

# G Cardiovascular Infections

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## Endocarditis and Intravascular Infections

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### SHORT VIEW SUMMARY

#### Definition

- *Infective endocarditis* (IE) is an infection of the endocardial surface of the heart.

#### Epidemiology

- It is traditionally associated with heart valves damaged by rheumatic heart disease.
- In the current era, health care contact and injection drug use are the primary risk factors.

#### Microbiology

- *Staphylococcus aureus* is now the leading cause of IE in most of the industrialized world.
- Historically, viridans-group streptococci were the most common cause of endocarditis.
- *Bartonella* spp. are the most common cause of culture-negative IE in the United States. Other common causes of culture-negative IE are summarized in Table 80.6.

#### Diagnosis

- Results of blood cultures remain the cornerstone of diagnosis of endocarditis.
- Clinical evaluation alone is insufficient to exclude the possibility of endocarditis.

- Echocardiography, particularly transesophageal echocardiography, has greatly improved the clinician's ability to identify endocarditis.
- Diagnostic schema, such as the modified Duke criteria, are useful in establishing the presence of endocarditis.

#### Therapy

- Cardiac surgery is required in up to half of patients with endocarditis and improves patient outcome.
- Cardiac surgery is especially important in patients with endocarditis who have heart failure, paravalvular abscess, recurrent embolic events, or ongoing sepsis or who are infected with highly resistant or fungal pathogens.
- Although the timing of cardiac surgery, particularly after embolic events involving the central nervous system, remains controversial, emerging evidence supports the benefit of early valve replacement surgery for endocarditis.
- Antibiotic therapy involves extended courses of antibiotics. Treatment is highly pathogen

specific and is summarized in Table 80.7. Guidelines for treatment of IE were updated in 2015.<sup>1</sup>

- Addition of adjunctive low-dose, short-course gentamicin to standard antibiotic treatment of *S. aureus* native valve IE has been shown to confer high risk for nephrotoxicity without significant improvement in clinical outcomes and is not encouraged.
- Several observational studies support the use of high-dose ceftriaxone in combination with ampicillin for the treatment of ampicillin-susceptible, aminoglycoside-resistant enterococcal endocarditis or for patients with underlying renal disease.

#### Prevention

- Prevention of endocarditis involves reduction of bloodstream infections, especially in the health care setting.
- The role of antibiotic prophylaxis for the prevention of endocarditis is controversial. Guidelines were published by the American Heart Association in 2015.

### INFECTIVE ENDOCARDITIS

The term *infective endocarditis* (IE) denotes infection of the endocardial surface of the heart and implies the physical presence of microorganisms in the lesion. Although the heart valves are affected most commonly, the disease also may occur within septal defects or on the mural endocardium. Infections of arteriovenous shunts and of arterioarterial shunts (patent ductus arteriosus) and infections related to coarctation of the aorta are included in the following discussion because the clinical manifestations are similar. The term *infective endocarditis*, first used by Thayer and later popularized by Lerner and Weinstein,<sup>2</sup> is preferable to the former term *bacterial endocarditis*, because nonbacterial pathogens, including fungi and perhaps even viruses, may be responsible for the syndrome.

In the past, IE was classified as *acute* or *subacute*. This distinction was based on the usual progression of the untreated disease and is mainly of historical interest. The acute form follows a fulminant course, usually with high fever, systemic toxicity, and leukocytosis; death occurs in several days to less than 6 weeks. It classically is associated with infection caused by *Staphylococcus aureus*, *Streptococcus pyogenes*, *Streptococcus pneumoniae*, or *Neisseria gonorrhoeae*. The subacute form (death occurring in 6 weeks to 3 months) and the *chronic* form (death occurring later than 3 months) usually are considered together. They commonly occur in the setting of prior valvular disease and are

characterized by a slow, indolent course with low-grade fever, night sweats, weight loss, and vague systemic complaints. These two forms of IE classically are caused by the viridans streptococci.

Although useful conceptually, this classification ignores the nonbacterial forms of IE and the frequent overlap in manifestations of infection by specific organisms, such as the enterococci. A classification based on the etiologic agent responsible is preferable because it has implications for the course usually followed, the likelihood of preexisting heart disease, and the appropriate antimicrobial agents to use.

Although IE is relatively uncommon, it has received considerable attention from clinicians and scientists for the past century. The clinical manifestations of IE are so varied that they may be encountered in any of the medical subspecialties. Successful management depends on the close cooperation of medical and surgical disciplines. Endocarditis services and therapeutic protocols have been created at several tertiary care centers in the United States and Europe. IE has attracted considerable investigative interest. Although the factors that influence its development now are identified more clearly, many questions remain about the unique aspects of this infection, in particular:

1. Why do organisms lodge specifically on the cardiac valves rather than elsewhere in the vascular tree?
2. What enables the microorganisms to survive on the valve surface after colonization?

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3. What are the primary host defenses against induction and progression of the infection?
4. Why do only a relatively few strains of bacteria produce most cases of IE whereas many others produce only bacteremia?
5. What factors are responsible for the marked variation in the manifestations of IE?
6. Why is the infection so difficult to eradicate with antibiotics even though the infecting organisms often are exquisitely sensitive to the drugs *in vitro*?

These questions are discussed in detail in the following sections.

## Epidemiology

The incidence of IE is difficult to determine, because the criteria for diagnosis and the methods of reporting vary with different series.<sup>3,4</sup> An analysis based on strict case definitions often reveals that only a small proportion (approximately 20%) of clinically diagnosed cases are categorized as definite. In a systematic review of IE epidemiology studies from 1980 to 2008, crude incidence of IE ranged between 1.5 and 11.6 cases per 100,000 people.<sup>5</sup> Of note, high-quality data were available only from 10 countries, most of which are high-income areas; the epidemiology of IE in lower-income regions is poorly characterized. With the use of the Nationwide Inpatient Sample, which approximates about a 20% sample of all US acute-care hospitals, several studies have reported significant increases in hospitalizations for IE, with most of this increase being attributable to *S. aureus*.<sup>6</sup> In the International Collaboration on Endocarditis–Prospective Cohort Study (ICE-PCS), the proportion of acute cases had increased from approximately 20% in the preantibiotic era to more than 75% in most of the industrialized world.<sup>7</sup>

## Age

The mean age of patients with IE has increased gradually in the antibiotic era. In 1926, the median age was younger than 30 years;<sup>8</sup> by 1943, it was 39 years, and currently more than half of patients are older than 50 years.<sup>7,9,10</sup> In ICE-PCS, among more than 2700 patients from 58 centers in 25 countries with definite IE according to the modified Duke criteria, the median age was 57.9 years.<sup>7</sup> The disease is uncommon in children, in whom it is associated primarily with (1) underlying structural congenital heart disease, particularly septal defects or complex lesions involving septal defects; (2) surgical repair of these defects; or (3) nosocomial catheter-related bacteremia, especially in infants.<sup>11,12</sup>

The mean age for men is 6 to 7 years older than that for women, and men are affected more commonly (54%–69% of cases); the mean male-to-female ratio is 1.7:1, with a range of 1:1 to 3:1 in 18 large series.<sup>13</sup> Among patients younger than 35 years, more cases occur in women. Many factors may be related to this shift in age distribution. First, there has been a change in the nature of the underlying heart disease owing to a decline in the incidence of acute rheumatic fever and rheumatic heart disease, countered by the increasing importance of degenerative heart disease in elderly patients. Second, the age of the population has been increasing steadily, and people with rheumatic or congenital heart disease are surviving longer. In addition, such patients increasingly are being subjected to prosthetic valve surgery, an important etiologic factor in the pathogenesis of IE.

## Health Care–Associated Infective Endocarditis

A relatively new form of the disease, health care–associated IE, has emerged secondary to the introduction of new therapeutic modalities (e.g., intravenous catheters, hyperalimentation lines, pacemakers, dialysis shunts).<sup>3,7,10,14–16,17</sup> In a prospective, multinational cohort study of more than 1600 patients with native valve endocarditis and no injection drug use, more than one-third of patients had health care–associated endocarditis, which in many cases was community acquired.<sup>17</sup> The emerging importance of health care–associated IE in industrialized nations has also influenced the microbiology of IE, with an increasing prevalence of *S. aureus* and decreasing prevalence of viridans streptococci in much of the industrialized world.

## Pattern of Valvular Involvement

The heart valve involved by the infection varies considerably with the proportion of acute cases reported in each series. The distribution ranges

from 28% to 45% of cases for the mitral valve alone, 5% to 36% for the aortic valve alone, and 0% to 35% for the aortic and mitral valves combined. The tricuspid valve rarely is involved (0%–6% of cases), and the pulmonary valve even less often (<1%).<sup>7,18</sup> Involvement of the aortic valve alone is increasing in frequency and correlates with the increase in acute cases; the incidence was 5% in 1938 and increased to 38% by 2000.<sup>7</sup>

## Predisposing Factors

Almost any type of structural heart disease may predispose to IE, especially if the defect results in turbulence of blood flow. Rheumatic heart disease was the underlying lesion in 37% to 76% of infections in the past, and the mitral valve is involved in more than 85% of cases related to rheumatic heart disease.<sup>13</sup> If the mitral valve alone is involved, women outnumber men by 2 to 1. The aortic valve is affected in approximately 50% of these cases; if it alone is involved, men outnumber women by 4 to 1. Right-sided endocarditis is rare (except in injection drug users and patients with indwelling transvenous pacemakers) and accounts for fewer than 10% of all cases occurring in patients with rheumatic heart disease. In developed countries, the proportion of cases related to rheumatic heart disease has continued to decline (to 5% or less in the past 2 decades),<sup>7</sup> whereas in developing countries rheumatic heart disease<sup>19,20</sup> remains the most common predisposing cardiac condition.<sup>21</sup>

Congenital heart disease (especially patent ductus arteriosus, ventricular septal defect, coarctation of the aorta, bicuspid aortic valve, tetralogy of Fallot, and, rarely, pulmonic stenosis) is responsible in 6% to 24% of endocarditis cases.<sup>7</sup> IE is uncommon in the secundum atrial septal defects, probably because this lesion results in a low-pressure shunt with little turbulence. The congenitally bicuspid aortic valve is an important condition in elderly patients (especially men).<sup>22</sup> In one prospective multicenter analysis, it was present in 16% of 310 cases of definite native valve endocarditis. Half of the patients with bicuspid aortic valve had perivalvular abscess, and 72% required valve surgery.<sup>23</sup> Surgical closure of a ventricular septal defect lowers the risk for IE.<sup>24</sup>

The degenerative cardiac lesions (e.g., calcified mitral annulus, calcific nodular lesions secondary to arteriosclerotic cardiovascular disease, post-myocardial infarction thrombus) assume greatest importance in the 30% to 40% of IE patients without underlying valvular disease. The actual contribution made by these lesions is unknown, but they occur with an increased incidence in the elderly. In one series, degenerative lesions were present in 50% of patients older than 60 years with native valve IE.<sup>25</sup> The contribution of these degenerative cardiac lesions to the development of IE was apparent in an analysis of 148 patients receiving treatment in London after 1970.<sup>26,27</sup> The underlying structural cardiac defects were as follows: rheumatic heart disease in 39 patients, congenital defects in 13, and normal or degenerate valves in 65. Although a calcified mitral annulus is fairly common in elderly women, this lesion rarely is complicated by IE (only 3 of 80 patients in one report).<sup>28</sup> When patients with acute IE are considered separately, more than 50% have no recognized underlying cardiac disease.<sup>29</sup>

Many other conditions, such as bicuspid aortic valve,<sup>22</sup> luetic heart disease, arterioarterial fistulas, hemodialysis shunts or fistulas, intracardiac pacemaker wires, and intracardiac prostheses, may predispose to IE. Prosthetic valve endocarditis is increasing in incidence in proportion to other forms of endocarditis. For example, it was present in one-fifth of the 2781 adults with definite IE in ICE-PCS (see Chapter 81).<sup>7</sup> Intravascular infections involving cardiac devices (e.g., permanent cardiac pacemakers, defibrillators) also have increased significantly since the 1990s and are discussed in Chapter 82.<sup>30,31</sup> IE also occurs more frequently among patients with extensive contact with the health care system.<sup>10,17</sup> As noted previously, injection drug users constitute another group with an increased risk for IE (see later discussion). In this population, there is the added problem of a rapidly rising prevalence of IE among persons with human immunodeficiency virus (HIV) infection. In addition, injection drug users are the group at greatest risk for recurrent and polymicrobial IE.<sup>13,32</sup> Although the contribution of invasive procedures (e.g., sigmoidoscopy, colonoscopy) has been debated, native valve IE seems to be more common among patients with active inflammatory bowel disease (6 of 213 patients in one report<sup>33</sup>).

Although it is not classically recognized as a condition leading to bacterial endocarditis, up to 5% of patients with idiopathic hypertrophic subaortic stenosis develop IE.<sup>34</sup> IE is more common in the subset of these patients who have hemodynamically severe forms of the disease, as manifested by a higher peak systolic pressure gradient and a high prevalence of symptoms. New murmurs develop in 36% of patients with idiopathic hypertrophic subaortic stenosis complicated by IE, and this new physical finding correlates with a higher mortality rate.<sup>34</sup> Among seven cases examined histologically, the infection was found on the aortic valve in three cases, on the mitral valve in two cases, on both valves in one case, and on the subaortic endocardium in one case. This distribution probably is related to the associated mitral regurgitation caused by displacement of the anterior leaflet by the abnormal ventricular architecture and by the turbulence of the jet stream affecting the aortic valve distal to the intraventricular obstruction.

An association has also been recognized between IE and mitral valve prolapse. Among 896 Olmsted County residents with mitral prolapse, the 15-year cohort risk of IE was 1.1%, which was more than eightfold higher than in the general population.<sup>35</sup> All IE cases occurred in patients with concurrent mitral regurgitation.

Mitral valve prolapse should be suspected in patients who have midsystolic clicks with or without a late systolic murmur. The condition is common and has been recognized in 0.5% to 20% of otherwise healthy people, especially young women. It has become apparent that mitral valve prolapse is only one component of a developmental syndrome. This lesion often is associated with a distinct habitus in women,<sup>36</sup> with von Willebrand disease, or with ophthalmoplegia. Some of these characteristics may be useful in identifying patients at high risk for IE. All 25 patients in one series who developed IE on a prolapsing mitral valve had a holosystolic murmur, and none had the isolated click without a murmur.<sup>37</sup>

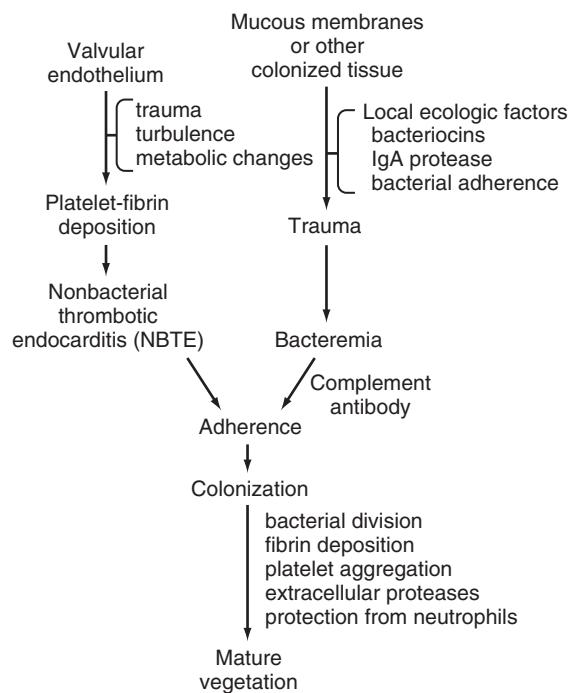
The risk for IE seems to be increased in the subset of patients with mitral valve prolapse who exhibit thickened leaflets with valvular redundancy.<sup>25</sup> In addition, men older than 45 years who have mitral valve prolapse are at increased risk for IE.<sup>38</sup> Nevertheless, the risk for IE is higher in patients with mitral valve prolapse. In a careful retrospective, epidemiologic, matched case-control analysis, the calculated odds ratio (8.2; 95% confidence interval [CI], 2.4–28.4) indicated a substantially higher risk for the development of IE in these patients than in controls.<sup>39</sup> It seems that when IE develops in people with mitral valve prolapse, the symptoms and signs are more subtle and the mortality rate is less than in left-sided IE of other types.<sup>40</sup>

## Pathogenesis and Pathophysiology

In vitro observations and studies in experimental animals have shown that development of IE probably requires the simultaneous occurrence of several independent events, each of which may be influenced by a cadre of distinct factors. The valve surface first must be "altered" to produce a suitable site for bacterial attachment and colonization. Valve surface changes may be produced by various local and systemic stresses, including blood turbulence (from underlying structural or inflammatory valvular disease) and the offending organism itself. These alterations result in the deposition of platelets, fibronectin, fibrin, and other matrix ligands in the formation of so-called sterile vegetation—the lesions of nonbacterial thrombotic endocarditis (NBTE). Bacteria then must reach this site and adhere to and invade the involved tissue to produce colonization and persistence. Certain strains seem to have a selective advantage in adhering to platelets, fibronectin, or fibrin and produce the disease with a lower inoculum. After microbial colonization, the surface is covered rapidly with a protective sheath of fibrin and platelets to produce an environment conducive to further bacterial multiplication and vegetative growth. It is important to point out that, at least for left-sided IE, neutrophils play little role in the pathogenesis of or defense against evolution of IE. The interaction of these events is depicted in Fig. 80.1. In the following sections, these factors are considered independently (for in-depth discussions, see references 41–45).

## Nonbacterial Thrombotic Endocarditis

Luschka, in 1852, first suggested that IE resulted when septic coronary emboli lodged in the vessels of the cardiac valve.<sup>46</sup> This hypothesis was



**FIG. 80.1** Proposed scheme for the pathogenesis of infective endocarditis. IgA, Immunoglobulin A.

discarded, because cardiac valves are poorly vascularized.<sup>43,47,48</sup> It now is clear that the initial colonization occurs on the damaged endothelial surface of the valve. In experimental animals, it is almost impossible to produce IE with intravenous injections of bacteria unless the valvular surface is first perturbed. If a polyethylene catheter is passed across the aortic valve of a rat or rabbit, IE is produced with intravenously injected bacteria or fungi.<sup>49,50</sup> Microscopic examination of this early lesion shows the organisms intimately adherent to fibrin-platelet deposits overlying interstitial edema and mild cellular distortion that have formed in areas of valvular trauma.<sup>51</sup> Scanning electron micrographs of the damaged valvular surface confirm the adhesion of microorganisms to these areas of fibrin-platelet deposition early in the disease course.<sup>52</sup> The organisms are covered rapidly by fibrin.<sup>53</sup>

Opossums and pigs are the only animals known to develop spontaneous IE readily (i.e., without experimentally induced valvular alteration).<sup>44,54</sup> The stress of captivity is apparently sufficient in these animals to produce subtle valvular changes that lead to spontaneous endocarditis and a markedly increased susceptibility to the disease after intravenous injection of bacteria. In other animals and probably in humans, alteration of the valve surface is a prerequisite for bacterial colonization. Angrist and Oka<sup>47</sup> first recognized the importance of these deposits as the crucial factor in allowing bacterial colonization of valve surfaces and suggested the term NBTE. Many forms of exogenous stress produce these lesions experimentally, including infection, hypersensitivity states, cold exposure, simulated high altitude, high cardiac output states, cardiac lymphatic obstruction, and hormonal manipulations.<sup>44</sup> These procedures all increase the susceptibility of the animals to IE.

NBTE has been found in patients with malignancy (particularly pancreatic, gastric, or lung adenocarcinoma) and other chronic wasting diseases, rheumatic and congenital heart disease,<sup>47</sup> uremia, and connective tissue diseases such as systemic lupus erythematosus (SLE) and rheumatoid arthritis; after the placement of intracardiac catheters (e.g., Swan-Ganz); and after a self-limited acute illness. NBTE generally reflects one of two pathogenic mechanisms: hypercoagulability (especially related to secondary antiphospholipid syndromes) or endothelial damage. In a careful analysis performed in Japan, NBTE was found in 2.4% of 3404 autopsies, especially in elderly people with chronic wasting disease.<sup>55</sup> Among patients at high risk for NBTE, the rate may be greater. Cardiac valvular vegetations were found in 19% of 200 nonselected ambulatory

patients with solid tumors undergoing prospective echocardiographic screening.<sup>56</sup> Valvular lesions were most common among patients with carcinoma of the pancreas or lung or lymphoma.

NBTE is most common on the low-pressure side of the cardiac valves along the line of closure, precisely the site most often involved in IE. Whether this lesion is always essential for the development of IE in humans is unknown. Secondary hypercoagulable states (e.g., as seen in secondary antiphospholipid syndromes in SLE) may contribute to the development and propagation of the NBTE lesion.<sup>57</sup>

### Hemodynamic Factors

When associated with valvular insufficiency, IE characteristically occurs on the atrial surface of the mitral valve and the ventricular surface of the aortic valve. Rodbard<sup>58</sup> showed that this localization is related to a decrease in lateral pressure (presumably with decreased perfusion of the intima) immediately downstream from the regurgitant flow. Lesions with high degrees of turbulence (e.g., small ventricular septal defect with a jet lesion, valvular stenosis resulting from insufficient valves) readily create conditions that lead to bacterial colonization, whereas defects with a large surface area (large ventricular septal defect), low flow (ostium secundum atrial septal defect), or attenuation of turbulence (chronic congestive heart failure [CHF] with atrial fibrillation) rarely are implicated in IE. Cures of IE achieved with ligation of an arteriovenous fistula or patent ductus arteriosus without further treatment also highlight the importance of hemodynamic factors. A hyperdynamic circulation itself, such as that developing after experimentally induced arteriovenous fistulas in dogs or after creation of fistulas and shunts in hemodialysis patients, may lead indirectly to IE by producing NBTE.<sup>43,44</sup> Finally, implantable intracardiac prosthetic material may well contribute to a turbulent blood flow state, as seen in intraventricular pacemakers and implantable cardioverter-defibrillators.

The degree of mechanical stress exerted on the valve also affects the location of the IE.<sup>59</sup> In 1024 autopsy cases of IE reviewed through 1952, the incidence of valvular lesions was as follows: mitral, 86%; aortic, 55%; tricuspid, 19.6%; and pulmonic, 1.1%. This incidence correlates with the pressure resting on the closed valve: 116, 72, 24, and 5 mm Hg, respectively.

### Transient Bacteremia

In the setting of preexisting NBTE, transient bacteremia may result in colonization of these lesions and may lead to the development of IE.<sup>60</sup> Transient bacteremia occurs whenever a mucosal surface heavily colonized with bacteria is traumatized, such as occurs with dental extractions and other dental procedures or with gastrointestinal, urologic, or gynecologic procedures (Table 80.1).<sup>60,61</sup> The degree of bacteremia is proportional to the trauma produced by the procedure and to the number of organisms inhabiting the surface; the organisms isolated reflect the resident microbial flora. The bacteremia usually is low grade ( $\leq 10$  colony-forming units [CFUs]/mL) and transient; the bloodstream usually is sterile in less than 15 to 30 minutes.

In two studies in which samples for blood cultures were drawn from patients with severe gingival disease before the dental procedure, spontaneous bacteremia was identified in 9% to 11% of the patients. Other studies have shown an even higher frequency of spontaneous bacteremia. Of the blood cultured from healthy people, 60% to 80% of specimens were positive when filters and anaerobic techniques were used.<sup>62</sup> The degree of bacteremia was low, however, with only 2 to 10 CFUs/5 mL of blood isolated. "Nonpathogenic" organisms, such as *Propionibacterium* (now *Cutibacterium*) *acnes*, *Actinomyces viscosus*, *Staphylococcus epidermidis*, and other *Actinomyces* or streptococcal species, were responsible. Frequent episodes of silent bacteremia also are suggested by the identification of circulating humoral antibodies to the resident oral flora and by the noted increase in sensitized peripheral T cells to the flora of dental plaque. The frequency of such silent bacteremias in the probable pathogenesis of IE has contributed to the current concept that individual dental procedures are uncommonly the cause of such infections.<sup>63</sup> In contrast, it is currently believed<sup>64</sup> that underlying gingivodental disease results in intermittent, low-level bacteremia that can seed damaged valvular endothelial lesions in an unpredictable scenario.

**TABLE 80.1 Incidence of Bacteremia After Various Procedures**

PROCEDURE OR MANIPULATION	% POSITIVE BLOOD CULTURES
<b>Dental</b>	
Dental extraction	18–85
Periodontal surgery	32–88
Chewing candy or paraffin	17–51
Tooth brushing	0–26
Oral irrigation device	27–50
<b>Upper Airway</b>	
Bronchoscopy (rigid scope)	15
Tonsillectomy	28–38
Nasotracheal suctioning or intubation	16
<b>Gastrointestinal</b>	
Upper gastrointestinal endoscopy	8–12
Sigmoidoscopy or colonoscopy	0–9.5
Barium enema	11
Percutaneous needle biopsy of liver	3–13
<b>Urologic</b>	
Urethral dilation	18–33
Urethral catheterization	8
Cystoscopy	0–17
Transurethral prostatic resection	12–46
<b>Obstetric or Gynecologic</b>	
Normal vaginal delivery	0–11
Punch biopsy of the cervix	0
Removal or insertion of intrauterine (contraceptive) device	0

Data from Everett ED, Hirschmann JV. Transient bacteremia and endocarditis prophylaxis: a review. Medicine (Baltimore). 1977;56:61.

Another crucial factor during the transient bacteremia stage is susceptibility of the potential pathogen to complement-mediated bactericidal activity. Only "serum-resistant," gram-negative aerobic bacilli (e.g., *Escherichia coli*, *Pseudomonas aeruginosa*, *Serratia marcescens*) reliably produce experimental IE in rabbits,<sup>65,66</sup> and this property is found in all isolates from human cases of IE. Although experimental IE can be induced in rats with "serum-sensitive" *E. coli*, the organisms are eliminated rapidly on catheter removal.<sup>66</sup>

### Microorganism–Nonbacterial Thrombotic Endocarditis Interaction

The ability of certain organisms to adhere to NBTE lesions is a crucial early step in the development of IE. Gould and associates<sup>67</sup> showed that organisms commonly associated with IE (enterococci, viridans streptococci, *S. aureus*, *S. epidermidis*, *P. aeruginosa*) adhered more avidly to normal canine aortic leaflets in vitro than did organisms uncommon in IE (*Klebsiella pneumoniae*, *E. coli*). In addition, *S. aureus* and the viridans streptococci produce IE more readily than does *E. coli* in the rabbit model of IE.<sup>68</sup> This observation correlates with the relative frequency with which these organisms produce the disease in humans. The rarity of IE due to gram-negative aerobic bacilli also may be related to their serum sensitivity, as noted previously.

Differences in the propensity to cause IE are apparent even within a single species. For example, specific clones of *S. aureus*, including clonal complexes 30<sup>69,70</sup> and 22,<sup>71</sup> have been reported to be associated with an increased risk for IE. In addition, only 2 of the 11 capsular serotypes of *S. aureus* described to date, serotypes 5 and 8, account for

approximately 75% of clinical isolates, whereas highly mucoid strains (e.g., serotypes 1 and 2) are rarely recovered. Nevertheless, mutant strains devoid of microencapsulation had significantly lower median infective dose ( $ID_{50}$ ) values in a rat (catheter-induced NBTE) IE model,<sup>72</sup> compared with wild-type parent strains. Microcapsule expression may attenuate *S. aureus* IE production by blocking bacterial cell surface adhesins, but this hypothesis requires confirmation. In addition, an increasing number of reports suggest that other specific pathogen characteristics in *S. aureus* are associated with the severity of infection caused by these strains in humans.<sup>73–77</sup>

Other studies using an elegant experimental model of IE after dental extraction in rats with sucrose-induced periodontitis, which closely resembles the presumed pathogenetic sequence in humans, also have suggested an important role for bacterial adhesion to NBTE in the early events. Although viridans streptococci were isolated much more commonly than group G streptococci in blood cultures obtained 1 minute after extraction, the latter strains caused 83% of the IE episodes in this rat model.<sup>78,79</sup> This propensity to cause IE was associated with an increased adhesion of group G streptococci to fibrin-platelet matrices in vitro.<sup>79</sup>

The adherence of oral streptococci to NBTE may depend on the production of a complex extracellular polysaccharide, dextran. This polymer plays an essential role in the pathogenesis of dental caries by *Streptococcus mutans*.<sup>80</sup> Dextran allows the organism to adhere tightly to the surface of dental enamel. The enhanced ability to adhere to inert surfaces also may be important in IE. In an analysis of 719 cases of streptococcal infections in the United Kingdom, 317 cases of IE were found.<sup>81</sup> The most common etiologic agents were *Streptococcus sanguinis* (16.4% of the cases), previously identified in *Streptococcus* subacute bacterial endocarditis, and *S. mutans* (14.2%). Ratios of endocarditis to nonendocarditis bacteremia caused by particular organisms have been derived (Table 80.2), allowing prediction of the relative propensity for a particular organism to cause IE. The ratios range from 14.2:1 for *S. mutans* to a reversed ratio of 1:32 for *S. pyogenes*. Only the first four organisms listed in Table 80.2 (all with ratios >3:1) produce extracellular dextran. This finding suggests that dextran production may be another virulence factor in the pathogenesis of IE.

The role of dextran in the adherence of oral streptococci to NBTE also has been studied in vitro with the use of artificial fibrin-platelet matrices (simulating NBTE). The amount of dextran produced by

organisms grown in broth correlated with adherence; the amount was increased by incubating the organism in sucrose (which stimulates dextran production) and decreased by the addition of dextranase (which removes the dextran from the cell surface). The addition of exogenous dextran to *S. sanguinis* grown in sucrose-free media increased adherence. Dextran production also correlated directly with the ability of these organisms to produce IE in vivo in the rabbit model.<sup>82</sup> The strain of *S. sanguinis* produced IE less readily when incubated in dextranase than did control strains, and a strain that produced large quantities of dextran produced endocarditis more easily than did a strain that produced relatively small quantities of dextran. Dextran production also increased the adherence of *S. mutans* to traumatized canine aortic valves in vitro,<sup>83</sup> an effect that was dependent on polymers of higher molecular weight.<sup>84</sup> Dextran formation (or, more properly, exopolysaccharide or glycocalyx production) by oral streptococci may be a virulence factor for the production of IE by these organisms.<sup>85</sup> Continued in vivo synthesis of exopolysaccharide during experimental IE correlated with vegetation size and resistance to antimicrobial therapy.<sup>86,87</sup> Measurement of cell-adherent glycocalyx with a quantitative spectrophotometric tryptophan assay among viridans streptococci isolated from blood cultures has potential value as an independent predictor of the likelihood of IE.<sup>88</sup> Non-dextran-producing streptococci may produce IE in humans and adhere to artificial fibrin-platelet surfaces in vitro,<sup>89</sup> suggesting that other microbial surface characteristics are instrumental for this early event. Whatever the role of the extracellular glycocalyx in microbial adhesion, its presence may retard antimicrobial therapy for streptococcal endocarditis (see later discussion).<sup>86,87,90</sup>

FimA, a surface adhesin expressed by viridans streptococci, has been shown to mediate the attachment of such organisms to platelet-fibrin matrices in vitro and to experimental NBTE lesions in the animal model of IE.<sup>91</sup> Homologues of the *fimA* gene are widely distributed among clinical strains of viridans streptococci and enterococci, suggesting its importance in IE.<sup>92</sup> Several lines of experimental evidence have confirmed further the key role of FimA in the pathogenesis of IE. Inactivation of the *fimA* gene has yielded viridans streptococcal mutants exhibiting a significant decrease in virulence in experimental IE compared with the parental strain having intact FimA expression.<sup>91</sup> In addition, animals either passively immunized with anti-FimA antibody or actively immunized with a FimA vaccine were significantly less susceptible to experimental IE than nonimmunized controls.<sup>92</sup>

#### Viridans-Group Streptococcal Interactions With Platelets

The viridans-group streptococci interact with human platelets through several mechanisms that may contribute to the pathogenesis of IE. A locus of *Streptococcus gordonii*, important for binding to human platelets,<sup>93</sup> encodes a large, serine-rich repeat (SRR) cell wall-anchored glycoprotein adhesin (GspB), which comprises four proteins mediating the glycosylation of the adhesin,<sup>94–96</sup> and a specialized, multicomponent transporter (the accessory Sec system) that mediates the export of the adhesin to the bacterial surface. GspB binds to platelets via its interaction with sialoglycans on the platelet receptor glycoprotein Ib.<sup>97,98</sup> Subsequent studies have shown that the GspB-accessory Sec locus is highly conserved in other species of oral streptococci implicated as causes of IE, including *S. sanguinis*, *Streptococcus mitis*, and *Streptococcus oralis*.<sup>99</sup> Most homologues of GspB in these organisms also appear to be sialoglycan-binding adhesins, but they can differ in the type and range of sialylated glycan bound.<sup>99,100</sup> Loss of GspB expression was linked with decreased virulence in experimental IE.<sup>101</sup> Similar results have been reported for Hsa, a homologue of GspB expressed by another strain of *S. gordonii*,<sup>102,103</sup> indicating that at least some of the SRR adhesins are conserved virulence factors in IE. Of note, several other SRR adhesins of gram-positive pathogens have been linked to virulence in the setting of IE and other infections.<sup>104–107</sup>

A second mechanism for the binding of viridans-group streptococci to platelets is through the surface expression of bacteriophage-encoded proteins. Studies with *S. mitis/oralis* strain SF100 found that three proteins of a lysogenic phage (SM1) enhanced platelet binding in vitro and contributed to virulence for IE.<sup>108,109</sup> PblA is a “tape measure protein” (important for phage morphogenesis), whereas PblB is a tail fiber protein.

**TABLE 80.2 Ratio of Infective Endocarditis Cases to Nonendocarditis Bacteremia Cases for Various Streptococci and Enterococci**

ORGANISM	ENDOCARDITIS:NONENDOCARDITIS RATIO
<i>Streptococcus mutans</i>	14.2:1
<i>Streptococcus bovis</i> I	5.9:1
Dextran-positive <i>Streptococcus mitior</i>	3.3:1
<i>Streptococcus sanguinis</i>	3:1
<i>S. mitior</i>	1.8:1
Unclassified viridans streptococci	1.4:1
<i>Enterococcus faecalis</i>	1:1.2
Miscellaneous streptococci	1:1.3
<i>S. bovis</i> II	1:1.7
<i>Streptococcus anginosus</i>	1:2.6
Group G streptococci	1:2.9
Group B streptococci	1:7.4
Group A streptococci	1:32

Modified from Parker MT, Ball LC. Streptococci and aerococci associated with systemic infection in man. J Med Microbiol. 1976;9:275.

Both proteins are linked to the bacterial surface through their interactions with choline groups within the cell wall. In addition, the phage lysin protein becomes similarly associated with the cell wall, and mediates platelet binding through its interaction with fibrinogen.<sup>110,111</sup> One puzzling issue was how these bifunctional phage proteins exit the bacterium and adhere to its surface. It appears that there is some constitutive, low-level expression of the phage lytic cycle, which results in the expression of phage holin and lysin.<sup>112</sup> The net effect is to render the bacteria more permeable, so that PblA, PblB, and lysin leak from the bacteria and then bind back to the surface, where they can serve as adhesins. This is a remarkable system, because it is perhaps the first example of a phage-encoded bacterial surface structure and adhesin, and because it suggests a coadaptation or coevolution of the bacterium and the phage, wherein the bacterium is essential for phage replication and the phage gives the bacterium a selective advantage by providing it with a critical adhesin to colonize cognate ligands on platelets.

#### Adhesion to Nonbacterial Thrombotic Endocarditis by Other Organisms

A similar important role of adhesion to NBTE in the pathogenesis of IE has been shown for yeasts. *Candida albicans* adheres to NBTE in vitro and produces IE in rabbits more readily than does *Candida krusei*, a nonadherent yeast rarely implicated in IE in humans.<sup>113</sup> Although microbial adhesion is a crucial early event in the pathogenesis of IE, the precise intracardiac loci are unknown and may differ among organisms. Most organisms probably adhere initially to a constituent of NBTE; some evidence implicates fibronectin as the host receptor within NBTE.<sup>114</sup> More recent studies<sup>115,116</sup> have supported this concept. Low-fibronectin-binding mutants of *S. aureus* and *S. sanguinis* had decreased ability to produce IE in rats, compared with high-fibronectin-binding parent strains. Other normal constituents of damaged endothelium or NBTE (e.g., fibrinogen, laminin, type IV collagen<sup>117</sup>) also may serve to bind circulating bacteria. *Abiotrophia defectiva*, a major species isolated in cases of IE caused by *Abiotrophia* and *Granulicatella* spp.<sup>118</sup> (previously referred to as nutritionally variant streptococci, and discussed later), bound the extracellular matrix of fibroblasts and endothelial cells in a saturable-specific manner, whereas *Granulicatella adiacens* and other *Granulicatella* strains did not bind.<sup>119</sup> A study also documented binding of *S. mutans*, *S. mitis*, *S. sanguinis*, and *Enterococcus faecalis* to this extracellular matrix. Laminin-binding proteins (e.g., a 145-kDa protein found in *S. gordonii*) were identified on the cell walls of organisms recovered from patients with IE,<sup>120</sup> and the level of protein expression seemed to be regulated by the presence of extracellular matrix proteins.

#### Pathogenesis of *Staphylococcus aureus* Infective Endocarditis

Other organisms may bind directly to, or become ingested by, endothelial cells as the initial event.<sup>121–124</sup> This sequence appears to be important in the initiation of IE by *S. aureus* on “normal” cardiac valves or on native endothelial surfaces adjacent to damaged endothelial sites. Many studies in experimental IE using *S. aureus* as the study organism have shed additional light on the importance of microbial binding to specific matrix proteins found within the NBTE lesion on the development of IE. It seems that the key adhesin possessed by the organism for induction of IE is one or more of its several fibrinogen-binding proteins (e.g., clumping factor, coagulase<sup>125,126</sup>). Adhesins for other matrix molecules (e.g., fibronectin, collagen, thrombospondin<sup>127–129</sup>) are not involved pivotally in initial attachment of the organism to damaged endothelium but are crucial in persistence of the microbe at this site. Additional virulence factors produced by this organism ( $\alpha$ -toxin<sup>130</sup>) have been identified in the experimental IE model as important for persistence and proliferation of the organism within maturing vegetations in the next stage of infection, after valvular colonization. The fibronectin-binding adhesins of *S. aureus* seem to be crucial in the ability of the organism to invade cardiac endothelium and induce endothelial apoptosis,<sup>131–133</sup> although the specific microbial surface-host receptor ligand relationship remains incompletely defined for all the major IE pathogens. This is an active area of investigation, because inhibition of these events may provide novel prophylactic strategies.

