



# Infective Endocarditis

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## LEARNING OBJECTIVES

1. Evaluate patients for causative pathogens based on risk factors associated with infective endocarditis.
2. Evaluate patients for the pathophysiology of infective endocarditis.
3. Assess a patient for infective endocarditis based on clinical presentation and diagnostic testing.
4. Design an antimicrobial treatment plan for a patient with infective endocarditis including drug selection, dosing, and duration of therapy.

### ABBREVIATIONS IN THIS CHAPTER

HACEK	<i>Haemophilus</i> species, <i>Aggregatibacter actinomycetemcomitans</i> , <i>Cardiobacterium hominis</i> , <i>Eikenella corrodens</i> , <i>Kingella</i> species
MSSA	Methicillin-susceptible <i>Staphylococcus aureus</i>
MRSA	Methicillin-resistant <i>Staphylococcus aureus</i>
TEE	Transesophageal echocardiography
TTE	Transthoracic echocardiography
VGS	Viridans group streptococci

[Table of other common abbreviations.](#)

## INTRODUCTION

Infective endocarditis, an infection of the cardiac endothelium, remains a challenging disease that is associated with significant morbidity and mortality and affects both children and adults worldwide. Although the exact incidence is difficult to quantify because of the varying criteria used to define infective endocarditis, recent population-based studies have reported annual incidence rates ranging from 2–15 cases per 100,000 person-years (Pant 2015; Bin Abdulhak 2014; Duval 2012). The most common bacterial causes of infective endocarditis are *Staphylococcus* spp., *Streptococcus* spp., and *Enterococcus* spp. In specific patient populations, however, clinicians must also increasingly consider drug-resistant pathogens, atypical bacteria, and fungi.

Infective endocarditis is traditionally classified by the onset and severity of clinical symptoms. Acute endocarditis is a rapidly progressive form that manifests with signs of systemic illness, including high fever and sepsis (Wang 2018; Cahill 2016). In subacute or chronic infective endocarditis, nonspecific symptoms such as generalized fatigue, weight loss, and a low-grade fever can manifest over weeks to months. Although the timeline of presentation can be helpful to identify possible causative pathogens, empiric antibiotic therapy should be directed at the most likely causative pathogens. In addition, the following should be considered: history of heart valve surgery or cardiac devices, presence of a native or prosthetic valve, source of infection, and patient-specific factors (Wang 2018; Cahill 2016; Baddour 2015; Habib 2015).

## RISK FACTORS

Risk factors for infective endocarditis vary globally. In low-income countries, rheumatic heart disease remains a major risk factor (Marijon 2007). In high-income countries, endocarditis is more common among older adult patients and those with a predisposing condition such as structural heart disease, including degenerative valvular disease or congenital heart disease. Patients with prosthetic valves or implantable cardiac devices are also at higher risk (Bor 2013). Recurrent

infective endocarditis is a concern as well, particularly in patients with several risk factors. Increasing use of chronic indwelling catheters, including hemodialysis lines, constitutes another at-risk population (Toyoda 2017; Fernández-Hidalgo 2008). Furthermore, patients with poor oral hygiene and periodontal diseases are at risk of community-acquired infective endocarditis (Lockhart 2009). The diagnosis of endocarditis is more likely in male versus female patients. Lastly, intravenous drug use is associated with an increasing proportion of endocarditis cases. In a study at a single tertiary care center, intravenous drug use–associated infective endocarditis increased from 14% to 56% between 2009 and 2014 (Hartman 2016), which parallels the increase in opioid use across the United States (Fleischauer 2017; Wurcel 2016).

## PATHOPHYSIOLOGY

Infective endocarditis is precipitated by injury to the cardiac endothelium, which can be caused by valve sclerosis, rheumatic valvulitis, or direct invasion by bacteria (Werdan 2014). This injury is followed by a release of inflammatory cytokines

and tissue factors. Subsequently, fibronectin expression leads to formation of a platelet-fibrin microthrombotic lesion called a *sterile vegetation* (Widmer 2006). Bacteria in the bloodstream can then bind and colonize the lesion. These bacteria then replicate, leading to additional platelet and fibrin deposition, forming an infected vegetation. The production of a biofilm, which is clustered bacteria embedded in a polysaccharide and proteinaceous matrix, allows for the persistence of bacteria in the vegetation. Both the composition of the infected vegetation and biofilm make effective antibiotic penetration difficult (Flemming 2010). As the infected vegetation grows in size, the likelihood increases that the patient will develop high-grade bacteremia and experience an embolization. Cardiac complications such as poor valvular function and heart failure can subsequently develop (Chambers 2020).

## MICROBIOLOGY

Table 1 shows the etiology of definite endocarditis in a large international cohort study (Murdoch 2009). Despite regional variations, gram-positive pathogens remain the leading cause and account for up to 90% of cases. Of these pathogens, *Staphylococcus aureus* is the most commonly isolated

### BASELINE KNOWLEDGE STATEMENTS

Readers of this chapter are presumed to be familiar with the following:

- Traditional blood culturing practices, including organism identification and antimicrobial susceptibility testing
- Antibiotic spectrum of activity, mechanism of action, adverse effects, and basic pharmacokinetic and pharmacodynamic principles
- Therapeutic drug monitoring of vancomycin and aminoglycosides
- Diagnostic technologies, including echocardiography

[Table of common laboratory reference values.](#)

### ADDITIONAL READINGS

The following free resources have additional background information on this topic:

- Baddour L, Wilson W, Bayer A, et al. [Infective endocarditis in adults: diagnosis, antimicrobial therapy, and management of complications: a scientific statement for healthcare professionals from the American Heart Association.](#) *Circulation* 2015;132:1435-86.
- 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 \(ESC\).](#) *Eur Heart J* 2015;36:3075-128.

**Table 1.** Etiology of Infective Endocarditis in a Large International Cohort

Organism	n (%)
<i>Staphylococcus aureus</i>	869 (31%)
Coagulase-negative staphylococci	304 (11%)
Viridians group streptococci	483 (17%)
Enterococci	283 (10%)
Culture negative	277 (10%)
<i>Streptococcus bovis</i>	165 (6%)
Other Streptococci	162 (6%)
HACEK	44 (2%)
Fungi/yeast	45 (2%)
Other	121 (4%)
Total cases	2781

HACEK = *Haemophilus* spp., *Aggregatibacter actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens*, *Kingella* spp.

Information from Mori M, Brown KJ, Bin Mahmood SU, et al. Trends in infective endocarditis hospitalizations, characteristics, and valve operations in patients with opioid use disorders in the United States: 2005–2014. *J Am Heart Assoc* 2020;9:e012465.

microorganism in cases of native and prosthetic valve endocarditis in high-income countries and is the cause in up to 40% of cases in the United States and 31% of cases internationally (Pant 2015; Murdoch 2009). Increasing health care exposures and intravenous drug use have contributed to the rise in *S. aureus* infection. In a study of 1779 patients with definite endocarditis, intravenous drug use (OR 9.3; 95% CI, 6.3–13.7) and health care–associated infection (OR 2.9; 95% CI, 2.1–3.8) were factors identified as independently associated with *S. aureus* endocarditis (Fowler 2005). Furthermore, in a study evaluating characteristics of patients with infective endocarditis and opioid use disorders in the United States, *Staphylococcus* was the causative pathogen in 55.3% of cases.

