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.[578] 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.[568,569] 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.[568,569]

If treatment with β-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.[334] 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.[579] A 4-week regimen of high-dose teicoplanin has been efficacious in a few patients with streptococcal IE,[580] 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 μg/mL or by Enterococci

Enterococci are a common cause of IE and can be highly resistant to therapy. The mortality rate still approximates 20%,[578] and relapses are common. With broth dilution susceptibility tests, the MIC determinations for many enterococci are as follows: penicillin, 0.4 to 12.5 μg/mL; ampicillin, less than 0.4 to 3.1 μg/mL; cephalothin, 12.5 to 25 μg/mL; vancomycin, 0.78 to 3.1 μg/mL; streptomycin, 3.1 to greater than 50 μg/mL; and gentamicin, 6.25 to 25 μg/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 μg/mL (in 80% of cases, >100 μg/mL); cephalothin, greater than 100 μg/mL; streptomycin, greater than 25 μg/mL; vancomycin, greater than 100 μg/mL; and gentamicin, 25 μg/mL or less.[581] *E. faecium* strains are more resistant to β-lactams than are *E. faecalis* strains.[582] 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.[583,584] As stated earlier, all β-lactams, including imipenem, are bacteriostatic against enterococci in vitro, and combination regimens are used in treating IE whenever possible.[585]

A new mechanism of penicillin resistance among *E. faecalis* strains was described in 1983: plasmid-mediated β-lactamase production. These strains remain relatively rare.[586,587] *E. faecalis* predominates, but β-lactamase production was documented in *E. faecium*.[588] Ampicillin-sulbactam overcomes the β-lactamase production and appears to be equivalent to vancomycin[589,590] (or teicoplanin[591]) in experimental IE involving these organisms and superior to therapy with ticarcillin-clavulanate.[591] Most β-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 β-lactamase production related to perturbations in various penicillin-binding proteins; experimental IE caused by these organisms responds to therapy with daptomycin or vancomycin.[592] To date, the number of reported cases of enterococcal IE caused by β-lactamase–producing strains or cases with high-level penicillin resistance on a nonenzymatic basis is low. The traditional view of β-lactam tolerance among enterococci has been challenged[593] 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[594] suggest that "low-dose" streptomycin (peak serum concentrations of 9.1 μg/mL) in combination with penicillin is sufficient to treat streptomycin-susceptible enterococcal IE. "High-level" streptomycin resistance (MIC >2000 μg/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.[595] These highly resistant strains show synergism between a penicillin and gentamicin in vitro[596,597] 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 μg/mL, respectively) in the treatment of experimental streptomycin-resistant enterococcal IE.[598] Early reports[599,600] revealed high-level gentamicin resistance among enterococci in 14% of isolates beginning in 1979. This phenomenon has become increasingly prevalent in many areas[601–603] beginning with *E. faecalis,* but now also includes *E. faecium*.[603–605] High-level gentamicin resistance (MIC ≥2000 μg/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.[603] Although these strains seldom cause IE, they present major problems in nosocomial infections,[606] and, because resistance to multiple aminoglycosides is common, they represent a formidable therapeutic challenge.[607] 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[608] 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[609] and two open-label trials (see later discussion) of high-dose ceftriaxone (2 g IV twice daily) plus ampicillin[610,611] now strongly support the efficacy of a double β-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,[607,612] 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[613,614] 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%.[615] 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.[598] Vancomycin combined with rifampin had an indifferent effect against enterococci (43 of 48 strains) in vitro; antagonism was observed rarely.[616] 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[617]) as an important cause of nosocomial infections. The genetics of vancomycin resistance[618] is described elsewhere (see Chapter 30) and

has been reviewed,[619] 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.[617] 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[620] but has been reported in a variety of clinical settings,[621,622] including transplanted hearts.[623]

The therapy for vancomycin-resistant enterococcal IE is not established.[334] 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[624–626]—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,[621] a combination of quinupristin-dalfopristin plus ampicillin and gentamicin in addition to aortic root replacement,[627] and chloramphenicol plus minocycline.[622] A triple combination of high-dose penicillin plus vancomycin plus gentamicin seems promising in animal models of IE induced by such resistant enterococci[628,629] 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).[610,611] The older-generation quinolones (e.g., ciprofloxacin) do not seem promising for the treatment of enterococcal IE.[630]

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.[560] 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.[631,632]

Wilson and associates[633] 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.[334] 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.[334] 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[634] 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.[635,636] 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.[634] A study from Denmark has essentially confirmed the equivalent efficacies and reduced renal toxicities of the shorter-term aminoglycoside strategy for enterococcal IE.[637]

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[610] 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.[611] 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 (MIC >0.2 μg/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.[638] The addition of gentamicin produced a synergistic effect against *S. aureus* in vitro and in experimental staphylococcal IE in rabbits.[639] However, the combination did not improve the survival rate (60%) over that observed with a penicillin derivative alone in a small group of patients.[407] Combination therapy did not improve the results of therapy for staphylococcal IE in injection drug users,[640] 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[641] 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,[641] the findings of three randomized, prospective trials of short-course regimens in this disease were subsequently published, comprising 121 patients (summarized by DiNubile).[642,643] The combination regimens included intravenously administered cloxacillin with either gentamicin or amikacin.[644,645,646] The overall clinical and microbiologic cure rates exceeded 90% in these studies. In patients with HIV seropositivity (most having $CD4^+$ counts greater than 300×10^6 cells) and in patients with large tricuspid vegetations (≥10 mm in diameter), such regimens had excellent efficacy.[646] Ribera and coworkers[646] showed an efficacy of intravenously administered cloxacillin that was equivalent to that of the cloxacillin plus gentamicin regimen. These data suggested that parenteral β-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).[334] 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.[647]

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.[648] 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., ≥8 mg/kg daptomycin) for the treatment of left-sided IE,[649] 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.[650,651] In each study, including one in which more than 70% of patients were HIV seropositive,[651] 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.[652] 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,*[653] 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,[1] based in part on a report that even brief courses of gentamicin for these syndromes are associated with increased risks of nephrotoxicity.[654] 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.[654] 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.[655] If the organism is susceptible to penicillin (MIC <0.1 μg/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.[404]

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.[656] 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[657] 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.[657] 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 intravegetation densities. Vancomycin therapy for complicated SAB also has been associated with relapses, as confirmed with pulsed-field gel electrophoresis.[658] Failure rates of approximately 40% have been documented in patients with *S. aureus* IE treated with vancomycin[659] despite right-sided involvement. In another study[660] 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 ≥1.5 μg/mL[661] or as 2 μg/mL[662]) had a worse clinical outcome than patients whose bloodstream MRSA isolates had a lower vancomycin MIC value.[663] The full implications of these findings, however, are not yet established,[664] 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.[665,666] Daptomycin is an alternative to vancomycin in the treatment of SAB and IE.[667] 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.[667] Clinicians should be aware of the possibility of treatment-emergent resistance during daptomycin therapy, and patients should be carefully monitored for this possibility.[668] 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.[669] For MSSA IE in patients with anaphylactoid-type β-lactam allergy and suboptimal responses to vancomycin, the need for β-lactam desensitization should be considered.[670,671]

The use of clindamycin to treat staphylococcal IE is associated with an unacceptable relapse rate and is not recommended.[672] The optimal therapy for IE due to "tolerant" strains of *S. aureus* is controversial.[673,674] One retrospective study[675] 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,[676] 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.[677] 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.[678] 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.[679] 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,[680] 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.[681,682] 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,[683–685] although resistance to the quinolones has emerged during therapy, and frank failures have been recorded.[671,686,687] 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,[648] linezolid, quinupristin-dalfopristin, minocycline, trimethoprim-sulfamethoxazole,[688] fosfomycin plus imipenem,[689] or ceftaroline alone or in combination with trimethoprim-sulfamethoxazole.[690,691] 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[671,692] 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.[402] 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[342] 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[343] 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.[10,14–16,693,694] 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,[695,696] and soft tissue infections due to vancomycin-resistant *S. aureus*[697,698] 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.[668] Most of these strains (87%) are methicillin resistant when isolated within 1 year after valve implantation. One study[699] 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[700] 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.[227] 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.[334] 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,[701] 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,[702] but not ceftriaxone-sulbactam[703]) 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.[704,705] Endovascular *Salmonella* infections, including IE, also may respond to third-generation cephalosporins (see later discussion).[706] Left-sided IE due to *S. marcescens* is often refractory to medical therapy alone.[432]

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 valvulectomy or "vegetectomy"[707] without valve replacement is indicated.[708] Although valve replacement often is necessary for a cure of left-sided IE due to *P. aeruginosa,*[709] medical therapy alone occasionally is curative.[256,430] Studies in animals with experimental *Pseudomonas* IE[710] 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[711]; (2) isolates

showing aminoglycoside resistance due to permeability defects emerge during therapy[712]; (3) no postantibiotic effect of β-lactams against *P. aeruginosa* is evident in vivo,[713] 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.[714]

Treatment failures in *Pseudomonas* IE in humans also have been related to the selection of isolates with an enhanced production of type Id β-lactamase.[715] Based on clinical experience,[413,433,434] 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 μg/mL and 2 μg/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[711] and in humans,[716] 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,[717] 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,[718] 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.[334] Despite limited clinical data, ciprofloxacin is an accepted alternative therapy.[334] Duration of treatment for HACEK IE should be at least 4 weeks for native and prosthetic valve infections.[334] 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.[476,477] However, only about one-third of *B. fragilis* strains show an MIC for penicillin that is less than 0.25 μg/mL; and penicillin is only a bacteriostatic agent against these strains (the MBC is invariably >100 μg/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.[478]

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.[719] IE without meningitis due to intermediate (MIC >0.1–1.0 μg/mL) or high-level (MIC ≥2.0 μg/mL) penicillin-resistant pneumococci can be treated with high-dose penicillin or a third-generation cephalosporin.[334] If IE and meningitis are simultaneously present, high doses of cefotaxime or ceftriaxone (2 g IV every 12 hours) should be used.[334] IE due to pneumococcal isolates resistant to cefotaxime (MIC ≥2.0 μg/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.[334]

The gonococci that cause systemic infection usually are highly susceptible to penicillin.[720] 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 β-lactamase production or chromosomally mediated mechanisms) has not been reported, ceftriaxone has been used successfully to treat gonococcal IE.[721]

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.[501] Although the survival rate in patients treated before 1974 was less than 20%,[305] survival in the current era has increased to 40% to 70%, coincident with improved diagnostic techniques.[501,722] 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.[334,503,723]

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.[724] 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 valvulectomy 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.[725] On the basis of animal model data,[726] high-dose itraconazole may be of value in the treatment of *Aspergillus* IE but valve replacement probably will remain imperative for a cure.[727] Amphotericin B is more effective than fluconazole for the prophylaxis and treatment of experimental *Candida* IE,[728] 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[503,729–731] 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.[732]

Q Fever Endocarditis

More than 1300 well-documented cases of Q fever have been reported[733]; the mortality rate exceeds 65%.[480,481,483,484,485] Prolonged therapy (≥4 years) with doxycycline and either trimethoprim-sulfamethoxazole or rifampin was considered to be the regimen of choice in the past (see Chapter 188).[480,734–736] A fluoroquinolone may be a useful addition to doxycycline.[480,736] The acidic conditions of the phagolysosome, where the organism resides, may inhibit antibiotic activity.[736] 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.[480] 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.[733] 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.[737] 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.[334] Early (≤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 cefepime (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).[334] 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.[334] 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[518]: 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.[7] 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.[334] Patients with IE and CHF should be immediately evaluated for potential surgical therapy.[334,738] 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[739–741] in adults and children.[742] 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.[741] 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.[743]

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) periannular extension of infection (e.g., paravalvular abscess or fistula); and (6) large (>1 cm in diameter) anterior mitral valve vegetations.[334] 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.[744] The most common causes of death in IE, in approximate order, are CHF,[738] neurologic events,[227] septic complications,[745] embolic phenomena, rupture of a mycotic aneurysm, complications of cardiac surgery, lack of response to antimicrobial therapy, and prosthetic valve IE.[334]

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[540] found that early valve surgery is associated with increased survival in patients with IE. These findings were confirmed in a pivotal clinical trial[746] 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.[747] 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.[345] 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.[748] 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.[749]

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.[750] 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.[745] 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[217] 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.[751]

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.[334] 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).[752] 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).[753] 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.[1] 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 valvulectomy or vegetectomy with valvuloplasty is the procedure of choice for refractory right-sided IE.[754,755] 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 valvulectomy in this setting.[756] 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.[757]

Outstanding reviews on the indications for surgery during therapy for IE are available.[740,758–761] 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[758] 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.[762]

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,[763] 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.[764] It is estimated that more than half of the 40 million patients admitted to US hospitals each year undergo intravascular catheterization.[765] 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,[766–769] 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).[770,771] Seven cases were recognized during an 18-month period in Charleston, South Carolina, and 35 cases were identified over 7 years in Louisville, Kentucky.[772] 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.[773] 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.[774] Using data from the National Nosocomial Infection Study, Rhame and associates[775] 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).[776] This condition is unusual during childhood[777] 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.[778,779] 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 (≤24%).[780] 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.[781] 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.[782] The role of hypercoagulability due to gene polymorphisms in catheter-associated infection and thrombosis has been evaluated[783] but is unresolved. At least 50 cases of suppurative thrombophlebitis of the great thoracic veins have been reported in the literature,[784–786] 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.[787] 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.[788] Septic atrial thrombosis, occasionally with a coexistent Budd-Chiari syndrome, has complicated Broviac catheter insertion in infants.[789]

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,[790,791] 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.[791] 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[762]) 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.[765] 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,[767,768] 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.[792] 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[793]); 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. Microabscesses may be present in the vein wall or in the surrounding tissue.[772,794] 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.[767,769] 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.[766,768] 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.[795] In these series, less than 50% of the cases were diagnosed antemortem.[767]

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).[776] In a retrospective series of 21 children with superficial suppurative thrombophlebitis, 48% involved an upper extremity.[796] 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.[775,776] The frequency of catheter manipulations also has been linked to catheter infections.[797]

Subperiosteal abscesses of adjacent long bones may complicate superficial suppurative thrombophlebitis in children.[798] 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.[791] 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.[790,792] 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.[799] 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[799] 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.[126] ^{111}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.[798] 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[800,801] and the portal vein[778]; gas may be detected in the venular lumen, which is diagnostic of this condition. Experience with MRI[802] and ^{111}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.[803,804] MRI may be even more sensitive and can differentiate fresh thrombus (≤1 week old) from organizing or subacute thrombus.[805] 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, ^{111}In-labeled leukocyte scanning, and laparoscopy, still are undefined. Because bacteremia is shown in only 20% to 30%[754,755,770] 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.[770,776] 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.[775,776]

Suppurative thrombophlebitis due to gram-negative pathogens and *E. faecalis* is more common (than *S. aureus*) in patients with significant intraabdominal pathology.[774] *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.[806] 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[807,808]; 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,[808] 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.[808]

Malassezia furfur also is seen as an opportunistic pathogen of deep vein catheters, especially in premature infants[809] 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.[810] All authorities strongly endorse surgical excision as an integral part of treatment. In a review of 24 patients,[767] 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.[807,808] 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 (≤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.[774] 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.[784,787,810] The recommended approach is catheter removal, full-dose anticoagulation with heparin,[810,811] and parenteral antibiotic therapy. Although tissue plasminogen activator therapy has been used successfully in this setting,[812] 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.[793]

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.[788] 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,[811] 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,[787] 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.[813] In one series of 46 patients with pelvic suppurative thrombophlebitis,[791] 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[792] 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,[814] use of this combination agent has not shown consistent benefit with intravenous cannulas.[815]

A detailed discussion of prevention strategies for vascular catheters has been published by the Centers for Disease Control and Prevention.[816] 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[799]; 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.[817] 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,[818] 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,[819] only 6 were believed to be of infectious origin. Similarly, in a review[820] 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,[821] 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%.[822]

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%.[823–826] Two percent to 4% of IE patients develop intracranial mycotic aneurysms,[826,827] 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.[828,829] 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.[830] 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.[830]

In addition, aortic root complications, including abscess or mycotic aneurysm, are associated with a poor outcome from IE. In one review,[831] 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[832] 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.[833] The infecting organism is usually staphylococcal. By 1992, 34 cases had been reported, with the following distribution[833]: descending thoracic aorta, 14 cases; abdominal aorta, 10 cases; iliac arteries, 6 cases; and multiple sites, 4 cases.

