Infective Endocarditis: A Contemporary Review

Scott A. Hubers, MD; Daniel C. DeSimone, MD; Bernard J. Gersh, MBChB, DPhil; and Nandan S. Anavekar, MBBCh

Abstract

Infective endocarditis (IE), initially described more than 350 years ago, involves infection of the endocardial surface of the heart. The clinical manifestations of IE can involve every organ system, and the cardiac manifestations can include valvular vegetation, abscess, periannular extension of infection, and myopericarditis. Echocardiography is crucial in the diagnosis of IE, but alternative imaging modalities are playing an increasing role in the diagnosis and management of IE. Multidisciplinary care is imperative to the management of IE, often requiring the expertise of cardiologists, cardiothoracic surgeons, infectious diseases specialists, radiologists, and neurologists. We performed a literature search of the PubMed database from January 1st, 2000, to September 30th, 2019, using the terms infective endocarditis, diagnosis, and management to find the most pertinent and highest-quality evidence. This review summarizes key aspects of IE, with a focus on emerging advances in diagnosis. We also highlight growing patient populations at risk for IE, including patients with intracardiac devices and congenital heart disease.

Infective endocarditis (IE) is a disease of the endocardial surface of the heart. Infection typically involves the cardiac valves (native or prosthetic) or an indwelling cardiac device. It was first described more than 350 years ago, and important contributions to the understanding of the disease have been made by notable physicians such as William Osler and Emanuel Libman (see Figure 1). Infective endocarditis is typically classified as acute (symptoms occurring for days and up to 6 weeks), subacute (symptoms occurring between 6 weeks and 3 months), and chronic (symptoms of >3 months).

The present review summarizes key aspects of IE, with a focus on emerging advances in diagnosis. In addition, we look at specific growing at-risk patient populations, including adults with congenital heart disease (CHD) and patients supported with mechanical circulatory devices such as left ventricular assist devices (LVADs). Finally, we highlight the emerging role of artificial intelligence (AI) in the care of patients with IE.

We used the PubMed database to search the literature from January 1st, 2000, to September 30th, 2019, using the terms “infective endocarditis” AND “diagnosis” OR “management.” Studies selected for inclusion in this review were clinical trials and observational studies, although we also reviewed reference articles cited in guideline statements on the diagnosis and management of IE published by the American Heart Association (AHA) and the European Society of Cardiology. Select studies published before 2000 were included if they were considered pertinent to this review.

Epidemiology

The annual incidence of IE between 1970 and 2000 was estimated at approximately 5 to 7 cases per 100,000 person-years. The incidence has increased since 2000, approaching 15 cases per 100,000 population in 2011. Male individuals are more commonly diagnosed with IE than female individuals, particularly older men with a mean age of 67 years, in a typical Western
population. Despite being more common in older individuals, IE can affect younger patients, typically those from developing countries and Western countries from underprivileged socioeconomic demographic groups or with risk factors for the disease such as intravenous drug use (IVDU). Hospitalization for IE due to IVDU increased from 2000 to 2013, with the largest increase in those between the age of 15 and 34 years. Other than IVDU, risk factors for IE include degenerative valve disease, prosthetic valves, indwelling catheters and implanted cardiac devices, diabetes, immunosuppression, and CHD. Rheumatic heart disease remains a predisposing risk factor in the developing world, whereas IE due to rheumatic heart disease in the developed world is much less common and continues to decline.

DIAGNOSIS

Clinical Features

Diagnosis of IE relies on the Duke criteria, which were originally described in 1994 and modified in 2000. Components of the modified Duke criteria are summarized in Table 1. Despite the widespread use of these criteria for the diagnosis of IE, there are considerable limitations, and a substantial proportion of patients fall into the “possible IE” category. Furthermore, the presence of prosthetic valves reduces the sensitivity of the Duke criteria, likely related to challenges with imaging prosthetic valves. Significant advancements in technology with the use of cardiac computed tomography (CT) and positron emission tomography (PET) have improved diagnostic accuracy of IE and will be further discussed below.

The clinical manifestations of IE are protean and can involve every organ system. The cardiac manifestations could include valvular vegetation, abscess, periannular extension of infection, and myopericarditis. Mycotic aneurysms are an important vascular manifestation of IE as the mortality associated with unruptured and ruptured mycotic aneurysms is 30% and 80%, respectively. Embolic phenomena are common and can affect up to 50% of individuals with IE. Initiation of antibiotic therapy substantially decreases the risk of embolic events.

