Infective Endocarditis: A Comprehensive Overview

Todd L. Kiefer, MD, PhD, Thomas M. Bashore, MD
Division of Cardiology, Duke University Medical Center, Durham, NC

Infective endocarditis (IE) is an infection of a heart valve or other cardiac structure at a site of endothelial damage. The definition has been also expanded to include infected cardiac devices. A variety of organ systems may be adversely affected in patients with IE. Although advances have improved the diagnostic accuracy for IE, morbidity and mortality remain remarkably high. This article reviews the pathophysiology, complications, diagnosis, and management of IE with recent updates to the literature and the major cardiovascular society guidelines. The increasingly prevalent clinical problem of intracardiac device-related IE is addressed, along with the recent changes to the IE prophylaxis guidelines.

[Rev Cardiovasc Med. *2012;13(2/3): e105-e120 doi: 10.3909/ricm0633]*

KEY WORDS

Infective endocarditis • Bacteremia • Injection drug use • Valvular heart disease • Cardiac device infection

The first description of infective endocarditis (IE) was reported in the 17th century by Lazarus Riverius after reviewing autopsies.[1] Over the course of several centuries, significant advances have been made in our understanding of IE. However, most of this knowledge is based on observational data because there have been very few randomized trials of diagnostic or therapeutic approaches to IE. Despite improvements in antimicrobial therapy and cardiac surgical technique, IE is still associated with significant morbidity and mortality.

Pathophysiology

The hallmark of IE predisposition is endothelial damage. Subsequently, a complex of platelets and fibrin may be deposited at sites of endothelial damage,

which serves as a substrate for bacterial adherence during an episode of bacteremia. Areas of endothelial injury occur at the sites of valvular coaptation, so the process most commonly affects the ventricular side of the aortic and pulmonary valves and/or the atrial side of the mitral and tricuspid valves.[2] Likewise, endothelium exposed to turbulent jet lesions, such as the atrial wall with mitral regurgitation, the mitral chordae in aortic regurgitation, or the septal leaflet of the tricuspid valve with a ventricular septal defect, are sites favorable for the development of IE (Figure 1).[2] Once bacteria colonize a site of endothelial damage, neutrophils attach to the complex of bacteria-platelets-fibrin and valve destruction and invasion of adjacent myocardium may ensue. Occasionally, IE (particularly due to organisms with adhesive molecules on their surface) may develop in locations without any clinically evident preexisting endocardial abnormality.[3] The presence of infected vegetations is crucial to the diagnosis of IE (Figure 1).

Epidemiology

Various studies from different geographic regions published over the past 20 years have reported an IE incidence of 3.1 episodes per 100,000 person-years to 9.29 episodes per 100,000 person years.[4,5] There appears to be a trend of increasing IE in the elderly population, with 20.4 episodes per 100,000 person-years in the United States Medicare population in 1998.[6] Furthermore, more than half of IE cases in the United States and Europe are diagnosed in patients older than 60 years.[7] Many of these cases are related to the increasing use of intracardiac devices such as pacemakers and defibrillators in elderly patients.[8,9]

Several baseline characteristics are associated with the development of IE. Numerous studies have demonstrated that IE occurs more commonly in men, with a male to female sex ratio of 3.2:1 to 9:1.[7,10,11] Moreover, approximately 75% of patients diagnosed with IE have some form of structural heart disease (valvular or congenital abnormality).[12,13] In the early to mid 20th century, rheumatic valve disease was a major predisposing risk factor for IE, but this has decreased greatly in the Western world.[13] Injection drug use (IDU) is a well-characterized risk factor for IE and infection may occur without obvious preexisting valvular pathology. Nosocomial and non-nosocomial, health care–associated contacts are also increasingly recognized as important risk factors for the acquisition of endocarditis.[14]

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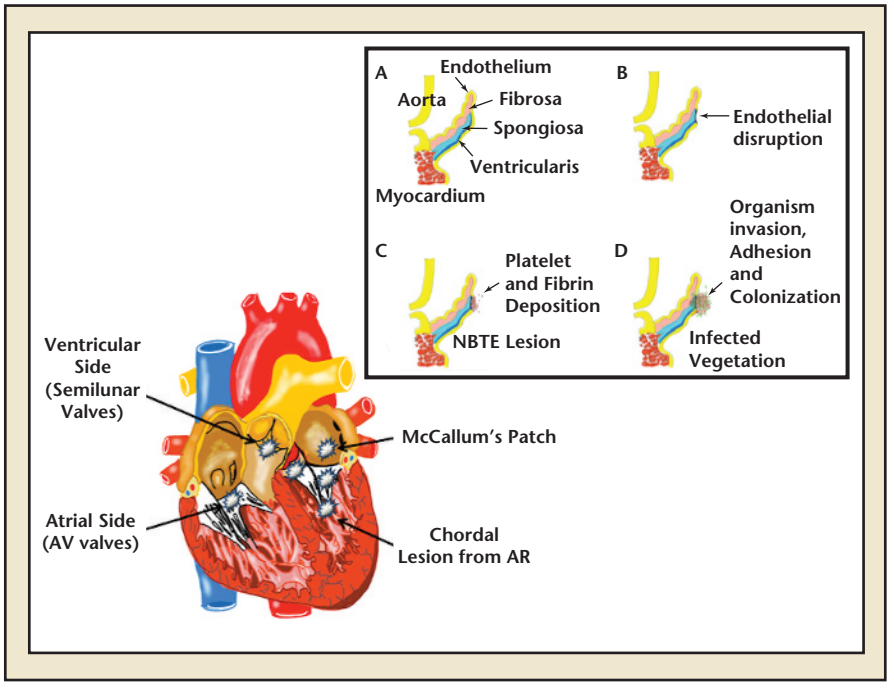
The valvular distribution of IE reveals slightly more cases of aortic IE (38%) than mitral valve IE (34%), with both valves involved in 8% of cases.[15] Isolated tricuspid valve IE is estimated to represent 4% of IE episodes and is more common in intravenous (IV) drug users, those on hemodialysis, and those with a pacemaker lead across the valve.[15] IE involving the pulmonary valve is exceedingly rare. In cases of aortic valve IE, the underlying predisposing lesion is aortic regurgitation in 10% to 18% of cases and aortic stenosis in 17% to 30% of cases.[15,16] Meanwhile, in mitral valve endocarditis, mitral regurgitation is the predisposing lesion in 21% to 33% of cases.[15,16]

Other clinically important predisposing cardiac conditions include congenital heart disease and prosthetic valve replacement. A history of congenital heart disease is associated with 4% to 18% of IE episodes, with cyanotic forms being at the highest risk.[16] In addition, prosthetic valve IE accounts for 12% to 30% of all cases of endocarditis.[16] Analysis of data from prosthetic valve patients shows that

Figure 1. Depiction of common sites of endothelial damage where IE may develop (left) with an illustration of the pathophysiologic process at the tissue level (right, inset). AR, aortic regurgitation; AV, atrioventricular; IE, infective endocarditis; NBTE, nonbacterial thrombotic endocarditis.



there is no difference in IE risk for patients with mechanical versus bioprosthetic valves.[17] However, individual patient characteristics, in particular renal insufficiency, prior IE, younger age, and perioperative wound infection, are associated with a heightened risk for prosthetic valve endocarditis.[18]

Several noncardiac risk factors linked to the acquisition of IE have been reported. IDU is a well-recognized risk factor for IE, with most cases involving the tricuspid valve, although one series did report left-sided valve infection in 57% of IDU patients.[19] Other IE predisposing risk factors include indwelling catheters, poor dentition, diabetes mellitus, AIDS, chronic skin infection, alcoholic liver cirrhosis, solid organ transplant, and genitourinary infections or procedures.[20] Patients with end-stage renal disease on chronic hemodialysis are particularly at increased risk for acquiring IE.[21-23] This is related to bacteremia from repeated use of the vascular access, calcium deposition on valve leaflets, and immunological abnormalities that are associated with chronic kidney disease.