Recently, the expression, structure, and binding activity of the two major *S. aureus* fibronectin-binding proteins (FnBPA, FnBPB) were determined in clinical isolates from patients with persistent bacteremia (frequently IE) or resolving bacteremia.<sup>134</sup> The persistent bacteremia isolates formed significantly stronger bonds with immobilized fibronectin as determined by dynamic binding measurements performed with atomic force microscopy. Several notable differences were also observed when the results were grouped by clonal complex 5 (CC5) strains versus CC45 strains. Fibronectin-binding receptors on CC5 formed stronger bonds with immobilized fibronectin. The *fnaA* gene was expressed at higher levels in CC45, whereas *fnaB* was found in only CC5 isolates. Sequencing of *fnaA* revealed discrete differences within high-affinity, fibronectin-binding repeats (FnBRs) of FnBPA that included (1) 5-amino-acid polymorphisms in FnBR-9, FnBR-10, and FnBR-11 involving charged or polar side chains; (2) an extra, 38-amino-acid repeat inserted between FnBR-9 and FnBR-10 exclusively seen in CC45 isolates; and (3) CC5 isolates that had the SVDFFED epitope in FnBR-11 (a sequence shown to be essential for fibronectin binding), whereas this sequence was replaced in all CC45 isolates with GIDFVED (a motif known to favor host cell invasion at the cost of reduced fibronectin binding). These complementary sequence and binding data suggest that differences in *fnaA* and *fnaB*, particularly polymorphisms and duplications in FnBPA, give *S. aureus* two distinct advantages in human endovascular infections: (1) FnBPs similar to that of CC5 enhance ligand binding and foster initiation of disease, and (2) CC45-like FnBPs promote cell invasion, a key attribute in persistent endovascular infections.

#### Effect of Antibiotics on Development of Infective Endocarditis

The importance of adherence characteristics in the development of IE also has been examined through the use of preincubation of organisms with antibiotics. Many classes of drugs, after incubation even at subinhibitory concentrations, decrease the adhesion of streptococcal species to fibrin-platelet matrices and damaged canine valves in vitro.<sup>135</sup> Several elegant studies in animal models verified the significance of this in vitro observation: preincubation of the organism in subinhibitory antibiotic concentrations prevented the development of IE in vivo.<sup>136,137</sup> This finding has direct relevance to the chemoprophylactic prevention of IE (see Chapter 83). In one study, subinhibitory concentrations of penicillin were found to result in a loss of streptococcal lipoteichoic acid, with reduced adhesion to NBTE-involved tissue and an impaired ability to produce IE in vivo.<sup>138</sup> Antibiotics may prevent IE by at least two mechanisms: bacterial killing and inhibition of adhesion to NBTE-involved tissue.<sup>139</sup>

#### Platelets and the Pathogenesis of Infective Endocarditis

Because platelets and fibrin are the major constituents of NBTE, the role of the platelet in the pathogenesis of IE also has been studied. Some strains of bacteria have been found to be potent stimulators of platelet aggregation and the release reaction.<sup>140</sup> In general, IE-producing strains of staphylococci and streptococci more actively aggregate platelets than do other bacteria that less frequently produce IE. Bacteria-platelet aggregates have been found in the peripheral blood of patients with bacteremia. The importance of these aggregates in the formation of the vegetation (or, conversely, the effect of the aggregation on the rate of removal of organisms from the circulation) is unknown. In one study, even small numbers of platelets greatly increased the adherence of oral streptococci to fibrin in vitro.<sup>81</sup> Other studies<sup>141</sup> showed that *S. sanguinis*, an important cause of IE, aggregates platelets and adheres to these blood components by means of protease-sensitive components, not dextrans. A platelet receptor for ligands on certain strains of *S. sanguinis* was suggested. However, this platelet aggregation by viridans streptococci requires direct platelet binding and plasma components.<sup>142</sup> Other experiments implicated immunoglobulin G (IgG) in this specific streptococcal bacteria-platelet interaction and suggested that platelet activation is mediated through the platelet surface Fc receptor, with a molecular weight of 40,000 daltons.<sup>143</sup>

After colonization of the valve occurs and a critical mass of adherent bacteria develops, the vegetation enlarges by further platelet-fibrin

deposition and continued bacterial proliferation. There is a complex interplay among factors responsible for bacteria-platelet adhesion and aggregation. The ability of *S. sanguinis* to induce platelet aggregation in vitro is conferred by two bacterial cell surface antigens: (1) class I antigen, which promotes adhesion of *S. sanguinis* to platelets ( $\text{adh}^+$ ), and (2) coexpression of class II antigen, which promotes platelet adhesion or platelet aggregation ( $\text{agg}^+$ ). At least nine  $\text{adh}/\text{agg}$  phenotypes have been identified among naturally occurring variants, reflecting a range of platelet interactivity. Intravenous inoculation of  $\text{agg}^+$  *S. sanguinis* strains into rabbits with catheter-induced aortic valve trauma led to larger vegetations, a more severe clinical course, more gross lesions in major organs, and greater mortality than inoculation with an  $\text{agg}^-$  strain or with the  $\text{agg}^+$  strains pretreated with Fab fragments specific for the platelet interactivity phenotype.<sup>144</sup> Platelet aggregation induced by *S. sanguinis* in vivo seems to be an important virulence determinant of vegetation development and disease progression. Streptococcal exopolysaccharide production inversely correlates with platelet adhesion while inhibiting aggregation,<sup>145</sup> indicating that these surface molecules may enhance endocarditis at some pathogenic steps but not at others.

The manner in which *S. aureus* interacts with platelets in the pathogenesis of IE differs substantially from that of the viridans streptococci. This interaction does not require the presence of specific antistaphylococcal antibody and is not amplified by the platelet Fc receptor.<sup>146</sup> Platelet-*S. aureus* interactions for executing aggregation require fibrinogen as a bridging molecule but are independent of the primary platelet fibrinogen-binding site, the glycoprotein IIb/IIIa integrin receptor. In addition, it seems that *S. aureus* can bind to platelets via platelet-derived von Willebrand factor or directly to von Willebrand factor receptor, at von Willebrand factor-binding domain.<sup>147-149</sup> In addition, platelet surface-expressed gC1qR can serve as a key “docking site” for staphylococci, predominantly through bridging molecules such as protein A and von Willebrand factor.<sup>150</sup> In experimental IE, transposon inactivation of the putative *S. aureus* platelet-binding adhesin gene resulted in mutants with diminished capacity to adhere to platelets in vitro in either suspension or surface-bound monolayers.<sup>151</sup> In experimental IE caused by such low-platelet-binding mutants, the induction rates of IE were equivalent to the induction rates of the parental strain, presumably because of the microbe’s ability to attach to damaged endothelium by multiple adhesive mechanisms. However, the capacity of the mutant to persist and proliferate within experimental vegetations and to disseminate hematogenously to the kidneys was markedly impaired in the mutant strain.<sup>151</sup> This transposon defect was found to reside within the staphylococcal fibrinogen adhesin gene, clumping factor A (*clfA*).<sup>152</sup>

Platelets also may play a role in host defense within the cardiac vegetation during IE.<sup>153</sup> It is underappreciated that platelets can actually phagocytose circulating staphylococci into engulfment vacuoles, in which the organism can persist.<sup>154</sup> Moreover, after specific exposure to thrombin (which is plentiful at the surface of damaged endothelium), release of  $\alpha$ -granule-derived platelet microbicidal proteins (PMPs) or thrombocidins with bactericidal activity against most gram-positive cocci that cause IE has been shown.<sup>155</sup> PMPs appear to be homologues of platelet factor 4,<sup>156</sup> whereas thrombocidins evolve from the platelet basic peptide lineage and are truncates of the chemokines NAP-2 and CTAP-3.<sup>157</sup> Although the ability of *S. aureus* to adhere to and aggregate platelets is a related property, the resistance to PMPs is an independent phenotypic characteristic and a potential virulence factor.<sup>158</sup> PMPs are low-molecular-weight (8–10 kDa) cationic proteins that act primarily on the bacterial cell membrane or cell wall, synergistically with antibiotics, to kill bacteria. PMPs also have shown fungicidal activity against some yeasts in vitro.<sup>159</sup>

Microbial resistance to the microbicidal activity of PMPs may contribute to the pathogenesis of IE. This hypothesis was supported by a reduction in vegetation weight and bacterial concentration in rabbits with experimental aortic valve *S. aureus* endocarditis after treatment with aspirin.<sup>160</sup> In addition, three studies in experimental IE confirmed the importance of the relationship of PMP resistance and the pathogenesis of IE. In experimental viridans streptococcal IE and *S. aureus* IE, PMP-resistant strains exhibited an enhanced capacity to persist at sites of valvular damage.<sup>161,162</sup> In addition, *S. aureus* strains exhibiting the PMP

resistance phenotype in vitro were able to proliferate within the vegetation and hematogenously seeded extracardiac foci (kidneys, spleen) to a significantly greater extent than their isogenic counterparts, which were PMP susceptible in vitro.<sup>163,164</sup>

Several clinical studies also emphasized the important association between PMP resistance and the pathogenesis of intravascular infections. Bloodstream isolates of viridans streptococci and *S. aureus* from patients with IE tended to be substantially more resistant to PMPs in vitro.<sup>162</sup> *S. aureus* bloodstream isolates arising from an intravascular source (catheter or IE) were significantly more resistant than bloodstream isolates arising from a deep tissue source.<sup>165</sup> Furthermore, PMP-resistant *S. aureus* bloodstream isolates from patients with IE were significantly more likely to have arisen from an intravascular catheter source.<sup>166</sup> In addition, data have shown fusion of PMP-rich  $\alpha$ -granules with platelet engulfment vacuoles noted earlier, implicating the intrinsic PMP-resistance phenotypes of engulfed staphylococci in their ultimate intraplatelet survival outcomes.<sup>154</sup> Should the engulfed organism be intrinsically PMP-resistant, the platelet could serve as a “Trojan horse” vehicle to disseminate the organism. In contrast, if the phagocytosed staphylococci were PMP susceptible, this mechanism could eliminate the organism from the circulation.<sup>154</sup> Lastly, when methicillin-resistant *S. aureus* (MRSA) isolates derived from patients with “persistent bacteremia” (>7 days of positive blood cultures despite in vitro susceptibility to the antibiotic being administered [usually vancomycin]) are examined, such strains tend to be more PMP resistant than MRSA from patients with rapidly resolving bacteremia.<sup>167,168</sup> Not surprisingly, such “persistent bacteremia” patient populations are enriched for underlying IE.<sup>169</sup>

## Interactions Between Bacteria and the Growing Vegetation

In IE, the bacterial colonies are found beneath the surface of the vegetation (at variable depth, depending on the intracardiac location<sup>170</sup>) and infiltration by phagocytic cells is minimal; the vegetation creates an environment of impaired host resistance. These conditions allow for relatively unbridled bacterial growth, resulting in extremely high colony counts of  $10^9$  to  $10^{11}$  bacteria per 1 g of tissue. Bacteria deep within the fibrin matrix have been shown by autoradiography to reach a state of reduced metabolic activity.<sup>171</sup> Studies by Yersin<sup>172</sup> and Meddens<sup>173</sup> and their colleagues suggested that impairment of host defenses (e.g., neutropenia, corticosteroids) potentiates progression of the disease when the tricuspid but not the aortic valve is involved but is largely dependent on the intracardiac location of the vegetation.<sup>174</sup>

The role of granulocytes within the vegetation is unknown. When vegetation formation is retarded with anticoagulants in experimental animals with IE, the organisms seem to divide on the surface, total bacterial titers are lower, and the clinical disease is more explosive.<sup>175,176</sup> In addition, it has been suggested that phagocytosis of microorganisms by monocytes on or within the vegetation generates tissue thromboplastin formation; thromboplastin then acts as a stimulant to fibrin deposition and growth of the vegetation.<sup>177</sup> However, the best evidence suggests that coagulation activation initiated by tissue factor,<sup>178</sup> with subsequent local thrombus formation, is responsible for the initiation of vegetation growth and persistence on the cardiac valve. It seems that some organisms (e.g., *S. aureus*) induce tissue factor production by endothelium without the necessity for host cytokines.<sup>179</sup>

Many important studies have elucidated the interactions among the invading microbe, the endothelium, and the monocyte in the pathogenesis of IE. After internalization by endothelial cells in vitro, microbes such as *S. aureus* evoke a potent proinflammatory chemokine response, including, for example, increased expression of interleukin (IL)-6 or IL-8 or of monocyte chemotactic peptide.<sup>180,181</sup> This event also is associated with increased expression on the endothelial cell surface of several key adhesion molecules, especially intercellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion molecule 1 (VCAM-1).<sup>124,180,181</sup> Among other cells, monocytes are drawn into this endothelial cell microenvironment; via their appropriate counterreceptors, monocytes can bind avidly to such microbe-activated endothelial cells.<sup>181</sup> Extracellular bacteria circulating in the vascular system then bind directly to the monocyte surface, inducing the release of tissue thromboplastin (tissue factor).<sup>182,183</sup> This latter molecule participates in the catalytic conversion

of prothrombin to thrombin, amplifying the procoagulant cascade at the site of endothelial cell colonization and leading to progressive evolution of the vegetative lesion in IE. Several studies have emphasized that organisms with low protease production (e.g., enterococci) are associated with larger, more friable vegetations with an increased tendency for embolization. This property was underscored in an elegant animal study by inducing IE with an enterococcus with low proteolytic activity and virulence to analyze the role of host proteases in vegetation growth. Matrix metalloprotease 9, elastase, and plasminogen activators were all present at higher concentrations in septic vegetations. These results suggest that the continuous attractant signals coming from bacterial colonies can result in chronic injury of myocardial tissues by host proteases.

### Immunopathologic Factors

IE results in stimulation of humoral and cellular immunity, as manifested by hypergammaglobulinemia, splenomegaly, and the presence of macrophages in the peripheral blood. The possibility that preformed antibody can increase the likelihood of the development of IE was suggested by the spontaneous occurrence of IE in horses receiving repeated immunizations with live pneumococci.<sup>184</sup> It was suggested that these antibodies produced bacterial agglutination in vivo, which increased the chances of valvular colonization. Studies in animals have suggested a protective role for circulating antibody. Rabbits preimmunized with heat-killed streptococci plus Freund adjuvant had a significantly higher ID<sub>50</sub> than that noted for nonimmunized controls after aortic valve trauma.<sup>185</sup> Other studies yielded similar results with *S. sanguinis*, *S. mutans*, and *S. pneumoniae*.<sup>186,187</sup> In additional experiments, antibody directed against cell surface components (including mannan) reduced the adhesion of *C. albicans* to fibrin and platelets in vitro and reduced IE production in vivo.<sup>188</sup> This effect may depend on the infecting organism, however, because antibody to *S. epidermidis* or *S. aureus* did not prevent the development of IE in immunized animals and did not result in reduced bacterial concentrations in infected vegetations or kidneys,<sup>189</sup> perhaps because of the inability of immune sera to enhance opsonophagocytosis of staphylococci. The role of preformed antibody in the pathogenesis of IE is unclear. Intravascular agglutination of bacteria may decrease the frequency of IE by reducing the actual number of circulating organisms, but cross-protection was not achieved with passive transfer of high-titer immune globulin from *Streptococcus defectivus*-immunized rabbits to control animals.<sup>187</sup> Nitrogen mustard-treated immunized rabbits lost their ability to clear *S. defectivus* efficiently from the circulation, a process partially restored by neutrophil transfusion.<sup>190</sup>

The role of the glycocalyx of *S. aureus*, and of antibodies directed against this exopolysaccharide, in the pathogenesis of IE is controversial. Most experimental studies suggest that microencapsulation of strains by the common capsular types (5 and 8) may mitigate virulence of the organism in IE by obscuring key surface-expressed adhesins involved in colonization or persistence at endovascular damage sites.<sup>191</sup>

Several more recent studies suggested a salutary effect of active or passive immunization strategies against this glycocalyx in diminishing the induction, progression, or metastatic infection phases of experimental IE.<sup>192,193</sup> However, large clinical trials have not been able to document salutary outcomes using active or passive immunization strategies directed against the staphylococcal capsule or candidate surface adhesins (e.g., clumping factor).<sup>194–197</sup>

One relatively unexplored area of pathogenesis of IE is dietary impacts on susceptibility to this infection. It is known that diet, and specifically dietary metals, can modify the risk of infection. However, for example, the mechanisms by which manganese (Mn), a common dietary supplement, alters infection remain undefined. The Skaar laboratory<sup>198</sup> has reported that dietary Mn levels can dictate the outcome of experimental *S. aureus* cardiac infections. Mice fed a high-Mn diet displayed increased Mn levels, with preferential localization in and around cardiac abscesses. Although the canonical mammalian Mn-sequestering protein calprotectin surrounded such lesions, it was not released into the abscess nidus and did not limit Mn within cardiac abscesses. Consequently, excess Mn was bioavailable to the organism in the depths of these lesions. Bioavailable Mn is used by *S. aureus* to detoxify reactive oxygen species and

protect the organism from neutrophil killing. Therefore a single dietary modification (i.e., Mn restriction) may be able to help amplify host antistaphylococcal defenses in patients at risk for *S. aureus* IE. Of interest, companies are focusing vaccine efforts to include components designed to raise antibodies against the *S. aureus* Mn receptor.<sup>199</sup>

Rheumatoid factor (anti-IgG IgM antibody) develops in about 50% of patients with IE of longer than 6 weeks' duration.<sup>200</sup> Rheumatoid factors were found at the time of admission in 24% of patients with acute staphylococcal IE (<6 weeks' duration), and the frequency increased to 40% if fever persisted for 2 weeks after the initiation of antibiotic therapy.<sup>201</sup> More than two-thirds of the patients became seronegative after 6 weeks of therapy, and two patients with a second episode of acute IE promptly redeveloped positive rheumatoid factors. The titers correlated with the level of hypergammaglobulinemia and decreased with therapy. Rheumatoid factor may play a role in the disease process by blocking IgG opsonic activity (i.e., by reacting with the Fc fragment), stimulating phagocytosis, or accelerating microvascular damage. Rheumatoid factor (IgM) has not been eluted from the immune complex glomerulonephritis associated with IE.<sup>202</sup> Antinuclear antibodies also occur in IE and may contribute to the musculoskeletal manifestations, low-grade fever, or pleuritic pain.<sup>203</sup>

Similar to malaria, schistosomiasis, syphilis, kala-azar, and leprosy, IE is associated with a constant intravascular antigenic challenge, and the development of several classes of circulating antibody is not unexpected. Opsonic (IgG), agglutinating (IgG, IgM), and complement-fixing (IgG, IgM) antibodies and cryoglobulins (IgG, IgM, IgA, C3, fibrinogen); various antibodies to bacterial heat-shock proteins; and macroglobulins all have been described in IE.<sup>204–206</sup> Antineutrophil cytoplasmic antibodies (ANCA) were present in 12 of 50 patients (24%) in a recent series and were associated with longer duration of symptoms before IE diagnosis.<sup>207</sup> Circulating immune complexes have been found in high titers in almost all patients with IE.<sup>208</sup> Circulating immune complexes are found with increased frequency in connection with a long duration of illness, extravascular manifestations, hypocomplementemia, and right-sided IE. Levels decrease and become undetectable with successful therapy. Patients with IE and circulating immune complexes may develop a diffuse glomerulonephritis that is analogous to the nephritis seen with infected ventriculoatrial shunts.<sup>209</sup> Corticosteroids have been used in a few patients with glomerulonephritis associated with IE.<sup>210</sup> Immune complexes plus complement are deposited subepithelially along the glomerular basement membrane to form a “lumpy-bumpy” pattern. Immune globulin eluted from these lesions has been shown to cross react with bacterial antigens.<sup>211</sup> In addition, bacterial antigens have been shown within circulating immune complexes.<sup>212</sup>

Some of the peripheral manifestations of IE, such as Osler nodes, also may result from a deposition of circulating immune complexes. Pathologically, these lesions resemble an acute Arthus reaction. The finding of positive culture aspirates in Osler nodes<sup>213</sup> suggests, however, that they may be caused by septic emboli rather than immune complex deposition. In some diffuse purpuric lesions in IE, immune complex deposits (IgG, IgM, and complement) have been shown in the dermal blood vessels by immunofluorescence.<sup>214</sup> Quantitative determinations of serum immune complex concentrations are useful in gauging the response to therapy. Effective treatment leads to a prompt decrease, with eventual disappearance of circulating immune complexes.<sup>215</sup> Conversely, therapeutic failures or relapses are characterized by rising titers or a reappearance of circulating immune complexes.<sup>216</sup>

### Pathologic Changes Heart

The classic vegetation of IE usually is located along the line of closure of a valve leaflet on the atrial surface of atrioventricular valves or on the ventricular surface of semilunar valves. Vegetations may be single or multiple; they are a few millimeters to several centimeters in size and vary in color, consistency, and gross appearance. Microscopically, the lesion consists primarily of fibrin, platelet aggregates, and bacterial masses; neutrophils and red blood cells are rare. Killed bacteria detectable with Gram stain within these vegetations sometimes persist for months after therapy.<sup>217</sup> Destruction of the underlying valve may coexist. With treatment, healing occurs by fibrosis and occasionally calcification. The

vegetation in acute cases is larger, softer, and more friable and may be associated with suppuration, more necrosis, and less healing than in subacute cases.<sup>46,218</sup>

This infection may lead to perforation of the valve leaflet or rupture of the chordae tendineae, interventricular septum, or papillary muscle. Staphylococcal IE frequently results in valve ring abscesses<sup>219</sup> with fistula formation into areas of the myocardium or pericardial sac. Aneurysm of the valve leaflet or sinus of Valsalva also is common. Valvular stenosis may result from large vegetations. Myocarditis, myocardial infarction, and pericarditis<sup>218,219</sup> are found frequently at autopsy. Myocardial abscesses are found in 20% of the autopsy cases and are associated primarily with acute staphylococcal IE with hectic fever, a rapid onset of CHF, and conduction disturbances. Myocardial infarcts are found in 40% to 60% of the autopsied cases, often without diagnostic changes on the electrocardiogram. Pericarditis is much more common in patients with acute IE.

Echocardiographic abnormalities are commonly observed in patients with acquired immunodeficiency syndrome (AIDS), but pericardial disease (pericarditis, effusions), myocardial disease leading to heart failure or arrhythmias, NBTE, and Kaposi sarcoma all are generally more frequent than IE. AIDS patients with IE usually are injection drug users with right-sided involvement and have an increased prevalence of cases due to *S. aureus* or fungi.<sup>220</sup> The clinical course in AIDS patients often is more fulminant than that of IE in injection drug users without AIDS; pneumonia and sepsis are common. IE also has been described in the transplanted heart.<sup>221</sup>

Emolic phenomena are common in IE. In the preantibiotic era, 70% to 95% of patients had clinically demonstrable embolic events, but this has decreased to 15% to 35% today. Pathologic evidence of embolization still is detected in 45% to 65% of autopsies, most frequently involving the renal, splenic, coronary, or cerebral circulation. Emboli and immune complex deposition contribute to the extracardiac manifestations of IE and may involve almost any organ system. If large emboli occlude major vessels, fungal endocarditis, marantic endocarditis, or an intracardiac myxoma should be suspected.

## Kidney

Three pathologic processes may be found in the kidney in patients with IE: abscess, infarction, and glomerulonephritis. Abscesses are uncommon, but infarctions have been seen in 56% of the autopsy cases.<sup>2</sup> The kidney usually is normal in size but may be slightly swollen, and petechiae may be found in the capsule. When renal biopsy specimens are obtained during active IE, the renal architecture is abnormal in *all* cases,<sup>222</sup> even in the absence of clinical or biochemical evidence of renal disease. "Focal" glomerulonephritis is found in 48% to 88% of the cases but is rare in acute IE. It is a focal, local, and segmental process characterized by endothelial and mesangial proliferation, hemorrhage, neutrophilic infiltration, fibrinoid necrosis, crescent formation, and healing by fibrosis. Diffuse glomerulonephritis is found in 17% to 80% of the cases and consists of generalized cellular hyperplasia in all glomerular tufts. A less common condition, termed *membranoproliferative glomerulonephritis*, is associated with IE due to *S. epidermidis* and is characterized by marked mesangial proliferation and by splitting of the glomerular basement membrane. Renal interstitial cellular infiltration is common.<sup>222</sup>

Between 10% and 15% of patients with IE exhibit an immune complex glomerulonephritis similar to that seen in SLE.<sup>209,211,215,216</sup> The evidence for immune complex deposition rather than a recurrent embolic phenomenon as the primary pathogenic mechanism includes the following:

1. Bacteria are rarely, if ever, seen in the lesions.
2. Glomerulonephritis can occur with right-sided IE.
3. Glomerulonephritis is rare in acute IE, even though large, friable vegetations result in widespread metastatic abscess formation.
4. Immunofluorescent staining with antiimmunoglobulin antibody reveals the typical lumpy-bumpy distribution seen in other forms of immune complex nephritis.
5. In diffuse glomerulonephritis, subepithelial electron-dense deposits are seen with electron microscopy and IgG, IgM, IgA, or complement is shown in these deposits with immunofluorescence.
6. Specific antibacterial antibody can be eluted from the lesions.<sup>211</sup>

7. Anti-glomerular basement membrane antibody has been found in a single case of IE with nephritis.
8. The glomerulonephritis often is accompanied by hypocomplementemia, with a positive result on serum assay for rheumatoid factor.
9. All of these abnormalities usually resolve with successful antimicrobial therapy as the concentration of circulating immune complexes declines.

## Mycotic Aneurysms

Mycotic aneurysms usually develop during active IE but occasionally are detected months or years after successful treatment. They are more common with viridans streptococcal infections and are found in 10% to 15% of autopsied cases. They may arise by any of several mechanisms: (1) direct bacterial invasion of the arterial wall with subsequent abscess formation or rupture, (2) septic or bland embolic occlusion of the vasa vasorum, or (3) immune complex deposition with resultant injury to the arterial wall. The aneurysms tend to occur at bifurcation points. They are found most commonly in the cerebral vessels (primarily the peripheral branches of the middle cerebral artery), but they also occur in the abdominal aorta; the sinus of Valsalva; a ligated patent ductus arteriosus; and the splenic, coronary, pulmonary, and superior mesenteric arteries. Mycotic aneurysms usually are clinically silent until rupture occurs; consequently, their true incidence in active IE is unknown.<sup>223</sup> Magnetic resonance angiography is a sensitive method for detection of mycotic aneurysms. For example, a prospective single-center study that evaluated 130 consecutive IE patients with cerebral magnetic resonance imaging (MRI) with angiography regardless of symptoms found 10 additional aneurysms that were clinically silent.<sup>224</sup>

## Central Nervous System

Cerebral emboli are the most common neurologic manifestation of IE.<sup>225</sup> Although 20% to 30% of patients with IE have clinically apparent cerebral emboli, the actual rate of cerebrovascular complications is significantly higher. In a study from Sweden, patients with left-sided IE were prospectively evaluated with cerebral MRI regardless of neurologic symptoms. The total cerebrovascular complication rate was 65%, including 35% that were symptomatic and 30% that were clinically silent.<sup>226</sup> This finding was externally validated in a French study that prospectively evaluated 130 IE patients with cerebral MRI with angiography within 7 days of admission and prior to any potential surgical intervention. MRI identified cerebral lesions in 82% of patients and led to changes in the diagnostic or therapeutic plan in 28% of the study patients.<sup>224</sup> A multinational, prospective cohort investigation of 1437 cases of definite left-sided IE found that the crude incidence of stroke in patients receiving appropriate antimicrobial therapy was 4.82 cases per 1000 patient-days in the first week and fell to 1.71 per 1000 patient-days in the second week.<sup>227</sup> The middle cerebral artery and its branches are involved most commonly.<sup>46</sup> Three percent of the cerebral emboli from all causes are secondary to IE. Cerebral infarction, arteritis, abscesses, mycotic aneurysms, intracerebral or subarachnoid hemorrhage, encephalomalacia, cerebritis, and meningitis have been reported.<sup>228</sup> Hemorrhagic transformation of an ischemic infarct due to septic emboli is the most common mechanism leading to fatal intracerebral hemorrhage during IE.<sup>229</sup> True acute purulent meningitis is rare except in pneumococcal endocarditis, but multiple microabscesses (cerebritis) due to *S. aureus* are relatively common in acute staphylococcal IE.

## Spleen

Splenic infarctions have been reported in 44% of autopsy cases but often are clinically silent.<sup>46</sup> Splenic abscesses are an uncommon complication of IE and typically manifest as fever, left upper quadrant abdominal pain, and leukocytosis. Diagnosis is established with computed tomography (CT) or ultrasonography.<sup>230,231</sup> Although splenectomy is a standard therapy for splenic abscess, percutaneous drainage may be an alternative in selected patients.<sup>232</sup> Splenic enlargement is common, and virtually all cases are associated with hyperplasia of the lymphoid follicles, an increase in secondary follicles, proliferation of reticuloendothelial cells, and scattered focal necrosis.<sup>218</sup> Spontaneous rupture of the spleen has occasionally been observed.

## Lung

When right-sided IE is present, pulmonary embolism with or without infarction, acute pneumonia, pleural effusion, or empyema is common. These septic pulmonary emboli commonly manifest on chest radiographs as rounded, "cannonball" lesions. Emboli may be septic or bland.<sup>220</sup>

## Skin

Petechiae are found in 20% to 40% of cases (Fig. 80.2) (see later discussion). Osler nodes consist microscopically of arteriolar intimal proliferation with extension to venules and capillaries and may be accompanied by thrombosis and necrosis. A diffuse perivascular infiltrate consisting of neutrophils and monocytes surrounds the dermal vessels. Immune complexes have been shown in the dermal vessels. Janeway lesions consist of bacteria, neutrophilic infiltration, necrosis, and subcutaneous hemorrhage (Fig. 80.3). Janeway lesions (see later description) are caused by septic emboli and reveal subcutaneous abscesses at histologic examination.<sup>233</sup>

## Eye

Roth spots consist microscopically of lymphocytes surrounded by edema and hemorrhage in the nerve fiber layer of the retina (Fig. 80.4).<sup>234</sup>

## Clinical Manifestations

The interval between an event likely to produce high-grade bacteremia and the onset of symptoms of IE, contrary to older estimates, is quite short. The so-called incubation period in 84% of 76 cases of streptococcal IE was less than 2 weeks.<sup>235</sup> On the other hand, the time from onset of symptoms to diagnosis in the subacute form of IE is quite long, with a median interval of approximately 5 weeks. Symptom duration of cases managed in community hospitals is often shorter than in patients referred to a tertiary care center, reflecting referral bias.<sup>4</sup>

The symptoms and signs of IE (Table 80.3) can be protean, and essentially any organ system may be involved. Four processes contribute to the clinical picture<sup>46</sup>: (1) the infectious process on the valve, including the local intracardiac complications; (2) bland or septic embolization to virtually any organ; (3) constant bacteremia, often with metastatic foci of infection; and (4) circulating immune complexes and other

immunopathologic factors.<sup>41–44,46</sup> As a result, the clinical presentation of patients with IE is highly variable and the differential diagnosis often is broad. Because of its many manifestations, the diagnosis of IE may be delayed; occasionally, it is not clinically suspected and is identified only at postmortem examination.<sup>236–238</sup> In a recent postmortem study of IE cases, in 38.2% IE was not diagnosed until autopsy. Important to note, Fernández Guerrero and colleagues found no significant difference in rates of "clinically occult" IE diagnoses before (1970–1985) and after (1986–2008) the availability of echocardiography at their institution (35% vs. 42.8%, respectively).<sup>239</sup> Fever is common but may be absent (5% of cases), especially in the setting of CHF, renal failure, a terminal disease, older age,<sup>240,241</sup> or previous antibiotic therapy. The fever pattern is usually remittent, and the patient's temperature rarely exceeds 40°C (104°F), except in acute IE. Persistent fever during antimicrobial therapy for IE is



**FIG. 80.2** Conjunctival petechiae in a patient with bacterial endocarditis.



**FIG. 80.3** Janeway lesions in a patient with *Staphylococcus aureus* endocarditis. (From Sande MA, Strausbaugh LJ. Infective endocarditis. In: Hook EW, Mandell GL, Gwaltney JM Jr, et al, eds. Current Concepts of Infectious Diseases. New York: Wiley Press; 1977.)



**FIG. 80.4** Retina from a patient with viridans streptococcal endocarditis showing Roth spots. (From Sande MA, Strausbaugh LJ. Infective endocarditis. In: Hook EW, Mandell GL, Gwaltney JM Jr, et al, eds. Current Concepts of Infectious Diseases. New York: Wiley Press; 1977.)

**TABLE 80.3 Clinical Findings in More Than 2700 Patients With Definite Endocarditis**

SIGNS	PATIENTS (%)
Fever	96
Heart murmur	85
Changing murmur	20
New murmur	48
Vascular embolic event	17
Osler nodes	3
Splinter hemorrhages	8
Janeway lesion	5
Splenomegaly	11
Roth spots	2
Hematuria	26
Conjunctival hemorrhage	5

Modified from Murdoch DR, Corey GR, Hoen B, et al. Clinical presentation, etiology, and outcome of patients with infective endocarditis in the 21st century: the International Collaboration on Endocarditis—Prospective Cohort Study. *Arch Intern Med.* 2009;169:463.

relatively uncommon but may be an ominous sign. In a review<sup>242</sup> of 123 cases of IE managed in Cleveland from 1972 to 1984, approximately half of the patients became afebrile within 3 days after the initiation of antibiotics; approximately 75% had defervesced after 1 week of treatment and 90% did so after 2 weeks of treatment. Prolonged fever (of 2 weeks' duration) is associated with specific etiologic agents (i.e., *S. aureus*, gram-negative bacilli, fungi, culture-negative IE) and, perhaps more important, with microvascular phenomena, embolization of major vessels, intracardiac (e.g., myocardial abscess) or peripheral complications, tissue infarction, a need for cardiac surgery, and a higher mortality rate.<sup>242,243</sup> Pulmonary emboli (bland), drug reactions, and nosocomial infection unrelated to IE also are causes of prolonged fever in this patient population.

Nonspecific symptoms, such as anorexia, weight loss, malaise, fatigue, chills, weakness, nausea, vomiting, and night sweats, are common, especially in subacute cases. These nonspecific symptoms often result in an incorrect diagnosis of malignancy, collagen vascular disease, tuberculosis, or other chronic diseases.

### Cardiac Murmurs

Traditionally, audible heart murmurs occurred in more than 85% of IE cases. However, recent changes in the epidemiology and microbiology of IE appear to have altered the presentation of IE. For example, in the ICE-PCS experience with more than 2700 prospectively identified IE patients, only 48% had a detectable "new" cardiac murmur, whereas a further 20% exhibited worsening of an existing murmur.<sup>7</sup> Moreover, murmurs may well be absent with right-sided or mural IE. When present, the classic "changing murmur" and "new regurgitant murmur" (usually aortic insufficiency) are diagnostically useful signs, often complicating IE caused by more virulent valvular pathogens such as *S. aureus*, group B streptococci, or pneumococci. New or changing murmurs are less common in elderly patients and often lead to diagnostic confusion.<sup>240,244</sup> More than 90% of patients who show a new regurgitant murmur develop CHF. CHF is the leading complication of IE.<sup>245</sup> Pericarditis is rare but, when present, usually is accompanied by myocardial abscess formation as a complication of staphylococcal infection. Although valvular regurgitation is the most important hemodynamic complication of IE, hemodynamically significant valvular obstruction requiring surgery may occur rarely, even without a prior history of valvular stenosis.<sup>246</sup>

### Peripheral Manifestations of Infective Endocarditis

Although the classic peripheral manifestations previously were found in half of cases, their prevalence has decreased in recent years. Clubbing is present in 10% to 20% of patients with subacute IE, especially if the

disease is of long duration, and may recede with therapy. The complete syndrome of hypertrophic osteoarthropathy is rare. Splinter hemorrhages are linear, red-to-brown streaks in the fingernails or toenails and are found commonly in IE. They are a nonspecific finding and are seen often in elderly patients and in patients with occupation-related trauma. These lesions are most suggestive of IE when they are located proximally in the nailbed. Petechiae are found in 20% to 40% of cases, particularly after a prolonged course, and usually appear in crops on the conjunctivae (see Fig. 80.2), buccal mucosa, palate, and extremities. These lesions initially are red and nonblanching but become brown and barely visible in 2 to 3 days. Petechiae may result from local vasculitis or from emboli. Osler nodes are small, painful, nodular lesions usually found in the pads of fingers or toes and occasionally in the thenar eminence. They are 2 to 15 mm and frequently are multiple and evanescent, disappearing in hours to days. Osler nodes are rare in acute cases of IE but occur in 10% to 25% of subacute cases. They are not specific for IE, because they may be seen in SLE, marantic endocarditis, hemolytic anemia, and gonococcal infections and in extremities with cannulated radial arteries. Janeway lesions (see Fig. 80.3) are hemorrhagic, painless macules with a predilection for the palms or soles. They persist for several days and are believed to be embolic in origin; they occur with greater frequency in staphylococcal IE. Roth spots (see Fig. 80.4) are oval, pale, retinal lesions surrounded by hemorrhage and usually are located near the optic disk. They occur in fewer than 5% of patients with IE and also may be found in patients with anemia, leukemia, or connective tissue disorders such as SLE.

### Splenomegaly

The frequency of splenomegaly in IE patients has declined significantly in the current era. Among 2662 prospectively enrolled patients with definite IE in whom the finding was recorded, 11% had splenomegaly.<sup>7</sup> In part, this changing frequency may reflect the much shorter time to diagnosis and treatment today and the predominance of acute rather than subacute IE. Splenic septic emboli are common during IE, but localized signs and symptoms are absent in approximately 90% of patients with this complication.<sup>247</sup> Abdominal CT is highly sensitive and should be employed if prolonged fever or sepsis is present. Serial CT studies usually can be used to distinguish between bland septic emboli and splenic abscess.<sup>248</sup>

### Musculoskeletal Manifestations

Musculoskeletal manifestations are common in IE. In a review of 192 cases,<sup>249</sup> 44% of patients had musculoskeletal symptoms. These symptoms usually occurred early in the disease and were the only initial complaint in 15% of cases. They included proximal oligoarticular or monarticular arthralgias (38%), lower-extremity monarticular or oligoarticular arthritis (31%), low back pain (23%), and diffuse myalgias (19%). The back pain may be severe, limiting movement, and may be the initial complaint in 5% to 10% of cases.<sup>250</sup> These findings may mimic those of rheumatic disease, resulting in a diagnostic delay.