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

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"),[834] (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.[835] 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.[823]

Trauma to the arterial wall with subsequent infection has been documented in injection drug users (needle trauma)[836] and has been associated with gunshot wounds, vascular surgery, cardiac catheterization, percutaneous transluminal coronary angioplasty,[837,838] intravascular stent placement,[839] radial artery catheterization,[840] implantable ports for intraarterial chemotherapy,[841] and puncture of a femoral artery for analysis of arterial blood gases.[817] 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[821] 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

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.[842] 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,[829,831] 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[843]), 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[844] also are unusual. Multiple lesions are identified in many IE patients with mycotic aneurysms.[834] Saccular forms seem to be more common than fusiform ones.[818] 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[823] 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[845] 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*.[833,838] 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.[834,846,847] Subclavian artery aneurysms may be present, with systemic findings plus unilateral upper extremity rash or splinter hemorrhages.[848] Nineteen cases of intracavernous carotid artery aneurysms have been reported,[849] 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.[850] 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.[851,852]

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[826–830,852] 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.[827]

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.[853] A sudden focal deficit consistent with embolism is seen in approximately 23% of patients and should prompt arteriography.[853] 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.[854] Stroke syndromes may be seen and manifest as focal neurologic deficits, headache, confusion, meningismus, seizures, or coma.[828,829] 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.[828] 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.[855] 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[835] 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.[856] 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[857] or hemobilia.[858] 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 hemothorax.[859]

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.[860] 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.[836] 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.[822] Only 50% of these patients are febrile on admission.[822] A superimposed septic arthritis also may be present.[861]

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.[862] In a large series of 2816 patients undergoing repair of abdominal aortic aneurysms, 127 (4.5%) had inflammatory abdominal aortic aneurysms.[863] 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.[824,835] 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.[864] 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[828,829]; 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,[865] magnetic resonance angiography,[829,866] and the less dangerous and invasive procedure of intravenous digital subtraction angiography[867] 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.[868]

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.[823] The abdominal aorta is noted to be calcified on abdominal radiographs in 47%,[825] 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[869]) 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.[870,871] Gas in the aortic wall is diagnostic but rare.

Although the sensitivity is unknown, ^{67}Ga- and ^{111}In-labeled leukocyte imaging have been used to localize intraarterial infections.[872] Occult infected aneurysms have been identified in patients with fever of unknown origin and negative results on CT or MRI studies with gallium[873] or leukocyte scintigraphy,[874] and these procedures may enable seroma or hematoma to be distinguished from adjacent infection. Leukocyte imaging with ^{99m}Tc-labeled cells also seems promising, but false-positive results have been noted.[875] Positron emission tomography labeled with ^{18}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.[876] 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.[877] Infective endarteritis or mycotic aneurysm in the vicinity of a patent ductus arteriosus also has been visualized successfully with 2D and Doppler echocardiography.[878,879] 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.[857]

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,[825] 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.[880] 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.[881] Lumbar osteomyelitis due to *Salmonella* was present in one-third of cases. The presumed portal of entry is the gastrointestinal tract.[882] *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.[883] *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.[884,885]

Arizona spp. (especially *Arizona hinshawii*) are closely related to *Salmonella* spp., cause similar clinical syndromes, and infect aortic aneurysms in elderly diabetic men.[886] The following organisms also produce infection in atherosclerotic aneurysms: *E. coli, P. aeruginosa,*[887] *Proteus* spp., *Citrobacter freundii, Klebsiella-Enterobacter* spp., *Brucella* spp.,[888] *S. marcescens, C. fetus,*[889] *L. monocytogenes* (17 reported cases[890,891]), *B. fragilis,* gonococci, group B streptococci,[892] corynebacteria, *C. burnetii,*[893] *Clostridium septicum,*[894] enterococci, and pneumococci.[895] *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.[896]

Fungal mycotic aneurysms are rare in the intracranial compartment, and only 13 definite cases had been reported by 1981.[897] 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,[898] and may complicate intracranial surgery. *Aspergillus* mycotic aneurysms have occurred after transsphenoidal resections. Fungi also may cause endarteritis in the aorta or on aortic grafts, including *Aspergillus* or *Bipolaris* spp.[899,900] Mycotic aneurysms with subarachnoid bleeding may complicate the course of neurobrucellosis.[901] 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.[836]

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,[902] 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,[827] but patients were selected only after subarachnoid hemorrhage had occurred. In a review of 13 intracranial mycotic aneurysms,[827] 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.[826] Endovascular stent-grafts combined with antibiotic therapy have been used in a few patients with mycotic aneurysms of the descending thoracic aorta.[903] 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.[902] Surgery is indicated for aneurysms that are increasing in size on serial angiographic studies[904–906] 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).[828,829]

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.[836] 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.[907]

The mortality rate in patients with infected atherosclerotic aneurysms often exceeds 90%; approximately 40 long-term survivors were reported from 1962 to 1988.[908–911] 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,[908,910] 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[912–915] 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.[916]

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.[909,911]

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,[917] 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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81 Prosthetic Valve Endocarditis

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SHORT VIEW SUMMARY

Definition
- Prosthetic valve endocarditis (PVE) is a potentially life-threatening infection that involves a valve prosthesis or annuloplasty ring.

Epidemiology
- PVE is an uncommon but well-recognized complication of valve replacement or repair.
- Health care–associated PVE is increasing in incidence.
- *Staphylococcus aureus* is the most common cause of PVE.

Microbiology
- Early-onset (illness onset within 1 year of valve surgery) PVE is usually caused by microorganisms acquired perioperatively, such as *S. aureus* and coagulase-negative staphylococci (CoNS). Nosocomial gram-negative pathogens (many of which are multidrug resistant), enterococci, and fungi may cause early-onset PVE.
- Late-onset PVE is usually caused by organisms that are part of endogenous microbiota such as CoNS, *S. aureus,* viridans-group streptococci, and enterococci.
- *S. aureus* and CoNS have become common pathogens of late-onset PVE, in part because of an increase in frequency of health care–associated exposure in the late period.

Diagnosis
- Modified Duke criteria, initially proposed for epidemiologic purposes, have been validated clinically in evaluation of patients for diagnosis of PVE.
- Blood cultures are critical in both diagnosis and management of PVE. The identification of microbial pathogen and drug susceptibility testing are crucial for selection of appropriate pathogen-directed antibiotic therapy.
- Transesophageal echocardiography (TEE) is the preferred imaging modality to support a diagnosis and to identify complications such as severe valve dysfunction and perivalvular extension of infection, which may warrant surgical intervention.

Therapy
- Parenteral antimicrobial therapy specifically targeting the identified microbe for a minimum of 6 weeks is recommended (see Table 81.1).
- During antimicrobial therapy, serial clinical evaluations are important; if complications that would prompt surgical intervention are clinically suspected, TEE may need to be repeated in order to identify them.
- Early surgical intervention should be considered in complicated PVE with perivalvular extension, severe heart failure, severe valve dysfunction or dehiscence, multiple emboli, unresponsive infection, and PVE due to multidrug-resistant organisms or fungi (see Table 81.6).

Prevention
- Perioperative antibiotic prophylaxis, strict infection control measures, good surgical technique, and limiting the use of central venous catheters are important in preventing early-onset PVE.
- Maintenance of good oral hygiene is important to prevent late-onset community-acquired PVE.
- Although there has been no randomized, placebo-controlled trial to define the efficacy and safety of antibiotic prophylaxis, it is recommended for any dental procedure that involves manipulation of the gingival or periapical region of teeth or perforation of oral mucosa, targeting viridans-group streptococci.
- Antibiotic administration may be reasonable for invasive procedures involving the respiratory tract or infected skin or skin structures and/or musculoskeletal tissue; in such cases, antibiotics should be administered before and after the invasive procedure ("after" as a treatment regimen). Coverage for viridans-group streptococci and possibly additional organisms may be needed in the setting of respiratory tract procedures, contingent on known colonization status or presence of infection. For infected skin or skin structures and/or musculoskeletal tissue, coverage for *S. aureus* and β-hemolytic streptococci should be provided.

Prosthetic valve endocarditis (PVE), a microbial infection involving the valve prosthesis or repaired native heart valve with placement of an annuloplasty ring, is an uncommon but potentially lethal complication of prosthetic valve surgery. Despite diagnostic and therapeutic advances over the past decades, PVE continues to be characterized by high rates of relapse, morbidity, and mortality.

Because of the increase in prosthetic valve implantations performed for degenerative valvular disease in elderly patients and longer survival of patients with prosthetic valves, the number of patients at risk of PVE will continue to increase in the developed world.

PROSTHETIC VALVES

During the first half of 20th century, the management of patients with heart diseases saw dramatic breakthroughs with many medical innovations such as cardiac catheterization, invention of the heart-lung machine, and discovery of heparin.[1] During a person's lifetime, the four heart valves have to open and close approximately 2.5 billion times to maintain efficient unidirectional blood flow. As the average life span increases, the risk of structural degeneration of heart valves escalates. For patients with valvular heart disease, surgical interventions such as valvuloplasty and surgical decalcification procedures had poor results, and the need for valve replacement was realized. Valve replacement operations have dramatically improved survival and quality of life among patients with valvular heart disease. In the developed world, age-related degenerative valve disease now is the most common indication for valve replacement.[2–4]

An ideal prosthetic valve is one that can be placed in the heart, is compatible with cardiac physiology, and is chemically inert, nonimmunogenic, nonthrombogenic, and durable for decades.

Mechanical Valves

The initial step in the development of prosthetic valves occurred in 1954, when Hufnagel reported surgical correction of aortic insufficiency with a polymethyl methacrylate aortic ball valve that was implanted in the descending aorta with use of proximal and distal fixation rings.[5] Despite initial success, this surgical intervention was limited by embolization, thrombosis of valve, significant mechanical noise, and lower reduction in cardiac workload. Albert Starr and Dwight Harken developed a mechanical caged-ball valve made of a stainless steel cage, a knitted Teflon cloth fixation ring, and a heat-cured Silastic ball. On September 21, 1960, the first successful orthotropic valve placement was done by

Starr in the mitral position and subsequently by Harken in the aortic position.[6–8] The main problem with mechanical valves that remains to date is the high rate of thromboembolic complications. Starr, along with mechanical engineer M. Lowell Edwards, worked to reduce thromboembolic complications by pursuing design modifications such as reducing metal exposure area, coating surfaces with heparin, and altering the fabric to induce growth of the endothelium.[1] These design changes over time reduced the rate of thromboembolic episodes but did not eliminate the need for lifelong anticoagulation. Additional limitations of mechanical caged-ball valves are the substantial energy requirement and myocardial oxygen consumption required to open the ball valve and maintain cardiac output. In the late 1960s, mechanical valves with tilted disks with lower resistance to open the valve were introduced. A mechanical valve with a bileaflet mechanism was introduced in 1977 and has the advantage of unimpeded central flow of blood when the valve is in open positions. Mechanical valves now come in three designs: ball cage, tilted disk, and bileaflet.

Bioprosthetic Valves

The successful implantation of a cadaveric valve in the subcoronary aortic position by Donald Ross in 1962 was promising.[9] Subsequently, Binet and colleagues reported that five patients who received mercurochrome-formalin–preserved heterografts survived without anticoagulants. Heterograft valves from pigs and cows resemble human valves in size and structure. However, the enthusiasm for the hemodynamic and biologic advantages of biologic tissue valves was dampened by their poor midterm durability. Carpentier sought to improve durability while maintaining low thrombogenicity by combining biologic and mechanical structures, advancing a concept of bioprosthesis.[10] The durability of tissue valve was improved by chemical treatment of the porcine heart valve—washing the valve in Hank's solution and using an oxidizing agent to reduce antigenic components and glutaraldehyde treatment to stabilize collagen by establishing cross-links. The chemically treated porcine valve was then supported by a fabric-covered metal frame and a sewing ring, creating a hybrid bioprosthesis. Further advances included introduction of tissue substitutes such as bovine pericardium and new fixation strategies designed to maintain the molecular structure of tissue valves while limiting mineralization. Despite these significant advances, bioprostheses are prone to late structural degeneration and failure.[11,12]

Transcatheter Expandable Valves

Transcatheter aortic valve implantation (TAVI) has revolutionized the field during the past decade by combining the technologic advances in stent design, balloon angioplasty, interventional cardiology, and noninvasive real-time cardiac imaging.[13,14] In this technique, a bioprosthetic valve is delivered to the aortic position by means of a percutaneous catheter and then secured in place within the diseased valve with an expandable stent. A transfemoral approach is most common, but transapical and transsubclavian approaches may be considered in patients with difficult femoral access. Since US Food and Drug Administration (FDA) approval was granted in 2012, more than 50,000 patients have benefited from this procedure in the United States.[13] The two transcatheter aortic valves that are currently commercially available are (1) the Edwards SAPIEN valve, which is made of bovine pericardial trileaflets mounted on a balloon-expandable stainless steel stent, and (2) the Medtronic CoreValve, which is composed of a porcine pericardial valve with a self-expandable nitinol stent. TAVI was initially approved for patients with severe symptomatic aortic stenosis considered to be at high or greater risk of death or serious complications from open heart surgery.[15] In 2016 the indication was expanded to patients at intermediate risk.[16] The pivotal TAVI trials have shown promise in high-risk patients, with reduction in the 1-year mortality rate and improvements in quality-of-life measures.[17–20] Severe complications include cerebral embolism, need for a pacemaker after TAVI, infection, and aortic dissection or rupture.[17,19] Active endocarditis is considered an absolute contraindication for TAVI. A major limitation of first-generation TAVI is that the valve cannot be repositioned or retrieved once deployed. Suboptimal positioning of the valve may result in regurgitation, occlusion of coronary ostia, or conduction abnormalities.[13] Hopefully, the future generation valves can overcome this limitation and improve the success rate and safety profile of this technique.[21,22]

Transcatheter mitral and pulmonary valves have been introduced more recently.[23,24] In 2017 the FDA approved an expanded indication for the SAPIEN 3 valve for patients with symptomatic heart disease due to failure of a previously placed bioprosthetic aortic or mitral valve in whom risk of death or severe complications prohibits repeat valve replacement surgery.