Microbiology

The microbiology of IE varies depending on whether a native valve, prosthetic heart valve, or intracardiac device is infected. Also, microbiology varies with patient predisposing characteristics, such as IV drug abuse. The vast majority of cases of native valve IE are now caused by *Staphylococcus, Streptococcus,* or *Enterococcus* species.[24] Other much less common organisms causing native valve IE include gram-negative bacilli and HACEK (*Haemophilus*, *Actinobacillus*, *Cardiobacterium*, *Eikenella*, *Kingella* species) organisms. In IDUs, *S aureus* is the responsible organism in >80% of IDU-related tricuspid valve IE cases.[24] Less commonly, IDU-related tricuspid valve IE is due to *Pseudomonas* or *Candida* species.[25] Following prosthetic heart valve insertion, microbial etiology for IE varies with time after surgery. In the past, prosthetic valve IE was classified as early (<6 weeks) or late following surgery. However, more recently, three distinct postoperative intervals of early (<2 months), mid (2-12 months), and late (>12 months) have been identified.[26] Early prosthetic valve IE is usually caused by nosocomial organisms such as *Staphylococcus* species and gram-negative bacilli, whereas mid-term infections involve nosocomial organisms and more traditional organisms of native valve IE, and the microbiology of late prosthetic valve IE parallels that of native valve IE with Viridans Streptococci, *Staphylococcus* species, and *Enterococcus* species accounting for most cases.[26] Infections of intracardiac devices, such as pacemakers and defibrillators, are caused by *Staphylococcus* species in the vast majority of cases.[27]

Investigation into the cell biology of host-microorganism interactions has advanced our understanding of the development of IE. Sites of endothelial damage are a favorable substrate for platelet-fibrin deposition, which then may serve as a matrix for bacterial adhesion. Various molecules are involved in this process. It has been shown that *Streptococci* species, which produce specific cell surface dextrans and glucans, are more frequently associated with IE.[28] Adhesion receptors on various microorganisms also bind to endothelial fibronectin to facilitate the development of IE.[28] In addition, *S aureus* may also express factors that bind to fibrinogen in platelet thrombi and stimulate the production of tissue factor by endothelial cells in order to promote bacterial adhesion.[28] Future work in this area will improve our understanding of the pathogenesis of IE and potentially lead to targets for pharmacologic therapy.

Diagnosis

IE is frequently considered in the differential diagnosis of patients presenting with fever, weight loss, or other constitutional symptoms. In patients with a confirmed diagnosis of IE, fever is the most common presenting symptom in approximately 60% to 90% of cases, although this is less common in elderly patients.[29] The frequency of

TABLE 1

Summary of Clinical Findings With IE

Cardiac	Heart murmur (80%-85%)
Neurologic	Altered mentation (10%-20%) Headache (15%-40%) Focal neurologic deficit (30%-40%)
Cutaneous	Splinter hemorrhages (5%-15%) Janeway lesions (6%-10%) Osler's nodes (7%-23%) Petechial lesions (10%-40%)
Systemic	Fever (60%-90%) Weight loss (25%-35%) Musculoskeletal pain (15%-40%)

IE, infective endocarditis.

associated clinical findings in IE is summarized in Table 1. A heart murmur is reported in 80% to 85% of cases of endocarditis.[26] This may be subtle in cases of IE involving the aortic valve with acute severe aortic regurgitation with the rapid equalization of pressures between the aorta and left ventricle, resulting in a soft, short duration diastolic murmur. Similar findings with a subtle murmur may also be observed with acute severe mitral regurgitation. Several classic cutaneous manifestations of IE that have been recognized for over a century are being seen with less frequency as patients present to medical attention earlier. These include splinter hemorrhages, though these are so nonspecific that they were not included in the Duke Criteria. In general, splinters in the proximal portion of the nailbed are less likely to be from injury than those in the distal portion. Other lesions occasionally observed include Janeway lesions, conjunctival or mucosal hemorrhages, which are all nonpainful embolic events, and Osler's nodes, which are an immunologic reaction distinguished by tender lesions on the distal pads of the fingers or toes. Left upper abdominal pain should suggest splenic infarction or splenic abscess. Roth spots may be observed on the retina. Neurologic symptoms, with embolic stroke being most common, are reported in one-third to one-half of IE patients, but nonspecific muscle and joint pain may also be evident in some patients. Renal dysfunction also commonly occurs with IE. From a pathophysiologic perspective, renal embolic events and immune complex glomerulonephritis are responsible for the majority of cases of renal insufficiency associated with IE.[30]

Many of these features have been used to develop diagnostic criteria to confirm IE. The latest, the Duke Criteria, were originally published in 1994 and subsequently have been modified and validated in several populations.[5,31-36] The rationale for the Duke Criteria diagnostic algorithm rests on demonstrating evidence of infection with a characteristic microorganism and evidence of valve, implanted cardiac device, or intracardiac infection. These characteristics are considered the major criteria (Table 2). Additional supporting evidence of IE from the various systemic manifestations, associated inflammatory markers, and from known predisposing conditions is included in the minor criteria. The diagnosis of definite IE depends on the presence of pathology evidence or two major criteria, one major and three minor criteria, or five minor criteria.[34] Possible IE is present when one major and one minor criterion or three minor

TABLE 2

Modified Duke Criteria for the Diagnosis of IE

Major Growth of typical bacterium for IE from two separate blood cultures:

- Viridans streptococci
- *Streptococcus bovis*
- HACEK organism
- *Staphylococcus aureus*
- Community-acquired enterococci

Persistent positive blood cultures with a bacterium consistent with IE

- 2 positive blood cultures $>$ 12 h apart
- 3 of 3 or a majority of $\geq$ 4 blood cultures

Coxiella burnetti IgG titer $>$1:800 or growth from blood culture

Endocardial involvement

Echocardiographic characteristic

- Oscillating mass
- Abscess
- New evidence of prosthetic valve dehiscence

New murmur of valve regurgitation

Minor Predisposing condition

- IV drug abuse
- Prior valve disease

Fever $>$ 38°C

Immunologic manifestation

- Osler's nodes
- Glomerulonephritis
- Roth's spots
- Positive rheumatoid factor serology

Vascular manifestation

- Embolic event
- Janeway lesion
- Mycotic aneurysm
- Intracranial hemorrhage

Microbiologic data not meeting major criteria

HACEK, *Haemophilus, Actinobacillus, Cardiobacterium, Eikenella, Kingella* species; IE, infective endocarditis; IgG, immunoglobulin G; IV, intravenous.

criteria are present.[34] A status of rejected IE is assigned when an alternative diagnosis has been made, complete resolution of findings suggesting IE occurs with ≤ 4 days of antibiotic treatment, or there is absence of pathologic evidence for IE on a surgical or autopsy specimen following ≤ 4 days of antibiotic treatment.[34] In the future, other markers, including C-reactive protein, which has been associated with adverse outcomes when persistently elevated in IE,[37] procalcitonin level, which identifies the presence of a bacterial infection,[38] and molecular diagnostics, including ProteinChip arrays, may play a confirmatory role in the diagnosis of IE.[39, 40]

Complications

Complications include valvular/myocardial dysfunction, embolization, or inflammatory/immune-mediated sequelae. Congestive heart failure (HF) is the most common complication of IE and occurs in approximately 50% to 60% of cases.[25] Endocarditis involving the aortic valve more often than the mitral or tricuspid valve results in HF.[41] Acute mitral regurgitation with IE is tolerated better from the hemodynamic standpoint as it results in left ventricular (LV) afterload reduction despite the LV volume overload.[42] Conversely, acute aortic regurgitation is associated with both LV pressure and volume overload. Premature closure of the mitral valve may occur due to the rapid elevation in the LV diastolic pressure and has been shown to signal the need for early surgical intervention (Figure 2).[24]

