Infective Endocarditis

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KEYWORDS

• Infective endocarditis • Native valve endocarditis • Prosthetic valve endocarditis

KEY POINTS

- The incidence of infective endocarditis (IE) is rising with the increased availability of prosthetic valves and intracardiac devices.
- Increasing mortality from IE among younger individuals may be attributable to higher rates of comorbid substance use.
- Staphylococcus aureus is the leading cause of IE worldwide.
- The diagnosis of IE relies on positive pathologic examination of involved tissue or the demonstration of consistent clinical, microbiologic, laboratory, and imaging findings.
- Management of IE involves prolonged antimicrobial therapy and, in certain cases, heart valve surgery or cardiac device removal.

INTRODUCTION

Centuries after descriptions of valvular vegetations first appeared in medical literature, infective endocarditis (IE) remains an uncommon but severe infection with high mortality. IE is defined as an infection of the endocardium, the vascular endothelium, a valvular prosthesis, or a nonvalvular indwelling cardiac device. A variety of clinical manifestations are possible, and positive blood cultures are the signature laboratory finding. Historically, streptococci and enterococci were the primary pathogens in IE, and patients were typically young or middle-aged with underlying rheumatic or congenital heart disease (CHD). As prosthetic valves and cardiac implantable electronic devices (CIEDs) became increasingly common, however, the epidemiology of IE shifted toward older patients with more comorbidities, particularly in industrialized nations. Along the same timeline, staphylococci emerged as the predominant pathogens. Early recognition, appropriate antibiosis, and timely surgical management, when indicated, are critical to managing this high-risk condition. This review summarizes the epidemiology, diagnostic considerations, and management options for patients with IE.

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Abbreviations	
18F-FDG	fluorine-18-fludeoxyglucose
AHA	American Heart Association
BCNIE	blood culture-negative infective endocarditis
CHD	congenital heart disease
CIED	cardiac implantable electronic device
CoNS	coagulase-negative staphylococci
ECMA	extracranial mycotic aneurysm
ESC	European Society of Cardiology
GPC	gram-positive cocci
ICH	intracranial hemorrhage
ICMA	intracranial mycotic aneurysm
IDU	injection drug use
IE	infective endocarditis
ISCVID	International Society for Cardiovascular Infectious Disease
MA	mycotic aneurysm
mNGS	metagenomic next-generation sequencing
NVE	native valve endocarditis
PCR	polymerase chain reaction
POET	Partial Oral Treatment of Endocarditis
PVE	prosthetic valve endocarditis
TEE	transesophageal echocardiography
TTE	transthoracic echocardiography

EPIDEMIOLOGY

Burden of Disease

The incidence of IE is rising, with more than 1.09 million cases diagnosed globally in 2019.[1] In the United States, the age-standardized incidence rate increased from 10.2 cases per 100,000 population in 1990 to 14.4 per 100,000 in 2019, driven by a 112.7% increase in cases among adults older than 55. The growing use of surgical and transcatheter valve replacements, CIEDs, and left ventricular assist devices is a driving factor, with prosthetic valve endocarditis (PVE) accounting for up to 30% of total IE cases and device-related IE accounting for 10%.[2]

There were 54,405 hospitalizations for IE in the United States in 2016 according to the Nationwide Inpatient Sample, an all-payer claims-based database, up from 34,488 hospitalizations in 2003. Health care expenditures for IE hospitalizations increased accordingly, from $1.58 billion in 2003 to $2.34 billion in 2016.[3] Estimates of in-hospital mortality from IE range from 15% to 30%.[4] Predictors of mortality include older age, infection with staphylococci or enterococci, PVE, presence of heart failure, vegetation size greater than 10 mm, cerebral complications, and inability to undergo cardiac surgery despite meeting guideline-recommended indications.[2,5] Though a national cross-sectional study in the United States found an overall decline in IE-related mortality from 1999 to 2020, there was an increase in mortality among 25-year to 44-year olds.[6] Death certificate data identified a significant increase in comorbid substance use disorder in that age group, suggesting that rising IE mortality among younger adults is related to the opioid crisis.