EPIDEMIOLOGY

The incidence of PVE ranges from 1% to 6% of prosthetic valve implantations, or 0.3% to 0.6% per patient-year.[25–27] PVE accounts for 16% to 33% of all definite cases of infective endocarditis (IE), according to data from retrospective studies of single and multicenter tertiary care units in developed countries[27–34] and from prospective national,[35–37] European,[33] and international multicenter observational studies.[38] Risk factors associated with the development of PVE include male sex, previous native valve endocarditis (NVE), and long cardiopulmonary bypass time for prosthetic valve placement.[39–41] The cumulative risk of developing PVE is highest within the initial 12 months after replacement surgery, with a peak during the first 2 months.[38,41–45]

The prosthetic valve and annulus are vulnerable to secondary microbial seeding during the early postimplantation period when they lack an endothelial lining. The mean age of patients with PVE is 65 years; the range is 50 to 74 years.[35,38] The risk of PVE is higher in patients who undergo valve replacement surgery during active IE, especially in the setting of an unknown pathogen or insufficient antibiotic treatment.[32,40,43,45–47]

The mechanical prostheses appear to have a slightly higher risk during the first 3 months after operation, and the bioprosthetic valves appear to have a slightly higher risk after 12 months after operation, likely as a result of degenerative changes in the bioprosthetic leaflets.[40,41,48] The cumulative risk of PVE appears similar between mechanical and bioprosthetic valves.[41–43,48,49] However, a very large observational study of 38,500 elderly patients (age ≥65 years) demonstrated that those with bioprosthetic aortic valves had a higher risk of IE than did patients with mechanical aortic valves at 12-year follow-up.[50] The frequency of PVE is similar for both aortic and mitral prosthetic valves during the first year after operation.[41–43,47,51,52]

Prosthetic Valve Endocarditis After Transcatheter Valve Replacement

The incidence of early PVE after TAVI has ranged from 0.5% to 3.1%, similar to the incidence of PVE after open heart surgical valve replacements.[53–56] One proposed source of endothelial damage favoring subsequent endocarditis is the presence of residual aortic regurgitation, a major limitation of the first generation of transcatheter aortic valves.[53] Indeed, moderate-to-severe residual aortic regurgitation was identified as a characteristic associated with PVE in a review of 250 patients with PVE who underwent TAVI (22.4% vs. 14.7%; hazard ratio [HR], 2.05; 95% confidence interval [CI], 1.28–3.28).[56] A systematic review of 60 patients with PVE noted that most were men and had a higher risk profile with multiple comorbidities, such as diabetes mellitus, renal failure, and immunocompromise. Most patients with PVE were diagnosed between 3 and 9 months after implantation, with a median time of 5 months. Enterococci and *Staphylococcus aureus* were the predominant pathogens, followed by gram-negative organisms and fungi. Approximately half of the patients with PVE did not have a clear source or portal of entry of the pathogen. The most common presenting symptoms were fever and heart failure, followed by septic embolic lesions. Approximately 58% of patients with PVE had vegetations demonstrated with transesophageal echocardiography (TEE) and a significantly higher proportion of patients had perivalvular complications, such as abscesses (47%), fistulas (9%), and involvement of other valves (22%), comparable to rates of such complications in historical cohorts of PVE after open heart surgery.[53] Despite the high frequency of perivalvular complications, only 41% of patients underwent surgery, likely explained by the high-risk profile of patients who underwent surgical intervention, and in-hospital mortality neared 34%.[53]

MICROBIOLOGY

The microbiology of PVE depends on (1) time of onset of PVE (early vs. late PVE) and (2) site of acquisition (community-acquired vs. health care–associated PVE).

Early- and Late-Onset Prosthetic Valve Endocarditis

PVE has been categorized as early-onset PVE and late-onset PVE on the basis of the time period between prosthetic valve replacement and the manifestation of endocarditis. The microbiologic features of early- and late-onset PVE are different. Early-onset PVE has been due to microorganisms acquired intraoperatively or during the immediate postoperative period. *S. aureus* and coagulase-negative staphylococci (CoNS) are the most common pathogens in early PVE, followed in incidence by diphtheroids, fungi, and nosocomial aerobic gram-negative bacilli.[34,38,57–62] In the past, the time limit was arbitrarily chosen as 60 days, to differentiate perioperative infections from late community-acquired infections.[31,38,46] However, less virulent organisms acquired perioperatively may manifest many months after surgery. The peak incidence of CoNS endocarditis is between 60 and 365 days after valve implantation.[38] Hence, 1 year appears to be a better reference point to distinguish between early and late PVE. There has been a sharp decline in the proportion of early PVE, from 60% of all PVE cases in studies published in the 1970s[59,60,62] to about 10% to 20% in more recent studies,[38,58] without significantly affecting the overall rate of PVE.[26,38,41,61] The reduced early PVE rate is the consequence of better infection prevention and control practices, appropriate use of antimicrobial prophylaxis, improvements in design of prosthetic valves, and better surgical techniques.

Late PVE is usually considered to have been acquired in the community, unrelated to surgery or the perioperative period, with microbiologic findings resembling those of NVE. However, as a result of changes in the health care delivery system and the longer survival of patients with prosthetic valves, health care–associated PVE cases are increasing in the late period.[34] In some regions of the world, staphylococci have surpassed streptococci as the most frequent causative organisms of late PVE. In some hospitals, enterococci have surpassed viridans-group streptococci and thus are the third most common etiologic agent of late PVE.[34,38,58]

Health Care–Associated Prosthetic Valve Endocarditis

Health care–associated infections have become the most important risk factor for development of PVE in recent years.[34,38,63–65] Health care–associated PVE constituted about 37% of all cases in a prospective, multinational cohort.[38] *S. aureus* is now the leading causative organism of PVE, with increases in frequency of methicillin-resistant strains across geographic regions.[38] Nosocomial bacteremia and fungemia are high-risk factors for subsequent development of PVE.[63,66–68] Major risk factors for health care–associated PVE include presence of intravascular devices and hemodialysis. About 70% of health care–associated PVE cases are diagnosed within the first year after prosthetic valve implantation, and more than 60% occur beyond 60 days after operation.[38] Many aerobic gram-negative bacilli can cause health care–associated PVE, and multidrug resistance is common. Among this group, *Pseudomonas, Serratia, Acinetobacter,* and *Stenotrophomonas* spp. predominate. Fungal PVE due to *Candida* spp. can occur with health care exposure. *Candida albicans* and *Candida parapsilosis* are the most frequently isolated fungal pathogens of PVE.[69–72] Other non-*albicans Candida* spp. such as *Candida glabrata* and *Candida krusei* can cause PVE.[70]

Community-Acquired Prosthetic Valve Endocarditis

Most community-acquired PVE is caused by enterococci, viridans-group streptococci, and fastidious organisms including the HACEK group (*Haemophilus parainfluenzae, Aggregatibacter aphrophilus*, *Aggregatibacter actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens,* and *Kingella* spp.),[35,37,73–76] a similar constellation to those causing NVE in the community.

Late-onset PVE has been rarely caused by *Mycobacterium* spp., *Coxiella, Brucella, Tropheryma, Bartonella, Legionella* spp., *Enterovirus,* and *Aspergillus* spp. but can be difficult to identify as causal organisms. Fungal stains of the resected tissue can show characteristic fungal hyphal elements. Other rare fungal pathogens include *Scopulariopsis, Cryptococcus neoformans,* and *Histoplasma capsulatum.*[77–82] Rare cases of PVE with *Listeria,*[83–85] *Salmonella,*[86] and other gram-negative pathogens have been reported.

Outbreaks of Nontuberculous Mycobacterial Infections

Rapidly growing nontuberculous mycobacteria (NTM; *Mycobacterium fortuitum, Mycobacterium chelonae, Mycobacterium wolinskyi*) have been associated with several outbreaks of surgical site infections after heart surgery.[87–90] Potential sources include prosthetic valve implant contamination during the manufacturing process, contaminated water used to cool the cardioplegia solution, and contaminated heater-cooler units used during open heart surgery.[91] Examples of potential contamination of implants during the manufacturing process include an outbreak of PVE due to *M. chelonae* and an outbreak of *M. fortuitum* infection involving patches used for repairing septal defects.[88,89]

A prolonged outbreak of infection was identified to be due to *Mycobacterium chimaera*, a member of the *Mycobacterium avium* complex, after open heart surgery. The outbreak involved multiple hospitals in several countries and has been traced to heater-cooler units from a single manufacturer, likely contaminated during the manufacturing process.[91] Many patients with *M. chimaera* PVE present several months to years after operation (median, 21 months), and high clinical suspicion is important in the diagnosis of infection.[92] This outbreak was identified after the local infection control team was alerted to two cases of unusually invasive *M. chimaera* infection, which prompted a subsequent outbreak investigation and was critical in the ultimate recognition of a global infection-control problem.

NTM are resistant to frequently used disinfectants such as chlorine and ozone.[93] They also have the propensity to form biofilms, contributing to their persistence in the hospital and in home water systems. Colonization of the hospital environment, especially the water systems, with NTM is common.[94] Aerosolization of these bacteria from the contaminated heater-cooler units used during the open heart surgical procedure was hypothesized to be the likely mode of transmission in the recent outbreak.[91]

PATHOGENESIS

PVE can occur as a result of direct microbial contamination of a prosthetic valve at the time of surgery or as a consequence of secondary hematogenous seeding from a distant infectious focus. The prosthetic valve and perivalvular tissue are vulnerable for secondary microbial seeding during the early postimplantation period, when they lack protective endothelial lining.

The pathogenesis of PVE consists of several steps including (1) microbial adherence to the prosthetic valve, damaged endothelium, platelet-fibrin aggregate, and/or periprosthetic tissue; (2) recruitment and activation of monocytes and platelets and activation of extrinsic coagulation cascade, resulting in an infected coagulum called a vegetation, the characteristic lesion of endocarditis; (3) persistence and growth of the microorganism within cardiac lesions, leading to local tissue destruction and invasion; and (4) dislodgement of the vegetations, which may occur and result in septic emboli in distant organs such as the brain, skin, spleen, and kidneys or in the musculoskeletal system.[95,96]

Microbial Adherence

Microbial adherence is a critical step in the pathogenesis of endocarditis and involves complex interactions between microbial surface proteins and host extracellular matrix molecules. The endothelial lining of the heart is usually resistant to microbial infection. However, during the early postimplantation period, the prosthetic valve, cardiac annulus, periannular tissue, sewing ring, and sutures are not endothelialized. The foreign material is often coated with extracellular host matrix molecules (e.g., fibrinogen, fibrin, fibronectin, collagen, elastin, plasma proteins, platelet proteins) that can serve as ligands for microorganisms.[97] Microorganisms can also adhere to and infect the sterile platelet-fibrin aggregate formed after injury or inflammation of the endothelium. The aging bioprosthesis, sutures, and sewing cuff fabric of a valve prosthesis are thrombogenic and favor deposition of fibrinogen-fibrin, fibronectin, plasma proteins, and platelets.

The microbial surface proteins that can bind to the host extracellular matrix proteins are called "microbial surface components recognizing adhesive matrix molecules" (MSCRAMMs).[98] These surface components play a key role in the initiation of endovascular infections, bone and joint infections, and prosthetic device infections. The usual pathogens of PVE (*S. aureus,* CoNS, streptococci) possess abundant MSCRAMMs. CoNS possess several adhesins, including autolysin/adhesins AtlE and Aae,[99,100] the fibrinogen-binding protein Fbe/SdrG,[101,102] the giant 1-MDa fibrinogen-binding protein Embp, and lipase GehD.[103] Additional protein and polysaccharide components such as autolysin AtlE are involved in primary attachment to polymers. CoNS have emerged as important pathogens in modern clinical practice, primarily because of their ability to adhere to biomaterials and form a stable biofilm.[104–106] Biofilm is a slimy, slippery coat formed by a structured community of bacterial cells enclosed in a self-produced extracellular polymeric matrix adherent to solid surfaces.[107,108]

S. aureus has many surface proteins and nonprotein adhesins[108] that play a crucial role in the pathogenesis of IE. These include clumping factor A (ClfA), fibrinogen-binding adhesins, and the bifunctional fibrinogen/fibronectin-binding protein A (FnBPA).[109–111] The microbial surface proteins of streptococci that have been studied in experimental models of IE include glucans *(Streptococcus sanguis, Streptococcus mutans, Streptococcus gordonii)*[112]; Fim A *(Streptococcus parasanguis)*[113]; Ace, an adhesin for collagen type IV, collagen type I, and laminin; endocarditis; and Hsa, a sialic acid–binding protein *(S. gordonii).*[114] Enterococci have biofilm-associated proteins *(Enterococcus faecalis),*[115,116] Acm and Scm, and collagen adhesins *(Enterococcus faecium).*[117]

Formation and Growth of Vegetations

The microbial growth within a platelet-fibrin aggregate leads to activation of the extrinsic coagulation cascade and recruitment of monocytes and platelets that result in the formation of vegetation. The adherent bacteria activate the extrinsic coagulation pathway by triggering release of tissue factor from monocytes that adhere to early vegetations[118,119] and from endothelial cells surrounding the infected valves.[120–122] They also influence recruitment and activation of monocytes.[123–125] For example, the FnBPA proteins of staphylococci interact with the endothelial cells and help in recruitment of monocytes by triggering the expression of intercellular adhesion molecule (ICAM-1) and vascular cell adhesion molecule (VCAM-1), interleukin (IL)-6, IL-8, monocyte chemotactic protein (MCP-1), and tissue factor.