The next most frequent complication is embolization, with stroke

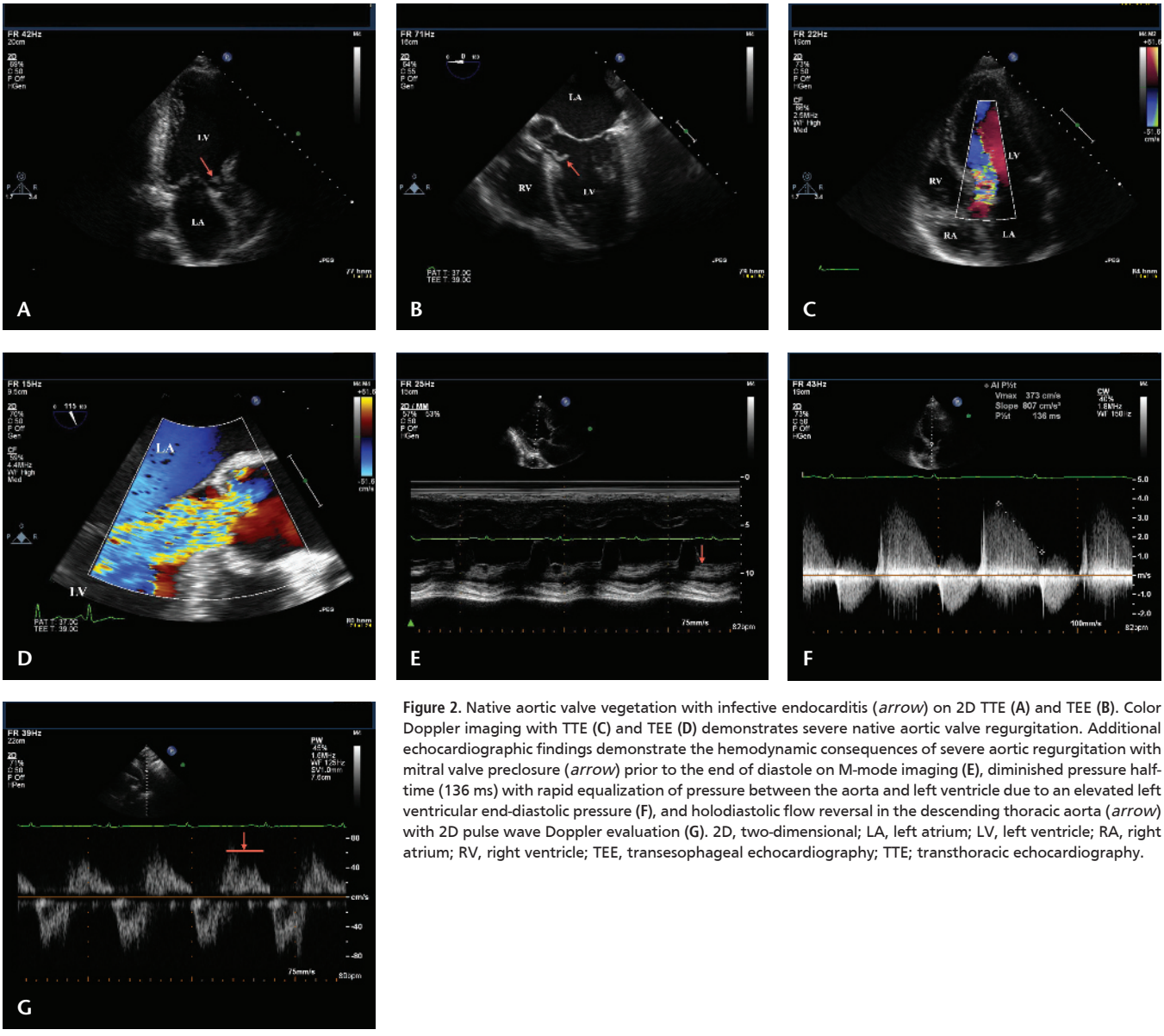


Figure 2. Native aortic valve vegetation with infective endocarditis (*arrow*) on 2D TTE **(A)** and TEE **(B)**. Color Doppler imaging with TTE **(C)** and TEE **(D)** demonstrates severe native aortic valve regurgitation. Additional echocardiographic findings demonstrate the hemodynamic consequences of severe aortic regurgitation with mitral valve preclosure (*arrow*) prior to the end of diastole on M-mode imaging **(E)**, diminished pressure half-time (136 ms) with rapid equalization of pressure between the aorta and left ventricle due to an elevated left ventricular end-diastolic pressure **(F)**, and holodiastolic flow reversal in the descending thoracic aorta (*arrow*) with 2D pulse wave Doppler evaluation **(G)**. 2D, two-dimensional; LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle; TEE, transesophageal echocardiography; TTE; transthoracic echocardiography.

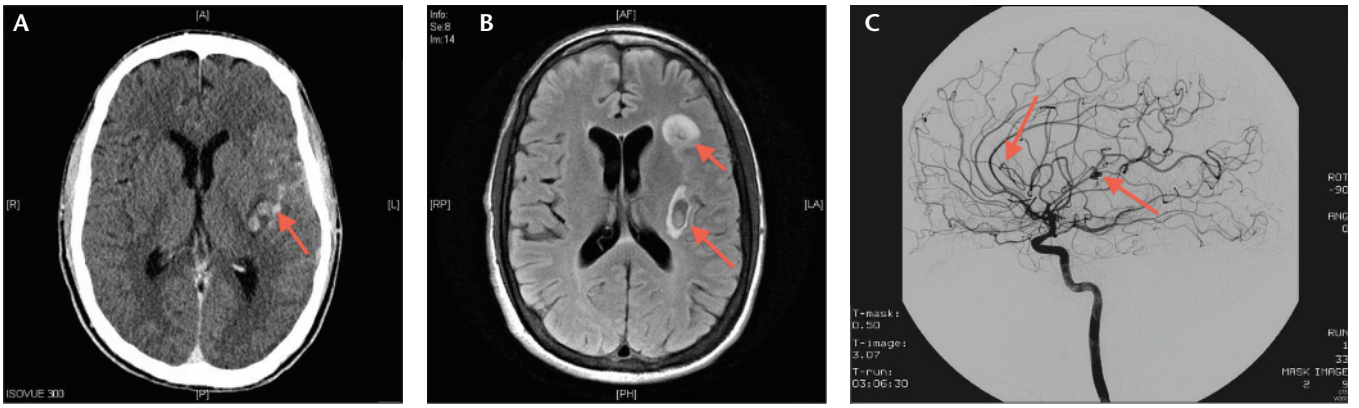


Figure 3. Mycotic aneurysm with rupture and intracranial hemorrhage (*arrow*) on brain computed tomographic imaging **(A)**. Brain magnetic resonance imaging **(B)** showing intracranial hemorrhage (*arrow*) from a ruptured mycotic aneurysm in the same patient. Cerebral angiogram **(C)** from this patient showing the mycotic aneurysms (*arrows*) of the M2 and M3 segments of the left middle cerebral artery.