Coagulase-negative staphylococci (e.g., *Staphylococcus epidermidis*) that colonize the skin can adhere to indwelling lines and invasive devices leading to bacteremia and potentially hospital-acquired endocarditis in certain hosts (Chu 2008, 2004). In addition, these bacteria are a more common cause of prosthetic valve endocarditis (Alonso-Valle 2010; Chu 2009; López 2007). Viridans group streptococci, including *Streptococcus mutans*, *Streptococcus salivarius*, *Streptococcus anginosus*, *Streptococcus mitis*, and *Streptococcus sanguinis*, which as part of the normal flora of the oral cavity and gastrointestinal system, are the second leading cause of native valve endocarditis and are the pathogens in 17% of cases. Enterococci are the third leading cause of native valve infection, accounting for 11% of cases. Most of these cases are caused by *Enterococcus faecalis* (Murdoch 2009).

Less common causes of infective endocarditis are gram-negative bacteria, such as *Pseudomonas aeruginosa*, and may lead to severe disease. The HACEK organisms—*Haemophilus* spp., *Aggregatibacter actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella* spp.—are a group of fastidious gram-negative bacteria that colonize the oropharynx and can cause endocarditis (Das 1997). Fungal pathogens such as *Candida* spp. or *Aspergillus*

spp. are rare but potentially fatal causes of endocarditis. Lastly, endocarditis can be caused by zoonotic organisms, such as *Coxiella burnetii* and *Brucella* spp. found in farm animals, *Bartonella henselae* in cats, and *Chlamydia psittaci* in birds (Murdoch 2009).

## CLINICAL PRESENTATION

Infective endocarditis can present as either acute or subacute disease. Acute infective endocarditis progresses quickly over days to weeks, and patients present with rapid onset of high-grade fever, sepsis, and systemic complications such as congestive heart failure, stroke, and septic or pulmonary embolization. A new-onset heart murmur, present in up to 75% of cases, is a hallmark sign of acute infective endocarditis when accompanied with the signs and symptoms mentioned previously. Subacute infective endocarditis can be much more difficult to recognize because patients develop nonspecific symptoms such as fatigue, dyspnea, low-grade fever, malaise, chills, sweats, back pain, arthralgias, or weight loss over several weeks to months. Microembolic or immunologic phenomena as described in Table 2 are rare findings but can support an endocarditis diagnosis. In addition, arterial emboli and pulmonary infarcts may be present in more progressive disease. Assessing a patient’s timeline of clinical presentation and risk factors may aid the clinician in identifying the pathogen. For example, *S. aureus* endocarditis tends to be associated with acute and severe presentation whereas viridans group streptococci (VGS) are traditionally associated with less severe and more subacute presentation (Servy 2014; Werdan 2014; Silverman 2007; Murdoch 2009).

## DIAGNOSIS

The diagnosis of infective endocarditis is based on clinical presentation, microbiological findings, and imaging. The primary diagnostic criteria used for endocarditis are the modified

**Table 2.** Microembolic and Immunologic Phenomena

Condition	Description
<b>Vascular or Microembolic Phenomena</b>	
Splinter hemorrhage	Broken blood vessels found under the nails
Conjunctival hemorrhage	Broken blood vessels found in the eye conjunctiva
Mycotic aneurysm	Infection of the arterial wall
Janeway lesion	Irregular, nontender hemorrhagic lesions located on palms of the hands and soles of the feet
<b>Immunologic Phenomena</b>	
Roth spots	Hemorrhages with pale centers in the retina
Osler nodes	Painful, erythematous nodules on the tips of fingers and toes
Glomerulonephritis	Inflammation of glomeruli in the kidney; presents as acute kidney injury

**Table 3.** Modified Duke Criteria for Endocarditis

**PATHOLOGICAL CRITERIA**

- Microorganisms demonstrated by culture or histological examination of a vegetation, a vegetation that has embolized, or an intracardiac abscess
- Vegetation or intracardiac abscess confirmed by histological examination showing active endocarditis

**CLINICAL CRITERIA**

**Major Criteria**

**Blood culture positive for infective endocarditis**

Typical microorganisms consistent with infective endocarditis from two separate blood cultures:

- Viridans streptococci, *Streptococcus gallolyticus*, the HACEK group, *Staphylococcus aureus*, or community-acquired enterococci, in absence of a primary focus

Microorganisms consistent with infective endocarditis from persistently positive blood cultures:

- $\geq 2$  positive cultures of blood samples drawn  $>12$  hours apart  
—or—
- All of 3 or a majority of  $\geq 4$  separate cultures of blood, with first and last sample drawn at least 1 hour 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 by visualizing any one of more of the following:

- Oscillating intracardiac mass on valve or supporting structures, in the path of regurgitant jets or on implanted material in absence of an alternative anatomic explanation
- Abscess
- New partial dehiscence of prosthetic valve
- New valvular regurgitation; a preexisting murmur worsening or changing is insufficient to meet the criteria

**Minor Criteria**

Predisposition, predisposing heart condition, or injection drug use

Fever, temperature  $>100.4^{\circ}\text{F}$  ( $38^{\circ}\text{C}$ )

Vascular phenomena: major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, Janeway lesions

Immunologic phenomena: glomerulonephritis, Osler nodes, Roth spots, rheumatoid factor

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

Echocardiographic minor criteria eliminated

<b>Definite Endocarditis</b>	<b>Possible Endocarditis</b>	<b>Rejected Endocarditis</b>
2 major criteria	1 major and 1–2 minor criteria	0 major and 1–2 minor criteria
—or—	—or—	—or—
1 major and $\geq 3$ minor criteria	3–4 minor criteria	1 major and 0 minor criteria
—or—		
5 minor criteria		

Information from: Li J, Sexton D, Mick N, et al. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. Clin Infect Dis 2000;30:633-8.

Duke criteria (Table 3) (Li 2000). The algorithm classifies the diagnosis as *definite*, *possible*, or *rejected* endocarditis based on the number of major and minor criteria met by a patient. The modified Duke criteria are widely used in clinical practice;

however, because studies have shown a sensitivity between 70% and 79%, use of this tool should not be the sole method of diagnosis (Shrestha 2017). A constellation of clinical symptoms make up the minor criteria.

A key to successfully treating endocarditis is identification of the infective organism. Whenever possible, blood cultures should be drawn promptly on presentation—ideally before antibiotic administration. Providers should obtain three blood cultures from different venipuncture sites because the yield increases with the number of cultures obtained. Sensitivity increases from 73%–80% with one culture to 85%–98% with three cultures (Lee 2007). Furthermore, identification of certain pathogens in the blood, such as *S. aureus*, should always prompt evaluation for endocarditis given its strong association (Joseph 2013). When blood cultures are negative in patients with clinical syndromes consistent with endocarditis, alternative mechanisms of pathogen identification can be used, including serologic studies, universal bacterial PCR (using 16S rRNA primers) of cardiac valves from tissue samples obtained during surgery, and histopathology. In patients with definite endocarditis and negative blood cultures, the sensitivity of the universal bacterial (using 16S rRNA) or fungal (using 28S rRNA) PCR assay is as high as 80% (Shrestha 2015).

Imaging is another major component of diagnosis. Transthoracic echocardiography (TTE) is a noninvasive imaging modality that can screen patients for endocarditis. Unfortunately, many patient factors can limit the image quality; therefore, the overall sensitivity of TTE is around 70% in native valves (Habib 2010). In patients with prosthetic valve endocarditis, the TTE image quality is poor given the structural components of the prosthesis. In addition, TTE is often inadequate for assessment of the perivalvular area. Therefore, the sensitivity of TTE is closer to 50% for prosthetic valve endocarditis (Habib 2010). Transesophageal echocardiography (TEE), although more invasive, is the preferred imaging modality for diagnosis. Both American Heart Association and European Society of Cardiology endocarditis guidelines recommend that both TTE and TEE be obtained for patients with moderate to high risk of endocarditis, for those with prosthetic valves, and for those with endocarditis diagnosed based on TTE alone to identify abscess, pseudoaneurysm, or fistula (Baddour 2015; Habib 2015). Although not widely available, positron emission tomography is an imaging modality with particularly high diagnostic value in patients with prosthetic valve endocarditis (Pizzi 2015).

