvement, or central nervous system infection, otherwise a 6-week regimen is indicated.[5]

Although previous guidelines emphasized combination therapy with an aminoglycoside for the 2-week duration based on earlier studies, the current recommendation for monotherapy is based on data showing that a 2-week regimen of an antistaphylococcal or penicillinase-resistant penicillin alone, without the addition of an aminoglycoside, is as effective as combined therapy in MSSA tricuspid valve endocarditis.[93] Combination treatment (daptomycin plus 4 days of gentamicin) was no different in success rates but had higher rates of renal toxicity compared to daptomycin monotherapy.

Alternative treatment approaches for staphylococcal endocarditis in PWID using oral antibacterial therapies (ciprofloxacin and rifampin) or long-acting lipoglycopeptides (eg, dalbavancin or oritavancin) have demonstrated efficacy.[94–96] However, concerns with resistance (eg, ciprofloxacin), patient adherence, and limited published data prohibit their routine use for the treatment of infective endocarditis in PWID.[5]

Staphylococcal Endocarditis: Prosthetic Valves

PVE accounts for 10% to 30% of all infective endocarditis cases.[6,15] Staphylococci (*S. aureus* and coagulase-negative staphylococci), gram-negative bacilli, and fungi are the main causes of early PVE, while the microbiology of late PVE mirrors that of NVE. An episode of PVE occurring within 2 months of surgery strongly suggests that the cause is staphylococci implanted during the procedure. Yet the risk of staphylococcal endocarditis remains elevated for up to 12 months after valve replacement.[97] Because this type of infective endocarditis is typically a nosocomial infection, methicillin-resistant organisms are common, and vancomycin is the cornerstone of therapy. Combination antimicrobials are recommended because of the high morbidity and mortality associated with PVE and its refractoriness to therapy.[5,68] Although the addition of rifampin to an antistaphylococcal or penicillinase-resistant penicillin or vancomycin does not result in predictable bacterial synergism, rifampin may have unique activity against staphylococcal infection that involves prosthetic material, where its addition results in a higher microbiologic cure rate.[5] Combination therapy also decreases the emergence of resistance to rifampin, which frequently occurs when it is used alone. For methicillin-resistant staphylococci (both MRSA and coagulase-negative staphylococci), vancomycin is recommended with rifampin for 6 weeks or more (Table 134-9). Due to the risk of developing on therapy resistance, rifampin should not be started until blood cultures have sterilized.[98] Gentamicin is added for the first 2 weeks if the organism is aminoglycoside susceptible; traditional dosing should be used as once-daily regimens have not been adequately evaluated in PVE and are not recommended.[5]

For MSSA, an antistaphylococcal or penicillinase-resistant penicillin is administered in place of vancomycin. PVE responds poorly to medical treatment and has a higher mortality compared with NVE. Valve dehiscence and incompetence can result in acute heart failure, and surgery is often a component of treatment.[5,60]

The use of anticoagulation is controversial in PVE. In general, those who require anticoagulation for a prosthetic valve should continue the anticoagulant cautiously during endocarditis therapy, unless a contraindication to therapy exists. It is recommended to hold all anticoagulation for at least 2 weeks for patients with *S. aureus* PVE if a recent CNS embolic event has occurred.[5]

Enterococcal Endocarditis

Enterococci are the third leading cause of infective endocarditis, but they are more resistant to therapy than staphylococci and streptococci.[78,80,99] Enterococci are noteworthy as no single antimicrobial is bactericidal. In addition, monotherapy with penicillin for infective endocarditis caused by

enterococci results in relapse rates of 50% to 80%.[5,80,99] Thus, combination therapy consisting of a cell-wall–active agent such as a penicillin or vancomycin and an aminoglycoside (or cephalosporin with ampicillin) are necessary for bactericidal activity. Additionally, resistance to all available drugs is increasing.

Enterococcal endocarditis requires 4 to 6 weeks of IV ampicillin or IV penicillin G plus an aminoglycoside for cure (Table 134-10). IV ampicillin plus ceftriaxone is as effective and better tolerated as IV ampicillin plus gentamicin and should be considered as a treatment option.[5,6] A 6-week course is recommended for patients with symptoms lasting longer than 3 months and those with PVE. Streptomycin and gentamicin have similar efficacy, but gentamicin is preferred due to the inability to obtain streptomycin serum concentrations in most laboratories.[5,80] In the treatment of enterococcal endocarditis, relatively low serum concentrations of aminoglycosides appear adequate for successful therapy, such as a gentamicin peak concentration of approximately 3 to 4 µg/mL (mg/L; 6.3-8.4 µmol/L).[5,80,81] Treatment of enterococcal endocarditis does not have the high success rate seen with infective endocarditis caused by viridans group streptococci, presumably because the organism is more resistant to killing.

Although some data support the use of extended-interval aminoglycoside dosing for other types of endocarditis (eg, streptococci), the data are more vague regarding this strategy in enterococcal endocarditis.[80] Some studies suggest that extended-interval aminoglycoside dosing and short-interval (traditional) dosing are clinically equivalent, discordant studies imply otherwise.[77,81,100] Extended-interval dosing is appropriate in the setting of non-high-level aminoglycoside resistant (MIC <500 µg/mL [mg/L]) *E. faecalis* infective endocarditis and this strategy has been adopted by the new ESC Guidelines.[6,100] This recommendation differs from the current AHA guidelines, which continue to support traditional dosing.[5]

Resistance among enterococci to penicillins and aminoglycosides is increasing.[5] Enterococci that exhibit high-level resistance to streptomycin (MIC >2,000 µg/mL [mg/L]) are not synergistically killed by penicillin and streptomycin because the aminoglycoside either no longer binds to the ribosome or is inactivated by an aminoglycoside-modifying enzyme, streptomycin adenylase.[80] Because enterococci will appear resistant to aminoglycosides on routine susceptibility testing, the only way to distinguish high-level from low-level resistance is by performing special susceptibility tests using 500 to 2,000 µg/mL (mg/L) of the aminoglycoside.[78] High-level streptomycin-resistant enterococci occur with a frequency approaching 60%, and high-level resistance to gentamicin is now found in 10% to 50% of isolates. Although most gentamicin-resistant enterococci are resistant to all aminoglycosides (including amikacin), 30% to 50% remain susceptible to streptomycin.[80] The incidence of high-level aminoglycoside resistance is increasing; however, data on appropriate therapy are sparse, and therapeutic options are few.[77,80,81]

In addition to isolates with high-level aminoglycoside resistance, β-lactamase-producing enterococci (especially *E. faecium*) have been reported. If these organisms are discovered, use of vancomycin or ampicillin-sulbactam in combination with gentamicin should be considered. Treating multidrug-resistant enterococci, such as VRE, is difficult, and data on appropriate therapy are sparse. Guidelines suggest either linezolid or daptomycin (at least 10 mg/kg), although use of either agent has produced conflicting results.[5,6] Surgery and replacement of the infected cardiac valve may be the only cure.

HACEK Group

Fastidious gram-negative bacteria from the group of bacteria including *Haemophilus parainfluenzae*, *Haemophilus aphrophilus*, *Aggregatibacter* species, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella kingae* (HACEK group) account for 0.8% to 6% of infective endocarditis cases.[101] Frequently, these types of infective endocarditis present as subacute illnesses with large vegetations and emboli. These oropharyngeal organisms are slow growing and should be considered as possible causes of “culture-negative” endocarditis. With proper treatment, infectious endocarditis caused by HACEK organisms has a low mortality rate. β-Lactamase–producing organisms are occurring more often; hence, HACEK organisms should be considered resistant to ampicillin alone and should not be used unless in vitro susceptibility testing is adequate. Ceftriaxone, or an alternate third- or fourth-generation cephalosporin, is the preferred treatment in most cases. Ciprofloxacin may be considered as an option if a hypersensitivity to cephalosporins is present (Table 134-11).[5,6] Treatment is usually for 4 weeks, but it should be extended to 6 weeks in PVE caused by one of these organisms.

