Chapter 32

Infective Endocarditis

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The incidence of IE infection is difficult to determine because the criteria for diagnosis vary among the numerous series that have been reported. Estimates from the American Heart Association place the annual incidence of IE at 10,000 to 20,000 new cases per year. The mean age of patients has increased—from younger than 30 years in 1926 to older than 50 years currently. This change is likely due to dramatic decreases in the incidence of rheumatic fever because of the development of antimicrobial therapy. Degenerative valvular heart disease is now the major predisposing factor for endocarditis (see also chapters 27–31). The mitral valve is most commonly affected, followed by the aortic valve. The tricuspid and pulmonic valves are only rarely involved, usually in association with injection drug use.

ETIOLOGY AND PATHOGENESIS

The development of IE requires two events. First, the surface of the heart valve must be damaged, creating a suitable site for platelet and fibrin deposition. Subsequently, bacteria must reach the site and adhere to the lesion (Fig. 32-1). Transient bacteremia occurs when an area heavily colonized with bacteria (and usually distant to the heart) is traumatized. The most common of such areas includes the oropharynx, the gastrointestinal tract, and the genitourinary tract. Bacteremia can occur in areas where skin breakdown accompanies bacterial colonization or after manipulation of the area (for instance, after dental cleaning, cystoscopy or endoscopy, or colonoscopy with biopsy). After colonization of the valve, bacteria replicate to a critical mass, and the vegetation enlarges by deposition of platelets and fibrin and continued bacterial replication (Fig. 32-2).

Patient Population

Approximately 60 to 80% of patients with endocarditis have an identifiable predisposing cardiac lesion such as degenerative or congenital heart disease, mitral valve prolapse, or rheumatic heart disease. The exception to this is patients with infective endocarditis associated with intravenous drug abuse. These individuals typically present with IE of the right heart valves, involving the tricuspid or pulmonic valves that were probably structurally normal before infection. Although the typical patient with IE secondary to intravenous drug abuse is young and male, intravenous drug abuse should be considered in any individual with tricuspid valve endocarditis. In addition to these causes, bacteremia from intravenous catheters, TPN indwelling catheters, arteriovenous shunts (used for hemodialysis), pacemakers, postoperative wound infections, and genitourinary manipulation have become an important cause of IE in chronically ill patients.

CLINICAL PRESENTATION

Four processes contribute to the clinical picture of IE: the infectious process on the heart valve, including local intracardiac complications; bland or septic embolization to virtually any organ; persistent bacteremia, possibly with metastatic foci of infection; and circulating immune complexes and other immunopathologic factors (Fig. 32-3). Fever is present in approximately 95% of patients, but may be absent in those with congestive heart failure (CHF), renal failure, liver disease, and history of antibiotic usage, as well as in elderly individuals. Fever lasting longer than 2 weeks despite adequate antimicrobial therapy is
Bacterial Endocarditis

Deposit of platelets and organisms (stained dark), edema, and leukocytic infiltration in very early bacterial endocarditis of aortic valve.

Development of vegetations containing clumps of bacteria on tricuspid valve.

Early vegetations of bacterial endocarditis on bicuspid aortic valve.

Early vegetations of bacterial endocarditis at contact line of mitral valve.
Common Portals of Bacterial Entry in Bacterial Endocarditis

- Dental infections
- Genitourinary infections
- Cutaneous infections
- Pulmonary infections

Bloodstream

Mild residual changes of rheumatic mitral valve disease

Tetralogy of Fallot

Bicuspid aortic valve (congenital or acquired)

Small ventricular septal defect (probe): “Jet lesion” opposite

Coarctation of aorta and/or patent ductus (arrow)

Common Predisposing Lesions
Bacterial Endocarditis

Advanced bacterial endocarditis of aortic valve: Perforation of cusp; extension to anterior cusp of mitral valve and chordae tendineae; “Jet lesion” on septal wall.