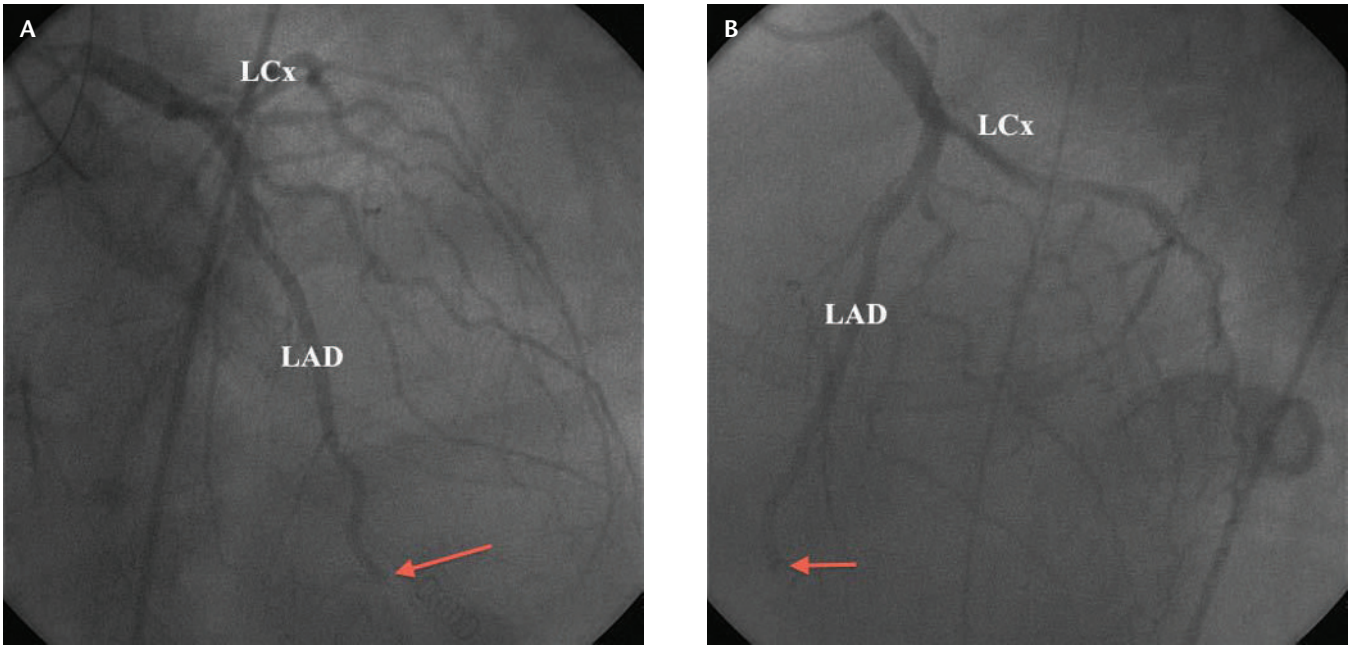
the greatest concern. In 14% of patients with IE a central nervous system (CNS) embolic event is the presenting feature.[43] Stroke may be due to large vessel occlusion or to a mycotic aneurysm, likely due to embolic occlusion of the vasa vasorum (Figure 3). Emboli are more frequent in mitral valve IE compared with aortic valve IE.[44,45] The risk for an embolic event with IE is highest prior to diagnosis and at the initiation of antimicrobial therapy; it subsequently declines quickly once the patient is on appropriate antibiotic therapy.[46] Over the past few years, two small studies of patients with definite aortic or mitral valve IE revealed evidence of subclinical embolic events on brain magnetic resonance imaging (MRI) in 30% to 48% of patients.[47,48] Embolic events may also be noted in the liver, spleen, kidneys, extremities, vertebral bodies, and coronary arteries (Figure 4). Septic pulmonary emboli may occur with tricuspid valve IE or be related to an intracardiac device infection. Additionally, extension of the original focus of infection may lead to abscess formation, valve leaflet perforation, fistula formation, or prosthetic valve dehiscence.

Inflammatory and immune-mediated complications are also well characterized in association with IE. These include renal insufficiency from immune complex-mediated glomerulonephritis and inflammatory-mediated myalgias, arthralgias, and tenosynovitis.

Echocardiography in the Diagnosis of IE and IE-Related Complications

Echocardiography is integral to the diagnosis of IE and is a component of the major criteria in the Duke Criteria. However, as with

Figure 4. Coronary angiography with anteroposterior cranial angulation **(A)** and left anterior oblique cranial angulation **(B)** showing distal LAD coronary artery cut-off (*arrow*) from embolism of an IE vegetation. IE, infective endocarditis; LAD, left anterior descending coronary artery; LCx: left circumflex coronary artery.



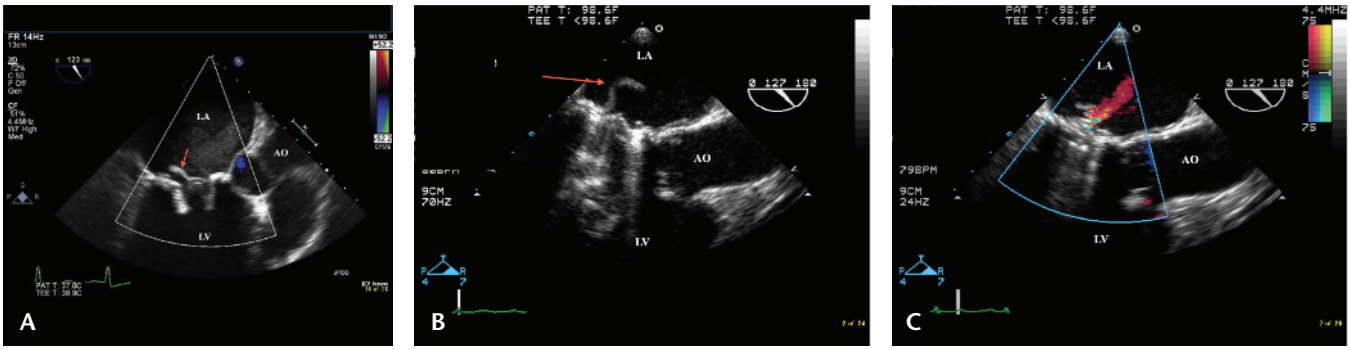


Figure 5. Bioprosthetic mitral valve vegetation **(A)** with infective endocarditis visualized by transesophageal echocardiography. Prosthetic bileaflet mechanical mitral valve infective endocarditis vegetation visualized by transesophageal echocardiography **(B)** with prosthetic mitral regurgitation shown by color flow Doppler imaging **(C)**. AO, proximal ascending aorta; LA, left atrium; LV, left ventricle.

any diagnostic test, the utility of the test is related to the pretest probability of the disease in question. Several years ago, it was reported that, in patients without evidence of a vasculitic/embolic event, central venous catheter, recent history of IDU, prosthetic heart valve, or positive blood cultures, there was a zero probability of transthoracic echocardiography (TTE) evidence for IE.[49] Transesophageal echocardiography (TEE) is more sensitive and specific for detecting a vegetation than TTE. For TTE, the sensitivity is 46% and the specificity is 95%, whereas with TEE the sensitivity is 93% and the specificity is 96%.[25] Furthermore, TEE may be necessary for a complete imaging evaluation. In patients with prosthetic heart valves, TEE may be necessary to fully evaluate the valve due to artifact and acoustic shadowing from the prosthetic material (Figure 5).

Additional analysis led to examining the cost effectiveness of a diagnostic strategy of initial TTE versus TEE. In one such study, it was reported that an initial diagnostic approach using TEE was superior to an algorithm with initial TTE and subsequent TEE or empiric antibiotic therapy alone.[50] Another study suggested that TEE was associated with greater cost effectiveness in patients with catheter-associated *S aureus* bacteremia than an empiric course of 2 or 4 weeks of antibiotic therapy.[51] In addition, TEE provides improved imaging in patients with prosthetic valves, suspected paravalvular abscess, or in patients with poor sound transmission (obesity, lung hyperinflation). The indications for TEE in addressing potential complications is summarized in Table 3.

This use of both TTE and TEE has also been addressed by the most recent update to the American College of Cardiology (ACC)/American Heart Association (AHA) Valvular Heart Disease Guidelines.[24] Class I indications for TTE and TEE are listed in Table 4.