## THERAPEUTIC MANAGEMENT

Antimicrobials represent the mainstay of treatment for infective endocarditis. In general, selection of optimal therapy depends on the isolated pathogen, presence of antimicrobial resistance, development of extracardiac disease, and involvement of prosthetic material. Every effort to obtain blood cultures prior to the initiation of empiric antimicrobial therapy should be attempted. Empiric therapy should also be based on specific patient considerations, including past infection history, current suspected source of infection, risk factors, drug allergy, and exposures. For most patients presenting

with native valve endocarditis, a regimen covering *S. aureus*, VGS, *Enterococcus* spp., and gram-negative bacilli is reasonable, which may include vancomycin and ceftriaxone or cefepime, depending on the risk of *P. aeruginosa*. In patients with prosthetic valve endocarditis who present within 1 year of prosthetic valve placement, a regimen of vancomycin, rifampin, gentamicin, and cefepime to cover *Staphylococcus* spp. and other hospital-acquired pathogens is reasonable. If symptoms occur more than 1 year after prosthetic valve placement, a regimen of vancomycin and ceftriaxone to cover *Staphylococcus* spp., VGS, and *Enterococcus* spp. may be considered (Baddour 2015). Although the final antimicrobial regimen should be tailored to the isolated pathogen, these regimens may be continued in the setting of culture-negative endocarditis. The following section will review antimicrobial treatments for each of the main causes of infective endocarditis with standard guideline-concordant antibiotic therapies summarized in tables.

### Viridans Group Streptococci

Viridans group streptococci are fastidious organisms, and the most clinically significant species of the group are *S. anginosus*, *S. mitis*, *S. mutans*, *S. salivarius*, and *S. sanguinis*. They are part of the normal human flora in the upper respiratory tract and oral cavity, the female genital tract, and the gastrointestinal tract. Given their presence in the oral cavity, dextran-producing VGS strains can cause transient bacteremia after tooth brushing, dental procedures, or in the setting of poor oral hygiene, dental caries, or abscesses. Furthermore, bacteremia caused by an intraabdominal source can lead to endocarditis with VGS, usually in patients with other predisposing cardiac conditions.

The VGS remain highly susceptible to penicillin and other  $\beta$ -lactam antibiotics. Thus, penicillin G remains the mainstay of therapy for VGS endocarditis. First-line treatment recommendations for native valve endocarditis caused by VGS include penicillin G, either given alone or in combination with gentamicin depending on the MIC of the organism, as shown in Table 4. Combination therapy may also be necessary in isolates with higher MICs for penicillin. The combination of penicillin or ceftriaxone with gentamicin results in synergistic killing and can allow for shorter treatment durations. Treatment duration of either 2 or 4 weeks should be considered based on patient characteristics. In general, 2 weeks of therapy may be appropriate in relatively uncomplicated cases of native valve endocarditis caused by highly penicillin-susceptible VGS and in patients at low risk of toxicity caused by aminoglycosides (Sexton 1998; Murray 1986). In patients with complicated cardiac or extracardiac abscesses or complications and those at risk of nephrotoxicity from gentamicin, including older adult patients or those with pre-existing renal dysfunction, 4 weeks of therapy is appropriate. In cases of prosthetic valve endocarditis caused by VGS, the recommended treatment is penicillin or ceftriaxone for 6 weeks with

**Table 4.** Treatment of Native and Prosthetic Valve Endocarditis Caused by Viridans Group Streptococci

Pathogen Characteristics	Antibiotic Therapy	Duration of Therapy	Comments
<b>Native Valve</b>			
Penicillin MIC $\leq$ 0.12 mg/L	<b>Preferred:</b> Penicillin G 12–18 million units IV per 24 hr –or– Ceftriaxone 2 g IV every 24 hr	4 wk	Ampicillin may be considered as an alternative to penicillin in setting of severe penicillin shortage.
	<b>Preferred (alternative):</b> Penicillin G 12–18 million units IV per 24 hr + gentamicin IV –or– Ceftriaxone 2 g IV every 24 hr + gentamicin IV	2 wk	Avoid 2-wk regimen with gentamicin in known cardiac or extracardiac abscess or CrCl < 20 mL/min Once-daily gentamicin (3 mg/kg IV every 24 hr) is preferred
	<b>Alternative for severe <math>\beta</math>-lactam allergy:</b> Vancomycin IV 10–20 mg/kg IV every 8–24 hr (dosing based on therapeutic drug monitoring)	4 wk	–
Penicillin MIC > 0.12 to < 0.5 mg/L	<b>Preferred:</b> Penicillin G 24 million units IV per 24 hr + gentamicin IV for first 2 wk –or– Ceftriaxone 2 g IV every 24 hr	4 wk	Once-daily gentamicin (3 mg/kg IV every 24 hr) is preferred Ampicillin may be considered as an alternative to penicillin in setting of severe penicillin shortage.
	<b>Alternative for severe <math>\beta</math>-lactam allergy:</b> Vancomycin IV 10–20 mg/kg IV every 8–24 hr (dosing based on therapeutic drug monitoring)	4 wk	–
Penicillin MIC $\geq$ 0.5 mg/L	<b>Preferred (if susceptible):</b> Ceftriaxone 2 g IV every 24 hr + gentamicin IV	4–6 wk	Once-daily gentamicin (3 mg/kg IV every 24 hr) is preferred
	<b>Preferred (alternative):</b> Penicillin G 24 million units IV per 24 hr (or ampicillin 2 g IV every 4 hr) + gentamicin IV	4–6 wk	
	<b>Alternative for severe <math>\beta</math>-lactam allergy:</b> Vancomycin IV 10–20 mg/kg IV every 8–24 hr (dosing based on therapeutic drug monitoring)	4–6 wk	–
<b>Prosthetic Valve</b>			
Penicillin MIC $\leq$ 0.12 mg/L	<b>Preferred:</b> Penicillin G 24 million units IV per 24 hr $\pm$ gentamicin IV for first 2 wk –or– Ceftriaxone 2 g IV every 24 hr $\pm$ Gentamicin IV for first 2 wk	6 wk	Once-daily gentamicin (3 mg/kg IV every 24 hr) is preferred Ampicillin may be considered as an alternative to penicillin in setting of severe penicillin shortage.
	<b>Alternative for severe <math>\beta</math>-lactam allergy:</b> Vancomycin IV 10–20 mg/kg IV every 8–24 hr (dosing based on therapeutic drug monitoring)	6 wk	–
Penicillin MIC > 0.12 mg/L	<b>Preferred:</b> Penicillin G 24 million units IV per 24 hr + gentamicin IV –or– Ceftriaxone 2 g IV every 24 hr + gentamicin IV	6 wk	Once-daily gentamicin (3 mg/kg IV every 24 hr) is preferred Ampicillin may be considered as an alternative to penicillin in setting of severe penicillin shortage.
	<b>Alternative for severe <math>\beta</math>-lactam allergy:</b> Vancomycin IV 10–20 mg/kg IV every 8–24 hr (dosing based on therapeutic drug monitoring)	6 wk	–

IV = intravenous.

or without gentamicin for at least the first 2 weeks in isolates with low MICs for penicillin. However, use of the combination therapy is recommended in isolates with higher MICs (greater than 0.12 mg/L). Very few cases exist of endocarditis with VGS strains exhibiting higher penicillin MICs (greater than 0.12 mg/L). Thus, treatment recommendations are based on in vitro experiments and case reports (Baddour 2015).