Vegetations of bacterial endocarditis on underaspect as well as on atrial surface of mitral valve.

Advanced lesion of mitral valve: Vegetations extending onto chordae tendineae with rupture of two chordae; also extension to atrial wall and contact lesion on opposite cusp.
associated with specific etiologic agents, such as *Staphylococcus aureus*, gram-negative rods, fungi, culture-negative IE, embolization, myocardial abscess, tissue infarction, the need for cardiac surgery, and a higher mortality rate.

**Heart murmurs** can be detected in more than 85% of cases because of the predisposing valvular or congenital abnormality. In patients with IE diagnosed at an early stage, a documented change in their murmur or the appearance of a new murmur is uncommon and predicts an adverse outcome. CHF results primarily from progressive valvular insufficiency, and CHF develops in more than 90% of patients who demonstrate a new regurgitant murmur. Heart block, arrhythmias, pericarditis, abscesses, fistulas, and perforations can also occur (Fig. 32-4).

**Peripheral manifestations** are found in up to half of the cases and often reflect serious systemic consequences of IE. These include splinter hemorrhages, petechiae, Osler nodes, Janeway lesions, Roth spots, and clubbing (Fig. 32-5). Splenomegaly and musculoskeletal symptoms are also common.

**Embolic episodes** occur in at least one third of cases, and the clinical findings are unique to the organ involved. Neurologic manifestations (20–40% of cases) are associated with increased mortality. Embolic stroke is more commonly observed than other systemic emboli, due to the sensitivity of the brain to ischemic damage. Neuroemboli may result in hemiplegia, sensory loss, ataxia, aphasia, or an alteration in mental status (Fig. 32-5).

Many patients have symptoms for weeks to months before diagnosis because symptoms and signs can be nonspecific. The diagnosis of IE should be considered in any patient with persistent fever, weight loss, or unexplained failure to thrive.

### MICROBIOLOGY

#### Streptococci

Streptococci are the pathogens in 55% of cases of native valve IE (if IE is excluded due to intravenous drug abuse). Approximately 35% of all cases are due to *Streptococcus viridans*, a normal inhabitant of the oropharynx.

*Streptococcus bovis* is a normal inhabitant of the human gastrointestinal tract. *S. bovis* endocarditis is more likely to develop in elderly individuals, and more than one third of those infected have a predisposing malignant or premalignant gastrointestinal tract lesion. To screen for underlying colon cancer, colonoscopy is indicated when *S. bovis* is recovered from the bloodstream.

*Streptococcus pneumoniae* is a rare cause of IE seen more commonly with alcohol abuse; its course is usually fulminant. Presentation may be associated with perivalvular abscess formation, pericarditis, or concurrent meningitis. Left-sided involvement is the rule, with a predilection for the aortic valve. The overall mortality rate remains high, with death resulting from rapid valvular destruction and hemodynamic compromise.

Enterococcal endocarditis usually has a subacute course, similar to the viridans streptococci. It is more common in older men after genitourinary manipulation and in younger women after obstetric procedures. More than 40% of the patients have no underlying heart disease, although a heart murmur develops in more than 95% during the illness. Classic peripheral manifestations are uncommon. Resistance of enterococci to conventional antimicrobial therapy makes the infection more difficult to treat.

#### Staphylococci

Staphylococci are responsible for at least 20 to 30% of the cases of IE, and 80 to 90% of these are due to the coagulase-positive *S. aureus*. Endocarditis resulting from this organism may involve previously normal heart valves. *S. aureus* endocarditis progresses rapidly and carries with it a high risk. Rapid valve destruction, widespread metastatic infections, myocardial abscesses, purulent pericarditis, and valve ring abscesses—and hemodynamic compromise—are more common with this agent than with more common
Bacterial Endocarditis: Cardiac Sequelae

Figure 32-4

Adhesion of mitral valve cusp to ventricular wall resulting from vegetations on undersurface of valve