During an echocardiographic examination of a patient with suspected IE, there are several salient features to address. First, a thorough evaluation for the presence of a mobile vegetation on a valve leaflet or intracardiac device should be performed. When the diagnosis

TABLE 3

Complications of IE	
Valvular/myocardial dysfunction	Congestive heart failure Valve regurgitation Fistula formation Leaflet perforation Prosthetic valve dehiscence Abscess formation Conduction abnormalities
Embolic	Stroke Mycotic aneurysm Central nervous system abscess Spleen Kidneys Extremities Vertebral bodies Coronary arteries Lungs (right-sided IE)
Inflammatory/immune-mediated	Glomerulonephritis Tenosynovitis

IE, infective endocarditis.

TABLE 4

Class I ACC/AHA Indications for TTE and TEE in the Evaluation of IE

TTE	Detection of vegetations for diagnosis Assessment of valve and ventricular dysfunction with definite IE Diagnosis of mechanical cardiac complications of IE Repeat imaging of high-risk patients with definite IE
TEE	Inconclusive TTE results with symptomatic IE Equivocal TTE results with suspected IE for additional supportive diagnostic evidence Evaluation of mechanical complications of IE Imaging of suspected prosthetic valve IE Preoperative and intraoperative evaluation with definite IE

ACC, American College of Cardiology; AHA. American Heart Association; IE, infective endocarditis; TEE, transesophageal echocardiography; TTE, transthoracic echocardiography.

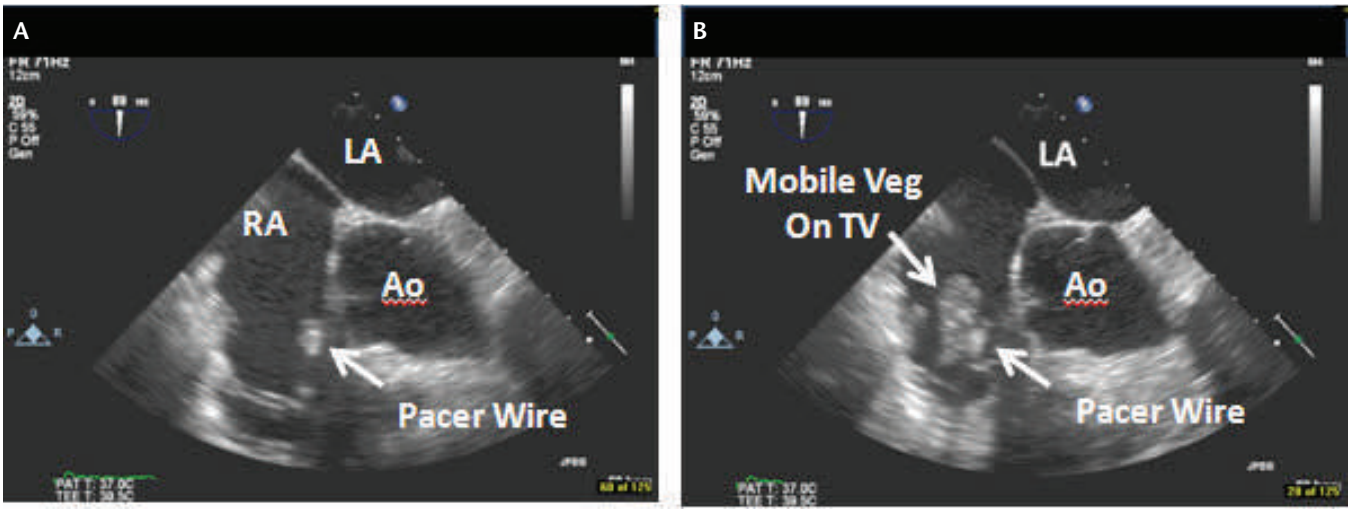
of device-related IE is suspected, careful evaluation of pacemaker and defibrillator wires along their entire course with particular attention to the superior vena cava-right atrial junction and where the leads cross the tricuspid valve is imperative (Figure 6). Also, it is important to note that not all mobile masses represent IE. Other explanations for mobile masses include marantic endocarditis, annular or valvular calcium, Libman-Sacks endocarditis, ruptured chordae, cardiac tumors (eg, fibroelastomas), and Lambl excrescences on native valves along with suture material on prosthetic valves. Echocardiography also provides ventricular dimensions and function, an estimate of the severity of the valvular regurgitation (or stenosis), an estimate of pulmonary artery pressure, and a measure of the ventricular diastolic properties.

Vegetation size can also be estimated by echocardiography. Though controversial, some studies have shown a correlation between vegetation size and risk of thromboembolism.[52-54] A vegetation size >1 cm has been used as a threshold of higher risk for embolization, acknowledging that significant interobserver variability exists regarding the measurement of vegetations.[55]

Abscess formation from extension of infection into adjacent myocardium is associated with increased morbidity and mortality when it complicates IE. It is more common with IE of the aortic valve, where it may be initially detected by electrocardiographic (ECG) abnormalities due to damage of adjacent conduction tissue. In aortic valve endocarditis, a new prolongation of the ECG PR interval should be presumed to be due to an aortic abscess until proven otherwise. Extension of infection into paravalvular tissue is also associated with significantly higher operative mortality.[56] When an abscess is present, an echo-lucent space is often seen on echocardiography, with or without evidence of color Doppler flow into the space. TEE is the recommended imaging modality for evaluation if abscess is suspected. One clue to the diagnosis is the presence of persistent bacteremia.

In rare cases, destruction of surrounding tissues with IE leads to fistula formation between cardiac chambers, such as with sinus of Valsalva rupture into a

Figure 6. Native tricuspid valve and pacemaker lead vegetations on TEE during diastole **(A)** and systole **(B)**. Ao, aortic valve; LA, left atrium; RA, right atrium; TEE transesophageal echocardiography.



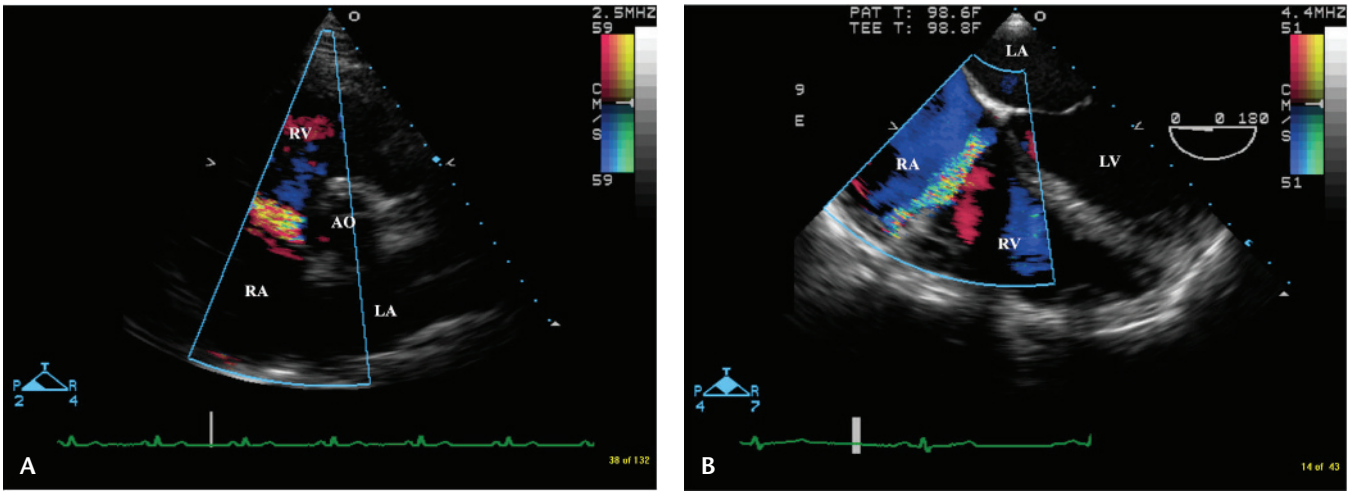


Figure 7. Fistula from the noncoronary sinus of Valsalva into the RA seen on TTE **(A)** and TEE **(B)** with color flow Doppler imaging. AO, aortic valve; LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle; TEE, transesophageal echocardiography; TTE; transthoracic echocardiography.

cardiac chamber or the pericardium (Figure 7). Initially, this may be suggested by a new continuous murmur on physical examination and/or deteriorating hemodynamic status. The diagnosis is confirmed with echocardiography using transducer sweeps and color-flow Doppler imaging to search for potential abnormal communication between cardiac structures. This approach should be used in the echocardiographic examination of any patient with IE. The presence of a fistula is an accepted indication for emergency surgery.