Risk Factors

Risk factors for IE include male sex, age greater than 60 years, injection drug use (IDU), poor dentition, and structural heart disease. IE is more often diagnosed in male patients, though female patients have increased risk of mortality and are less likely to be managed with cardiac surgery.[7,8] Among younger individuals, IDU and CHD drive

IE risk.[9,10] The proportion of IE cases associated with IDU nearly doubled between 2010 and 2015, increasing from 15.3% to 29.1%.[11]

Corrective cardiac procedures have improved the prognosis of CHD, allowing 95% of newborns with CHD to survive to adulthood. However, prosthetic material used in corrective procedures and residual structural abnormalities predispose adults with CHD to IE.[12] Rheumatic heart disease with mitral stenosis, once a common predisposing condition for IE among younger patients, has become less prevalent in developed countries. However, other forms of structural heart disease, including mitral valve prolapse with mitral regurgitation, aortic stenosis, and aortic regurgitation, remain important risk factors for IE.[13]

Microbiology

Gram-positive cocci (GPC) account for nearly 80% of cases of IE.[13] In the EURO-ENDO registry, a cohort of 3116 adult patients admitted for IE across 40 countries, the most common causes of IE were staphylococci (44.1%), enterococci (15.8%), oral streptococci (12.3%), and *Streptococcus gallolyticus* (6.6%).[2] *Staphylococcus aureus* is the most commonly isolated organism in both native valve endocarditis (NVE) and PVE, in IDU-associated IE, and across geographic regions.[13] *S aureus* and enterococci are associated with higher risk of mortality when compared with other organisms.[14] Among the oral streptococci, risk of IE can be further classified based on the infecting streptococcal species.[15]

The microbiology of PVE is classically stratified by the timing of infection after implantation. *S aureus* and coagulase-negative staphylococci (CoNS) are the most common culprits in the first year. Gram-negative bacilli and *Candida* are infrequent causes of PVE but may be seen in the first 2 months after implantation due to health care exposures. Beyond 1-year postimplantation, the causes of PVE more closely mirror the microbiology of NVE, with *S aureus* and streptococci isolated most frequently.[16] In a retrospective study of 780 PVE cases in the Swedish Registry on IE, however, no differences in microbiology were identified between early and late PVE. The most common causative organisms in this cohort were alpha-hemolytic streptococci (29%), *S aureus* (22%), enterococci (14%), CoNS (12%), and *Cutibacterium acnes* (6%).[17] The microbiology of PVE following transcatheter aortic valve implantation as compared with surgical aortic valve replacement is not significantly different.[18]

Less common causes of IE should be considered based on patient risk factors and exposures (**Table 1**).[19–23] HACEK organisms (*Haemophilus*, *Aggregatibacter*, *Cardiobacterium*, *Eikenella corrodens*, and *Kingella*) are fastidious, gram-negative bacteria classically known for causing blood culture-negative infective endocarditis (BCNIE). They account for less than 2% of IE cases and are associated with prosthetic valves.[13,24] Though fungal IE is rare, a recent systematic review of 250 cases estimated mortality at 40%.[25] *Bartonella* spp, *Brucella* spp, *Coxiella burnetii*, and *Tropheryma whipplei* are obligate intracellular organisms that do not typically grow on blood cultures and are implicated in BCNIE, particularly in patients with subacute presentations.

CLINICAL PRESENTATION

Cardiac and Vascular Manifestations

IE is a clinically protean condition that can affect every organ system and mimic a variety of other medical conditions. Four processes are responsible for the development of most of the clinical features: (1) infection of the involved cardiac valve; (2) embolization; (3) bacteremia and metastatic infection; and (4) immune complex formation.[26]

