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Management Considerations in Infective Endocarditis
A Review

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IMPORTANCE Infective endocarditis occurs in approximately 15 of 100 000 people in the United States and has increased in incidence. Clinicians must make treatment decisions with respect to prophylaxis, surgical management, specific antibiotics, and the length of treatment in the setting of emerging, sometimes inconclusive clinical research findings.

OBSERVATIONS Community-associated infective endocarditis remains the predominant form of the disease; however, health care accounts for one-third of cases in high-income countries. As medical interventions are increasingly performed on older patients, the disease incidence from cardiac implanted electronic devices is also increasing. In addition, younger patients involved with intravenous drug use has increased in the past decade and with it the proportion of US hospitalization has increased to more than 10%. These epidemiological factors have led to *Staphylococcus aureus* being the most common cause in high-income countries, accounting for up to 40% of cases. The mainstays of diagnosis are still echocardiography and blood cultures. Adjunctive imaging such as cardiac computed tomographic and nuclear imaging can improve the sensitivity for diagnosis when echocardiography is not conclusive. Serological studies, histopathology, and polymerase chain reaction assays have distinct roles in the diagnosis of infective endocarditis when blood culture have tested negative with the highest yield obtained from serological studies. Increasing antibiotic resistance, particularly to *S aureus*, has led to a need for different antibiotic treatment options such as newer antibiotics and combination therapy regimens. Surgery can confer a survival benefit to patients with major complications; however, the decision to pursue surgery must balance the risks and benefits of operations in these frequently high-risk patients.

CONCLUSIONS AND RELEVANCE The epidemiology and management of infective endocarditis are continually changing. Guidelines provide specific recommendations about management; however, careful attention to individual patient characteristics, pathogen, and risk of sequela must be considered when making therapeutic decisions.

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Supplemental content

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Endocarditis is an infection of the cardiac endothelium and can present as either acute or subacute disease. Acute infective endocarditis advances rapidly, presenting with a sudden onset of high fever, rigors, sepsis, and systemic complications. This presentation alone is indistinguishable from other causes of sepsis, but when there is also a new-onset heart murmur, a diagnosis of acute infective endocarditis should be considered. In contrast, subacute infective endocarditis can be difficult to diagnose. Patients develop nonspecific symptoms such as fatigue, dyspnea, or weight loss over several weeks to months. Fever may or may not be present. Although endocarditis is commonly associated with a heart murmur due to valve regurgitation, new murmurs are present in less than half of cases (**Table 1**).[1,2] Janeway lesions or Osler nodes are classic diagnostic findings (**Figure 1**), but they are present in fewer than 5% of cases. Imaging can reveal embolic phenomena such as pulmonary and splenic emboli (**Figure 2**). Infective endocarditis should be suspected when patients present with either an acute or subacute illness when infective endocarditis risk factors are present (**Box 1**). In general, *Staphylococcus aureus* infection causes acute, aggressive infections, and the more indolent pathogens, viridans group streptococci or coagulase-negative staphylococci, cause subacute infective endocarditis.

Methods

We conducted a literature search of the PubMed database from January 2008 through March 2018. The selection, including clinical trials, observational studies, review articles, and society guidelines, was limited to studies published in English. We reviewed the reference articles that were cited in the guidelines

for the management of infective endocarditis from the American Heart Association and European Society of Cardiology. Because infective endocarditis is a disease with numerous categories (based on infecting microorganism and defined subtypes of native- vs prosthetic valve–infection and community- vs health care–associated infection), we present a broad overview of this disease with a focus on select contemporary issues. Studies published prior to 2008 that were considered (by V.H.C. and A.W.) to be pertinent to this narrative review were also included.

Clinical Features

Changes in Epidemiology

Infective endocarditis is more common now than in the past, with its incidence in the United States increasing from 9.3 per 100 000 population in 1998 to 15 per 100 000 in 2011.[10] This increased incidence results, in part, from more frequent health care–associated disease (Box 1).[3,12] In a large multicenter, multinational study, health care–associated infective endocarditis accounted for 34% of cases. Hemodialysis, non–hemodialysis intravascular catheters, and invasive procedures are often associated with the infection.[12,13] Furthermore, the proportion of cases related to prosthetic valves and implantable cardiac devices is increasing.[13,14]

Community-associated infective endocarditis still accounts for approximately 70% of cases and is mostly associated with oral, gastrointestinal, and cutaneous bacteria.[1,15] Intravenous drug use accounts for an increasing proportion of community-associated cases. Administrative data from the Nationwide Inpatient Sample showed that infective endocarditis resulting from intravenous drug use increased in the United States from 7% to 12% of hospitalizations between 2000 and 2013.[16] This study, which relied on *International Classification of Diseases, Ninth Revision (ICD-9)* coding to capture drug use, may have underestimated the proportion stemming from intravenous drug use. At a single tertiary center in North Carolina (a state with statistically the same drug overdose death rate as the national rate, 2016),[17] a study based on electronic chart review showed intravenous drug use–associated infective endocarditis increased from 14% to 56% of infective endocarditis hospitalizations between 2009 and 2014.[18] In parallel with the opioid epidemic in the United States, young white intravenous drug users between ages 15 and 34 years are associated with increasing rates of hospitalization for infective endocarditis.[16,19]