Microorganisms also engage and activate platelets either directly or through bridging molecules. For example, *S. aureus* induces platelet activation by several surface proteins. ClfA/clumping factor B (ClfB) and FnBPA/fibronectin-binding protein B (FnBPB) are the major platelet-activating modulins.[126–128] *S. sanguis* activates platelets by either direct interaction between the serine-rich glycoprotein A (SrpA) and the glycoprotein Ib receptor (von Willebrand factor [vWF])[129] or specific antibody and complement assembly that link the surface proteins to platelet FcγRIIA and complement receptors.[130] Strains of *S. gordonii* stimulate platelet aggregation directly by binding to glycoproteins Ib and IIb through the serine-rich surface glycoproteins GspB and the sialic acid–binding adhesins (Hsa).[131,132]

These processes result in an enhanced procoagulant and inflammatory activity in the vicinity of the infection. The thrombus serves as a focus for adherence of additional bacteria and platelets, leading to growth of the vegetation.

Persistence and Growth of Microorganisms

Microorganisms are able to persist and grow within vegetations by using many mechanisms to evade the host defense system. The usual pathogens of IE have reduced susceptibility to platelet-microbicidal proteins in vitro.[133–135] ClfA of *S. aureus* inhibits phagocytosis by human polymorphonuclear leukocytes in the absence of fibrinogen.[136] Fibrin-adherent streptococci are not engulfed by monocytes.[137] *S. aureus* can internalize into intact endothelial cells through a fibronectin bridge between FnBPA and the endothelial $\alpha_5\beta_1$ integrins (fibronectin receptors). This internalization of *S. aureus* can lead to persistent or recurrent infection by avoiding host defense and membrane-active antimicrobial agents, such as β-lactams and glycopeptides.

The biofilm over the prosthetic valve also provides a protective environment for the bacteria. The sessile bacteria within the biofilm are less susceptible to the host immune system and antibiotics than the free-floating (planktonic) bacteria. The polymeric matrix acts as a diffusion barrier to retard the diffusion of antibiotics and reactive oxidants of phagocytic cells. Bacteria within the biofilm exhibit an altered phenotype with different patterns of growth, gene expression, and protein production. Nutrient-deficient bacteria in the biofilm switch to a slow-growing metabolically quiescent persister phenotype, which is less susceptible to antimicrobial agents.[137]

Tissue Destruction and Invasion

Microorganisms produce various toxins and tissue-degrading enzymes that result in invasion and tissue destruction. The extent and rapidity of tissue destruction depend on the virulence of the microorganisms. *S. aureus,* the most common pathogen of PVE, is a virulent organism capable of inducing significant tissue destruction in a short period of time. In *S. aureus,* the secretion of tissue-degrading enzymes and toxins is coordinated in a growth phase–dependent manner by global regulator loci such as accessory gene regulator *(Agr),* the stress response regulon (SigB), and staphylococcal accessory regulator *(SarA).*[109,138,139]

PATHOLOGY

The clinicopathologic findings of PVE usually differ between mechanical and bioprosthetic valves. Mechanical heart valves are primarily made of metal or carbon alloys and are classified according to their structure as caged-ball, single-tilting disk, or bileaflet-tilting disk valves.[140] Metal or carbon alloys are usually not well suited for microbial adherence. The infection of mechanical prostheses usually starts at the interface between the sewing cuff and the native tissue. The perivalvular tissue invasion can result in loosening of the sutures, causing periprosthetic leaks, or in ring abscesses (Fig. 81.1). Annular abscess or paravalvular leak was more common in mechanical PVE than in bioprosthetic PVE.[141] In a retrospective multicenter study at 16 tertiary referral hospitals, 148 (17%) of 872 patients with PVE had perivalvular complications of the aortic ring, including aortocavitary fistulas in 19% and nonruptured abscess in 81%.[142] The ring abscess may dislodge the prosthesis from its anchorage (Fig. 81.2) and give rise to the echocardiographic appearance of a "dancing" prosthesis. Acute ventricular decompensation and congestive heart failure (CHF), due to either valve obstruction or incompetence, are important complications of PVE requiring surgery. In one study, 45% of all patients with PVE developed prosthetic dehiscence with moderate or severe valve regurgitation.[142] Aortic PVE may also result in third-degree heart block if the infectious process extends to the conducting system of the heart. Ruptured ring abscesses may form fistulous tracks into cardiac chambers or into the intraventricular septum and lead to intracardiac shunting. The aortic PVE may result in aneurysms of the sinus of Valsalva by extending to the aortic root or aneurysms of the anterior leaflet of the mitral valve by extending through

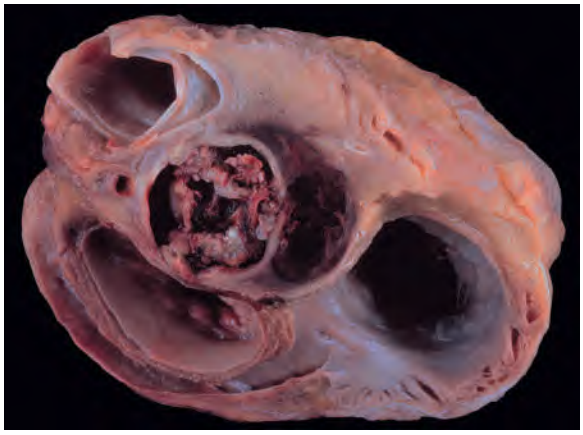

FIG. 81.1 Aortic prosthetic valve endocarditis with valvular stenosis and paravalvular ring abscess. *(Courtesy Dr. William D. Edwards, Mayo Clinic.)*

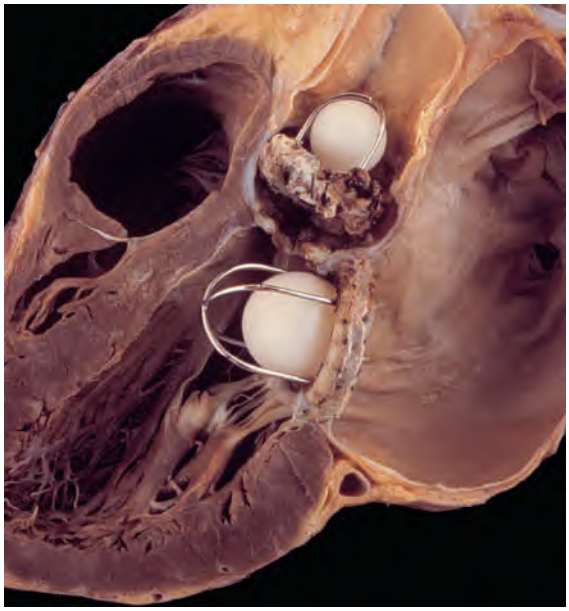

FIG. 81.2 Mechanical aortic prosthetic valve endocarditis with dehiscence and paravalvular leak. *(Courtesy Dr. William D. Edwards, Mayo Clinic.)*

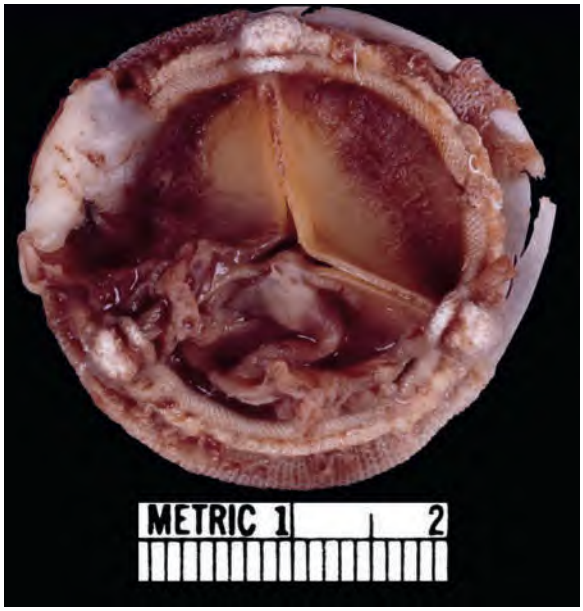

FIG. 81.4 Aortic bioprosthetic endocarditis involving the cusps. *(Courtesy Dr. William D. Edwards, Mayo Clinic.)*

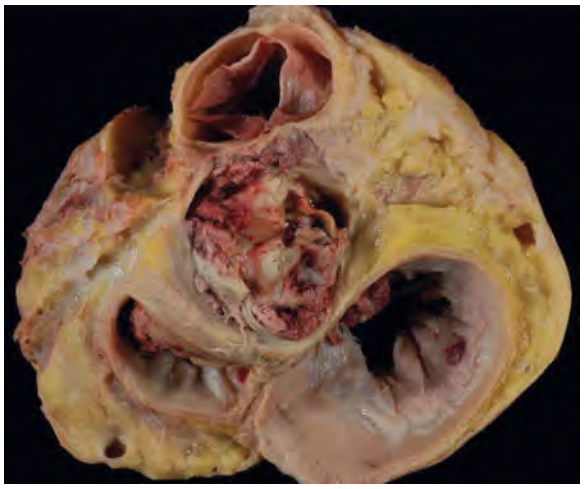

FIG. 81.3 Aortic prosthetic valve endocarditis extending to involve other native valves. *(Courtesy Dr. William D. Edwards, Mayo Clinic.)*

mitral-aortic fibrous continuity. The infection may also extend to involve the other valves, resulting in multivalvular endocarditis (Fig. 81.3).

Bioprosthetic valves are homografts (preserved human aortic valves) or heterografts (bovine pericardial or porcine valve tissue mounted on a metal support), and the infection is usually restricted to the cusps (Fig. 81.4). The growth of thrombotic vegetations in the biosynthetic material can lead to cusp rupture, perforation, leak, and vegetations. However, if the sewing cuff is involved in infection, the pathologic process is similar to that of mechanical prosthetic valve infection.

The sizes and types of vegetations appear to be correlated with the virulence of the causative microorganism. *S. aureus* usually results in smaller vegetations but causes significant destruction and invasion of the tissue. Viridans-group streptococci have been associated with larger vegetations with slower, milder destruction of tissue. Fungi form large, bulky vegetations.[142] Large vegetations are also associated with the HACEK group of organisms.

CLINICAL PRESENTATION

The clinical presentation of PVE is variable, determined by the virulence of the pathogen and the time of presentation. Common clinical presentations include fever, new or changing murmur, heart block, congestive heart failure (CHF), and embolic events.[143] Fever is the most common symptom and sign of PVE and is present in 73% to 92% of patients. However, fever is often absent in patients with renal failure, elderly patients, and those taking antibiotic or antipyretic medications. New or changing murmur or CHF may be indicative of complications of PVE such as prosthetic valve dehiscence, fistulas, or perivalvular abscess.[144–147] New ventricular dysrhythmias or conduction abnormalities may arise if the infectious process (perivalvular abscess) extends into the electrical conduction system of the heart.[148,149] Perivalvular extension of the aortic PVE into the intraventricular septum can disrupt the proximal ventricular conduction system and result in complete heart block. Embolic stroke or brain abscess, or both, may be the initial presentation of PVE. In patients with left-sided endocarditis, both symptomatic (35%) and clinically silent (30%) cerebrovascular complications are common.[150] Mycotic aneurysms involving the cerebral vasculature are uncommon, but serious complications of PVE can result in intracranial hemorrhage.[151,152] Secondary metastatic abscess can develop in the musculoskeletal system (psoas abscess, vertebral osteomyelitis, and diskitis), kidneys, spleen, joints, and so on. Right-sided endocarditis involving the tricuspid or pulmonic prosthesis may result in septic pulmonary emboli. Glomerulonephritis or arthritis can be a manifestation of a systemic immune response but is uncommon in acute presentations.

DIAGNOSIS

Classic oslerian manifestations may often be absent in acute PVE because patients present during the early stage of the disease before the evolution of immunologic and embolic manifestations. The diagnosis of PVE can be challenging because atypical presentations are common in the elderly population with prosthetic valves. A high index of suspicion and comprehensive clinical, microbiologic, and echocardiographic evaluations are important for prompt diagnosis of PVE and its complications. Modified Duke criteria should be used as a clinical guide to evaluate all patients suspected to have PVE.[153,154] Since the Duke criteria were initially established for epidemiologic and clinical research purposes rather than to assist in clinical practice, clinical judgment should be used when they are applied in the management of patients.

Echocardiography

TEE is recommended in all cases of suspected PVE.[154] One of the two major criteria in the modified Duke diagnostic schema is echocardiographic evidence of oscillating intracardiac mass on the valve or

supporting structures, new partial dehiscence of prosthetic valve, or intracardiac abscess.[153] The utility of transthoracic echocardiography (TTE) is limited in the evaluation of patients with suspected PVE for two reasons.[155] First, reverberations and other artifacts created by the prosthesis hamper the quality of the TTE images. Second, TTE is not sensitive enough to evaluate for perivalvular complications, which is critical in the management of PVE. TEE has a higher sensitivity of 86% to 92% to detect vegetations when compared with TTE (17%–36%).[156–159] TEE is also superior to TTE for the detection of complications such as perforations, prosthetic valve dehiscence, perivalvular abscesses, and fistulas.[160] Thus, TEE is important to both establish the diagnosis of PVE and identify high-risk patients who may require early surgery.

False-negative TEE may occur in the early course of illness if the vegetations or perivalvular abscesses are too small to be detected.[161] If the clinical suspicion persists despite negative TEE, TEE should be repeated after 7 days, although again it can be falsely negative as a result of the intervening therapy. The interpretation of TEE is sometimes difficult because differentiation among thrombus, vegetation, or degenerative strand is not always obvious.

Complications of PVE such as valve dehiscence, perivalvular abscess, fistulas, and pseudoaneurysm may evolve over time despite negative initial TEE. Persistent fever despite appropriate antibiotic treatment and/or new conduction abnormalities should raise the suspicion for intracardiac perivalvular abscess. New or worsening heart failure may suggest mechanical valve dehiscence or perforation or rupture of the bioprosthetic valve cusp. TEE should be repeated promptly whenever there is a change in clinical condition that raises the suspicion of PVE complications. TEE may depict pseudoaneurysms as a pulsatile, echocardiographic-free sac around the prosthesis communicating with a cardiac chamber (Fig. 81.5).

Nuclear Medicine Imaging Techniques

Echocardiography is operator dependent and may be falsely negative if it is performed too early in the pathogenesis of PVE when vegetation and/or structural valve damage are not yet apparent.[162] Up to 30% of patients who undergo echocardiography because of clinical suspicion of PVE have inconclusive findings. To overcome this limitation, several nuclear medicine imaging procedures have been examined over the past few years, including labeled leukocyte scintigraphy, single-photon emission computed tomography (SPECT), and fluorine-18 fluorodeoxyglucose positron emission tomography (PET) with either computed tomography (^{18}F-FDG-PET/CT) or computed tomography angiography (CTA)[163] (Fig. 81.6).