### Embolic Events

Major embolic episodes, as a group, are second only to CHF as a complication of IE and occur in almost one-fourth of cases.<sup>7</sup> Splenic artery emboli with infarction may result in left upper quadrant abdominal pain with radiation to the left shoulder, a splenic or pleural rub, or a left pleural effusion. Renal infarctions may be associated with microscopic or gross hematuria, but renal failure, hypertension, and edema are uncommon. Retinal artery emboli are rare (<2% of cases) and may manifest with a sudden complete loss of vision. A panophthalmitis has been reported with pneumococcal IE. Pulmonary emboli secondary to right-sided IE constitute a common feature in narcotic addicts (see later discussion). Coronary artery emboli usually arise from the aortic valve and may cause myocarditis with arrhythmias or myocardial infarction. This finding may be overlooked, especially given the time constraints of interventions such as thrombolytic therapy or angioplasty during acute myocardial infarction, resulting in serious complications in patients with IE presenting with an acute myocardial infarction.<sup>250</sup> Major vessel emboli (affecting the femoral, brachial, popliteal, or radial artery) are more common in fungal endocarditis.

## Neurologic Manifestations

Neurologic manifestations occur in 20% to 40% of all IE cases. In IE cases admitted to intensive care units, however, neurologic manifestations are the most common IE complication, occurring in 55% of patients.<sup>251</sup> Patients with *S. aureus* IE, mitral valve IE, or nonneurologic embolic events are at increased risk for neurologic complications. Of patients with neurologic complications, 50% present with these signs and symptoms as the heralding features of their illness.<sup>252,253</sup> In a Finnish survey of 218 episodes of definite or possible IE, neurologic complications were identified in 55 episodes (25%), with an embolic event as the most common manifestation (23 of 55 patients, or 42%). Among critically ill IE patients, however, over half may have a neurologic complication.<sup>251</sup> In most episodes (76%), the neurologic manifestation was evident before antimicrobial treatment was started, being the first sign of IE in 47% of episodes.<sup>254</sup> The development of clinical neurologic deterioration during IE is associated with a twofold to fourfold increase in mortality for the implicated etiologic microbe.<sup>215</sup> Mycotic aneurysms of the cerebral circulation occur in 2% to 10% of cases. They usually are single, small, and peripheral and may lead to devastating subarachnoid hemorrhage. Other features include seizures, severe headache, visual changes (particularly homonymous hemianopsias), choreoathetoid movements, mononeuropathy, and cranial nerve palsies. Toxic encephalopathy with symptoms ranging from a mild change in personality to frank psychosis may occur, especially in elderly patients.

## Renal Manifestations

Patients with IE may have symptoms of uremia. In the preantibiotic era, renal failure developed in 25% to 35% of the patients, but presently fewer than 10% are affected. When uremia does develop, diffuse glomerulonephritis with hypocomplementemia usually is found, but focal glomerulonephritis also has been implicated. Renal failure is more common with long-standing disease but usually is reversible with appropriate antimicrobial treatment alone. IE may be confused with thrombotic thrombocytopenic purpura if neurologic signs, fever, renal failure, anemia, and thrombocytopenia are present.<sup>255</sup>

## Infective Endocarditis in Drug Addicts

Acute infection accounts for approximately 60% of hospital admissions among injection drug users, and IE is implicated in 5% to 15% of these episodes.<sup>256</sup> It has proved difficult to predict accurately the presence of IE in a febrile drug addict,<sup>257</sup> especially from history and physical examination findings alone,<sup>258</sup> although cocaine use by an injection drug user should heighten the suspicion of IE.<sup>259</sup> Cocaine was associated strongly with the presence of IE in 102 injection drug users in San Francisco when findings were analyzed with logistic regression analysis, but no such correlation was found among febrile addicts who did not use cocaine. The most reliable predictors of IE in febrile parenteral drug users are visualization of vegetations with echocardiography and the presence of embolic phenomena.<sup>258</sup> Although many of the aforementioned clinical manifestations are seen in addicts with IE, several distinctions are noteworthy. In this group of patients, two-thirds have no clinical evidence of underlying heart disease and there is a predilection for the infection to affect the tricuspid valve. Only 35% of addicts who ultimately proved to have IE showed heart murmurs on admission.<sup>256</sup> The frequency of valvular involvement is as follows: tricuspid alone or in combination with others, 52.2%; aortic alone, 18.5%; mitral alone, 10.8%; and aortic plus mitral, 12.5%. Left-sided involvement has been more common in some series, however.<sup>260</sup>

Of patients with tricuspid valve infection, 30% have pleuritic chest pain; pulmonary findings may dominate the clinical picture, and the chest radiograph shows abnormalities (e.g., infiltrates, effusion) in 75% to 85% of the cases.<sup>261</sup> Radiographic evidence of septic pulmonary emboli is eventually present in 87% of cases.<sup>262</sup> Signs of tricuspid insufficiency (gallop rhythm, systolic regurgitant murmur louder with inspiration, large V waves, or a pulsatile liver) are present in only one-third of cases. Most of these patients are 20 to 40 years old (80%), and men predominate in a ratio of 4:1 to 6:1. Almost two-thirds of these patients have extravalvular sites of infection, which are helpful in the diagnosis.<sup>261–263</sup> The course of acute staphylococcal IE in an addict tends to be less

severe than in nonaddicts,<sup>261</sup> although this may not be true in AIDS patients. HIV-seropositive patients acquire IE by one of two mechanisms: through injection drug abuse or as a complication of long-term central venous catheterization for administration of medications (e.g., for cytomegalovirus [CMV] retinitis). In either situation, *S. aureus* is the most common etiologic organism. IE is more common among injection drug users with advanced HIV immunosuppression (CD4<sup>+</sup> count, <200 cells/mm<sup>3</sup>), even after accounting for injection drug use behaviors.<sup>264</sup> Conversely, among HIV-infected persons who do not practice injection drug use, IE is rare despite the increasing number of HIV-infected patients worldwide.<sup>220</sup> In the absence of injection drug abuse, HIV-seropositive patients develop left-sided and right-sided IE with equal frequency.<sup>265</sup> In contrast, in the setting of injection drug abuse, HIV-seropositive patients develop predominantly right-sided IE. The IE-related morbidity and mortality rates in HIV-seropositive patients who do not have an AIDS-defining illness or criteria are similar to the rates in HIV-seronegative counterparts.<sup>265</sup>

## Laboratory Findings

Hematologic parameters often are abnormal in IE, but none is diagnostic. Anemia is almost always present (70%–90% of cases), especially in subacute IE, and has the characteristics of the anemia of chronic disease, with normochromic normocytic indices, a low serum iron concentration, and a low iron-binding capacity. The anemia tends to worsen with the duration of the illness. Thrombocytopenia occurs in 5% to 15% of cases but is common in neonatal IE. Leukocytosis is present in 20% to 30% of cases but is rare in the subacute variety, whereas counts of 15,000 to 25,000 cells/mm<sup>3</sup> are common in acute IE. The differential count usually is normal, but there may be a slight shift to the left. Leukopenia is uncommon (5%–15%); when present, it usually is associated with splenomegaly. Large mononuclear cells (histiocytes) can be detected in the peripheral blood in approximately 25% of patients, but the yield is higher in blood obtained by earlobe puncture. This finding is nonspecific, because similar cells have been found in malaria, typhus, typhoid fever, and tuberculosis.

The erythrocyte sedimentation rate is elevated in approximately 60% of contemporary IE cases.<sup>7</sup> In the absence of renal failure, CHF, or disseminated intravascular coagulation, a normal erythrocyte sedimentation rate is evidence against a diagnosis of IE. Hypergammaglobulinemia is detected in 20% to 30% of the cases and may be accompanied by a plasmacytosis in the bone marrow aspirate. A positive result on assay for rheumatoid factor is found in 40% to 50% of cases, especially when the duration of the illness is more than 6 weeks.<sup>200</sup> Hypocomplementemia (reported in 5%–15% of cases) parallels the incidence of abnormal renal function test results (elevated creatinine concentration in 5%–15%). A false-positive result on Venereal Disease Research Laboratory (VDRL) testing is uncommon (0.2%). Lyme serologic test results may be positive in patients with IE who are living in areas endemic for Lyme disease and may be reflective of remote exposure to the pathogen, leading to diagnostic confusion and delay.<sup>266</sup>

The urinalysis frequently is abnormal; proteinuria occurs in 50% to 65% of cases, and microscopic hematuria occurs in 30% to 60% of cases. Red blood cell casts may be seen in 12% of cases. Gross hematuria, pyuria, white blood cell casts, and bacteriuria also may be found.

Circulating immune complexes can be detected in most cases of IE but also are found in 32% of patients who have septicemia but no endocarditis, in 10% of healthy persons, and in 40% of noninfected narcotic addicts.<sup>200</sup> However, levels of aggregated human immune globulin equivalent to or greater than 100 µg/mL were found only in IE (35% of the cases). Detection of high levels of immune complexes may be useful in the diagnosis of right-sided IE in narcotic addicts or in culture-negative cases. In addition, because the levels decline with appropriate treatment, serial measurement of immune complexes may assist in management of the disease.<sup>215,216</sup> Mixed-type cryoglobulins are detectable in 84% to 95% of patients with IE, but this also constitutes a nonspecific finding. Serial determination of the serum C-reactive protein concentration, although nonspecific and virtually always elevated in IE, may be useful to monitor therapy and detect intercurrent complications or infections.<sup>267</sup>

A number of nuclear imaging studies have been evaluated in the diagnosis of IE, including gallium 67 (<sup>67</sup>Ga) myocardial,<sup>268</sup> technetium 99m (<sup>99m</sup>Tc)-labeled antibacterial antibody,<sup>269</sup> indium 111 (<sup>111</sup>In)-labeled platelets<sup>270</sup>; and fluorine 18 (<sup>18</sup>F)-fluorodeoxyglucose-labeled positron emission tomography.<sup>271</sup> This last technique has been recommended to enhance diagnostic acumen in cases of suspected prosthetic valve IE.<sup>272</sup>

The blood culture is the most important laboratory test performed in a diagnostic workup for IE. The bacteremia is usually continuous and low grade (80% of patients have <100 CFUs/mL of blood).<sup>273</sup> When bacteremia is present, the first two blood cultures yield the etiologic agent more than 90% of the time. In a prospective cohort of more than 2700 prospectively identified contemporary patients with definite IE, 88.8% had positive blood cultures.<sup>7</sup> In streptococcal endocarditis, the first blood culture was positive in 96% of cases, and one of the first two cultures was positive in 98%. When antibiotics had been administered during the previous 2 weeks, the rate of positive cultures declined from 97% to 91% ( $P < .02$ ).<sup>274</sup> The influence of outpatient antibiotic administration on blood culture positivity was more significant in another retrospective analysis;<sup>275</sup> 64% of 88 cultures were positive in 17 patients receiving antibiotics before hospitalization, compared with 100% of cultures in 15 patients without antibiotic exposure. In nonstreptococcal IE, the first blood culture was positive in 86% of the cases; when two cultures were taken, the first culture was positive in 100%. Most blood cultures contained only a few organisms; more than 50% contained 1 to 30 bacteria per milliliter. Only 17% of the cultures yielded more than 100 bacteria per milliliter. The bacteremia also was constant, with little variation in quantitative culture determinations in any individual patient. The sensitivity of blood cultures for the detection of streptococci is particularly susceptible to prior antibiotic therapy and is affected by the media used.<sup>276</sup> Continuous-monitoring blood culture systems such as BACTEC (Becton Dickinson, Mississauga, Ontario) and BacT/ALERT (Organon Teknika, Scarborough, Ontario) are significantly more sensitive than conventional methods.

On the basis of these studies, the following procedures for culturing blood are recommended. At least three blood culture sets (no more than two bottles per venipuncture) should be obtained in the first 24 hours. More specimens may be necessary if the patient has received antibiotics during the preceding 2 weeks. At least 10 mL of blood (if feasible) should be injected into trypticase soy (or brain-heart infusion) and thioglycolate broth.<sup>277,278</sup> Supplementation with 15% sucrose (in an attempt to isolate cell wall-deficient forms) or the use of prereduced anaerobic media is unrewarding.<sup>279</sup> The newer commercial media are effective, but comparative data are few. In general, culture of arterial blood offers no advantage over use of venous blood. Inspection for macroscopic growth should be performed daily, and routine subcultures should be done on days 1 and 3. Specialized methods, and not extended incubation times, are recommended for recovery of fastidious agents of IE.<sup>280</sup> When gram-positive cocci grow on the initial isolation but fail to grow on subculture, *Abiotrophia* or *Granulicatella* spp. should be suspected.<sup>281</sup> In this event, subculture inoculation should be onto media supplemented with either 0.05% to 0.1% L-cysteine or 0.001% pyridoxal phosphate.

Ribitol teichoic acids are major constituents of the cell wall of staphylococci. Gel diffusion and counterimmunoelectrophoresis techniques have been used to detect teichoic acid antibodies in the serum of patients with suspected *S. aureus* IE. Because of problems with false-positive and false-negative results, this test rarely is used now.

### Special Diagnostic Tests

Special diagnostic tests are not used routinely (with the exception of echocardiography) in all cases of IE but may be useful in the diagnostic approach to culture-negative IE and in decisions about surgical intervention during active infection. The incidence of so-called blood culture-negative endocarditis has ranged from 2.5% to 31% in published series.<sup>282,283</sup> If the patient has not received previous antibiotic therapy and the blood cultures are obtained as outlined, these cases should represent less than 5% of the total.<sup>3</sup> Some of the aforementioned tests (e.g., assays for rheumatoid factor and teichoic acid antibodies, examination of earlobe blood specimens for histiocytes) may be helpful in identifying such cases, but other procedures often are necessary. If the

patient has received antibiotics, blood cultures in hypertonic media may allow detection of cell wall-defective organisms.

Supplementation of media with vitamin B<sub>6</sub> or with cysteine may assist in the recovery of *Abiotrophia* and *Granulicatella* spp. The lysis-centrifugation blood culture technique assists in the detection of staphylococci<sup>284</sup> and fungi, but *Abiotrophia* and *Granulicatella* spp. do not survive this procedure, and yields of pneumococci and anaerobes are decreased.<sup>285</sup> Routine use of this technique is not indicated, but it may be helpful in suspected culture-negative cases of IE. Because of improvements in blood culture media and automated blood culture incubation systems, extended incubation times of blood cultures are no longer necessary to recover HACEK organisms (see later discussion).<sup>286,288</sup> Special efforts to neutralize or inactivate antimicrobial agents present in blood, such as the addition of penicillinase or of antibiotic-removal resins, do not substantially enhance the yield of positive blood cultures in IE, and they increase the incidence of laboratory contamination of the blood culture. These maneuvers are not recommended routinely.<sup>285</sup>

Cultures of bone marrow or urine rarely may be positive when blood cultures are negative. Serologic studies are necessary for the diagnosis of Q fever or murine typhus.<sup>287</sup> Psittacosis endocarditis usually is diagnosed with serologic methods, but one case<sup>288</sup> yielded positive blood and pharyngeal cultures. Special culture techniques (e.g., for *Legionella* spp.<sup>289</sup>) are indicated in patients with suspected prosthetic valve IE if initial cultures are "negative."

*Bartonella*, recognized as an important cause of apparent blood culture-negative IE (especially in homeless alcoholic patients), also can be isolated by prolonged incubation and subculture of the aerobic broth media (see Chapter 234).<sup>290-294</sup> Serologic strategies also may assist in the diagnosis of *Bartonella* IE.<sup>291</sup> In addition to blood culture and serodiagnostic strategies, as outlined previously, culture of valvular tissue or vegetations that have embolized to peripheral arteries and have been removed surgically may yield the causative organism. Microscopy of these tissues, including direct fluorescence antibody techniques and electron microscopy, may assist in making the etiologic diagnosis, particularly in cases caused by fastidious or intracellular pathogens, such as *Tropheryma whipplei*,<sup>295</sup> *Chlamydia*, *Coxiella burnetii*,<sup>296</sup> and *Legionella*.<sup>297</sup>

Molecular techniques to recover specific DNA or 16S ribosomal RNA from valve tissue samples have been useful diagnostically in selected cases,<sup>298</sup> and polymerase chain reaction (PCR) studies performed on blood or serum may be highly useful for the diagnosis of IE caused by difficult-to-grow pathogens.<sup>299</sup> In an investigation comparing broad-range PCR results on resected endocardial specimens from 49 patients with suspected IE with results of culture and Gram staining of resected specimens and Duke criteria, bacterial DNA was shown within cardiac tissue in 18% of patients with sterile blood cultures.<sup>300</sup> Other tests to exclude collagen vascular diseases usually are necessary in patients undergoing evaluation for culture-negative native valve IE.<sup>301</sup>

Although still rare, fungal IE is increasing in frequency and usually affects narcotic addicts, patients with prosthetic valves, or hospitalized patients receiving antibiotics or hyperalimentation or both.<sup>302</sup> Low-birth-weight neonates seem particularly prone to *Candida* IE, predominantly on the tricuspid valve or right atrial mural endocardium.<sup>303</sup> The rate of prosthetic valve endocarditis among fungemic patients with prosthetic heart valves was approximately 25% in one retrospective series.<sup>304</sup> Historically, over half of cases of fungal IE exhibited negative blood cultures.<sup>305</sup> The Castaneda principle (a culture of blood in a bottle containing agar and liquid broth) has been shown to increase the yield of fungal cultures.<sup>279</sup>

Various serologic procedures have been used in an attempt to substantiate a diagnosis of fungal IE. Tests for the determination of anti-*Candida* antibody are poorly standardized, variably sensitive, often nonspecific, and difficult to interpret.<sup>306</sup> Tests for mannan antigenemia (a constituent of the cell wall of *Candida*) or enolase by hemagglutination inhibition and by enzyme-linked immunosorbent assay<sup>307,308</sup> have been reported as helpful in the diagnosis of disseminated candidiasis. In addition, a reliable radioimmunoassay for the detection of *Aspergillus* antigenemia is under investigation. If embolism to major vessels occurs, an embolectomy should be performed, and the material should be

examined with special fungal stains and culture. Identification of the fungus by either technique is diagnostic of fungal IE even if blood cultures are sterile.

### Echocardiography

The use of echocardiography in the diagnosis of IE first was reported in 1973.<sup>309</sup> The use of two-dimensional (2D), cross-sectional, real-time techniques improved the diagnostic accuracy over M-mode methods.<sup>310</sup> The characteristic finding is a shaggy, dense band of irregular echoes in a nonuniform distribution on one or more leaflets, with full unrestricted motion of the valve. The smallest vegetation detected was approximately 2 mm, but the acoustic impedance of the mass relative to the surrounding structures is a more important factor than size in identifying the vegetation. If the vegetation is calcified (which may occur early and independent of the healing process), the sensitivity of echocardiography may be increased. Echocardiography has localized vegetations correctly in culture-negative cases. Echocardiography may be of special value in detection of the large, friable vegetations characteristic of fungal IE. Use of M-mode or 2D transthoracic techniques with prosthetic heart valves has been disappointing, however, because of the difficulty in resolution around the prosthetic device.

Many reports<sup>311</sup> have evaluated the role of transthoracic echocardiography (TTE) in the diagnosis and management of suspected IE and have been summarized in cogent analyses.<sup>312</sup> It seems from most analyses that TTE should be performed in all patients in whom IE seems to be a reasonable diagnosis. In contrast, TTE is not an appropriate screening test in the evaluation of febrile patients in whom IE is unlikely on clinical grounds or in bacteremic patients with organisms that rarely cause IE (e.g., *E. coli*), particularly if there is another obvious focus to explain the clinical syndrome; TTE may be overused in such low-risk situations.<sup>313</sup> TTE may be technically inadequate in 20% of adult patients owing to obesity, chronic obstructive pulmonary disease, or chest wall deformities. These studies also suggest the following: (1) TTE has variable sensitivity for the detection of vegetations (<50% to >90% positive), indicating that a negative study does not exclude IE; (2) the sensitivity of TTE for detecting vegetations is highest in right-sided IE, because the tricuspid and pulmonic valves lie relatively close to the chest wall; (3) false-positive results are extremely rare; (4) only technically adequate studies are of value, a characteristic that depends on examiner experience; (5) echocardiography is extremely valuable in assessing local complications of IE, especially surrounding the aortic valve, although the sensitivity for detecting these complications is relatively low for TTE (see later discussion); and (6) patients with a “vegetation” identified with echocardiography are at an increased risk for subsequent systemic emboli, CHF, need for emergency surgery, and death, especially with aortic valve involvement. This apparent influence on prognosis has hastened earlier surgery in some cases,<sup>314</sup> but this point is controversial.<sup>315</sup>

Positive findings on the echocardiogram in a patient with IE should serve as adjunctive evidence, together with clinical parameters, in favor of surgical intervention. In one analysis from the Mayo Clinic,<sup>316</sup> emboli were not statistically more common in patients with left-sided native valve IE and echocardiographically documented vegetations within 72 hours after beginning antimicrobial therapy than in patients without vegetations visualized by transthoracic techniques. The occurrence of emboli was correlated positively with the infecting microorganism, being more common in IE due to viridans streptococci than in IE due to *S. aureus*. Most studies have suggested that mitral valve vegetations (particularly vegetations attached to the anterior leaflet), regardless of size, are associated with higher rates of embolization (25%) than are aortic valve vegetations (10%). This association implicates the mechanical effects of abrupt mitral valve leaflet excursions, occurring twice per heartbeat, in enhancing the embolic potential of vegetations.<sup>317</sup> Visualization of vegetations by echocardiography is not sufficient to prompt early surgery.<sup>318</sup> Serial echocardiograms often reveal the persistence of vegetations after successful therapy, but sequential studies may be useful in the timing of surgical intervention. Although the finding is still controversial, larger vegetation size has been associated with an increased risk for cerebral emboli. One large meta-analysis incorporating data from 10 studies involving 738 patients showed that large vegetation

size (>1 cm) was associated independently with an increased risk for stroke.<sup>319</sup> Short-term changes in vegetation size during therapy do not correlate well with clinical outcome.<sup>320</sup>

One study suggested that an increase in vegetation size, as seen with echocardiography during treatment of IE, can identify a subset of patients with a higher rate of complications, independent of the presence of persistent bacteremia or overt clinical stigmata of IE.<sup>321,322</sup> Some studies have suggested that highly mobile vegetations constitute an independent increase in risk for complications in IE.<sup>323</sup> In other studies, vegetation mobility at echocardiography has not been an important independent risk factor for embolic events in IE, because it is correlated strongly with vegetation size.<sup>288,314</sup>

One problem in considering the significance of these echocardiographic characteristics is the high degree of interobserver variability in interpreting the echocardiographic images.<sup>324</sup> Inexperienced physicians do not understand this issue. In one investigation involving four readers independently interpreting TTE studies from 41 cases of IE, Heinle and colleagues reported that investigators agreed on vegetation mobility in 57% of the cases, vegetation shape in 36%, and vegetation attachment in 40%.<sup>325</sup> In a more recent study of intraobserver and interobserver agreement for a random sample of 110 echocardiograms from the ICE registry, interobserver agreement was highest for aortic abscess ( $\kappa = 1.0$ ) and vegetation location ( $\kappa = 0.95$ ) and lowest for mobility ( $\kappa = 0.69$ ).<sup>326</sup> This overall improved agreement relative to the Heinle study was attributed to digital image acquisition and inclusion of transesophageal echocardiograms.

### Transesophageal Echocardiography

Transesophageal echocardiography (TEE) has altered the diagnostic approach to some patients with suspected IE.<sup>327–332</sup> TEE uses a 5-MHz phased-array transducer with Doppler and color flow encoding capabilities mounted on the tip of a flexible endoscope. Biplane (horizontal and longitudinal) or omniplane imaging is preferred over TTE imaging because of (1) better spatial resolution with a higher-frequency transducer, (2) lack of acoustic interference (e.g., from lungs, chest wall), and (3) proximity to posterior structures (e.g., mitral valve, left atrium, interatrial septum, descending aorta).<sup>329</sup> TEE has proved useful in a wide variety of clinical situations, including detection of possible sources of emboli, diagnosis of thoracic aortic dissection, detection of prosthetic valve dysfunction, and evaluation of IE.<sup>327–329</sup> Intraoperative TEE imaging has become a valuable new tool, often providing real-time feedback to the surgical team during the procedure. Three-dimensional (3D) TEE has emerged as a potential adjunct to characterize valvular lesions. However, in one prospective cohort of 144 consecutive patients, 3D TEE was less sensitive than 2D TEE, with only one additional case of a vegetation detected with 3D TEE but not 2D TEE.<sup>333</sup>

TEE is also more sensitive than conventional TTE in the detection of intracardiac vegetations (approximately 95% vs. 60%–65%, respectively), particularly in the setting of prosthetic valves (see Chapter 81). In one report of 96 patients with IE,<sup>330</sup> the sensitivity of TEE was 100%, compared with 63% for TTE, and the specificity values were identical (98%). The advantage of TEE was particularly evident for vegetations smaller than 10 mm in diameter. In another study,<sup>331</sup> vegetations were detected with TEE in 82% of the cases, compared with 69% for TTE. Although negative results on TEE do not exclude IE,<sup>327–329,332</sup> the procedure should be considered in patients with suspected IE and negative results on TTE. Potential sources of false-negative TEE studies include small vegetations and previous embolization of vegetations. If the clinical suspicion of IE is high and the results of an initial TEE examination are negative, another TEE study is warranted within 7 to 10 days.<sup>334</sup> TEE also has become the procedure of choice for the detection of perivalvular extension of infection in patients with IE.<sup>335,336</sup> Daniel and colleagues<sup>336</sup> reported a diagnostic sensitivity of 87% and a specificity of 95% for TEE in the detection of IE-related abscess, compared with 28% and 99% for TTE. Other investigations have shown TEE to be superior in the diagnosis of valvular perforation,<sup>337</sup> pacemaker IE,<sup>338</sup> eustachian valve IE,<sup>339</sup> IE in the elderly,<sup>340</sup> and other presentations. TEE should be performed (unless contraindicated, as by significant esophageal disease) in all IE patients with a complicated course if perivalvular extension is suspected. MRI also seems promising for the detection of

these complications,<sup>335</sup> but clinical experience with this modality is limited.

TEE is not a screening or noninvasive procedure but is generally safe<sup>341</sup> in experienced hands, and it may alter management in selected patients with proved or suspected IE. Two cost-effectiveness analyses favored the increased use of TEE.<sup>342,343</sup> Using outcomes among a cohort of consecutive patients with intravascular catheter-associated *S. aureus* bacteremia (SAB), Rosen and colleagues<sup>343</sup> found that TEE was a cost-effective method of defining the duration of antibiotic therapy (2 weeks vs. 4 weeks), compared with empirical courses of either 2 weeks or 4 weeks. Similarly, a decision analysis by Heidenreich and coworkers<sup>342</sup> found TEE to be more cost-effective than TTE among patients with a high pretest probability of endocarditis (defined as 4%–60%).

In an effort to identify a subset of patients with suspected native valve IE who may not require TEE, one study compared a standard definition of a negative TTE (no vegetation present) with a strict definition (at least moderate ultrasound quality, normal cardiac anatomy, no valvular stenosis, at most trivial valvular regurgitation, at most mild simple pericardial effusion, absence of implanted hardware or central venous catheter, and no evidence of vegetation). In a retrospective analysis of 790 TTE/TEE pairs, 104 (13.2%) met strict negative criteria. Use of the strict definition improved sensitivity (from 43% to 98%) and negative predictive value (from 87% to 97%), at the expense of specificity (from 90% to 16%) and positive predictive value (from 53% to 22%).<sup>344</sup>

In conjunction with the physical examination, phonocardiography, and electrocardiography, the echocardiogram may play an important role in assessing the severity of acute aortic insufficiency in cases of active IE.<sup>345</sup> In this setting, classic signs, such as a wide pulse pressure and bounding pulses, often are absent; however, there is usually a reduction in intensity of the first heart sound, and Austin Flint murmurs may be audible. Findings on the chest radiograph and electrocardiogram may be normal. The degree of mitral valve preclosure (as determined with echocardiography) correlates with the acute elevation in left ventricular end-diastolic pressure. If this event occurs before the Q wave on the electrocardiogram, urgent surgical intervention is recommended.

### Cardiac Catheterization

Cardiac catheterization provides valuable hemodynamic and anatomic information in patients with IE when surgical intervention is being considered.<sup>263</sup> If properly performed, the procedure is safe, as was shown by the lack of postcatheterization emboli or hemodynamic deterioration in 35 consecutive patients in one series.<sup>346</sup>

### Diagnostic Criteria

Diagnostic criteria for IE (the Beth Israel criteria) were published in 1982 by von Reyn and colleagues,<sup>3</sup> but these criteria did not use echocardiographic findings in the case definitions, despite major improvements in echocardiographic technology (see previous discussion). In addition, the isolation of a “typical” IE pathogen from blood cultures was not considered in the Beth Israel definitions. Many presumptive cases of IE were classified as not *definite* but *probable*. With improved methodology and recognition of the central role of echocardiography in the evaluation of suspected IE, new case definitions and diagnostic criteria (the Duke criteria), initially were proposed in 1994.<sup>347</sup> Modifications to the Duke criteria were published in 2000<sup>348</sup> and are now used widely (Table 80.4). The Duke criteria (modeled after the Jones criteria for diagnosing rheumatic fever<sup>349</sup>) improve on the Beth Israel criteria by including echocardiographic demonstration of vegetations or paravalvular complications of IE and the isolation of typical IE pathogens from blood cultures as “major criteria” for the clinically definite categorization of IE. In addition, the presence of recent injection drug use is included in the Duke criteria as a “minor criterion” for diagnosis of IE, recognizing the increased risk for IE in this patient population. Direct comparisons of the Duke and Beth Israel criteria have been done in 11 major studies, including almost 1400 patients. Patient populations from diverse geographic areas with presumed IE have been studied, including young, middle-aged, and elderly adults; pediatric patients; patients with native or prosthetic valve involvement; and patients with and without a history of injection drug use. These studies confirmed the increased

**TABLE 80.4 Definition of Infective Endocarditis (IE) According to Modified Duke Criteria**

#### Definite Infective Endocarditis

##### *Pathologic Criteria*

- Microorganisms demonstrated by culture or histologic examination of a vegetation, a vegetation that has embolized, or an intracardiac abscess specimen; or
- Pathologic lesions; vegetation or intracardiac abscess confirmed by histologic examination showing active endocarditis

##### *Clinical Criteria (See Below for Definitions)*

- 2 major criteria; or
- 1 major criterion and 3 minor criteria; or
- 5 minor criteria

#### Possible Infective Endocarditis

- 1 major criterion and 1 minor criterion; or
- 3 minor criteria

#### Rejected

- Firm alternate diagnosis explaining evidence of IE; or
- Resolution of IE syndrome with antibiotic therapy for ≤4 days; or
- No pathologic evidence of IE at surgery or autopsy, with antibiotic therapy for ≤4 days; or
- Does not meet criteria for possible IE, as above

#### Major Criteria

##### *Blood Culture Positive for Infective Endocarditis*

- Typical microorganisms consistent with IE from two separate blood cultures: viridans streptococci, *Streptococcus bovis*, HACEK group, *Staphylococcus aureus*; or
- Community-acquired enterococci, in the absence of a primary focus; or
- Microorganisms consistent with IE from persistently positive blood cultures, defined as follows:
  - At least two positive cultures of blood samples drawn >12 h apart; or
  - All of three or a majority of four or more separate cultures of blood (with first and last sample drawn at least 1 h apart)
  - Single positive blood culture for *Coxiella burnetii* or antiphase I IgG antibody titer >1:800

#### Evidence of Endocardial Involvement

- Echocardiogram positive for IE (TEE recommended in patients with prosthetic valves, rated at least “possible IE” by clinical criteria, or complicated IE [paravalvular abscess]; TTE as first test in other patients), defined as follows:
  - Oscillating intracardiac mass on valve or supporting structures, in the path of regurgitant jets, or on implanted material in the absence of an alternative anatomic explanation; or
  - Abscess; or
  - New partial dehiscence of prosthetic valve
  - New valvular regurgitation (worsening or changing of preexisting murmur not sufficient)

#### Minor Criteria

- Predisposition, predisposing heart condition or injection drug use
- Fever, temperature >38°C (100.4°F)
- Vascular phenomena, major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, and Janeway lesions
- Immunologic phenomena: glomerulonephritis, Osler nodes, Roth spots, and rheumatoid factor
- Microbiologic evidence: positive blood culture but does not meet a major criterion as noted above<sup>a</sup> or serologic evidence of active infection with organism consistent with IE
- Echocardiographic minor criteria eliminated

<sup>a</sup>Excludes single positive cultures for coagulase-negative staphylococci and organisms that do not cause endocarditis.  
HACEK, *Haemophilus*, *Aggregatibacter* (formerly *Actinobacillus*), *Cardiobacterium*, *Eikenella*, *Kingella*; IgG, immunoglobulin G; TEE, transesophageal echocardiography; TTE, transthoracic echocardiography.

Modified from Li JS, Sexton DJ, Mick N, et al. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. Clin Infect Dis. 2000;30:633.

sensitivity of the Duke criteria in the clinical diagnosis of IE and the diagnostic usefulness of echocardiography in the identification of clinically definite cases.<sup>334</sup> Modifications of the Duke criteria, to provide a floor for diagnosis of putative cases as possible IE, have added more specificity to the schema.<sup>348</sup>

## Etiologic Agents

### Streptococci

A plethora of microorganisms have been implicated in IE, but streptococci and staphylococci account for 80% to 90% of the cases in which an identification is made. The most common etiologic agents are listed in Table 80.5. Streptococci were once the most common overall cause of IE and continue to be the predominant etiologic agents in the developing world.<sup>19,20</sup> Staphylococci have assumed increasing importance among isolates in community hospitals in recent years, however (see later discussion).<sup>29,350</sup> Viridans streptococci remain the major cause of IE in children. The disease usually runs a subacute course with multiple nonspecific symptoms (see Table 80.3). More than 80% of these patients have underlying heart disease. Viridans streptococci are the most commonly isolated pathogens in IE cases associated with mitral valve prolapse,<sup>351</sup> and IE in young women with isolated mitral valve involvement is almost universally caused by viridans streptococci. Approximately 20% of cases that come to the physician's attention are seen because of embolic phenomena. With modern medical and surgical management, the cure rate should exceed 90% in nonenterococcal streptococcal IE, although complications may ensue in more than 30% of cases.

The nomenclature of the streptococci is confusing, and the terminology varies among authors. As detailed in Chapter 202, current names for the  $\alpha$ -hemolytic streptococci other than *S. pneumoniae* (i.e., viridans streptococci) causing IE are *S. mitis*, *S. sanguinis*, *S. mutans*, *Streptococcus salivarius*, *Abiotrophia* and *Granulicatella* spp., and some isolates of the *Streptococcus intermedius* group (*S. intermedius* and *Streptococcus anginosus*). *Streptococcus morbillorum* now is classified as *Gemmella morbillorum*; *Streptococcus mitior* now is considered to be a "genospecies" of *S. mitis*. The name *S. mitior* is embedded so deeply in the endocarditis literature, however, that it is retained in the discussion that follows. Group D streptococci are sometimes  $\alpha$ -hemolytic, depending on the conditions and the isolate, but are not included among the viridans streptococci. Streptococci of the viridans group (not a true species) are  $\alpha$ -hemolytic and usually nontypeable by the Lancefield system.

The streptococci most commonly isolated from cases of IE are *S. sanguinis*, *Streptococcus bovis* (we will continue to use this name here, although the human strains have been reclassified as *Streptococcus*

*gallolyticus*), *S. mutans*, and *S. mitior*.<sup>81</sup> In a series of 317 cases of streptococcal IE, the breakdown was as follows:  $\alpha$ -hemolytic, 45%; nonhemolytic, non-group D, 21%; group D, 25%; pyogenic (groups A, B, C, G), 5%; miscellaneous, 3%; and aerococci, 1.3%. The  $\alpha$ -hemolytic strains included *S. sanguinis* (16.4% of all cases of IE), non-dextran-producing *S. mitior* (13.2%), dextran-positive *S. mitior* (7.3%), and an unclassified group (7.9%). Some isolates of *S. sanguinis*, formerly called *Streptococcus* SBE, are in Lancefield group H; however, most are nontypeable. *S. mutans* (14.2%), *S. anginosus* (5.4%), and *S. salivarius* (1.3%) are the nonhemolytic, non-group D strains. Group D organisms include the enterococci (8%) and *S. bovis* (17%). In another analysis,<sup>352</sup> viridans streptococci caused 58% of cases of IE at The New York Hospital from 1970 to 1978. The various responsible species were as follows: *S. mitior*, 31%; *S. bovis*, 27%; *S. sanguinis*, 24%; *S. mutans*, 7%; vitamin B<sub>6</sub>-dependent *S. mitior*, 5%; *S. anginosus*, 4%; and others, 2%—all of which were slightly different from the species reported from the United Kingdom. By contrast, group D streptococci constituted 25% of all cases of IE within six regions of France representing 16 million inhabitants.<sup>353</sup> Among 1242 consecutive episodes of IE from 1996 to 2013 in three Spanish centers, 294 were streptococcal, of which 47 were *S. bovis* (3.8%), 134 viridans-group streptococci (10.8%), and 113 enterococcal (9.1%).<sup>354</sup>

There seems to be no correlation between clinical outcome and the species involved,<sup>268</sup> with the exception of nutritionally deficient strains (see later discussion). The relative role of each species overall is problematic, however, because species designations of identical strains among laboratories often are disparate, and most blood and cerebrospinal fluid isolates of viridans or nonhemolytic streptococci are not from patients with IE.<sup>355</sup>

*S. mutans*, a normal member of the oral microbiota, is microaerophilic, pleomorphic, and fastidious. Two-thirds of *S. mutans* strains hydrolyze bile-esculin,<sup>356</sup> a test used to identify group D organisms, and may be confused with enterococci. Other characteristics of *S. mutans* include the absence of group D antigen (some strains are positive for group E), production of acid from mannitol, failure to hydrolyze hippurate, and formation of gelatinous deposits (dextran) in media containing 5% sucrose. This organism may be difficult to isolate and to identify. It often requires more than 3 days for primary isolation, grows best on horse blood agar in 5% to 10% carbon dioxide on subculture, and is pleomorphic, resulting in confusion with diphtheroids. *S. mutans* first was isolated in 1924 by Clark from dental caries lesions of humans and first was reported in 1928 to cause IE. The central importance of this organism in dental caries has been amply documented.