Table 1
Common causes of blood culture-negative infective endocarditis

Pathogen	Associated Risk Factors
HACEK organisms (*Haemophilus, Aggregatibacter, Cardiobacterium, Eikenella corrodens,* and *Kingella*)	Prosthetic valves
Non-HACEK gram-negative bacilli, including enteric organisms and *Pseudomonas aeruginosa*	IDU, nosocomial infection, malignancy, hemodialysis
Fungal organisms, including *Candida* spp and *Aspergillus* spp	IDU, immunosuppression, prior heart surgery, prosthetic valves
Bartonella spp	Homelessness, alcohol use disorder, human immunodeficiency virus (HIV), exposure to dogs, cats, and lice
Brucella spp	Consumption of unpasteurized data, exposure to bodily fluids from infected animals
Coxiella burnetii	Exposure to farm animals
Tropheryma whipplei	Preexisting valvular heart disease, immunosuppression

Patients with IE may present acutely and follow a fulminant course, or they may present more subacutely over a period of weeks to months with nonspecific symptoms such as chills, night sweats, malaise, arthralgia, weight loss, and anorexia. Although classifying IE as "acute" or "subacute" is helpful conceptually, overlapping manifestations can be seen. As a result, IE is typically classified by etiologic agent.

The most common symptoms of IE are fever and cardiac murmur, which are present in 78% to 95% and 65% to 70% of patients, respectively.[2,13] Absence of fever tends to be associated with older age or previous antibiotic therapy.[27] Valvular dysfunction from IE most frequently manifests as valvular regurgitation, and heart failure is a common complication.[2,28] The presence of conduction abnormalities in a patient with suspected or confirmed IE should raise concern for a perivalvular abscess most likely involving the aortic valve.[29] Progressive heart block and myopericarditis may arise before or during therapy.

Mycotic aneurysms (MAs) are uncommon vascular complications of IE that arise from septic embolization of vegetations to the arterial vasa vasorum, leading to spread of infection to the arterial wall with subsequent aneurysmal dilation. Arterial branching points are especially high risk for MA formation.[30] Many MAs are asymptomatic until rupture, which happens in around 50% of cases.[31] Intracranial MAs (ICMAs) are more common than extracranial MAs (ECMAs) and are associated with higher mortality. Among ECMAs, the involvement of the intra-abdominal arteries and arteries of the lower extremities is most common.[31] Because of the high mortality associated with ICMAs, cerebrospinal imaging is recommended in all patients with IE who develop headache, neurologic deficits, or meningeal signs.[30]

Embolic and Immunologic Phenomena

Major embolic events are the second most common IE complication after heart failure and occur in around 25% of cases.[2,13] Embolization occurs more frequently in patients with left-sided IE, and the involvement of the cerebral, splenic, and renal circulation is most common.[2] Patients with splenic infarction from splenic artery emboli may develop left upper quadrant pain with radiation to the left shoulder, and patients

with renal infarctions from renal artery emboli may develop microscopic or gross hematuria. Among patients with right-sided IE, pulmonary embolization may occur. Septic pulmonary emboli can be solitary or multiple peripheral or subpleural densities with variable degrees of central cavitation.

Up to 5% to 10% of patients with IE present with microembolic or immunologic phenomena.[13] Splinter hemorrhages, conjunctival hemorrhages, Janeway lesions (nontender macules on the palms and soles), Osler nodes (tender nodules on the distal fingers and toes), Roth spots (hemorrhagic retinal lesions), and immune complex-mediated glomerulonephritis may be seen. Patients with suspected IE who develop microscopic hematuria and/or proteinuria should undergo urine microscopy to evaluate for dysmorphic erythrocytes and erythrocyte casts.

DIAGNOSIS

Microbiologic, Serologic, and Molecular Studies

A positive blood culture is the most important laboratory test in diagnosing and treating IE. At least 3 blood culture sets should be collected before the initiation of antibiotic therapy, with the first and last samples drawn at least 1 hour apart.[30] Over 90% of native IE cases will have positive blood cultures.[32] Receipt of antibiotics in the preceding 2 weeks may impact blood culture positivity, particularly in the case of streptococcal IE.[33]

BCNIE is most frequently caused by recent administration of antibiotics and by intracellular organisms that cannot be cultured on standard blood culture media. The HACEK bacteria, historically a cause of BCNIE, can be isolated within 5 days using conventional automatic blood culture systems.[34] The nutritionally variant streptococci associated with IE, *Abiotrophia* spp and *Granulicatella* spp, should be suspected if gram-positive cocci grow on initial culture isolation but fail to grow on subculture. Subculture with vitamin B_6 or with cysteine may aid in their recovery.[35]

In the context of consistent epidemiologic clues and negative blood cultures, serologic testing for obligate intracellular bacteria (eg, *C burnetii*, *Bartonella* spp, and *Brucella* spp) should be performed. For patients with prosthetic valves or underlying immunocompromise, serologic testing for fungi, *Legionella* spp, and *Mycoplasma pneumoniae* can be considered.