Thickening and erosion of mitral valve with stumps of ruptured chordae tendineae: Enlargement of L. atrium

Erosion and perforation of aortic valve cusp; perforation of anterior cusp of mitral valve (ruptured mycotic aneurysm): “Jet lesion” on septum; L. ventricular hypertrophy
Bacterial Endocarditis: Remote Embolic Effects

Infarct of brain with secondary hemorrhage from embolism to right anterior cerebral artery; also small infarct in left basal ganglia

Embolus in vessel of ocular fundus with retinal infarction; petechiae

Multiple petechiae of skin and clubbing of fingers

Petechiae of mucous membranes

Petechiae and gross infarcts of kidney

Mycotic aneurysms of splenic arteries and infarct of spleen; splenomegaly
## Table 32-1
### Duke Criteria

#### Definite IE

**Pathologic criteria**
- Microorganism: demonstrated by culture or histology in a vegetation, in a vegetation that has embolized, or in an intracardiac abscess **or**
- Pathologic lesions: vegetation or intracardiac abscess, confirmed by histology showing active endocarditis

**Clinical criteria**
- Two major criteria **or**
- One major and three minor criteria **or**
- Five minor criteria

#### Possible IE

Findings consistent with IE that fall short of “definite” but not rejected

#### Rejected IE

Firm alternate diagnosis for manifestations of endocarditis **or**

Resolution of manifestations of endocarditis, with antibiotic therapy for 4 days or less **or**

No pathologic evidence of IE at surgery or autopsy after antibiotic therapy for 4 days or less

#### Major criteria

1. Positive blood cultures for IE
   - Typical microorganism for IE from two separate blood cultures in absence of a primary focus
     - Viridans streptococci
     - *Streptococcus bovis*, including nutritional variant strains
     - HACEK group
     - Community-acquired *Staphylococcus aureus* or enterococci
   - Persistently positive blood culture, defined as recovery of a microorganism consistent with IE from:
     - Blood cultures drawn more than 12 hours apart **or**
     - All of three or a majority of four or more separate blood cultures, with first and last drawn at least 1 hour apart

2. Evidence of endocardial involvement
   - Positive echocardiogram for IE
     - Oscillating intracardiac mass, on valve or supporting structures, or in the path of regurgitant jets, or on implanted material, in the absence of an alternate anatomic explanation **or**
     - Abscess **or**
     - New partial dehiscence or prosthetic valve **or**
   - New valvular regurgitation (increase or change in preexisting murmur not sufficient)

#### Minor criteria

1. Predisposition: predisposing heart condition or intravenous drug use
2. Fever 38.0°C or higher (100.4°F)
3. Vascular phenomena: major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, Janeway lesions
4. Immunologic phenomena: glomerulonephritis, Osler nodes, Roth spots, rheumatoid factor
5. Microbiologic evidence: positive blood culture but not meeting major criterion as noted previously or serologic evidence of active infection with organism c/w IE
6. Echocardiogram consistent with IE but not meeting major criterion

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IE indicates infective endocarditis.

causes of endocarditis. In many cases, urgent or emergent surgery is needed to remove the infected valve and surrounding area. *S. aureus*, including methicillin-resistant *S. aureus*, is the most common pathogen in conjunction with intravenous drug abuse. Coagulase-negative staphylococci, generally less virulent, are important pathogens in prosthetic valve IE.

**Gram-Negative Bacilli**

Persons who inject drugs or have prosthetic valves or cirrhosis are at increased risk for gram-negative bacillary IE. *Salmonella* species have an affinity for abnormal heart valves and may cause valvular perforation or destruction, atrial thrombi, myocarditis, and pericarditis. *Pseudomonas* IE is seen mainly in patients who inject drugs and tends to affect normal valves. Common complications include major embolic phenomena, inability to sterilize valves, neurologic complications, ring and annular abscesses, splenic abscesses, bacteremic relapse, and heart failure. Early surgery is recommended for left-sided disease.