Labeled Leukocyte Scintigraphy

Inflammatory cells migrate avidly to the site of infection by chemotaxis. Radiolabeled white blood cell (WBC) scans use this phenomenon to localize the site of infection by planar imaging. Labeled leukocyte scintigraphy techniques, such as indium 111 (^{111}In), gallium (^{67}Ga) with SPECT views, and technetium 99m (^{99m}Tc) hexamethyl propylene amine oxidase (HMPAO) with SPECT/CT acquisitions, have been reported to be helpful in identifying PVE or perivalvular abscesses even among patients with negative echocardiographic results.[164–168] One study showed the added value of ^{99m}Tc HMPAO with SPECT/CT in the management of IE by improving the performance of the modified Duke criteria.[167] ^{99m}Tc-labeled monoclonal anti–human granulocyte antibody–labeled leukocytes for diagnosis of PVE have been used in a small case-control study.[169] Limitations of WBC scans include poor spatial resolution and variable sensitivity affected by viability of leukocytes after the in vitro labeling process and rate of migration of leukocytes to the site of infection. The WBC labeling process is also time consuming, labor intensive, expensive, and slow; the imaging is performed 24 hours or later after injection of the radiolabeled leukocytes.[163]

Positron Emission Tomography/Computer Tomography

^{18}F-FDG-PET/CT combines the measurement of metabolic activity of tissue and anatomic evaluation of CT to achieve a diagnosis of PVE. Advantages of ^{18}F-FDG-PET/CT over WBC scans include high spatial and target-to-background contrast resolution without any requirement for labor-intensive in vitro WBC labeling processes. ^{18}F-FDG-PET/CT relies on the phenomenon that glucose uptake transporters (GLUT1) are overexpressed in the activated inflammatory cells (neutrophils, macrophages, lymphocytes) at the site of infection and hence accumulate FDG in high concentration.[170–172] In a prospective study of 72 patients with suspected PVE, ^{18}F-FDG-PET/CT had a sensitivity of 73% and specificity of 80% and it identified all cases of PVE in which pathologic diagnosis was confirmed after valve surgery. If ^{18}F-FDG-PET/CT is included as a major criterion in the modified Duke criteria, the sensitivity of the diagnostic scheme might rise to 97% from 70% by reclassification a number of "possible" cases to "definite" PVE.[173]

The addition of CTA to ^{18}F-FDG-PET has been proposed as a better imaging modality than nongated CT/^{18}F-FDG-PET to diagnose PVE and perivalvular complications such as mycotic aneurysm, myocardial abscess, fistula, and thrombosis, and for preoperative evaluation of coronary arteries.[174–176] ^{18}F-FDG-PET/CTA can help in the surgical decision process by identifying complications that may necessitate urgent surgical intervention.[177] However, well-controlled comparisons of diagnostic accuracy are not currently available.

Limitations of Positron Emission Tomography/Computer Tomography

Many unanswered questions remain regarding ^{18}F-FDG-PET/CT imaging procedures. The standard protocol employed in most nuclear medicine

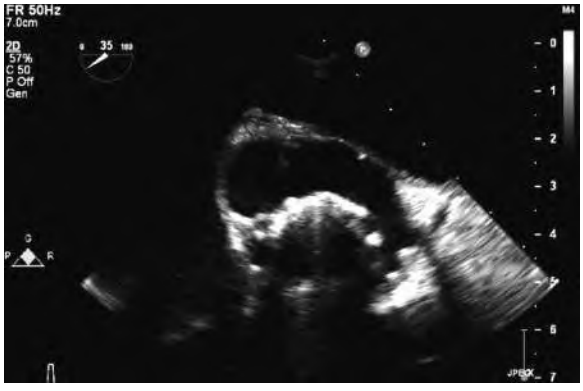

FIG. 81.5 Transesophageal echocardiography image showing pseudoaneurysm. *(Courtesy Dr. Nandan Anavekar, Mayo Clinic.)*

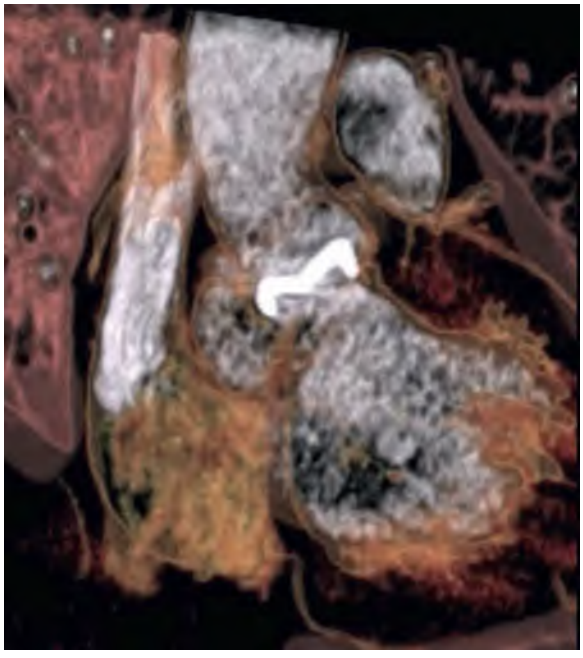

FIG. 81.6 Multislice computed tomography scan showing perivalvular abscess. *(Courtesy Dr. Nandan Anavekar, Mayo Clinic.)*

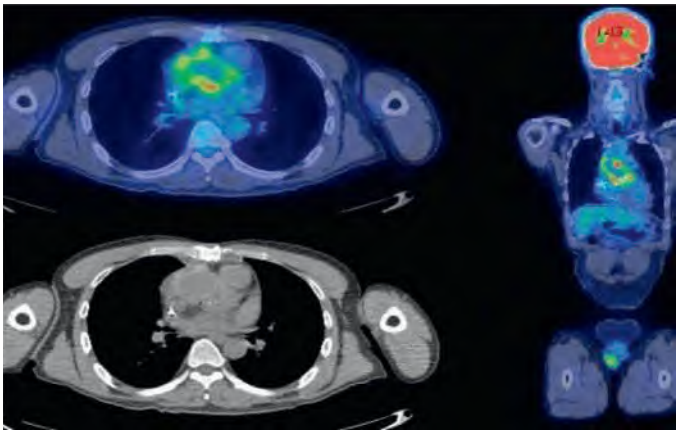

FIG. 81.7 Fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG-PET/CT) scan positive for prosthetic aortic root endocarditis. ^{18}F-FDG-PET/CT relies on the phenomenon that glucose uptake transporters (GLUT1) are overexpressed in the activated inflammatory cells (neutrophils, macrophages, lymphocytes) at the site of infection and hence accumulate FDG in high concentration. This figure shows focal and heterogeneous FDG uptake around the prosthetic aortic root that appears to signify infection. *(Courtesy Dr. Maryam Mahmood, Mayo Clinic.)*

centers is designed to detect metastatic lesions, which have higher metabolic activity than infected tissue. Some authors have suggested that modifications in the protocol (delayed image acquisition at 2–3 hours after injection of glucose rather than at 1 hour) will increase the sensitivity of ^{18}F-FDG-PET/CT through better detection of glucose uptake by monocytes and macrophages at the level of infection.[178] The pattern and distribution of FDG uptake (focal, heterogeneous rather than diffuse) appear to signify infection more than the intensity of FDG uptake (maximum standardized uptake value [SUV_{max}]), and there is no established SUV cutoff value available (Fig. 81.7). A major concern with ^{18}F-FDG-PET/CT is the potential for false-positive results during the early postoperative period, because there is significant functional glucose uptake in the perivalvular tissue.[163,179,180] There are few available data about the normal evolution of FDG uptake in the perivalvular tissue in the early postoperative period. Use of BioGlue to seal aortic graft anastomoses has produced significantly high FDG uptake.[181] The inflammatory reaction and metabolic activity after cardiac surgery appear to be idiosyncratic, and therefore the FDG uptake pattern in the early postoperative period may not be generalizable. Current guidelines recommend deferring ^{18}F-FDG-PET/CT for up to 3 months after cardiac surgery. Physiologic myocardial FDG uptake and cardiac motion could interfere with results. Sensitivity of ^{18}F-FDG-PET/CT appears to be lower with small vegetation size, and antibiotic treatment may reduce inflammatory reaction, resulting in false-negative results.[182] Available studies of ^{18}F-FDG-PET/CT in the evaluation of PVE are limited by lack of controls,[173] and well-designed prospective studies are needed to further delineate its role in the management of patients with suspected PVE. Standardization of dietary protocols, timing of image acquisition, image processing protocols, and image interpretation criteria are important and needed. The current European guidelines for diagnosis of IE have included ^{18}F-FDG-PET/CTA in the diagnostic algorithm.[183] It appears to be useful especially among patients in whom clinical suspicion of PVE is high despite normal or inconclusive echocardiographic results. Among patients with "possible" PVE according to modified Duke criteria, ^{18}F-FDG-PET/CTA can help to reclassify them conclusively to either "rejected" or "definite" PVE.

Nuclear medicine imaging techniques examine the whole body. ^{18}F-FDG-PET/CT can be valuable in identifying subclinical extracardiac metastatic infectious lesions such as vertebral osteomyelitis, psoas abscess, pyomyositis, splenic abscess, and septic arthritis, with the exception of septic brain lesions.[184,185]

Identification of the Pathogen

Blood Cultures

Blood cultures remain the most valuable test in establishing the etiologic diagnosis of PVE. In clinically stable patients, at least three sets of blood cultures should be collected before the initiation of antibiotics. Blood cultures can be obtained at any time and are not necessarily timed with fever or chills because the bacteremia in endocarditis is low grade and continuous.[186,187] Growth of the microorganism in blood culture allows one to perform antimicrobial susceptibility testing, which is crucial in the selection of the most effective antibiotic regimen.

Blood cultures are positive in about 78% to 91% of patients with PVE.[32,38,57] Advances in bacterial culture techniques, with prolonged incubation times, presence of carbon dioxide, and use of enriched culture media have improved the yield of blood cultures. However, the prevalence of blood "culture-negative" PVE is still significant. Recent antibiotic administration is the most common cause of blood "culture-negative" PVE.[38] Routine blood cultures may also fail to detect fastidious microorganisms such as HACEK, *Bartonella, Brucella, Abiotrophia, Granulicatella* spp., and noncultivable microorganisms such as *Chlamydia* spp., *Coxiella burnetii, Legionella* spp., *Mycobacterium* spp., *Mycoplasma pneumoniae, Tropheryma whipplei,* and fungi.[188]

Valve Culture

If a patient undergoes surgery, surgical specimens, including vegetations, tissue fragments of bioprosthesis, periprosthetic tissues and abscesses, and embolic fragments, should be sent for histopathologic evaluation and cultures. Cultures of the valves are often negative owing to prior antibiotic administration.[189,190] Valve culture results should be interpreted with caution because contamination during handling from surgical resection to laboratory processing is possible.

Serologic Methods

Serologic methods can be used to complement culture-based methods to identify a pathogen. Modified Duke criteria have included specific serologic data as surrogate markers for positive blood cultures to establish an etiologic diagnosis in "culture-negative" endocarditis. An anti–phase I immunoglobulin G antibody titer of greater than or equal to 1:800 by microimmunofluoresence to *C. burnetii* is a major criterion in the modified Duke criteria for Q fever endocarditis.[154] Serologic tests are available for *Brucella melitensis, Bartonella* spp., *Legionella* spp., *M. pneumoniae,* and *Chlamydia* spp., and an antigen assay for *Aspergillus* spp. may be useful.[191]

Broad-Range Polymerase Chain Reaction Based on the Bacterial 16S rRNA Gene

Approximately 9% to 13% of patients with IE have negative blood cultures, and the rate is higher among patients who had received prior antibiotic therapy.[35,192] Without an identified causative pathogen, it is difficult to select an optimal antimicrobial regimen, often resulting in an empirical broad-spectrum combination regimen that may be suboptimal with a lower success rate while potentially increasing the risk of drug adverse events. Molecular diagnostic methods such as 16S ribosomal RNA (rRNA) polymerase chain reaction (PCR) and sequencing may help to identify the pathogen among the culture-negative IE group.[193] The 16S rRNA genes comprise both highly conserved and variable regions. With use of broad-range PCR primers to amplify the conserved region of 16S rRNA genes, it is theoretically possible to identify a majority of bacterial pathogens.[194] PCR amplification of conserved sequences in the panfungal small subunit rRNA internal transcribed spacer sequence can be used to identify fungal microorganisms.[195] To enable identification of microorganisms at the subspecies level, the highly variable ribosomal intergenic sequences can be targeted for PCR amplification. In addition, this amplification can be extremely useful in defining whether a pathogen has genes that encode for antimicrobial resistance; this would be helpful, for example, in the case of identification of a *Staphylococcus* and whether it is oxacillin resistant. Other genes such as the 23S rRNA, 16S-23S intergenic spacer, and rpoB have been successfully used.[194]

PCR-based techniques have been used to detect microorganisms in blood specimens in addition to resected heart valve tissue.[196–200] Microbial

DNA can be present in valve tissue for several weeks after initiation of an appropriate antimicrobial agent.[198,201]

Studies evaluating user-developed 16S rRNA gene assays have reported a wide range of performance with varying sensitivities (range, 41.2%–100%) and specificities (range, 61.5%–100%) among patients with definite IE.[202] Two commercial assays are available but have been evaluated in only a small number of patients.[203,204] The sensitivity of broad-range 16S rRNA gene PCR assays has been lower among patients with prosthetic valve IE compared with those with native valve IE.[189,192,202] Limitations of molecular methods include potential contamination and cross-reaction of primers within the 16S rRNA gene with human DNA in clinical samples.[202,205] PCR-based methods also do not differentiate between viable and dead microorganisms.

Molecular techniques cannot replace culture-based methods but are additional tools that can be used to improve the etiologic diagnosis of IE. Currently, culture is indispensable for antimicrobial susceptibility testing.