Less Common Types of Infective Endocarditis

Atypical Microorganisms

Endocarditis caused by organisms, such as *Bartonella* spp., *C. burnetii*, *Brucella* spp., *Candida* spp., and *Aspergillus* spp., *Legionella* spp., and gram-negative bacilli (eg, *Pseudomonas*), is relatively uncommon. Medical therapy for infective endocarditis caused by these organisms is usually unsuccessful.[5,6] Consultation with an infectious diseases expert is warranted when these microorganisms are identified.

In addition to *Pseudomonas* spp., other gram-negative bacilli that have been implicated include *Salmonella* spp., *E. coli, Citrobacter* spp., *Klebsiella* spp., *Enterobacter* spp., *Serratia marcescens, Proteus* spp., and *Providencia* spp. These infections have a poor prognosis, with mortality rates as high as 60% to 80%. Cardiac surgery in concert with an extended duration of combination antibacterial therapy is recommended (class IIa; level of evidence: B) for most patients with gram-negative bacillary infective endocarditis. Readers are referred to the AHA guidelines for more extensive review of treatment regimens for infective endocarditis due to *Pseudomonas* spp. and unusual gram-negative bacteria.[5]

Fungi cause less than 2% of endocarditis cases; most patients with fungal endocarditis have undergone recent cardiovascular surgery, are PWID, have received prolonged treatment with indwelling central venous catheters, or are immunocompromised.[102] *Candida* spp. and *Aspergillus* spp. are the most commonly involved, and the mortality rate is high (>80%) for the following reasons: (1) large, bulky vegetations that often form, (2) systemic septic embolization that may occur, (3) the tendency of fungi to invade the myocardium, (4) poor penetration of vegetations by antifungals, (5) the low toxic-to-therapeutic ratio of agents such as amphotericin B, and (6) the lack of consistent fungicidal activity of available antifungal agents.[5,6,102] When fungal infective endocarditis is identified, a combined medical–surgical approach is warranted. Because these infections occur infrequently, scant clinical data are available to make solid treatment recommendations. Amphotericin B with or without flucytosine or high dose echinocandin is the recommended pharmacologic approach for *Candida* spp. endocarditis while voriconazole is suggested for those with *Aspergillus* spp. endocarditis.[5,6,84,103] Greater than 6 weeks of therapy is usually recommended, followed by life-long suppressive therapy with an oral azole in most cases.

C. burnetii (Q fever), an obligate intracellular bacterium, is most likely to be identified via serology or PCR testing since it cannot be isolated from routine blood cultures. It is a common cause of infective endocarditis in certain areas of the world where goat, cattle, and sheep farming are widespread. The most favorable therapy for Q fever is unknown but may include doxycycline with hydroxychloroquine, trimethoprim/sulfamethoxazole, rifampin, or fluoroquinolones for at least 18 months.[104] *Brucella* spp. are facultative intracellular gram-negative bacilli. Humans are infected by this organism after ingesting infected unpasteurized dairy products or undercooked meat, inhaling infectious aerosols, or contacting infected tissues. This type of infective endocarditis is more common in veterinarians and livestock handlers. Cure requires valve replacement and antimicrobial agents including doxycycline with streptomycin, gentamicin, or doxycycline with trimethoprim–sulfamethoxazole or rifampin for an extended period (6 weeks to months).[105]

Culture-Negative Endocarditis

Sterile blood cultures are reported in up to 40% of patients with infective endocarditis if strict diagnostic criteria are used.[2,6,41] This type of infective endocarditis may occur as a result of previous antimicrobial therapy (most common), unidentified subacute right-sided infective endocarditis, slow-growing fastidious organisms, non-bacterial etiologies (eg, fungi), non-infective endocarditis, and improperly collected blood cultures. When blood cultures from patients suspected of infective endocarditis show no growth after 48 to 72 hours, cultures should be held for up to a month and special testing techniques (eg, serological analysis, PCR) pursued to detect fastidious or non-bacterial organisms.[5,43]

The AHA guidelines provide general recommendations for culture-negative infective endocarditis (Table 134-11) and suggest that therapy should be guided based on the individual patient's medical history and epidemiological risks identified. Selection of treatment can be difficult, balancing the need to cover all likely organisms against potential toxic drug effects (eg, aminoglycosides). Antimicrobial selection should involve consultation with an infectious diseases specialist. Irrespective of the chosen treatment, extended antimicrobial therapy is required. The empirical approaches for culture-negative infective endocarditis highlight the need for proper collection and monitoring of blood cultures and an extensive medication history.

EVALUATION OF THERAPEUTIC OUTCOMES

The evaluation of patients treated for bacteremia or infective endocarditis includes assessment of disease signs and symptoms, blood cultures, microbiologic tests, inflammatory markers, serum drug concentrations, and other tests to evaluate organ function. Table 134-10

Signs and Symptoms

Time to clinical improvement in patients with bacteremia largely depends on the infectious etiology, primary source of infection, presence of secondary metastatic foci, and degree of source control. In general, patients with gram-negative bacteremia clinically improve at a faster rate than those with gram-positive bacteremia, especially *S. aureus*.[30]

Fever usually subsides within 1 week of initiating therapy for patients with infective endocarditis.[23] Persistence of fever may indicate ineffective antimicrobial therapy, emboli, right-sided endocarditis, intravascular catheter infections, or drug reactions. For some patients, fever may persist even with appropriate antimicrobial therapy. With defervescence, the patient should begin to feel better, and other symptoms, such as lethargy or weakness, should subside. Echocardiography, typically a TTE, should be performed when antimicrobial therapy has been completed to determine new baseline cardiac function (eg, ventricular size and function).[5]

Blood Cultures

After initiating antimicrobial therapy, follow-up blood cultures should be obtained every 24 to 48 hours until sterile in most patients as duration of bacteremia may impact duration of therapy.[30] With *S. aureus* bacteremia, positive follow-up blood cultures are associated with increased mortality.[106] Additionally, positive follow-up blood cultures, indicative of prolonged duration of bacteremia, may suggest that the antimicrobials are inactive against the pathogen, the doses are not producing adequate concentrations at the site of infection, or lack of source control in some patients.[107] In most situations, the duration of therapy should be determined beginning on the first day blood cultures were negative in patients with previously positive blood cultures. Alternatively, the duration of therapy should be counted from the first postoperative day in patients who undergo valve surgery with intraoperative findings of a paravalvular abscess or resultant positive culture from the valve tissue. During the remainder of therapy, frequent blood cultures are not necessary but should be obtained if fever recurs.[4]

However, positive follow-up blood cultures in gram-negative bacteremia are uncommon.[30,108] As a result, follow-up blood cultures may be unnecessary except in patients who remain febrile despite antimicrobial therapy, relapse, or lack source control. In these cases, duration of therapy should begin on the first day of active therapy based on antimicrobial susceptibility testing.

Microbiologic Tests

10 Identification and susceptibility testing should be performed on all organisms isolated from blood cultures to guide definitive therapy in patients with bacteremia or infective endocarditis.[5,49,65] The agent being used should be tested, as well as alternatives that may be required if intolerance, allergy, or resistance occurs. Occasionally, it is useful to determine whether synergy exists for antimicrobial combinations, although synergistic regimens usually can be predicted from the literature.

Inflammatory Markers

Inflammatory markers are commonly used in infectious diseases processes for diagnosing, monitoring of clinical outcomes, and assisting clinicians with evaluating the efficacy of antibacterial therapy. Only one inflammatory marker, rheumatoid factor (RF), is part of the Modified Duke Criteria for diagnosis. Other inflammatory markers, such as ESR, CRP, and procalcitonin (PCT), have all been investigated for evaluating the outcomes of patients with bacteremia and infective endocarditis.[109,110] While these markers may be beneficial in assessing clinical outcomes, further evidence is needed to establish routine use for infective endocarditis.

Serum Drug Concentrations

Of the agents used for bacteremia and infective endocarditis, therapeutic drug monitoring is routinely available for aminoglycosides (except streptomycin) and vancomycin. Few data, however, support attaining any specific serum concentrations for patients with infective endocarditis. In general, serum concentrations of the antibacterial should exceed the MIC of the organisms.