### ***Enterococcus* spp.**

The primary *Enterococcus* spp. that cause clinical infection leading to endocarditis are *Enterococcus faecium* and *E. faecalis*. Enterococci are normal gastrointestinal and genitourinary commensal organisms. Few antibiotic options exist for the treatment of endocarditis caused by *Enterococcus* spp. because of intrinsic mechanisms of resistance. However, most *E. faecalis* are susceptible to penicillin and ampicillin. Of note,  $\beta$ -lactam antibiotics alone are not bactericidal against *Enterococcus* spp. Instead, they must be combined with aminoglycosides to achieve bactericidal activity. However, nephrotoxicity and ototoxicity because of aminoglycosides remains a major concern, and resistance is also rising (Fernández-Hidalgo 2013; Gavalda 2007). In cases for which combination with gentamicin is not indicated, use of streptomycin (if susceptible) can be considered or clinicians can initiate double  $\beta$ -lactam therapy. In vitro studies of experimental endocarditis demonstrated that the combination of ampicillin and ceftriaxone was effective against gentamicin-susceptible and highly gentamicin-resistant *E. faecalis* (Gavalda 1999). Ampicillin and ceftriaxone have synergistic activity because of their different binding affinities for penicillin-binding proteins. Ampicillin binds to penicillin-binding proteins 1, 4, and 5 whereas ceftriaxone saturates 2 and 3; therefore, use of the two agents in combination leads to greater antimicrobial activity (Werth 2015). Two key observational studies conducted in patients with gentamicin-resistant *E. faecalis* endocarditis provide evidence for use of this regimen. Although limitations exist, these studies showed similar success rates and less nephrotoxicity in patients treated with ampicillin and ceftriaxone compared with outcomes for patients treated with ampicillin and gentamicin (Fernandez-Hidalgo 2013; Gavalda 2007).

Multidrug resistance to penicillin, vancomycin, and aminoglycosides is common in isolates of *E. faecium*. Linezolid and daptomycin have activity against multidrug-resistant enterococci. Few data exist evaluating outcomes after the use of linezolid for treatment of enterococcal endocarditis, and case series show conflicting data (Tsigrelis 2007; Falgas 2006; Schentag 2003). Daptomycin has bactericidal activity against *Enterococcus* spp. The emergence of isolates nonsusceptible to daptomycin is of concern and significantly limits use of this agent (Woods 2018). Although optimal dosing is controversial, for most isolates of *E. faecium*, higher doses of 10–12 mg/kg/day should be used to achieve adequate concentrations for efficacy and to prevent the emergence of resistant subpopulations (Britt 2017). Combination therapy can also be considered in patients with enterococcal endocarditis

that is multidrug resistant, including daptomycin and ampicillin or ceftaroline (Sakoulas 2014b, 2013, 2012). Optimal treatment of multidrug-resistant enterococcal endocarditis remains unclear. Treatment duration for native valve endocarditis caused by *Enterococcus* spp. ranges from 4 to 6 weeks. Guidelines recommend 6 weeks of therapy for patients with native valve endocarditis caused by *Enterococcus* spp. who have symptoms lasting longer than 3 months. In patients with prosthetic valve endocarditis, antibiotic selection is the same as native valve endocarditis, but treatment duration is typically at least 6 weeks. Table 5 summarizes the treatment of native and prosthetic valve endocarditis caused by enterococci.

### ***Staphylococcus* spp.**

Both coagulase-positive (*S. aureus*) and coagulase-negative staphylococci (*S. epidermidis*, *Staphylococcus lugdunensis*) can cause infective endocarditis. The most common cause of endocarditis in developed countries is *S. aureus*. Exposures increasing the risk of infection are intravascular catheters, surgical wounds, indwelling prosthetic devices, hemodialysis, and intravenous drug use (Murdoch 2009; Fowler 2005). Endocarditis caused by *S. aureus* can be life-threatening by leading to myocarditis, peripheral and pulmonary septic emboli, and cardiogenic and/or septic shock. Oxacillin or methicillin resistance is common and occurs for about half of the *S. aureus* isolates. Similar health care exposures are risk factors for coagulase-negative staphylococci. Infection with *S. lugdunensis* typically causes a more virulent form of endocarditis with a higher rate of complications than other coagulase-negative staphylococci (Liu 2010; Anguera 2005; Seenivasan 2003). Coagulase-negative staphylococci are mostly resistant to oxacillin or methicillin.

Treatment of staphylococcal endocarditis is presented in Table 6. The recommended therapy for patients with left-sided, native valve infective endocarditis caused by methicillin-susceptible *S. aureus* (MSSA) is 6 weeks of an antistaphylococcal penicillin such as nafcillin or oxacillin, or cefazolin. Historically, the use of cefazolin for treatment of MSSA infective endocarditis was avoided because of concern for clinical failure caused by the inoculum effect. The *inoculum effect* refers to a laboratory phenomenon whereby the activity of an agent or MIC determined in the presence of a high bacterial density ( $\geq 10^8$  CFU/mL) is significantly greater than that measured using a standard inoculum ( $10^5$  CFU/ml) (Sabath 1975).  $\beta$ -Lactamase is produced by MSSA, and cefazolin may test as susceptible with a standard inoculum but may be inactivated in the presence of a high inoculum. However, clinical data supporting the use of cefazolin for the treatment of MSSA bacteremia have emerged recently (Weis 2019). A meta-analysis of seven studies in which 4391 patients with MSSA bacteremia were evaluated showed that treatment with cefazolin was associated with similar 30-day all-cause mortality (9.1% vs. 12.3%; RR 0.70; 95% CI,

**Table 5.** Treatment of Native and Prosthetic Valve Endocarditis Caused by Enterococci

Pathogen Characteristics	Antibiotic Therapy	Duration of Therapy	Comments
<b>Native Valve</b>			
<b>Susceptible to penicillin and gentamicin</b>	<b>Preferred:</b> Ampicillin 2 g IV every 4 hr + gentamicin IV —or— Penicillin G 18–30 million units IV per 24 hr + gentamicin IV	4–6 wk	Request susceptibility testing for penicillin if used  4-wk treatment with ampicillin and aminoglycoside is indicated only if symptom onset of infection is ≤ 3 mo duration  Traditional gentamicin dosing is preferred: 1 mg/kg IV every 8 hr
	<b>Preferred (alternative):</b> Ampicillin 2 g IV every 4 hr + ceftriaxone 2 g IV every 12 hr	6 wk	Consider ampicillin and ceftriaxone regimen in renal insufficiency
	<b>Alternative for severe penicillin allergy:</b> Vancomycin IV 10–20 mg/kg IV every 8–24 hr (dosing based on therapeutic drug monitoring) + gentamicin IV	6 wk	Traditional gentamicin dosing is preferred: 1 mg/kg IV every 8 hr
<b>Susceptible to penicillin and resistant to gentamicin</b>	<b>Preferred:</b> Ampicillin 2 g IV every 4 hr + Ceftriaxone 2 g IV every 12 hr	4–6 wk	—
	<b>Alternative for severe penicillin allergy (for streptomycin susceptible):</b> Vancomycin IV 10–20 mg/kg IV every 8–24 hr (dosing based on therapeutic drug monitoring) + streptomycin IV	6 wk	Streptomycin dose 7.5 mg/kg IV every 12 hr is preferred
<b>Resistant to penicillin</b>	<b>Preferred:</b> Vancomycin IV 10–20 mg/kg IV every 8–24 hr (dosing based on therapeutic drug monitoring) + gentamicin IV	6 wk	Traditional gentamicin dosing is preferred: 1 mg/kg IV every 8 hr
<b>Resistant to vancomycin, aminoglycosides, and penicillin</b>	<b>Preferred:</b> Daptomycin 10–12 mg/kg IV every 24 hr —or— Linezolid 600 mg IV/PO every 12 hr	6 wk	Consider combination therapy with daptomycin and ampicillin or ceftaroline for persistent disease
<b>Prosthetic Valve</b>			
See native valve section for antimicrobial selection		≥ 6 wk	—

IV = intravenous; PO = oral.