*S. bovis* is a normal inhabitant of the gastrointestinal tract of humans and many animal species. The genetic diversity among organisms historically classified as *S. bovis* has been clarified to include biotypes I and II, *S. salivarius*, and *Streptococcus macedonicus*.<sup>357</sup> In addition, *S. bovis* has been subdivided further into *S. gallolyticus* subsp. *gallolyticus*, *S. gallolyticus* subsp. *pasteurianus*, and *Streptococcus infantarius*.<sup>358</sup> It is important to differentiate *S. bovis* from the other members of group D (the enterococci), because the respective therapeutic approaches to infection with these organisms are different (see later discussion). Group D organisms are identified presumptively by bile-esculin hydrolysis.<sup>359,360</sup> Only the enterococci (*E. faecalis* and its varieties, *Enterococcus zymogenes* and *Enterococcus liquefaciens*; *Enterococcus faecium*; and *Enterococcus durans*) grow in 6.5% sodium chloride, whereas *S. bovis* and *Streptococcus equinus* (a rare cause of IE) are salt sensitive. Seventy-five percent of strains of *S. bovis* are heat tolerant, and they may grow and produce acid in *E. faecalis* broth; these methods are unreliable for separation.<sup>361</sup> Arginine hydrolysis by enterococci and starch hydrolysis by *S. bovis* are other means for reliable separation. The association of bacteremia due to *S. bovis* with carcinoma of the colon and other lesions of the gastrointestinal tract suggests that a colonoscopy should be performed if this organism is isolated from blood cultures.<sup>362,363</sup> Interesting to note, this association appears to be higher with *S. gallolyticus* subsp. *gallolyticus*.<sup>358</sup>

### Enterococci

Enterococci are normal inhabitants of the gastrointestinal tract and occasionally of the anterior urethra. All enterococci are in Lancefield group D; they are catalase negative and nonmotile; and they may exhibit

**TABLE 80.5 Etiologic Agents in 1779 Patients With Definite Infective Endocarditis**

AGENT	CASES (%)
<i>Staphylococcus</i>	
<i>Staphylococcus aureus</i>	31.6
Coagulase-negative staphylococci	10.5
<i>Streptococcus</i>	
Viridans-group streptococci	18.0
<i>Streptococcus bovis</i>	6.5
Other streptococci	5.1
Enterococci	10.6
HACEK group	1.7
Non-HACEK gram-negative bacteria	2.1
Fungi	1.8
Polymicrobial	1.3
Other species	3.1
Culture negative	8.1

HACEK, *Haemophilus*, *Aggregatibacter* (formerly *Actinobacillus*), *Cardiobacterium*, *Eikenella*, *Kingella*.

Data from Fowler VG Jr, Miro JM, Hoen B, et al. *Staphylococcus aureus endocarditis throughout the world: a consequence of medical progress. The International Collaboration on Endocarditis Prospective Cohort Study*. JAMA. 2005;293:3012.

$\alpha$ -,  $\beta$ -, or  $\gamma$ -hemolysis on blood agar. They grow well in sodium azide (SF [*Streptococcus faecalis*] broth), 40% bile, 6.5% sodium chloride, and 0.1% methylene blue and can survive at 56°C for 30 minutes or at a pH of 9.6.<sup>364</sup> Enterococci are responsible for 5% to 18% of the cases of IE, and the incidence seems to be increasing.<sup>7,365,366,367</sup> The disease usually runs a subacute course and affects older men (mean age, 59 years) after genitourinary manipulation or younger women (mean age, 37 years) after obstetric procedures. The mean duration of nonspecific symptoms, such as malaise, fatigue, anorexia, and weight loss, was 140 days in one review. More than 40% of the patients have no underlying heart disease, although more than 95% develop a heart murmur during the course of the illness. Classic peripheral manifestations are uncommon (<25% of the cases). Bacteriuria with enterococci is a helpful diagnostic clue and was found in 4 of 15 patients in one study.<sup>364</sup> Cure is difficult because of the intrinsic resistance to many antibiotics, and a high mortality rate persists in this disease. With the increasing use of third-generation cephalosporins, which are relatively inactive against enterococci *in vitro*, and other contributing factors (e.g., use of indwelling urinary catheters), an alarming increase in enterococcal bacteremias has been documented during the past 2 decades.<sup>367–369</sup> Most enterococcal bacteremias are health care associated, are often polymicrobial (42% in one large series<sup>370</sup>), and are associated with serious underlying disorders. Factors that suggest IE in patients with enterococcal bacteremia include (1) community acquisition, (2) preexistent valvular heart disease, (3) cryptogenic source, and (4) absence of polymicrobial bacteremia.<sup>370</sup> Antibiotic usage patterns, the aging of the population, and more invasive procedures in hospitalized adults all portend a continued increase in serious enterococcal infections, including IE, in the future.

### **Streptococcus pneumoniae**

Before 1945, *S. pneumoniae* was responsible for approximately 10% of the cases of IE, but the prevalence has decreased to approximately 1% to 3% currently.<sup>371</sup> The course usually is fulminant and often (in approximately one-third of cases) is associated with perivalvular abscess formation or pericarditis or both. Left-sided involvement is the rule, and there is a predilection for the aortic valve (approximately 70% of cases). Many patients with pneumococcal IE are alcoholics (approximately 40%), and concurrent meningitis is present in about 70% of cases.<sup>371–373</sup> The overall mortality rate is approximately 50% (60%–65% in children<sup>374</sup>), with death usually caused by rapid valvular destruction and hemodynamic compromise,<sup>375</sup> although indolent presentations of pneumococcal IE with a favorable outcome have been described.<sup>376</sup>

*Abiotrophia* and *Granulicatella* spp. can cause difficulties in isolation and were implicated in 1.5% of all IE cases at one Spanish medical center over a 15-year period.<sup>377</sup> The organisms do not grow on subculture unless L-cysteine or pyridoxal vitamin B<sub>6</sub> is provided. IE due to nutritionally deficient streptococci is almost always indolent in onset and associated with preexisting heart disease.<sup>378</sup> Therapy is difficult, because systemic embolization, relapse, and death are common (occurring in 17%–27% of cases). A closely related species, *S. mitis*, although not nutritionally deficient, also causes serious infections, including IE, in adults<sup>379</sup> and has emerged as an important causative agent of IE among drug addicts in some areas (e.g., New York City<sup>380</sup>).

### **$\beta$ -Hemolytic Streptococci**

Group B streptococci (*Streptococcus agalactiae*) are normal inhabitants of the mouth, vagina, and anterior urethra in 5% to 12% of the general population. In 149 patients with group B streptococcal infections, the serotypes isolated were Ia in 46%, II in 22%, and III in 11%.<sup>381</sup> Although the organism has long been recognized as a cause of bacteremia and meningitis in neonates, serious *S. agalactiae* infections in adults also have been emphasized.<sup>382,383</sup> Risk factors for group B streptococcal sepsis and IE in adults include diabetes mellitus, carcinoma, alcoholism, hepatic failure, elective abortion, and injection drug use.<sup>383–385</sup> As with *S. bovis*, occasional cases occur in association with villous adenomas of the colon.<sup>386</sup> More than 90 cases of group B streptococcal IE have been reported.<sup>384–388</sup> Underlying heart disease is common, the male-to-female ratio is 1.4:1, the mean age is approximately 54 years, and left-sided involvement predominates. The overall mortality rate is almost 50%. The organism does not produce fibrinolysin, which may

be responsible for the large, friable vegetations and frequent major systemic emboli.

A similar clinical picture with a destructive process, left-sided predominance, frequent complications, and high mortality (approximately 40%) has been observed in the 47 cases of group G streptococcal IE reported in the literature.<sup>389,390</sup> Most human infections with *Streptococcus suis* have presented as meningitis (with a striking predilection to cause deafness as a sequela) and sepsis with accompanying arthritis or endophthalmitis, but two cases of IE due to serotype 2 have been described.<sup>391</sup> A history of pig or raw pork contact was a feature in both patients. Several cases of IE due to *Streptococcus canis*, a zoonotic group G streptococcal species associated with dogs, have also been reported.<sup>392</sup>

Group A streptococci remain a rare cause of IE associated with a high complication rate in adults and children.<sup>393</sup> *S. anginosus* is a rare cause of IE (6%–7% of cases), but this species is unusual among these streptococci in that it has a predilection to cause suppurative complications, including brain, liver, perinephric, and other abscesses and cholangitis, peritonitis, and empyema.<sup>394–396</sup> Some of these complications occur during IE due to this organism and may require surgical attention.

Approximately 50% of *S. anginosus* strains carry the group F antigen.<sup>395</sup> IE caused by *S. anginosus* may result in virulent intracardiac complications (e.g., myocardial abscess, purulent pericarditis) more typical of *S. aureus* infections.<sup>397</sup>

### **Gemella**

IE due to *Gemella haemolysans* also has been reported.<sup>398</sup> This organism now is placed in genus V of the family Streptococcaceae. *Gemella* should be suspected if blood cultures reveal a variable morphology (with some organisms resembling diphtheroids) and an indeterminate Gram stain. The antimicrobial susceptibility of *Gemella* spp. is similar to that of the viridans streptococci. Although misidentification in the microbiology laboratory is presumably common, six cases of IE due to *G. haemolysans* have been reported since 1982.<sup>399</sup>

### **Aerococci**

Aerococci are uropathogens frequently misidentified as streptococci, staphylococci, or enterococci. With improved microbiologic techniques, IE due to *Aerococcus urinae* and *Aerococcus sanguinicola*, primarily occurring in older patients with underlying urinary tract diseases, has been described.<sup>400,401</sup>

### **Staphylococci**

*S. aureus* is now the most common cause of IE in most of the industrialized world.<sup>10</sup> Rates of *S. aureus* IE are rising in the United States.<sup>350</sup> A primary cause of this fundamental shift in the microbiology of IE relates to the growing importance of health care contact as a risk factor for bacteremia and, increasingly, IE.<sup>10,17</sup> This species is the causative agent in most cases of acute IE, but only 10% to 12% of patients with SAB have IE.<sup>402,403</sup> The organism may attack normal heart valves (defined as those having no clinically detectable cardiac disease) in approximately one-third of the patients. The course frequently is fulminant when it involves the mitral or aortic valve, with widespread metastatic infection, and results in death in approximately 40% of patients.<sup>404–407</sup>

As noted, the proportion of cases of IE due to *S. aureus* seems to be increasing at both community and university hospitals.<sup>14,15,29,365,408</sup> Traditionally, most cases of *S. aureus* IE were believed to be community acquired.<sup>409</sup> In the late 1990s, however, a small report of *S. aureus* IE from Duke University suggested a demographic shift among patients with this infection.<sup>410</sup> Over half of cases were associated with health care contact, and many were associated with intravascular catheters. These observations were validated in a multinational cohort of more than 1700 patients with definite IE. *S. aureus* was the most common cause of IE, accounting for 32% of all cases. Among the *S. aureus* cases, 39% were presumed to be health care associated, and in 28% the presumed source was an intravascular device.<sup>10</sup> These statistics emphasize that the finding of health care-associated SAB should prompt a complete evaluation for underlying IE.

Myocardial abscesses (with conduction disturbances), purulent pericarditis, and valve ring abscesses are more common in staphylococcal

endocarditis than in other forms of IE. Peripheral foci of suppuration (e.g., lung, brain, spleen, kidney) are common and affect more than 40% of these patients.<sup>404,407,408</sup> These extravascular sites of involvement may offer clues to an early diagnosis, especially in narcotic addicts.<sup>261,262</sup> This disease often is clinically unsuspected in older patients, and mortality rates frequently exceed 50% in patients older than 50 years, especially when the infection is nosocomially acquired.<sup>408,411</sup> The rare entity of neonatal IE also is often caused by *S. aureus*<sup>412</sup>; survival is unusual.

IE in narcotic addicts usually is due to *S. aureus*, but the disease tends to be less severe, with mortality rates of 2% to 6%.<sup>261,262</sup> The lower mortality is related directly to the preponderance of cases affecting the tricuspid valve, a syndrome that responds to antimicrobial therapy in most cases.<sup>409</sup> The emergence of MRSA in addicts with staphylococcal IE was first documented in the Detroit area in the mid-1980s.<sup>256,413</sup> Among 180 bacteremic addicts admitted to the Detroit Medical Center in 1 year, 24% grew MRSA and 41% of the patients overall had IE. Previous hospitalizations, long-term addiction (particularly in men), and nonprescribed antibiotic use were predictive of MRSA acquisition (odds ratio, 8.6:1).<sup>413</sup> Injection of newer psychoactive substances, including synthetic cannabinoids and synthetic cathinones, was associated with higher incidence of *S. aureus* IE and cavitating pulmonary lesions compared with findings in those who injected only opiates.<sup>414</sup>

### Coagulase-Negative Staphylococci

Although *S. epidermidis* was traditionally an important agent in prosthetic valve IE (see Chapter 81) and in infants with IE related to umbilical venous catheters in neonatal intensive care units,<sup>415</sup> studies from the ICE-PCS have confirmed that it also is an emerging cause of native valve IE. Approximately 8% of patients with definite native valve IE and no history of injection drug use were infected with coagulase-negative staphylococci.<sup>416,417</sup> Health care contact was the primary risk factor for infection. Many of these patients also had preexisting valvular disease. Although surgical treatment occurred more frequently in patients infected with coagulase-negative staphylococci than in those with *S. aureus* infection, mortality in these two groups was similar.<sup>416</sup> Data from a *Caenorhabditis elegans* model support the possibility that *S. epidermidis* isolates from patients with native valve IE constitute a more virulent subset within this species.<sup>418</sup>

Separation of IE from uncomplicated bacteremia due to *S. epidermidis* (implicated in approximately 50% of cases of native valve coagulase-negative staphylococcal IE) can be difficult. IgG antibodies to a novel 30-kDa cloned protein, termed *staphylococcal secretory antigen*, were demonstrated in patients with *S. epidermidis* IE but not in patients with uncomplicated *S. epidermidis* bacteremia or IE due to other pathogens.<sup>419</sup> Extensive laboratory evaluation<sup>420</sup> revealed that most *S. epidermidis* IE isolates are distinct and do not represent common-source outbreaks, despite the frequent shift to a small-colony variant by many strains *in vivo*<sup>421</sup> and the description of polyclonal *S. epidermidis* IE.<sup>422</sup>

Rare cases of IE due to other coagulase-negative staphylococci (e.g., *Staphylococcus saprophyticus*, *Staphylococcus capitis*) have been reported.<sup>423,424</sup> A growing number of reports of IE caused by the coagulase-negative *Staphylococcus lugdunensis* have been published.<sup>425–428</sup> This organism tends to cause a substantially more virulent form of IE than coagulase-negative staphylococci, with high morbidity rates despite almost uniform *in vitro* susceptibilities to most antibiotics, including penicillins and cephalosporins.<sup>425–428</sup> These strains frequently are misidentified as *S. aureus* because they often are yellow pigmented and yield complete hemolysis on blood agars. Their *in vitro* hemolytic capacities relate to the production of synergistic hemolysin. Differentiation of *S. lugdunensis* from *S. aureus* in the microbiology laboratory depends on the tube coagulase test and the ability of the former strains to cause ornithine decarboxylation. Distinguishing *S. lugdunensis* from other coagulase-negative staphylococci can be difficult with commercial identification schemata.<sup>429</sup>

### Gram-Negative Bacilli

Gram-negative aerobic bacilli now cause approximately 2% of cases of IE. Among more than 2700 patients with definite endocarditis prospectively enrolled into ICE-PCS from 60 centers in 28 countries, 49 patients

(1.8%) had endocarditis due to non-HACEK gram-negative bacilli.<sup>430</sup> Traditionally, injection drug use has been regarded as the primary risk factor for enteric gram-negative bacterial endocarditis<sup>413,431–436</sup> and injection drug users remain a high-risk population in specific locations.<sup>437</sup> However, experience from the large, contemporary, and multinational ICE-PCS demonstrated that health care contact, and not injection drug use, was the most common risk factor for enteric gram-negative IE. In this definitive study, more than half of the patients with IE due to non-HACEK gram-negative bacilli had health care-associated infection, whereas injection drug use was rare (4%). Prosthetic valves and implanted endovascular devices were frequently associated with non-HACEK gram-negative bacillary IE. Patients with cirrhosis<sup>438</sup> also seem to be at an increased risk for the development of gram-negative bacillary IE.

The duration of illness is usually less than 6 weeks, most patients are 40 to 50 years old, and men and women are affected equally.<sup>439</sup> In gram-negative septicemia, the bloodstream usually is cleared by therapy with appropriate antimicrobial agents. In contrast, in IE due to gram-negative bacilli, persistent bacteremia is common, even with high levels of antimicrobial activity. CHF is common, and the prognosis is poor. Older series reported a mortality rate of 60% to 83% for IE due to gram-negative bacilli.<sup>439</sup> However, contemporary experience indicates a substantially better prognosis, with in-hospital mortality rates of 24%.<sup>430</sup> This improved mortality rate is perhaps due in part to high rates of cardiac surgery (51%).

A heart murmur noted during an episode of gram-negative sepsis with unexplained anemia or the persistence of positive blood cultures despite adequate levels of antibiotics may indicate IE. In the early postoperative period after prosthetic valve replacement, sustained gram-negative bacteremia does not imply IE,<sup>440</sup> and other foci of infection (e.g., sternal wound, pneumonia, urinary tract, intravenous catheters) should be sought carefully.

Traditionally, *Salmonella* spp. were important causes of gram-negative bacterial IE among the Enterobacteriaceae. These organisms have an affinity for abnormal cardiac valves, usually on the left side of the heart.<sup>439,441</sup> Although many serotypes have been implicated, most cases are caused by *Salmonella enterica* serotypes Choleraesuis, Typhimurium, and Enteritidis. Valvular perforation or destruction, atrial thrombi, myocarditis, and pericarditis are common, and the outlook is grave. *Salmonellae* also may produce endarteritis in aneurysms of major vessels (see later discussion).

Although historically regarded as a rare cause of endocarditis because of its poor endothelial cell-binding capacity, *E. coli* now appears to predominate among the Enterobacteriaceae as a cause of IE.<sup>430</sup> This may reflect the growing importance of health care contact as a risk factor for enteric gram-negative IE. Other species of Enterobacteriaceae can also rarely cause IE.<sup>439</sup> In the 1970s, a total of 36 cases of IE due to *S. marcescens* were reported from San Francisco; 32 (88%) were associated with injection drug use.<sup>431,432</sup> The cases were characterized by large vegetations with near-total occlusion of the valve orifice in the absence of significant underlying valvular destruction. The overall mortality rate ranged from 68% to 73%, because a cure of left-sided IE caused by a member of the Enterobacteriaceae is uncommon with medical therapy alone. Valve replacement after 7 to 10 days of antibiotics was recommended for these difficult infections.<sup>432</sup> Approximately 12 cases of IE due to *Campylobacter fetus* have been reported since the first case in 1955.<sup>442</sup>

The first case of *Pseudomonas*-induced IE was recognized in 1899; more than 200 cases have been reported since then.<sup>256,413,433–438</sup> Although historical reports of pseudomonal IE (95%) were primarily associated with injection drug use,<sup>413,433–436</sup> more contemporary reports confirm health care contact as the current primary risk factor.<sup>17,443</sup> The male-to-female ratio is 2.5:1, and the mean age is 30 years. Major embolic phenomena, inability to sterilize valves, neurologic complications (53%), ring and annular abscesses, splenic abscesses, bacteremic relapses, and rapidly progressive CHF are common. Ecthyma gangrenosum, the necrotizing cutaneous lesion characteristic of *Pseudomonas* bactemia, occasionally has been noted, especially in cases of IE due to *Pseudomonas (Burkholderia) cepacia*.<sup>444</sup> The disease carries the highest mortality if the patient is older than 30 years (73%, compared with 33% in younger

patients), if the duration of illness is less than 5 days (76%, compared with 41% for shorter durations), and if there is left-sided cardiac involvement.<sup>434,436,445</sup> Because of the poor prognosis and frequent complications,<sup>256</sup> early surgery is recommended by many authorities for left-sided pseudomonal IE.<sup>334</sup> In contrast, high-dose regimens of antipseudomonal penicillins combined with aminoglycosides have had a salutary effect in many patients with isolated right-sided pseudomonal IE (see “Antimicrobial Therapy”). Almost all addicts with *P. aeruginosa* IE in more recent reports<sup>65,413,435,436</sup> have abused tripeptenamine and pentazocine (“Ts and blues”).

#### HACEK Group Bacteria (*Haemophilus*, *Aggregatibacter* [Formerly *Actinobacillus* spp.], *Cardiobacterium*, *Eikenella*, *Kingella*)

*Haemophilus* spp. historically accounted for 0.8% to 1.3% of all cases of IE,<sup>446–449</sup> although some have been reclassified into the genus *Aggregatibacter*. These infections usually run a subacute course and occur in the setting of preexisting valvular disease. Emboli to major peripheral arteries were found in six of seven cases of *Haemophilus parainfluenzae* IE.<sup>446</sup> Major central nervous system complications are relatively common.<sup>449</sup> *Aggregatibacter aphrophilus* produces a similar clinical pattern and has been transmitted from dogs to humans. Single cases of IE due to *Aggregatibacter segnis* and *Haemophilus influenzae* biogroup *aegyptius* have been reported from Denmark and Israel.<sup>450,451</sup> A closely related organism, *Aggregatibacter actinomycetemcomitans*, is a rare cause of subacute IE (with approximately 35 cases reported) and carries a mortality rate of 34%.<sup>452,453</sup> IE due to *Cardiobacterium hominis*<sup>454</sup> resembles the disease caused by *Haemophilus* spp.; 26 cases of *C. hominis* IE were reported by 1983. Only one extravascular infection due to *C. hominis* has been documented (meningitis during IE).

At least 28 cases of *Kingella* endocarditis (caused by *Kingella kingae*, 25 cases; *Kingella denitrificans*, 2 cases; and *Kingella indologenes*, 1 case) have been reported.<sup>455</sup> Invasive *Kingella* infections are increasingly recognized in children. Approximately 50% of patients develop complications, including acute stroke in approximately 25%. A dozen cases of IE due to *Eikenella corrodens* have been reported; injection drug use (especially of amphetamines) was implicated in five patients.<sup>456,457</sup> Dental infection or a history of dental procedures may be a feature, and drug users often have “cleaned” the injection site with saliva; *E. corrodens* is a usual inhabitant of the oropharynx. The disease generally has an indolent course, but presentation may be acute.<sup>457</sup>

All of the aforementioned HACEK bacteria can be reliably isolated with standard blood culture incubation periods using conventional automated blood culture systems.<sup>280,286</sup> The clinical syndrome produced by this group is virtually identical to that observed in subacute IE: large friable vegetations, frequent emboli, development of CHF, and often the eventual need for valve replacement.<sup>458</sup>

#### Other Gram-Negative Bacteria

IE produced by several other gram-negative species has received attention recently. *N. gonorrhoeae* was responsible for at least 5% to 10% of the cases of IE before the introduction of penicillin but now is implicated rarely. In the older series, half of the patients with gonococcal IE had involvement of the right side of the heart and exhibited the characteristic double-quotidian fever pattern. Of the cases of gonococcal IE reported since 1949,<sup>459–461</sup> most occurred in young men. Skin manifestations consistent with the gonococcal arthritis-dermatitis syndrome or IE have been documented in only 20% of the cases. Most cases of gonococcal IE now follow an indolent course, in contrast to the often fulminant progression in the preantibiotic era. Aortic valve involvement, large vegetations seen with TTE, associated valve ring abscesses, CHF, and nephritis are common.<sup>461</sup> A high frequency of late complement component deficiencies has been observed in patients with gonococcal IE. Sudden hemodynamic deterioration despite appropriate therapy may occur,<sup>459–461</sup> and the mortality rate is approximately 20%. “Nonpathogenic” *Neisseria* spp.—*N. perflava*, *N. flava*, *N. pharyngis*, *N. mucosa*, *N. sicca*, *N. flavescens*, and especially *Moraxella* (*Neisseria*) *catarrhalis*, and *Neisseria elongata* subsp. *nitroreducens*—now are isolated more frequently in IE than are gonococci, but they usually produce infection on abnormal or prosthetic heart valves.<sup>462–464</sup>

#### Gram-Positive Bacilli

IE due to various species of corynebacteria (diphtheroids) is uncommon and usually occurs on damaged or prosthetic valves,<sup>465</sup> although native valve infections (e.g., *Arcanobacterium* [*Corynebacterium*] *haemolyticum* in a drug addict) are reported rarely. About 19 cases of IE due to *Corynebacterium pseudodiphtheriticum* (previously *Corynebacterium hofmannii*) have been reported; native valves were involved in approximately half of these cases.<sup>466</sup> *Corynebacterium xerosis* is a very rare cause of native valve IE. Nontoxicogenic *Corynebacterium diphtheriae* IE has been reported in more than 40 patients. A cluster of 7 cases in 1 year from New South Wales, Australia,<sup>467</sup> emphasized the aggressive nature of the infection, including major vascular complications, the frequent occurrence of septic arthritis (in four of seven patients), and involvement of native valves. Injection drug use also is a predisposing factor.

The isolation of *Listeria monocytogenes* has been reported in 44 cases of IE.<sup>468,469</sup> Most cases of IE due to *Listeria* spp. have occurred in patients without any underlying defect in host defenses, although preexisting heart disease is present in approximately 50%. The mean age in the reported series was 51 years, and the overall mortality rate was 48%.<sup>469</sup>

*Propionibacterium* (now called *Cutibacterium*) species are typically part of normal skin microbiota, but have been implicated in approximately 70 cases of IE, generally involving prosthetic material.<sup>470</sup>

Lactobacilli also have been reported to cause a subacute form of IE, but these cases are rare (only 41 reported).<sup>471,472</sup> Despite an initial response to therapy, relapse of this infection is not unusual (approximately 60% of cases). Most cases occur on structurally abnormal native valves after dental manipulation.<sup>472</sup> Therapy with single agents is often unsatisfactory because lactobacilli, similar to enterococci, are tolerant to penicillins. Medical cure has been difficult to achieve in the past. These organisms also may require several weeks for isolation on blood culture.

More than 90% of 49 serious infections caused by *Erysipelothrix rhusiopathiae* were characterized as IE.<sup>473</sup> Occupational or vocational animal or fish exposure is a major risk factor, and approximately one-third of patients are alcoholic. Most patients are men. A characteristic erysipeloid skin lesion is present in approximately 40% of cases, and the organism exhibits significant aortic valve tropism (involved in 70% of patients).<sup>473</sup> The overall mortality rate is 38%.

Most cases of *Bacillus* IE involve the tricuspid valve in narcotic addicts, but nonaddicts and prosthetic valve recipients also have been affected.<sup>474</sup> *Rothia dentocariosa* is a rare cause of IE (approximately 20 cases reported) but has led to significant central nervous system complications.<sup>475</sup>

#### Anaerobic Bacteria

Nonstreptococcal anaerobic bacteria were responsible for 1.3% of all the cases of IE in 1970.<sup>476</sup> *Bacteroides fragilis* was the predominant pathogen in a review of 67 cases from the literature.<sup>477</sup> The following organisms were isolated: *B. fragilis*, 35.8%; *Bacteroides oralis*, 3%; *Prevotella melaninogenica* (*Bacteroides melaninogenicus*), 3%; *Fusobacterium necrophorum*, 13.4%; *Fusobacterium nucleatum*, 9%; *Clostridium* spp., 13.4%; *P. acnes*, 7.5%; *Dialister granuliformans*, 1.5%; and unidentified, 16.4%. More than one-third of the unidentified cases also were believed by the authors to represent *B. fragilis*. Approximately 25% of these cases were polymicrobial, usually mixed with anaerobic or microaerophilic streptococci. The portal of entry for *B. fragilis* was probably the gastrointestinal tract, whereas *B. oralis*, *P. melaninogenica*, and fusobacteria originated from the mouth or upper respiratory tract. Two-thirds of the patients were older than 40 years and had preexisting heart disease.

The course usually is subacute except for that with infection due to *F. necrophorum*, which characteristically produces a more fulminant disease. These organisms usually cause extensive valve destruction, CHF, and major systemic emboli (in 60%–70% of the cases). Thromboembolic episodes are especially common in infections caused by *B. fragilis*, a phenomenon that may be related to the heparinase produced by this organism. The mortality rate in cases of anaerobic IE has ranged from 21% to 46%.<sup>477</sup> One series from California noted no deaths among seven patients with anaerobic or microaerophilic IE<sup>478</sup>; these cases constituted 10.6% of the IE cases seen. This is similar to a 7.7% incidence reported

by other investigators<sup>3</sup> and suggests that anaerobic IE may be more prevalent now than it was in 1970.<sup>479</sup> Isolation of these organisms may be improved by the newer anaerobic culture techniques currently in use.

## Other Bacteria

### *Coxiella burnetii*

IE due to *C. burnetii* (the cause of Q fever) is well documented in the United Kingdom, the United States, Canada, France, the Middle East, and Australia<sup>480–482</sup> (see Chapter 188). Ten cases of Q fever IE were recognized in four Dublin teaching hospitals during a period of 3 years.<sup>481</sup> Q fever usually is a self-limited respiratory illness caused by the inhalation of infected aerosols.<sup>483</sup> The first IE cases were reported in 1959. Men outnumber women by 6 to 1, and 90% of patients have preexisting heart disease. Most cases of *C. burnetii* IE are chronic, with a history of an influenza-like illness occurring 6 to 12 months previously. Risk factors may include exposure to parturient cats or rabbits, previous valvulopathy, and pregnancy.<sup>482</sup> The aortic valve is involved in more than 80% of the cases. Hematuria is uncommon, although it is observed frequently in acute Q fever. Hepatosplenomegaly and hepatitis, common features in other types of Q fever, are seen in about half of patients with IE caused by this organism. Other important clues are thrombocytopenia (seen in 90% of cases) and hypergammaglobulinemia. Immune complex-mediated glomerulonephritis develops in approximately 25% of cases.<sup>480,481,484</sup> Histologically, *C. burnetii* IE is characterized by significant fibrosis and calcifications, slight inflammation and vascularization, and small or absent vegetations.<sup>296</sup> *Coxiella* were shown histologically in the valve tissue in 62% of the cases, and the organism was isolated in 83%, although this poses a significant laboratory hazard.<sup>298</sup> The diagnosis is best made serologically; a positive titer of antibody to the phase I antigen as measured with complement fixation or enzyme-linked immunosorbent assay indicates chronic infection, whereas a fourfold rise in titer of antibody to the phase II antigen is associated with active current infection. A phase I antibody titer (usually IgG or IgA or both) greater than 1:800 is considered virtually diagnostic of *C. burnetii* IE and may be useful to monitor the response to therapy.<sup>480,485</sup> Isolation of *C. burnetii* by inoculation of valve suspensions into a human fetal diploid fibroblast cell line seems to be a promising technique.<sup>486</sup> DNA probes are under development. The prognosis with medical therapy alone is poor, and valve replacement often is necessary for a cure (see later discussion). This agent also may cause endarteritis. A single case of IE due to the causative agent of murine typhus has been reported.<sup>287</sup>

### *Chlamydia psittaci*

*Chlamydia psittaci*, the agent of psittacosis, has been implicated in at least 10 well-documented cases of IE.<sup>487</sup> This organism also may cause myocarditis or pericarditis. Most cases have been associated with psittacine bird exposure; in one case, chlamydiae were found in the liver of the suspected budgerigar. Transmission from pet cats also has been proposed. The course is subacute, and the diagnosis often is made retrospectively. Most patients had preexisting heart disease, with a striking propensity for aortic valve involvement, and rapid valvular destruction leading to surgical intervention or death. A diagnosis can be established with the demonstration of complement-fixing antibodies. Cure usually requires valve replacement and prolonged antibiotic therapy. The mortality rate in this small group was 40%. Two well-documented cases of IE due to *Chlamydia trachomatis* have been reported.<sup>488</sup> Microimmunofluorescence tests are necessary for a diagnosis. Several cases of probable *Chlamydia pneumoniae* IE have been reported.<sup>489</sup> IE due to *Mycoplasma pneumoniae* was proposed in one case report, but cultural confirmation was lacking.<sup>490</sup>

### *Tropheryma whipplei*

*T. whipplei* is the causative agent of Whipple disease. Although its precise ecologic niche is unclear, there is increasing evidence to suggest that *T. whipplei* may be a component of the microbiota of the human respiratory tract, especially in patients with HIV. *T. whipplei* is an occasional cause of IE and has been cultivated from human valvular tissue.<sup>491</sup> In a review of 35 reported cases of Whipple IE, CHF, fever, and preceding

valvular abnormalities all were less common in patients with Whipple IE than in patients with IE due to other pathogens.<sup>295</sup>

A study from Germany involving heart valves found that *T. whipplei* was the most common cause of culture-negative IE. The study evaluated 1135 heart valves, which were analyzed for bacterial infection by means of conventional culture techniques, PCR amplification of the bacterial 16S rRNA gene, and subsequent sequencing. *T. whipplei*-positive heart valves were confirmed with specific PCR, fluorescence in situ hybridization, immunohistochemistry, histologic examination, and culture for *T. whipplei*. The investigators found that *T. whipplei* was the most common cause of culture-negative IE, accounting for 6.3% of such cases.<sup>492</sup> However, other investigators have emphasized the principal role of *Bartonella* and *C. burnetii* as etiologic agents in culture-negative IE.<sup>493</sup> Thus the etiology of culture-negative IE may vary significantly by geographic region.

### *Brucella* species

*Brucella* spp. continue as important etiologic agents in Spain and in Saudi Arabia, where these organisms are responsible for approximately 10% of IE cases.<sup>494</sup> Aggressive medical therapy with valve replacement usually is necessary for a cure of *Brucella* IE.<sup>495</sup>

### Unusual Bacterial Causes of Infective Endocarditis

Five cases of IE due to *Spirillum minus*, a spirochete, have been reported.<sup>496</sup> This organism is distributed widely in nature, especially in fresh or salt water with organic debris. *S. minus* is the etiologic agent of rat-bite fever (sodoku), but rodent transmission was not documented in the cases of IE. Preexisting heart disease or severe underlying disease (e.g., aplastic anemia) was usually present, although one case occurred in an otherwise healthy person.

Many other bacteria have been described in cases of IE; however, consideration of these organisms separately is beyond the scope of this chapter. These infectious agents include *Acinetobacter* (approximately 20 reported cases; a maculopapular rash on the palms and soles may be present),<sup>497</sup> *Actinomyces*,<sup>498</sup> *Alcaligenes*, *Bordetella*, *Flavobacterium*, *Micrococcus*, *Moraxella*, *Paracolon*, *Stomatococcus mucilaginosus* (4 cases of IE),<sup>499</sup> *Streptobacillus moniliformis* (16 cases; usually damaged native valves are involved),<sup>500</sup> *Vibrio*, and *Yersinia*.

## Fungi

Fungal IE is rare. Data from ICE-PCS showed that fewer than 1% of more than 2700 patients with definite IE were infected with *Candida* species.<sup>501</sup> Although injection drug use was traditionally an important risk factor for candidal IE,<sup>305</sup> health care contact has now emerged as the primary risk factor for most patients with this infection.<sup>302,501</sup> For example, 51% of patients from the ICE-PCS data with candidal IE had extensive health care contact as a risk factor, whereas only 12% had a history of injection drug use.<sup>501</sup> *Candida parapsilosis* and other non-*C. albicans* species have been reported to be more common in addicts, whereas *C. albicans* and *Aspergillus* spp. tend to predominate in health care-associated infections.<sup>302,305</sup>

The overall cure rate in cases of fungal IE is poor. The poor prognosis may be due to (1) large, bulky vegetations; (2) tendency for fungal invasion of the myocardium; (3) widespread systemic septic emboli; (4) poor penetration of antifungal agents into the vegetation<sup>502</sup>; (5) low toxic-to-therapeutic ratio of the available antifungal agents; and (6) usual lack of fungicidal activity with these compounds. A cure is almost impossible without surgical intervention (see later discussion).<sup>503</sup> The role of promising antifungal agents, including caspofungin<sup>504</sup> and voriconazole,<sup>505</sup> in the management of fungal IE remains to be defined.

In a review of 25 cases of *Aspergillus*-induced IE in which cultures were made,<sup>506</sup> the organisms isolated were as follows: *A. fumigatus*, 14; *A. flavus*, 4; *A. niger*, 3; and *A. ustus*, *A. sydowi*, *A. terreus*, and *A. glaucus*, 1 each. Only 5 of 34 patients in this series had positive blood cultures, and only one patient survived. A few cases, usually fatal, of *Aspergillus* IE after coronary artery bypass surgery have been described; *A. clavatus* was isolated in 1 case.

Other fungi that have caused IE include *Histoplasma*, *Blastomyces*, *Coccidioides*, *Cryptococcus*, *Hansenula*, *Fonsecaea* (*Hormodendrum*), *Lomentospora prolificans* (formerly *Scedosporium prolificans*), *Mucor*,

*Paecilomyces*, and *Phialophora*. *Histoplasma capsulatum* IE has been diagnosed rapidly using direct application of AccuProbe (Hologic Gen-Probe, San Diego, CA) on an excised cardiac valve.<sup>507</sup> Of the eight reported cases of IE due to *Trichosporon beigelii*, six occurred on prosthetic valves; only two patients have survived with a combined medical-surgical approach.<sup>508</sup> *Pseudallescheria boydii* has caused IE in approximately five reported patients; all were immunosuppressed (e.g., liver transplant, AIDS) or had received prosthetic heart valves.<sup>509</sup> A single case of *Trichoderma longibrachiatum* has been reported from a cardiac device-related IE.<sup>510</sup>

IE also has been rarely caused by higher bacteria, such as *Actinomyces*, *Nocardia*, and *Mycobacterium* spp.

## Viruses

The role of viruses in IE is unknown. Experimentally, coxsackievirus B has been shown to produce valvular and mural endocarditis in mice and cynomolgus monkeys.<sup>511</sup> In these studies, the viral antigen was identified in the valvular tissue by immunofluorescence techniques. Although the enteroviruses commonly are implicated in cases of myocarditis or pericarditis in humans, there is no proof that viral infections produce IE in humans. Adenoviruses also are capable of producing IE in mice. Persand<sup>512</sup> described a case of "cytomegalovirus endocarditis," but bacteria also were cultured from a mural lesion. Another potential case of CMV endocarditis was reported in a patient with CMV viremia and viral inclusions in resected valve leaflet tissue.<sup>513</sup> In this case, the patient had also been recently treated for group G streptococcal bacteremia, limiting the ability to confidently establish CMV as the primary pathogen.