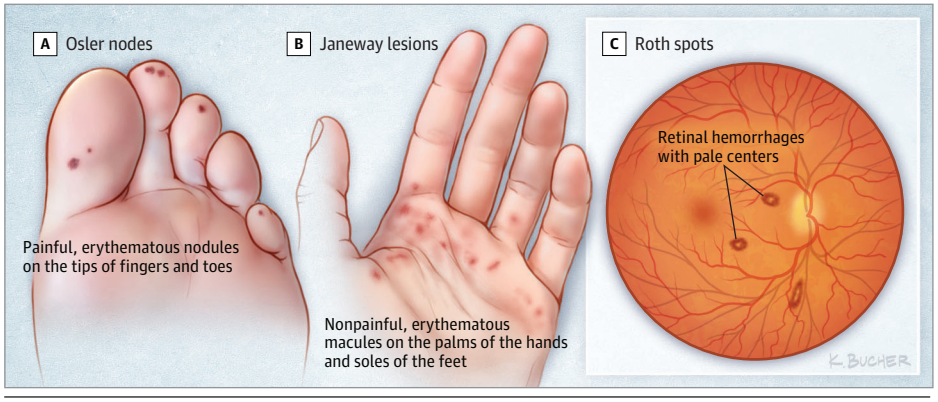
The rise in the incidence is also related to, in part, increased use of cardiac implantable electrophysiological devices (CIEDs).[20-22] Infective endocarditis stemming from implantable devices is defined as an infection involving the intravascular electrode leads with or without involvement of a cardiac valve or endocardial surface and is usually caused by *S aureus* or coagulase-negative staphylococci.[22,23] This may be associated with device pocket infection in which the skin and soft tissue at the implant site are infected during implantation, with surgical manipulation, or with device erosion through the skin; however, CIED endocarditis can also be caused by hematogenous seeding from transient bacteremia. Although both permanent pacemakers and implantable cardioverter-defibrillators lacking transvenous leads are now available, the effect of these newer systems on cardiac implant infections is unknown.

Table 1. Clinical Signs and Complications of Infective Endocarditis

Sign	Patients, %
Fever	86-96
New murmur	48
Worsening of old murmur	20
Hematuria	26
Vascular embolic event	17
Splenomegaly	11
Splinter hemorrhages	8
Osler nodes	3
Janeway lesions	5
Roth spots	2
Complication	
Stroke	17-20
Nonstroke embolization	23-33
Heart failure	14-33
Intracardiac abscess	14-20
New conduction abnormality	8

Adapted from Murdoch et al[1] and Selton-Suty et al.[2]

Figure 1. Classic, but Uncommon, Signs of Infective Endocarditis

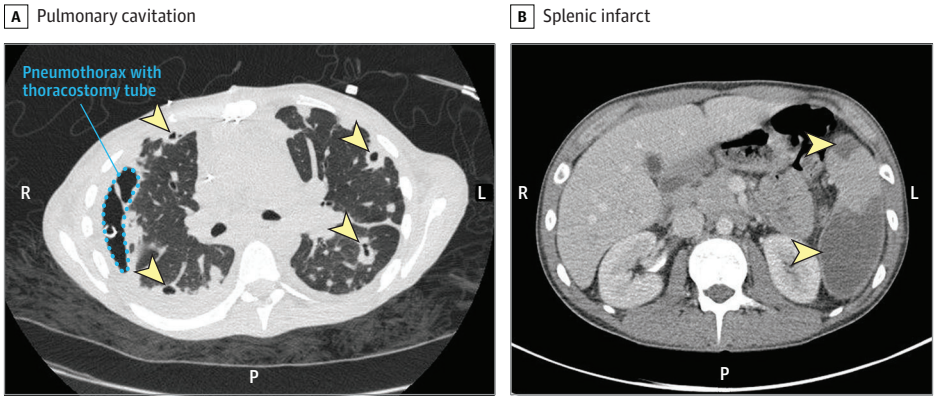


A, Osler nodes (shown on the foot) present as painful, erythematous nodules on the tips of the fingers and toes.

B, Janeway lesions (shown on the hand) present as nonpainful, erythematous macules on the palms of the hands and soles of the feet.

C, Roth spots are hemorrhages with pale centers that are found on the retina.

Figure 2. Embolic Phenomena of Infective Endocarditis as Seen on Computed Tomographic Images: Peripheral Signs of Infective Endocarditis



A, Computed tomographic image of a patient with endocarditis with septic emboli. This image shows many pulmonary nodules (designated by the yellow arrows), most of which are subpleural and cavitated, a finding consistent with septic emboli. This patient also has anasarca, mediastinal and hilar lymphadenopathy, and a large pneumothorax that has a chest tube in it. The many cavitating lesions from the septic emboli might have created bronchopleural fistulae resulting in the pneumothorax.

B, Computed tomographic image of a patient with endocarditis with septic emboli. This image shows an enlarged spleen with splenic infarcts (designated by the yellow arrows), indicative of splenic emboli.