0.54–0.91) as treatment with antistaphylococcal penicillins. Among the six studies reporting nephrotoxicity, 1188 patients were analyzed and cefazolin was associated with lower rates of nephrotoxicity (RR 0.36; 95% CI, 0.21–0.59); however, the number of patients with endocarditis in these studies was small (Weis 2019). In endocarditis subgroup analysis, 90-day all-cause mortality was assessed for only 42 patients; despite fewer events in patients treated with cefazolin (0% vs. 34.3%; RR 0.71; 95% CI, 0.12–4.05), only limited conclusions can be made because of the small sample size. In an analysis of 652

patients with MSSA endocarditis, 30-day all-cause mortality was similar in patients treated with cefazolin compared with those treated with antistaphylococcal penicillins (10.9% vs. 17.2%; RR 0.71; 95% CI, 0.37–1.34) (Weis 2019).

Use of combination therapy with gentamicin and/or rifampin is no longer recommended in the guidelines for treatment of native valve endocarditis because of concerns for toxicity and a lack of data supporting efficacy. For individuals who use intravenous drugs and develop right-sided endocarditis, uncomplicated cases may be treated for as short as 2 weeks



**Table 6.** Treatment of Native and Prosthetic Valve Endocarditis Caused by Staphylococci

Pathogen Characteristics	Antibiotic Therapy	Duration of Therapy	Comments
<b>Native Valve</b>			
<b>Methicillin-susceptible (MSSA or MSSE)</b>	<b>Preferred:</b> Nafcillin or oxacillin 2 g IV every 4 hr	6 wk	—
	<b>Alternative for penicillin allergy (nonanaphylaxis):</b> Cefazolin 2 g IV every 8 hr	6 wk	Do not use cefazolin if central nervous system disease is present
	<b>Alternative for penicillin allergy (anaphylaxis):</b> Vancomycin 10–20 mg/kg IV every 8–24h (dosing based on therapeutic drug monitoring) —or— Daptomycin ≥8 mg/kg IV every 24 hr	6 wk	—
<b>Methicillin-resistant (MRSA or MRSE)</b>	<b>Preferred:</b> Vancomycin 10–20 mg/kg IV every 8–24 hr (dosing based on therapeutic drug monitoring) —or— Daptomycin ≥8 mg/kg IV every 24 hr	6 wk	Vancomycin dosing should target an AUC goal of 400-600 mg·h/L for serious MRSA infections including infective endocarditis.
<b>Prosthetic Valve</b>			
<b>Methicillin-susceptible (MSSA or MSSE)</b>	<b>Preferred:</b> Nafcillin or oxacillin 2 g IV every 4 hr + rifampin 300 mg PO/IV every 8 hr + gentamicin IV for first 2 wk	≥ 6 wk	Traditional gentamicin dosing is preferred: 1 mg/kg IV every 8 hr
<b>Methicillin-resistant (MRSA or MRSE)</b>	<b>Preferred:</b> Vancomycin 10–20 mg/kg IV every 8–24h (dosing based on therapeutic drug monitoring) + rifampin 300 PO/IV every 8 hr + gentamicin IV for first 2 wk	≥ 6 wk	Traditional gentamicin dosing is preferred: 1 mg/kg IV every 8 hr

IV = intravenous; MRSA = methicillin-resistant *Staphylococcus aureus*; MRSE = methicillin-resistant *Staphylococcus epidermidis*; MSSA = methicillin-susceptible *Staphylococcus aureus*; MSSE = methicillin-susceptible *Staphylococcus epidermidis*; PO = oral.

(Ribera 1996). In patients with prosthetic valve endocarditis, gentamicin should be added for the first 2 weeks of therapy and rifampin should be used for the entire duration of 6 or more weeks in combination with the chosen  $\beta$ -lactam.

Limited data exist for the treatment of refractory MSSA bacteremia. In these rarer cases of persistent MSSA bacteremia despite treatment with standard antibiotics, a combination of cefazolin and ertapenem has emerged as a potential treatment option. Clinical experience with this combination is limited to case reports and case series. In a report of 11 cases with persistent bacteremia ranging from 4–9 days, use of the combination after previous antibiotic regimens resulted in successful clearance for all cases. Six patients had confirmed endocarditis. In addition, in a rat model of MSSA endocarditis the geometric mean bacterial concentration in vegetations was about 4-log lower with the combination than with cefazolin alone (Ulloa 2020).

In patients with confirmed  $\beta$ -lactam allergy, several studies have shown poorer outcomes in patients treated with vancomycin compared with those treated with a  $\beta$ -lactam for MSSA infections. In a retrospective cohort study using propensity score matching, 294 patients with MSSA bacteremia were included. Infection-related mortality was significantly higher in patients treated with vancomycin compared with those treated with a  $\beta$ -lactam (37% vs. 18%,  $p=0.02$ ) (Kim 2008). Daptomycin can be used as an alternative; although optimal dosing in this setting has not been established, higher doses of 8 mg/kg/day or more are recommended. Endocarditis caused by methicillin-susceptible coagulase-negative staphylococci can be treated the same as MSSA.

For native-valve methicillin-resistant *S. aureus* (MRSA) endocarditis, vancomycin or daptomycin can be used alone for 6 weeks. In patients with prosthetic valve infections, gentamicin and rifampin should be used in combination as just presented (see Table 6). Endocarditis caused by methicillin-

resistant coagulase-negative staphylococci can be treated the same as MRSA. Outcomes associated with MRSA bacteremia, especially in cases of infective endocarditis, remain poor despite widespread use of standard antibiotic therapy with vancomycin and daptomycin.

Ceftaroline is a  $\beta$ -lactam antibiotic with activity against MRSA. Clinical experience with use of this agent for treatment of infective endocarditis is limited. Recently, results were published from the Clinical Assessment Program and Teflaro Utilization Registry (CAPTURE), a multicenter retrospective study evaluating real-world clinical use of ceftaroline including use for treatment of infective endocarditis caused by gram-positive organisms (Destache 2019). Of the 55 patients evaluated, 80% had MRSA, 7.3% had MSSA, and 7.3% had coagulase-negative staphylococci. Most patients received ceftaroline as second-line or salvage therapy, and monotherapy was used for 23 (41.8%) patients. Overall clinical success was achieved in 70.9% of all study patients and 82.6% of patients treated with monotherapy (Destache 2019). Although conclusions are limited given the small sample size and lack of a comparator, future studies evaluating use of ceftaroline monotherapy for treatment of MRSA infective endocarditis are needed.

In patients with persistent and/or refractory MRSA bacteremia, several combination therapies have been proposed. In vitro studies have shown synergistic activity when daptomycin or vancomycin is combined with antistaphylococcal  $\beta$ -lactam antibiotics (Davis 2015; Sakoulas 2014a; Werth 2013a, 2013b; Mehta 2012). Although several retrospective cohort studies and case series have reported improved clinical outcomes with use of combination therapy, the optimal combination of antibiotics and its role in the treatment of MRSA bacteremia and endocarditis remain unclear.

Four recent studies have evaluated various combination therapies (Pujol 2021; Jorgensen 2020; Tong 2020; Geriak 2019). In a randomized open-label trial, a combination regimen of daptomycin plus ceftaroline was compared with vancomycin for treatment of MRSA bacteremia. This study had 40 patients enrolled at the time of termination. This investigation was stopped early when an unanticipated mortality difference was seen between the groups (0 of 17 in the combination arm vs. 6 of 23 in the vancomycin arm;  $p=0.029$ ). Because of early termination, limited conclusions can be drawn from this study (Geriak 2019). However, these data support the need for future investigation into the role of combination therapy.