When aminoglycosides are administered for infective endocarditis caused by gram-positive cocci with a traditional three-times-daily regimen, peak serum concentrations are recommended to be on the low side of the traditional ranges (3-4 µg/mL [mg/L; 6.3-8.4 µmol/L] for gentamicin). If extended-interval dosing is used, which is only recommended in streptococcal infective endocarditis, the most appropriate method of monitoring has not been

determined. When vancomycin is administered, the primary goal is to ensure adequate concentrations, based on area under the curve (AUC)-guided or trough-guided serum concentration monitoring.

PREVENTION

Antimicrobial prophylaxis is used as an attempt to prevent infective endocarditis for patients who are at the highest risk (Table 134-14).[5–7] The use of antimicrobials for this purpose requires consideration of (1) cardiac conditions associated with endocarditis, (2) procedures causing bacteremia, (3) organisms likely to cause endocarditis, and (4) pharmacokinetics, spectrum, cost, adverse effects, and ease of administration of available antimicrobial agents. The objective of prophylaxis is to diminish the likelihood of infective endocarditis in high-risk individuals from procedures that result in bacteremia. Although there are no prospective, controlled human trials demonstrating that prophylaxis in high-risk individuals protects against the development of endocarditis during bacteremia-inducing procedures, animal studies suggest possible benefit.[7] Furthermore, many causes of infective endocarditis appear not to be secondary to an invasive procedure. Bacteremia as a consequence of daily activities may be the major culprit, and the value of antimicrobial prophylaxis before bacteremia-causing procedures has been questioned. The effectiveness or ineffectiveness of antimicrobial prophylaxis has not been proven, and the common practice of using antimicrobial therapy in this setting remains controversial. The mechanism of a beneficial effect in humans is unclear, but antimicrobials may decrease the number of bacteria at the surgical site, kill bacteria after they are introduced into the blood, and prevent adhesion of bacteria to the valve.

TABLE 134-14

Prophylaxis of Infective Endocarditis

Highest Risk Cardiac Conditions	Presence of a prosthetic heart valve Prosthetic material used for cardiac valve repair Prior diagnosis of infective endocarditis Cardiac transplantation with subsequent valvulopathy Congenital heart disease (CHD)[a]	
Types of procedures	Dental procedures that require perforation of the oral mucosa or manipulation of the periapical region of the teeth of gingival tissue Invasive respiratory procedures involving an incision or biopsy Invasive procedures involving infected skin, skin structures, or musculoskeletal tissue	
Antimicrobial Options	**Adult Doses[b]**	**Pediatric Doses[b] (mg/kg)**
Oral amoxicillin	2 g	50
IM or IV ampicillin[c]	2 g	50
IM or IV cefazolin or ceftriaxone[c–e]	1 g	50
Oral cephalexin[d–f]	2 g	50
Oral doxycycline[e]	100 mg	<45 kg, 4.4 mg/kg or >45 kg, 100 mg
Oral azithromycin or clarithromycin[e]	500 mg	15
IV vancomycin[b,c,e]	15 to 20 mg/kg (not to exceed 2 g per dose)	15 (maximum dose of 1 g)

[a]Includes only the following: unrepaired cyanotic CHD, prophylaxis within the first 6 months of implanting prosthetic material to repair a congenital heart defect, and repaired CHD with residual defects at or adjacent to prosthetic material.

[b]All one-time doses administered 30-60 minutes prior to initiation of the procedure except for IV vancomycin which should be administered 120 minutes prior to the procedure.

[c]For patients unable to tolerate oral medication.

[d]Should be avoided in patients with immediate-type hypersensitivity reaction to penicillin or ampicillin (eg, anaphylaxis, urticaria, or angioedema).

[e]Option for patients with non-immediate hypersensitivity reaction to penicillin or ampicillin.

[f]May substitute with an alternative first- or second-generation cephalosporin at an equivalent dose.

Data from References 7,111.

Regardless of the controversy about whether prophylactic antimicrobials should be used, infective endocarditis prophylaxis is recommended in select situations in those with underlying high-risk cardiac conditions. The AHA released updated guidelines that better define who should and should not receive infective endocarditis prophylaxis.[7]

Key points are that (1) only a small number of cases of infective endocarditis might be prevented with antimicrobial prophylaxis for dental procedures, even if 100% effective; (2) infective endocarditis prophylaxis should be recommended only for patients with underlying cardiac conditions associated with the highest risk, which includes presence of a prosthetic heart valve, prosthetic material used for cardiac valve repair, prior diagnosis of infective endocarditis, cardiac transplantation with subsequent valvulopathy, CHD, for dental procedures involving manipulation of gingival tissue or the periapical region of teeth or perforation of the oral mucosa, invasive respiratory procedures involving an incision or biopsy, or invasive procedures involving infected skin, skin structures, or musculoskeletal tissue; (3) prophylaxis is not recommended based solely on an increased lifetime risk of acquisition of infective endocarditis; and (4) administration of antimicrobials solely to prevent endocarditis is not recommended for patients who undergo a gastrointestinal tract or genitourinary procedure.

To determine whether a patient should receive prophylactic antimicrobials, one needs to assess the patient's risk and whether he or she is undergoing a procedure resulting in bacteremia. When antimicrobial prophylaxis is appropriate, a single 2-g dose of amoxicillin is recommended for adult patients at risk, given 30 to 60 minutes before undergoing procedures associated with bacteremia. Because the duration of antimicrobial prophylaxis appears to be relatively short, guidelines do not advocate a second oral dose of amoxicillin, which was recommended previously. Alternative prophylaxis regimens for patients with hypersensitivity to penicillins or those unable to take oral medications are also provided. Clindamycin is no longer recommended for prophylaxis for dental procedures due to greater risk of adverse reactions compared to other prophylactic antimicrobials. A summary of guideline recommendations is available in Table 134-11. Refer the full AHA guideline for more detailed information.[7]

ABBREVIATIONS

AHA	American Heart Association
ANC	absolute neutrophil count
CDIE	cardiac device infective endocarditis
CHD	congenital heart disease
CPK	creatinine kinase
CRP	c-reactive protein
ESBL	extended spectrum β-lactamase
ESC	European Society of Cardiology
ESR	erythrocyte sedimentation rate
HACEK	the group of bacteria including *Haemophilus parainfluenzae*, *Haemophilus aphrophilus*, *Aggregatibacter* species, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella kingae*
IE	infective endocarditis
MBC	minimum bactericidal concentration
MIC	minimum inhibitory concentration

MRSA	methicillin-resistant *Staphylococcus aureus*
MSSA	methicillin-susceptible *Staphylococcus aureus*
NVE	native valve endocarditis
OPAT	outpatient antimicrobial therapy
PCR	polymerase chain reaction
PCT	procalcitonin
PVE	prosthetic valve endocarditis
PWID	persons who inject drugs
RF	rheumatoid factor
SBT	serum bactericidal titer
TEE	transesophageal echocardiography
TTE	transthoracic echocardiography
ULN	upper limit of normal
VRE	vancomycin resistant enterococcus

REFERENCES

1. Coburn B, Morris AM, Tomlinson G, Detsky AS. Does this adult patient with suspected bacteremia require blood cultures? *JAMA.* Aug 1 2012;308(5):502–511. doi: 10.1001/jama.2012.8262.

2. Thuny F, Grisoli D, Cautela J, Riberi A, Raoult D, Habib G. Infective endocarditis: Prevention, diagnosis, and management. *Can J Cardiol.* Sep 2014;30(9):1046–1057. doi: 10.1016/j.cjca.2014.03.042.

3. Sandoe JAT, Watkin RW, Elliott TSJ, Dayer MJ. Infective endocarditis in the adult patient. *Medicine*. 2017;45(11):678–682. 2017/11/01. doi: https://doi.org/10.1016/j.mpmed.2017.08.004.

4. Fernández Guerrero ML, Álvarez B, Manzarbeitia F, Renedo G. Infective endocarditis at autopsy: A review of pathologic manifestations and clinical correlates. *Medicine (Baltimore)*. May 2012;91(3):152–164. doi: 10.1097/MD.0b013e31825631ea.

5. Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis in adults: Diagnosis, antimicrobial therapy, and management of complications. *Circulation* 2015;132(15):1435–1486. doi: 10.1161/CIR.0000000000000296.