Microbiology

Regional variation exists regarding the causative microorganisms in IE. Staphylococcus aureus is the leading cause of IE in most of the world, present in approximately 31% of cases, followed by viridans group streptococci at 17% and Enterococcus species. Streptococcus gallolyticus (bovis) endocarditis is more common in Europe than in North America, whereas endocarditis due to the HACEK organisms (Haemophilus species, Aggregatibacter actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens, Kingella species) is relatively rare in North America. Viridans group streptococci are responsible for 26% of cases of IE in South America compared with 9% in North America, a difference felt to be related to higher rates of rheumatic heart disease.

Culture-negative endocarditis is an important entity to recognize and predictably is often difficult to diagnose. Generally, cases of blood culture—negative endocarditis fall into one of the following categories: sterilized blood cultures from previous antibiotic use; slow growth of fastidious organisms such as HACEK bacteria, Catibacterium (formerly Propionibacterium) acnes, and Candida species; endocarditis due to...
intracellular organisms such as *Bartonella* species, *Chlamydia* species, and *Tropheryma whipplei*; and noninfectious endocarditis. In a prospective study of culture-negative endocarditis, serology identified the causative microorganism in almost half of the cases, with *Coxiella burnetii* and *Bartonella* species being the most common pathogens. Rarely, non-IE, including nonbacterial thrombotic (marantic) endocarditis, could be due to autoimmune or neoplastic conditions.

**Imaging**

Echocardiography is the cornerstone of imaging modalities in the diagnosis of IE. Transthoracic echocardiography (TTE) should be performed in all cases of suspected endocarditis. Transesophageal echocardiography (TEE) has an important role in the diagnosis of IE when TTE is negative and in characterizing lesions and identifying local complications. The sensitivity of TTE in patients with prosthetic valves is approximately 50%, likely because of shadowing from the structural components of the prosthetic valve. The utility of TEE in these patients is significant, as sensitivity is more than 90% for the detection of endocarditis. Despite the improved sensitivity of TEE for the detection of endocarditis, TTE may perform similarly to TEE in evaluating anterior structures of the heart, including the tricuspid valve and right ventricular outflow tract. In a study of intravenous drug users with suspected right-sided endocarditis, TTE performed as well as TEE in the detection of vegetations.

Appropriate use criteria for echocardiography, published in 2011, support the use of TTE for the initial evaluation in patients with suspected IE and positive blood cultures or a new murmur. In addition, TTE is recommended for reevaluation of patients with a high risk of progression of IE or with a change in clinical status while routine surveillance of uncomplicated IE with TTE is inappropriate when no change in management is expected. These criteria also note that TEE is appropriate as the initial or supplemental diagnostic test when there is a moderate to high pretest probability of IE (staphylococcal bacteremia, prosthetic heart valves, or intracardiac devices). The 2017 Appropriate Use Criteria for Multimodality Imaging in Valvular Heart Disease also addressed IE. Although similar to the 2011 guidelines on echocardiography in IE, the 2017 guidelines state that repeating TTE may be appropriate to evaluate for interval change after antibiotic therapy even when no change in therapy is anticipated.

The use of 3-dimensional (3D) echocardiography provides added value to the...
evaluation of IE and complements conventional 2D echocardiography. The main advantage of 3D echocardiography is the improved spatial resolution of cardiac structures, allowing for a better visualization of vegetations, abscesses, and valvular deformities. In a small study of patients with valvular vegetations undergoing cardiac surgery, 3D echocardiography localized vegetations more accurately and better characterized the complications of IE compared with 2D echocardiography.

Three-dimensional echocardiography is also helpful in surgical planning. For example, 3D imaging allows for the visualization of the mitral valve in the “surgeon’s view” (viewing the mitral valve from the left atrium) and may enhance previously unrecognized abnormalities, such as mitral valve clefts and commissural mitral regurgitation. Although limitations of 3D echocardiography include reduced temporal resolution and the presence of artifacts, 3D echocardiography has evolved as an important adjunct to 2D echocardiography.

Intraoperative TEE has become widely used in cardiac surgery operating rooms and is valuable for patients undergoing surgery for IE. This was seen in a retrospective study from Israel in which intraoperative TEE affected surgical management in nearly 36% of cases. Specifically, the prepump intraoperative TEE changed surgical management in 6 of 52 cases (even when all patients had TEE within 2 weeks of operation), and postpump imaging led to a second bypass run in 10.2% of cases. The benefit of intraoperative TEE becomes clear when acknowledging the dynamic nature of IE with changing vegetation sizes and the rapid potential to develop local complications. Therefore, intraoperative TEE should be routinely performed at the time of surgery for IE.