**HACEK Organisms**

Bacteria in the HACEK group include *Haemophilus* species, *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella kingae*. All of these organisms are fastidious and may require 2 to 3 weeks of incubation for isolation from blood. The typical clinical syndrome produced includes large friable vegetations, frequent emboli, and the development of heart failure.

**Fungi**

Most patients with fungal endocarditis have predisposing factors, such as intravenous drug abuse, reconstructive cardiovascular surgery, or prolonged intravenous therapy. *Candida parapsilosis* and *Candida tropicalis* predominate in those persons injecting drugs, whereas *Candida albicans* and *Aspergillus* species predominate in others. Fungal endocarditis carries a poor prognosis secondary to large bulky vegetations, a tendency for myocardial invasion, widespread systemic septic emboli, and inadequate antifungal therapy due to poor penetration and lack of fungicidal activity. Surgical intervention is usually necessary.

**Culture-Negative Infective Endocarditis**

The most common causes of culture-negative IE include recent administration of antibiotics, slow growth of fastidious organisms or organisms that are difficult to culture (HACEK organisms, *Brucella*, *Coxiella*, *Mycoplasma*, *Chlamydia*, *Bartonella*, *Legionella*), fungal endocarditis, and non-infective endocarditis or alternative diagnoses.

**DIAGNOSTIC APPROACH**

**Blood cultures** remain the single most important laboratory test in the diagnosis of IE. Bacteremia is usually continuous and low grade; blood cultures are positive for growth in 85 to 95% of cases. At least three sets of blood cultures should be drawn in the first 24 hours. More cultures may be necessary if the patient has received antibiotics in the preceding 2 weeks. Negative blood culture results are usually secondary to previous antibiotic usage, but some organisms, such as those in the HACEK group and *Brucella*, grow slowly and may require up to 4 weeks’ incubation. Blood cultures are more likely to be negative when fungi are the pathogens. If embolization to a major vessel occurs, embolectomy should be performed and material should be sent for routine bacterial and fungal stains and culture. Serologic studies may be necessary for the diagnosis of Q fever, brucellosis, legionellosis, and psittacosis.

**Echocardiography** should be performed in all patients. Transthoracic echocardiography (TTE) is a rapid, noninvasive test with excellent specificity for vegetations (98%). However, the sensitivity of TTE is variable (from <50% to >90% positive). Transesophageal echocardiography (TEE) is substantially more sensitive (76–100%) and is particularly useful in patients with suboptimal TTE due to pulmonary disease, obesity, or chest wall deformsities and for evaluating tricuspoid, pulmonic, and prosthetic valves. TEE is also superior for evaluating complications of IE, such as extravalvular extension of infection and abscess. Negative TEE and TTE confer a 95% negative predictive value. However, when clinical suspicion of IE is high and the result of initial echocardiography is negative, a repeat examination in 7 to 10 days is warranted.

**Laboratory abnormalities** are common but nonspecific in IE. Hematologic parameters are
often abnormal, but none are diagnostic. Normochromic, normocytic anemia is usually present, characteristic of an anemia of chronic disease. The erythrocyte sedimentation rate is elevated in most patients (90–100%), and positive rheumatoid factor is found in 40 to 50% of cases, particularly when illness duration is more than 6 weeks. Other findings include thrombocytopenia, leukocytosis or leukopenia, hypergammaglobulinemia, and abnormal urinalysis results.

MANAGEMENT AND THERAPY

Antimicrobial Therapy
Empiric, broad-spectrum antibiotic therapy—directed against the most likely causative agents—should be initiated after blood cultures have been obtained. Subsequent selection of antimicrobial agents is based on susceptibility testing of the causative microbe. Treatment requires prolonged use of bactericidal antibiotics; the parenteral route is usually indicated (Table 32-2).