Assessment and Diagnosis

Microbiology

Originally developed for research purposes, the modified Duke criteria (**Box 2**)[11,25] provide a framework for the clinical diagnosis of infective endocarditis. Determination of the causative pathogen (Figure 1 in the Supplement) is of prime importance. This enables clinicians to narrow and tailor therapy to the target pathogen and helps identify the source of the bloodstream infection. Every effort should be made to maximize the yield of blood cultures. At least 3 sets of blood cultures from separate venipuncture sites should be obtained prior to starting antibiotic therapy. At least 20 mL of blood should be obtained per venipuncture because the relative yield increases linearly with the volume of blood cultured.[26]

S aureus is the leading cause of native and prosthetic valve infection in high-income countries, causing 40% of US cases in 2011[10] and 31% of cases in a large, international cohort.[1] This pathogen poses a treatment challenge because of antimicrobial resistance[27-29] and predilection for acute complications such as stroke.[30-32] Viridans group streptococci (17%) and enterococci (11%) are the next leading causes of native valve infection.[1] Coagulase-negative staphylococci, on the other hand, have a prominent role related to prosthetic valves and cardiac devices.[33] Unique, more challenging-to-treat pathogens such as gram-negative bacteria and fungi have accounted for a minor, but increasing, proportion of cases.[10]

The HACEK (*Haemophilus* species, *Aggregati bacter actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens*, *Kingella* species) organisms can cause infective endocarditis[34] and are a group of fastidious gram-negative bacteria that used to require long times to grow in culture. This is no longer the case because with contemporary blood culture systems, HACEK bacteria should grow within the first 5 days of routine blood cultures.[35] Fungal infective endocarditis, predominantly caused by *Candida* and *Aspergillus*, can be difficult to diagnose because of the poor sensitivity of blood cultures.[36,37] While *Candida* may be detected by blood culture, *Aspergillus* usually is not and it's diagnosis often relies on valve culture and histopathology or biopsy of a peripheral embolic lesion.

Blood cultures that are negative for endocarditis can pose a diagnostic challenge. The etiology varies according to region, reflecting differences in local pathogens, initiation of antibiotics prior to taking blood cultures, and use of diagnostic testing. Evaluation aims at identifying pathogens that are either nonculturable or difficult to culture (ie, slow growing or require special growth media). This diagnostic workup includes serological studies, polymerase chain reaction (PCR) assays of cardiac valves, and histopathology (**Table 2**).[38-40] In a large prospective study of 759 patients with blood cultures that tested negative, a systematic diagnostic protocol identified a causative organism in 62%. Of these, 75% were diagnosed by blood serology (either *Coxiella* or *Bartonella* species). Polymerase chain reaction assays of the heart valves were second highest in yield, for which 66% of patients tested positive by 16S rDNA assays. Polymerase chain reaction assays of the blood (16S rDNA assays) were positive for 13.6% of patients, and autoimmunohistochemistry had a much lower diagnostic yield.[39]

Imaging

Echocardiography is the most important imaging modality for the diagnosis of infective endocarditis and its complications. Echocardiographic features include vegetations, abscess, fistula, leaflet perforation, valvular regurgitation, and prosthetic valve dehiscence. The sensitivity of transthoracic echocardiography for establishing a diagnosis of native valve endocarditis is approximately 70% but is only 50% for diagnosing prosthetic valve endocarditis because of its relatively low resolution.[41] The negative predictive value of transthoracic echocardiography is high (97%) when adequate ultrasound quality is achieved and imaging shows no cardiac abnormalities that predispose to endocarditis or that suggest intracardiac infection (ie, the absence of intracardiac catheters or other

prosthetic material, abnormal valve anatomy or function, cardiac congenital abnormalities, pericardial effusion, and vegetation).[42] However, a completely normal transthoracic echocardiographic result is more likely in patients with a low pretest probability (eg, absence of a heart murmur) but is less common in patients with an intermediate or high pretest probability (eg, prosthetic heart valve or acute valve regurgitation) who may still require transesophageal echocardiography for its higher spatial resolution.

Transesophageal echocardiography has better visualization and greater spatial resolution resulting in higher sensitivity (95%) and similar specificity (90%) than does transthoracic echocardiography for establishing a diagnosis.[41,43] Transesophageal echocardiography is preferred when the sensitivity of transthoracic echocardiography is not optimal, such as when a prosthetic valve or electrophysiological implants are present. In patients with inadequate transthoracic echocardiography or with an intermediate or a higher probability of infective endocarditis after transthoracic echocardiography (eg, possible infective endocarditis by modified Duke criteria, *S aureus* bacteremia with unexplained source), transesophageal echocardiography is appropriate and clinically useful.[44] Because of the low sensitivity of transthoracic echocardiography for the diagnosis of intracardiac abscess, transesophageal echocardiography should be performed in all cases of suspected abscess, a cause for endocarditis that must be treated surgically.