In CAMERA-2, an open-label, randomized trial of 352 patients with MRSA bacteremia, daptomycin or vancomycin monotherapy was compared with either agent used in combination with a  $\beta$ -lactam for the initial 7 days of treatment. Most patients received vancomycin and flucloxacillin. Notably, only 42 (11.9%) study patients had infective endocarditis. The study was terminated early because of an increased incidence of acute kidney injury in the combination arm. At the time of study termination, the primary end point of composite failure of therapy was similar between the treatment groups; 59 of

170 (35%) versus 68 of 175 (39%) patients did not respond to combination or standard monotherapy, respectively ( $-4.2%$ ; 95% CI  $-14.3$  to  $6.0$ ;  $p=0.42$ ). Persistent bacteremia at day 5 was significantly reduced among the patients receiving combination therapy (11% vs. 20%,  $p=0.02$ ) (Tong 2020).

A recent retrospective cohort study of 229 patients with MRSA bacteremia compared treatment with daptomycin and a  $\beta$ -lactam to daptomycin alone. Of note, 35.4% of patients included in the study had endocarditis. In an adjusted analysis, the composite failure rate was lower in patients treated with combination therapy (adjusted OR 0.386; 95% CI, 0.175–0.853) (Jorgensen 2020). Although none of the three studies presented provide conclusive evidence, combinations of vancomycin or daptomycin and a  $\beta$ -lactam such as ceftaroline or cefazolin should be considered in cases of refractory infection. Larger studies of combination therapy in patients with infective endocarditis are warranted.

The efficacy of a newer combination, daptomycin and fosfomycin, was evaluated in a randomized, multicenter, phase 3, superiority, open-label clinical trial of adult inpatients with MRSA bacteremia at 18 hospitals in Spain. In this study, 74 patients received daptomycin 10 mg/kg/day intravenously plus fosfomycin 2 g every 6 hours intravenously and 81 received daptomycin 10 mg/kg/day intravenously alone. Treatment success at the test of cure visit (6 weeks after end of therapy) was achieved in 54.1% of patients who received combination therapy compared with 42% of patients who received daptomycin alone (RR 1.29; 95% CI, 0.93–1.8). Of interest, patients receiving combination therapy had fewer positive blood cultures at day 3 compared with those receiving daptomycin monotherapy (2.7% vs. 18.5%; RR 0.15; 95% CI, 0.04–0.63). Similarly, the rate of complicated bacteremia was lower in the combination group compared with the daptomycin monotherapy group (16.2% vs. 32.1%; RR 0.51; 95% CI, 0.28–0.94). The rate of any adverse events leading to treatment discontinuation was higher in the combination therapy group (17.6% vs. 4.9%; RR 3.56; 95% CI, 1.21–10.44). Cardiac failure ( $n=4$ ) and hypokalemia (defined as less than 3 mmol/L;  $n=2$ ) were the most common serious adverse events in the combination therapy group. A diagnosis of left-sided endocarditis was made for 18 (11.6%) study patients; despite this small sample size, subgroup analysis of this population was performed and showed no difference between the two groups for treatment success at test of cure. Of note, the intravenous formulation of fosfomycin has not been approved for use in the United States at the time of publication.

### **Other Less Common Pathogens: HACEK, Gram-Negative Bacilli, Fungal Pathogens**

The HACEK organisms are fastidious gram-negative bacilli that are rarer causes of community-acquired native valve endocarditis. These microorganisms grow slowly in standard blood culture media and were traditionally difficult to isolate. However, with advances in the clinical microbiology laboratory, identification of the HACEK organisms has

become more likely. Data supporting antibiotic selection and treatment duration for endocarditis caused by HACEK organisms are limited to observational studies. In the absence of antimicrobial susceptibility testing, ceftriaxone can be used for 4 weeks in patients with native valve endocarditis and 6 weeks in patients with prosthetic valve endocarditis (Baddour 2015).

Although infective endocarditis caused by non-HACEK gram-negative bacilli is rare, outcomes are poor with high mortality rates. In a retrospective cohort of 43 patients with infections primarily caused by *Pseudomonas aeruginosa* (68%) or *Serratia marcescens* (9%), 12-month all-cause mortality and hospital readmission were 30% and 54%, respectively (Veve 2020). The optimal antibiotic therapy is unknown, and the guidelines recommend cardiac surgery for most cases in addition to the use of antibiotics. Current recommendations include  $\beta$ -lactam antibiotics in combination with either an aminoglycoside or fluoroquinolone for at least 6 weeks (Baddour 2015; Morpeth 2007). Final selection of agents should be tailored to the antibiotic susceptibility of the isolated pathogen.

Fungal endocarditis is also rare but certain host factors and exposures can increase risk. *Candida* spp. and *Aspergillus* spp. account for most cases, and immunocompromised hosts and individuals who use intravenous drugs are at-risk populations. In addition, health care exposures, such as use of central venous catheters, implanted cardiac devices, and long hospitalizations, can increase risk of *Candida* spp. (Pierotti 2002; Ellis 2001). Optimal treatment regimens are unclear, and mortality rates are exceedingly high at almost 50% (Badiee 2014). Thus, fungal endocarditis alone is an indication for surgical intervention. Treatment of *Candida* endocarditis includes amphotericin B and flucytosine or high-dose micafungin as initial therapy with lifelong suppressive therapy using oral azole antifungals (Baddour 2015, 2001; Steinbach 2005). Even less is known about optimal treatment for *Aspergillus* endocarditis; however, amphotericin B or voriconazole are the first-line treatment options. Use of combination therapy with expanded spectrum azoles or echinocandins may be considered. Step-down to lifelong therapy with oral azoles, including voriconazole, may be necessary. Treatment with intravenous antifungals usually occurs for more than 6 weeks (Baddour 2015; Patterson 2016).

## ADDITIONAL TREATMENT CONSIDERATIONS

The use of intravenous antimicrobials has been the standard for treatment of infective endocarditis. However, a recent randomized controlled trial demonstrated that outcomes for infective endocarditis caused by gram-positive organisms were similar for patients treated with either oral or intravenous antibiotics, after completing an initial course of 2 weeks

of intravenous therapy. Certain populations were not represented in this study, including patients with right-sided endocarditis, MRSA infection, cardiac abscess, persistent leukocytosis or C-reactive protein, and extracardiac sites of infection. Despite these limitations, this evaluation suggests that transition to oral antibiotics may be considered in carefully selected patients who have completed a 2-week course of intravenous antibiotics (Iversen 2019).

Although treatment durations for infective endocarditis have ranged from 4–6 weeks, data supporting the use of shorter durations of antibiotics postoperatively are accumulating. Current guidelines recommend that treatment duration be determined from the date of the first negative blood cultures or from a positive valve culture, whichever occurs later (Baddour 2015). In a retrospective evaluation of 182 episodes of infective endocarditis in patients requiring surgery, the rate of relapse within 1-year follow up was low at 1.1%. Of note, patients were primarily infected with *Streptococcus* spp (42.3%), *Staphylococcus aureus* (19.8%), or coagulase-negative staphylococci (14.8%). Early reoperation was necessary in 5% of patients, and the 1-year mortality rate was 9.9%. Using multivariable logistic regression modeling, the authors showed similar complication rates between patients receiving either less than 2 weeks or greater than 2 weeks of antibiotic therapy postoperatively (OR 1.01; 95% CI, 0.42–2.53) (Rao 2019). In another retrospective evaluation of 358 patients who underwent valve surgery for infective endocarditis, relapse of infection following surgery was low (three episodes, 0.8%) and unrelated to the duration of antibiotic therapy before or after surgery. The authors concluded that the traditional 4–6 weeks of antibiotic therapy administered postoperatively may be unnecessary (Morris 2005). Although controversial, shorter durations in certain populations may be considered.