## Culture-Negative Endocarditis

As discussed earlier, sterile blood cultures have been noted in 2.5% to 31% of cases of IE.<sup>514,515</sup> However, blood cultures are negative in only approximately 5% of patients who have IE confirmed by strict diagnostic criteria.<sup>516,517</sup> Sterile blood cultures may be the result in several conditions: (1) subacute right-sided IE; (2) cultures taken toward the end of a chronic course (>3 months); (3) uremia supervening in a chronic course; (4) mural IE, as in ventricular septal defects, post-myocardial infarction thrombi, or infection related to pacemaker wires; (5) slow growth of fastidious organisms, such as anaerobes, *Haemophilus* spp., *Actinobacillus* spp., *Cardiobacterium* spp., *Abiotrophia* and *Granulicatella* spp., or *Brucella* spp.; (6) prior administration of antibiotics<sup>514,517</sup>; (7) fungal IE; (8) IE caused by obligate intracellular parasites, such as *Coxiella*, Chlamydiae, *T. whipplei*,<sup>295</sup> and perhaps viruses; or (9) noninfective endocarditis or an incorrect diagnosis. Table 80.6 summarizes common causes of culture-negative IE. Attention to the proper collection of blood culture specimens, care in the performance of serologic tests, and use of newer diagnostic techniques may reduce the proportion of culture-negative cases.

## Polymicrobial Endocarditis

The proportion of IE cases due to more than one pathogen may be increasing. In a literature review spanning the 1980s,<sup>518</sup> 101 cases of polymicrobial IE were found. *S. aureus* and viridans-group streptococci were the most common identified organisms. The mean age was 36.5 years, the male-to-female ratio was almost 2:1, and 71 of the patients were injection drug users. As expected, tricuspid valve involvement with septic pulmonary emboli was common. Left-sided involvement, two organisms (vs. three or more), and older age were associated with a higher mortality rate.

## Etiology of Infective Endocarditis in Injection Drug Users

The organisms responsible for IE in injection drug users require separate consideration, because the distribution differs from that in other patients with IE. The frequencies of the etiologic agents isolated before 1977 in seven major series were as follows: *S. aureus*, 38%; *P. aeruginosa*, 14.2%; *Candida* spp., 13.8%; enterococci, 8.2%; viridans streptococci, 6%; *S. epidermidis*, 1.7%; gram-negative aerobic bacilli, 1.7% to 15%; other bacteria, 2.2%; mixed infections, 1.3%; and culture negative, 12.9%. In addition, there was an unexplained geographic variation in the causal

**TABLE 80.6 Causes of Culture-Negative Endocarditis**

ORGANISM	EPIDEMIOLOGY AND EXPOSURES	DIAGNOSTIC APPROACHES
<i>Aspergillus</i> and other noncandidal fungi	Prosthetic valve	Lysis-centrifugation technique; also culture and histopathologic examination of any emboli
<i>Bartonella</i> spp.	<i>B. henselae</i> : exposure to cats or cat fleas <i>B. quintana</i> : louse infestation; homelessness, alcohol abuse	Most common cause of culture-negative IE in United States; serologic testing (may cross-react with <i>Chlamydia</i> spp.); PCR assay of valve or emboli is best test; lysis-centrifugation technique may be useful
<i>Brucella</i> spp.	Ingestion of unpasteurized milk or dairy products; livestock contact	Blood cultures ultimately become positive in 80% of cases with extended incubation time of 4–6 wk; lysis-centrifugation technique may expedite growth; serologic tests are available
<i>Chlamydia psittaci</i>	Bird exposure	Serologic tests available but exhibit cross-reactivity with <i>Bartonella</i> ; monoclonal antibody direct stains on tissue may be useful; PCR assay now available
<i>Coxiella burnetii</i> (Q fever)	Global distribution; zoonosis, wide range of mammals	Serologic tests (high titers of antibody to both phase I and phase II antigens); also PCR assay on blood or valve tissue
<i>HACEK</i> spp.	Periodontal disease or preceding dental work	Although traditionally a cause of culture-negative IE, <i>HACEK</i> species are now routinely isolated from most liquid broth continuous monitoring blood culture systems without prolonged incubation times
<i>Legionella</i> spp.	Contaminated water distribution systems; prosthetic valves	Serology available; periodic subcultures onto buffered charcoal yeast extract medium; lysis-centrifugation technique; PCR assay available
<i>Abiotrophia</i> and <i>Granulicatella</i> spp.	Slow and indolent course	Supplemented culture media or growth as satellite colonies around <i>Staphylococcus aureus</i> streak; antimicrobial susceptibility testing often requires processing specialized microbiology laboratory
<i>Tropheryma whipplei</i> (Whipple disease)	Typical signs and symptoms include diarrhea, weight loss, arthralgias, abdominal pain, lymphadenopathy, central nervous system involvement; IE may be present without systemic symptoms	Histologic examination of valve with periodic acid-Schiff stain; valve cultures may be done using fibroblast cell lines; PCR assay on vegetation material
HACEK, <i>Haemophilus</i> , <i>Aggregatibacter</i> (formerly <i>Actinobacillus</i> ), <i>Cardiobacterium</i> , <i>Eikenella</i> , <i>Kingella</i> ; IE, infective endocarditis; PCR, polymerase chain reaction.		

agents of IE associated with injection drug use. *S. aureus* predominated in New York City, Chicago, Cincinnati, and Washington, DC; *P. aeruginosa* IE was traditionally encountered in Detroit and has recently resurfaced there,<sup>437</sup> but MRSA still predominates. A 1990 compilation from Detroit indicated the distribution of causative agents in addicts with IE ( $n = 74$ ) as follows: *S. aureus*, 60.8%; streptococci, 16.2%; *P. aeruginosa*, 13.5%; polymicrobial, 8.1%; and *Corynebacterium JK*, 1.4%.<sup>519</sup>

Polymicrobial IE (as many as eight different pathogens have been recovered from blood cultures of an individual patient) is fairly common among drug addicts. Some authors have speculated that HIV infection

predisposes injection drug users to IE owing to unusual bacteria, including *Corynebacterium* and *Neisseria* spp.<sup>519</sup> Although *S. aureus* IE in this population usually was tricuspid, streptococci infected left-sided valves significantly more often than the other pathogens. Biventricular and multiple-valve infections occurred most commonly in *Pseudomonas* IE, and all of these patients abused “Ts and blues.” Left-sided IE due to *P. aeruginosa* is a devastating disease and usually manifests as an acute illness refractory to seemingly optimal antimicrobial regimens. Complications, including ring and annular abscesses, neurologic sequelae, CHF, and splenic abscesses, are common; surgery is often necessary for cure.<sup>520</sup> The overall mortality rate still approaches 60%, however.

*S. marcescens* was an important historical pathogen in San Francisco,<sup>432</sup> although *S. aureus* now predominates in this patient population (HF Chambers, personal communication). These differences do not correlate with contamination of “street” heroin.<sup>521</sup> The high incidence of staphylococcal endocarditis may be explained partially by an increase in nasal and oral carriage of this organism.<sup>522</sup> Heroin use during the previous week was associated with an *S. aureus* isolation rate of 35% from skin, nose, or throat cultures; this rate declined to 11% (not significantly different from that in controls) if heroin had not been injected in the preceding 2 weeks. This suggests an endogenous source for the infecting organism, because *S. aureus* is infrequently (in <5% of cases) isolated from street heroin or injection paraphernalia.

The exact incidence of IE in injection drug use is unknown. A conservative estimate is 1.5 to 2 cases of IE per 1000 addicts at risk per year.<sup>523</sup> Injection drug use is the most common risk factor for the development of recurrent native valve IE; 43% of 281 patients surveyed from 1975 to 1986 with this syndrome were addicts (see earlier discussion).<sup>524</sup> A nested case-control study from Johns Hopkins University found that IE was more common among injection drug users with advanced immunosuppression, even after accounting for injection drug use behaviors. Analyses have shown that although *S. aureus* remains the most common cause of right-sided IE in injection drug users, cases of left-sided IE in this population are also commonly caused by viridans-group streptococci.

## THERAPY FOR INFECTIVE ENDOCARDITIS

The response to antimicrobial therapy for IE is unique among bacterial infections. Although the organisms may exhibit exquisite susceptibility in vitro to the antibiotics used, complete eradication takes weeks to achieve, and relapse is not unusual. There are two possible explanations for these phenomena: (1) The infection exists in an area of impaired host defense and is encased tightly in a fibrin meshwork in which the bacterial colonies divide relatively free from interference from phagocytic cells, and (2) the bacteria in these vegetations reach tremendous population densities (often  $10^9$  to  $10^{10}$  CFUs/g). At these high populations, the organisms may exist in a state of reduced metabolic activity and cell division, as was suggested by Durack and Beeson<sup>171</sup> in studies of L-alanine incorporation into bacterial cell walls. A similar finding is observed in broth in vitro after 18 hours of incubation. In both situations, the bacteria are less susceptible to the bactericidal action of penicillin or other drugs that require cell wall synthesis and division for maximal activity. The relative importance of antimicrobial penetration into vegetations in the response to therapy is unresolved. Although multiple studies have examined antibiotic concentrations in human cardiac valve tissue obtained during surgery<sup>525</sup> and they have usually been found to be in close agreement with concurrent serum concentrations, the relevance of these data to therapy for IE is unknown, so current recommendations remain unaltered.

Information on antimicrobial concentration in vegetations, either in experimental models or in humans with IE, is sparse. Experiments involving a single dose of a radiolabeled antimicrobial agent with autoradiographic analysis of drug dispersion within vegetations of animals with experimental IE revealed three patterns<sup>526</sup>: (1) concentration at the periphery of the vegetation without diffusion into the core (e.g., teicoplanin); (2) progressive diffusion, but with a high gradient from periphery to core (e.g., ceftriaxone); or (3) homogeneous diffusion throughout the vegetation (e.g., several fluoroquinolones). The predictive value of these observations with regard to therapeutic efficacy is

unknown. The suboptimal clinical efficacy of teicoplanin in several clinical trials treating intravascular *S. aureus* infections may relate to the maldistribution of this agent within vegetations.<sup>527</sup> Analysis of pharmacodynamic variables (e.g., concentration-dependent bactericidal activity, postantibiotic effect) also may assist in the rational selection of regimens for the treatment of IE.<sup>526</sup> Studies in animals have confirmed that when vegetation formation is inhibited with anticoagulants, the organisms are eradicated more rapidly with penicillin treatment than in control animals with larger vegetations.<sup>175</sup> Enzymatic modification of the glycocalyx in the vegetations of experimental streptococcal IE by in vivo dextranase administration facilitated the bactericidal activity of penicillin by more rapid sterilization of the lesion.<sup>528</sup> In contrast, tissue-type plasminogen activator produced a concentration-dependent lysis of fibrin clots or vegetations infected with *S. epidermidis* or *S. sanguinis* but did not enhance antimicrobial activity in *in vitro* models.<sup>529,530</sup> Several studies in experimental IE have confirmed the utility of aspirin in reducing the size of vegetations and the microbial densities within aortic vegetations.<sup>531,532</sup> In addition, one clinical study in patients with established IE suggested that aspirin could mitigate the growth of vegetative lesions (as monitored echocardiographically) and prevent cerebral emboli.<sup>533</sup>

## General Principles

Certain general principles have been accepted that provide the framework for the current recommendations for treatment of IE. Parenteral antibiotics are recommended over oral drugs in most circumstances because of the importance of sustained antibacterial activity. Erratic absorption with many classes of agents makes oral drugs less desirable. Short-term therapy has been associated with relapse, and most current recommendations emphasize extended drug administration. Early studies by the British Medical Research Council<sup>534</sup> first emphasized the necessity for prolonged treatment. Bacteriostatic antibiotics are generally ineffective in the treatment of bacterial IE. Their use has been associated with frequent relapses, failure to control the infection, or both. A symptomatic response to agents such as tetracycline, erythromycin, or in some cases clindamycin should not be accepted as indicative of successful treatment, because relapse is common after treatment with these agents is discontinued. Likewise, antibiotic combinations should produce a rapid bactericidal effect. This is seen with synergistic combinations, such as penicillin plus an aminoglycoside effective against most viridans streptococci or enterococci. In experimental animals, the rate of bactericidal action expressed by a drug or combination of drugs in broth is predictive of the relative rate at which the organisms are eradicated from the cardiac vegetations *in vivo*. Antagonistic combinations, such as penicillin plus chloramphenicol, which are less rapidly bactericidal, are less effective in experimental IE than the single bactericidal drug (penicillin) alone.<sup>535</sup> General guidelines for the evaluation of new antimicrobial agents for the treatment of IE were published in 1992.<sup>536</sup> Guidelines for outpatient parenteral antibiotic therapy for IE have been published. These guidelines outline a conservative approach (inpatient or daily outpatient follow-up) during the critical phase (weeks 0–2 of treatment), when complications are most likely, followed by outpatient parenteral antibiotic therapy for the continuation phase of antibiotic therapy.<sup>537</sup>

Patients with IE may have an associated myocarditis complicated by cardiac arrhythmias and CHF. These patients (with IE plus CHF) require close observation in an intensive care unit with electrocardiographic monitoring. As discussed later, the selection of antibiotics should be based on antimicrobial susceptibility tests and the treatment should be monitored clinically and with determination of antimicrobial blood levels when indicated. Blood cultures should be obtained during the early phase of therapy to ensure eradication of the bacteremia and in patients with persistent or recurrent fever during therapy. The use of anticoagulants during therapy for native valve IE has been associated with fatal subarachnoid hemorrhage and other bleeding complications. Most authorities agree that anticoagulant administration in this setting is contraindicated, but this conclusion is controversial. In cases of IE localized to mechanical prosthetic valves, many clinicians maintain anticoagulation within therapeutic range, provided that the patient has no evidence of major vascular emboli (e.g., central nervous system



signs or symptoms). One study concluded that oral anticoagulation should be discontinued in patients with *S. aureus* prosthetic valve IE until the septic phase of the disease is resolved (approximately 10 days after initiation of antimicrobial therapy).<sup>538</sup>

Patients with left-sided IE should be managed at least initially in facilities with access to cardiothoracic surgery. Although persistent or recurrent fever despite appropriate antimicrobial therapy may be due to pulmonary or systemic emboli or drug hypersensitivity, the most common cause is extensive valve ring or adjacent structure infection or metastatic infection.<sup>539</sup> Approximately one-third of patients with left-sided IE require surgery during the acute stages of infection for either valve replacement or metastatic infection.<sup>547</sup> Close monitoring of and early surgical consultation for patients with IE, particularly those with signs of heart failure or persistent fever, are essential. The critical role of early cardiac surgery in many cases of IE has been clearly reiterated by a large, well-designed propensity study<sup>540</sup> and one randomized trial.<sup>541</sup> However, this latter study has been criticized for study design issues that limited generalizability, including infrequency of *S. aureus* IE and a relatively young and healthy patient population.

### Tests Useful for Antimicrobial Treatment Monitoring

Management of IE demands careful consideration of the choice, dose, and duration of antimicrobial therapy. The following laboratory tests can help the physician to monitor treatment and can aid in rational therapeutic decisions. In every case of bacterial IE, the etiologic agent must be isolated in pure culture and the minimal inhibitory concentration (MIC) and minimal bactericidal concentration (MBC) must be determined for the usual antibiotics used (see later discussion). Standard

disk sensitivity testing is unreliable in the context of treating IE, and results may be misleading without the quantitative information provided from the MIC and MBC.

In some forms of IE, combinations of antibiotics are used routinely.<sup>542</sup> These regimens are based on synergy studies performed in vitro and on results obtained in experimental animal models of IE. In difficult cases with a slow therapeutic response and in cases caused by unusual organisms, a determination of synergistic combinations of antibiotics may be helpful. In these cases, tests for bactericidal synergism may be undertaken by standard techniques, such as broth dilution, microtiter "checkerboards," or time-kill curves in broth. Proper attention to standardized techniques, especially inoculum size, is crucial for a meaningful interpretation of the results.

When aminoglycosides are used in therapy, the concentration of antibiotic in the serum should be determined periodically. These agents have a low toxic-to-therapeutic ratio, especially in elderly patients and in patients with renal disease. Peak and trough concentrations should be measured, and the dose should be altered accordingly. This method is superior to reliance solely on nomograms for dosage changes. If synergy with another agent is demonstrable, serum concentrations of the aminoglycosides lower than those generally considered "therapeutic" may be adequate, lessening the potential for toxicity.

### Antimicrobial Therapy

The treatment recommendations contained in this chapter are summarized in Table 80.7 and are based on published guidelines from the American Heart Association Committee on Endocarditis published in October 2015.<sup>1</sup> The role of aminoglycosides and other agents in combination therapy for IE also has been reviewed.<sup>543</sup>

**TABLE 80.7 Summary of Treatment Options for Endocarditis**

ORGANISM	REGIMEN <sup>a</sup>	COMMENTS
<b><i>Staphylococcus aureus</i></b>		
<b>Native Valve</b>		
Methicillin-susceptible	Nafcillin or oxacillin, 2 g IV q4h × 4–6 wk Cefazolin, 2 g IV q8h × 4–6 wk	Use of gentamicin in native valve <i>S. aureus</i> IE is associated with significant nephrotoxicity without clear clinical benefit and is discouraged. Acceptable in setting of penicillin allergy other than immediate hypersensitivity. See above cautions about gentamicin use.
Methicillin-resistant	Vancomycin, 15–20 mg/kg IV q8–12h × 6 wk <sup>b</sup> Daptomycin, 6 mg/kg IV qd × 4–6 wk <sup>b</sup>	Also acceptable in setting of immediate hypersensitivity or anaphylaxis to penicillin; goal vancomycin trough level 10–20 µg/mL is recommended with careful monitoring of renal function. Daptomycin is FDA approved for treatment of right-sided <i>S. aureus</i> IE; for adults, some experts recommend 8–10 mg/kg IV.
<b>Prosthetic Valve</b>		
Methicillin-susceptible	Nafcillin or oxacillin, 2 g IV q4h × ≥6 wk, plus gentamicin, 1 mg/kg IV q8h × 2 wk, plus rifampin, 300 mg PO/IV q8h × ≥6 wk	Some authorities recommend delaying the initiation of rifampin therapy for several days in an attempt to prevent treatment-emergent resistance to rifampin.
Methicillin-resistant	Vancomycin, 15–20 mg/kg IV q8–12h × ≥6 wk plus gentamicin, 1 mg/kg IV q8h × 2 wk, plus rifampin, 300 mg PO/IV q8h × ≥6 wk	Goal vancomycin trough level 10–20 µg/mL is recommended with careful monitoring of renal function. Some authorities recommend delaying the initiation of rifampin therapy for several days in an attempt to prevent treatment-emergent resistance to rifampin.
<b>Injection Drug Use</b>		
Methicillin-susceptible	Nafcillin or oxacillin, 2 g IV q4h × 2 wk; plus gentamicin, 1 mg/kg IV q8h × 2 wk	Two-week regimen only for use in injection drug users with infection limited to tricuspid valve, no renal insufficiency, and no extrapulmonary infection. Two weeks of monotherapy with antistaphylococcal penicillin has also been successfully used in these patients.
Methicillin-resistant	Vancomycin, 15–20 mg/kg IV q8–12h × 4 wk Daptomycin, 6 mg/kg IV qd × 4–6 wk	Use of gentamicin in this setting is not recommended. Goal vancomycin trough level 10–20 µg/mL is recommended with careful monitoring of renal function. Daptomycin is FDA approved for treatment of right-sided <i>S. aureus</i> IE; for adults, some experts recommend 8–10 mg/kg IV.
<b>Coagulase-Negative Staphylococci</b>		
<b>Native Valve</b>		
Methicillin-susceptible	Nafcillin or oxacillin, 2 g IV q4h × 4–6 wk	
Methicillin-resistant	Vancomycin, 15–20 mg/kg IV q8–12h × 6 wk	Also acceptable in setting of immediate hypersensitivity or anaphylaxis to penicillin. Goal vancomycin trough level 10–20 µg/mL is recommended with careful monitoring of renal function.

**TABLE 80.7 Summary of Treatment Options for Endocarditis—cont'd**

ORGANISM	REGIMEN <sup>a</sup>	COMMENTS
<b>Prosthetic Valve</b>		
Methicillin-susceptible	Nafcillin or oxacillin, 2 g IV q4h × ≥6 wk, plus gentamicin, 1 mg/kg IV q8h × 2 wk, plus rifampin, 300 mg PO/IV q8h × ≥6 wk	Some authorities recommend delaying the initiation of rifampin therapy for several days in an attempt to prevent treatment-emergent resistance to rifampin.
Methicillin-resistant	Vancomycin, 15–20 mg/kg IV q8–12h × ≥6 wk, plus gentamicin, 1 mg/kg IV q8h × 2 wk, plus rifampin, 300 mg PO/IV q8h × ≥6 wk	Goal vancomycin trough level 10–20 µg/mL is recommended with careful monitoring of renal function. Some authorities recommend delaying the initiation of rifampin therapy for several days in an attempt to prevent treatment-emergent resistance to rifampin.
<b>Penicillin-Susceptible Viridans Streptococci (MIC ≤0.1 µg/mL) and <i>Streptococcus bovis</i> (<i>S. gallolyticus</i>)</b>		
	Penicillin, 2–3 million units IV q4h × 4 wk, or ampicillin, 2 g IV q4h × 4 wk Ceftriaxone, 2 g IV qd × 4 wk	Also effective for other penicillin-susceptible nonviridans streptococci (e.g., group A streptococci) For penicillin allergy; patients with uncomplicated viridans streptococcal IE are candidates for outpatient therapy. Uncomplicated native valve IE only; not acceptable for <i>Abiotrophia</i> and <i>Granulicatella</i> spp.
<i>Abiotrophia</i> and <i>Granulicatella</i> spp.	Penicillin, 2–4 million units IV q4h × 4 wk, plus gentamicin, 1 mg/kg IV q8h × 2 wk Vancomycin, 15–20 mg/kg IV q8–12h × 4 wk	For prosthetic valve IE, give 6 wk of penicillin. <i>Abiotrophia</i> and <i>Granulicatella</i> spp. are often penicillin tolerant. For penicillin allergy. No published guidelines exist for vancomycin trough targeting for treatment of streptococcal or enterococcal infections.
<b>Relatively Penicillin-Resistant Viridans Streptococci (MIC 0.12 to &lt;0.5 µg/mL)</b>		
	Penicillin, 4 million units IV q4h × 4 wk, plus gentamicin, 1 mg/kg IV q8h × 2 wk Vancomycin, 15–20 mg/kg IV q8–12h × 4 wk	For penicillin allergy or to avoid gentamicin. No published guidelines exist for vancomycin trough targeting for treatment of streptococcal or enterococcal infections.
<b>Enterococci<sup>c</sup> and Penicillin-Resistant Viridans Streptococci (Penicillin MIC &gt;0.5 µg/mL)</b>		
Penicillin-susceptible, aminoglycoside-susceptible enterococci	Penicillin <sup>d</sup> 3–5 g IV q4h × 4–6 wk, plus gentamicin, 1 mg/kg IV q8h × 4–6 wk; or Ampicillin, 2 g IV q4h, plus gentamicin, 1 mg/kg IV q8h × 4–6 wk	Increase duration of both drugs to 6 wk for prosthetic valve infection or for enterococcal IE with symptoms >3 mo. For older patients and those with underlying renal disease, can consider shortening the duration of gentamicin to 2 wk.
Penicillin-resistant, vancomycin-susceptible, aminoglycoside-susceptible enterococci	Vancomycin, 15–20 mg/kg IV q8–12h × 6 wk, plus gentamicin, 1 mg/kg q8h × 6 wk <sup>e</sup>	Also for patients with penicillin allergy. This regimen is associated with enhanced risk of nephrotoxicity. Penicillin desensitization should be considered as an alternative to this regimen when possible. No published guidelines exist for vancomycin trough targeting for treatment of streptococcal or enterococcal infections.
Penicillin-susceptible, aminoglycoside-resistant enterococci	Ampicillin, 2 g IV q4h, plus ceftriaxone, 2 g IV q12h	Useful for patients with significant underlying renal disease.
Penicillin-resistant, vancomycin-resistant enterococci	No standard therapy; daptomycin, linezolid, and quinupristin-dalfopristin have been used	Consult infectious diseases specialist.
<b>HACEK Strains</b>		
	Ceftriaxone, 2 g IV qd × 4 wk Ampicillin-sulbactam, 3 g IV q6h × 4 wk (if β-lactamase producing strain) <sup>a</sup>	Increase duration to 6 wk for infections involving prosthetic valves. Increase duration to 6 wk for infections involving prosthetic valves.
<b>Non-HACEK Gram-Negative Bacilli<sup>f</sup></b>		
Enterobacteriaceae	Extended-spectrum penicillin (e.g., piperacillin-tazobactam) or cephalosporin plus aminoglycosides for susceptible strains	Treat for a minimum of 6–8 wk. Some species exhibit inducible resistance to third-generation cephalosporins. Valve surgery is often required for patients with left-sided IE caused by gram-negative bacilli, especially for prosthetic valve IE. Consultation with an infectious diseases specialist is recommended.
<i>Pseudomonas aeruginosa</i>	Antipseudomonal penicillin (e.g., piperacillin) plus high-dose tobramycin, 8 mg/kg/day IV or IM in once-daily doses; or High-dose ceftazidime, cefepime, or imipenem	Goal tobramycin peak and trough concentrations of 15–20 µg/mL and ≤2 µg/mL, respectively. Treat for a minimum of 6–8 wk. Early valve surgery usually required for left-sided <i>Pseudomonas</i> IE; consultation with a specialist in infectious diseases is recommended.
<b>Fungi<sup>g</sup></b>		
	Treatment with a parenteral antifungal agent (usually an amphotericin B-containing product) is usually recommended as initial therapy	Fungal endocarditis is usually an indication for valve replacement surgery. Long-term/lifelong suppressive therapy with oral antifungal agents is often required. Consultation with a specialist in infectious diseases is recommended.

<sup>a</sup>Dosages assume normal renal function. For patients with renal insufficiency, adjustments must be made for all antibiotics except nafcillin, rifampin, and ceftriaxone. Gentamicin doses should be adjusted to achieve a peak serum concentration of approximately 3 µg/mL 30 minutes after dosing and a trough gentamicin level of <1 µg/mL.

<sup>b</sup>Primarily relevant to left-sided IE.

<sup>c</sup>Enterococci must undergo antimicrobial susceptibility testing. These recommendations are for enterococci susceptible to penicillin, gentamicin, and vancomycin except as indicated.

<sup>d</sup>Ampicillin, 12 g/day, can be used instead of penicillin.

<sup>e</sup>The need to add an aminoglycoside has not been demonstrated for penicillin-resistant streptococci.

<sup>f</sup>Limited data exist.

FDA, US Food and Drug Administration; HACEK, *Haemophilus*, *Aggregatibacter* (formerly *Actinobacillus*), *Cardiobacterium*, *Eikenella*, *Kingella*; IE, infective endocarditis; MIC, minimal inhibitory concentration.

Modified from Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis: diagnosis, antimicrobial therapy, and management of complications: a scientific statement for healthcare professionals from the American Heart Association. Circulation. 2015;132:1435.

## Penicillin-Sensitive Streptococcal Endocarditis

Most strains of viridans streptococci, "other" streptococci (including *S. pyogenes*), and nonenterococcal group D streptococci (primarily *S. bovis*) are exquisitely sensitive to penicillins, with an MIC of less than 0.12 µg/mL. Of viridans streptococci, 15% to 20% are "resistant" to this arbitrary concentration of penicillin.<sup>352,377</sup> In addition, approximately 15% of the strains of *S. mutans* show a low MIC for penicillin (<0.1 µg/mL), but the MBC is considerably higher (1.25–50 µg/mL).<sup>356</sup> These organisms probably should be considered "penicillin tolerant" and should be treated accordingly. Although results depend on the in vitro methodology employed,<sup>344</sup> studies beginning in the 1980s suggested that tolerance to penicillin among viridans streptococci was more prevalent than previous reports had indicated.<sup>345</sup> Of viridans streptococci cultured from gingiva and blood after dental procedures, 19% were tolerant,<sup>346</sup> especially among *S. mutans* (27%) and *S. mitior* (20%) isolates. Almost identical figures were reported among blood culture isolates of viridans streptococci,<sup>347</sup> with tolerance defined as a penicillin MBC-to-MIC ratio exceeding 10:1. Almost all strains of nutritionally dependent streptococci were tolerant to penicillin.<sup>348,349</sup> The influence of the tolerance phenomenon on the response to penicillin therapy in experimental IE is not known; two studies yielded conflicting results.<sup>350,351</sup> Data on human infections with tolerant strains and the therapeutic results are unavailable. Except for *Abiotrophia* and *Granulicatella* spp., we do not believe that the demonstration of tolerance by an isolate of viridans streptococci influences therapeutic decisions.

With broth dilution susceptibility tests, the usual MBC determinations for the so-called penicillin-sensitive streptococci are as follows: penicillin, 0.1 to 1 µg/mL; cephalothin, 0.15 to 1.25 µg/mL; vancomycin, 0.15 to 0.4 µg/mL; streptomycin, 6.25 to 50 µg/mL; and gentamicin, 1.56 to 3.12 µg/mL.<sup>352,353</sup> *S. bovis* is 10 to 5000 times more susceptible to penicillin than the other group D species (enterococci). They also are relatively susceptible to oxacillin, methicillin, and lincomycin, whereas the enterococci are resistant.<sup>360</sup> Most streptococci in this group show synergism in vitro between penicillin or vancomycin and streptomycin, gentamicin, or kanamycin (see later discussion).<sup>354,355</sup> The first strains of viridans streptococci with high-level streptomycin resistance (MIC ≥1000 µg/mL) were reported in 1982 from Paris.<sup>356</sup> Although these strains are rare (2%–8% of isolates in some locales),<sup>356</sup> the documentation of aminoglycoside-modifying enzymes and the lack of penicillin-streptomycin synergy in vitro and in experimental animal models<sup>356,357</sup> are alarming. These penicillin-susceptible strains may be killed synergistically by penicillin-gentamicin combinations. Significant antibiotic antagonism was shown with the combination of clindamycin and gentamicin for *S. mutans* IE. The in vitro synergism between penicillin and aminoglycosides was found to correlate with a more rapid rate of eradication of bacteria from cardiac vegetations in vivo in the rabbit endocarditis model<sup>358,359</sup> for the common viridans streptococci. All of these studies have been summarized in reviews.<sup>360–362</sup> Low-level penicillin resistance (defined in this study as MIC 0.2–2 µg/mL) was found in 31% of viridans streptococci in Madrid in 1988 and 1989, and an additional 17% of strains showed high-level resistance.<sup>363</sup> Perhaps most important, streptomycin and cefotaxime resistance also was found to be "common."<sup>32</sup> The authors suggested a vancomycin-gentamicin regimen for IE due to viridans streptococci in Spain.

The combination of penicillin and streptomycin was used in more than 200 historical cases at The New York Hospital–Cornell Medical Center without a documented relapse.<sup>354</sup> This clinical experience has been confirmed elsewhere, but the overall reported relapse rate is 1.4%.<sup>361</sup> This regimen is as follows: aqueous penicillin G, 10 million to 20 million units given intravenously daily, or procaine penicillin G, 1.2 million units given intramuscularly every 6 hours, for 4 weeks, combined with streptomycin, 0.5 g intramuscularly every 12 hours for the first 2 weeks. Studies by Wilson and colleagues at the Mayo Clinic<sup>364,365</sup> showed that a 2-week course of intramuscular procaine penicillin (1.2 million units every 6 hours) and streptomycin (0.5 g every 12 hours) cured at least 99% of patients with penicillin-sensitive streptococcal IE. These results were similar to those obtained with therapy consisting of β-lactams alone for a total of 4 weeks<sup>366,367</sup> but significantly better than results obtained with penicillin alone for 2 weeks. The latter regimen was

associated with a 50% relapse rate if low doses of penicillin were used and improved to 17% with higher penicillin dosages. The 2-week penicillin-streptomycin regimen has been the most cost-effective and the preferred therapy among these three regimens in uncomplicated penicillin-sensitive (MIC ≤0.12 µg/mL) streptococcal IE in young patients. However, since the advent of ceftriaxone-based regimens (featuring 2 weeks of ceftriaxone plus an aminoglycoside), many clinicians have opted for this approach (see later discussion).<sup>368,369</sup> Four weeks of penicillin (or ceftriaxone; see later discussion) alone is recommended for patients with impaired renal function and for those who are particularly susceptible to the low risk for streptomycin-induced ototoxicity (i.e., the elderly). The Cornell regimen (4 weeks of penicillin with an initial 2 weeks of streptomycin) has been recommended for patients with a complicated course, a history of disease exceeding 3 months' duration, or prosthetic valve IE caused by these sensitive strains and when susceptibility testing reveals the rare penicillin-resistant streptococci.<sup>370</sup> The preferred regimen for IE due to penicillin-tolerant streptococci is not established.

Most of the published clinical data with β-lactam-aminoglycoside regimens for the treatment of viridans streptococcal IE involve the use of penicillin or ampicillin plus either streptomycin or gentamicin. On the basis of extensive in vitro and animal data and for a variety of other reasons, however, the American Heart Association has deemed gentamicin preferable to streptomycin in this context.<sup>237</sup> First, gentamicin currently is more widely available and is used more often clinically than streptomycin in viridans streptococcal IE. Second, gentamicin (but not streptomycin) serum level determinations are performed routinely in most hospital laboratories. Because in vitro synergy against most viridans streptococci with penicillin or ampicillin in combination with gentamicin occurs at low gentamicin concentrations (1–3 µg/mL), most authorities recommend using gentamicin at a total daily dose of no more than 3 mg/kg/day (IM or IV), split into either a twice-daily (every 12 hours) or a thrice-daily (every 8 hours) dosage regimen. However, one study using ceftriaxone plus gentamicin given as a once-daily dose reported excellent efficacy against penicillin-susceptible streptococcal IE with no increases in aminoglycoside-associated nephrotoxicity.<sup>369</sup> Despite the apparent safety of once-daily aminoglycoside dosing in this study and in clinical trials involving patients with other infectious disorders,<sup>371</sup> the total number of patients receiving such regimens for 2 weeks or longer has been relatively limited. As with any patients receiving aminoglycosides, appropriate clinical and blood level monitoring to mitigate ototoxicity and nephrotoxicity should be used. Nomograms for prudent monitoring and adjustment of aminoglycoside doses when once-daily regimens are used have been published.<sup>370</sup>

We believe that gentamicin, at a total daily dose of 3 mg/kg, should be substituted for streptomycin in the aforementioned regimens when combination therapy is deemed advisable. In addition, a penicillin-gentamicin regimen is indicated for viridans streptococcal IE if high-level streptomycin resistance is present<sup>356,357</sup> and for strains that are relatively resistant to penicillin (MIC >0.12 µg/mL and ≤0.5 µg/mL).<sup>334</sup> Infections caused by strains with a penicillin MIC greater than 0.5 µg/mL should be treated as for enterococcal IE (see later discussion). Because of the enhanced rate of bacterial killing in animal models<sup>372,373</sup> and the high relapse rate of about 17%,<sup>374</sup> we also believe that the Cornell regimen (using gentamicin as the preferred aminoglycoside) should be employed for all patients with IE due to *Abiotrophia* and *Granulicatella* spp. Although temafloxacin plus tobramycin was as effective as penicillin plus tobramycin against experimental IE caused by *G. adiacens* in rabbits,<sup>375</sup> quinolones are best avoided for IE due to streptococci pending further data.

In a penicillin-allergic patient for whom a cephalosporin is deemed safe, several regimens are acceptable for IE caused by penicillin-susceptible viridans streptococci: (1) cefazolin, 2 g IM or IV every 8 hours for 4 weeks, combined with streptomycin, 0.5 g IM or IV every 12 hours; or (2) gentamicin, administered IM or IV in two or three daily doses for a total of no more than 3 mg/kg daily, for the initial 2 weeks; or (3) ceftriaxone alone, 2 g IV or IM given daily for 4 weeks. This last regimen has been proven efficacious against penicillin-sensitive streptococcal IE.<sup>376,377</sup> In one uncontrolled trial in Europe, 55 of 59 patients completed treatment with 4 months to 5 years of follow-up; treatment was completely

uneventful in 71% of patients, whereas valve replacement eventually was required in 10 patients. This regimen may permit outpatient therapy in most stable patients with this disease. In addition, ceftriaxone plus an aminoglycoside has shown in vivo synergy in experimental viridans streptococcal IE.<sup>578</sup> Combination regimens of 2 weeks, including ceftriaxone (2 g once daily) plus an aminoglycoside (netilmicin or gentamicin), which allow for shortened, predominantly outpatient regimens, have been studied in penicillin-susceptible viridans streptococcal IE.<sup>568,569</sup> These trials, performed in Europe and North and South America, documented efficacy in this form of IE comparable to that achieved with other 2-week or 4-week regimens.<sup>568,569</sup>

If treatment with  $\beta$ -lactams is contraindicated, the regimen of choice is vancomycin, 30 mg/kg/24 h in two equally divided doses (not to exceed 2 g/24 h, unless serum concentrations are inappropriately low) for 4 weeks.<sup>334</sup> Because patients, particularly obese patients, who are receiving a fixed dose of vancomycin regularly received inadequate doses of the antibiotic, weight-based dosing strategies are preferred.<sup>579</sup> A 4-week regimen of high-dose teicoplanin has been efficacious in a few patients with streptococcal IE,<sup>580</sup> but the occurrence of drug fever and infection with teicoplanin-tolerant *S. bovis* is cause for concern.