Cardiac computed tomographic angiography has excellent spatial resolution enabling visualization of paravalvular complications such as abscess or aneurysm and has potentially less imaging artifact from the prosthetic valve than does transesophageal echocardiography (**Table 3**).[45,46] However, it is less sensitive than transesophageal echocardiography for detecting small vegetations.[47] Radiolabeled leukocyte scintigraphy or ^{18}F-fluorodeoxyglucose positron emission tomographic–computed tomographic (FDG-PET/CT) scanning can be helpful with the detection of peripheral embolic and cardiac and extracardiac sites of infection.[48] In one study, PET/CT improved the sensitivity of the modified Duke criteria by reclassifying possible diagnoses to definite infective endocarditis.[49]

Box 1. Risk Factors for Acquisition of Infective Endocarditis and Health Care–Associated Infective Endocarditis

Risk Factors for Acquisition of Infective Endocarditis

- Age older than 60 years
- Male sex
- Structural heart disease
  - Valvular disease (eg, rheumatic heart disease, mitral valve prolapse, degenerative)
  - Congenital heart disease (eg, ventricular septal defect, bicuspid aortic valve)
- Prosthetic valve
- Prior infective endocarditis
- Intravenous drug use
- Chronic hemodialysis
- Intravascular catheter
- Indwelling cardiovascular device
- Skin infection
- Oral hygiene or dental pathology

Definitions of Health Care–Associated Endocarditis

Nosocomial

Occurring in a patient hospitalized for more than 48 hours prior to the onset of signs or symptoms consistent with infective endocarditis

Non-nosocomial

Occurring in a patient in which signs or symptoms consistent with infective endocarditis developed prior to hospitalization in patients with extensive out-of-hospital contact with health care interventions or systems, defined as the following:

- Receipt of intravenous therapy, wound care, or specialized nursing care at home within the 30 days prior to the onset of native valve endocarditis
- Receipt of hemodialysis or intravenous chemotherapy in the 30 days before the onset of native valve endocarditis
- Hospitalization for 2 or more days in the 90 days before the onset of native valve endocarditis or
- Residence in a nursing home or long-term care facility

Adapted from Lockhart et al,[4] Durante-Mangoni et al,[5] Hill et al,[6] McKinsey et al,[7] Strom et al,[8] and Chen et al.[9]

Treatment

Antibiotics

Pathogen-specific recommendations for antibiotics are complex and are well summarized in a recent guideline.[50] Optimal therapy of infective endocarditis requires bactericidal antibiotics for a prolonged period. The exact duration and use of single-drug vs combination drug therapy varies according to the pathogen, presence of antibiotic resistance (as discussed below), and whether the infection involves a native or prosthetic valve.

Antibiotic treatment decisions for *S aureus* infective endocarditis hinge on the presence or absence of antibiotic resistance. An antistaphylococcal beta-lactam such as nafcillin is recommended for the treatment of methicillin-susceptible *S aureus* (MSSA) because antistaphylococcal beta-lactam agents are associated with higher cure rates for MSSA bacteremia than is vancomycin.[51] Cefazolin can be substituted for nafcillin to treat patients who have a nonanaphylactoid allergy to penicillin. For methicillin-resistant *S aureus* (MRSA), vancomycin is the recommended antibiotic. Daptomycin is an acceptable alternative; however, special attention to dosing is needed.[28,52] The US Food and Drug Administration has approved a 6-mg/kg dose of daptomycin to treat *S aureus* bacteremia and right-sided infective endocarditis. However, daptomycin is usually tolerated at higher doses. For example, the Infectious Diseases Society of America guideline for the treatment of MRSA bacteremia recommends 8 to 10 mg/kg of daptomycin and the European guidelines recommend 10 mg/kg or higher.[41,53] For *native* valve infective endocarditis, adjunctive therapy with an aminoglycoside is not recommended because it does not reduce mortality and it is associated with renal toxicity.[54,55] Similarly, rifampin is not recommended as adjunctive therapy because of hepatotoxicity and drug interactions.[56,57] For *S aureus*–infected prosthetic valves, combination therapy (an antistaphylococcal beta-lactam agent or vancomycin, as appropriate, plus an aminoglycoside and rifampin) is recommended.

Box 2. Modified Duke Criteria for Diagnosis of Infective Endocarditis

Definite Infective Endocarditis

Pathologic Criteria

Microorganisms demonstrated by culture or histologic examination of a vegetation, a vegetation that has embolized, or an intracardiac abscess specimen; or

Pathologic lesions; vegetation or intracardiac abscess confirmed by histologic examination showing active endocarditis

Clinical Criteria

2 Major criteria; or

1 Major criterion and 3 minor criteria; or

5 Minor criteria

Possible Infective Endocarditis

1 Major criterion and 1 minor criterion; or

3 Minor criteria

Rejected

Firm alternative diagnosis explaining evidence of infective endocarditis; or

Resolution of infective endocarditis syndrome with antibiotic therapy for 4 or fewer days; or

No pathological evidence of infective endocarditis at surgery or autopsy, with antibiotic 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, *Streptococcus bovis*, or HACEK (*Haemophilus* species, *Aggregati bacter actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens*, *Kingella* species) group, *Staphylococcus 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 2 positive cultures of blood samples drawn more than 12 hours apart; or
- All of 3 or a majority of 4 or more separate cultures of blood (with first and last sample drawn ≥1 hours apart)
- Single positive blood culture for *Coxiella burnetti* or antiphase I IgG antibody titer of more than 1:800

Evidence of Endocardial Involvement

Echocardiogram positive for infective endocarditis defined as follows

- Oscillating intracardiac mass on a 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 of more than 38°C

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

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

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

From Li et al.[11] Reprinted by permission of Oxford University Press.

[a] Excludes single positive cultures for coagulase–negative staphylococci and organisms that do not cause infective endocarditis.