Indications for Cardiac Surgery
Indications for surgical therapy of infective endocarditis are shown in Table 32-3. Deciding whether and when to proceed to surgery can be difficult. Most often, complications occur suddenly and the first embolic event can be devastating (one significant embolic episode is an indication for surgery). Ideally, surgical therapy proceeds when a serious complication is imminent but has not yet occurred. Predicting which patients are at highest risk is as much art as it is science. The size and mobility of vegetations imaged by echocardiography can be helpful, but is not absolute. Thus, the decision to proceed with surgery must be made carefully, with early discussion among cardiologists, infectious disease physicians, and cardiac surgeons, after well-informed input from patients and families.

Course of Endocarditis
Symptomatic improvement, a decrease in fever, and clearance of bacteremia are usually prompt with appropriate antibiotic therapy. Anemia usually persists through therapy, and it may take weeks or months to resolve. Recurrent or persistent fever may be secondary to failure to control infection, metastatic abscess formation, recurrent emboli, IV-related phlebitis, superimposed infections, or medication (most likely antibiotic) related. The most frequent causes of death in IE are neurologic and septic complications, CHF, embolic phenomena, rupture of mycotic aneurysm, and complications from cardiac surgery.

Special Considerations

Prosthetic Valve Endocarditis
Prosthetic valve endocarditis (PVE) accounts for 10 to 15% of all cases of IE. It is classified as early when the infection occurs within the first 2 months after surgery and as late thereafter. Early PVE infection is believed to result from organisms acquired at the time of surgery or in the early postoperative period. Coagulase-negative staphylococci such as *Staphylococcus epidermidis* are the most common organisms, with occasional infections caused by *S. aureus*, diphteroids, Gram-negative rods, and fungi. Late PVE is presumably caused by bacteremia unrelated to the initial surgical procedure. Although the pathogens overlap with those of early PVE, the more usual agents of endocarditis, such as *S. viridans* and enterococci, also are found.

The clinical signs and symptoms of PVE are similar to those encountered in patients with native valve endocarditis. Because TTE typically fails to adequately visualize prosthetic valves, TEE is generally necessary.

Treatment of infective endocarditis is much more challenging when it involves the foreign material of a prosthetic valve. Empiric treatment usually includes a combination of vancomycin, gentamicin, and rifampin, but effective therapy frequently also necessitates removal and replacement of the prosthesis.

Prophylaxis
Antimicrobial prophylaxis is recommended for patients with increased risk of endocarditis from underlying cardiac conditions who undergo invasive procedures likely to generate bacteremia. For dental procedures, the recommendation for adults is a single 2.0-g dose of amoxicillin to be administered 1 hour before the anticipated procedure. For details regarding prophylaxis for other procedures, see the American Heart Association Web site: http://www.americanheart.org.
### Antimicrobial Therapy for Infective Endocarditis