Histology

Histologic examination of resected perivalvular and valvular tissues remains the gold standard for the diagnosis of PVE. Histologic criteria of PVE include demonstration of microorganisms in the resected specimens and pathologic lesions such as vegetations and inflammatory infiltrates, with or without annular abscess.[206] In situ visualization of causative agents in the resected valve specimens can be done with immunohistochemical methods. Autoimmunohistochemistry is an immunohistochemical method in which a patient's own serum is used as a source of antibodies that can be used to detect microorganisms in heart valve specimens.[207] Fluorescence in situ hybridization using fluorescent peptide nucleic acid (PNA) probes can penetrate into gram-positive bacteria within the resected valve tissue and can help to visualize the organism in situ.[208] If histologic examination fails to demonstrate microorganisms and vegetations, computer-assisted quantitative analysis of digitized microscopic images of the inflammatory pattern may assist in differentiating infective and noninfective inflammatory valve processes. Excessive neovascularization and a pattern composed of $CD15^+$ leukocytes exceeding 2% of the mechanical valve surface and exceeding 1.5% of the total bioprosthetic valve surface are highly predictive (90% and 98%, respectively) and specific (90% and 94%, respectively) for an acute infection.[206,209]

The management of PVE consists of effective pathogen-specific antimicrobial therapy and timely surgical intervention, when indicated. TEE is used to assess prosthetic valve function and vegetation size and to identify perivalvular complications that may require surgical intervention. It should be repeated during antimicrobial therapy when clinically indicated to monitor for development of complications of PVE. As discussed earlier, ^{18}F-FDG-PET/CTA can help in the surgical decision process by identifying perivalvular complications that may necessitate urgent surgical intervention.[177]

All patients suspected of having PVE should be hospitalized initially for close clinical monitoring. As previously discussed, pathogen identification, usually by isolation from blood cultures, is critical in defining an optimal treatment regimen. Because the infection is life-threatening, it is reasonable to initiate empirical antimicrobial therapy targeting the most likely pathogens after obtaining at least three sets of blood cultures. It is suggested that the empirical antimicrobial regimen be chosen to target the most likely pathogens of PVE, considering the time of onset of PVE and the likely site of acquisition.

ANTIMICROBIAL THERAPY

In vitro susceptibility testing should be used to define the most effective, pathogen-specific antimicrobial regimen. A microbicidal regimen is preferred for the treatment of PVE. At least two sets of blood cultures should be drawn every 24 to 48 hours until clearance of bloodstream infection is documented.[154] No randomized controlled trials have been conducted to establish the optimal duration of antimicrobial treatment. The duration of antimicrobial therapy is a minimum of 6 weeks and should be counted from the day of first negative blood cultures in culture-positive PVE.[154,183] If the resected valve or tissue culture or both are positive, it is reasonable to administer an entire course of antimicrobial therapy. In regimens that include multiple agents, they should be administered in temporal proximity to achieve maximal synergistic microbicidal effect.

Staphylococcal Prosthetic Valve Endocarditis

The antimicrobial regimens recommended for PVE due to *S. aureus* and CoNS are identical—based mainly on in vitro susceptibility testing (Table 81.1). A triple-drug combination antimicrobial regimen is recommended for the optimal treatment of staphylococcal PVE. The principal drug is a cell wall–active agent, chosen on the basis of methicillin susceptibility.[154] Vancomycin is the principal drug of choice for methicillin-resistant organisms, whereas semisynthetic penicillin (nafcillin, oxacillin) should be chosen for methicillin-susceptible organisms.[154] Cefazolin is used in patients who have a well-defined history of nonanaphylactoid reaction to penicillins. The second drug in combination therapy is rifampin, which is important in the treatment of staphylococcal foreign-body–related infections. In vitro studies, animal models of staphylococcal prosthetic device infections, and clinical studies have provided evidence supporting the role of rifampin in eradicating staphylococci adherent to prosthetic devices.[210–214] Rifampin resistance can easily develop owing to mutation of the ribosomal gene responsible for rifampin site of action.[212] The probability of this mutation and hence selection of rifampin-resistant strains is high when a large, highly dense, rapidly dividing bacterial population is exposed to ineffective rifampin-containing regimens. Hence, it is reasonable to initiate rifampin only after effective two-drug combination antistaphylococcal therapy has been administered for at least 2 days. If the *Staphylococcus* is not susceptible to two other drugs, a single agent can be used for 3 to 5 days before initiation of rifampin. The goal of this strategy is to reduce the number of organisms and hence lower the risk of selection of rifampin-resistant subpopulation. The third drug in the combination regimen is either an aminoglycoside or a fluoroquinolone. Gentamicin is recommended for

TABLE 81.1 Therapy for Prosthetic Valve Endocarditis Caused by Staphylococci, Suggested by the American Heart Association

REGIMEN	DOSAGE AND ROUTE	DURATION
Methicillin-Susceptible Staphylococci		
Nafcillin or oxacillin[a] *Plus*	2 g IV q4h	≥6 wk
Rifampin[b] *Plus*	300 mg PO or IV q8h	≥6 wk
Gentamicin[c]	3 mg/kg IV/IM q24h in 2 or 3 equally divided doses	2 wk
Methicillin-Resistant Staphylococci		
Vancomycin[d] *Plus*	15 mg/kg IV q12h	≥6 wk
Rifampin[b] *Plus*	300 mg PO or IV q8h	≥6 wk
Gentamicin[c]	3 mg/kg IV/IM in 2 or 3 equally divided doses	2 wk

[a]Cefazolin 2 g IV q8h can be used in non–immediate-type allergic reaction to penicillin. Consider skin testing for patients with history of immediate-type allergy to penicillin. Vancomycin is recommended only in patients unable to tolerate penicillins and cephalosporins.
[b]It is recommended to initiate rifampin therapy only after susceptibility results are known and ideally after 2 days of effective combination therapy, in an attempt to reduce the risk of emergence of rifampin resistance.
[c]Gentamicin should be administered in close proximity to vancomycin, nafcillin, or oxacillin to maximize synergy. Renal function and serum gentamicin concentrations should be closely monitored. Goal trough level is <1 μg/mL and peak level (1 h postdose) is 3–4 μg/mL.
[d]Vancomycin dosage should be adjusted to a trough level of 10–20 μg/mL. Dosages recommended are for patients with normal renal function.
From Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis in adults: diagnosis, antimicrobial therapy, and management of complications: a scientific statement for healthcare professionals from the American Heart Association: endorsed by the Infectious Diseases Society of America. Circulation. *2015;132:1435–1486.*

the initial 2 weeks of therapy, although there are only limited clinical data to support this addition. In the case of gentamicin resistance, another aminoglycoside can be substituted if the organism is susceptible. If the organism is resistant to all aminoglycosides or if the patient is intolerant to aminoglycosides, a fluoroquinolone may be used as a substitute if the strain is susceptible.[212,213,215]

In vitro susceptibility testing should be repeated when there is failure of an antimicrobial regimen. Clinical failure with vancomycin therapy for methicillin-resistant *S. aureus* (MRSA) PVE can occur as a result of heterogeneous-type vancomycin-intermediate *S. aureus* (VISA) strains, and the optimal antimicrobial therapy in such cases is unknown.[216] Higher vancomycin minimal inhibitory concentrations (MICs) have been associated with worse clinical outcomes in both patients with MRSA infections treated with vancomycin and those with methicillin-susceptible *S. aureus* infections treated with β-lactams.[217,218] Higher vancomycin MICs may be surrogate markers for undefined host- or pathogen-specific factors that contribute to worse clinical outcome in some patients. Clinical experience is limited in the treatment of PVE with newer agents such as high-dose daptomycin and linezolid.[219–221] The role of ceftaroline or a combination regimen of daptomycin and ceftaroline in the treatment of staphylococcal PVE has yet to be defined. Staphylococcal PVE is often complicated by perivalvular extension or prosthetic valve dysfunction, necessitating surgical intervention for optimal management.

Streptococcal Prosthetic Valve Endocarditis

The antimicrobial regimens recommended by the American Heart Association (AHA) for the treatment of PVE caused by viridans-group streptococci, *Streptococcus gallolyticus,* or other penicillin-susceptible streptococci are listed in Table 81.2. The primary drug for treatment of streptococcal PVE is either penicillin or ceftriaxone, given for a minimum of 6 weeks. For PVE caused by highly penicillin-susceptible streptococci (MIC ≤0.12 μg/mL), the addition of gentamicin for the initial 2 weeks is optional because the combination regimen has not been shown to have superior cure rates compared with β-lactam monotherapy.[154] If the strain does not have high-level gentamicin resistance, intravenous (IV) once-daily gentamicin may be administered for the initial 2 weeks in patients who can tolerate aminoglycosides. For patients with PVE caused by streptococci with relative or high-level penicillin resistance (MIC >0.12 μg/mL), *Gemella, Abiotrophia,* or *Granulicatella* spp., a combination of penicillin or ceftriaxone with gentamicin is recommended for a minimum duration of 6 weeks. It is suggested to continue gentamicin for 6 weeks if the patient can tolerate it without significant nephrotoxicity. Monotherapy with vancomycin for a minimum of 6 weeks is recommended only for patients who cannot tolerate both penicillin and ceftriaxone.

PVE caused by *Streptococcus pneumoniae, Streptococcus pyogenes,* and group B, C, F, and G β-hemolytic streptococci are uncommon. In patients with PVE caused by penicillin-susceptible *S. pneumoniae,* 6 weeks of IV penicillin, cefazolin, or ceftriaxone is recommended. For PVE caused by *S. pneumoniae* with high penicillin resistance (MIC ≥2 μg/mL), 6 weeks of IV therapy—high-dose penicillin, cefotaxime, or ceftriaxone—is recommended. Cefotaxime or ceftriaxone is preferred if *S. pneumoniae* PVE is complicated with meningitis, because these agents have higher penetration into cerebrospinal fluid. In *S. pneumoniae* PVE with resistance to cefotaxime (MIC >2 μg/mL), IV vancomycin and rifampin can be added to cefotaxime or ceftriaxone.

TABLE 81.2 Therapy of Prosthetic Valve Endocarditis Caused by Streptococci as Suggested by the American Heart Association

REGIMEN	DOSAGE AND ROUTE	DURATION	COMMENTS
Penicillin-Susceptible (MIC ≤0.12 μg/mL) Strain of Viridans-Group Streptococci, *Streptococcus gallolyticus (bovis)*			
Either			Gentamicin is optional. Combination of penicillin or ceftriaxone with gentamicin has not been shown to be superior to monotherapy. Gentamicin should not be administered if creatinine clearance is <30 mL/min.
Aqueous crystalline penicillin G	24 million units/24 h IV, either continuously or in 4–6 equally divided doses	6 wk	
Or			
Ceftriaxone	2 g IV/IM q24h	6 wk	
With or without			
Gentamicin	3 mg/kg IM or IV single daily dose	2 wk	
Relatively or Fully Resistant to Penicillin (MIC >0.12 μg/mL) Strain of Viridans-Group Streptococci and *Streptococcus gallolyticus (bovis)*			
Either			Ampicillin 2 g IV q4h is a reasonable option if there is shortage of penicillin. See below for patients with β-lactam allergy.[a]
Aqueous crystalline penicillin G	24 million units/24 h IV, either continuously or in 4–6 equally divided doses	6 wk	
Or			
Ceftriaxone	2 g IV/IM q24h	6 wk	
Plus			
Gentamicin	3 mg/kg IM or IV single daily dose	6 wk	

[a]Monotherapy with IV vancomycin 15 mg/kg q12h for 6 wk is recommended only for patients unable to tolerate penicillin and ceftriaxone.
MIC, Minimal inhibitory concentration.
Dosages recommended are for patients with normal renal function.
From Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis in adults: diagnosis, antimicrobial therapy, and management of complications: a scientific statement for healthcare professionals from the American Heart Association: endorsed by the Infectious Diseases Society of America. Circulation. *2015;132:1435–1486.*

Enterococcal Prosthetic Valve Endocarditis

The regimens recommended by the AHA for the treatment of enterococcal PVE are listed in Table 81.3. In contrast to streptococci, enterococci are relatively resistant to treatment with penicillin, ampicillin, or vancomycin, and monotherapy is not bactericidal. The synergistic effect achieved by combination of a cell wall agent (penicillin, ampicillin, or vancomycin) with an aminoglycoside is bactericidal against susceptible strains of enterococci.[222]

Enterococci are relatively impermeable to aminoglycoside, but cell wall–active agents increase this permeability, producing synergistic bactericidal effects. For synergism, the strain should be susceptible to the cell wall–active agent and not have high-level resistance to the aminoglycoside. High-level resistance is defined as growth at high concentrations of aminoglycoside (500 μg/mL of gentamicin or 1000 μg/mL of streptomycin).[154] All enterococci should be tested for susceptibility to cell wall–active agents (penicillin and vancomycin), and for high-level aminoglycoside resistance (both gentamicin and streptomycin). For susceptible strains, the combination of penicillin or ampicillin with gentamicin for 6 weeks has been the preferred regimen for several decades. However, aminoglycoside-containing regimens have higher risk of nephrotoxicity, especially in elderly patients with enterococcal PVE who also have multiple comorbidities. Guidelines have included a dual β-lactam option with ampicillin plus ceftriaxone (2 g IV every 12 hours) as a treatment regimen that should be administered for 6 weeks. If an aminoglycoside-containing regimen is chosen, the aminoglycoside should be given in multiple divided doses each day. Once-daily aminoglycoside administration has not been demonstrated to be as effective as multiple-daily administration in enterococcal endocarditis. Hence, in contrast to streptococcal PVE, once-daily administration is not recommended for enterococcal PVE. For patients with normal renal function, gentamicin should be administered every 8 hours.[223] The serum concentrations should be monitored closely, especially in patients with reduced renal function. The dosage should be adjusted to achieve a 1-hour serum concentration of approximately 3 μg/mL and a serum trough concentration of less than 1 μg/mL. A higher dosage of gentamicin increases the risk of nephrotoxicity without providing any additional enhanced bactericidal effect on enterococci.[224] About one-third of high-level gentamicin-resistant strains are susceptible to high levels of streptomycin and can be used for achieving synergy with cell wall–active agents.[224,225] Streptomycin is not favored owing to the higher risk of ototoxicity and the extremely limited availability of serum drug

TABLE 81.3 Therapy of Prosthetic Valve Endocarditis Caused by Enterococci as Suggested by the American Heart Association