Table 2. Diagnostic Tests for Blood Culture–Negative Infective Endocarditis

Diagnostic Test	Pathogen	Comments
Serology	*Coxiella burnetii* *Bartonella* species *Chlamydophila* species *Brucella* species *Mycoplasma* species *Legionella pneumophila* *Aspergillus* species	The majority of pathogens identified by serology are *C burnetii* and *Bartonella* spp, the prevalence of which varies according to region. There is cross-reactivity between Bartonella and Chlamydophila serologies
Histopathology of resected cardiac valve tissue	*Bartonella* species *Tropheryma whipplei* *Coxiella burnetii* Fungi (*Candida* species, *Aspergillus* species)	Streptococci and staphylococci can be identified if blood culture negativity was due to use of antibiotics
Polymerase chain reaction assay of cardiac valve tissue	*Bartonella* species *Tropheryma whipplei* *Coxiella burnetii* Fungi (*Candida* species, *Aspergillus* species)	Streptococci and staphylococci can be identified if blood culture negativity was due to use of antibiotics

Adapted from Brouqui and Raoult,[38] Fournier et al,[39] and Tattevin et al.[40]

Increasing antibiotic resistance complicates the treatment of *S aureus* infective endocarditis. Reduced susceptibility to vancomycin (where the isolate has a high minimum inhibitory concentration [eg, 1.5 mg/L-2 mg/L] but is still within the range of susceptibility) is associated with worse clinical outcomes for both MRSA and MSSA bacteremia.[58-60] Heterogeneous vancomycin-intermediate *S aureus* (heteroVISA) are subpopulations of MRSA that have intermediate vancomycin resistance and may be found in 29%[29] of MRSA–infective endocarditis cases. Successful treatment of a patient with pacemaker–related infective endocarditis due to

Table 3. Major Diagnostic Tools Available for Infective Endocarditis Diagnosis: Imaging

Diagnostic Imaging Test	Indications	Sensitivity and Specificity	Limitations
TTE	Bacteremia with regurgitant heart murmur Recurrent fever with regurgitant heart murmur Recurrent fever with possible cardioembolic events Quantitation of severity of valve dysfunction (regurgitation or stenosis)	Sensitivity 40%-66%, specificity 94%	Low sensitivity for prosthetic valve infective endocarditis (20%-46%) Low sensitivity for abscess
TEE	Abnormal TTE suggestive of infective endocarditis Bacteremia with prior prosthetic valve replacement, valve repair, or CIED Normal TTE with high clinical suspicion for infective endocarditis Evaluation of possible structural complications of infective endocarditis (abscess, fistula, perforation, prosthetic valve dehiscence) Evaluation of vegetation size Suspected prosthetic valve or CIED endocarditis Quantitation of severity of valve dysfunction	Sensitivity 90%-100%, specificity 90%-100%	Diagnosis of paravalvular complications in prosthetic infective endocarditis (differentiating abscess from postsurgical changes around sewing ring) Higher sensitivity and specificity in native valve infective endocarditis
Nuclear cardiac imaging (radiolabeled leukocyte scintigraphy, FDG-PET/CT)	Suspected prosthetic device (valve, CIED, or graft) infection with nondiagnostic TEE Extracardiac complications (eg, abscess)	Sensitivity 40%-100%, specificity 71%-100%	Availability of cyclotron False positive due to noninfective inflammation (especially after recent valve replacement) Radiation exposure Higher sensitivity and specificity if CT angiography performed Higher sensitivity and specificity for prosthetic or device infective endocarditis
Cardiac computed tomographic angiography	Suspected prosthetic device (valve, CIED, or graft) infection with nondiagnostic TEE	Sensitivity 93%, specificity 88%	Radiation exposure Iodinated contrast administration Rapid or irregular heart rate Visualization of small vegetation (<4 mm) or valve perforation

Abbreviations: CIED, cardiac implantable electrophysiological devices; CT, computed tomography; FDG, ^{18}F-fluorodeoxyglucose; PET, positron emission tomography; TEE, transesophageal echocardiography; TTE, transthoracic echocardiography.

a non–daptomycin susceptible strain of VISA has been described.[61] There is very limited evidence regarding nontraditional treatments for unusually resistant staphylococcal infections or persistent MRSA bacteremia–infective endocarditis. Successes with vancomycin plus beta-lactam,[62] daptomycin plus beta-lactam,[63,64] ceftaroline,[65-67] linezolid,[68] and telavancin have been published in case reports or small-series reports of patients.[69]