### Endocarditis Caused by Streptococci With Penicillin Minimal Inhibitory Concentration Greater Than 0.5 $\mu\text{g}/\text{mL}$ or by Enterococci

Enterococci are a common cause of IE and can be highly resistant to therapy. The mortality rate still approximates 20%,<sup>578</sup> and relapses are common. With broth dilution susceptibility tests, the MIC determinations for many enterococci are as follows: penicillin, 0.4 to 12.5  $\mu\text{g}/\text{mL}$ ; ampicillin, less than 0.4 to 3.1  $\mu\text{g}/\text{mL}$ ; cephalothin, 12.5 to 25  $\mu\text{g}/\text{mL}$ ; vancomycin, 0.78 to 3.1  $\mu\text{g}/\text{mL}$ ; streptomycin, 3.1 to greater than 50  $\mu\text{g}/\text{mL}$ ; and gentamicin, 6.25 to 25  $\mu\text{g}/\text{mL}$ . Ampicillin is approximately twice as active as penicillin by weight. In contrast, the usual MBC determinations are as follows: penicillin, greater than 6.25  $\mu\text{g}/\text{mL}$  (in 80% of cases, >100  $\mu\text{g}/\text{mL}$ ); cephalothin, greater than 100  $\mu\text{g}/\text{mL}$ ; streptomycin, greater than 25  $\mu\text{g}/\text{mL}$ ; vancomycin, greater than 100  $\mu\text{g}/\text{mL}$ ; and gentamicin, 25  $\mu\text{g}/\text{mL}$  or less.<sup>581</sup> *E. faecalis* strains are more resistant to  $\beta$ -lactams than are *E. faecalis* strains.<sup>582</sup> In general, these agents are bacteriostatic against the enterococci and should not be administered alone in this disease. This bacteriostatic action of agents known to inhibit cell wall synthesis is the result of a defective bacterial autolytic enzyme system.<sup>583,584</sup> As stated earlier, all  $\beta$ -lactams, including imipenem, are bacteriostatic against enterococci in vitro, and combination regimens are used in treating IE whenever possible.<sup>585</sup>

A new mechanism of penicillin resistance among *E. faecalis* strains was described in 1983: plasmid-mediated  $\beta$ -lactamase production. These strains remain relatively rare.<sup>586,587</sup> *E. faecalis* predominates, but  $\beta$ -lactamase production was documented in *E. faecium*.<sup>588</sup> Ampicillin-sulbactam overcomes the  $\beta$ -lactamase production and appears to be equivalent to vancomycin<sup>589,590</sup> (or teicoplanin<sup>591</sup>) in experimental IE involving these organisms and superior to therapy with ticarcillin-clavulanate.<sup>591</sup> Most  $\beta$ -lactamase-producing organisms also display high-level aminoglycoside resistance, further compromising and complicating the choice of available regimens (see later discussion). Still other enterococci, particularly *E. faecium* and *Enterococcus raffinosus*, may display high-level penicillin resistance in the absence of  $\beta$ -lactamase production related to perturbations in various penicillin-binding proteins; experimental IE caused by these organisms responds to therapy with daptomycin or vancomycin.<sup>592</sup> To date, the number of reported cases of enterococcal IE caused by  $\beta$ -lactamase-producing strains or cases with high-level penicillin resistance on a nonenzymatic basis is low. The traditional view of  $\beta$ -lactam tolerance among enterococci has been challenged<sup>593</sup> in that some strains show "paradoxical" tolerance (i.e., there is a higher percentage of survivors at higher antibiotic concentrations). This phenomenon is shown more easily in vitro at high bacterial densities in stationary growth phase, a situation presumably reflecting the in vivo conditions in the vegetation, and may be important in bacterial persistence or relapse during or after therapy for enterococcal IE.

Cell wall-active antibiotics plus an aminoglycoside are synergistic and produce a bactericidal effect in vitro against most enterococcal

strains. Although successful treatment of enterococcal IE requires such combinations, aminoglycoside-associated nephrotoxicity and ototoxicity confer significant risk to patients whose antibiotic regimen includes an aminoglycoside. Studies in experimental models<sup>594</sup> suggest that "low-dose" streptomycin (peak serum concentrations of 9.1  $\mu\text{g}/\text{mL}$ ) in combination with penicillin is sufficient to treat streptomycin-susceptible enterococcal IE. "High-level" streptomycin resistance (MIC >2000  $\mu\text{g}/\text{mL}$ ) is demonstrable in at least 60% of current enterococcal strains. This resistance correlates with an inability to show in vitro synergism between penicillin and streptomycin.<sup>595</sup> These highly resistant strains show synergism between a penicillin and gentamicin in vitro<sup>596,597</sup> at clinically achievable serum concentrations. Enhanced activity with the penicillin and gentamicin combination was seen in vivo for streptomycin-resistant and streptomycin-sensitive enterococci in the rabbit model of IE. No differences in results were seen when penicillin was combined with low-dose versus high-dose gentamicin (peak serum levels of 3.06 and 8.05  $\mu\text{g}/\text{mL}$ , respectively) in the treatment of experimental streptomycin-resistant enterococcal IE.<sup>598</sup> Early reports<sup>599,600</sup> revealed high-level gentamicin resistance among enterococci in 14% of isolates beginning in 1979. This phenomenon has become increasingly prevalent in many areas<sup>601–603</sup> beginning with *E. faecalis*, but now also includes *E. faecium*.<sup>603–605</sup> High-level gentamicin resistance (MIC  $\geq$ 2000  $\mu\text{g}/\text{mL}$ ) now accounts for at least 35% of enterococcal blood isolates in many hospitals. The resistance is plasmid mediated through the production of aminoglycoside-modifying enzymes and can be transferred among strains. A clonal dissemination is not the cause of the increased frequency of these resistant strains, because gentamicin resistance appears in a wide variety of different conjugative and nonconjugative plasmids among enterococci.<sup>603</sup> Although these strains seldom cause IE, they present major problems in nosocomial infections,<sup>606</sup> and, because resistance to multiple aminoglycosides is common, they represent a formidable therapeutic challenge.<sup>607</sup> In addition, penicillin-aminoglycoside or vancomycin-aminoglycoside synergy is not apparent against these organisms in vitro.

The optimal therapy for IE due to these highly resistant strains has not been established. None of the currently recommended regimens is bactericidal against these isolates, and valve replacement<sup>608</sup> may be necessary for a cure. When these isolates are encountered, all available aminoglycosides must be tested separately, because the organism may be susceptible to one but resistant to others. Some isolates are sensitive to quinolones or daptomycin, but these agents have received scant attention in human enterococcal infections. Traditionally, long-term therapy (8–12 weeks) with high dosages of penicillin (20–40 million units IV daily in divided doses) or ampicillin (2–3 g IV every 4 hours or by continuous infusion) for IE due to these multiple aminoglycoside-resistant enterococci was recommended. However, in vitro data<sup>609</sup> and two open-label trials (see later discussion) of high-dose ceftriaxone (2 g IV twice daily) plus ampicillin<sup>610,611</sup> now strongly support the efficacy of a double  $\beta$ -lactam combination in the setting of ampicillin-sensitive, aminoglycoside-resistant enterococcal IE data. Although results vary among experimental animal models of IE with these strains,<sup>607,612</sup> continuous infusion of high-dose ampicillin throughout the 24-hour period may be more effective than a divided-dose regimen and merits a trial in recalcitrant cases. Even higher-dose aminoglycosides and trimethoprim-sulfamethoxazole were ineffective in animal models<sup>613,614</sup> and cannot be recommended.

Vancomycin also is bacteriostatic against enterococci and exhibits synergy with the aminoglycosides in vitro. The vancomycin-streptomycin combination synergistically kills 40% to 80% of enterococcal strains, whereas the vancomycin-gentamicin combination shows synergy against 93% to 98%.<sup>615</sup> In one study, vancomycin therapy alone was ineffective in eradicating enterococci from cardiac vegetations in the rabbit model of IE, but the combination of vancomycin plus gentamicin rapidly achieved a bactericidal effect.<sup>598</sup> Vancomycin combined with rifampin had an indifferent effect against enterococci (43 of 48 strains) in vitro; antagonism was observed rarely.<sup>616</sup> Glycopeptide-resistant strains of enterococci first were isolated in France in 1986 and since then have emerged rapidly in many geographic areas worldwide (e.g., New York City<sup>617</sup>) as an important cause of nosocomial infections. The genetics of vancomycin resistance<sup>618</sup> is described elsewhere (see Chapter 30) and

has been reviewed,<sup>619</sup> but multiple phenotypes exist that may confer cross-resistance to related agents (e.g., teicoplanin, daptomycin). Molecular analyses suggest that a highly mobile genetic element (i.e., a transposon) is responsible for the rapid spread of vancomycin-resistant enterococci.<sup>617</sup> The molecular basis for some forms of this resistance (substitutions of D-alanine-D-lactate for D-alanine-D-alanine in the terminal pentapeptide chain) has been defined. IE due to vancomycin-resistant enterococci is unusual<sup>620</sup> but has been reported in a variety of clinical settings,<sup>621,622</sup> including transplanted hearts.<sup>623</sup>

The therapy for vancomycin-resistant enterococcal IE is not established.<sup>334</sup> All suspected strains should be tested quantitatively (e.g., by determination of MIC or MBC) in vitro for susceptibility to glycopeptides, penicillins, and aminoglycosides. Teicoplanin—or, potentially, linezolid or daptomycin<sup>624–626</sup>—may be useful, in combination with gentamicin, against some isolates with low-level vancomycin resistance that do not exhibit cross-resistance. Anecdotal cases have been reported of cures after therapy with linezolid,<sup>621</sup> a combination of quinupristin-dalfopristin plus ampicillin and gentamicin in addition to aortic root replacement,<sup>627</sup> and chloramphenicol plus minocycline.<sup>622</sup> A triple combination of high-dose penicillin plus vancomycin plus gentamicin seems promising in animal models of IE induced by such resistant enterococci<sup>628,629</sup> and should be considered if in vitro susceptibility test results suggest multiply resistant isolates. The cephalosporins are relatively inactive against enterococci, even in combination with an aminoglycoside, and should not be used in this disease except potentially in place of an aminoglycoside and in combination with ampicillin (see later discussion).<sup>610,611</sup> The older-generation quinolones (e.g., ciprofloxacin) do not seem promising for the treatment of enterococcal IE.<sup>630</sup>

Native or prosthetic valve enterococcal IE caused by strains susceptible to penicillin, gentamicin, and vancomycin should be treated with combination antimicrobial therapy for at least 4 to 6 weeks.<sup>560</sup> The recommended regimen is as follows: aqueous penicillin G, 18 to 30 million units IV daily in divided doses (or ampicillin 12 g/24 h in six equally divided doses), plus gentamicin 3 mg/kg/24 h in three equally divided doses, for 4 to 6 weeks. Gentamicin should not be given once daily for enterococcal IE. Experimental studies in enterococcal IE models show a greater reduction in vegetation bacterial densities when the aminoglycoside is administered in multidose rather than once-daily regimens.<sup>631,632</sup>

Wilson and associates<sup>633</sup> analyzed the experience at the Mayo Clinic with 56 patients who received treatment for 4 weeks with aqueous penicillin G (20 million units IV daily) combined with either streptomycin, 0.5 g IM every 12 hours, for enterococcal IE due to streptomycin-sensitive strains, or gentamicin, 1 mg/kg IM every 8 hours, for IE due to streptomycin-resistant strains. Relapse rates were high (12.5%) for both regimens; however, all patients who experienced relapse had had symptoms suggestive of IE for longer than 3 months. Relapses also occurred only in patients with mitral valve involvement. All patients who received more than 3 mg/kg daily of gentamicin developed reversible nephrotoxicity (defined as a twofold increase in serum creatinine concentration), and 19% of patients receiving streptomycin for 4 weeks developed irreversible vestibular toxicity. Although this was not a prospective randomized trial, we believe that in selected cases enterococcal IE may be managed with 4 weeks of combination therapy. Exceptions include mitral valve involvement, duration of symptomatic illness exceeding 3 months, enterococcal prosthetic valve endocarditis, and relapses of enterococcal IE.

A penicillin-allergic patient presents the clinician with a difficult therapeutic dilemma. Vancomycin as a single drug in a dose of 30 mg/kg/24 h in two equally divided doses up to 1 g IV every 12 hours, unless serum vancomycin levels are inappropriately low, is recommended for the treatment of enterococcal IE when patients are unable to tolerate penicillin or ampicillin, or if the infecting pathogen is resistant to these preferred agents.<sup>334</sup> Experience is limited, however, and because of its lack of bactericidal activity in vitro and poor performance in experimental IE, vancomycin should be combined with gentamicin or streptomycin.<sup>334</sup> This combination is potentially more nephrotoxic, and clinical proof of the superiority of such regimens over vancomycin alone is not available. The other therapeutic option in the allergic patient is “penicillin desensitization” followed by the administration of penicillin and an

aminoglycoside. The treatment of enterococcal IE caused by highly aminoglycoside-resistant or glycopeptide-resistant strains was discussed earlier.

### Alternatives to Full-Course Aminoglycoside Therapy for Enterococcal Infective Endocarditis

The significant risk for nephrotoxicity accompanying the traditional 4- to 6-week course of aminoglycoside therapy recommended for enterococcal IE has prompted a number of investigators to consider potentially safer alternatives. Olaison and colleagues<sup>634</sup> conducted a 5-year nationwide prospective cohort study in Sweden in which 93 episodes of enterococcal IE were identified. Although current American Heart Association guidelines for the treatment of enterococcal IE recommend combined treatment with penicillin or ampicillin plus an aminoglycoside for 4 to 6 weeks, these investigators evaluated the clinical outcomes when the total duration of aminoglycoside therapy was reduced. Patients in this observational study had a median of 15 days of combined penicillin-ampicillin plus aminoglycoside. The overall cure rate of 81% (75 of 93) compared favorably with most historical control studies of enterococcal IE.<sup>635,636</sup> The authors concluded that reducing the aminoglycoside duration to approximately 2 weeks would maintain clinical efficacy while reducing potential toxicities in this high-risk patient population with enterococcal IE.<sup>634</sup> A study from Denmark has essentially confirmed the equivalent efficacies and reduced renal toxicities of the shorter-term aminoglycoside strategy for enterococcal IE.<sup>637</sup>

A second aminoglycoside-sparing strategy for ampicillin-susceptible enterococcal IE involves pairing ampicillin with high-dose ceftriaxone (2 g IV every 12 hours) instead of gentamicin. This approach takes advantage of the fact that the combination of ceftriaxone and ampicillin can saturate at least four of the five major penicillin-binding proteins of enterococci. In a prospective observational cohort study involving 13 centers in Spain, Gavalda and coworkers<sup>610</sup> initially reported a 3-month cure rate of 67.4% in 43 patients with ampicillin-susceptible *E. faecalis* IE who received a 6-week course of intravenous ampicillin, 2 g every 4 hours, plus intravenous ceftriaxone, 2 g every 12 hours. This experience was replicated in a second observational, nonrandomized cohort study involving 246 consecutive adults with *E. faecalis* IE from 18 Spanish and Italian hospitals.<sup>611</sup> Of the 246 patients, 159 patients received ampicillin and ceftriaxone and 87 received ampicillin and an aminoglycoside. Although there were no significant differences between the two patient groups in 3-month mortality or relapses, interruption of antibiotic treatment because of adverse events was much more frequent in patients treated with ampicillin and an aminoglycoside than in those receiving ampicillin and ceftriaxone (25% vs. 1%,  $P < .001$ ), primarily owing to the emergence of new renal failure (23% vs. 0%,  $P < .001$ ). Based on these reports, we believe that the combination of ampicillin and ceftriaxone appears to be effective and safe for treating high-level aminoglycoside-resistant ampicillin-susceptible *E. faecalis* IE and represents a reasonable option for patients with non-high-level aminoglycoside-resistant *E. faecalis* IE who are at increased risk for nephrotoxicity.

### Staphylococcal Endocarditis

The mortality rate in acute staphylococcal IE still approximates 25% to 40%, and the preferred antibiotic regimen is controversial. Mortality is highest for men, for patients older than 50 years, and for patients with left-sided involvement or central nervous system manifestations. In addition, injection drug users seem to have a lower mortality than do nonaddicts. Most *S. aureus* isolates, whether community or hospital acquired, are now resistant to penicillin G ( $\text{MIC} > 0.2 \mu\text{g/mL}$ ). The current recommended regimen includes a penicillinase-resistant penicillin (nafcillin or oxacillin, 2 g IV every 4 hours) or a cephalosporin (cephalothin, 2 g IV every 4 hours, or cefazolin, 2 g IV every 8 hours) given for 6 weeks.<sup>638</sup> The addition of gentamicin produced a synergistic effect against *S. aureus* in vitro and in experimental staphylococcal IE in rabbits.<sup>639</sup> However, the combination did not improve the survival rate (60%) over that observed with a penicillin derivative alone in a small group of patients.<sup>407</sup> Combination therapy did not improve the results of therapy for staphylococcal IE in injection drug users,<sup>640</sup> but the

mortality rate is low (2%–8%) in this subgroup of patients with this disease.

A number of studies have evaluated whether combination therapy permitted a shorter duration of therapy in injection drug users with *S. aureus* IE. Two weeks of nafcillin (2 g IV every 4 hours) plus tobramycin (1 mg/kg IV every 8 hours) cured 47 (94%) of 50 injection drug users who had right-sided IE<sup>641</sup> without evidence of renal failure, extrapulmonary metastatic infectious complications, aortic or mitral involvement, meningitis, or infection with MRSA. After this original experience with “short-course” parenteral therapy for right-sided *S. aureus* IE in addicts,<sup>641</sup> the findings of three randomized, prospective trials of short-course regimens in this disease were subsequently published, comprising 121 patients (summarized by DiNubile).<sup>642,643</sup> The combination regimens included intravenously administered cloxacillin with either gentamicin or amikacin.<sup>644,645,646</sup> The overall clinical and microbiologic cure rates exceeded 90% in these studies. In patients with HIV seropositivity (most having CD4<sup>+</sup> counts greater than  $300 \times 10^6$  cells) and in patients with large tricuspid vegetations ( $\geq 10$  mm in diameter), such regimens had excellent efficacy.<sup>646</sup> Ribera and coworkers<sup>646</sup> showed an efficacy of intravenously administered cloxacillin that was equivalent to that of the cloxacillin plus gentamicin regimen. These data suggested that parenteral  $\beta$ -lactam short-course therapy, with or without aminoglycoside, is adequate for the treatment of uncomplicated right-sided IE caused by methicillin-susceptible *S. aureus* (MSSA).<sup>334</sup> By contrast, another investigation confirmed the relative ineffectiveness of a short-course regimen based on a glycopeptide (teicoplanin or vancomycin) plus gentamicin for right-sided *S. aureus* IE.<sup>647</sup>

### Daptomycin for Staphylococcal Infective Endocarditis

In 2006, daptomycin, 6 mg/kg IV once daily, was shown to be noninferior to low-dose, short-course gentamicin plus either vancomycin or nafcillin, as appropriate, for the treatment of SAB and right-sided IE.<sup>648</sup> Based on the results of this clinical trial, daptomycin received approval from the U.S. Food and Drug Administration (FDA) for the treatment of SAB, including right-sided native valve IE. Because of concerns about treatment-emergent resistance to daptomycin, some authorities use daptomycin at higher doses (e.g., 8–10 mg/kg IV once daily) than those currently approved when treating complicated *S. aureus* infections. Although a single observational study from the ICE-PCS described the use of high dose (e.g.,  $\geq 8$  mg/kg daptomycin) for the treatment of left-sided IE,<sup>649</sup> there are currently insufficient data on the use of daptomycin for left-sided IE to provide a recommendation for this indication.

### Other Antibiotics for Staphylococcal Infective Endocarditis

Two studies have evaluated the use of predominantly oral 4-week antibiotic regimens (ciprofloxacin plus rifampin) for the treatment of uncomplicated right-sided *S. aureus* IE in injection drug users.<sup>650,651</sup> In each study, including one in which more than 70% of patients were HIV seropositive,<sup>651</sup> cure rates exceeded 90%.

Anecdotal case reports in nonaddicts with staphylococcal IE suggest that the addition of gentamicin may be beneficial if there is no response to nafcillin therapy.<sup>652</sup> In a multicenter, prospective trial comparing nafcillin alone with nafcillin plus gentamicin (for the initial 2 weeks) in the treatment of IE due to *S. aureus*,<sup>653</sup> most of the patients were nonaddicts who had left-sided IE. Although the combination therapy resulted in a more rapid rate of eradication of the bacteremia, the incidence of nephrotoxicity was increased and no improvement in mortality was achieved. The 2015 American Heart Association treatment guidelines concluded that adjunctive gentamicin therapy should not be used for either left- or right-sided *S. aureus* native valve IE,<sup>1</sup> based in part on a report that even brief courses of gentamicin for these syndromes are associated with increased risks of nephrotoxicity.<sup>654</sup> In that report, 236 patients from 44 centers in four countries were randomized to receive either daptomycin monotherapy or initial low-dose gentamicin (e.g., 3 mg/kg/24 h IV in three equally divided doses for 3–5 days). In a post hoc analysis of the study results, Cosgrove and colleagues addressed the issue of gentamicin-induced nephrotoxicity.

In their analysis, 22% of patients receiving initial low-dose gentamicin, versus 8% of patients not receiving this adjunct therapy, experienced decreased creatinine clearance ( $P = .005$ ). Receipt of any gentamicin was independently associated with clinically significant decreases in creatinine clearance.<sup>654</sup> Based on these results and on the minimal existing data supporting its benefit, we believe that initial low-dose gentamicin should no longer be used for SAB or native valve endocarditis in most clinical scenarios. The role of initial low-dose gentamicin remains unresolved in a number of other settings not addressed in Cosgrove and colleagues’ study, including pediatric populations, patients with left-sided IE or prosthetic valve IE, infections caused by high-vancomycin MIC MRSA isolates (e.g., vancomycin-intermediate-resistant *S. aureus* [VISA]), and infections with persistent bacteremia.<sup>655</sup> If the organism is susceptible to penicillin (MIC  $<0.1$   $\mu$ g/mL), this agent in a dose of 20 to 24 million units IV daily should be used. The response to treatment may be slow, often with fever and positive blood cultures lasting 1 week.<sup>404</sup>

The therapy for staphylococcal IE in penicillin-allergic patients and in cases in which the isolate is methicillin-resistant (i.e., MRSA) is problematic. A decision analysis concluded that patients with a questionable history of immediate-type hypersensitivity to penicillin and methicillin-sensitive *S. aureus* IE should be skin tested before starting antibiotic therapy.<sup>656</sup> First-generation cephalosporins (as noted previously) generally are recommended in patients with non-life-threatening penicillin allergy, but nafcillin is more active in experimental MSSA endocarditis<sup>657</sup> and is preferred if the results of skin tests for penicillin allergy are negative. With the exception of ceftazidime, the in vivo efficacy of cephalosporins in experimental *S. aureus* IE has a positive correlation with in vitro activity (MIC) and the percentage of time during the dosing interval in which the drug serum level exceeds the MIC.<sup>657</sup> Vancomycin still is recommended for the treatment of *S. aureus* IE in patients with life-threatening penicillin allergy (e.g., anaphylaxis) or anaphylactoid reactions (e.g., giant urticaria) and when MRSA strains are involved; however, more recent experience suggests caution, because suboptimal outcomes have been associated with the use of this agent in MRSA IE. Vancomycin is less rapidly bactericidal than nafcillin in vitro against *S. aureus*, especially at high inocula (approximately  $10^7$  CFUs), mimicking intravascular densities. Vancomycin therapy for complicated SAB also has been associated with relapses, as confirmed with pulsed-field gel electrophoresis.<sup>658</sup> Failure rates of approximately 40% have been documented in patients with *S. aureus* IE treated with vancomycin<sup>659</sup> despite right-sided involvement. In another study<sup>660</sup> using vancomycin-based regimens (with or without rifampin), blood cultures remained positive after 7 days of therapy in approximately 50% of patients, despite right-sided involvement and negative results in many echocardiographic studies. Patients with bacteremia or IE due to MRSA with high, but still “fully susceptible,” vancomycin MICs (defined as  $\geq 1.5$   $\mu$ g/mL<sup>661</sup> or as  $2$   $\mu$ g/mL<sup>662</sup>) had a worse clinical outcome than patients whose bloodstream MRSA isolates had a lower vancomycin MIC value.<sup>663</sup> The full implications of these findings, however, are not yet established,<sup>664</sup> because the same association of worse clinical outcome in infections caused by such “high vancomycin MIC” *S. aureus* strains has also been documented in patients infected with MSSA who were treated with antistaphylococcal penicillins instead of vancomycin.<sup>665,666</sup> Daptomycin is an alternative to vancomycin in the treatment of SAB and IE.<sup>667</sup> When daptomycin is used for the treatment of *S. aureus* IE, many authorities use higher doses than the FDA-approved dose of 6 mg/kg.<sup>667</sup> Clinicians should be aware of the possibility of treatment-emergent resistance during daptomycin therapy, and patients should be carefully monitored for this possibility.<sup>668</sup> Of interest, a recent investigation reported improved clinical outcomes in patients with “high vancomycin MIC” MRSA bacteremia who received early substitution of daptomycin for vancomycin.<sup>669</sup> For MSSA IE in patients with anaphylactoid-type  $\beta$ -lactam allergy and suboptimal responses to vancomycin, the need for  $\beta$ -lactam desensitization should be considered.<sup>670,671</sup>

The use of clindamycin to treat staphylococcal IE is associated with an unacceptable relapse rate and is not recommended.<sup>672</sup> The optimal therapy for IE due to “tolerant” strains of *S. aureus* is controversial.<sup>673,674</sup> One retrospective study<sup>675</sup> suggested that patients with IE due to these tolerant strains had a more complicated course; however, combination

therapy did not seem to be beneficial. Tolerance does seem to influence the response to therapy in some experimental animal models of *S. aureus* IE,<sup>676</sup> and the use of combination regimens seems prudent when these strains are recovered from patients, but this is not universally accepted. Another controversial area is the adjunctive role of rifampin.<sup>677</sup> Because of the emergence of resistant strains, this drug is ineffective alone. Results of in vitro studies on rifampin combinations with either β-lactam agents or vancomycin frequently are contradictory, and clinical outcomes with experimental IE induced by *S. aureus* depend on which drug in the combination exerts the greatest bactericidal activity in vivo.<sup>678</sup> The question of the role of rifampin for SAB was definitively addressed in the ARREST trial, a randomized double-blind trial of 758 adults with SAB (including 33 with IE), who were randomized to receive either rifampin or placebo, in addition to standard therapy. Adjunctive rifampicin did not provide any clinical benefit but was associated with an increased frequency of adverse events.<sup>679</sup> Given the results of the ARREST trial, rifampin should not be recommended in patients with SAB or native valve IE.

#### Therapy for Highly Resistant Staphylococci

The therapy for IE due to *S. aureus* displaying borderline susceptibility to antistaphylococcal penicillins, first described by McDougal and Thornsberry in 1986,<sup>680</sup> is also a matter of debate. Experimental models of IE induced with these isolates suggest that nafcillin (or oxacillin) or ampicillin-sulbactam should be effective.<sup>681,682</sup> Several agents, including teicoplanin, fosfomycin, and fluoroquinolones, are active against MRSA in vitro and are as rapidly bactericidal as vancomycin in experimental animal models of IE due to MRSA,<sup>683–685</sup> although resistance to the quinolones has emerged during therapy, and frank failures have been recorded.<sup>671,686,687</sup> For patients with MRSA IE not responding to vancomycin, several choices are available, including the addition of rifampin or gentamicin (or both) or other regimens including daptomycin,<sup>648</sup> linezolid, quinupristin-dalfopristin, minocycline, trimethoprim-sulfamethoxazole,<sup>688</sup> fosfomycin plus imipenem,<sup>689</sup> or ceftaroline alone or in combination with trimethoprim-sulfamethoxazole.<sup>690,691</sup> Ceftaroline is active against MRSA with reduced susceptibility to vancomycin and daptomycin, including heteroresistant VISA (hVISA), VISA, vancomycin-resistant *S. aureus* (VRSA), and daptomycin-nonsusceptible *S. aureus* (DNSSA). *S. aureus* also displays a “seesaw” effect in which isolates display increased susceptibility to nafcillin as vancomycin susceptibility decreases—also seen with ceftaroline—which led to improved results with ceftaroline against hVISA and VISA strains in an in vivo model. Experience with these drugs in humans with left-sided or prosthetic *S. aureus* IE is limited.

#### Treatment of *S. aureus* Bacteremia Without Proven Infective Endocarditis

Bayer and associates<sup>671,692</sup> identified four parameters predictive of the presence of IE in 72 patients with SAB in a prospective study: (1) the absence of a primary site of infection, (2) community acquisition of infection, (3) metastatic sequelae, and (4) valvular vegetations detected with echocardiography. In another study of 724 prospectively identified patients with SAB, Fowler and associates observed key clinical identifiers of complicated bacteremia, including (1) community acquisition, (2) persistent fever at 72 hours, (3) skin examination suggesting the presence of acute systemic infection, and (4) positive blood culture 48 to 96 hours after the initial positive blood culture.<sup>402</sup> Although these clinical identifiers are useful methods to assist in the identification of clinically unsuspected IE, the role of echocardiography increasingly is being recognized.

Two decision analyses have shown the role of TEE in identifying the presence of IE and in helping to define the duration of antibiotic therapy. Heidenreich and colleagues<sup>342</sup> found that in patients whose prior probability of IE was between 4% and 60%, initial use of TEE provided the greatest quality-adjusted survival at a cost within the range for commonly accepted health interventions. Rosen and colleagues<sup>343</sup> found that the use of TEE to determine the duration of therapy (2 weeks vs. 4 weeks) in patients with intravascular catheter-associated SAB was cost-effective and provided better outcomes than empirical 2-week or 4-week treatment strategies. While definitive trials are awaited, short-term

therapy should be used only if IE can be excluded reasonably by methods previously discussed. Although older studies suggested that occult IE in patients with nosocomial SAB was uncommon, the increasing importance of health care-associated *S. aureus* IE has now been definitively established.<sup>10,14–16,693,694</sup> In these patients, classic manifestations of IE are uncommon and TEE is useful in diagnosis of IE. IE due to glycopeptide-intermediate *S. aureus* has been reported,<sup>695,696</sup> and soft tissue infections due to vancomycin-resistant *S. aureus*<sup>697,698</sup> have been reported and are cause for concern.

#### Coagulase-Negative Staphylococci

*S. epidermidis* is the second most common etiologic agent in cases of prosthetic valve IE.<sup>668</sup> Most of these strains (87%) are methicillin resistant when isolated within 1 year after valve implantation. One study<sup>699</sup> suggested that the optimal antimicrobial regimen for these infections is vancomycin plus rifampin, usually with the addition of an aminoglycoside. The emergence of vancomycin resistance among coagulase-negative staphylococci<sup>700</sup> is cause for concern. These concepts are discussed further in Chapter 81.

#### Endocarditis Due to Enterobacteriaceae or *Pseudomonas* Species

Approximately 2% of contemporary IE cases are caused by aerobic gram-negative bacilli.<sup>227</sup> Health care contact and cardiac devices seem to have largely replaced injection drug use as the primary risk factors for acquisition of IE due to these bacteria. The prognosis is especially poor with left-sided cardiac involvement. Certain combinations of penicillins or cephalosporins and aminoglycosides have been shown to be synergistic against many of these strains and usually are recommended.<sup>334</sup> For IE caused by most strains of *E. coli* or *Proteus mirabilis*, a combination of a penicillin, either ampicillin (2 g IV every 4 hours) or penicillin (20–24 million units IV daily), and an aminoglycoside, usually gentamicin or a broad-spectrum cephalosporin, is suggested. Third-generation cephalosporins are extremely active against *E. coli* in vitro, and some (e.g., ceftriaxone) have proved effective in experimental animal models of *E. coli* IE,<sup>701</sup> even when long dosing intervals were used. This group of agents merits further evaluation in humans for IE due to susceptible gram-negative bacilli.

A combination of a third-generation cephalosporin and an aminoglycoside (either gentamicin or amikacin) is recommended for *Klebsiella* IE. IE due to carbapenem-resistant *Klebsiella* has been successfully treated with a combination of colistin and gentamicin in one case report. Certain β-lactam/β-lactamase inhibitor combinations (e.g., piperacillin-tazobactam,<sup>702</sup> but not ceftriaxone-sulbactam<sup>703</sup>) are active in vivo in experimental models of *Klebsiella* IE in animals induced by TEM-3-producing isolates and merit further evaluation in combination with an aminoglycoside in humans with this disease. The specific aminoglycoside used is a crucial variable and cannot be predicted totally from MIC data alone, because pharmacodynamic characteristics differ markedly in animal models of IE caused by gram-negative aerobic bacilli.<sup>704,705</sup> Endovascular *Salmonella* infections, including IE, also may respond to third-generation cephalosporins (see later discussion).<sup>706</sup> Left-sided IE due to *S. marcescens* is often refractory to medical therapy alone.<sup>432</sup>

*P. aeruginosa* is a rare but potentially devastating cause of IE in at-risk populations. Medical therapy may be successful in *P. aeruginosa* IE involving the right side of the heart in 50% to 75% of cases. If the disease is refractory to antibiotics, tricuspid valvectomy or “vegetectomy”<sup>707</sup> without valve replacement is indicated.<sup>708</sup> Although valve replacement often is necessary for a cure of left-sided IE due to *P. aeruginosa*,<sup>709</sup> medical therapy alone occasionally is curative.<sup>256,430</sup> Studies in animals with experimental *Pseudomonas* IE<sup>710</sup> offer a partial explanation for these disparate results: the penetration into vegetations and the time during which antibiotic concentrations exceeded the MBC were significantly greater with tricuspid vegetations than with aortic vegetations for ceftazidime and tobramycin.

Problems have emerged with all potential regimens in animal models of this disease: (1) therapy with β-lactams (e.g., ceftazidime) has failed, owing to the selection of clones within valve vegetations that exhibit constitutive hyperproduction of type Id β-lactamase<sup>711</sup>; (2) isolates

showing aminoglycoside resistance due to permeability defects emerge during therapy;<sup>712</sup> (3) no postantibiotic effect of  $\beta$ -lactams against *P. aeruginosa* is evident in vivo,<sup>713</sup> necessitating frequent (or continuous) drug administration; and (4) the alginate exopolysaccharide inhibits clearance of mucoid strains from the vegetation via cellular or antimicrobial mechanisms. This inhibition can be reversed partially by the coadministration of alginase in animal models of *Pseudomonas* IE.<sup>714</sup>

Treatment failures in *Pseudomonas* IE in humans also have been related to the selection of isolates with an enhanced production of type Id  $\beta$ -lactamase.<sup>715</sup> Based on clinical experience,<sup>413,433,434</sup> however, the preferred regimen for IE due to *P. aeruginosa* is high-dose tobramycin (8 mg/kg/day IV or IM in divided doses every 8 hours), with maintenance of peak and trough concentrations of 15 to 20  $\mu$ g/mL and 2  $\mu$ g/mL or less, respectively, in combination with either an extended-spectrum penicillin (e.g., ticarcillin, piperacillin, azlocillin) or ceftazidime or cefepime in full doses. The toxicity associated with this regimen is low; combination treatment should be given for a minimum of 6 weeks. The use of quinolones (in combination with an aminoglycoside) seems promising for the treatment of *Pseudomonas* IE on the basis of favorable results in animal models<sup>711</sup> and in humans,<sup>716</sup> but the development of stepwise resistance during therapy may limit the efficacy of this class of drugs in the future. Based on limited experimental data,<sup>717</sup> ceftazidime-tobramycin is preferred over aztreonam-tobramycin for this disease. Approximately seven cases of *P. aeruginosa* IE have been treated successfully with imipenem plus an aminoglycoside,<sup>718</sup> but the potential for the development of resistance exists with any of these regimens.

Ceftriaxone or ampicillin-sulbactam should be considered treatments of choice for IE due to HACEK group bacteria.<sup>334</sup> Despite limited clinical data, ciprofloxacin is an accepted alternative therapy.<sup>334</sup> Duration of treatment for HACEK IE should be at least 4 weeks for native and prosthetic valve infections.<sup>334</sup> The previously mentioned recommendations offer only a rough guide for initial treatment. It is imperative that each isolate be subjected to quantitative sensitivity testing in vitro to ensure the optimal selection of antibiotics.

### Endocarditis Due to Anaerobic Bacilli

Although IE caused by anaerobic bacilli is uncommon, the mortality rate is high. *B. fragilis* is isolated in many of these cases and is responsible for most fatalities. Most strains of anaerobic bacilli, with the exception of *B. fragilis*, are sensitive to penicillin in vitro, and use of this agent, at a dose of 20 to 24 million units IV daily, is the recommended therapy.<sup>476,477</sup> However, only about one-third of *B. fragilis* strains show an MIC for penicillin that is less than 0.25  $\mu$ g/mL; and penicillin is only a bacteriostatic agent against these strains (the MBC is invariably >100  $\mu$ g/mL), and relapse is common. Although clindamycin and chloramphenicol readily inhibit most strains of *B. fragilis*, they lack bactericidal activity and they are poor therapeutic choices, although several patients have been cured with high-dose penicillin, chloramphenicol (1 g IV every 6 hours), or clindamycin (600 mg IV every 6 hours). Owing to excellent bactericidal activity in vitro and the serum concentrations attained, metronidazole, ticarcillin plus clavulanic acid, piperacillin plus tazobactam, imipenem, and meropenem are reasonable choices for therapy for anaerobic IE.<sup>478</sup>

### Pneumococcal, Gonococcal, and Meningococcal Endocarditis

IE caused by pneumococci, gonococci, or meningococci is now very rare. Pneumococcal IE must be considered in any patient with pneumococcal bacteremia, especially if meningitis is present. This form of IE is most common in alcoholics; the organism generally attacks the aortic valve and results in valvular insufficiency, often with perivalvular abscess formation or pericarditis. Type 12 pneumococci cause more than 20% of the cases of pneumococcal IE but are a rare (5% of cases) cause of pneumococcal pneumonia. Penicillin, 20 to 24 million units IV daily, cefazolin (2 g IV every 8 hours), or a third-generation cephalosporin for 4 weeks is recommended to treat IE due to highly penicillin-susceptible pneumococcus. Although the impact of penicillin resistance on the outcome of pneumococcal IE is unresolved, one series of 63 patients with pneumococcal IE found that left-sided heart failure, but not penicillin resistance, was associated independently with a higher risk for death.<sup>719</sup> IE

without meningitis due to intermediate (MIC >0.1–1.0  $\mu$ g/mL) or high-level (MIC  $\geq$ 2.0  $\mu$ g/mL) penicillin-resistant pneumococci can be treated with high-dose penicillin or a third-generation cephalosporin.<sup>334</sup> If IE and meningitis are simultaneously present, high doses of cefotaxime or ceftriaxone (2 g IV every 12 hours) should be used.<sup>334</sup> IE due to pneumococcal isolates resistant to cefotaxime (MIC  $\geq$ 2.0  $\mu$ g/mL) should be treated with vancomycin plus rifampin. Important to note, these recommendations are based on current levels of resistance and could be revised based on future MIC characteristics.<sup>334</sup>

The gonococci that cause systemic infection usually are highly susceptible to penicillin.<sup>720</sup> IE due to these organisms and the meningococci can be treated effectively with the same penicillin regimen recommended for pneumococcal IE. Although IE due to penicillin-resistant gonococci (on the basis of either  $\beta$ -lactamase production or chromosomally mediated mechanisms) has not been reported, ceftriaxone has been used successfully to treat gonococcal IE.<sup>721</sup>

### Fungal Endocarditis

Since the 1990s, the incidence of fungal sepsis has undergone a striking increase. Fungal IE now occurs principally in the setting of health care contact (e.g., after surgery or prolonged parenteral therapy, in compromised hosts such as neonates), whereas the importance of injection drug use as a risk factor for this condition has apparently diminished in recent series.<sup>501</sup> Although the survival rate in patients treated before 1974 was less than 20%,<sup>303</sup> survival in the current era has increased to 40% to 70%, coincident with improved diagnostic techniques.<sup>501,722</sup> The preferred mode of therapy has not been determined. The use of antifungal agents alone has been almost universally unsuccessful in achieving a cure of this disease. The addition of surgical measures to antifungal therapy may result in an improvement in prognosis, but to date there is insufficient clinical experience. If fungal IE is diagnosed, a combined medical-surgical approach is usually recommended.<sup>334,503,723</sup>

Historically, the mainstay of antifungal drug therapy is amphotericin B. This agent is toxic and produces multiple side effects, including fever, chills, phlebitis, headache, anorexia, anemia, hypokalemia, renal tubular acidosis, nephrotoxicity, nausea, and vomiting. Drug toxicity is common and often necessitates alterations in the regimen. To reduce toxicity, lipid formulations of amphotericin B are preferred.<sup>724</sup> Dosages and the technique of administration are given in Chapter 40A.