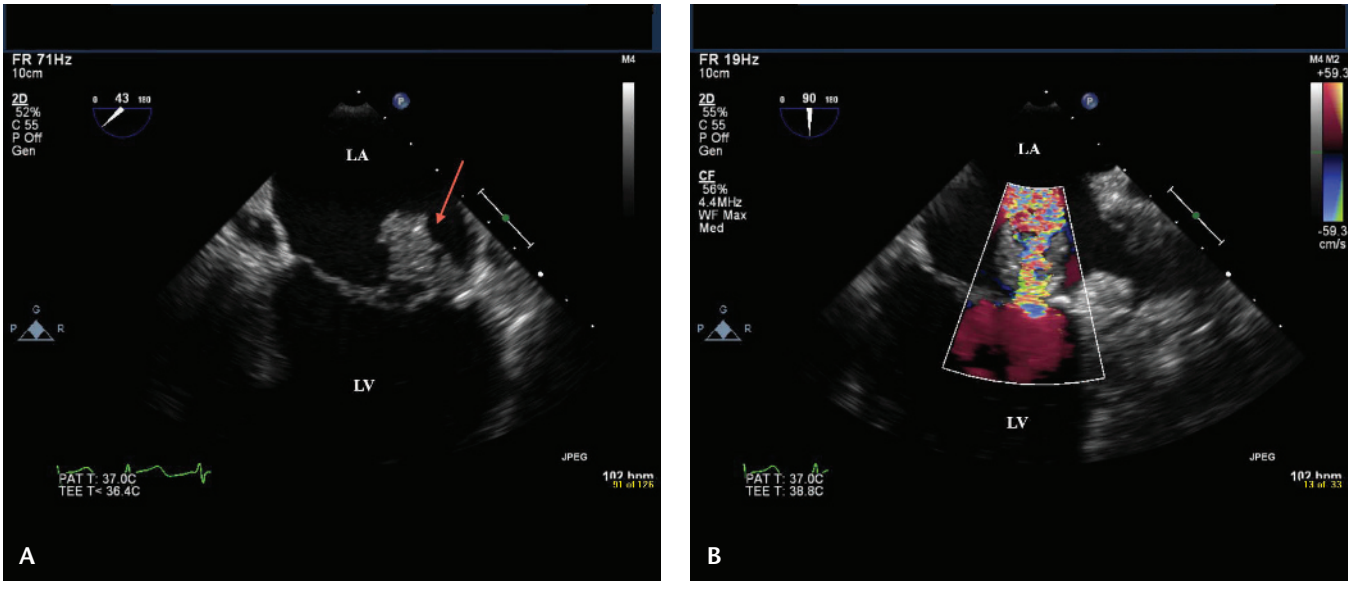
The echocardiographic examination should also search for any evidence of valve leaflet perforation (Figure 8). This is often associated with a virulent microorganism such as *S aureus*. Valve leaflet perforation is commonly linked to worsening regurgitation and hemodynamic status.

Dehiscence of a prosthetic valve is defined as rocking of a prosthesis on imaging $>$ 15 degrees in any plane. Quite frequently there is significant paravalvular regurgitation and concomitant hemodynamic compromise. Prosthetic valve dehiscence is regarded as an urgent indication for cardiac surgery with IE.

Treatment and Outcomes

IE is associated with significant complications and in-hospital mortality. Empiric antibiotic coverage should be instituted as soon as the diagnosis is considered and after the requisite sets of blood cultures are obtained. The growth of an isolated organism and its pattern of antibiotic sensitivity are critical to guiding pharmacotherapy decisions. Hence, infectious disease

Figure 8. Native mitral valve IE vegetation (*arrow*) on 2D TEE **(A)** with leaflet perforation seen by color flow Doppler imaging **(B)**. 2D, two-dimensional; IE, infective endocarditis; LA, left atrium; LV, left ventricle; TEE, transesophageal echocardiography.



consultation is essential to the care of a patient with IE.

A detailed discussion of the specific antibiotic regimens and duration of treatment for the various microorganisms that cause IE is beyond the scope of this review but have been reviewed in the recent ACC/AHA guideline documents[24] and are available in the 2012 guidelines from the British Society of Antimicrobial Therapy.[57] In general, native valve endocarditis should be treated with 4 weeks of IV antibiotic therapy and prosthetic valve infection for 6 weeks. Many patients can complete the course of treatment for IE as outpatient therapy after initial hospitalization. Successful resolution of infection without an increase in adverse events has been reported with outpatient antibiotic infusion therapy at home for patients with Viridans streptococcus, *S aureus*, and *Enterococcal* IE.[58-61] It is also worth mentioning that since publication of the aforementioned treatment guidelines, long-term treatment data for Q fever IE have been reported.[62] These data suggest that, in Q fever endocarditis, an 18-month duration of therapy for native valve and 24 months for prosthetic valve infection results in successful resolution.[62] Recurrences are known to occur, however.

Several recent updates in the treatment of IE have also been reported. Approximately 5 years ago, an important publication documented the noninferiority of the bactericidal antimicrobial agent, daptomycin, in the management of patients with *S aureus* bacteremia with or without IE in a randomized trial.[63] Furthermore, there was a lower incidence of renal injury with daptomycin therapy.[63] Subsequently, additional research with daptomycin has suggested a role in the management of right-sided IE as well.[64] The utility of daptomycin in the outpatient management of patients with IE has also been suggested by a recent analysis.[59] From the cost-effectiveness perspective, daptomycin has a similar economic cost as vancomycin plus gentamicin therapy for patients with methicillin-resistant *S aureus* bacteremia and/or IE.[65] At the present time, daptomycin is not included in the most recent version of the ACC/AHA IE management guidelines. The potential endorsement of daptomycin for the treatment of IE by future society guideline statements is likely.

Anticoagulants have not been shown to improve outcome in IE[66] and the medical management of patients with IE may be complicated for those maintained on chronic warfarin anticoagulation therapy. Most clinicians discontinue warfarin therapy upon diagnosis of IE, and once the international normalized ratio is <2.0, anticoagulate with unfractionated or low molecular weight heparin. If valve surgery is not planned, then warfarin may be restarted after 7 days of antimicrobial therapy. There are recent data suggesting that continuing the warfarin may not result in an increase in CNS bleeding complications.[67] Imaging of the brain with a computed tomography scan or MRI should be performed to exclude a CNS bleed if the patient develops any focal neurologic symptoms or severe headache.

Surgery

The appropriate use and timing of surgery in patients with IE is an important clinical question that has never been subjected to study with randomized clinical trials. Hence, most of the data from which to draw conclusions regarding valve surgery for IE are derived from observational data with the inherent selection bias that is problematic with this type of analysis. Several observational studies have shown that the mortality benefit of valve surgery appears to be most relevant in patients with moderate to severe HF or those in the highest propensity quintile for predicted surgery based on baseline characteristics.[68,69] In addition, an analysis published in 2010 of prospective, multicenter, international data on 1552 patients with definite IE revealed a statistically significant survival benefit for patients having valve surgery during the initial hospitalization compared with medical therapy alone. This result persisted after careful statistical evaluation using propensity matching, survivor bias adjustment, and instrumental variable adjustment.[70]

Guideline recommendations for the use of surgery in patients with IE have been published in the most recent ACC/AHA Valvular Heart Disease Management document and are summarized in Table 5.[24] Most experts consider symptomatic HF with left-sided IE due to valve dysfunction or other mechanical complication a clear indication for valve surgery. In addition, clinicians often consider on a case-by-case basis surgical intervention for recurrent embolic events, for a mobile vegetation >10 mm, or for organisms known to be resistant to usual medical therapy.