Enterococcal infective endocarditis is the third most common cause of endocarditis worldwide.[70-72] Inherent characteristics of enterococci and increasing antibiotic resistance[73-75] pose unique treatment challenges for enterococcal infective endocarditis. Enterococci have higher minimum inhibitory concentrations to cell-wall active agents such as penicillin, ampicillin, and vancomycin than do other streptococci. They are also relatively impermeable to aminoglycosides. Thus, killing of susceptible strains requires the synergistic action of a cell-wall active agent such as ampicillin and an aminoglycoside such as gentamicin.[76,77] Complicating this approach is that some isolates have high-level resistance to aminoglycosides, and the incidence of infection with these isolates is increasing worldwide.[73,74,78] In infective endocarditis due to these isolates, synergy with an aminoglycoside is not an option. Guidelines recommend 4 to 6 weeks of penicillin or ampicillin plus gentamicin for treatment of infective endocarditis caused by beta-lactam and aminoglycoside-susceptible enterococci. This therapeutic regimen is associated with significant risk of nephrotoxicity. A newer regimen, ampicillin plus ceftriaxone, uses ceftriaxone (by itself, ineffective against enterococci) to saturate penicillin-binding sites. Because of the apparent efficacy and lower toxic effects[71,73,75] of the ampicillin-ceftriaxone regimen, guidelines recommend either ampicillin-gentamicin or ampicillin-ceftriaxone for enterococcal infective endocarditis that is susceptible to penicillin and aminoglycosides. For ampicillin-susceptible and aminoglycoside-resistant Enterococcal infective endocarditis, the ampicillin-ceftriaxone regimen is recommended.[50] As detailed in the guidelines, vancomycin can be substituted for ampicillin when the enterococcal strain is resistant to penicillin. Linezolid or daptomycin can be used for strains that are resistant to penicillin and vancomycin.[50]

Surgical Intervention

Guidelines for surgical treatment of infective endocarditis are largely based on observational studies.[41,46,50] Indications for surgical valve repair or replacement include acute complications, such as valve dysfunction resulting in heart failure, which are associated with a higher risk of mortality or major morbidity than if treated with antibiotic therapy alone. Surgery is performed during the index hospitalization in about half of left-sided infections (infection of a native or prosthetic mitral or aortic valve)[1]

Table 4. Valve Surgery for the Management of Native and Prosthetic Valve Infective Endocarditis: Summary of Recommendations[a]

	Class[b]	Level[c]
Early valve surgery is indicated in the following cases of patients[d]		
Valve dysfunction resulting in symptoms or signs of heart failure	I	B
Symptoms or signs of heart failure resulting from valve dehiscence, intracardiac fistula, or severe prosthetic valve dysfunction	I	B
Infective endocarditis complicated by heart block, annular or aortic abscess, or destructive penetrating lesions	I	B
Evidence of persistent infection (ie, persistent bacteremia or fever lasting >5-7 d and provided that other sites of infection and fever have been excluded) after the start of appropriate antibiotic therapy	I	B
Early valve surgery should be considered or is a reasonable strategy		
Infective endocarditis caused by fungi or resistant organisms (eg, VRE, MDR gram-negative bacilli)	I	B
Recurrent emboli and persistent or enlarging vegetations despite appropriate antibiotic therapy	IIa	B
Severe valvular regurgitation and mobile vegetations >10 mm	IIa	B
Mobile vegetations >10 mm, particularly when involving the anterior leaflet of the mitral valve and associated with other relative indications for surgery	IIb	C
Relapsing prosthetic valve infective endocarditis	IIa	C

Abbreviations: MDR, multidrug resistant; VRE, vancomycin-resistant enterococci.

[a] Adapted from Baddour et al.[50]

[b] Class I indicates that the treatment or procedure is beneficial and should be performed; class IIa, treatment or procedure is beneficial and it is reasonable to perform the procedure; class IIb, there is more benefit than risk and the procedure may be considered; class III, there is no benefit and could cause harm.

[c] Level A indicates that multiple populations have been evaluated and data were derived from multiple randomized clinical trials or meta-analyses; level B, limited populations were evaluated and data were derived from a single randomized trial or nonrandomized studies; level C, very limited populations were evaluated; and data were derived from only consensus opinions of experts, case studies, or standard of care.

[d] Early surgery is defined as having occurred during the initial hospitalization and before completion of a full course of antibiotics.

Box 3. Antibiotic Prophylaxis for Infective Endocarditis Guidelines[a]

Procedures for Which Infective Endocarditis Prophylaxis Is Recommended

Antibiotic prophylaxis is reasonable for all dental procedures that involve manipulation of gingival tissue, manipulation of the periapical region of teeth, or perforation of the oral mucosa for patients considered to be at highest risk (below)

Patients With the Following Are at Highest Risk

Prosthetic cardiac valves, including transcatheter-implanted prostheses and homografts

Prosthetic material used for cardiac valve repair, such as annuloplasty rings and chords

Previous infective endocarditis

Unrepaired cyanotic congenital heart disease or repaired congenital heart disease, with residual shunts or valvular regurgitation at the site of or adjacent to the site of a prosthetic patch or prosthetic device

Cardiac transplant with valve regurgitation due to structurally abnormal valve

[a] Adapted from the American Heart Association/American College of Cardiology Focused Update 2017.[24]

most commonly for heart failure due to acute, severe valvular regurgitation.[79] Other complications not effectively treated or cured with antibiotic therapy alone include abscess, recurrent embolic events with residual vegetation, multidrug-resistant organism, or persistent bacteremia (**Table 4**).[41,46] In all cases of left-sided, prosthetic valve, device, or complicated endocarditis, consultation by a cardiac surgeon should be sought to assess operative risk and treatment options.