Molecular diagnosis using real-time polymerase chain reaction (PCR) to recover specific DNA, 16S ribosomal RNA (for bacteria), or 18S ribosomal RNA (for fungi) may also aid in the identification of causative organisms in BCNIE. Excised valve tissues or vegetation specimens are the preferred samples for molecular diagnostics due to the higher concentration of bacterial or fungal DNA than in blood. Broad-range bacterial PCR using primers for the 16S rRNA gene has a reported sensitivity of 33% to 100% and a reported specificity of 77% to 100%.[36,37] Organism-specific PCR, which is available for *Bartonella* spp, *C burnetii*, and *T whipplei*, generally demonstrates superior sensitivity.[37]

Metagenomic next-generation sequencing (mNGS) is growing in prominence as a novel diagnostic platform to identify pathogens in BCNIE. When applied to resected valve tissue, the sensitivity of mNGS is 86% to 100%, and the specificity is 72% to 100%. Plasma mNGS is less sensitive (reportedly 47%–80%) but similarly specific (72%–100%).[38] Because mNGS can detect nonviable or unculturable bacteria if microbial nucleic acids are present, it is particularly advantageous in BCNIE due to recent antibiotic administration. Further study is needed to better understand the limitations of mNGS in this context.

Pathologic examination of resected valve tissue or embolic fragments is the gold standard for diagnosing IE. All specimens obtained during surgical valve debridement

or resection should be collected in a sterile container without fixative and sent to the microbiology laboratory and the pathology department, where stains for bacteria, mycobacteria, and fungi may aid in microorganism identification. Immunohistochemical stains can also be useful for diagnosis.

Imaging Studies

Echocardiography is the primary imaging modality for diagnosing IE. Transthoracic echocardiography (TTE) has a sensitivity of around 75% for the diagnosis of vegetations, whereas transesophageal echocardiography (TEE) has a sensitivity of 85% to 90% for the same. Both TTE and TEE have high specificity for IE (>90%). In a patient with suspected IE, TEE should be performed if initial TTE is negative, if there is a prosthetic valve or intracardiac device present, or if complications such as paravalvular lesions or fistulae are suspected.[2,39] However, if vegetations are small or if echocardiography is performed very early in a patient's illness, TEE may be negative.[30] Therefore, if clinical suspicion for IE remains high after a negative initial TTE or TEE, then echocardiography should be repeated within a short-time interval.

Because of its improved spatial resolution, cardiac computed tomography (CT) has a higher sensitivity for diagnosing pseudoaneurysm or abscess compared with TEE (78% vs 69%). While TEE is more sensitive than cardiac CT for vegetations (94% vs64%), cardiac CT can be considered when TEE is contraindicated or inconclusive.[40] Cardiac CT can also provide a noninvasive assessment of coronary artery disease before surgery in patients with IE.[4]

Fluorine-18-fludeoxyglucose (18F-FDG) PET/CT is an emerging imaging modality for IE best reserved for patients with nondiagnostic echocardiography. In patients with NVE, 18F-FDG-PET/CT has a sensitivity of 22% to 31% and a specificity of 98% to 100%. For patients with PVE, sensitivity of 18F-FDG-PET/CT for diagnosing IE increases to 86% to 93%; specificity is 84% to 90%.[41,42] If a patient is within 3 months of prosthetic valve implantation, positive 18F-FDG-PET/CT may reflect postoperative inflammation rather than infection, which must be taken into account.[43] The specificity of 18F-FDG-PET/CT in diagnosing CIED-related IE is around 85% when there is abnormal FDG uptake on CIED leads.[42] A negative scan does not rule out CIED infection, however. Whole body 18F-FDG-PET/CT may additionally identify sites of metastatic infection in patients with IE and can be considered in monitoring response to treatment in select cases.[4]