REGIMEN	DOSAGE AND ROUTE	DURATION	COMMENTS
Enterococci Susceptible to Penicillin, Gentamicin, and Vancomycin			
Either ampicillin	2 g IV q4h	6 wk	Recommended for patients with renal clearance >50 mL/min. Vancomycin 15 mg/kg IV q12h can be substituted for ampicillin or penicillin only in patients unable to tolerate penicillin and ampicillin.
Or Aqueous crystalline penicillin G	18–30 million units/24 h, either continuously or in 6 equally divided doses	6 wk	
Plus Gentamicin[a]	1 mg/kg IV or IM q8h	6 wk	
Or Double β-Lactam Regimen—Ampicillin *Plus*	2 g IV q4h	6 wk	Double β-lactam regimen is recommended for patients with renal clearance <50 mL/min.
Ceftriaxone	2 g IV q12h	6 wk	
Enterococci Resistant to Penicillin but Susceptible to Gentamicin and Vancomycin *β-Lactamase–Producing Strain*			
Ampicillin-sulbactam *Plus*	3 g IV q6h	6 wk	β-Lactamase–producing strains of enterococci are extremely rare. Confirmation will be necessary before selecting ampicillin-sulbactam as part of the treatment regimen. Vancomycin 15 mg/kg IV can be substituted for ampicillin-sulbactam in patients unable to tolerate ampicillin-sulbactam.
Gentamicin[a]	1 mg/kg IV or IM q8h	6 wk	
Intrinsic Penicillin Resistance			
Vancomycin *Plus*	15 mg/kg IV q12h	6 wk	Monitor renal function closely.
Gentamicin[a]	1 mg/kg IV or IM q8h	6 wk	
Enterococci Resistant to Penicillin, Aminoglycoside, and Vancomycin			
Linezolid *Or*	600 mg IV or PO q12h	≥6 wk	Monitor for myelosuppression, neuropathy, and drug interactions.
Daptomycin	10–12 mg/kg IV q24h	≥6 wk	Severe myalgia may occur.
Enterococci Susceptible to Penicillin, Resistant to Aminoglycosides, or Gentamicin Resistant and Susceptible to Streptomycin			
Ceftriaxone sodium *Plus*	2 g IV/IM q12h	≥6 wk	Streptomycin may be used along with ampicillin if renal clearance >50 mL/min, normal eighth cranial nerve function, and availability of rapid streptomycin serum concentration testing.
Ampicillin sodium	2 g IV q4h	≥6 wk	

[a]Gentamicin should be given in 3 divided doses rather than a single daily dose.
Dosages recommended are for patients with normal renal function.
From Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis in adults: diagnosis, antimicrobial therapy, and management of complications: a scientific statement for healthcare professionals from the American Heart Association: endorsed by the Infectious Diseases Society of America. Circulation. *2015;132:1435–1486.*

assay–monitoring capacity. Streptomycin should be avoided if renal clearance is less than 50 mL/min. Streptomycin should be administered every 12 hours in patients with normal renal function. The dosage should be adjusted to achieve a 1-hour serum concentration of 20 to 30 μg/mL and a trough concentration of less than 10 μg/mL.[224]

Double β-lactam combinations (ceftriaxone or cefotaxime or imipenem plus ampicillin) have been shown to have synergistic bactericidal activity against *E. faecalis* strains and have been considered as an alternative regimen for strains with high-level resistance to gentamicin and streptomycin but susceptible to penicillin.[226] An observational, nonrandomized, multicenter cohort study compared ampicillin plus ceftriaxone combination with ampicillin plus gentamicin for treatment of IE caused by *E. faecalis,* including 89 cases of *E. faecalis* PVE. The study did not find any difference in mortality, treatment failure, or relapse between the two groups, but the rate of interruption of antibiotic treatment due to adverse events (renal failure, elevation in creatinine) was higher in patients receiving ampicillin plus gentamicin. The authors concluded that the double β-lactam combination (ampicillin plus ceftriaxone) can be used safely to treat IE caused by both susceptible and high-level aminoglycoside-resistant strains of *E. faecalis.*[227]

For PVE caused by enterococci that are intrinsically resistant to penicillin but susceptible to aminoglycoside and vancomycin, a combination regimen of vancomycin with aminoglycoside for 6 weeks is suggested. Renal function should be closely monitored because this combination has a higher risk of renal toxicity. In extremely rare strains of *E. faecalis,* penicillin resistance may be due to inducible β-lactamase production rather than alteration in penicillin-binding proteins. For these β-lactamase–producing strains, ampicillin-sulbactam is the preferred cell wall–active agent, and vancomycin is recommended only for those who cannot tolerate ampicillin-sulbactam.[154]

Therapeutic options are limited in patients with PVE caused by enterococci that are resistant to penicillin, aminoglycoside, and vancomycin. Only case reports of treatment success with linezolid, quinupristin-dalfopristin, and daptomycin have been reported.[228–230] Combination therapy of ampicillin with daptomycin even in cases of ampicillin resistance might be a potential salvage regimen in patients unable to undergo surgery.[231,232] In patients with PVE caused by strains for which there is no effective bactericidal regimen, surgical intervention with valve replacement followed by a long (at least 8-week) course of postoperative antimicrobial therapy may be considered.

HACEK Prosthetic Valve Endocarditis

The regimens recommended by the AHA for treatment of HACEK PVE are listed in Table 81.4. Ceftriaxone or ampicillin-sulbactam is recommended as the preferred initial agent until susceptibility data are available because strains resistant to ampicillin due to β-lactamase production are increasing in frequency.[154] Fluoroquinolones have activity against HACEK organisms in vitro, but clinical efficacy data are limited. Antimicrobial therapy alone usually results in successful treatment of HACEK PVE if there is no perivalvular complication or valve dysfunction.[233]

Diphtheroid Prosthetic Valve Endocarditis

Diphtheroids are members of *Corynebacterium* species that are usually nonpathogenic commensals of the skin and mucous membranes (other

TABLE 81.4 Therapy of Prosthetic Valve Endocarditis Caused by HACEK as Suggested by the American Heart Association

REGIMEN	DOSAGE AND ROUTE	DURATION
Ceftriaxone *Or*	2 g q24h	6 wk
Ampicillin	2 g IV q4h	6 wk
Ciprofloxacin[a]	500 mg PO or 400 mg IV q12h	6 wk

HACEK, Haemophilus parainfluenzae, Aggregatibacter aphrophilus, Aggregatibacter actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens, and *Kingella* spp.
[a]Ciprofloxacin is recommended only for patients unable to tolerate cephalosporin and ampicillin-sulbactam.
Dosages recommended are for patients with normal renal function.

than *Corynebacterium diphtheriae*) but have been known to cause PVE. Combination of penicillin or ampicillin with gentamicin for a minimum of 6 weeks is the recommended regimen for PVE caused by strains of diphtheroids (*Corynebacterium* spp.) that are susceptible to both penicillin and gentamicin. If the strain is resistant to gentamicin or penicillin, bactericidal synergism is not possible.[234] In patients with PVE caused by diphtheroid strains that are resistant to either penicillin or gentamicin and in patients who cannot tolerate penicillin, monotherapy with vancomycin for at least 6 weeks is recommended.

Enteric Gram-Negative Bacillary Prosthetic Valve Endocarditis

For PVE caused by enteric gram-negative bacilli, the optimal antibacterial regimen should be selected based on in vitro susceptibility tests.[154,183] Whenever possible, the combination of two effective agents should be administered for at least 6 weeks. In patients with PVE caused by multidrug-resistant gram-negative bacilli or *Pseudomonas* spp., surgical débridement and replacement of the infected valve followed by antimicrobial therapy is recommended.[235]

Fungal Prosthetic Valve Endocarditis

Candida spp. is the predominant pathogen that causes fungal PVE. Fungal PVE is associated with high rates of treatment failure, relapse, and mortality. Large, dense vegetations and frequent embolic events are characteristic features. Medical therapy alone is not sufficient to cure fungal PVE. Early surgical intervention is recommended by most authorities to improve survival and cure rate of fungal PVE.[70,154] Fungal PVE can recur even after this aggressive combined surgical-medical intervention, and prolonged, possibly lifelong suppressive therapy with oral antifungal agents is recommended by some experts.[70,81,236–239] If surgical intervention is not feasible, lifelong suppressive therapy is suggested. The antifungal regimen should be based on the fungal species and in vitro susceptibility data. Amphotericin B has been the drug of choice for fungal PVE for a long time. Lipid formulations of amphotericin have less nephrotoxicity and can be used. Echinocandins have been used in patients who cannot tolerate an amphotericin B formulation.[70] In a few case reports, combination antifungal therapy (e.g., caspofungin plus fluconazole, amphotericin B plus fluconazole) successfully cured candidal PVE without surgical intervention.[238,240,241]

Prosthetic Valve Endocarditis Due to Nontuberculous Mycobacteria

Rapidly growing NTM *(M. fortuitum, M. chelonae, Mycobacterium abscessus)* may cause PVE as a result of nosocomial acquisition and should be suspected in culture-negative PVE because blood cultures may be negative in as many as 40% of patients with NTM PVE.[92,242,243] The treatment of PVE due to NTM is poorly defined and often involves early surgical replacement of the infected prosthetic valve followed by several months of combination antibiotic therapy.[244–246] Antimicrobial regimens should be chosen based on identification and in vitro susceptibility testing of NTM isolates, despite the well-known limitations.[247] Combination of at least two active drugs (amikacin, carbapenems, macrolides, and fluoroquinolones) is suggested, and optimal duration of treatment is unknown. Relapse of NTM bacteremia can occur after discontinuation of antibiotics, prompting the suggestion of lifelong suppression by some authors.[245]

Culture-Negative Prosthetic Valve Endocarditis

The treatment regimen for culture-negative PVE should cover the most likely pathogens, considering prior antibiotic use, time of onset of PVE, and clinical and local epidemiologic clues. For early-onset PVE (<1 year after prosthetic valve surgery), the recommended empirical regimen includes vancomycin, gentamicin, cefepime, and rifampin, aiming to cover staphylococci, enterococci, and aerobic gram-negative bacilli including *Pseudomonas* spp.[154] Late onset of PVE (>1 year after prosthetic valve surgery) is usually caused by staphylococci, viridans-group streptococci, or enterococci. For late-onset PVE, AHA and Infectious Diseases Society of America guidelines suggest a combination of vancomycin and ceftriaxone.[154] In cases of suspected *Bartonella* PVE, empirical treatment with ceftriaxone, gentamicin, and doxycycline is recommended. Uncommon pathogens such as *Bartonella* spp., *Brucella* spp., *C. burnetii, Chlamydia* spp., *Legionella* spp., *T. whipplei,* NTM, and fungi should also be considered on the basis of clinical and epidemiologic clues (Table 81.5).[205,248,249] If there is no clinical improvement with an empirical regimen, surgical intervention for resection of the infected valve and obtaining samples for microbiologic and histopathologic evaluation should be considered.

SURGICAL INTERVENTION

Indications for Surgical Intervention

Current guidelines recommend surgical intervention in patients with hemodynamic instability, heart failure, and significant valve dysfunction or perivalvular complications.[154,250] Among those PVE patients with persistent bloodstream infection with antimicrobially resistant pathogens or those with a persistent large vegetation (>1 cm) after an embolic event, surgical intervention has been suggested as an option. Approximately 42% to 49% of patients with PVE undergo surgical interventions.[38,251] No randomized controlled trial has been conducted to evaluate the optimal management of PVE, so the recommended indications for surgical intervention in patients with PVE are based on data from observational studies, cohort studies, and expert opinion.[252] Some authorities recommend surgical intervention for all patients with mechanical PVE, and surgical intervention has been noted to be associated with higher survival rates than historical controls in some studies.[252–254] In an international prospective database of 1025 patients with PVE, 490 (47.8%) underwent surgical intervention during their index hospitalization, and early surgery was associated with lower in-hospital mortality in the unadjusted analysis and after controlling for selection bias.[255] However, analysis after adjustment for survivor bias did not show benefit with surgical intervention in in-hospital and 1-year mortality rates compared with rates in patients who were managed with medical therapy alone.[255] A systematic review and meta-analysis of 32 studies (retrospective or observational) analyzed 2636 patients with definite PVE to compare medical and surgical management.[256] The surgical intervention group included 1320 patients, was significantly younger, and had a higher number of men and patients with heart failure, prosthetic valve vegetation and perivalvular complications. The medical therapy group included 1316 patients and had a significantly higher number of patients with PVE due to *S. aureus.* Aortic PVE was the most common entity, and there was no significant difference between the two groups in incidence of early IE, fungal endocarditis, or embolic events. The mean time from diagnosis of PVE to surgical intervention was 16 days; follow-up data were available in 14 studies, with a mean duration of 22 months. In the pooled analysis, lower 30-day mortality (25% vs. 34%; relative risk [RR], 0.73) and higher survival at follow-up (69% vs. 58%; RR, 1.27) were noted in the surgical intervention group, mainly driven by data from the more recent studies (published after year 2000). There was no significant difference in the relapse rate of PVE between the two groups.[256] It should be noted that the surgical group had a higher prevalence of heart failure and paravalvular complications for which surgical intervention is recommended in the current guidelines. The results of the meta-analysis appear to support those

TABLE 81.5 Epidemiological Clues to Consider in Selecting Empirical Regimen for Culture-Negative Prosthetic Valve Endocarditis

EPIDEMIOLOGIC CLUE	ORGANISMS
Early-onset (≤1 year) PVE	Coagulase-negative staphylococci (CoNS), *Staphylococcus aureus,* aerobic gram-negative bacilli, fungi, *Corynebacterium* species, *Legionella* species
Late-onset (>1 year) PVE	CoNS, *S. aureus,* viridans-group streptococci, *Enterococcus* species, fungi, *Corynebacterium* species
Intravenous drug use	*S. aureus*, CoNS, β-hemolytic streptococci, fungi, gram-negative bacilli including *Pseudomonas aeruginosa*
Indwelling vascular device	*S. aureus*, CoNS, gram-negative bacilli, *Corynebacterium* species
Genitourinary disorders, infection, and manipulation	*Enterococcus* species, Group B streptococci, gram-negative bacilli, *Neisseria gonorrhea*
Chronic skin disorders	*S aureus*, β-hemolytic streptococci
Poor dental health, dental procedures	Viridans-group streptococci, nutritionally variant streptococci, *Abiotrophia defectiva Granulicatella* species, *Gemella* species, HACEK organisms
Alcoholism, cirrhosis	*Bartonella* species, *Aeromonas* species, *Listeria* species, *Streptococcus pneumoniae,* β-hemolytic streptococci
Diabetes mellitus	*S. aureus,* β-hemolytic streptococci, *S. pneumoniae*
Burn	*S. aureus,* gram-negative bacilli including *P. aeruginosa*, fungi
Dog or cat exposure	*Bartonella* species, *Pasteurella* species, *Capnocytophaga* species
Exposure to contaminated milk or infected farm animals	*Brucella* species, *Coxiella burnetii, Erysipelothrix* species
Homelessness, body lice	*Bartonella* species
AIDS	*Salmonella* species, *S. pneumoniae, S. aureus*
Pneumonia, meningitis	*S. pneumoniae*
Solid organ transplantation	*S. aureus, Aspergillus fumigatus, Enterococcus* species, *Candida* species
Gastrointestinal lesions	*Streptococcus gallolyticus (bovis), Enterococcus* species, *Clostridium septicum*

HACEK, Haemophilus parainfluenzae, Aggregatibacter aphrophilus, Aggregatibacter actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens, and *Kingella* spp.
Modified from Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis in adults: Diagnosis, antimicrobial therapy, and management of complications: a scientific statement for healthcare professionals from the American Heart Association: endorsed by the Infectious Diseases Society of America. Circulation. *2015;132:1435–1436.*

TABLE 81.6 Indications for Consideration of Surgical Intervention

- Severe heart failure; mild-moderate heart failure unresponsive to medical therapy
- Valvular dehiscence, obstruction, or leaflet perforation
- Perivalvular extension of infection leading to myocardial abscess, fistula, or shunt
- New severe conduction defects suggestive of perivalvular extension
- Multiple (>1) systemic emboli despite appropriate antimicrobial therapy
- Uncontrolled infection—persistent fever and positive blood cultures for >5 days
- Fungus, *Pseudomonas* spp., or other multidrug-resistant organisms

recommendations. It remains unclear whether patients with persistent bloodstream infection (>7 days) or a large vegetation (>1 cm) without other complications would benefit from early valve surgery. The decision for surgical intervention should be individualized for each patient after careful risk-benefit analysis (Table 81.6).