Contemporary research into optimal management strategies for patients with IE has shown the effectiveness of an organized, multidisciplinary management approach. A group of investigators created a consensus algorithm for the medical and/or surgical management of IE patients using guideline statements and the input of cardiologists, infectious disease consultants, and cardiac surgeons. This work demonstrated a decrease in mortality, renal failure, deaths from embolic events, and multisystem organ failure when compared with outcome data obtained a few

TABLE 5

Class I ACC/AHA Indications for Surgery in Patients With Native or Prosthetic Valve IE

Acute IE with symptomatic HF from valve dysfunction (stenosis or regurgitation)
Acute mitral or aortic regurgitation with evidence of increased left atrial or left ventricular end-diastolic pressures
Fungal IE or infection with other antimicrobial-resistant organism
Complications of IE
Abscess
Fistula
Valve leaflet perforation
Prosthetic valve dehiscence
Heart block

ACC, American College of Cardiology; AHA, American Heart Association; HF, heart failure; IE, infective endocarditis.

years earlier at the same institution prior to the use of this systematic approach.[71]

Prognosis

Even with modern antimicrobial therapy and the use of valve surgery in selected patients, mortality in-hospital and following hospital discharge remains quite high. Mortality has been observed at 15% to 20% in-hospital and 30% to 40% at 1 year even in the modern era.[25] Right-sided endocarditis, though much less common than left-sided, carries a better prognosis with in-hospital mortality $< 10\%$,[72] except in patients with AIDS, in whom mortality approaches 50%.[73] Several investigators have performed analyses in an attempt to better comprehend the risk of death in patients with IE. One such study demonstrated that an embolic event, diabetes mellitus, and *S aureus* infection independently predicted in-hospital mortality with IE.[74] Likewise, others have reported that altered mental status, Charlson comorbidity index ≥ 2 (scoring system to predict 1-year mortality based on the presence of a variety of coexisting medical conditions), moderate to severe HF, *S aureus* or other nonviridans infection, or medical therapy without surgery predicted mortality using a scoring system at 6 months following diagnosis.[75] Other work has shown that patients with end-stage renal disease on hemodialysis also have an increased risk of death with IE.[76,77] For patients with prosthetic valve IE, a single-center series published in 2010 of 122 patients demonstrated an in-hospital mortality rate of 29%, which was independently associated using multivariate logistic regression analysis with the presence of HF and echocardiographic evidence of abscess.[78] A recent large-scale analysis of 19,543 surgeries performed for IE in the Society of Thoracic Surgeons database from 2002 to 2008 was used to develop risk scores for operative mortality and a 30-day composite of mortality and major morbidity with C-statistics of 0.757 and 0.728, respectively; it is summarized in Figure 9.[79] With more than 28 risk factor points as defined in the table within the figure, there was a $> 50\%$ 30-day combined morbidity and mortality.[79]

Special Considerations

Cardiac Device Infections

With advances in medical device technology and the increasing life expectancy of the elderly population, there has been an increase in the number of implanted cardiac devices and device-related infections. As a group, these are often referred to as cardiovascular implantable electronic device (CIED) infections and range from isolated pocket infections to device-related IE. Analysis of Medicare databases from the 1990s showed a 42% increase in cardiac device procedures, but a 124% increase in device infections during the same decade.[80] This trend has continued with more recent work using the National Hospital Discharge Survey database, which reports a 12% increase in cardiac device implantation from 2004 to 2006 and a 57% increase in cardiac device-related infection (Figure 10).[81] Not surprisingly, device-related IE is associated with increased morbidity, mortality, and financial burden.[82]

The microbiology of CIED is related to coagulase-negative staphylococci or *S aureus* infection in over two-thirds of cases.[27] In a recent analysis of a small cohort of patients with *S aureus* bacteremia and an implanted cardiac device, 35% had evidence for a pocket infection or device-related IE and 19% had evidence for device-related IE.[83] Therefore, empiric antimicrobial therapy should include coverage for the aforementioned organisms with subsequent tailoring of therapy contingent on microbial culture and sensitivity data and infectious disease consultant recommendations. Additional decisions to be considered in the management of CIED involve device explant and timing of new device implant, if necessary.

Risk Factor	Points for Major Morbidity and Operative Mortality
Operative status of emergency, salvage, or with cardiogenic shock	17
Creatinine > 2.0 or renal failure	12
IABP or inotropes preoperatively	12
Surgery on more than one valve	7
Insulin-dependent diabetes mellitus	7
Active IE	7
NYHA class IV status	6
Operative status of urgent or emergency without cardiogenic shock	6
History of prior CABG	5
History of prior valve surgery	5
Female	5
Arrhythmia	5
Age > 60 years	4
Body surface area > 1.9 cm^2	1

A

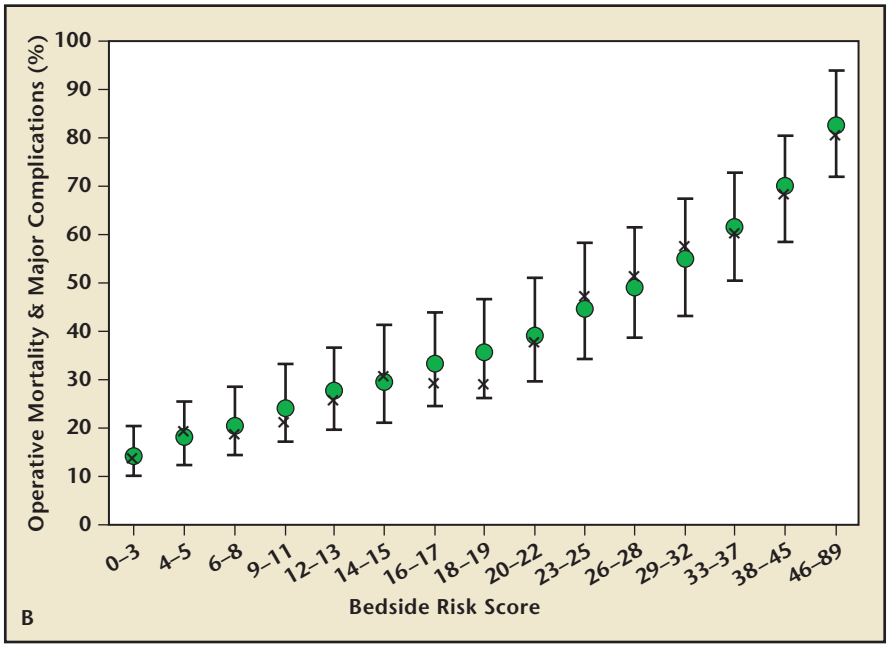


Figure 9. Scoring system for predicting 30-day morbidity and mortality in patients with IE (A) and corresponding risk with an increasing score depicted in (B). CABG, coronary artery bypass graft; IABP, intra-aortic balloon pump; IE, infective endocarditis; NYHA, New York Heart Association. Reprinted from *The Journal of Thoracic and Cardiovascular Surgery*, Volume 141, Gaca JG et al, "Outcomes for endocarditis surgery in North America: a simplified risk scoring system," pages 98-106, 2011, with permission from Elsevier.[79]

Several risk factors have been identified through multivariate analyses to be independently associated with intracardiac device infection. In one study, history of immunosuppression, history of chronic corticosteroid use, hemodialysis, and another focus of infection were independent predictors of CIED IE.[84] A small study of patients having biventricular pacemaker placement for cardiac resynchronization therapy (CRT) reported a device infection incidence of 1.7% per year.[85] CRT device infection was independently associated with longer procedure time, hemodialysis, repeat procedure after device implantation, and CRT-implantable defibrillator versus CRT-pacemaker placement.[85] Additionally, for those who do develop a device-related infection, multivariate analysis demonstrated a higher in-hospital mortality with older age and renal failure.[86]