2023 Duke Criteria

Given the highly variable clinical presentation of IE, the Duke criteria were developed in 1994 and modified in 2000 to help standardize the definition of IE for research purposes.[44,45] While pathologic confirmation of IE remains the gold standard for diagnosis, the modified Duke criteria provide a clinical framework diagnosing IE that has been used for more than 2 decades. Over this timeframe, the epidemiology of IE has changed and the use of diagnostic imaging modalities such as 18F-FDG-PET/CT and cardiac CT have become more widespread. In response to a growing need to modify the diagnostic criteria for IE in light of these changes, the 2023 Duke-International Society for Cardiovascular Infectious Diseases Criteria for Infective Endocarditis (ISCVD) were presented as an update to the modified Duke criteria.[43] The 2023 Duke-ISCVID criteria are summarized in **Box 1**.

Across several validation studies, the 2023 criteria are more sensitive than the 2000 criteria for definite IE with slightly reduced specificity overall.[46–50] As a result, patients without IE might be classified as having definite or possible IE. Because a false negative diagnosis of IE has more devastating consequences than a false positive, the

Box 1
2023 Duke International Society for Cardiovascular Infectious Disease (ISCVID) criteria for infective endocarditis[a]

Major Criteria

Microbiologic Major Criteria

Positive blood cultures

Typical microorganisms isolated from ≥ 2 separate blood culture sets: *S aureus*, *S lugdunensis*, *E faecalis*; all streptococcal spp except *S pneumoniae* and *S pyogenes*; *Granulicatella* and *Abiotrophia* spp; *Gemella* spp; HACEK (*Haemophilus* spp, *Aggregatibacter* spp, *Cardiobacterium* spp, *Eikenella corrodens*, *Kingella* spp)

In the setting of intracardiac prosthetic material, typical microorganisms include: coagulase-negative staphylococci, *C striatum*, *C jeikeium*, *S marcescens*, *P aeruginosa*, *C acnes*, nontuberculous mycobacteria (especially *M chimaera*), and *Candida* spp.

or

Nontypical microorganisms isolated from ≥ 3 separate blood culture sets

Positive laboratory tests

PCR or other nucleic-acid based test[b] from blood for *Coxiella burnetii*, *Bartonella* spp

or

Tropheryma whipplei or single blood culture with *Coxiella burnetii* or positive for phase I immunoglobulin (IG) G antibody (Ab) titer > 1:800

or

IgM or IgG Abs by immunofluorescence assay to *Bartonella* spp with IgG titer ≥ 1:800

Imaging Major Criteria

Echocardiography and/or cardiac CT imaging

Vegetations, valvular/leaflet perforation or aneurysm, abscess, pseudoaneurysm, or intracardiac fistula

or

New valvular regurgitation (worsening/changing preexisting murmur is not sufficient)

or

New partial dehiscence of a prosthetic valve

[18F]FDG PET/CT imaging

Abnormal activity involving a native or prosthetic valve, ascending aortic graft,[c] or intracardiac device leads

Surgical Major Criteria

Evidence of IE on direct inspection during heart surgery

Minor Criteria

Presence of a predisposing cardiac condition, cardiac implantable electronic device, or injection drug use

Temperature ≥ 38.0°C (100.4°F)

Vascular phenomena, including arterial emboli, septic pulmonary infarcts, cerebral or splenic abscess, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhage, or Janeway lesions

Immunologic phenomena, including positive rheumatoid factor, Osler nodes, Roth spots, or glomerulonephritis

Microbiologic evidence, falling short of a major criterion

Positive blood cultures that do not meet major criteria

or

Positive culture, PCR, or other nucleic acid-based test[b] for a typical IE organism from a sterile site other than cardiac tissue, cardiac prosthesis, or arterial embolus; or positive PCR for a skin bacterium on a valve or wire