The use of intracardiac echocardiography (ICE) has been described in patients with IE. Intracardiac echocardiography involves the use of a catheter equipped with a transducer, typically inserted into the femoral vein, to visualize intracardiac structures. A prospective study evaluating patients who were referred for transvenous lead extraction in the setting of suspected cardiac device infection found that ICE performed better than TEE in identifying intracardiac masses, specifically identifying masses not seen by TEE in 11% of patients with possible IE.

The specificity of ICE for IE may be reduced because of false positives from thrombi, strands, and noninfective vegetations, and

<table>
<thead>
<tr>
<th>Major criteria</th>
<th>Minor criteria</th>
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<tbody>
<tr>
<td>Positive blood culture for IE with a typical organism from 2 separate blood cultures</td>
<td>Predisposition: predisposing heart condition or IVDU</td>
</tr>
<tr>
<td>Persistently positive blood cultures for any organism (at least 2 positive cultures of samples drawn &gt;12 h apart)</td>
<td>Fever ≥38.0°C</td>
</tr>
<tr>
<td>Single positive blood culture for Coxiella burnetii or anti-phase I IgG antibody titer of &gt;1:800</td>
<td>Vascular phenomena: arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, and Janeway lesions</td>
</tr>
<tr>
<td>Echocardiogram positive for IE including vegetation, abscess, new partial dehiscence of a prosthetic valve, or new valve regurgitation</td>
<td>Microbiological evidence that does not meet major criteria</td>
</tr>
<tr>
<td>Echocardiogram positive for IE including vegetation, abscess, new partial dehiscence of a prosthetic valve, or new valve regurgitation</td>
<td>Positive blood culture not meeting major criteria</td>
</tr>
<tr>
<td>Echocardiogram positive for IE including vegetation, abscess, new partial dehiscence of a prosthetic valve, or new valve regurgitation</td>
<td>Immunological phenomena (Osler nodes, Roth spots, rheumatoid factor, or glomerulonephritis)</td>
</tr>
</tbody>
</table>

*IE = infective endocarditis; IVDU = intravenous drug use.

*Definite IE is defined as meeting 2 major clinical criteria, 1 major criterion with 3 minor criteria, or 5 minor criteria. Possible IE is defined as meeting 1 major criterion with 1 minor criterion or 3 minor criteria. Of note, a diagnosis of IE is rejected when a firm alternative diagnosis is present, when signs/symptoms resolve with ≤4 days of antibiotic therapy, when there is absence of pathological evidence for IE at the time of surgery (with antibiotic therapy of ≤4 days), and when criteria for possible IE are not met.
this study did not use pathological specimens to confirm IE. Regardless, ICE may become a useful imaging modality for IE if its advantages are confirmed in future prospective studies.

Alternative imaging modalities are playing an increasing role in the diagnosis and management of IE. One particularly useful modality is cardiac CT. In 1 study, multislice CT had a similar diagnostic accuracy for detecting the presence of valvular vegetations compared with TEE, although small vegetations (<4 mm) were more commonly missed by CT. An advantage of CT over TEE is in the detection of perivalvular extension of infection and pseudoaneurysms. Two studies found that multislice CT was superior to TEE in the identification of abscesses and pseudoaneurysms and provided more accurate anatomical information. The improved accuracy of CT compared with TEE in the detection of perivalvular abscesses and pseudoaneurysms is thought to be due to superior spatial resolution. Cardiac CT is also valuable in surgical planning, as it can provide a noninvasive assessment for coronary artery disease. Despite the advantages of cardiac CT, TEE has been found to be better at evaluating valve perforation and the presence of intracardiac fistula. Ultimately, TEE and cardiac CT provide complementary information in the diagnosis and management of patients with IE.

The main role of magnetic resonance imaging (MRI) in the management of IE is with the detection of cerebral embolic events. Magnetic resonance imaging can lead to earlier diagnosis of IE, as it is a minor criterion in the modified Duke criteria. Findings from cerebral MRI upgraded the diagnosis for patients to “definite IE” from “nondefinite IE” in approximately 26% of patients from a prospective cohort in France. Cerebral MRI can also affect surgical planning, particularly the timing of surgery.

Positron emission tomography scanning has emerged as an important tool in the diagnosis of IE. The rationale behind PET scanning for IE is based on the uptake of 18F-fluorodeoxyglucose (FDG) by cells such as leukocytes and monocytes at the site of infection. In a study by Saby et al, cases of “possible IE” were significantly reduced with the use of FDG PET/CT when used in patients with suspected prosthetic valve endocarditis. In addition, FDG PET/CT imaging can be helpful in the evaluation of cardiac device infection. Recent surgery, vasculitis, and other inflammatory states can potentially result in false positives from FDG PET/CT imaging. Despite these limitations, PET/CT will continue to be a powerful tool in the evaluation and management of IE.