## MANAGEMENT CONSIDERATIONS

### The Endocarditis Team

The management of infective endocarditis can be complex given the complicated patient presentation and high mortality of the disease. As a result, endocarditis cases may be best managed by a multidisciplinary endocarditis team. The ideal composition of an endocarditis team includes cardiac surgeons, cardiologists, infectious disease physicians, addiction specialists, neurologists, infectious diseases pharmacists, and radiologists. These individuals work collaboratively to appropriately diagnose and select patients for surgical intervention as well as optimize antimicrobial therapy including selection of definitive therapy, dosing, and duration. Studies have evaluated the impact of such a team and have demonstrated decreased in-hospital mortality by more than 50% (Carrasco 2014; Chirillo 2013; Botelho 2009).

Although most of the data exist in centers outside of the United States, a recent study was published evaluating the

## Patient Care Scenario

A 52-year-old man, J.Q., presents to the ED with a 3-day history of high fevers, chills, and general fatigue. His medical history is significant for hemodialysis dependence for past 2 years, mitral valve replacement less than 1 year ago, and a previous episode of infective endocarditis caused by MRSA. In the ED, J.Q. is febrile and hemodynamically unstable. Empiric antibiotics are initiated and three sets of blood cultures are collected. He is transferred to the ICU for further management. Blood cultures

### ANSWER

J.Q. has several notable risk factors for infective endocarditis, as follows: male sex, continuous healthcare exposure from hemodialysis, an indwelling catheter from hemodialysis, recent surgery, prosthetic mitral valve, and a previous history of endocarditis.

The modified Duke criteria should be used for diagnosis. J.Q. has the following major criteria: *S. aureus* identified from two separate blood cultures and echocardiogram positive for endocarditis. The following minor criteria are present as well: fever and predisposing heart condition. Thus, based on the presence of two major criteria, the diagnosis of definite endocarditis is made.

Based on the patient's history, including the recent valve replacement less than 1 year ago and a previous episode

of infective endocarditis caused by MRSA, an appropriate empiric antibiotic regimen for prosthetic valve endocarditis should include vancomycin, rifampin, gentamicin, and cefepime. Once MRSA is identified, cefepime should be discontinued. Vancomycin and rifampin should be continued for at least 6 weeks and the gentamicin should be continued for the first 2 weeks of treatment. Given the patient's history of hemodialysis, if there is a concern that his current clinical condition may cause further insult to his kidney function, daptomycin can be used as an alternative for vancomycin. Furthermore, if his MRSA infection persists and becomes refractory to this regimen, addition of an antistaphylococcal  $\beta$ -lactam should be considered, such as cefazolin, nafcillin, or ceftaroline.

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implementation of an endocarditis team in a U.S.-based tertiary care center. The team, consisting of infectious disease physicians, infectious disease pharmacists, cardiologists, cardiothoracic surgeons, neurologists, and substance abuse specialists, developed an evidence-based algorithm for management and met weekly. Outcomes in 56 patients with definite infective endocarditis who were admitted in the year after implementation of the team approach were compared with 68 patients with definite endocarditis admitted during the historical control period. In-hospital mortality decreased from 29.4% in the historical group to 7.1% in the team approach group ( $p < 0.0001$ ) (El-Dalati 2021). This study demonstrates the importance of multidisciplinary care for improving outcomes in patients with an often fatal infectious disease.

### Surgery

Although antimicrobial treatment is the cornerstone of management for infective endocarditis, surgical intervention is often necessary (Baddour 2015). Current guidelines list the indications for early surgery, defined as during initial hospitalization and before completion of a full course of antibiotics (Box 1).

## CONCLUSION

Infective endocarditis remains a challenging infectious disease for clinicians given its complex pathophysiology, long durations of antibiotic therapy, and the high mortality rate if not treated promptly. Careful attention to diagnosis should be made including assessment of cardiac and extracardiac disease and identification of the causative pathogen. Treatment should be based on patient factors, the isolated pathogen, and clinical manifestations of endocarditis. Although guidelines exist providing specific treatment recommendations based on the isolated pathogens, antibiotic resistance is increasingly making selection of definitive antibiotic therapy more difficult. Furthermore, better quality evidence evaluating various regimens, particularly combination therapies for MRSA infections are warranted to help optimize therapy. Surgical intervention is often necessary to eradicate infection. Therefore, implementation of a structure such as that described for the multidisciplinary team is of vital importance.

## Box 1. Recommendations for Early Surgery

### Recommendation: Indicated

- Patients with endocarditis who present with valve dysfunction resulting in symptoms or signs of heart failure
- Patients with endocarditis complicated by heart block, annular or aortic abscess, or destructive penetrating lesions
- Patients with persistent infection (manifested by persistent bacteremia or fever lasting more than 5–7 days and after exclusion of other sites of infection and fever) after the start of appropriate antimicrobial therapy

### Recommendation: Consider

- Patients with endocarditis caused by fungi or highly resistant organisms (e.g., vancomycin-resistant *Enterococcus* and multidrug-resistant gram-negative bacilli)
- Patients with mobile vegetations larger than 10 mm, particularly involving the anterior leaflet of the mitral valve and associated with other relative indications for surgery

### Recommendation: Reasonable

- Patients who present with recurrent emboli and persistent or enlarging vegetations despite appropriate antibiotic therapy
- Patients with severe valvular regurgitation and mobile vegetations larger than 10 mm
- Patients with relapsing prosthetic valve endocarditis

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## Practice Points

Infective endocarditis remains a challenging disease state for clinicians. Clinical pharmacists play a critical role in the management of these patients given their expertise in optimizing pharmacotherapy. Although high-quality data evaluating novel treatments and combinations are limited, several key principles are important to keep in mind:

- The leading cause of infective endocarditis in the United States is *S. aureus* because of increases in health care exposures and intravenous drug use.
- The modified Duke criteria are still used in the diagnosis of infective endocarditis. However, clinical presentation and history should be considered. Of importance, identification of the infective pathogen remains key to successful treatment of endocarditis. For case in which blood culture are negative, alternative diagnostic approaches should be used including serological studies, PCR assays of cardiac valves, and histopathology.
- National treatment guidelines can be used as a reference to identify an antibiotic regimen for most cases of infective endocarditis when a pathogen is identified. However, infectious diseases pharmacists can aid in the selection of an optimal regimen based on patient characteristics, pharmacokinetic and pharmacodynamic principles, and adverse effect profile. Furthermore, infection with uncommon pathogens such as those with multi-drug resistance or gram-negative organisms can occur, and pharmacists play a leading role in selection of an optimal therapeutic regimen.
- In patients with persistent and/or refractory MRSA infection, combination therapy with daptomycin or vancomycin and an antistaphylococcal  $\beta$ -lactam antibiotic should be considered.
- Lastly, because the care of patients with endocarditis can be complex, management by a multidisciplinary endocarditis team is ideal.

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# Self-Assessment Questions

## Questions 1 and 2 pertain to the following case.

J.T., a 65-year-old man, is admitted to the hospital with a 3-week history of low-grade fever and chills. He has a significant cardiac history including mitral valve regurgitation which led to mitral valve replacement 2 years ago. His medical history is otherwise noncontributory. J.T. is slightly hypotensive and febrile but otherwise stable. Cardiology and infectious diseases consults are ordered. The infectious diseases team arrives first and performs a thorough physical examination. The examination is notable for poor oral dentition including cavities and an oral abscess in J.T.'s mouth.