After 1 to 2 weeks of amphotericin B therapy at full dosages, surgery probably should be performed. If isolated tricuspid IE is present, total tricuspid valvectomy usually can be considered in individual cases. Rarely, removal of the vegetation alone is curative. Valve replacement is necessary for left-sided fungal IE. The duration of antifungal therapy after surgery is empirical, but 6 to 8 weeks usually is recommended.

It is possible that combination antifungal therapy may improve the poor survival rate associated with fungal IE. Some strains of *Candida* spp. and *Cryptococcus neoformans* are inhibited in vitro by concentrations of 5-fluorocytosine achieved with the oral administration of 25 mg/kg/dose 4 times daily. Synergism between 5-fluorocytosine and amphotericin B has been documented for these yeasts in vitro and in the treatment of cryptococcal meningitis. This combination was fungicidal and perhaps instrumental in the cure of one case of *Aspergillus* IE. In the rabbit model of IE due to *C. albicans*, however, the addition of 5-fluorocytosine did not improve the rate of eradication of fungal organisms from the vegetation over the rate observed with amphotericin B alone. Potentiation of amphotericin B activity by rifampin has been noted for virtually all strains of *Candida* spp. tested and for a few isolates of *H. capsulatum*. The therapeutic advantage of the addition of 5-fluorocytosine or rifampin to amphotericin for fungal IE requires further investigation, but initial results in animal models of disseminated candidiasis are not encouraging.<sup>725</sup> On the basis of animal model data,<sup>726</sup> high-dose itraconazole may be of value in the treatment of *Aspergillus* IE but valve replacement probably will remain imperative for a cure.<sup>727</sup> Amphotericin B is more effective than fluconazole for the prophylaxis and treatment of experimental *Candida* IE,<sup>728</sup> and it remains the agent of choice. However, the use of fluconazole apparently has led to long-term cures of *Candida* IE in a limited number of patients<sup>503,729–731</sup> when valve replacement was considered to be contraindicated. This agent should be tried after an initial course of amphotericin B in this

setting or used for long-term suppressive therapy. The roles of lipid and liposomal amphotericin complexes and voriconazole in the treatment of fungal IE are largely unknown. Recent data of echinocandins for the treatment of fungal IE are encouraging, however, and suggest that this class of antifungal agents may be reasonable in selected cases of fungal IE.<sup>732</sup>

### **Q Fever Endocarditis**

More than 1300 well-documented cases of Q fever have been reported<sup>733</sup>, the mortality rate exceeds 65%.<sup>480,481,483,484,485</sup> Prolonged therapy ( $\geq 4$  years) with doxycycline and either trimethoprim-sulfamethoxazole or rifampin was considered to be the regimen of choice in the past (see Chapter 188).<sup>480,734-736</sup> A fluoroquinolone may be a useful addition to doxycycline.<sup>480,736</sup> The acidic conditions of the phagolysosome, where the organism resides, may inhibit antibiotic activity.<sup>736</sup> Cure of the IE after treatment with a combination of doxycycline and hydroxychloroquine to alkalinize the phagolysosome for 1 year was reported in 20 patients.<sup>480</sup> Valve replacement often is required, and long-term prognosis is guarded. Careful follow-up to detect recrudescence of infection is essential. A combination regimen of doxycycline plus hydroxychloroquine for at least 18 months allowed shortening the duration of therapy and resulted in reduction in the number of relapses.<sup>733</sup> The Raoult group recently published their results with more than 100 patients with Q fever endocarditis followed over 26 years (median follow-up, 100 months). Based on their results, we believe that doxycycline plus hydroxychloroquine are the drugs of choice and that 18 months of therapy is adequate for treatment of native valve Q fever endocarditis versus 24 months for prosthetic valve endocarditis unless certain serologic markers persist (requiring sequential monitoring of these parameters).

### **Infective Endocarditis Due to Chlamydiae**

Based on limited experience, a combination of valve replacement and prolonged ( $>3$  months) tetracycline therapy seems justified in IE due to chlamydiae. Rifampin has cured at least one case of chlamydial IE after therapy with tetracyclines failed, but exposure to this agent rapidly induces the emergence of drug resistance in *C. trachomatis* in tissue culture.<sup>737</sup> The role of combination regimens (e.g., rifampin plus erythromycin or tetracycline) merits further study.

### **Culture-Negative Endocarditis**

The therapy for culture-negative IE in nonaddicts is controversial, but the regimen usually used "covers" enterococci, the HACEK group, and *Abiotrophia* and *Granulicatella* spp. For native valve culture-negative IE, this regimen consists of a combination of ampicillin-sulbactam, 12 g/24 h in four equally divided doses, plus gentamicin 3 mg/kg/24 h in three equally divided doses plus ciprofloxacin for 4 to 6 weeks.<sup>334</sup> Early ( $\leq 1$  year) culture-negative prosthetic IE should be treated with appropriately dosed vancomycin (for 6 weeks) plus gentamicin (at doses indicated previously for 2 weeks) plus ceftazidime (6 g IV daily in three equally divided doses for 6 weeks) plus rifampin (900 mg PO or IV daily in three equally divided doses for 6 weeks).<sup>334</sup> Culture-negative IE involving prosthetic valves that have been in place for longer than 1 year should be treated as listed previously for native valve endocarditis.<sup>334</sup> If staphylococcal IE is likely, a penicillinase-resistant penicillin or a cephalosporin in full dosage should be substituted in the aforementioned regimen. If clinical improvement occurs, some authorities recommend discontinuation of treatment with the aminoglycoside after 2 weeks. The other agents should be continued for a full 6 weeks of treatment. Continued surveillance for the causative agent and careful follow-up are mandatory. An analysis of any correlation between the response to empirical antimicrobial therapy and survival was performed in 52 patients with culture-negative IE<sup>518</sup>: 92% of the patients who became afebrile within the first week of therapy survived, compared with only 50% of those whose fever persisted longer than 7 days. Most deaths were caused by major systemic emboli or uncontrollable CHF due to valvular insufficiency.

### **Surgical Therapy**

Valve replacement has become an important adjunct to medical therapy in the management of IE and now is used in almost half of the cases.<sup>7</sup>

Decisions regarding surgical intervention in patients with IE should be individualized and should be made with input from the infectious diseases physician, the cardiologist, and the cardiovascular surgeon.<sup>334</sup> Patients with IE and CHF should be immediately evaluated for potential surgical therapy.<sup>334,738</sup> Other generally accepted indications for potential surgical intervention during active IE are as follows: (1) more than one serious systemic embolic episode; (2) uncontrolled infection; (3) ineffective antimicrobial therapy (e.g., in fungal IE); (4) resection of mycotic aneurysms; (5) most cases of prosthetic valve IE caused by more antibiotic-resistant pathogens (e.g., staphylococci, enteric gram-negative bacilli); and (6) local suppurative complications, including perivalvular or myocardial abscesses. The major indications in the past have been persistent infection and CHF<sup>739-741</sup> in adults and children.<sup>742</sup> CHF during active IE was the indication for surgery in 86% of 108 patients undergoing valve replacement at Stanford University Medical Center from 1963 to 1984.<sup>741</sup> The importance of individualizing decisions for valve replacement surgery among patients with *S. aureus* prosthetic valve IE, basing these decisions on the presence of traditional indications (e.g., heart failure), has been recently emphasized.<sup>743</sup>

Despite the widespread use of TTE and TEE in patients with IE, the indications for surgical intervention based on echocardiographic features remain controversial. The American Heart Association Committee on IE, working from data reported in the recent literature, identified the following echocardiographic features in IE as being associated with a potential increased need for surgical intervention: (1) persistent vegetations after a major systemic embolic episode; (2) increase in vegetation size after appropriate antibiotic therapy; (3) acute mitral insufficiency; (4) valve dehiscence, perforation, or rupture; (5) perianular extension of infection (e.g., paravalvular abscess or fistula); and (6) large ( $>1$  cm in diameter) anterior mitral valve vegetations.<sup>334</sup> However, findings of a recent study suggest that early surgery based solely on large vegetation size in patients with left-sided native valve IE was associated with worse clinical outcome.<sup>744</sup> The most common causes of death in IE, in approximate order, are CHF,<sup>738</sup> neurologic events,<sup>227</sup> septic complications,<sup>745</sup> embolic phenomena, rupture of a mycotic aneurysm, complications of cardiac surgery, lack of response to antimicrobial therapy, and prosthetic valve IE.<sup>334</sup>

Owing to the inherent differences between medically managed patients with IE and patients undergoing surgical intervention for IE, the optimal role and timing of valve surgery in IE are controversial. However, a growing body of evidence supports the importance of early surgical intervention. A large, well-designed propensity analysis<sup>540</sup> found that early valve surgery is associated with increased survival in patients with IE. These findings were confirmed in a pivotal clinical trial<sup>746</sup> randomizing 76 patients with left-sided endocarditis, severe valve disease, and large vegetations to early surgery (within 48 hours of randomization) or conventional treatment. The primary end point—a composite of in-hospital death, embolic events within 6 weeks of randomization, or recurrence of IE at 6 months—was significantly less frequent in the early-surgery group than in the conventional-treatment group (3% vs. 28%;  $P = .02$ ). Limitations of this trial, such as the infrequency of cases caused by *S. aureus* and the relatively young and otherwise healthy study subjects, reduced the generalizability of the findings. A retrospective cohort study stratified adults with complicated left-sided native valve IE, using baseline features, into four groups of prognostic severity.<sup>747</sup> When acute aortic regurgitation complicated by CHF supervenes in IE, the mortality rate still exceeds 50%. The classic physical findings associated with chronic aortic regurgitation often are absent in these patients.<sup>345</sup> The current trend is to perform early surgery in this group of patients, because nothing is gained by delay. The merits of early valve replacement surgery were confirmed in 1972.<sup>748</sup> In a series of 28 patients from Birmingham, Alabama, with acute aortic regurgitation, 4 had no CHF and were managed medically, and all survived. In contrast, 7 of 11 patients with mild CHF and 7 of 8 patients with moderate-to-severe CHF died during medical therapy, often suddenly and with pathologic evidence of coronary emboli and myocardial infarction. Four of five patients with moderately severe CHF who underwent surgery survived. These data suggest that early surgical intervention may improve survival in this setting. Valvular regurgitation on Doppler echocardiography is not predictive of death in the absence of CHF.<sup>749</sup>

The hemodynamic status of the patient, not the activity of the infection, is the crucial determining factor in the timing of cardiac valve replacement; that is, development of CHF in the setting of IE generally dictates valvular surgery regardless of the acuteness of the infection or the amount of antibiotics already received by the patient.<sup>750</sup> The hemodynamic severity of the acute aortic regurgitation may be assessed by determining the degree of mitral valve preclosure by echocardiography. If premature closure of the mitral valve occurs before the Q wave of the electrocardiogram, the left ventricular end-diastolic pressure is very high, and surgical intervention is required urgently. Nothing is gained by temporizing, even if only a few hours of antibiotics can be administered. If CHF persists despite digoxin, diuretics, and other therapeutic modalities (e.g., left ventricular afterload reduction), surgery also is indicated. In 80 patients subjected to aortic valve replacement for IE, the surgical cure rate was 72%. There were no instances of subsequent infection of the prosthesis, but 16% of the patients developed paravalvular regurgitation. This latter complication usually was controlled easily with medical therapy. Organisms visible on Gram stain, positive cultures, or annular abscesses at the time of surgery are associated with late complications.<sup>745</sup> Although the topic has not been systematically studied, most authorities suggest that if there is evidence of active IE at the time of valve replacement surgery, antibiotic therapy should be continued postoperatively for at least several weeks. Such evidence might include vegetations that remain culture positive and vegetations with significant polymorphonuclear inflammation. An investigation by Morris and colleagues<sup>217</sup> found that dead bacteria may persist for months in sterile vegetations and concluded that only valve cultures should be considered when determining the duration of antibiotic therapy after valve replacement for IE. By contrast, routine valve cultures in patients undergoing native valve replacement for indications other than clinically suspected IE do not seem warranted.<sup>751</sup>

The optimal timing of valve replacement surgery for left-sided IE is another unresolved clinical question. Because of the observed decrease in embolic risk during the initial 1 to 2 weeks of medical therapy, early surgical intervention could potentially avoid a devastating embolic event while subjecting the patient to the risks of valve replacement surgery. Therefore the strategy for surgical intervention to avoid major embolization remains individualized.<sup>334</sup> The importance of timing of surgery following cerebral emboli in IE patients was evaluated in 198 patients. Fifty-eight patients who underwent surgery within 1 week of stroke were compared with 140 patients who underwent surgery 8 or more days after stroke. After adjustment for other confounding factors, no statistically significant difference in 1-year mortality was present among the early-surgery recipients (95% CI, 0.802–1.650).<sup>752</sup> The high risk of exacerbation is prohibitively high in the first month after hemorrhagic stroke. In a multicenter study of IE with hemorrhagic stroke, mortality was higher when valve surgery was performed within 4 weeks of the hemorrhagic event, compared with later surgery (75% vs. 40%, respectively).<sup>753</sup> Based on these data, the American Heart Association Committee on Endocarditis has made the following recommendations: Valve surgery may be performed in IE with stroke or subclinical cerebral emboli without delay if intracranial hemorrhage has been excluded with imaging studies and neurologic damage is not severe (i.e., coma). In patients with major ischemic stroke or intracranial hemorrhage, it is reasonable to delay valve surgery for at least 4 weeks.<sup>1</sup> It is important to emphasize that these recommendations are intended to serve as general guidelines in the absence of definitive evidence.

In contrast to left-sided IE, in which CHF is the usual indication for surgical intervention, persistent infection is the indication for surgery in more than 70% of patients with right-sided IE. Most patients are injection drug users, with IE caused by organisms that are difficult to eradicate with antimicrobial therapy alone (e.g., fungi, gram-negative aerobic bacilli). Tricuspid valvectomy or vegetectomy with valvuloplasty is the procedure of choice for refractory right-sided IE.<sup>754,755</sup> Valve replacement at a second operation is advised only if medical management fails to control the hemodynamic manifestations and the patient has ceased using illicit drugs. Combination antimicrobial therapy should be continued for 4 to 6 weeks postoperatively. These patients may develop mild-to-moderate right-sided heart failure, but this is tolerated easily, and the success rate with this approach is greater than 70%. Eventual

tricuspid valve replacement usually is required, however, owing to progressive right-sided heart failure. Persistent fever, recurrent pulmonary emboli, or vegetations demonstrable with echocardiography usually do not necessitate tricuspid valvectomy in this setting.<sup>756</sup> In addition, many surgeons contend that a return to the use of illicit drugs and reinfection of the valve after initial cure are contraindications to reoperation.<sup>757</sup>

Outstanding reviews on the indications for surgery during therapy for IE are available.<sup>740,758–761</sup> The rationale for surgical intervention, including major and minor criteria for valve replacement, is discussed in detail. A point system weighting multiple factors was devised by Alsip and colleagues<sup>758</sup> to assist in decision making concerning surgery in patients with active IE. The value of this system remains to be defined. It has become apparent that most patients with prosthetic valve IE (except patients with late disease caused by penicillin-sensitive viridans streptococci) require valve replacement for consistent cures. Valve replacement also is necessary in a significant proportion of patients with IE on native valves after a medical cure; aortic involvement is a predictor of the need for surgery.<sup>762</sup>

### Suppurative Thrombophlebitis

Suppurative thrombophlebitis is an inflammation of the vein wall that is caused by the presence of microorganisms and frequently associated with thrombosis and bacteremia. In the following discussion, suppurative thrombophlebitis is differentiated from catheter-related sepsis. Suppuration of the vein wall usually is absent in intravenous catheter-related sepsis and in bacteremia secondary to contaminated intravenous fluid, although it does occur. Suppurative thrombophlebitis may be classified into four forms: superficial, central (including pelvic), cavernous sinus, and infection of the portal vein (pyelophlebitis). The last two conditions have become rare since the introduction of antibiotics. In contrast, superficial suppurative thrombophlebitis has been increasing steadily in incidence since the introduction of the plastic intravenous cannula. Superficial suppurative thrombophlebitis secondary to intravenous fluid therapy first was described in 1947,<sup>763</sup> when 93 cases were reported, 43 of which were amenable to surgical therapy.

### Epidemiology

In 1973, approximately 1 of every 4 hospitalized patients received intravenous therapy, for a total of more than 10 million patients annually in the United States.<sup>764</sup> It is estimated that more than half of the 40 million patients admitted to US hospitals each year undergo intravascular catheterization.<sup>765</sup> Suppurative thrombophlebitis is a particular problem in burned patients, for whom it represents a common cause of death due to infection. In several large series of burned patients,<sup>766–769</sup> suppurative thrombophlebitis developed in 4% to 8% and increased in frequency if cutdowns were performed. Suppurative thrombophlebitis also is found in other hospitalized patients (especially patients with cancer and those receiving corticosteroid therapy).<sup>770,771</sup> Seven cases were recognized during an 18-month period in Charleston, South Carolina, and 35 cases were identified over 7 years in Louisville, Kentucky.<sup>772</sup> Eight cases were encountered during an 8-month period in Johannesburg, and suppurative thrombophlebitis was estimated to represent a minimum incidence of 0.12% of all admissions.<sup>773</sup> In a study using strict diagnostic criteria, 29 episodes of suppurative thrombophlebitis in 27 patients were identified in a large Air Force hospital over a period of 4 years.<sup>774</sup> Using data from the National Nosocomial Infection Study, Rhame and associates<sup>775</sup> estimated the overall incidence of suppurative thrombophlebitis as 88 cases per 100,000 discharges, but this disease is underreported. Suppurative thrombophlebitis also is common among drug addicts, particularly when injections are made in large, central veins (e.g., jugular or subclavian veins).<sup>776</sup> This condition is unusual during childhood<sup>777</sup> but may occur as a complication related to intravenous therapy.

Catheter-related sepsis without suppurative thrombophlebitis is much more common and affects at least 50,000 to 100,000 patients per year in the United States.<sup>778,779</sup> The risk for this complication is approximately 40 times higher with plastic cannulas (8%) than with steel or “scalp vein” cannulas (0.2%). Irritation to the vein wall, with the subsequent development of suppurative thrombophlebitis, is more common with

Polyethylene catheters than with catheters constructed of Teflon or Silastic material. Central venous catheterization has been employed for more than 35 years for hemodynamic monitoring, total parenteral nutrition, and infusion of drugs. The exact incidence of suppurative thrombophlebitis of the central veins commonly cannulated (i.e., jugular, subclavian, *venae cavae*) is unknown. However, recent evidence clearly shows that catheter-associated thrombosis is common in specific populations. For example, in a recent prospective cohort study, venous ultrasonography and targeted physical examination were blindly performed in 48 patients with upper torso central venous catheter-associated SAB to identify the prevalence of venous thrombosis. With ultrasonography, definite or possible thrombosis was present in 34 (71%) of 48 patients. The sensitivity of all physical examination findings, either alone or in combination, was low ( $\leq 24\%$ ).<sup>780</sup> Autopsy series have revealed central venous thrombosis in 37% of catheterized subjects, but this diagnosis rarely is recognized, because most patients are asymptomatic. When examined with phlebography at the time of catheter withdrawal, 42% of catheters were found to have sleeve thrombi and another 8% revealed veno-occlusive thrombi.<sup>781</sup> In addition, sepsis has been reported in approximately 7% of patients receiving total parenteral nutrition and other medications by the central route.

When thrombosis and bacterial or fungal contamination or sepsis coexist, suppurative thrombophlebitis may intervene.<sup>782</sup> The role of hypercoagulability due to gene polymorphisms in catheter-associated infection and thrombosis has been evaluated<sup>783</sup> but is unresolved. At least 50 cases of suppurative thrombophlebitis of the great thoracic veins have been reported in the literature,<sup>784–786</sup> but this is almost certainly a gross underestimate of the problem. Eight cases in 8 years due to *Candida* spp. alone were observed at the University of Wisconsin.<sup>787</sup> As another example, 53 cancer patients with catheter-related SAB were identified from 1986 to 1989 at the MD Anderson Cancer Center; septic thrombosis was diagnosed in 12 (23%) and suspected in another 3 (6%) of these patients. Five of the 12 patients developed deep-seated complications, including septic pulmonary emboli and endocarditis, compared with 2 of the 38 patients without septic thrombosis ( $P < .01$ ). Persistent fever despite appropriate antistaphylococcal agents was an early clue to the diagnosis.<sup>788</sup> Septic atrial thrombosis, occasionally with a coexistent Budd-Chiari syndrome, has complicated Broviac catheter insertion in infants.<sup>789</sup>

Superficial suppurative thrombophlebitis is a complication of either dermal infection or use of an indwelling intravenous catheter. Pelvic suppurative thrombophlebitis is associated with parturition, abortion, gynecologic surgery, or a pelvic abscess. This is a disease of women of childbearing age, with most cases occurring between the ages of 15 and 40 years (mean, 20 years). In 123 cases in two reports,<sup>790,791</sup> the predisposing conditions were as follows: vaginal delivery, 39 cases; cesarean section, 19 cases; abortion, 33 cases; and major gynecologic surgery, 32 cases. During a 9-year period in Atlanta, 27 cases of postpartum septic pelvic thrombophlebitis were identified in more than 54,000 deliveries.<sup>791</sup> The relative risks for this condition were as follows: parturition, 1 in 2000 (highest in the inner-city population); septic abortion, 1 in 200; and major gynecologic surgery, 1 in 800. The incidence of suppurative thrombophlebitis increases proportionally with the degree of trauma to the pelvic tissues.

## Pathogenesis

The pathogenesis of suppurative thrombophlebitis (discussed in detail by Tornos and colleagues<sup>762</sup>) is poorly understood. A thrombus may act as a nidus for local entrapment and colonization of bacteria that gain access to the site from another focus. This is analogous to the proposed role of NBTE in the pathogenesis of IE. When superficial suppurative thrombophlebitis is associated with intravascular cannulas, the route of infection may involve (1) migration from the skin between the catheter wall and perivascular tissue, (2) contamination of intravenous fluid, (3) contamination of the hub, or (4) hematogenous dissemination from an infected focus elsewhere. The relative contributions of these four routes are unknown, although most investigators believe that migration of organisms down the external surface of the catheter is the most important route of invasion.<sup>765</sup> The predominant organism in burn wounds, *P. aeruginosa*, is a rare cause of suppurative thrombophlebitis,

and suppurative thrombophlebitis usually develops days to weeks after the cutdown incision is healed,<sup>767,768</sup> arguing against a local cutaneous source in burn patients.

The venous system draining the pelvis includes the intervertebral venous plexus, the lumbar venous plexus, the superficial and deep veins of the abdominal wall, and the hemorrhoidal plexus. Any component of this system may be affected in pelvic suppurative thrombophlebitis, but the veins draining the uterus, including the ovarian veins and the inferior vena cava, are involved most often.<sup>792</sup> Thrombus formation may result from stasis of blood flow due to the gravid uterus or from the hypercoagulable state of parturition. Normal residents of the vaginal or perineal bacterial flora gain access to the thrombus via the bloodstream or regional lymphatics. There often is an associated endometritis or parametritis. Septic pulmonary emboli and metastatic abscess formation are common. Septic thrombosis of the portal vein often is associated with hepatic abscess (occurring in five of seven patients in one series<sup>793</sup>); an obvious extrahepatic source of intraabdominal infection is usually absent.

## Pathologic Changes

Regardless of the vein involved, the pathologic changes are similar. The vein is enlarged, tortuous, and thickened. There may be associated perivascular suppuration or hemorrhage or both, and the vein lumen usually contains pus and thrombus. Microscopically, endothelial damage, fibrinoid necrosis, and thickening of the vein wall are evident. Micro-abscesses may be present in the vein wall or in the surrounding tissue.<sup>772,794</sup> Gross periphlebitic abscesses are not unusual and may be evident on physical examination. Thrombi frequently extend beyond the area of suppuration. In an autopsy series of peripheral suppurative thrombophlebitis in burned patients, extension of the clot into the great central veins was found in 18% of the cases.<sup>767,769</sup> Metastatic abscess formation and septic pulmonary emboli with infarction are found in more than 50% of the fatal cases. These conditions may result from bacterial liquefaction and fragmentation of affected thrombi within the vein, because clot liquefaction is noted commonly in autopsy series.

## Clinical Manifestations

Superficial suppurative thrombophlebitis often is difficult to identify, because local findings of inflammation may be absent. The disease occurs more frequently when plastic catheters are inserted in the lower extremities, a common practice in burned patients. In 132 cases of superficial suppurative thrombophlebitis reported from the burn center at Fort Sam Houston, Texas, the distribution of affected vessels was as follows: lower extremity (predominantly saphenous system), 100; upper extremity (predominantly antecubital fossa), 32; jugular vein, 7; and iliac vein, 4. The mean duration of preceding venous cannulation was 4.81 days, and the latent interval from removal of the catheter to the development of symptoms ranged from 2 to 10 days.<sup>766,768</sup> Fever was present in more than 70% of the cases, but rigors were rare. Local findings, such as warmth, erythema, tenderness, swelling, or lymphangitis, were present in only 32% of the patients; however, bacteremia with signs of systemic sepsis was found in 84%. Septic pulmonary emboli with secondary pneumonia—often the first diagnostic clue—occurred in 44%. Pneumonia, sepsis, or metastatic abscess formation was the only manifestation of this disease in two-thirds of the cases. The late onset of pneumonia or sepsis in a burned patient demands the careful inspection of all previously cannulated veins, because untreated suppurative thrombophlebitis is associated with a high mortality rate. In another report, a dramatic increase in the overall insulin daily requirement heralded the onset of suppurative thrombophlebitis.<sup>795</sup> In these series, less than 50% of the cases were diagnosed antemortem.<sup>767</sup>

In contrast to the experience with suppurative thrombophlebitis in burned patients, most medical and postoperative patients develop the disorder in the upper extremities and signs of local inflammation are present more commonly (94% in one series).<sup>776</sup> In a retrospective series of 21 children with superficial suppurative thrombophlebitis, 48% involved an upper extremity.<sup>796</sup> Many of the affected patients are elderly with debilitating diseases, and often they are receiving antibiotics when superficial suppurative thrombophlebitis supervenes. As noted, the duration of intravenous catheterization is an important risk factor; 68%

of implicated cannulas had been left in place for at least 5 days.<sup>775,776</sup> The frequency of catheter manipulations also has been linked to catheter infections.<sup>797</sup>

Subperiosteal abscesses of adjacent long bones may complicate superficial suppurative thrombophlebitis in children.<sup>798</sup> The local findings in this condition, including bone tenderness, erythema, warmth, and limitation of motion with occasional extension into the joint space, may overshadow the suppurative thrombophlebitis itself. Septic deep vein thrombosis of the femoral vessels with swollen, tender, and inflamed inguinal areas has been described in injection drug users of heroin and cocaine. Contiguous pelvic bone osteomyelitis is unusual.

Suppurative thrombophlebitis of the thoracic central veins occurs in critically ill patients with central catheters in place, in patients receiving total parenteral nutrition, and in patients after long-term cannulation with Broviac, Hickman, and other devices. The systemic findings associated with sepsis overshadow any local findings in venous occlusion (e.g., superior vena cava syndrome), which are rare in this setting. This syndrome should be suspected in any septic patient if bacteremia or fungemia fails to resolve on removal of the central catheter and institution of appropriate antimicrobial therapy.

Pelvic suppurative thrombophlebitis usually develops 1 to 2 weeks after delivery or postoperatively and is associated with high fever, chills, anorexia, nausea, vomiting, abdominal pain, and a protracted course.<sup>791</sup> Flank pain may result from ureteral obstruction by enlarged veins. Abdominal tenderness, usually in the right lower quadrant, may be mild to severe. Approximately 80% of cases are unilateral on the right side, 14% are bilateral, and only 6% are unilateral and left sided. This distribution is believed to result from compression of the right ovarian vein at the pelvic brim by the enlarged uterus with retrograde flow on the left and protection from ascending infection. The physical examination findings may be normal, however. A tender vein can be palpated in 30% of the cases at pelvic or abdominal examination.<sup>790,792</sup> The uterus usually is freely movable. Spread of the process to the femoral vein with edema and tenderness of the lower extremity is unusual. Many of these patients are extremely ill, with an acute or chronic course characterized by little or no response to antibiotics and the development of multiple small septic pulmonary emboli. Because many of the manifestations are nonspecific, the differential diagnostic listing is broad and includes acute appendicitis, ureteral obstruction, torsion of an ovarian cyst, pyelonephritis, broad ligament hematoma, parametritis, endometritis, perinephric abscess, pelvic abscess, small bowel volvulus, pelvic inflammatory disease, sickle cell crisis, and ectopic pregnancy.

## Laboratory Findings

Bacteremia is a hallmark of superficial suppurative thrombophlebitis, occurring in 80% to 90% of patients with the diagnosis. Gross pus within the vein lumen is found in about half of the cases, and this finding establishes a diagnosis of suppurative phlebitis. If infection of a venous catheter is suspected, the catheter should be removed and cultured. The results may be misleading, however, because even though bacteria are isolated in 60% of the cases, a positive culture does not correlate with inflammation.<sup>799</sup> The following semiquantitative culture technique was developed in an attempt to differentiate catheter-related sepsis from suppurative thrombophlebitis. After preparing the skin with alcohol, the catheter is removed with sterile forceps (avoiding skin contact) and is placed in a sterile tube for transport. The catheter then is cut aseptically into 5.7-cm pieces, and each section is rolled across the surface of a 5% sheep blood agar plate. The growth of more than 15 colonies on the plate correlates well<sup>799</sup> with the presence of venous infection. In the few cases of suppurative thrombophlebitis studied by means of this technique, all catheters yielded confluent growth. Because the standard 5.7-cm catheter retains 0.7 to 1.5 mg of moisture on its surface and the plate growth has exceeded 1000 colonies in every case of suppurative thrombophlebitis, bacterial counts must exceed  $10^6$  organisms per gram in the catheter wound. These titers are similar to those found with other types of infected wounds. This technique is simple, rapid, and inexpensive and may prove useful in establishing the need for exploratory venotomy. Simple needle aspiration of the suspected vein also may be diagnostic.<sup>126</sup>  $^{111}\text{In}$ -labeled leukocyte imaging

studies have been used to detect superficial suppurative thrombophlebitis, but experience is limited.

Other laboratory findings in patients with superficial suppurative thrombophlebitis (e.g., leukocytosis) are nonspecific. The chest radiograph may reveal multiple peripheral densities or a pleural effusion consistent with pulmonary emboli, infarction, abscess, or empyema. The diagnosis of an associated subperiosteal abscess is difficult; bone and gallium scans usually reveal hyperperfusion without definite osteomyelitis, routine radiographs almost always show no abnormalities, and CT scans often show only soft tissue swelling with obliteration of tissue planes. The use of high-resolution CT scans may improve these results.<sup>798</sup> The diagnosis of deep central vein suppurative thrombophlebitis in the thorax is established with venography, with the demonstration of thrombi in a patient with positive blood cultures, but CT with contrast enhancement is probably just as sensitive and is noninvasive. CT scans are useful in the diagnosis of suppurative phlebitis of the great central veins<sup>800,801</sup> and the portal vein;<sup>778</sup> gas may be detected in the venular lumen, which is diagnostic of this condition. Experience with MRI<sup>802</sup> and  $^{111}\text{In}$ -labeled leukocytes is meager.

In most cases of pelvic suppurative thrombophlebitis, there is a peripheral blood leukocytosis, and the urinalysis is usually normal. The chest radiograph may reveal multiple septic pulmonary emboli. Intravenous pyelography can be useful in disclosing ureteral obstruction. Real-time ultrasonography is helpful in delineating the location and extent of the thrombus, but the ileus that often is associated with this infection may render interpretation difficult. Ultrasonography also may show the presence of a periuterine, adnexal, or tubo-ovarian mass. CT reveals low attenuation with contrast enhancement in suppurative venous thrombosis and is sensitive in the diagnosis of pelvic suppurative thrombophlebitis.<sup>803,804</sup> MRI may be even more sensitive and can differentiate fresh thrombus ( $\leq 1$  week old) from organizing or subacute thrombus.<sup>805</sup> These sensitive and noninvasive techniques may lead to an increased recognition of pelvic suppurative thrombophlebitis, earlier diagnosis, and improved outcome. The roles of newer diagnostic techniques, such as pelvic venography, transuterine phlebography,<sup>111</sup> $\text{In}$ -labeled leukocyte scanning, and laparoscopy, still are undefined. Because bacteremia is shown in only 20% to 30%<sup>754,755,770</sup> of cases of pelvic suppurative thrombophlebitis, negative blood cultures do not exclude the diagnosis.

## Etiologic Agents

*S. aureus* was the causative agent in 65% to 78% of the cases of superficial suppurative thrombophlebitis reported before 1968. Many cases now are also caused by a member of Enterobacteriaceae, especially *Klebsiella-Enterobacter* spp.<sup>770,776</sup> These agents are acquired nosocomially and often are resistant to multiple antibiotics. Almost all patients with superficial suppurative thrombophlebitis due to gram-negative aerobic bacilli or fungi are receiving broad-spectrum antibiotics at the time the disease manifests. In a review of 86 cases compiled from the literature reported in the 1970s, the organisms isolated were as follows: *Klebsiella-Enterobacter* spp., 34 cases; *Providencia* spp., 5 cases; *Proteus* spp., 5 cases; *Serratia* spp., 3 cases; *E. coli*, 6 cases; *P. aeruginosa*, 3 cases; *S. aureus*, 15 cases; *C. albicans*, 9 cases; *S. epidermidis*, 4 cases; and enterococci, 2 cases.<sup>775,776</sup>

Suppurative thrombophlebitis due to gram-negative pathogens and *E. faecalis* is more common (than *S. aureus*) in patients with significant intraabdominal pathology.<sup>774</sup> *S. aureus*, other gram-positive cocci, and *Candida* spp. were more common when this risk factor was absent. Multiple organisms are isolated in 14% of cases. Anaerobic isolates are extremely rare but have been described in pediatric patients.<sup>806</sup> A distinct clinical syndrome of suppurative thrombophlebitis due to *C. fetus*, typically in immunocompromised patients, has been described. An increase in the incidence of superficial suppurative thrombophlebitis due to *Candida* spp. has been reported<sup>807,808</sup>; all patients were receiving antibiotics without hyperalimentation. None was neutropenic, and none was receiving corticosteroids. In one series of seven patients observed in a 15-month interval<sup>808</sup> all had concomitant or preceding bacterial infections and had received multiple antibiotics (mean, five antibiotics) for at least 2 weeks. Preceding candidal colonization at other sites (e.g., sputum, urine) often was present.<sup>808</sup>

*Malassezia furfur* also is seen as an opportunistic pathogen of deep vein catheters, especially in premature infants<sup>809</sup> and other pediatric patients receiving lipid emulsions, but this risk factor is not present in all patients.

The responsible agents in pelvic suppurative thrombophlebitis are poorly defined because blood cultures often are negative, and most investigators did not use adequate anaerobic techniques. The organisms that have been isolated, in approximate order of frequency, are *Bacteroides* spp., microaerophilic or anaerobic streptococci, *E. coli* and other coliforms, and β-hemolytic streptococci. The predominance of *Bacteroides* may be related to the heparinase produced by this organism. A prolonged latent period (3 weeks) may occur before blood cultures become positive. The more extensive use of anaerobic isolation techniques and routine culturing of surgical specimens may serve to clarify the role of anaerobic bacteria in this entity.

### Presumptive Therapy

Superficial suppurative thrombophlebitis is a lethal iatrogenic disease, and surgery often is necessary for cure. The first reported successful cure of suppurative thrombophlebitis followed surgical ligation of the vein by Hunter in 1784.<sup>810</sup> All authorities strongly endorse surgical excision as an integral part of treatment. In a review of 24 patients,<sup>767</sup> 14 were managed medically alone, and all died, either directly from suppurative thrombophlebitis with persistent bacteremia or secondary to metastatic complications. Of 10 patients who underwent surgical exploration, 7 survived, and only one of the three deaths was attributable to suppurative thrombophlebitis. Antibiotics also should be used in the treatment of this disease; initial empirical treatment with a semisynthetic penicillin (e.g., nafcillin, 2 g IV every 4–6 hours) plus either an aminoglycoside (e.g., gentamicin, 1.0–1.7 mg/kg IV or IM every 8 hours) or a third-generation cephalosporin (e.g., cefotaxime) or a quinolone (e.g., ciprofloxacin) is recommended, because members of Enterobacteriaceae or staphylococci are the usual etiologic agents. The optimal duration of therapy is unknown and largely empirical. The role of antifungal therapy for superficial suppurative thrombophlebitis due to *C. albicans* is controversial.<sup>807,808</sup> Most of these infections can be cured by vein excision. However, because of the propensity of this pathogen to disseminate hematogenously to organs (e.g., retina, kidneys), a 10- to 14-day course of amphotericin B, echinocandin, or fluconazole is advised postoperatively, pending further data. Antifungal therapy is mandatory in immunosuppressed patients or if signs of metastatic complications (e.g., endophthalmitis) develop.

If superficial suppurative thrombophlebitis is a likely diagnosis, an exploratory venotomy may be necessary. This procedure should be performed proximal to the suspected site; the vein should be ligated and then “milked” in an attempt to express purulent material for inspection by Gram stain and culture. If no pus is apparent, further surgical exploration is necessary to establish the diagnosis. In older literature, simple ligation was thought to be sufficient, but the rate of relapse with ongoing sepsis was high. The segment of vein and all its involved tributaries should be totally excised. Radical surgery from the ankle to the groin may be required in some burn patients. Nevertheless, local or regional anesthesia alone often is sufficient (approximately 90% of cases) for vein excision. Backbleeding, indicative of a patent lumen, should be evident at the point of vein transection. Vein excision usually is followed by prompt ( $\leq 24$  hours) defervescence. If systemic symptoms, bacteremia, or marked local manifestations persist after vein excision, reexploration is necessary, with careful attention to total removal of all involved veins and drainage of contiguous (e.g., periphlebitic, subperiosteal) abscesses.