MANAGEMENT

Antibiotics
Optimal antimicrobial therapy involves the prolonged (>4 weeks) use of bactericidal agents in an attempt to eradicate infection.

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TABLE 2. Empirical Antibiotic Regimens for Infective Endocarditis

<table>
<thead>
<tr>
<th>Condition</th>
<th>Antibiotic regimen</th>
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<tbody>
<tr>
<td>Native valve endocarditis</td>
<td>IV vancomycin 20 mg/kg loading dose and then 15 mg/kg every 12 h IV cefepime 2 g every 8 h</td>
</tr>
<tr>
<td>Prosthetic valve endocarditis</td>
<td>IV vancomycin 20 mg/kg loading dose and then 15 mg/kg every 12 h IV cefepime 2 g every 8 h</td>
</tr>
<tr>
<td>Culture-negative endocarditis</td>
<td>IV vancomycin IV ceftriaxone IV gentamicin 3 mg/kg every 24 h in 3 divided doses or doxycycline 100 mg twice daily</td>
</tr>
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</table>

\^HACEK = Haemophilus species, Aggregatibacter actinomycescomitans, Cardobacterium hominis, Eikenella corrodens, Kingella species; IV = intravenous.

\^Data from Circulation.
Initial antimicrobial therapy is often empirical and based on patient and epidemiological factors. Standard empirical antibiotic regimens are summarized in Table 2. Guidelines recommend consultation with an infectious disease specialist to guide antimicrobial selection and duration. The following paragraphs provide a brief overview of antimicrobial therapy for the most common microbiological causes of IE, but further recommendations can be found in the appropriate IE management guidelines.

Treatment of streptococcal IE due to viridans group streptococci or *Strep gallolyticus* (bovis) is dependent on penicillin minimum inhibitory concentration data. In strains of streptococci that are highly susceptible to penicillin, monotherapy with a parenteral penicillin or ceftriaxone has been found to be highly effective. Vancomycin is an acceptable alternative in those unable to tolerate penicillin therapy. The addition of gentamicin for the initial 2 weeks of treatment is reasonable for IE due to viridans group streptococci or *Strep gallolyticus* (bovis) that are not highly susceptible to penicillin and in patients with prosthetic valves or prosthetic material.

Antibiotic therapy for staphylococcal IE depends on whether staphylococci are coagulase positive (*Staph aureus*) or coagulase negative (ie, *Staphylococcus epidermidis* or *Staphylococcus lugdunensis*) and the presence or absence of prosthetic valves or prosthetic material. Native valve endocarditis due to methicillin-sensitive *Staphylococcus aureus* (MSSA) is typically treated with β-lactams such as nafcillin or cefazolin (for patients with non—anaphylactoid allergy to β-lactams). Vancomycin is the treatment of choice for native valve IE due to methicillin-resistant *Staphylococcus aureus* (MRSA). Daptomycin has been found to be as effective as the standard of care and is an acceptable alternative to vancomycin. Aminoglycosides and rifampin are not recommended for native valve endocarditis due to MRSA or MSSA. However, because of the biofilm formation on the surface of prosthetic material/devices, combination therapy of a β-lactam for MSSA (vancomycin for MRSA) and rifampin with the use of gentamicin for the initial 2 weeks is recommended for prosthetic valve endocarditis.

Endocarditis due to enterococci can be challenging to treat because of increasing resistance to penicillins and aminoglycosides. Combination therapy of penicillin and an aminoglycoside can result in bactericidal synergy, in which the presence of penicillin facilitates the intracellular uptake of the aminoglycoside. An alternative regimen of ampicillin with ceftriaxone is reasonable for IE due to aminoglycoside-resistant enterococcal strains, as well as situations where the risk of nephrotoxicity and ototoxicity are unacceptably high.

**Adjunctive Medical Therapy**
No randomized clinical trials have addressed anticoagulation management in patients with IE. However, a retrospective study found that patients with prosthetic valve endocarditis who were receiving anticoagulation had a significantly higher mortality than did those with native valve endocarditis, and most (73%) patients with prosthetic valve IE died of central nervous system complications. Therefore, the current recommendation is to discontinue anticoagulation in patients with IE and a mechanical valve who have had central nervous system complications.

<table>
<thead>
<tr>
<th>TABLE 3. Indications for Surgery in Infective Endocarditis</th>
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<tbody>
<tr>
<td><strong>General indication</strong></td>
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<tr>
<td>Heart failure</td>
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<tr>
<td>Persistent infection</td>
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<tr>
<td>Complication of infection</td>
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<tr>
<td>Prevention of embolism</td>
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**INFECTIVE ENDOCARDITIS**

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embolic events for at least 2 weeks.19 When reintroduction of anticoagulation is appropriate, it is generally accepted to initiate intravenous unfractionated heparin and then transition to warfarin. Anticoagulation management in patients with IE who have not had an intracerebral event remains controversial. Also, the safety of novel oral anticoagulants in IE has not been systematically studied.