6. Habib G, Lancellotti P, Antunes MJ, et al. 2015 ESC Guidelines for the management of infective endocarditis: The Task Force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by: European Association for Cardio-Thoracic Surgery (EACTS), the European Association of Nuclear Medicine (EANM). *Eur Heart J.* Nov 21 2015;36(44):3075–3128. doi: 10.1093/eurheartj/ehv319.

7. Nishimura RA, Otto CM, Bonow RO, et al. 2017 AHA/ACC Focused Update of the 2014 AHA/ACC guideline for the management of patients with valvular heart disease: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. Jun 20 2017;135(25):e1159–e1195. doi: 10.1161/cir.0000000000000503.

8. Baddour LM, Epstein AE, Erickson CC, et al. Update on cardiovascular implantable electronic device infections and their management. *Circulation* 2010;121(3):458–477. doi: 10.1161/CIRCULATIONAHA.109.192665.

9. Kern WV, Rieg S. Burden of bacterial bloodstream infection—A brief update on epidemiology and significance of multidrug-resistant pathogens. *Clin Microbiol Infect* 2020;26(2):151–157. doi: 10.1016/j.cmi.2019.10.031.

10. Laupland KB, Church DL. Population-based epidemiology and microbiology of community-onset bloodstream infections. *Clin Microbiol Rev.* 2014;27(4):647–664. doi: 10.1128/CMR.00002-14.

11. El Atrouni WI, Knoll BM, Lahr BD, Eckel-Passow JE, Sia IG, Baddour LM. Temporal trends in the incidence of *Staphylococcus aureus* bacteremia in Olmsted County, Minnesota, 1998 to 2005: A population-based study. *Clin Infect Dis.* Dec 15 2009;49(12):e130–e138. doi: 10.1086/648442.

12. Tong SY, Davis JS, Eichenberger E, Holland TL, Fowler VG Jr. Staphylococcus aureus infections: Epidemiology, pathophysiology, clinical manifestations, and management. *Clin Microbiol Rev.* Jul 2015;28(3):603–661. doi: 10.1128/cmr.00134-14.

13. Graff LR, Franklin KK, Witt L, et al. Antimicrobial therapy of gram-negative bacteremia at two university-affiliated medical centers. *Am J Med.* Feb 15 2002;112(3):204–211. doi: 10.1016/s0002-9343(01)01092-0

14. Cervera C, Almela M, Martinez-Martinez JA, Moreno A, Miro JM. Risk factors and management of Gram-positive bacteraemia. *Int J Antimicrob Agents*. 2009;34(Suppl 4):S26–S30. doi: 10.1016/S0924-8579(09)70562-X.

15. Pant S, Patel NJ, Deshmukh A, et al. Trends in infective endocarditis incidence, microbiology, and valve replacement in the United States from 2000 to 2011. *J Am Coll Cardiol.* May 19 2015;65(19):2070–2076. doi: 10.1016/j.jacc.2015.03.518.

16. Toyoda N, Chikwe J, Itagaki S, Gelijns AC, Adams DH, Egorova NN. Trends in infective endocarditis in California and New York State, 1998-2013. *JAMA.* Apr 25 2017;317(16):1652–1660. doi: 10.1001/jama.2017.4287.

17. Talha KM, Dayer MJ, Thornhill MH, et al. Temporal trends of infective endocarditis in North America from 2000 to 2017 – A systematic review. *Open Forum Infect Dis* 2021;8(11)doi: 10.1093/ofid/ofab479.

18. Elder RW, Baltimore RS. The changing epidemiology of pediatric endocarditis. *Infect Dis Clin North Am.* Sep 2015;29(3):513–524. doi: 10.1016/j.idc.2015.05.004.

19. Wang A, Gaca JG, Chu VH. Management considerations in infective endocarditis: A review. *JAMA.* Jul 3 2018;320(1):72–83. doi: 10.1001/jama.2018.7596.

20. Chirouze C, Hoen B, Duval X. Infective endocarditis epidemiology and consequences of prophylaxis guidelines modifications: The dialectical evolution. *Curr Infect Dis Rep.* Nov 2014;16(11):440. doi: 10.1007/s11908-014-0440-y.

21. Hoen B, Duval X. Infective endocarditis. *N Engl J Med.* Aug 22 2013;369(8):785. doi: 10.1056/NEJMc1307282.

22. Katan O, Michelena HI, Avierinos JF, et al. Incidence and predictors of infective endocarditis in mitral valve prolapse: A population-based study. *Mayo Clin Proc.* Mar 2016;91(3):336–342. doi: 10.1016/j.mayocp.2015.12.006.

23. Hill EE, Herijgers P, Herregods MC, Peetermans WE. Evolving trends in infective endocarditis. *Clin Microbiol Infect.* Jan 2006;12(1):5–12. doi: 10.1111/j.1469-0691.2005.01289.x.

24. Yardena S-I, Boaz F, Ruth O-W, et al. Reappraisal of community-acquired bacteremia: A proposal of a new classification for the spectrum of acquisition of bacteremia. *Clin Infect Dis.* 2002;34(11):1431–1439. doi: 10.1086/339809.

25. Rodríguez-Baño J, López-Prieto MD, Portillo MM, et al. Epidemiology and clinical features of community-acquired, healthcare-associated and nosocomial bloodstream infections in tertiary-care and community hospitals. *Clin Microbiol Infect.* 2010;16(9):1408–1413. doi: 10.1111/j.1469-0691.2010.03089.x.

26. Benito N, Miró JM, de Lazzari E, et al. Health care-associated native valve endocarditis: Importance of non-nosocomial acquisition. *Ann Intern Med.* May 5 2009;150(9):586–594. doi: 10.7326/0003-4819-150-9-200905050-00004.

27. Bin Abdulhak AA, Tleyjeh IM. Indications of surgery in infective endocarditis. *Curr Infect Dis Rep.* Mar 2017;19(3):10. doi: 10.1007/s11908-017-0569-6.

28. Thuny F, Grisoli D, Collart F, Habib G, Raoult D. Management of infective endocarditis: challenges and perspectives. *Lancet*. Mar 10 2012;379(9819):965–975. doi: 10.1016/s0140-6736(11)60755-1.

29. Christaki E, Giamarellos-Bourboulis EJ. The complex pathogenesis of bacteremia: From antimicrobial clearance mechanisms to the genetic background of the host. *Virulence*. Jan 1 2014;5(1):57–65. doi: 10.4161/viru.26514.

30. Fabre V, Sharara SL, Salinas AB, Carroll KC, Desai S, Cosgrove SE. Does this patient need blood cultures? A scoping review of indications for blood cultures in adult nonneutropenic inpatients. *Clin Infect Dis.* Aug 22 2020;71(5):1339–1347. doi: 10.1093/cid/ciaa039.

31. Siegman-Igra Y, Fourer B, Orni-Wasserlauf R, et al. Reappraisal of community-acquired bacteremia: A proposal of a new classification for the spectrum of acquisition of bacteremia. *Clin Infect Dis.* Jun 1 2002;34(11):1431–1439. doi: 10.1086/339809.

32. Klein M, Wang A. Infective endocarditis. *J Intensive Care Med.* Mar 2016;31(3):151–163. doi: 10.1177/0885066614554906.

33. Werdan K, Dietz S, Löffler B, et al. Mechanisms of infective endocarditis: Pathogen-host interaction and risk states. *Nat Rev Cardiol.* Jan 2014;11(1):35–50. doi: 10.1038/nrcardio.2013.174.

34. Athan E, Chu VH, Tattevin P, et al. Clinical characteristics and outcome of infective endocarditis involving implantable cardiac devices. *JAMA.* Apr 25 2012;307(16):1727–1735. doi: 10.1001/jama.2012.497.

35. Sexton DJ, Spelman D. Current best practices and guidelines. Assessment and management of complications in infective endocarditis. *Infect Dis Clin North Am.* Jun 2002;16(2):507–521, xii. doi: 10.1016/s0891-5520(01)00011-3.