Imaging criteria

Abnormal metabolic activity as detected by [18F]FDG PET/CT within 3 months of implantation of a prosthetic valve, ascending aortic graft,[c] intracardiac device leads, or other prosthetic material

Physical examination criteria

New regurgitation identified by auscultation if echocardiography is not available

[a]Table adapted from Fowler and colleagues.[43] A definite diagnosis of IE is based on 2 major, 5 minor, or 1 major plus 3 minor criteria. A possible diagnosis of IE is based on 3 minor clinical criteria or 1 major and 1 minor clinical criteria.[b]16S/18S sequencing *or* metagenomic (shotgun) sequencing.[c]With concomitant evidence of valve involvement.

decision about whether to treat possible IE cases rests on a combination of factors, including the specifics of the case, the clinical consequences of treating a false positive versus not treating a false negative, and the estimated prevalence of IE associated with the pathogen.[51]

TREATMENT

Empiric Antibiotics

In patients with suspected IE who are acutely ill, empiric antibiotics should be initiated after at least 2 (preferably 3) sets of blood cultures have been obtained. The most likely pathogens, local antibiogram, patient characteristics, epidemiologic risk factors, and involvement of prosthetic material must be considered when selecting a regimen. Consultation with an infectious disease specialist is recommended.

An empiric NVE regimen should cover for *S aureus*, viridans streptococci, *S gallolyticus*, enterococci, and gram-negative organisms, including the HACEK group. Vancomycin with either ceftriaxone or cefepime (for patients with nosocomial exposures) is appropriate coverage. If BCNIE is suspected, individual risk factors and exposures should be considered, and empiric coverage for organisms such as *Bartonella* spp, *Brucella* spp, and *C burnetii* may be initiated. An empiric PVE regimen consists of vancomycin plus gentamicin and rifampin.

Targeted Antibiotics and Treatment Duration

Antibiotics should be tailored to the culprit pathogen once identified by culture, serology, or other diagnostic method. Treatment recommendations for common IE pathogens are detailed in **Table 2**.[4,30]

The optimal duration of antibiotic treatment for IE is not well studied, but 4 to 6 weeks is recommended for most presentations, with the first day of effective therapy defined by when blood cultures are negative. Prolonged courses of bactericidal antibiotics are recommended to penetrate biofilms and sterilize vegetations that may contain a high burden of bacteria. In patients who undergo valve surgery, the resected valve tissue should be cultured. If tissue cultures are positive, a full course of antibiotics is warranted following surgery.[30]

Oral Antibiotics

Historically, the American Heart Association (AHA) and European Society of Cardiology (ESC) IE guidelines recommended that the entire IE treatment course be administered intravenously based on the premise that intravenous antibiotics reach high tissue and blood concentrations more rapidly and reliably than oral antibiotics. Lack of data on treatment efficacy with oral antibiotics has also precluded the switch from intravenous to oral regimens.[52]

The Partial Oral Treatment of Endocarditis (POET) trial was a randomized, multicenter trial that evaluated the efficacy of switching to oral antibiotics after an initial course of intravenous treatment for at least 10 days with clinical stabilization. The study enrolled 400 adults with left-sided IE due to GPCs, and the primary outcome was a composite of all-cause mortality, unplanned cardiac surgery, embolic events, and relapse of bacteremia in the 6 months following completion of antibiotics. Switch to oral antibiotics was noninferior to a full intravenous course. Study limitations included enrollment of only 5 participants who used injection drugs, zero cases of methicillin reistant *Staphylococcus aureus* (*MRSA*) IE, and exclusion of BCNIE and right-sided IE cases. This study suggests that transitioning to oral antibiotics may be appropriate in some cases, but generalizability is limited.[53]

Table 2
Antibiotic treatment regimens for common infective endocarditis pathogens[a]