The role of less radical surgery in therapy for superficial suppurative thrombophlebitis has not been addressed adequately. Although the literature supports vein excision, this experience stems largely from burn centers. Despite infection with gram-negative bacilli or *Candida* spp., six of eight children with superficial suppurative thrombophlebitis were cured by means of local incision and drainage of the involved site plus parenteral antimicrobial therapy.<sup>774</sup> Radical surgery with extensive excision perhaps can be reserved for patients in whom these measures fail. Delayed closure is preferred over primary wound closure. If osteomyelitis is documented in the adjacent long bones, antimicrobial

therapy should be continued for at least 6 weeks. Resection of the involved vasculature in most patients with suppurative thrombophlebitis of the great central veins is technically impossible. Medical therapy is usually sufficient.<sup>784,787,810</sup> The recommended approach is catheter removal, full-dose anticoagulation with heparin,<sup>810,811</sup> and parenteral antibiotic therapy. Although tissue plasminogen activator therapy has been used successfully in this setting,<sup>812</sup> experience is limited, and its use must be considered experimental. Septic thrombosis of the portal vein usually responds to systemic antimicrobial therapy directed at bowel flora with or without percutaneous drainage of any associated hepatic abscesses.<sup>793</sup>

The duration of therapy for septic phlebitis of deeper veins is unsettled: 2 to 3 weeks after catheter removal is suggested, with at least 4 weeks for *S. aureus* disease.<sup>788</sup> Experience with more potent agents (e.g., third-generation cephalosporins) for suppurative thrombophlebitis due to gram-negative bacilli is scant, but trials are indicated. Because heparin may precipitate vancomycin with a partial loss of antibacterial activity at concentrations present in intravenous lines,<sup>811</sup> these drugs should not be administered simultaneously through the same intravenous access line. In contrast to *Candida* IE, suppurative thrombophlebitis of the great central veins due to *Candida* spp. is curable medically, but antifungal regimens must be continued longer than is usually adequate for superficial suppurative thrombophlebitis. Based on limited data,<sup>787</sup> amphotericin B at a daily dose of 0.7 mg/kg, to a total dose of at least 22 mg/kg, plus 5-fluorocytosine (25 mg/kg/dose 4 times daily), is recommended after catheter removal. A lipid formulation of amphotericin is usually preferred to conventional amphotericin. Fluconazole (400 mg/day) or an echinocandin for 4 to 6 weeks is an alternative in patients who are not able to tolerate amphotericin B. Surgery may be essential in patients with suppurative thrombophlebitis of the thoracic or neck veins if perivascular collections are present.

The optimal therapy for pelvic suppurative thrombophlebitis still is controversial. Because anaerobic streptococci and *Bacteroides* spp. predominate, the initial antibiotics of choice are aqueous penicillin G (20 million units IV daily) plus either clindamycin (450–600 mg IV every 6 hours) or metronidazole (500–750 mg IV every 8 hours). The use of heparin is debated. The addition of heparin after several days of unsuccessful treatment with antibiotics itself may produce an antipyretic effect.<sup>813</sup> In one series of 46 patients with pelvic suppurative thrombophlebitis,<sup>791</sup> including 7 with massive ovarian vein involvement and 15 with septic pulmonary emboli, 42 patients become afebrile within 7 days (mean, 2.5 days) while receiving penicillin, chloramphenicol, and heparin. Four patients required exploratory laparotomy, and pelvic abscesses were found in 3 of them. These results argue strongly that medical therapy alone often is effective, but no controlled studies on the use of heparin have been done. If medical therapy is unsatisfactory, surgery with drainage of abscesses and, usually, ligation of the implicated venous system must be performed. Some authorities<sup>792</sup> believe that ligation of the inferior vena cava or ovarian vein, or both, should be performed in all of these cases, but the evidence for this approach is inconclusive.

### Prevention

The incidence of superficial suppurative thrombophlebitis can be reduced by the same preventive procedures that are used for intravenous cannulas in general (see Chapter 300). These include the use of “scalp vein” cannulas whenever possible; avoidance of lower-extremity cannulations; insertion under aseptic conditions; secure anchoring of the cannula; and frequent replacement (at least every 48–72 hours) of intravenous fluid bottles, cannulas, and connecting tubing. Although neomycin-polymyxin B–bacitracin ointment is effective in reducing the incidence of cutdown infections,<sup>814</sup> use of this combination agent has not shown consistent benefit with intravenous cannulas.<sup>815</sup>

A detailed discussion of prevention strategies for vascular catheters has been published by the Centers for Disease Control and Prevention.<sup>816</sup> When clinical signs of bacteremia occur in a patient receiving intravenous fluids, the following steps should be taken: (1) blood culture specimens should be obtained; (2) intravenous administration should be discontinued and all cannulas removed; (3) the intravenous fluid should be cultured; (4) the cannula should be cultured semiquantitatively on blood

agar, as described by Maki and associates<sup>799</sup>; and (5) appropriate antibiotic therapy should be instituted. If clinical signs of sepsis and bacteremia persist despite appropriate antibiotic therapy, an intravascular focus (e.g., suppurative thrombophlebitis at a previously cannulated vein) should be sought, as discussed previously.

## INFECTIVE ENDARTERITIS AND MYCOTIC ANEURYSMS

The term *mycotic aneurysm* was coined by Osler in 1885 to describe a mushroom-shaped aneurysm that developed in a patient with subacute bacterial endocarditis. At that time, the term *mycotic* was used to refer to all microorganisms. At present, the use of *mycotic* has been restricted specifically to fungal infections, but *mycotic aneurysm* still is used for all extracardiac (or intracardiac) aneurysms of infectious etiology except for syphilitic aortitis. This term also has been used to describe preexisting aneurysms secondarily infected from contiguous or distant foci and pseudoaneurysms arising from trauma or iatrogenic causes. *Endarteritis* refers to inflammation of the arterial wall, which may occur with or without coexistent aneurysmal dilation. Unless an aneurysm or coarctation of the aorta is present, infective endarteritis is usually a postmortem diagnosis. Because infected aneurysms differ in their pathogenesis, the various classifications (Table 80.8) are examined separately in the following discussion.<sup>817</sup> Infections of arterial prosthetic devices are discussed in detail in Chapter 82 and are not considered here.

## Epidemiology

Although incidence figures are unavailable, a localized suppurative process of the arterial wall is rare. Estimates derived from autopsy series of aortic aneurysms are available but ignore infections at other locations in the arterial tree. In a review of more than 22,000 autopsies performed at the Boston City Hospital from 1902 to 1951,<sup>818</sup> aortic aneurysms were found in 1.5%. Mycotic aneurysms constituted only 2.6% of these lesions, however. In another review of 178 aneurysms found among more than 20,000 autopsies at the Mayo Clinic from 1925 to 1954,<sup>819</sup> only 6 were believed to be of infectious origin. Similarly, in a review<sup>820</sup> of 77 pure iliac artery aneurysms in 48 patients from a 21-year period, only 2 aneurysms (4.2%) were mycotic in origin. In the preantibiotic era, infected aneurysms were confined predominantly to patients with IE; in a series of 217 cases reported in 1923,<sup>821</sup> 86% were associated with IE. With the advent of antibiotics, mycotic aneurysms in IE have become less prevalent and hematogenous seeding of a previously damaged arteriosclerotic vessel constitutes the most common mechanism. In a retrospective review of all emergency department cases seen at one city public hospital from 1994 to 1999, the annual prevalence of arterial mycotic aneurysms among injection drug users was 0.03%.<sup>822</sup>

Because most of these lesions arise in areas of severe atherosclerosis, they occur in men more often in a ratio of 3:1, and the average age at presentation has been 65 years. The mean age for mycotic aneurysms that occur with IE is younger (approximately 40 years), and men and women are affected approximately equally. Estimates of the incidence of mycotic aneurysms in patients with IE range up to 15%.<sup>823–826</sup> Two percent to 4% of IE patients develop intracranial mycotic aneurysms,<sup>826,827</sup> although a neurologic presentation is common in patients with IE (noted in 16%–23% of cases), and at least 30% of the patients develop neurologic manifestations.<sup>828,829</sup> As discussed previously, the presence of such

manifestations during IE has an adverse effect on the ultimate mortality rate. These lesions remain a significant cause of morbidity and mortality due to intracerebral and subarachnoid hemorrhage, especially in young people in developing countries, where acute rheumatic fever, rheumatic heart disease, and resultant IE still are prevalent.<sup>830</sup> Nine intracranial mycotic aneurysms associated with IE were treated in one neurosurgical unit in South Africa during an 18-month period, and five patients died.<sup>830</sup>

In addition, aortic root complications, including abscess or mycotic aneurysm, are associated with a poor outcome from IE. In one review,<sup>831</sup> aortic root complications were documented in 23 (46%) of 50 cases of aortic valve IE over a 6-year period; prosthetic valve involvement was common, and the surgical mortality rate and incidence of postoperative aortic regurgitation were higher in the group with aortic root complications.

Mycotic aneurysms are extremely rare in childhood<sup>832</sup> and when present are usually associated with IE, cardiovascular malformations, or connective tissue disorders. A specific disease entity first described in 1970 is aneurysm associated with umbilical artery catheterization in neonates.<sup>833</sup> The infecting organism is usually staphylococcal. By 1992, 34 cases had been reported, with the following distribution<sup>833</sup>: descending thoracic aorta, 14 cases; abdominal aorta, 10 cases; iliac arteries, 6 cases; and multiple sites, 4 cases.

## Pathogenesis

Four different mechanisms have been postulated to produce infection of the arterial wall: (1) formation of mycotic aneurysms secondary to septic microemboli to the vasa vasorum ("embolomycotic aneurysms"),<sup>834</sup> (2) extension from a contiguous infected focus, (3) hematogenous seeding of the intima during bacteremia originating from a distant infection, and (4) trauma to the arterial wall with direct contamination.<sup>835</sup> Embolomycotic aneurysms usually occur in patients with active IE, and the incidence of this type has declined since antibiotics became available. The source of infection is the cardiac vegetation, with production of arterial emboli that lodge in the vasa vasorum, often at points of bifurcation of the affected artery.

Contiguous foci of infection (e.g., a caseous tuberculous lymph node or pyogenic vertebral osteomyelitis) may extend directly to major vessels, with subsequent aneurysm formation. The normal arterial intima is very resistant to infection. If this lining is altered by congenital malformations (e.g., coarctation of the aorta) or by acquired disease (especially atherosclerotic plaques or ulcers), resistance to infection is lowered and the surface may become colonized by bloodborne organisms. This hypothesis is analogous to the central role of NBTE in the pathogenesis of IE. An intraluminal thrombus associated with an atherosclerotic vessel also may serve as a nidus for colonization. Atherosclerosis accounts for more than 74% of secondarily infected aneurysms. Luetic arteritis and cystic medial necrosis also have been associated with secondary infection.<sup>823</sup>

Trauma to the arterial wall with subsequent infection has been documented in injection drug users (needle trauma)<sup>836</sup> and has been associated with gunshot wounds, vascular surgery, cardiac catheterization, percutaneous transluminal coronary angioplasty,<sup>837,838</sup> intravascular stent placement,<sup>839</sup> radial artery catheterization,<sup>840</sup> implantable ports for intraarterial chemotherapy,<sup>841</sup> and puncture of a femoral artery for analysis of arterial blood gases.<sup>817</sup> These events, if associated with contamination, usually lead to pseudoaneurysm formation in a peripheral artery and a contiguous abscess in extravasated blood.

## Pathologic Changes

Infection of the arterial tree has been recognized by pathologists for more than a century. Virchow first showed local dilation of the arterial wall at the site of a septic embolus in 1847. Infection superimposed on an atherosclerotic aorta first was reported by Koch in 1851. Stengel and Wolfroth<sup>821</sup> collected 217 cases of mycotic aneurysms in 1923. These lesions probably are underreported, and pathologic material has been scant in recent years.

Most mycotic aneurysms that develop during the course of IE are situated in the sinus of Valsalva or in the supravalvular proximal thoracic aorta (>70% develop proximal to the aortic arch). Aneurysms are more

**TABLE 80.8 Classification of Mycotic Aneurysms**

PREEXISTENT ARTERIAL STATUS	SOURCE OF INFECTION
Normal	Intravascular
Atherosclerotic	Septic embolism from the heart
Aneurysm	Bacteremia with seeding
Arterial prosthesis	Extension from adjacent endocardial focus on erosion
	Extravascular
	Contiguous site of infection
	Iatrogenic

common in the right or posterior sinus and may be complicated by acquired shunts (rupture into the right ventricle is the most common), tamponade, coronary artery occlusion, or an atrioventricular conduction block.<sup>842</sup> Less commonly, major visceral, intracranial, and peripheral arteries are involved. Intracranial mycotic aneurysms characteristically develop in the distribution of the middle cerebral artery at peripheral bifurcation points,<sup>829,831</sup> as opposed to a more proximal location for most congenital aneurysms. Multiple intracranial lesions may be present. Mycotic aneurysm of the extracranial carotid arteries is rare (26 case reports<sup>843</sup>), but most develop in association with IE, usually due to *S. aureus*. Fewer than 10% are found in the upper extremities, but these arteries usually are not examined adequately with pathologic or radiologic techniques. Infrafemoral aneurysms during IE or after its treatment<sup>844</sup> also are unusual. Multiple lesions are identified in many IE patients with mycotic aneurysms.<sup>834</sup> Saccular forms seem to be more common than fusiform ones.<sup>818</sup> The aneurysms vary in size from 1 mm to more than 10 cm. As mentioned earlier, many of these aneurysms arise from emboli to the vasa vasorum, and occasionally the embolus can be shown grossly and microscopically. Acute and chronic inflammation is found diffusely through the arterial wall; necrosis, hemorrhage, abscess, and bacterial colonies all may be present in the sections. The elastica and muscularis layers usually are obliterated, but the intima often is intact. Rupture with surrounding hemorrhage and infection may be present.

Secondary infection of a preexisting aneurysm is found most commonly in the abdominal aorta (accounting for 70% of the cases), because this is the area most frequently and severely damaged by atherosclerosis. Ascending and descending aortic aneurysms each account for about 15% of the cases. The primary bacteremia most commonly originates from distal infections in soft tissue, lung, bone, or joint. The arterial infection usually begins in the distal abdominal aorta or iliac arteries as a focus of inflammation on an ulcerated atheromatous plaque. The wall of the aneurysm is thinned, and there is focal acute and chronic inflammation that may lead to arterial rupture. Even so-called bland aortic aneurysms commonly have some mild inflammation (characterized by a predominance of lymphocytes and mononuclear cells) in the wall; however, infected atherosclerotic aneurysms are characterized by acute inflammation with a predominance of polymorphonuclear leukocytes, necrosis, abscess formation, hemorrhage, and visible bacterial colonies. This lesion probably is underreported, because the focal suppuration may be limited in extent and overlooked unless routine culture and histologic sections are examined on every aortic aneurysm specimen. Erosion and rupture may be present without aneurysmal dilation. Lumbar or thoracic osteomyelitis is present in one-third of the cases<sup>823</sup> and may precede the aneurysm or develop secondary to contiguous spread from the vascular infection.

When contamination accompanies arterial injury, an infected pseudoaneurysm may result. These lesions are located in the extremities in more than 80% of the cases and are characterized by more extensive local tissue inflammation than is seen with the two types mentioned previously. Infection as a cause of pseudoaneurysm formation is increasing: 17 of 57 (30%) lesions seen in the 1980s<sup>845</sup> were infected. When endarteritis develops after angioplasty, it usually follows a second procedure or repuncture, and this scenario should suggest the diagnosis; all cases have been due to *S. aureus*.<sup>833,838</sup> Distal emboli, pseudoaneurysm, and coexistent osteomyelitis are present in more than 50% of the cases. Infective aortic root aneurysm also has occurred after coronary artery bypass graft surgery, with disastrous results.<sup>834,846,847</sup> Subclavian artery aneurysms may be present, with systemic findings plus unilateral upper extremity rash or splinter hemorrhages.<sup>848</sup> Nineteen cases of intracavernous carotid artery aneurysms have been reported,<sup>849</sup> usually occurring with meningitis with or without IE.

Of special interest are mycotic aneurysms in patients undergoing renal transplantation. Among 640 renal transplants performed at the University of Minnesota over 8 years, perinephric infections developed in 28 patients, and 8 of these patients developed mycotic aneurysms.<sup>850</sup> These lesions were evident clinically 1.5 to 4 months after transplantation. Six were located in the external iliac artery and one each in the internal iliac artery and aorta. All of these lesions were secondary to contiguous foci of infection in the deep tissues of the transplant wound.<sup>851,852</sup>

## Clinical Manifestations

When mycotic aneurysms occur during the course of IE, manifestations of the underlying disease may be evident. Peripheral middle cerebral artery aneurysms constitute 2.5% to 6.2% of all intracranial aneurysms<sup>826–830,852</sup> and usually are secondary to infection. Intracranial mycotic aneurysms are usually clinically silent. Hemorrhage results in severe headache of sudden onset with rapid deterioration in the level of consciousness. The time interval from diagnosis of IE to the onset of hemorrhage is variable (0–35 days), with a mean of 18 days.<sup>827</sup>

Some lesions produce premonitory or herald neurologic signs, including focal deficits and seizures. However, these findings are relatively common in patients who have IE without intracranial aneurysms, and the differential diagnosis and decisions regarding arteriography are difficult.<sup>853</sup> A sudden focal deficit consistent with embolism is seen in approximately 23% of patients and should prompt arteriography.<sup>853</sup> A high proportion of patients with intracranial mycotic aneurysm with severe, unremitting, localized headache, often in association with homonymous hemianopsia (as a herald sign), was reported in one series.<sup>854</sup> Stroke syndromes may be seen and manifest as focal neurologic deficits, headache, confusion, meningismus, seizures, or coma.<sup>828,829</sup> Contrary to popular belief, most intracranial hemorrhages associated with IE were found to be caused not by ruptured mycotic aneurysms but by septic necrotic arteritis.<sup>828</sup> Symptomatic intracranial hemorrhage was associated with a mortality rate of 60% to 90% in that study. Patients also may present with bilateral cortical blindness.

Unusual location or etiology of an intracranial mycotic aneurysm suggests a diagnosis other than IE.<sup>855</sup> Mycotic aneurysms tend to occur more commonly in women of a younger age than does IE in general. They must be differentiated from aneurysms secondary to tumor emboli (especially choriocarcinoma or atrial myxoma), trauma, arteritis, or moyamoya disease and congenital aneurysms. Visceral artery aneurysms are uncommon but when present are almost uniformly caused by infection<sup>835</sup> or by polyarteritis nodosa. The most common location is in the superior mesenteric artery. Although superior mesenteric artery aneurysms account for only 8% of visceral artery aneurysms overall, most are of infectious origin.<sup>856</sup> Symptoms include colicky abdominal pain of acute onset, but the presentation is variable. Hepatic artery aneurysms may produce colicky right upper quadrant pain, fever, jaundice, and gastrointestinal hemorrhage<sup>857</sup> or hemobilia.<sup>858</sup> More than 190 cases of this entity have been reported in the literature; 75% were extrahepatic, and 25% were intrahepatic. Ruptured mycotic aneurysm of the celiac artery may manifest as hemoptysis or hemotorax.<sup>859</sup>

If the external iliac artery is involved, a triad of clinical signs may be present: (1) pain in the lower extremity (especially the anterior aspect of the thigh) with quadriceps muscle wasting and a depressed knee jerk; (2) arterial insufficiency of the extremity with coolness, pallor, and depressed pulses; and (3) bacteremia.<sup>860</sup> Distal aneurysms (e.g., affecting the femoral artery) occasionally have unusual presenting manifestations, including arthritis and purpura in the affected limb. If more peripheral arteries are involved (usually with a pseudoaneurysm), a tender, diffusely indurated mass is present in 92% of cases. The mass is pulsatile, with an associated bruit, in 50% to 60% of patients, and 20% to 30% have decreased peripheral pulses, skin changes, or even frank gangrene.<sup>836</sup> Local suppuration, petechiae, and purpura are often present, and the lesion may be confused with localized cellulitis or an abscess without consideration of vascular involvement. In users of illicit drugs, the brachial, radial, or carotid arteries or arteries of the lower extremity may be involved.<sup>822</sup> Only 50% of these patients are febrile on admission.<sup>861</sup> A superimposed septic arthritis also may be present.

Although most infected aortic atherosclerotic aneurysms occur in elderly men, no pathognomonic findings exist to separate these patients from patients with bland, uninfected aneurysms. Fever is the most helpful differentiating sign (present in >70% of patients), because it is uncommon in patients with bland aneurysms. Back pain or abdominal pain occurs in about one-third of the cases. A draining cutaneous sinus may be present. Differentiation of an infected aneurysm from the entity of inflammatory abdominal aortic aneurysm may be difficult. Inflammatory abdominal aortic aneurysms first were described in 1935 and

account for 5% to 10% of abdominal aortic aneurysms; the lesions are usually infrarenal and often lead to ureteral obstruction, owing to the densely adherent fibrotic mass surrounding the vessel.<sup>862</sup> In a large series of 2816 patients undergoing repair of abdominal aortic aneurysms, 127 (4.5%) had inflammatory abdominal aortic aneurysms.<sup>863</sup> Most patients (123 of 127) were men and heavy smokers. Inflammatory abdominal aortic aneurysms are associated with an elevated erythrocyte sedimentation rate (73% of cases), weight loss, symptoms (back or abdominal pain in 30%–50%), and a high operative mortality rate.

Continuing bacteremia despite “appropriate” antimicrobial therapy in an elderly (especially diabetic) patient who has no signs of IE suggests an infected intravascular site. The aneurysm is palpable in 50% to 60% of the cases.<sup>824,835</sup> In most cases, the onset is insidious, and a low-grade fever may be present for several months before diagnosis. The nonspecificity of the clinical manifestations is reflected by the 75% preoperative rupture rate for this entity. Rupture may occur into the retroperitoneal space or peritoneal cavity (56%), pleural cavity (9%), duodenum (12%), esophagus (6%), mediastinum (3%), or pericardium (3%). The most common site of aortoenteric fistula is between the aorta and the third portion of the duodenum. Short periods of herald bleeding are common warning signs before exsanguinating hemorrhage occurs.<sup>864</sup> Severe pain and the rapid onset of shock usually accompany rupture of the aneurysm.

## Laboratory Findings

There are no characteristic laboratory abnormalities in this group of diseases. When mycotic aneurysms occur with IE, alterations suggesting the underlying disease may be present. CT is useful in patients with neurologic manifestations of IE, especially for the demonstration of intracranial hemorrhage. CT is not sufficiently sensitive for the detection of intracranial mycotic aneurysms<sup>828,829</sup>; however, these lesions are not likely when the appearance on CT scan is completely normal. Diagnosis of intracranial mycotic aneurysm can be established by four-vessel cerebral arteriography, although 2D and 3D helical CT angiography,<sup>865</sup> magnetic resonance angiography,<sup>829,866</sup> and the less dangerous and invasive procedure of intravenous digital subtraction angiography<sup>867</sup> are promising. Magnetic resonance angiography may detect aneurysms only 2 to 3 mm in diameter, but false-negative results occur in 8% to 10% of such studies; this modality cannot substitute for selective angiography, although techniques and resolution are evolving.<sup>868</sup>

Patients with infected aortic aneurysms usually have a leukocytosis (65%–83%), but this is nonspecific and may be present even if the aneurysm is bland. Bacteremia is found in 53% to more than 90% of the cases, is continuous, and usually does not clear with antibiotic therapy alone. Evidence for a primary source of bacteremia (e.g., pneumonia, osteomyelitis) may be present but is absent in 46% of the cases.<sup>823</sup> The abdominal aorta is noted to be calcified on abdominal radiographs in 47%,<sup>825</sup> and anterior vertebral body erosion has been shown in 18%. A lack of calcification suggests infection, because 70% to 80% of bland aneurysms show calcification on abdominal radiographs. Certain procedures (e.g., intravenous pyelography, ultrasonography, CT<sup>869</sup>) may reveal the presence of an aneurysm but often are not satisfactory for preoperative detail. The absence of intimal calcification, an associated perianeurysmal fluid collection or osteomyelitis (usually shown by CT), and the sudden appearance of an aneurysm in a septic patient are all features suggesting an infected abdominal aortic aneurysm.<sup>870,871</sup> Gas in the aortic wall is diagnostic but rare.

Although the sensitivity is unknown,<sup>67</sup>Ga- and <sup>111</sup>In-labeled leukocyte imaging have been used to localize intraarterial infections.<sup>872</sup> Occult infected aneurysms have been identified in patients with fever of unknown origin and negative results on CT or MRI studies with gallium<sup>873</sup> or leukocyte scintigraphy,<sup>874</sup> and these procedures may enable seroma or hematoma to be distinguished from adjacent infection. Leukocyte imaging with <sup>99m</sup>Tc-labeled cells also seems promising, but false-positive results have been noted.<sup>875</sup> Positron emission tomography labeled with <sup>18</sup>F-fluorodeoxyglucose shows great potential for the detection of endarteritis and infected vascular grafts and will likely become the nuclear medicine study of choice for this group of diseases. Nevertheless, preoperative angiography often is preferred to delineate precisely the extent of aneurysmal involvement.<sup>876</sup> This information may alter the operative approach and may minimize complications.

Two-dimensional echocardiography (TTE or TEE) is a useful noninvasive technique for documenting mycotic aneurysms in the vicinity of the aortic valve (e.g., sinus of Valsalva, supravalvular, subvalvular), and this technique is adjunctive to aortic root angiography preoperatively.<sup>877</sup> Infective endarteritis or mycotic aneurysm in the vicinity of a patent ductus arteriosus also has been visualized successfully with 2D and Doppler echocardiography.<sup>878,879</sup> Intraoperative epicardial echocardiography has been used to facilitate the surgical approach. If a hepatic aneurysm is suspected, liver scanning and ultrasonography performed before angiography may be helpful.<sup>857</sup>

## Etiologic Agents

Before the antibiotic era, mycotic aneurysms associated with IE usually were caused by the more “virulent” organisms, such as the β-hemolytic group A streptococci, pneumococci, or *H. influenzae*. With the decline of these organisms as causal agents in IE, most are now due to streptococci or staphylococci (≥60% of cases).

When bacteria seed a preexisting atherosclerotic vessel, the etiologic agents are markedly different from those found in mycotic aneurysms associated with IE. Gram-positive organisms cause approximately 60% of these lesions, but gram-negative bacilli (chiefly salmonellae) are isolated in 35%. Staphylococci are implicated in 40% of the cases overall,<sup>825</sup> and more than two-thirds of these are *S. aureus*. The risk for vascular infection in adult patients with non-Typhi *Salmonella* bacteremia has been reviewed.<sup>880</sup> Salmonellae cause 20% of the cases and involve, in order of frequency, the aorta and femoral and iliac arteries. Only 1 in 24 such cases reported before 1974 was above the renal arteries.<sup>881</sup> Lumbar osteomyelitis due to *Salmonella* was present in one-third of cases. The presumed portal of entry is the gastrointestinal tract.<sup>882</sup> *S. enteritidis* strains are isolated in 40% of cases, which is proportional to their overall rate of isolation in the United States. *S. enterica* serotype Choleraesuis, an uncommon clinical isolate, seems to be particularly pathogenic for this condition, because this species was isolated in 32% of the cases.<sup>883</sup> *S. enterica* serotype Typhi rarely is implicated in this disorder. *Salmonella* infections of aortic aneurysms first were reported in 1948. The predilection for involvement by this organism is not understood, but salmonellae tend to seed abnormal tissues during bacteremia (e.g., hematomas, malignant tumors, cysts, gallstones, bone infarcts, altered endothelium, aortic aneurysms). It has been estimated that 25% of patients older than 50 years with *Salmonella* bacteremia have an intravascular focus of infection.<sup>884,885</sup>

*Arizona* spp. (especially *Arizona hinshawii*) are closely related to *Salmonella* spp., cause similar clinical syndromes, and infect aortic aneurysms in elderly diabetic men.<sup>886</sup> The following organisms also produce infection in atherosclerotic aneurysms: *E. coli*, *P. aeruginosa*,<sup>887</sup> *Proteus* spp., *Citrobacter freundii*, *Klebsiella-Enterobacter* spp., *Brucella* spp.,<sup>888</sup> *S. marcescens*, *C. fetus*,<sup>889</sup> *L. monocytogenes* (17 reported cases<sup>890,891</sup>), *B. fragilis*, gonococci, group B streptococci,<sup>892</sup> corynebacteria, *C. burnetii*,<sup>893</sup> *Clostridium septicum*,<sup>894</sup> enterococci, and pneumococci.<sup>895</sup> *Mycobacterium tuberculosis* is a rare cause of aortic mycotic aneurysms. Of the 41 cases reported in the literature from 1945 to 1999, 75% seemed to result from erosion of the aortic wall by a contiguous focus and 25% seemed to result from direct seeding of the aortic intima or via the vasa vasorum.<sup>896</sup>

Fungal mycotic aneurysms are rare in the intracranial compartment, and only 13 definite cases had been reported by 1981.<sup>897</sup> The most common etiologic agents are *Aspergillus* spp., agents of mucormycoses, and *Candida* spp. The first two agents may involve intracranial arteries by direct extension from foci of sinusitis. One case of multiple intracranial aneurysms due to *Coccidioides immitis* that occurred during therapy for basilar meningitis has been described. Fungal mycotic aneurysms tend to involve larger, more proximal vessels at the base of the brain (11 [61%] of 18 cases were carotid or basilar), compared with those involved in bacterial cases of IE,<sup>898</sup> and may complicate intracranial surgery. *Aspergillus* mycotic aneurysms have occurred after trans-sphenoidal resections. Fungi also may cause endarteritis in the aorta or on aortic grafts, including *Aspergillus* or *Bipolaris* spp.<sup>899,900</sup> Mycotic aneurysms with subarachnoid bleeding may complicate the course of neurobrucellosis.<sup>901</sup> Tuberculous aneurysms are now uncommon; when present, they originate from contiguous foci of infection.

Pseudoaneurysms resulting from intraarterial or perivascular injection of illicit street drugs, often in addicts with sclerosed veins due to repeated intravenous inoculation, are associated with contiguous abscesses. The causative agents are *S. aureus* (in 76% of cases), *P. aeruginosa* (in 18%), and many others.<sup>836</sup>

## Therapy

No uniformly acceptable approach has been devised for the treatment of mycotic aneurysms in IE. The treatment of intracranial mycotic aneurysms is particularly controversial. Some of these lesions seem to resolve with antimicrobial therapy alone. In a review of 56 aneurysms occurring in 45 patients,<sup>902</sup> 3 of 20 patients died when treatment was limited to antibiotics alone. Mild-to-moderate neurologic deficits were observed in 8 of the 17 survivors. Likewise, 6 of 25 patients for whom treatment included antibiotics and surgery died and 9 of 19 survivors were left with mild-to-moderate neurologic deficits. In other studies, the investigators reported a different experience, with a higher mortality in the nonsurgical group,<sup>827</sup> but patients were selected only after subarachnoid hemorrhage had occurred. In a review of 13 intracranial mycotic aneurysms,<sup>827</sup> 6 of 8 patients who received treatment with antibiotics alone died; no deaths were observed in the surgical treatment group. In a review of 85 cases treated between 1954 and 1978, 20 of 38 patients managed solely with antibiotics died, compared with 8 of 30 patients who underwent surgery.<sup>826</sup> Endovascular stent-grafts combined with antibiotic therapy have been used in a few patients with mycotic aneurysms of the descending thoracic aorta.<sup>903</sup> The distal location of most intracranial mycotic aneurysms associated with IE may permit ligation and excision with fewer complications than are observed with surgery for berry aneurysms in the circle of Willis. The mortality rate was low (4 of 15) in patients with multiple aneurysms who received treatment with antibiotics alone. In one series, the mortality rate was 29% after rupture of an intracranial mycotic aneurysm.

The most important factor in the management of intracranial mycotic aneurysms is whether rupture is present. A definitive review found that mortality rates of medically and surgically managed patients with unruptured intracranial mycotic aneurysms due to IE were similar. If rupture was present, however, surgical or endovascular therapy appeared to be indicated, because the outcome of medically managed patients was poor. Based on these data, most authorities advise a conservative approach if the intracranial mycotic aneurysm is unruptured. Other factors influencing treatment decisions for intracranial mycotic aneurysms include aneurysm location, presence of increased intracranial pressure, and the extent of perfusion supplied by the affected artery. Interesting to note, aneurysm size is not helpful in determining when to operate immediately because small mycotic aneurysms may rupture and some large mycotic aneurysms may regress with medical management.

Serial imaging with angiography, magnetic resonance angiography, or CT angiography may be useful in monitoring these patients, because the aneurysms may change in size or new lesions may develop. Among 21 patients studied with angiography, the mycotic aneurysm increased in size in 5 patients, did not change in 1 patient, became smaller in 6 patients, and completely resolved in 11 patients; new aneurysms developed in 2 patients. More than 50% of these peripheral intracranial aneurysms resolved with antibiotic therapy alone during the treatment of IE.<sup>902</sup> Surgery is indicated for aneurysms that are increasing in size on serial angiographic studies<sup>904–906</sup> but may be deferred for 4 to 6 weeks for aneurysms that are remaining the same size (if the patient is an acceptable medical risk). The definitive treatment for aneurysms that are decreasing in size on serial angiographic studies repeated every 2 weeks is unclear. CT is not helpful in localizing the aneurysm but provides important information if hematomas, infarcts, or abscesses develop.

The choice of antibiotics is governed by the etiologic agent of the IE, but therapy for intracranial mycotic aneurysms, especially multiple lesions, must be individualized (see earlier discussion).<sup>828,829</sup>

Peripheral vessels usually are involved when arterial trauma (needle trauma, gunshot wound, iatrogenic injury) results in pseudoaneurysm formation with infection. Therapy with antibiotics, proximal ligation of the vessel, resection of the pseudoaneurysm, and appropriate drainage results in cures in 75% of the cases. Vascular reconstruction through uninfected tissue planes with autogenous grafts is necessary if limb viability depends on the affected vessel. This situation is encountered more frequently in the lower extremity. Severe ischemia developed in 9 of 28 patients after excision of mycotic aneurysms of the common femoral artery in one series of 52 cases.<sup>836</sup> Amputation was required in only 11% in a large series of 54 aneurysms among drug addicts seen at the Henry Ford Hospital; there were no deaths.<sup>907</sup>

The mortality rate in patients with infected atherosclerotic aneurysms often exceeds 90%; approximately 40 long-term survivors were reported from 1962 to 1988.<sup>908–911</sup> A high index of suspicion is necessary to allow surgical intervention before rupture occurs, because this complication is uniformly fatal and occurs in about 80% of the cases. If gram-negative bacilli are the cause of the infection, early rupture (e.g., within 2 weeks after the first positive blood culture) occurs much more frequently (84%) than if gram-positive bacteria are isolated (10%). Survival after surgery also is more common (75%) for patients with aneurysms infected with gram-positive cocci than for patients with gram-negative bacilli (25%). Antibiotics should be used in this disease, however, even if the lesion is sterilized (reported in only three cases). The aneurysm still may continue to enlarge and rupture, and surgery is required.

At surgery, the aneurysm and any intraluminal thrombus must be sectioned and Gram stain performed, and specimens must be submitted for culture. If infection is present, all aneurysmal tissue and surrounding areas of inflammation must be resected before grafting. Basic principles of grafting in this situation include the use of autogenous rather than synthetic grafts and insertion only in clean, noninfected tissue planes. If the graft is placed in the infected area, continued infection, leakage, thrombus formation, abscess formation, or rupture usually results. Although some authorities have achieved a successful result through restoration of vascular continuity in situ after radical débridement,<sup>908,910</sup> this approach is not recommended in most cases. Nevertheless, the type of reconstruction must be individualized, because results of in situ repair seem to be better for suprarenal<sup>912–915</sup> than for more distal aortic aneurysms if reconstruction is combined with prolonged courses of intravenously administered antimicrobial agents. Radical resection of intraabdominal aortic aneurysms without prosthetic material also has been used in a few cases.<sup>916</sup>

In a review of 24 patients with abdominal aortic aneurysms infected with salmonellae, 10 died after rupture without surgery and another 7 survived grafting only to die because of continued leakage from the anastomosis (only 5 patients were long-term survivors). If a graft is inserted in situ and persistent fever with bacteremia or embolism in the lower extremities ensues, reoperation with extraanatomic grafting is mandatory. Because the resected area is contaminated, special bypass techniques—especially for thoracoiliac, transpubic, and axillofemoral bypass—usually are required. If an axillofemoral approach is used, a single graft should be inserted for both lower extremities, because patency is prolonged under these circumstances.<sup>909,911</sup>

Bactericidal antibiotics should be continued for 6 to 8 weeks postoperatively. The choice of agents depends on the isolated organism (or the morphologic characteristics of the organisms in the surgical specimen) and on the results of in vitro susceptibility testing. Implantation of antibiotic-releasing carriers with in situ reconstruction has been used,<sup>917</sup> but only in a few patients without controlled trials; use of such carriers remains of unproved benefit in therapy for mycotic aneurysm.

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The complete reference list is available online at Expert Consult.

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**UPDATE****Partial Oral Antibiotics for Infective Endocarditis****Henry Redel, MD**

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The long-standing and general principle for the preferential use of parenteral antibiotics in the treatment of infective endocarditis has been challenged by the results of the Partial Oral Treatment of Endocarditis (POET) trial.<sup>1</sup> A multicenter, randomized, unblinded, noninferiority trial was performed in Denmark involving 400 patients with either native or prosthetic valve endocarditis due to *Streptococcus* species, *Enterococcus faecalis*, *Staphylococcus aureus*, or coagulase-negative staphylococci. The study subjects were randomized to either conventional parenteral treatment,

or to early switch to oral combination therapy with highly bioavailable agents. The primary outcome was a composite of all-cause mortality, unplanned cardiac surgery, clinically evident embolic events, or relapse of bacteremia at 6 months. Such bad outcomes occurred in 12.1% of the intravenous treatment group and 9.0% of the oral treatment group. This result met the noninferiority criterion. Four patients were switched from oral to intravenous therapy, and including these as treatment failure did not change the outcome of noninferiority. This study was heterogeneous, with many clinically relevant variables including the use of multiple treatment regimens for each bacterial species, and the inclusion of prosthetic and native valves. Such heterogeneity limited our ability to assess the efficacy of specific regimens. However, the concept of early switch to oral combination therapy in endocarditis appears to be safe and will be of interest to both patients and clinicians going forward. Further studies are needed to define the most effective regimens for these common gram-positive pathogens and with regard to regimens for prosthetic versus native valves.

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