Given that endocarditis vegetations are rich in platelets, there was initial optimism that antiplatelet agents would be effective adjunctive medical therapy in patients with IE. In a randomized clinical trial published in 2003, patients with IE were randomized to 325 mg daily aspirin or placebo.40 These investigators found no difference in rates of embolic events or development of intracranial lesions. However, a trend toward increased bleeding in the aspirin group was observed. In contrast, a retrospective study evaluating 600 patients with IE found a lower risk of symptomatic embolic events in patients who had received an antiplatelet medication for at least 6 months before hospitalization for IE. Therefore, guidelines currently recommend that antiplatelet agents should not routinely be initiated in patients with IE, although continuation of long-term antiplatelet agents in patients with low bleeding risk is reasonable.19

The use of statin therapy may have a role in the management of patients with IE. A retrospective study with propensity score matching evaluated the effect of statin therapy on the rate of embolic events in patient with IE. Previous treatment with statins was significantly associated with lower rates of embolic events (odds ratio, 0.30; 95% CI, 0.14-0.62; P = .001).42 The potential mechanisms to explain the benefit of statins were attributed to anti-inflammatory, antiplatelet, and immunomodulatory effects. A subsequent study in Taiwan replicated the benefit of statins in IE and found significantly lower in-hospital, 3-month, and 12-month mortality rates in statin users than in nonstatin users. Despite the promising results of these retrospective studies and a biologically plausible explanation for their benefit, no randomized trials have been performed to evaluate the effect of statin therapy in patients with IE and the current rationale for their use is not strong.

**Surgery**

Specific indications for the surgical management of IE are listed in Table 3. Broadly, the indications for surgery involve the presence of valve dysfunction causing heart failure, persistent bacteremia despite antimicrobial therapy, and IE with fungi or drug-resistant organisms. When an indication for surgical intervention is met, the next issue becomes the risk of surgery, and the greatest decision-making hurdle relates to the presence or absence of previous stroke that may represent a complication of the illness. Along with this, the timing of surgery is an important consideration (Figure 2). The optimal timing of surgical management in

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**FIGURE 2.** Decision tree for the surgical management of infective endocarditis. HF = heart failure; PVE = prosthetic valve endocarditis; Staph aureus = Staphylococcus aureus. Adapted in part from J Am Coll Cardiol,46 with permission.
IE is unknown. Evidence for the timing of the surgical management of IE came from a randomized clinical trial from South Korea in which patients with left-sided native valve endocarditis and severe valve disease with large vegetations were assigned to either early surgery (defined as within 48 hours of randomization) or conventional treatment. The primary outcome was a composite of in-hospital death or embolic events within 6 weeks of randomization. Among patients in the conventional treatment arm, 77% underwent surgery at some point, either during hospitalization or during follow-up. Those who underwent early surgery had a significant reduction in the composite end point (hazard ratio, 0.10; 95% CI, 0.01-0.82; \(P=0.03\)). However, limitations of this study include a small cohort (<40 patients in each group), and most cases were streptococci, which have lower rates of morbidity and mortality when compared with Staph aureus. The benefit of early surgery was confirmed by other observational studies, one of which used propensity score matching to exhibit that patients with native valve endocarditis who had surgery during index hospitalization had lower in-hospital mortality than did those treated medically.

The European and US guidelines on the management of IE differ in their definitions of surgical timing. In the European Society of Cardiology guidelines, surgical timing is defined as either emergent (within 24 hours), urgent (within a few days), or elective (after 1 to 2 weeks of antibiotic therapy). The 2015 AHA guidelines on the management of IE define early surgery as during initial hospitalization and before completion of a full course of antibiotics. Despite these differences, both guidelines recommend avoiding a delay in the surgical management of IE in the setting of hemodynamic compromise, uncontrolled infection as evidenced by persistent fever or perivalvular extension of infection, and prevention of embolism. A unique challenge is surgical timing in patients with previous stroke, especially hemorrhagic stroke, as postsurgical mortality in these patients is high in the first 4 weeks. In a retrospective analysis of a cohort of patients with left-sided endocarditis, patients with brain hemorrhage had a higher mortality when surgery was performed within 4 weeks as compared with delayed surgery. The recommendation of the AHA guidelines states that it is reasonable to delay surgical intervention for at least 4 weeks in patients with major stroke or intracranial hemorrhage.