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<th><strong>Etiology</strong></th>
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| **Viridans streptococci and *Streptococcus bovis* susceptible to penicillin (MIC ≤0.1 µg/mL)** | Penicillin G 12–18 million U/24 h IV in six doses* for 4 weeks or ceftriaxone 2 g IV once daily for 4 weeks  
**or**  
Penicillin G 12–18 million U/24 h IV in six doses* for 2 weeks **WITH** gentamicin 1 mg/kg IV every 8 h† for 2 weeks  
**or**  
Vancomycin 30 mg · kg⁻¹ · 24 h⁻¹ IV in two divided doses for 4 weeks (only recommended for patients allergic to β-lactams) |
| **Viridans streptococci and *Streptococcus bovis* relatively resistant to penicillin (MIC >0.01 to <0.5 µg/mL)** | Penicillin G 18 million U/24 h IV continuously or six doses for 4 weeks **WITH** gentamicin 1 mg/kg IV every 8 h for 2 weeks (First-generation cephalosporins may be substituted for penicillin in patients with penicillin hypersensitivity not of the immediate type.)  
**or**  
Vancomycin 30 mg · kg⁻¹ · 24 h⁻¹ IV in two divided doses for 4 weeks (only recommended for patients allergic to β-lactams) |
| **Enterococci (and viridans streptococci with penicillin MIC >0.5 µg/mL, nutrient variant viridans streptococci)** | Penicillin G 18–30 million U/24 h IV in six doses **WITH** gentamicin 1 mg/kg IV every 8 h for 4–6 weeks  
**or**  
Ampicillin 12 g/24 h in six doses **WITH** gentamicin 1 mg/kg IV every 8 h for 4–6 weeks  
**or**  
Vancomycin 30 mg · kg⁻¹ · 24 h⁻¹ IV in two divided doses for 4–6 weeks **WITH** gentamicin 1 mg/kg IV every 8 h for 4–6 weeks (Only recommended for patients allergic to β-lactams; cephalosporins are not acceptable alternatives for patients allergic to penicillin.)‡ |
| **Staphylococci (penicillin susceptible)** | Penicillin G 20 million U/24 h IV in six doses for 4–6 weeks* |
| **Staphylococci (methicillin susceptible, penicillin resistant)** | Nafcillin (or oxacillin) 2 g IV every 4 h* for 4–6 weeks **WITH** gentamicin 1 mg/kg IV every 3–5 days*  
**or**  
Cefazolin (or other first-generation cephalosporin) 2 g IV every 8 h for 4–6 weeks **WITH** gentamicin 1 mg/kg IV every 8 h for 3–5 days |
| **Staphylococci (methicillin resistant)** | Vancomycin 30 mg · kg⁻¹ · 24 h⁻¹ IV in two divided doses for 4–6 weeks |
| **HACEK microorganisms** | Ceftriaxone 2 g IV once daily for 4 weeks  
**or**  
Ampicillin 2 g every 4 h or 12 g/24 h IV continuously **WITH** gentamicin 1 mg/kg IV every 8 h for 4 weeks |

* Dosing of penicillin, nafcillin, and oxacillin is quite frequent and often considered problematic for patients stable enough for home therapy. However, because these drugs are stable for 24 h at room temperature, they may be given via a pump that remains continuously at the patient’s side, requiring adjustment by a nurse or other caregiver only once every 24 h.
†Aminoglycosides are used in endocarditis for synergy for gram-positive infections. Therefore, doses are lower than those used to treat gram-negative infections but require a continuous therapeutic level such that once-daily therapy is not an option.
‡ The infecting strain of *Enterococcus* bacteria must be tested for resistance to aminoglycosides. High-level resistance means loss of synergy, and thus, aminoglycosides should not be used in these instances. Therapy should be prolonged to 8–12 weeks.

The increase of antimicrobial resistance is likely to continue and will complicate treatment decisions in patients with IE. Future studies will be needed to evaluate treatment effectiveness for resistant species of streptococci, staphylococci, and enterococci. Some clinicians believe that the size of the vegetation and other echocardiographic characteristics may predict which patients are at risk for poor outcome and will need early surgery. Advances in imaging methods may make predictions based on characteristics of the vegetations more feasible. In addition, future studies will help to determine whether echocardiographic findings other than perivalvular or myocardial abscess should be added to the list of surgical indications.

**FUTURE DIRECTIONS**

The increase of antimicrobial resistance is likely to continue and will complicate treatment decisions in patients with IE. Future studies will be needed to evaluate treatment effectiveness for resistant species of streptococci, staphylococci, and enterococci. Some clinicians believe that the size of the vegetation and other echocardiographic characteristics may predict which patients are at risk for poor outcome and will need early surgery. Advances in imaging methods may make predictions based on characteristics of the vegetations more feasible. In addition, future studies will help to determine whether echocardiographic findings other than perivalvular or myocardial abscess should be added to the list of surgical indications.

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