1. Based J.T.'s risk factors and clinical presentation, which one of the following organisms is most likely the cause of J.T.'s infection?
  - A. *Staphylococcus aureus*
  - B. Viridans group streptococci
  - C. *Enterococcus faecalis*
  - D. *Pseudomonas aeruginosa*
2. On day 2 of J.T.'s admission, blood culture results reveal *Streptococcus anginosus* with penicillin MIC 0.06 mg/L. The TTE shows a mobile echodensity on the mitral valve. Which one of the following is best to recommend—with the narrowest spectrum and lowest toxicity potential—for J.T.?
  - A. Penicillin G 4 million units intravenously every 4 hours for 6 weeks
  - B. Penicillin G 4 million units intravenously every 4 hours for 2 weeks
  - C. Ceftriaxone 2 g plus gentamicin 3 mg/kg intravenously every 24 hours for 6 weeks
  - D. Vancomycin 15 mg/kg intravenously every 8 hours

## Questions 3 and 4 pertain to the following case.

L.K. is a 32-year-old woman with a history of significant intravenous drug use. She presents to the ED with a high-grade fever (temperature 102°F [38.9°C]), generalized malaise, hypotension, and erythema around her injection site. Three blood cultures are drawn in the ED, which later reveal methicillin-resistant *S. aureus* (MRSA). On physical examination, L.K.'s care team notices tender, erythematous nodules on her fingers and toes. A workup for endocarditis is initiated. A TTE is performed and does not reveal anything substantial. L.K. is unable to undergo a transesophageal echocardiogram (TEE) given clinical instability.

3. Using the modified Duke criteria, which of the following best assesses L.K.'s presentation?
  - A. Possible endocarditis by presence of 1 major and 2 minor criteria
  - B. Possible endocarditis by presence of 3 minor criteria

- C. Definite endocarditis by presence of 2 major criteria
  - D. Definite endocarditis by presence of 1 major and 3 minor criteria
4. L.K. is initiated on vancomycin intravenously. On day 4 of antibiotic therapy, her blood cultures are still positive and she is clinically declining. Which one of the following is best to recommend for L.K.?
    - A. Continue vancomycin intravenously
    - B. Add ceftaroline 600 mg intravenously every 8 hours
    - C. Add daptomycin 10 mg/kg/day intravenously
    - D. Change vancomycin to ceftaroline 600 mg intravenously every 8 hours
  5. Which one of the following patients is at highest risk of developing bacteremia leading to infective endocarditis?
    - A. 22-year-old woman with a UTI
    - B. 78-year-old man with an implanted cardiac device who is hemodialysis dependent
    - C. 25-year-old man with cardiac conduction abnormalities and a skin abscess
    - D. 45-year-old woman with an intra-abdominal abscess
  6. A 68-year-old woman has a medical history that includes prosthetic valve infective endocarditis. She presents to the hospital with fever, chills, and general malaise. Blood cultures are drawn and reveal *S. aureus*. She undergoes TTE, but the image quality is poor. Given her clinical instability, the patient is unable to undergo TEE. Which one of the following imaging modalities would best aid in a diagnosis of prosthetic valve endocarditis in this patient?
    - A. MRI
    - B. PET
    - C. Chest CT
    - D. Radiography
  7. You are a new member of the antimicrobial stewardship team at your hospital. The physician lead tasks you with creation of treatment guidelines and interventions to help improve outcomes in patients with infective endocarditis. Which one of the following interventions is best to recommend to reduce mortality in this population?
    - A. Routine use of PET scans
    - B. Routine use of PCR assays for pathogen identification
    - C. Implementation of a multidisciplinary endocarditis team
    - D. Elimination of modified Duke criteria for diagnosis

8. A 72-year-old man has a medical history that includes recurrent intraabdominal abscesses. Over the past year, he was frequently admitted to the hospital and has received several courses of intravenous antibiotics. Today, the patient presents to the ED with fever, night sweats, and chills. On physical examination, the physician notices abdominal pain and a new cardiac murmur. Blood samples are drawn and sent to the clinical microbiology laboratory for culture. Which one of the following potential causes of this patient's presentation is most likely to be resistant to vancomycin?

- A. *E. faecium*
- B. *E. faecalis*
- C. *S. anginosus*
- D. *Streptococcus gallolyticus*

9. A 38-year-old woman has a diagnosis of endocarditis caused by *E. faecium*. Today is day 6 of treatment with daptomycin 6 mg/kg intravenously every 24 h and blood cultures are still positive. Which one of the following is best to recommend for this patient?

- A. Change daptomycin to vancomycin.
- B. Increase the daptomycin dose to 10–12 mg/kg intravenously every 24h and add ampicillin.
- C. Change daptomycin to ceftaroline.
- D. Change daptomycin to ampicillin and gentamicin.

**Questions 10 and 11 pertain to the following case.**

K.R. is a 34-year-old woman who has recently relapsed on intravenous drug use. Unfortunately, she is now hospitalized with methicillin-susceptible *S. aureus* bacteremia and native valve endocarditis. K.R. has a penicillin allergy of mild rash noted in her chart.

10. After confirming that her penicillin allergy is real, which one of the following is best to recommend for K.R.?

- A. Ertapenem
- B. Vancomycin
- C. Daptomycin
- D. Cefazolin

11. Today is day 7 of antibiotic therapy as recommended above and K.R.'s blood cultures are still positive. Which one of the following is best to recommend for K.R.?

- A. Add gentamicin.
- B. Add rifampin.
- C. Add ertapenem.
- D. No change is necessary.

**Questions 12 and 13 pertain to the following case.**

R.Q. is a 51-year-old man with multiple recent health care exposures. He has a chronic indwelling catheter with redness around the insertion site. R.Q. presents with septic shock and acute kidney injury. Blood cultures reveal *C. albicans*.

After several days of persistent candidemia, an evaluation for endocarditis is conducted and TEE reveals a large mobile vegetation on the mitral valve.

12. Based on the identified pathogen and patient characteristics, which one of the following is best to recommend for R.Q.?

- A. Micafungin 150 mg intravenously every 24 hours with plan for lifelong suppressive therapy with fluconazole
- B. Liposomal amphotericin B 3 mg/kg intravenously every 24 hours and flucytosine 25 mg/kg orally every 6 hours with plan for lifelong suppressive therapy with fluconazole
- C. Micafungin 150 mg intravenously every 24 hours but no lifelong suppression
- D. Fluconazole 800 mg intravenously every 24 hours

13. Which one of the following best evaluates R.Q.'s endocarditis?

- A. It is likely to have good cure rates with antifungal treatment alone.
- B. It will likely require surgical intervention as fungal endocarditis alone is an indication for surgery.
- C. The patient is not a candidate for surgical intervention because fungal endocarditis is a contraindication for surgery.
- D. This case of *Candida* endocarditis has a low propensity to cause morbidity and mortality.

14. A 63-year-old man has native valve endocarditis caused by *E. faecalis*. He is started on a combination of ampicillin and gentamicin for treatment. About 2 weeks into his course, the patient develops significant nephrotoxicity. Which one of the following is best to recommend for this patient?

- A. Continue ampicillin and gentamicin because this is the only regimen with optimal efficacy.
- B. Continue ampicillin but change gentamicin to ceftriaxone.
- C. Continue ampicillin but change gentamicin to streptomycin.
- D. Change ampicillin and gentamicin to vancomycin alone.

15. Which one of the following patients with endocarditis would be most likely to benefit from a transition to a highly bioavailable oral antibiotic?

- A. 21-year-old with MRSA endocarditis
- B. 43-year-old with methicillin-susceptible *S. aureus* endocarditis and evidence of vertebral abscess
- C. 35-year-old with uncomplicated *S. anginosus* endocarditis who has completed 2 weeks of intravenous therapy
- D. 26-year-old with uncomplicated *S. anginosus* endocarditis who has completed 5 days of intravenous therapy