Pathogen	NVE	PVE
Methicillin-susceptible staphylococci	Nafcillin, oxacillin, or cefazolin for 6 wk[a] [a]For uncomplicated right-sided IE, 2-wk course sufficient Vancomycin for 6 wk if beta lactam allergy	Nafcillin or oxacillin for 6 wk + rifampin for 6 wk + gentamicin for first 2 wk Vancomycin may replace nafcillin or oxacillin if beta lactam allergy
Methicillin-resistant staphylococci	Vancomycin or daptomycin for 6 wk	Vancomycin for 6 wk + rifampin for 6 wk + gentamicin for first 2 wk
Penicillin-susceptible viridans streptococci and *S gallolyticus* (minimum inhibitory concentration [MIC] $\leq$0.12 μg/mL)	Penicillin G, ampicillin, or ceftriaxone for 4 wk Vancomycin for 4 wk if beta lactam allergy	Penicillin G, ampicillin, or ceftriaxone for 6 wk with or without gentamicin for first 2 wk Vancomycin for 6 wk if beta lactam allergy
Penicillin-resistant viridans streptococci and *S gallolyticus* (MIC >0.12 μg/mL)	Combination therapy: penicillin G or ampicillin for 4 wk + gentamicin for first 2 wk Monotherapy: ceftriaxone (if susceptible MIC) or vancomycin for 4 wk	Combination therapy: penicillin G, ampicillin, or ceftriaxone + gentamicin for 6 wk Monotherapy: vancomycin for 6 wk
Penicillin-susceptible and gentamicin-susceptible enterococci	Aminoglycoside combination: penicillin G or ampicillin + gentamicin (4 wk if symptoms < 3 mo, 6 wk if symptoms > 3 mo) Beta-lactam combination: ceftriaxone + ampicillin for 6 wk	Aminoglycoside combination: penicillin G or ampicillin + gentamicin for 6 wk Beta-lactam combination: ceftriaxone + ampicillin for 6 wk
Penicillin-resistant and gentamicin-susceptible enterococci	Vancomycin + gentamicin for 6 wk	Vancomycin + gentamicin for 6 wk
HACEK organisms	Ceftriaxone or ampicillin (if susceptible MIC) for 4 wk Ciprofloxacin or levofloxacin for 4 wk if unable to tolerate beta lactam	Ceftriaxone or ampicillin (if susceptible MIC) for 6 wk Ciprofloxacin or levofloxacin for 6 wk if unable to tolerate beta lactam

[a] Treatment recommendations adapted from the American Heart Association IE guidelines (Baddour et al).[30]

Long-Acting Parenteral Antibiotics

Dalbavancin is a novel glycopeptide antibiotic active against gram-positive organisms, including MRSA. Because of its long half-life, dalbavancin can be administered intravenously weekly or every other week, making it an appealing option for outpatient parenteral antibiotic therapy for IE. Initial data from nonrandomized studies are promising, with high rates of treatment success for NVE, PVE, and device-related IE.[54,55] Compared with standard of care, use of dalbavancin has also been shown to reduce both hospital length of stay and associated health care costs.[56]

Surgical Management

Cardiothoracic surgical consultation should be obtained for all patients with IE for consideration of valve replacement or repair. The primary indications for surgery are described in **Table 3**. The optimal timing of surgery is not well defined, and terminology for what constitutes early versus late surgery is variable across studies.

A randomized, controlled trial of 76 patients with left-sided NVE, severe valve disease, and vegetations greater than 10 mm compared early surgery within 48 hours of study randomization to conventional treatment. Early surgery significantly decreased the risk of the composite primary outcome of all-cause mortality, embolic events, or recurrence within 6 months, though this finding was driven entirely by decreased risk of embolic events.[57] A systematic review and meta-analysis of 21 studies comparing early surgery within 20 days to conservative management found that early surgery reduced the odds of mortality by 36%.[58]

Exceptions to the recommendation for early surgery are acute stroke or intracranial hemorrhage (ICH), in which case valve surgery should be delayed at least 4 weeks. In patients with ICH, risk of mortality is higher when surgery is performed within 4 weeks. There are also theoretic concerns that the anticoagulation required for cardiopulmonary bypass during cardiac surgery could result in hemorrhagic conversion of stroke, or that transient cerebral ischemia could occur in the setting of perioperative hypotension.[59]