36. Habib G, Hoen B, Tornos P, et al. Guidelines on the prevention, diagnosis, and treatment of infective endocarditis (new version 2009): The Task Force on the Prevention, Diagnosis, and Treatment of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and the International Society of Chemotherapy (ISC) for Infection and Cancer. *Eur Heart J.* Oct 2009;30(19):2369–2413. doi: 10.1093/eurheartj/ehp285.

37. Cheng MP, Stenstrom R, Paquette K, et al. Blood culture results before and after antimicrobial administration in patients with severe manifestations of sepsis: A diagnostic study. *Ann Intern Med.* Oct 15 2019;171(8):547–554. doi: 10.7326/M19-1696.

38. Doern GV, Carroll KC, Diekema DJ, et al. Practical guidance for clinical microbiology laboratories: A comprehensive update on the problem of blood culture contamination and a discussion of methods for addressing the problem. *Clin Microbiol Rev.* Dec 18 2019;33(1). doi: 10.1128/CMR.00009-19.

39. Lee A, Mirrett S, Reller LB, Weinstein MP. Detection of bloodstream infections in adults: How many blood cultures are needed? *J Clin Microbiol.* Nov 2007;45(11):3546–3548. doi: 10.1128/JCM.01555-07.

40. Pien BC, Sundaram P, Raoof N, et al. The clinical and prognostic importance of positive blood cultures in adults. *Am J Med.* Sep 2010;123(9):819–828. doi: 10.1016/j.amjmed.2010.03.021.

41. Durack DT, Lukes AS, Bright DK. New criteria for diagnosis of infective endocarditis: Utilization of specific echocardiographic findings. Duke Endocarditis Service. *Am J Med.* Mar 1994;96(3):200–209. doi: 10.1016/0002-9343(94)90143-0.

42. Li JS, Sexton DJ, Mick N, et al. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. *Clin Infect Dis.* Apr 2000;30(4):633–638. doi: 10.1086/313753.

43. Liesman RM, Pritt BS, Maleszewski JJ, Patel R. Laboratory diagnosis of infective endocarditis. *J Clin Microbiol.* Sep 2017;55(9):2599–2608. doi: 10.1128/jcm.00635-17.

44. Cunha BA. Empiric antimicrobial therapy for bacteremia: Get it right from the start or get a call from infectious disease. *Clin Infect Dis.* Oct 15 2004;39(8):1170–1173. doi: 10.1086/424525.

45. Price CN, Solomon DA, Johnson JA, Montgomery MW, Martin B, Suzuki J. Feasibility and safety of outpatient parenteral antimicrobial therapy in conjunction with addiction treatment for people who inject drugs. *J Infect Dis.* Sep 2 2020;222(Suppl 5):S494–S498. doi: 10.1093/infdis/jiaa025.

46. Tamma PD, Conley AT, Cosgrove SE, et al. Association of 30-day mortality with oral step-down vs continued intravenous therapy in patients hospitalized with enterobacteriaceae bacteremia. *JAMA Intern Med.* Mar 1 2019;179(3):316–323. doi: 10.1001/jamainternmed.2018.6226.

47. Iversen K, Ihlemann N, Gill SU, et al. Partial oral versus intravenous antimicrobial treatment of endocarditis. *N Engl J Med.* Jan 31 2019;380(5):415–424. doi: 10.1056/NEJMoa1808312.

48. Marshall JC. Principles of source control in the early management of sepsis. *Curr Infect Dis Rep.* Sep 2010;12(5):345–353. doi: 10.1007/s11908-010-0126-z.

49. Holland TL, Arnold C, Fowler VG Jr. Clinical management of staphylococcus aureus bacteremia: A review. *JAMA.* 2014;312(13):1330–1341. doi: 10.1001/jama.2014.9743.

50. Goto M, Schweizer ML, Vaughan-Sarrazin MS, et al. Association of evidence-based care processes with mortality in *Staphylococcus aureus* bacteremia at Veterans Health Administration Hospitals, 2003-2014. *JAMA Intern Med.* Oct 1 2017;177(10):1489–1497. doi: 10.1001/jamainternmed.2017.3958.

51. Bai AD, Showler A, Burry L, et al. Impact of infectious disease consultation on quality of care, mortality, and length of stay in *Staphylococcus aureus* bacteremia: Results from a large multicenter cohort study. *Clin Infect Dis.* May 15 2015;60(10):1451–1461. doi: 10.1093/cid/civ120.

52. Lee RA, Vo DT, Zurko JC, Griffin RL, Rodriguez JM, Camins BC. Infectious diseases consultation is associated with decreased mortality in enterococcal bloodstream infections. *Open Forum Infect Dis.* Mar 2020;7(3):ofaa064. doi: 10.1093/ofid/ofaa064.

53. Walensky RP, McQuillen DP, Shahbazi S, Goodson JD. Where is the ID in COVID-19? *Ann Intern Med.* Oct 6 2020;173(7):587–589. doi: 10.7326/M20-2684.

54. Wenzler E, Wang F, Goff DA, et al. An Automated, pharmacist-driven initiative improves quality of care for *Staphylococcus aureus* bacteremia. *Clin Infect Dis.* Jul 15 2017;65(2):194–200. doi: 10.1093/cid/cix315.

55. Gelsomino S, Maessen JG, van der Veen F, et al. Emergency surgery for native mitral valve endocarditis: The impact of septic and cardiogenic shock. *Ann Thorac Surg.* May 2012;93(5):1469–1476. doi: 10.1016/j.athoracsur.2011.11.025.

56. Manne MB, Shrestha NK, Lytle BW, et al. Outcomes after surgical treatment of native and prosthetic valve infective endocarditis. *Ann Thorac Surg.* Feb 2012;93(2):489–493. doi: 10.1016/j.athoracsur.2011.10.063.

57. Ramirez-Duque N, Garcia-Cabrera E, Ivanova-Georgieva R, et al. Surgical treatment for infective endocarditis in elderly patients. *J Infect.* Aug 2011;63(2):131–138. doi: 10.1016/j.jinf.2011.05.021.

58. Kiefer T, Park L, Tribouilloy C, et al. Association between valvular surgery and mortality among patients with infective endocarditis complicated by heart failure. *JAMA.* Nov 23 2011;306(20):2239–2247. doi: 10.1001/jama.2011.1701.

59. De Feo M, Cotrufo M, Carozza A, et al. The need for a specific risk prediction system in native valve infective endocarditis surgery. *Sci World J.* 2012;2012:307571. doi: 10.1100/2012/307571.

60. Byrne JG, Rezai K, Sanchez JA, et al. Surgical management of endocarditis: The society of thoracic surgeons clinical practice guideline. *Ann Thorac Surg.* Jun 2011;91(6):2012–2019. doi: 10.1016/j.athoracsur.2011.01.106.

61. Kang DH, Kim YJ, Kim SH, et al. Early surgery versus conventional treatment for infective endocarditis. *N Engl J Med.* Jun 28 2012;366(26):2466–2473. doi: 10.1056/NEJMoa1112843.

62. Safdar N, Handelsman J, Maki DG. Does combination antimicrobial therapy reduce mortality in gram-negative bacteraemia? A meta-analysis. *Lancet Infect Dis.* Aug 2004;4(8):519–527. doi: 10.1016/S1473-3099(04)01108-9.

63. Mogle BT, Beccari MV, Steele JM, Fazili T, Kufel WD. Clinical considerations for oral beta-lactams as step-down therapy for Enterobacteriaceae bloodstream infections. *Expert Opin Pharmacother.* Jun 2019;20(8):903–907. doi: 10.1080/14656566.2019.1594774.

64. Sutton JD, Stevens VW, Chang NN, Khader K, Timbrook TT, Spivak ES. Oral beta-lactam antimicrobials vs fluoroquinolones or trimethoprim-sulfamethoxazole for definitive treatment of enterobacterales bacteremia from a urine source. *JAMA Network Open*. Oct 1 2020;3(10):e2020166. doi: 10.1001/jamanetworkopen.2020.20166.

65. Al-Hasan MN, Rac H. Transition from intravenous to oral antimicrobial therapy in patients with uncomplicated and complicated bloodstream infections. *Clin Microbiol Infect.* Mar 2020;26(3):299–306. doi: 10.1016/j.cmi.2019.05.012.