Despite a progressive emphasis on earlier surgical intervention in distinct subgroups of patients with IE, a significant proportion still do not receive surgery, even in the absence of stroke. In a prospective cohort of 863 patients with left-sided endocarditis and an indication for cardiac surgery, 24% did not undergo surgery, with stroke being cited as the reason in nearly a quarter of cases. Several risk score models are available to assist with the decision regarding surgical management, and worse outcomes were present in older patients with multiple comorbidities including diabetes and renal disease.

CARDIAC IMPLANTABLE ELECTRONIC DEVICES

The use of cardiac implantable electronic devices (CIEDs) has risen significantly in the past few decades. Unfortunately, the rate of CIED-related infections has increased out of proportion to the increase in implantation of these devices. Cardiac implantable electronic device infection can occur at the device pocket site, CIED leads, and/or the endocardial surfaces. Risk factors for the development of CIED infection include device revision, device pocket hematoma, and patient comorbidities such as diabetes, cancer, heart failure, and corticosteroid use. The diagnosis of CIED infection relies on blood culture data and echocardiography, specifically TEE given its higher sensitivity for detecting lead and valvular vegetations as compared with TTE. Newer imaging modalities, including FDG PET/CT, can be helpful in diagnosing CIED infections, especially in the setting of equivocal TEE imaging. 18F-Fluorodeoxyglucose PET/CT is particularly useful in the diagnosis of device pocket infections, with sensitivity and
specifcity approaching 96% and 97%, respectively.53

Once CIED infection is confirmed, the mainstay of treatment involves antibiotics and complete extraction of the device and leads. Several studies have found improved outcomes in patients who underwent complete device system removal vs those treated with antibiotics alone.54,55 Cardiac implantable electronic device infection is common in patients with staphylococcal bacteremia, approaching 36% in one study.56 In patients with a need for ongoing cardiac pacing, a temporary pacemaker is typically placed while awaiting negative blood cultures. Recommendations on treatment strategies and other management of CIED infections are summarized in Figure 3. It should be noted that leadless pacemakers may be an alternative therapeutic option in select patients, particularly those with repeated infections from transvenous systems.57

Not uncommonly, masses and nonspecific strands are noted on the leads of CIEDs during TTE or TEE, raising the concern for CIED infection. In a Turkish study evaluating patients with pacemakers, nearly 30% were found to have “accretions,” defined as thin mobile masses on pacemaker leads.58 Importantly, 5-year outcomes of these patients were no different from those without accretions. In another study involving patients undergoing TEE for reasons other than endocarditis evaluation, 10% (13 of 136) were found to have masses on device leads, with only one case ultimately found to have CIED infection.59 In situations in which lead masses are present and CIED infection remains uncertain, there are

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**FIGURE 3.** General algorithm for the management of CIED infections. CIED = cardiac implantable electronic device; FDG PET/CT = 18F-fluorodeoxyglucose positron emission tomography/computed tomography; TEE = transesophageal echocardiography. aIncludes bacteremia due to *Staphylococcus aureus*, coagulase-negative staphylococci, *Cutibacterium* species and *Candida* species. bHigh-grade bacteremia defined as persistent bacteremia (at least 2 blood cultures drawn at separate times [<1 hour apart]) due to organisms typically associated with endocarditis, including alpha-hemolytic *Streptococcus*, beta-hemolytic *Streptococcus*, and *Enterococcus* species.
reports of using FDG PET/CT and even biopsy to characterize the mass.60-62

PREVENTION

The concept of using antibiotics to prevent IE has been around for more than 6 decades, dating back to AHA guidelines published in 1955, which recommended the use of intramuscular penicillin for individuals with rheumatic heart disease and CHD before dental procedures.63 Since then, multiple updates and revisions to these guidelines have been published. The most recent AHA guidelines from 2007 aimed to restrict antibiotic prophylaxis to patients at the highest risk of adverse outcomes from IE.64 The specific indications for antibiotic prophylaxis to prevent IE are summarized in Table 4. Of note, antibiotic prophylaxis of IE is not recommended for patients undergoing genitourinary or gastrointestinal tract procedures. It should be emphasized that there have been no randomized clinical trials evaluating the efficacy of antibiotic prophylaxis before dental procedures.

Studies examining the incidence of IE after the 2007 guideline changes have yielded conflicting results. Two studies from the United States65,66 and 1 from Canada67 found no increase in the incidence of IE after the guideline change. However, a study using the Nationwide Inpatient Sample database reported a significant rise in the incidence of streptococcal IE after the 2007 guidelines without any change in the rate of hospitalization or valve surgery for IE.3 The streptococcal group in this study included enterococci and Strep gallolyticus (bovis) rather than separate groups, which may explain the observed increase in IE after the guidelines rather than actual increase in viridans group streptococci—the predominant mouth organism and target of antibiotic prophylaxis. Despite the controversy, the current approach to antibiotic prophylaxis before dental procedures to prevent IE seems to appropriately weigh the risks and benefits of therapy and clearly targets high-risk individuals who would have significant adverse outcomes from IE.