Antithrombotic Agents

IE alone is not an indication to initiate antiplatelet or anticoagulant therapy, as no studies have demonstrated that these agents reduce the risk of thromboembolic complications. Long-term antiplatelet therapy may be continued after IE develops assuming that there are no major bleeding complications such as ICH. In patients with mechanical valve IE who have experienced a cerebral embolic event, anticoagulation should be paused for at least 2 weeks to reduce the risk of hemorrhagic transformation.[30]

PREVENTION

Antibiotic prophylaxis to prevent viridans streptococcal IE is recommended in individuals with cardiac conditions that confer high risk of adverse outcomes from IE who are undergoing invasive dental procedures. Invasive dental procedures involve manipulation of gingival tissue or the periapical region of teeth or perforation of oral mucosa,

Table 3
Indications for surgery in endocarditis[a]

Indications	Manifestations
Heart failure	Refractory pulmonary edema, cardiogenic shock
Paravalvular extension of infection	Annular or aortic abscess, penetrating lesion, heart block, or valve dehiscence
Difficult to treat organisms	Fungi, multidrug-resistant gram-negative bacilli, vancomycin-resistant enterococci
Persistent infection	Bacteremia or fever lasting > 5–7 d despite appropriate antibiotics
Prevention of embolism	Aortic or mitral valve mobile vegetation > 10 mm, or recurrent emboli

[a] Surgical indications adapted from the American Heart Association IE guidelines (Baddour et al).[30]

such as dental extractions, periodontal surgery, tooth implantation, or oral biopsies.[60] In a systematic review of 30 studies, prophylaxis following invasive dental procedures was associated with a 59% reduction in the risk of IE in high risk patients.[61] Cardiac conditions that constitute the highest risk of adverse outcome from viridans streptococcal IE include prosthetic cardiac material such as a valve, clip, or LVAD; previous, relapsed, or recurrent endocarditis; repaired or unrepaired congenital heart disease; and receipt of a cardiac transplant with subsequent cardiac valvulopathy. Prophylaxis is not routinely recommended for patients at intermediate risk of adverse outcomes, including those with valvular disease, hypertrophic cardiomyopathy, or a CIED. The preferred regimen is a single dose of oral amoxicillin administered 30 to 60 minutes prior to the procedure. Antibiotic prophylaxis to prevent IE is not recommended for patients undergoing genitourinary or gastrointestinal procedures due to lack of evidence supporting the efficacy of this practice.[60]

SUMMARY

With IDU on the rise and the growing use of prosthetic valves and intracardiac devices, the incidence of IE is increasing. Despite significant advances in diagnostic methodologies and options for treatment, IE remains a high-risk condition associated with significant morbidity and mortality. Effective antibiosis as well as surgery, in select cases, are the mainstays of treatment. There will likely be an increasing role for oral and long-acting injectable therapy for IE in years to come.

CLINICS CARE POINTS

- At least 3 blood culture sets should be collected before the initiation of antibiotic therapy, as over 90% of native infective endocarditis (IE) cases will have positive blood cultures. Serologic testing and molecular diagnostics such as real-time polymerase chain reaction and metagenomic next-generation sequencing may help identify blood culture-negative infective endocarditis.
- In a patient with suspected IE, transesophageal echocardiography should be performed if initial transthoracic echocardiography is negative, there is a prosthetic valve or intracardiac device present, or complications such as paravalvular lesions or fistulae are suspected.
- Vancomycin with either ceftriaxone or cefepime constitutes an appropriate empiric regimen for NVE, whereas vancomycin, rifampin, and gentamicin may be used empirically for PVE. Antibiotics should be tailored to the culprit pathogen once identified, with a 4-week to 6-week treatment course indicated in most cases.
- Indications for cardiac surgery include heart failure, paravalvular extension of infection, difficult to treat organisms, persistent infection, and prevention of embolism. Early surgery may reduce the risk of mortality and embolic events but is contraindicated in patients with acute stroke or intracranial hemorrhage.

DISCLOSURE

The authors have nothing to disclose.

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