Surgical recommendations for patients with *S aureus* and fungal infective endocarditis are evolving.[41,50,80] Patients with *S aureus* infection often have discrete indications for surgery such as acute valve dysfunction,[27] abscess, and risk of emboli.[31,81] Nevertheless, native or prosthetic valve endocarditis stemming from *S aureus* should not be deemed an absolute indication for surgery, despite conflicting statements in the guidelines[50,80]; rather, the need for surgery should be considered for each patient individually. Recent studies have shown that early surgery does not necessarily improve outcomes and that some patients can be cured without surgical intervention.[82-84]

Similarly, fungal infection historically has been considered a stand-alone indication for surgery. This is related to the poor outcomes associated with medical therapy for fungal infective endocarditis. However, a large meta-analysis of candida endocarditis showed that survival was similar among patients treated with combination antifungal therapy without surgery compared with patients treated with antifungal medical therapy with surgery.[85] A lack of benefit from surgical management was also demonstrated in 2 small but well-defined observational cohorts.[86,87] The availability of more tolerable antifungals such as echinocandins, use of combination therapy, and use of antifungal oral suppressive therapy following the initial course of intravenous treatment likely contributed to successful nonsurgical management of an otherwise very difficult-to-treat infection.[86,88,89] For *Candida*, the decision to treat surgically should be based on surgical indications, such as heart failure, heart block, annular abscess, or destructive lesions, similar to the way patients with other pathogens are treated. The situation differs for aspergillus endocarditis, which requires surgical treatment because of the high mortality associated with medical therapy alone.[90]

The optimal use of surgery for intravenous drug users is unclear. Because of concerns regarding drug use recidivism and relapsed infective endocarditis in this group, it is not clear that they should be routinely offered surgery. Single-center studies suggest that the outcomes following surgery are poor. One study showed that between 3 and 6 months after undergoing surgery, the hazard of death or reoperation was 10 times that of nonintravenous drug users.[91] Although patients with intravenous drug use–associated infective endocarditis may have low perioperative mortality,[92] longer-term mortality rates after surgical treatment can be as high as 45%.[93] Larger, more generalizable studies are needed to better define the optimal approach to surgical decision making in this group of patients.

Special Considerations

Prevention

For several decades, antibiotic prophylaxis has been a standard practice for the prevention of infective endocarditis. Dental procedures are thought to be a major source of bacteremia requiring antimicrobial prophylaxis for patients at risk of developing infective endocarditis but, in fact, bacteremia frequently occurs with routine daily activities,[94] and the cumulative effect of random bacteremia may be significantly greater than that from the occasional dental procedure.[95] Although antibiotics can reduce the incidence of bloodstream infection from dental procedures,[94] there are limited data demonstrating the effectiveness of antibiotic prophylaxis for infective endocarditis[96] and there are known failures of antibiotic prophylaxis.[97] Using antibiotics in an effort to avoid developing infective endocarditis is associated with a small risk of antibiotic–related adverse events.[98] Oral hygiene is important for prevention[4] and specific oral hygiene habits (eg, such as not toothbrushing after meals) have been associated with infective endocarditis due to oral streptococci.[94,99] Consequently, controversy exists regarding which populations should receive antibiotic prophylaxis. The American Heart Association[100] and European Society for Cardiology[101] now recommend prophylaxis when dental procedures are performed in patients who have cardiac conditions associated with the highest risk of adverse outcome if infective endocarditis occurs. The United Kingdom National Institute for Health and Care Excellence advises against routine antibiotic prophylaxis to prevent infective endocarditis.[102] Studies evaluating the association between changes in guideline recommendations for prophylactic antibiotics and incidence have not shown a clear and convincing association between a decreased use of prophylactic antibiotics and subsequent increased incidence of infective endocarditis.[10,97,103] How to optimally use antibiotics to prevent endocarditis remains unknown and is the subject of ongoing research. Nevertheless, for patients who have prosthetic valves or other conditions that place them at high risk of adverse outcomes, antibiotic prophylaxis may be beneficial (**Box 3**).[24] In addition, these patients should maintain the best possible oral health by pursuing regular professional dental care and appropriate maintenance of oral hygiene.[50]

Box 4. Challenges and Uncertainties in Infective Endocarditis

Prevention

Clarification of the benefit of antibiotic prophylaxis before dental procedures

Quantify the role of oral hygiene in the prevention of infective endocarditis

Defining and validating which patients should receive antibiotic prophylaxis (ie, which patients should be considered high risk)

Diagnosis

Differentiation of small vegetation vs noninfective changes in degenerative valve disease

Differentiation of infective vs postsurgical changes in possible prosthetic valve endocarditis

Differentiation of sterile thrombus or fibrin vs infected vegetation on cardiac implantable electrophysiological device lead

Improving yield of diagnostics (eg, polymerase chain reaction) for blood culture negative infective endocarditis

Treatment

Management of antiplatelet and anticoagulant therapies in acute infective endocarditis, particularly mechanical valve infection

Selection of optimal antibiotic therapy for infective endocarditis due to methicillin-resistant *Staphylococcus aureus* with reduced susceptibility to vancomycin

Role and benefit of surgery in patients with large vegetation after 1 week of antibiotic therapy on risk of embolic event

Treatment of infected transcatheter aortic valve replacement, especially in intermediate or high-risk surgical patients

Type of prosthetic valve replacement in patients with native valve endocarditis undergoing surgery

Determining and implementing strategies to prevent intravenous drug use–related, infective endocarditis

Use of surgery for left-sided infective endocarditis in patients with injection drug use