Device-related IE management guidelines were updated and published in 2010 by the ACC/AHA; Class I recommendations are summarized in Table 6.[87] Along these lines, a recent retrospective analysis suggests that percutaneous lead extraction is safe even if a lead vegetation is present.[88] Finally, the Class I recommendation on reimplantation advises careful assessment of the need for an intracardiac device, and if an indication is present, to place the device at a distant site from the prior location. A Class IIa recommendation is given to implantation of a new device after 72 hours of negative blood cultures for device infection, or 14 days with valvular IE.[87]

IE Prophylaxis

Old traditions die hard, and that is so with endocarditis prophylaxis. In fact, bacteremia from dental procedures pales in comparison with the bacteremia that occurs with routine activities such as eating or teeth brushing. In fact the 1-year cumulative exposure to bacteremia from daily activities is estimated to be 5.6 million times that of a single dental extraction.[89] If one examines the absolute risk of developing endocarditis, the highest-risk group includes those with a prosthetic valve implanted due to prior endocarditis. Even in that group, the absolute risk is only 1 in 95,000.[89] In addition, there are no data supporting the idea that prophylaxis actually works. In a 2-year

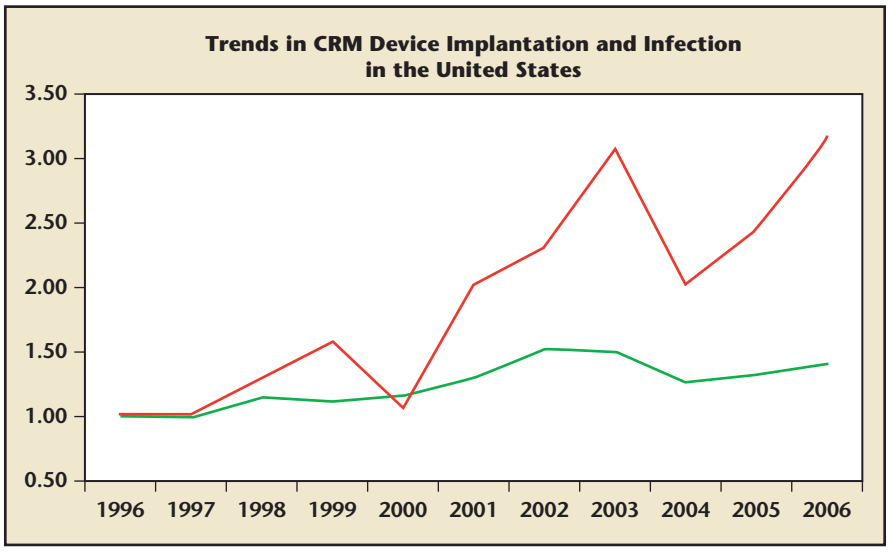


Figure 10. Rates of cardiac implantable electronic device infections (*red line*) plotted in relation to the overall number of devices implanted (*green line*) for the years 1996-2006. Reprinted with permission from Voigt A et al.[81]

case-control study by Van der Meer and colleagues,[90] 20 IE cases were found that occurred after dental procedures; in 5 of those cases, appropriate antibiotics were administered during the dental procedure.

Based on data such as these, an updated set of guideline recommendations from the ACC/AHA was published in 2007 that narrowed the spectrum of conditions and procedures for which IE antibiotic prophylaxis was indicated. The four conditions for which IE prophylaxis was recommended are a history of prior IE, the presence of a prosthetic heart valve or valve repair, cardiac transplant valvulopathy (an incredibly uncommon entity), and congenital heart disease with unrepaired cyanosis, residual shunt adjacent to repair with prosthetic material, or within the first 6 months of surgical or percutaneous repair.[89] Moreover, in the 2008 ACC/AHA management of adult congenital heart disease guidelines, antibiotic prophylaxis is also recommended (Class IIa) for the highest-risk patients with prosthetic heart valves, prosthetic material used for cardiac repair, or with unrepaired or palliated (surgical shunt/conduit) cyanotic congenital disease prior to vaginal delivery.[91]

TABLE 6

Class I ACC/AHA Recommendations for the Management of Cardiac Implantable Electronic Device Infections and IE

Diagnosis

- Obtain two sets of blood cultures prior to initiation of antimicrobial therapy
- Gram stain and culture of generator pocket tissue and lead tip at explant
- TEE with positive blood cultures or negative cultures and recent antibiotic therapy
- TEE for careful evaluation of left-sided heart valves for evidence of concomitant valvular IE

Management

Isolated pocket infection: 10-14 days of antibiotic therapy after device removal

Bacteremia and a device-related infection: minimum of 14 days after device removal

Device-related IE: 4-6 weeks of antibiotic therapy

Device and lead removal

- Definite CIED infection with a complicated pocket infection and abscess/erosion/or sinus tract even without evidence of lead infection
- Valvular IE even in the absence of obvious lead or device infection
- Unexplained *Staphylococcus* bacteremia

New device implant

- Assess need for intracardiac device
- Place new device at a site distant from prior device

ACC, American College of Cardiology; AHA, American Heart Association; CIED, Cardiac Implantable Electronic Device; IE, infective endocarditis; TEE, transesophageal echocardiography.

Aside from this exception for vaginal delivery for high-risk patients, the use of antibiotics is now only recommended prior to invasive dental procedures and not prior to routine bronchoscopy, gastrointestinal, genitourinary, or skin procedures.[89] The specific antibiotic prophylaxis regimens are also detailed in the guideline statement.[89] The European Society of Cardiology published a similar document in 2009 that excludes procedures other than invasive dental work.[92] The British National Institute for Health and Clinical Excellence no longer recommends antibiotic prophylaxis for any patient population or procedure.[93] The reality is that there are few data that any regimen of prophylaxis is meaningful to prevent IE.

Conclusions

Although advances in modern medicine have improved our ability to accurately diagnose IE, the morbidity and mortality associated with this infectious disease remain quite high. Observational data suggest that valve surgery lowers mortality in patients with congestive HF due to valve dysfunction related to IE. Management of patients with IE should involve a cooperative effort among cardiologists, infectious disease consultants, and cardiac surgeons. Guidelines to prevent endocarditis restrict prophylactic antibiotics to patients with select risk factors undergoing invasive dental procedures. Future work will continue to improve our understanding of the optimal treatment strategy (medical therapy or medical and surgical therapy) along with the timing of surgical intervention for individual patients with endocarditis. ■

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MAIN POINTS

- Infective endocarditis (IE) is associated with significant morbidity and mortality. More than half of IE cases in the United States and Europe are diagnosed in patients older than age 60 years, and many of these cases are related to the increasing use of intracardiac devices such as pacemakers and defibrillators.
- Factors that predispose individuals to IE include indwelling catheters, poor dentition, diabetes mellitus, AIDS, chronic skin infection, alcoholic liver cirrhosis, solid organ transplant, genitourinary infections, and intravenous drug use, among others.
- Diagnostic criteria have been developed to confirm IE. The rationale for the Duke Criteria diagnostic algorithm rests on demonstrating evidence of infection with a characteristic microorganism and evidence of valve, implanted cardiac device, or intracardiac infection (major criteria). Additional supporting evidence of IE from the various systemic manifestations, associated inflammatory markers, and from known predisposing conditions is included in the minor criteria.
- Transthoracic echocardiography and transesophageal echocardiography are integral to the diagnosis of IE.
- IE is associated with multiple complications involving a variety of organ systems. In general, these may be categorized as valvular/myocardial, embolic, or inflammatory/immune-mediated complications.

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