66. Yahav D, Franceschini E, Koppel F, et al. Seven versus 14 days of antimicrobial therapy for uncomplicated gram-negative bacteremia: A noninferiority randomized controlled trial. *Clin Infect Dis.* Sep 13 2019;69(7):1091–1098. doi: 10.1093/cid/ciy1054.

67. Gentry CA, Rodvold KA, Novak RM, Hershow RC, Naderer OJ. Retrospective evaluation of therapies for *Staphylococcus aureus* endocarditis. *Pharmacotherapy*. Sep-Oct 1997;17(5):990–997. [PubMed: 9324187]

68. Liu C, Bayer A, Cosgrove SE, et al. Clinical practice guidelines by the infectious diseases society of america for the treatment of methicillin-resistant *Staphylococcus aureus* infections in adults and children. *Clin Infect Dis.* Feb 1 2011;52(3):e18–e55. doi: 10.1093/cid/ciq146.

69. Minejima E, Mai N, Bui N, et al. Defining the breakpoint duration of *Staphylococcus aureus* bacteremia predictive of poor outcomes. *Clin Infect Dis.* Feb 3 2020;70(4):566–573. doi: 10.1093/cid/ciz257.

70. Rose W, Fantl M, Geriak M, Nizet V, Sakoulas G. Current paradigms of combination therapy in methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia: Does it work, which combination and for which patients? *Clin Infect Dis.* May 16 2021;doi: 10.1093/cid/ciab452.

71. Holland TL, Raad I, Boucher HW, et al. Effect of algorithm-based therapy vs usual care on clinical success and serious adverse events in patients with staphylococcal bacteremia: A randomized clinical trial. *JAMA.* Sep 25 2018;320(12):1249–1258. doi: 10.1001/jama.2018.13155.

72. Dagher M, Fowler VG Jr, Wright PW, Staub MB. A narrative review of early oral stepdown therapy for the treatment of uncomplicated *Staphylococcus aureus* bacteremia: Yay or nay? *Open Forum Infect Dis.* Jun 2020;7(6):ofaa151. doi: 10.1093/ofid/ofaa151.

73. Diekema DJ, Pfaller MA, Schmitz FJ, et al. Survey of infections due to Staphylococcus species: Frequency of occurrence and antimicrobial susceptibility of isolates collected in the United States, Canada, Latin America, Europe, and the Western Pacific region for the SENTRY Antimicrobial

Surveillance Program, 1997-1999. *Clin Infect Dis.* May 15 2001;32(Suppl 2):S114–S132. doi: 10.1086/320184.

74. Mermel LA, Allon M, Bouza E, et al. Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 Update by the Infectious Diseases Society of America. *Clin Infect Dis.* Jul 1 2009;49(1):1–45. doi: 10.1086/599376.

75. Babiker A, Li X, Lai YL, et al. Effectiveness of adjunctive clindamycin in beta-lactam antimicrobial-treated patients with invasive beta-haemolytic streptococcal infections in US hospitals: A retrospective multicentre cohort study. *Lancet Infect Dis.* May 2021;21(5):697–710. doi: 10.1016/S1473-3099(20)30523-5.

76. Arensman K, Shields M, Beganovic M, et al. Fluoroquinolone versus beta-lactam oral step-down therapy for uncomplicated streptococcal bloodstream infections. *Antimicrob Agents Chemother.* Oct 20 2020;64(11). doi: 10.1128/AAC.01515-20.

77. Beganovic M, Luther MK, Rice LB, Arias CA, Rybak MJ, LaPlante KL. A review of combination antimicrobial therapy for *Enterococcus faecalis* bloodstream infections and infective endocarditis. *Clin Infect Dis.* Jul 2 2018;67(2):303–309. 10.1093/cid/ciy064.

78. O'Driscoll T, Crank CW. Vancomycin-resistant enterococcal infections: Epidemiology, clinical manifestations, and optimal management. *Infect Drug Resist.* 2015;8:217–230. doi: 10.2147/IDR.S54125.

79. Britt NS, Potter EM, Patel N, Steed ME. Comparative effectiveness and safety of standard-, medium-, and high-dose daptomycin strategies for the treatment of vancomycin-resistant enterococcal bacteremia among veterans affairs patients. *Clin Infect Dis.* Mar 1 2017;64(5):605–613. doi: 10.1093/cid/ciw815.

80. Pericas JM, Zboromyrska Y, Cervera C, et al. Enterococcal endocarditis revisited. *Future Microbiol.* 2015;10(7):1215–1240. doi: 10.2217/fmb.15.46.

81. Arias CA, Contreras GA, Murray BE. Management of multidrug-resistant enterococcal infections. *Clin Microbiol Infect.* Jun 2010;16(6):555–562. doi: 10.1111/j.1469-0691.2010.03214.x.

82. Kim J, Lee Y, Park Y, et al. Anaerobic bacteremia: Impact of inappropriate therapy on mortality. *Infect Chemothe.* Jun 2016;48(2):91–98. doi: 10.3947/ic.2016.48.2.91.

83. Tattevin P, Revest M, Lefort A, Michelet C, Lortholary O. Fungal endocarditis: Current challenges. *Int J Antimicrob Agents*. Oct 2014;44(4):290–294. doi: 10.1016/j.ijantimicag.2014.07.003.

84. Pappas PG, Kauffman CA, Andes DR, et al. Clinical practice guideline for the management of candidiasis: 2016 update by the Infectious Diseases Society of America. *Clin Infect Dis.* Feb 15 2016;62(4):e1–e50. doi: 10.1093/cid/civ933.

85. Sexton DJ, Tenenbaum MJ, Wilson WR, et al. Ceftriaxone once daily for four weeks compared with ceftriaxone plus gentamicin once daily for two weeks for treatment of endocarditis due to penicillin-susceptible streptococci. Endocarditis Treatment Consortium Group. *Clin Infect Dis.* Dec 1998;27(6):1470–1474. doi: 10.1086/515038.

86. Falagas ME, Matthaiou DK, Bliziotis IA. The role of aminoglycosides in combination with a beta-lactam for the treatment of bacterial endocarditis: A meta-analysis of comparative trials. *J Antimicrob Chemother.* Apr 2006;57(4):639–647. doi: 10.1093/jac/dkl044.

87. Falagas ME, Manta KG, Ntziora F, Vardakas KZ. Linezolid for the treatment of patients with endocarditis: A systematic review of the published evidence. *J Antimicrob Chemother.* Aug 2006;58(2):273–280. 10.1093/jac/dkl219.

88. Fowler VG Jr, Boucher HW, Corey GR, et al. Daptomycin versus standard therapy for bacteremia and endocarditis caused by *Staphylococcus aureus*. *N Engl J Med.* Aug 17 2006;355(7):653–665. doi: 10.1056/NEJMoa053783.

89. Levine DP, Lamp KC. Daptomycin in the treatment of patients with infective endocarditis: Experience from a registry. *Am J Med.* Oct 2007;120(10 Suppl 1):S28–S33. doi: 10.1016/j.amjmed.2007.07.011.

90. Wu G, Abraham T, Rapp J, Vastey F, Saad N, Balmir E. Daptomycin: Evaluation of a high-dose treatment strategy. *Int J Antimicrob Agents*. Sep 2011;38(3):192–196. doi: 10.1016/j.ijantimicag.2011.03.006.

91. Durante-Mangoni E, Casillo R, Bernardo M, et al. High-dose daptomycin for cardiac implantable electronic device-related infective endocarditis. *Clin Infect Dis.* Feb 1 2012;54(3):347–354. doi: 10.1093/cid/cir805.

92. Carugati M, Bayer AS, Miro JM, et al. High-dose daptomycin therapy for left-sided infective endocarditis: A prospective study from the international collaboration on endocarditis. *Antimicrob Agents Chemother.* Dec 2013;57(12):6213–6222. doi: 10.1128/AAC.01563-13.

93. Yung D, Kottachchi D, Neupane B, Haider S, Loeb M. Antimicrobials for right-sided endocarditis in intravenous drug users: A systematic review. *J Antimicrob Chemother.* Nov 2007;60(5):921–928. doi: 10.1093/jac/dkm324.