Timing of surgery after nonhemorrhagic or hemorrhagic stroke

Timing of surgery in patients with nonemergency indication

Transcatheter Aortic Valve Replacement

The number of transcatheter aortic valve replacement (TAVR) procedures for aortic stenosis has rapidly increased in the United States over the past 5 years.[104] The reported incidence of infective endocarditis after TAVR ranges from 0.1% to 3.0%.[105] The rate in the PARTNER trials, which included 527 patients randomized to treatment with TAVR, was reported to be 0.7%.[106] Given the limited data available, it is likely that the incidence after TAVR is not very different from that of surgical aortic valve replacement, which has an incidence of 1% to 6%.[107]

The potential risk of infective endocarditis in patients who undergo a TAVR is influenced by various factors. The initial FDA approval for TAVR was for high-risk surgical patients.[104] These patients tended to be older (>80 years) and had many comorbidities such as heart failure, chronic obstructive lung disease, or hemodialysis that increased the risk of subsequently developing infective endocarditis. TAVR is associated with a higher rate of residual aortic insufficiency than is surgical aortic valve replacement. The presence of paravalvular aortic insufficiency may cause endothelial damage, predisposing infective endocarditis.[105]

TAVR is a fundamentally different procedure than surgical aortic valve replacement and the microbiology of infective endocarditis for the 2 procedures may differ. *Staphylococci* is the most common isolate in surgical aortic valve replacement.[108] The most common organism in patients who have undergone TAVR is *Enterococcus* (34.4%) with *Staphylococcus aureus* accounting for only 6.2% of all isolated organisms.[105] Because TAVR is generally done in high-risk patients, they are less likely to undergo subsequent surgical intervention should infective endocarditis develop than would patients who develop infective endocarditis after surgical aortic valve replacement (11% vs 50%).[108-110]

The most complete data available for infective endocarditis after TAVR comes from the Infectious Endocarditis after TAVR International Registry.[109] Of the 20 066 patients in the registry who underwent TAVR, 250 developed infective endocarditis. The risk factors associated with developing infective endocarditis included younger age, male sex, diabetes mellitus, and moderate to severe aortic regurgitation. *Enterococcus* was the most frequently

isolated organism. Surgery was performed in only 14.8% of patients, and the overall in-hospital mortality was 36%.

Cardiac Implantable Electronic Device Infection

Transesophageal echocardiography (TEE) can better diagnose lead infection than can transthoracic echocardiography because the extracardiac portion of these leads can only be visualized by transesophageal echocardiography.[23,111] Patients with staphylococcal bacteremia or endocarditis on other endocardial surfaces who have CIEDs are assumed to have an infected device. Because sensitivity of the modified Duke criteria for infective endocarditis and echocardiography is lower in CIED endocarditis (since it is harder to detect infection on the device electrode tip or endocardial areas in contact with the electrode tip), FDG-PET/CT or radiolabeled leukocyte scintigraphy imaging is the preferred means for establishing this diagnosis and should be performed when infective endocarditis is still suspected after a negative or equivocal transesophageal echocardiography study.[111]

Complete CIED hardware removal should be performed in all definite infective endocarditis cases.[41,112] Removal of the generator and transvenous lead extraction can be performed in most cases without the need to resort to surgery and is safe with mortality rates of less than 1% at experienced, high-volume centers.[113] Temporary pacing may be continued with a screw-in ventricular lead and temporary defibrillator function provided by a wearable external defibrillator for several weeks until risk of reinfection is reduced. Parenteral antibiotics are given,[112] but it is not known what the optimal timing is for reimplantation of another CIED. Blood cultures should be negative for at least 14 days if valvular vegetations are seen on echocardiography. Long-term survival after CIED endocarditis is reduced compared with other indications for CIED extraction,[113] likely related to comorbid host factors.

Prognosis

Infective endocarditis remains a lethal disease. The in-hospital mortality for infective endocarditis approximates 20% and the 6-month mortality is about 30%.[114] Despite advances in care, this mortality rate has not improved in the last 2 decades. The persistently high mortality is due to epidemiological shifts in the types of infective endocarditis (eg, health care–associated infective endocarditis), greater numbers of older patients who have significant comorbidities, and pathogens that have greater antibiotic resistance (**Box 4**). Prognostic factors for poor outcomes from infective endocarditis include host factors such as age and hemodialysis, infective endocarditis characteristics like prosthetic valve involvement or health care associated infective endocarditis, and having complications of infective endocarditis such as severe heart failure, stroke, or abscess development.[114] Early surgical intervention is associated with lower mortality,[114,115] although patients with higher operative risk have poorer long-term survival than patients with lower operative risk.[116] Patients with infective endocarditis have higher rates of all adverse cardiovascular events including stroke, myocardial infarction, rehospitalization for heart failure, and sudden death or ventricular arrhythmia compared with a matched cohort.[117]

Conclusions

The epidemiology and management of infective endocarditis are continually changing and many uncertainties remain. Guidelines provide specific recommendations about the management of infective endocarditis; however, careful attention to individual patient characteristics, the type of pathogen, and risk of the sequela of infective endocarditis must be considered when making therapeutic decisions.

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Submissions: We encourage authors to submit papers for consideration as a Review. Please contact Edward Livingston, MD, at Edward.livingston@jamanetwork.org or Mary McGrae McDermott, MD, at mdm608@northwestern.edu.

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