SPECIAL POPULATIONS

Left Ventricular Assist Device—Related Infection

The use of LVADs to manage patients with advanced heart failure continues to increase. In 2015, a total of 2754 LVADs were implanted and a higher proportion of LVADs were implanted for destination therapy as compared with 2008.68 The increase in device implants coupled with a longer duration of device therapy has led to an increase in device-related complications, including infection. Left ventricular assist device—related infection can occur at the driveline site, at the device pocket site, or on the internal surface of the pump near the endocardium.69 Driveline site infections are the most common type of LVAD-related

<table>
<thead>
<tr>
<th>TABLE 4. Indications for Antibiotic Prophylaxis Before Dental Proceduresa,b</th>
</tr>
</thead>
<tbody>
<tr>
<td>2007 AHA/ACC guidelines</td>
</tr>
<tr>
<td>Prosthetic heart valves</td>
</tr>
<tr>
<td>History of IE</td>
</tr>
<tr>
<td>Congenital heart disease (specifically unrepaired cyanotic heart disease or repaired congenital heart disease using prosthetic material [for 6 mo after surgery] or lifelong if the residual defect is present)</td>
</tr>
<tr>
<td>Patients with abnormal valve and valvular regurgitation who had undergone heart transplantation</td>
</tr>
</tbody>
</table>

*aACC = American College of Cardiology; AHA = American Heart Association; ESC = European Society of Cardiology; IE = infective endocarditis.

bDental procedures that specifically involve penetration of the oral mucosa and/or gingival tissue/periapical teeth.
infection, occurring approximately 1.31 to 1.42 per 100 patient-months. Importantly, patients with LVAD-related infections have 5.6 times greater mortality at 1 year and also have higher rates of other complications such as bleeding and stroke.

Treatment of LVAD-related infections is often based on expert opinion and is highly dependent on the specific clinical circumstances. Driveline infections are typically treated with debridement at the exit site and antibiotics, and device pocket infections are often treated with chronic suppressive antibiotics. In cases of persistent infection, pump exchange may be necessary. In a study of patients with either driveline infection or device pocket infection, pump exchange was associated with good outcomes with 100% survival at 30 days and low recurrence of infection. A published case series also reported good outcomes with pump exchange for persistent driveline infection. Many questions remain regarding LVAD-related infections, including identifying risk factors for infection, optimal treatment strategies, and infection prevention.

Transcatheter Valve Prosthetics and Other Intracardiac Devices
The past decade has seen an exponential rise in transcatheter procedures aimed to treat various cardiac conditions. The most common percutaneous interventions for treating valvular heart disease include transcatheter aortic valve replacement (TAVR), percutaneous valve repair, and paravalvular leak closure with vascular plugs. Given the relatively recent advances in these procedures, the full scope of the burden of endocarditis has yet to be revealed. However, data from trials of TAVR in intermediate- and high-risk surgical patients indicate that the risk of prosthetic valve endocarditis is similar between TAVR and surgical aortic valve replacement, estimated at 5.21 events per 1000 person-years in the population who underwent TAVR compared with 4.10 events per 1000 person-years in the population who underwent surgical aortic valve replacement (P=.44). In that study cohort of patients who underwent TAVR, specific risk factors for the development of prosthetic valve endocarditis included baseline cirrhosis, pulmonary disease, and renal insufficiency. A study evaluating outcomes after percutaneous mitral valve repair using transcatheter mitral-leaflet approximation with the MitraClip device (Abbott) found that the rate of IE at 90 days was 2.4% when the procedure was performed in low-volume centers (<3 procedures/y), which was significantly higher than that in high-volume centers (0.3%). There is a paucity of data on IE after paravalvular leak closure, but early experience in Europe suggests that the rate is low, with 1 case of IE in 259 patients after approximately 3 months of follow-up. The incidence of IE with even newer procedures, such as transcatheter mitral and tricuspid valve replacements, has yet to be studied.

Other intracardiac devices including patent foramen ovale and left atrial appendage closure devices are increasingly used to prevent thromboembolism. Patent foramen ovale and atrial septal defect closure devices have been used since the 1970s. The risk of IE is highest in the weeks to months after device implantation, and a lack of device endothelialization is thought to predispose patients to late bacterial endocarditis. Currently, no published studies have evaluated the incidence of IE after left atrial appendage closure device implantation. However, similar to patent foramen ovale and atrial septal closure devices, the risk of IE appears to be highest immediately after device implantation, leading the manufacturer of the device to recommend endocarditis prophylaxis for 6 months after placement.