94. Dworkin RJ, Lee BL, Sande MA, Chambers HF. Treatment of right-sided *Staphylococcus aureus* endocarditis in intravenous drug users with ciprofloxacin and rifampicin. *Lancet*. Nov 4 1989;2(8671):1071–1073. doi: 10.1016/s0140-6736(89)91083-0.

95. Heldman AW, Hartert TV, Ray SC, et al. Oral antimicrobial treatment of right-sided staphylococcal endocarditis in injection drug users: Prospective randomized comparison with parenteral therapy. *Am J Med.* Jul 1996;101(1):68–76. doi: 10.1016/s0002-9343(96)00070-8.

96. Thomas G, Henao-Martinez AF, Franco-Paredes C, Chastain DB. Treatment of osteoarticular, cardiovascular, intravascular-catheter-related and other complicated infections with dalbavancin and oritavancin: A systematic review. *Int J Antimicrob Agents*. Sep 2020;56(3):106069. doi: 10.1016/j.ijantimicag.2020.106069.

97. Casey JR, Kaur R, Friedel VC, Pichichero ME. Acute otitis media otopathogens during 2008 to 2010 in Rochester, New York. *Pediatr Infect Dis J.* Aug 2013;32(8):805–809. doi: 10.1097/INF.0b013e31828d9acc.

98. Riedel DJ, Weekes E, Forrest GN. Addition of rifampin to standard therapy for treatment of native valve infective endocarditis caused by *Staphylococcus aureus*. *Antimicrob Agents Chemother.* Jul 2008;52(7):2463–2467. doi: 10.1128/AAC.00300-08.

99. Reyes K, Zervos M. Endocarditis caused by resistant enterococcus: An overview. *Curr Infect Dis Rep.* Aug 2013;15(4):320–328. doi: 10.1007/s11908-013-0348-y.

100. Miro JM, Pericas JM, del Rio A, Hospital Clinic Endocarditis Study G. A new era for treating *Enterococcus faecalis* endocarditis: Ampicillin plus short-course gentamicin or ampicillin plus ceftriaxone: That is the question!. *Circulation*. Apr 30 2013;127(17):1763–1766. 10.1161/CIRCULATIONAHA.113.002431.

101. Chambers ST, Murdoch D, Morris A, et al. HACEK infective endocarditis: Characteristics and outcomes from a large, multi-national cohort. *PLoS One*. 2013;8(5):e63181. doi: 10.1371/journal.pone.0063181.

102. Pierrotti LC, Baddour LM. Fungal endocarditis, 1995-2000. *Chest*. Jul 2002;122(1):302–310. doi: 10.1378/chest.122.1.302.

103. Baeten JM, Palanee-Phillips T, Brown ER, et al. Use of a vaginal ring containing dapivirine for HIV-1 prevention in women. *N Engl J Med.* Dec 1 2016;375(22):2121–2132. doi: 10.1056/NEJMoa1506110.

104. Kersh GJ. Antimicrobial therapies for Q fever. *Expert Rev Anti Infect Ther.* Nov 2013;11(11):1207–1214. doi: 10.1586/14787210.2013.840534.

105. Solera J. Update on brucellosis: Therapeutic challenges. *Int J Antimicrob Agents*. Nov 2010;36(Suppl 1):S18–S20. doi: 10.1016/j.ijantimicag.2010.06.015.

106. Lopez Dupla M, Martinez JA, Vidal F, et al. Clinical characterization of breakthrough bacteraemia: A survey of 392 episodes. *J Int Med.* Aug 2005;258(2):172–180. doi: 10.1111/j.1365-2796.2005.01513.x.

107. Wiggers JB, Xiong W, Daneman N. Sending repeat cultures: Is there a role in the management of bacteremic episodes? (SCRIBE study). *BMC Infect Dis.* Jun 13 2016;16:286. doi: 10.1186/s12879-016-1622-z.

108. Clemmons AB, Young HN, Bland CM, et al. Incidence and utility of follow-up blood cultures in cancer patients with gram-negative bacteremia. *Diagn Microbiol Infect Dis.* Oct 2021;101(2):115444. doi: 10.1016/j.diagmicrobio.2021.115444.

109. Watkins R. The role for inflammatory markers in the diagnosis and management of infective endocarditis. *Infect Dis Clin Pract.* 03/01 2010;18. doi: 10.1097/IPC.0b013e3181aba67c.

110. von Dach E, Albrich WC, Brunel AS, et al. Effect of C-reactive protein-guided antimicrobial treatment duration, 7-day treatment, or 14-day treatment on 30-day clinical failure rate in patients with uncomplicated gram-negative bacteremia: A randomized clinical trial. *JAMA.* Jun 2 2020;323(21):2160–2169. doi: 10.1001/jama.2020.6348.

111. Wilson Walter R., Gewitz Michael, Lockhart Peter B., et al. Prevention of viridans group streptococcal infective endocarditis: A scientific statement from the American Heart Association. *Circulation* 2021;143 10.1161/cir.0000000000000969.

SELF-ASSESSMENT QUESTIONS

1. Which of the following are the two most important parameters for the diagnosis of infective endocarditis?
   A. Laboratory abnormalities and positive blood cultures
   B. Positive blood cultures and echocardiographic changes
   C. Electrocardiogram changes and positive physical findings
   D. Positive physical findings and positive blood cultures
2. Which of the following most likely represents a patient with true bacteremia?
   A. 62-year-old man admitted for diabetic ketoacidosis with *Staphylococcus epidermidis* isolated from 1 of 4 blood culture bottles
   B. 22-year-old woman with a history of intravenous drug use with *Staphylococcus aureus* isolated from 2 of 4 blood culture bottles
   C. 58-year-old woman admitted with a newly diagnosed DVT and *Bacillus* spp. isolated from both sets of blood cultures
   D. 99-year-old man admitted for failure to thrive with *Staphylococcus haemolyticus* isolated from 2 of 4 blood culture bottles
3. Which statement is *true* concerning echocardiography in the diagnosis of infective endocarditis?
   A. A negative transthoracic echocardiogram (TTE) excludes a diagnosis of infective endocarditis
   B. Transesophageal echocardiogram (TEE) has better sensitivity than transthoracic echocardiogram (TTE) for detecting vegetations
   C. Transesophageal echocardiogram (TEE) is unnecessary in patients with congenital heart disease, previous endocarditis, new murmur, or heart failure
   D. Transesophageal echocardiogram (TEE) has good sensitivity but poor specificity for detecting vegetations
4. 76-year-old man with a history of dental abscess was admitted to the clinic with persistent fever and malaise for the last month. A transthoracic echocardiogram (TTE) revealed a large mitral valve vegetation. Which of the following is the most likely etiology?
   A. Group A streptococci

B. Viridans group streptococci

C. *Staphylococcus epidermidis*

D. *Enterococcus faecalis*

5. 35-year-old man with a history of injection drug use was admitted with fevers and rigors and blood cultures revealed gram-positive cocci in pairs and clusters. He has no known drug allergies, has normal renal function, and appears in no apparent distress. Which of the following is the most appropriate empiric antibacterial therapy?

   A. Vancomycin

   B. Cefazolin

   C. Nafcillin

   D. Piperacillin/tazobactam

6. Which of the following is associated with the *highest* risk of developing infective endocarditis?

   A. Mitral valve prolapse with regurgitation

   B. Presence of a prosthetic heart valve

   C. Rheumatic fever without valvular defects

   D. Intravenous drug abuse

7. Which of the following represents the most likely primary source for *Escherichia coli* bacteremia?

   A. Urogenital procedure

   B. Skin and soft tissue infection

   C. Community acquired pneumonia

   D. Total knee arthroplasty

8. Which situation is *most* likely to lead to "culture-negative" infective endocarditis?

   A. Use of antimicrobials prior to blood culture sampling

   B. Gram-negative bacteria from the HACEK group (eg, *Kingella kingae*)

   C. Non-bacterial etiologies (eg, fungi)

   D. Unidentified subacute, left-sided infective endocarditis

9. A patient presents with complaints of fevers, chills, malaise, and dyspnea for the past 2 days. A grade 3/6 systolic murmur and thin, linear hemorrhages under the fingernail beds are discovered on examination. Based on these findings, the patient is suspected to have infective endocarditis. Which of the following would be the most appropriate empirical antimicrobial regimen?

   A. Cefazolin 2 g IV every 8 hours

   B. Vancomycin 15 mg/kg IV every 12 hours

   C. Vancomycin 15 mg/kg IV every 12 hours plus ampicillin/sulbactam 3 g IV every 6 hours

D. Vancomycin 15 mg/kg IV every 12 hours plus ceftriaxone 2 g IV every 12 hours

10. Which of the following would be the most appropriate antimicrobial regimen for methicillin-resistant *Staphylococcus aureus* (MRSA) prosthetic valve infective endocarditis?

A. Vancomycin 15 mg/kg IV every 12 hours for 6 weeks

B. Vancomycin 15 mg/kg IV every 12 hours plus gentamicin 1 mg/kg IV every 8 hours for 6 weeks

C. Vancomycin 15 mg/kg IV every 12 hours and rifampin 300 mg po every 8 hours for 6 weeks plus gentamicin 1 mg/kg IV every 8 hr for the first 2 weeks

D. Doxycycline 100 mg IV every 12 hours and rifampin 300 mg po every 8 hours for 6 weeks plus gentamicin 1 mg/kg IV every 8 hours for the first 2 weeks

11. In which of the following patients could intravenous antimicrobial therapy be transitioned to oral antimicrobial therapy to yield similar safety and efficacy outcomes?

A. 65-year-old man with methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia after recent total hip arthroplasty

B. 23-year-old woman with a pan susceptible *Klebsiella pneumoniae* bacteremia due to pyelonephritis

C. 47-year-old woman with fluoroquinolone-resistant *Pseudomonas aeruginosa* lifeport associated bacteremia

D. 62 year old man with methicillin-susceptible *Staphylococcus aureus* (MSSA) bacteremia due right lower extremity osteomyelitis

12. In which of the following patients would short course (7 days) of treatment for gram-negative bacteremia be most appropriate?

A. 24-year-old woman with a history of intravenous drug use with *Enterobacter cloacae* bacteremia and a paravalvular abscess

B. 66-year-old woman with *Escherichia coli* bacteremia due a urinary tract infection

C. 30-year-old man with *Serratia marcescens* bacteremia due to recent lumbar fusion

D. 40-year-old man with *Pseudomonas aeruginosa* bacteremia complicated by a prosthetic valve endocarditis

13. What is the *most* common organism causing infective endocarditis?

A. *Candida albicans*

B. *Enterococcus faecalis*

C. *Staphylococcus aureus*

D. *Viridans group streptococcus*

14. Which of the following represents a patient with uncomplicated *Staphylococcus aureus* bacteremia?

A. 26-year-old woman with no significant past medical history who developed a central line-associated MSSA bacteremia while being treated in the ICU for pancreatitis

B. 44-year-old man with a history of IV drug use with MRSA bacteremia and tricuspid infective endocarditis

C. 44-year-old man with persistent MSSA bacteremia secondary to prosthetic joint infection

D. 68-year-old woman with MRSA bacteremia and an infected cardiac implantable electronic device

15. Which of the following represents the most appropriate events in the management of *Staphylococcus aureus* bacteremia?:

A. infectious diseases consultation, source control, appropriate antimicrobial therapy

B. echocardiography, repeat blood cultures, appropriate antimicrobial therapy

C. infectious diseases consultation, echocardiography, source control, repeat blood cultures, appropriate antimicrobial therapy

D. infectious diseases consultation, echocardiography, repeat blood cultures, appropriate antimicrobial therapy

SELF-ASSESSMENT QUESTION-ANSWERS

1. **B.** Based on the Modified Duke Criteria, diagnosis of definite infective endocarditis requires positive blood cultures and evidence of endocardial involvement (Diagnosis section, Infective Endocarditis subsection, Table 134-6).

2. **A.** *Staphylococcus aureus* should always be considered pathogenic whereas *Staphylococcus epidermidis*, *Staphylococcus haemolyticus*, and *Bacillus* spp., are unlikely pathogens when recovered from blood cultures (Diagnosis section, Bacteremia subsection, Table 134-5).

3. **B.** Echocardiography is critical in diagnosis of infective endocarditis. While transthoracic echocardiograms (TTE) are performed first due to accessibility, transthoracic echocardiograms (TEE) are more sensitive and specific (90%-100% and 40%-66%, respectively). TEE should be performed in patients with CHD, previous endocarditis, new murmur, heart failure, or other stigmata of infective endocarditis (Diagnosis section, Infective Endocarditis subsection).

4. **B.** Viridans group streptococci are common inhabitants of the human mouth and gingiva, and they are especially common causes of endocarditis involving native valves which presents in a subacute fashion (Pharmacologic Therapy section, Infective Endocarditis subsection, Streptococcal Endocarditis).

5. **C.** Empirical therapy in patients with suspected *S. aureus* bacteremia based on gram-positive cocci in pairs and clusters from blood cultures, prior to susceptibility results, should include active against MRSA with either vancomycin or daptomycin in the majority of cases due to the increased rate of MRSA identified in hospital- and community-acquired bacteremias (Pharmacologic Therapy section, Bacteremia subsection, *Staphylococcus aureus*).

6. **A.** Presence of a prosthetic heart valve is associated with the greatest risk of infective endocarditis (Epidemiology section, Table 134-2).

7. **B.** Enterobacterales, which includes *E. coli*, bacteremia is most likely caused by genitourinary or gastrointestinal or respiratory tract sources, as well as translocation from genitourinary or gastrointestinal due to disruption or procedure (Non-pharmacologic Therapy section, Bacteremia subsection, Source control, Table 134-7).

8. **A.** "Culture-negative" infective endocarditis describes a patient in whom a clinical diagnosis of infective endocarditis is likely, but blood cultures do not yield a pathogen, which is most often due to previous antimicrobial therapy (Diagnosis section, Infective Endocarditis subsection).

9. **D.** In patients with acute presentations of infective endocarditis, IV vancomycin should be combined with cefepime to cover the most common causes of infective endocarditis, staphylococci, streptococci, enterococci, and aerobic gram-negative bacilli (Pharmacologic Therapy section, Infective Endocarditis subsection, Streptococcal Endocarditis).

10. **D.** 6 Weeks of IV vancomycin and PO rifampin should be combined with 2 weeks of IV gentamicin in patients with methicillin-resistant *Staphylococcus aureus* (MRSA) prosthetic valve endocarditis (Pharmacologic Therapy section, Infective Endocarditis subsection, Staphylococcal Endocarditis, Table 134-9).

11. **B.** Oral antimicrobial therapy is not recommended for patients with St*aphylococcus aureus* bacteremia. Although oral antimicrobial therapy can be used for gram-negative bacteremia, fluoroquinolones are the only oral option for *Pseudomonas aeruginosa* (Pharmacologic Therapy section, Bacteremia subsection)

12. **B.** Patients with uncomplicated gram-negative bacteremia can be treated with 7 days of antimicrobial therapy (Pharmacologic Therapy section, Bacteremia subsection, Gram-Negative Bacilli).

13. **C.** Endocarditis is most commonly caused by staphylococci, in particular *S. aureus* (Epidemiology section, Table 134-2).

14. **A.** To meet criteria for uncomplicated or low-risk *S. aureus* bacteremia, all of the following criteria must be met: (1) sterile repeat blood cultures 48 to 96 hr after the initial positive culture, (2) defervescence within 72 hr after initiation of active therapy, (3) exclusion of infective endocarditis/secondary metastatic infection, (4) no implanted prostheses (eg, prosthetic valves, cardiac devices, or arthroplasties), (5) not dependent on hemodialysis (Pharmacologic Therapy section, Bacteremia subsection, *Staphylococcus aureus*).

15. **C.** Treatment of *S. aureus* bacteremia includes source control, consultation with infectious diseases, echocardiography to evaluate for infective endocarditis, repeat blood cultures, and appropriate antimicrobial therapy. (Non-pharmacologic Therapy section, Bacteremia subsection, and Pharmacologic Therapy section, Bacteremia subsection, *Staphylococcus aureus*)