Hypertrophic Cardiomyopathy
Previous AHA guidelines recommended antibiotic prophylaxis before dental procedures in patients with hypertrophic cardiomyopathy because of the risk of IE in this population. It was thought that left ventricular outflow tract obstruction was a predisposing factor for the development of IE on the basis of a retrospective study of 10 patients with hypertrophic cardiomyopathy (all with left ventricular outflow tract obstruction) who developed IE. However,
a recent study evaluating 30 patients with hypertrophic cardiomyopathy who developed IE found similar rates of mitral and aortic valve IE, regardless of the presence of left ventricular outflow tract obstruction and systolic anterior motion of the mitral valve.81 One-year mortality in this patient population was low at 7%. Therefore, current guidelines do not recommend routine antibiotic prophylaxis before dental procedures in patients with hypertrophic cardiomyopathy.64

Congenital Heart Disease
The number of individuals living with CHD has substantially increased, mostly because of improvements in the diagnosis and management of children with congenital heart defects and advances in cardiac surgery. In 2010, it was estimated that 2.4 million people in the United States were living with CHD,82 a number that has almost certainly increased since then. Patients with CHD have an increased risk of IE, particularly those with residual cardiac shunts at the site of previous repair and those with uncorrected cyanotic heart disease.83 Specific predictors of IE in patients with CHD include those with valve-containing prosthetics (defined at prosthetic valves and valve-containing conduits), multiple defects, and male sex.84 Importantly, there was no long-term increase in the risk of IE in patients with non–valve-containing prosthetics, suggesting that repair may be preferred over valve replacement, if valve repair can be performed successfully.

KNOWLEDGE GAPS AND NEED FOR CENTERS OF EXCELLENCE
Multidisciplinary care is crucial to the diagnosis and management of IE. The presence of an “endocarditis team,” a multidisciplinary team made up of cardiologists, cardiothoracic surgeons, infectious diseases specialists, radiologists, and neurologists, has been found to improve prognosis.85,86 Cardiologists who are experts in echocardiography, including 3D TEE, and radiologists skilled in identifying the manifestations of IE using CT and nuclear imaging play an important role in the diagnosis of IE and related complications. For management decisions of patients with IE, a team approach is critical, involving specialists from cardiology, cardiothoracic surgery, neurology, and infectious disease. Our practice at Mayo Clinic has implemented a group of infectious disease physicians who are experts in the prevention, diagnosis, and management of IE. Their input is invaluable for decisions regarding antibiotics, surgical timing, and CIED management, among others. This team-based approach to care is instrumental not only during in-hospital care but also in the outpatient setting. Patients with a history of IE need close follow-up and education about how to avoid a relapse of IE.

Evidence-based research is needed to address a number of knowledge gaps in IE. As alluded to previously, the number of randomized clinical trials studying IE is limited, as it is a rare disease. Robust data are required to address a number of pressing questions in IE, including how to prevent IE, optimal timing of cardiac surgery, and how to reduce complications related to IE. More data on IE would also pave the way for use of AI in the management of patients with IE. This could include using data in the electronic health record to identify patients at highest risk for IE or characterizing vegetations to predict response to antibiotic therapy or risk of complications, specifically potential for emboli. In addition, AI could prove useful in management decisions, including the appropriateness of surgical intervention and surgical timing. An ongoing project in our group aims to develop an artificial neural network to predict the optimal timing of cardiac surgery in patients with IE as it affects mortality at 30 days and 1 year postsurgery. With similar AI models, we may be able to select patients who would benefit from antibiotic prophylaxis over other patients rather than broad categories. Artificial intelligence may allow us to individualize complex medical/surgical decisions, which could substantially affect the duration of intensive care and hospital lengths of stay and the duration of antibiotic therapy.
CONCLUSION
Infective endocarditis is a complex disease that requires the input of specialists from many fields. It is crucial to emphasize a multidisciplinary approach in IE, not only in the management of the disease but also in IE research. Despite advances in the past few decades in the diagnosis and management of IE, many unanswered questions remain, and randomized clinical trials are urgently needed to further our understanding of this challenging disease. Improvements in imaging technology and machine learning with AI offer hope to improve patient outcomes. Sir William Osler described IE as “one of the most formidable of cardiac affections,” leading to essentially all patients with IE in that era died of the disease. Although mortality has improved in the last century, IE continues to be a deadly disease, and further advancements in diagnosis and treatment are necessary to continue to improve outcomes.

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