Severe Heart Failure Due to Prosthetic Valve Dysfunction

Severe heart failure can be due to prosthetic valve dehiscence, cusp leak, perivalvular leak, intracardiac shunt, or valvular stenosis or obstruction by large vegetations. TEE is useful to assess the etiology of heart failure. Heart failure is independently associated with higher mortality, and early surgical intervention improves in-hospital and 1-year survival rates.[257] Medical management may be attempted for minimal or mild heart failure symptoms due to ventricular dysfunction. Urgent surgical intervention should be strongly considered for patients with severe heart failure, valve dehiscence, and perivalvular leak or for those whose condition did not improve with medical management. Patients with moderate-to-severe heart failure due to valve dehiscence rarely survive for more than a few months without surgical intervention.[148,253,254] Surgical intervention should not be delayed to prolong the preoperative antimicrobial regimen in an attempt to reduce the rate of postoperative infection because this strategy increases operative mortality and also does not reduce the rate of postoperative infection.[258–260] Patients with moderate-to-severe heart failure due to prosthetic valvular obstruction, insufficiency, or valvular perforation should undergo urgent surgical intervention.

Perivalvular Extension of Infection

Perivalvular extension of the infection is common in early PVE, staphylococcal PVE, infection of the mechanical valves, and aortic prosthesis.[38,141,261] TEE is the echocardiographic modality of choice to evaluate for perivalvular complications such as perivalvular abscess, pseudoaneurysm, shunt, and fistulas. TTE does not adequately evaluate for perivalvular complications. ^{18}F-FDG-PET/CT shows promise in identification of perivalvular complications of PVE. Even if the initial TEE is negative for perivalvular invasive infection, patients should be monitored carefully during antimicrobial therapy for development of any new clinical signs suggestive of perivalvular complications. Persistent fever or bacteremia, or both, despite appropriate antimicrobial therapy, and new-onset conduction block are suggestive of perivalvular invasive infection, and TEE should be repeated promptly. Early surgical intervention is indicated in patients with perivalvular invasive infection because these patients are associated with higher mortality and rarely cured with antibiotics alone.[262–265]

High-Grade Pathogens

Patients with early-onset PVE caused by *S. aureus, Staphylococcus lugdunensis,* or CoNS have a higher prevalence of perivalvular complications, which are associated with a high mortality rate with medical therapy alone.[27,266–268] Hence, many authorities have recommended early surgical intervention in these patients.[269–271] PVE due to *S. aureus* is associated with poorer outcomes, and some experts have recommended early valve surgery in all patients, even those without perivalvular complications or heart failure due to structural valve damage.[252,270,272] However, this topic is still debatable, and one study concluded that early valve surgery is indicated only for those with perivalvular complications or heart failure.[266] Chirouze and colleagues analyzed 168 patients with definite PVE due to *S. aureus* in the prospectively collected international endocarditis database.[273] As previously well documented, *S. aureus* PVE was associated with higher 1-year mortality compared with PVE due to other organisms (48.2% vs, 32.9%; $P = .003$), and a higher frequency of stroke and prosthetic dehiscence. After adjusting for propensity factors, prognostic comorbidity metrics, and survival bias, there was no benefit in in-hospital or 1-year mortality with early valve surgery.[273] Limitations of study size and the observational nature of the study precluded any identification of a subgroup of *S. aureus* PVE patients who might benefit from early valve surgery. With the available data, it is reasonable to recommend that all patients with *S. aureus* PVE be evaluated carefully for valvular damage, perivalvular complications, and heart failure, and a decision for early valve surgery should be made by a multidisciplinary team after carefully weighing

the patient's individual characteristics. Early valve surgery may not be essential for all patients with PVE due to *S. aureus*; medical management alone may suffice for patients without heart failure or intracardiac complications. In a subgroup analysis of a meta-analysis that included five studies of patients with *S. aureus* PVE, surgical intervention was shown to be beneficial with lower 30-day mortality (31% vs. 48%; RR, 0.65) and higher survival at follow-up (78% vs. 29%; RR, 2.58).[256] If the patient is clinically stable and the initial TEE evaluation is negative for perivalvular complications, medical management can be attempted with careful clinical monitoring. Serial TEE and close follow-up after completion of antimicrobial therapy should be done to look for signs of relapse of infection and/or valve dehiscence. Patients with *Pseudomonas* PVE also require surgical intervention if medical therapy fails. Surgical intervention is indicated when an effective bactericidal antimicrobial regimen is unavailable for patients with PVE caused by multidrug-resistant gram-negative bacilli or vancomycin-resistant or aminoglycoside-resistant enterococci. Fungal PVE caused by *Candida* or *Aspergillus* spp. is rarely cured by antimicrobial treatment alone, and surgery is usually indicated.[70,274] Many experts recommend surgery for PVE caused by *Coxiella* and *Brucella* spp.

Late-onset PVE caused by community-acquired pathogens, including viridans-group streptococci, other streptococci, enterococci, CoNS, and HACEK group microorganisms, has a more indolent clinical presentation, usually without perivalvular extension, and can often be managed with antimicrobial therapy alone.[149,262,264] Surgery is also indicated in relapse of PVE, especially if caused by staphylococci or gram-negative bacilli.

Multiple Emboli

In patients with IE, larger vegetations (>10 mm) and those on the anterior mitral valve are noted to be associated with a higher frequency of cerebral embolism.[275,276] In one study, the risk of embolization was noted to rise with larger vegetation size, particularly in staphylococcal and mitral valve endocarditis.[277] Increase in size of vegetation during appropriate antibiotic therapy was associated with a higher risk of an embolic event.[277] In a contemporary, multinational, prospective registry, about 34% of patients with PVE developed stroke.[38] In NVE, the risk of embolization declines rapidly with antimicrobial therapy and reaches a low-risk state by 2 weeks.[276] A study concluded that early surgical intervention in patients with NVE and a large vegetation (>10 mm) is associated with a lower rate (3% vs. 28%) of composite end point of all-cause death, embolic events, or recurrence of IE at 6 months.[278] However, surgery to remove a large vegetation to prevent stroke is still controversial and not recommended when no other indication for surgery is present. Similar to NVE, recurrent emboli and persistent vegetation after embolism despite effective antimicrobial therapy are indications for surgery in PVE.[262,279]

Timing of Surgery

The optimal timing of surgical intervention is not clearly defined, and the question is not answered by the available data. The surgical mortality rate increases with the degree of heart failure, hemodynamic instability, and renal and other organ dysfunction.[258,279] If a patient has severe heart failure and hemodynamic instability owing to prosthetic valve dehiscence, perivalvular leak, valvular obstruction, or fistula, surgical intervention should be done promptly. Delaying surgery for additional days of antibiotics worsens the survival rate and does not reduce the postoperative reinfection rate of the new prosthetic valve. The rate of postoperative PVE is low, even if the blood cultures are positive on the day of surgical débridement and placement of the new prosthesis.[280] In patients who do not require urgent surgical intervention, efforts should be made to medically optimize their cardiopulmonary status before surgery. Surgery should be performed once comorbid conditions are stabilized. If the comorbid conditions do not improve promptly, surgery should not be delayed.

Timing of Surgery in Patients With Central Nervous System Embolism

Neurologic complications may worsen owing to systemic heparinization and hypotension associated with cardiopulmonary bypass.[281] Embolic stroke can turn into hemorrhagic stroke during cardiopulmonary bypass and heparinization, resulting in high morbidity and mortality. The frequency of neurologic complication is high (40%) if surgery is performed within 1 week after embolic stroke. The risk diminishes to 10% if surgery is performed 10 to 15 days after stroke.[253] Hence, surgery should be delayed for 3 to 4 weeks after a central nervous system (CNS) embolic event if the patient is hemodynamically stable. However, if the patient develops severe heart failure, hemodynamic instability, or multiple emboli, surgery should be performed without delay.

Surgical Treatment

The goals of surgical intervention are to eliminate intracardiac foci of infection with radical débridement[282–285] and to restore hemodynamic stability by placement of a new prosthesis. Extensive débridement and resection of all infected valvular and perivalvular tissues are important to reduce the risk of reinfection of the newly implanted prosthesis. Major reconstruction of aortic and/or mitral annuli and left ventricular outflow tract (LVOT) may be needed after extensive débridement. Biologic tissues such as autologous pericardium, glutaraldehyde-fixed bovine pericardium, and pulmonary or aortic autograft have been preferred for use in the reconstruction. Abscess cavities are closed with a pericardial patch or filled with gelatin-resorcin-formol or gentamicin-saturated fibrin glue.[286] In complicated aortic PVE with abscesses, reconstruction of the aortic root and LVOT is usually done with a cryopreserved aortic allograft.[263,287] It is useful in patients with complicated PVE requiring extensive débridement because the allograft can be molded to replace valve and débrided tissue, restore continuity, and produce excellent hemodynamic performance.[287] The risk of postoperative infection is also lower with an aortic allograft because it is a biologic material without a prosthetic sewing ring and thus likely more resistant to infection than a mechanical prosthesis or Dacron graft.[286] The main disadvantage of a cryopreserved aortic allograft is its time-limited durability. Some have reported development of significant aortic valve regurgitation more than 5 years after implantation. Stentless bioprostheses, such as the Toronto stentless porcine valve (St. Jude, Minneapolis, MN) and Freestyle valve (Medtronic, Minneapolis, MN), are increasingly used as substitutes for aortic allografts in aortic PVE with perivalvular abscesses, with good results. Mechanical and bioprosthetic valves have also been used in aortic PVE after extensive débridement. The rate of recurrent endocarditis was 2.5% with no statistical difference between mechanical and bioprosthetic valves in one survey.[288]

Both mechanical and bioprosthetic valves have been used as replacements in mitral PVE with no difference in recurrent infection or long-term event-free survival rates.[288,289] Mitral homografts do not have synthetic material and hence may be more resistant to postoperative infection in the setting of mitral PVE.[286]

Outcome of Patients Treated Surgically for Prosthetic Valve Endocarditis

The reported mortality rate for surgery in PVE is 4% to 30%.[284,285,290,291] Earlier surgical intervention in complicated PVE, facilitated by early identification of valve dehiscence and perivalvular abscess through use of TEE, improved surgical techniques, use of cryopreserved aortic grafts, more effective combination antimicrobial therapy, and advancements in postoperative critical care, has resulted in better PVE survival rates. The overall long-term (>10-year) survival rate has been reported to be 41% to 73%, which is significantly better than the expected 100% mortality rate in patients with complicated PVE treated medically.[284,286] The overall rate of recurrent PVE (relapse or reinfection) after surgery is 6% to 15%.[292] The cryopreserved aortic allografts have a lower incidence of early postoperative infection and reinfection compared with mechanical valves or xenografts.[263,293] About 18% to 26% of patients who undergo new valve implantation require reoperation because of either sterile prosthetic valve dysfunction or recurrent PVE.[290,292,294]

Duration of Antimicrobial Therapy Postoperatively

Dead microorganisms and evidence of active inflammation (presence of polymorphonuclear leukocytes [PMLs]) may persist for weeks to months after microbiologic cure.[295] Positive Gram stain or PCR results may be due to nonviable microorganisms. If the culture of the resected

valve or perivalvular tissue is positive, the consensus is that patients might benefit from a full course of appropriate antimicrobial therapy after surgery, discounting the preoperative antibiotic course. If the surgical cultures are negative, then the recommended duration of antimicrobial therapy may include the preoperative antibiotic course (counting from the day of the first negative blood culture). Lifelong oral suppressive antifungal therapy is recommended for patients with fungal PVE after a full course of IV antifungal therapy.[274]

ANTICOAGULATION THERAPY

Chronic anticoagulation is required for patients with mechanical prostheses in order to prevent thromboembolic events.[296] Anticoagulation may be continued with close clinical monitoring in the setting of mechanical PVE because there is substantial risk of thromboembolism if discontinued.[297] In a recent analysis of eight studies evaluating the role of anticoagulation in mechanical PVE, the aggregate risk of thromboembolism was noted to be significantly higher in those patients without anticoagulation (42% vs. 11%; $P < .0001$), suggesting that anticoagulation reduced the risk of thromboembolism without any significant increase in the risk of cerebral hemorrhage.[298] If a patient develops a CNS septic embolic event, anticoagulation should be reversed because there is increased risk of hemorrhagic transformation of the embolic infarct and subsequent extension of hemorrhage. Once the patient is clinically stable and there is no further extension of the cerebral hemorrhage, anticoagulation might be resumed cautiously with IV unfractionated heparin or an antiplatelet drug. Patients with a bioprosthetic valve do not require chronic anticoagulation therapy. In the setting of bioprosthetic PVE, anticoagulation does not have additional benefit in preventing septic emboli and it should not be initiated unless there are other independent medical indications for anticoagulation therapy.

In *S. aureus* left-sided PVE, anticoagulation therapy is associated with increased risk of death due to neurologic complications.[299] Many experts suggest discontinuation of all anticoagulation in those who experience a stroke until they have received at least 2 weeks of antibiotic therapy.[154]

Prior long-term administration of antiplatelet and/or statin drugs before the onset of IE may reduce symptomatic embolic events.[300–302] However, in a randomized, double-blinded, placebo-controlled trial, aspirin initiated after the diagnosis of IE did not reduce risk of embolic events and was likely associated with increased risk of bleeding.[303] Therefore, initiation of aspirin or statin in established IE to prevent thromboembolic events is currently not recommended.

PREVENTION

PVE is an uncommon but life-threatening infection with a high mortality rate despite appropriate medical and surgical interventions. It is essential to make every effort to prevent this devastating complication of cardiac valve replacement surgery. The prevention strategies should take into consideration the mode of acquisition of the infection and the likely pathogens involved.

Early-onset PVE is acquired likely as a result of perioperative contamination of the prosthetic valve or secondary seeding from a distant focus of infection such as an IV catheter or wound infection. The main tools to prevent early-onset PVE are perioperative antibiotic surgical site infection prophylaxis, infection-control measures, and improvements in surgical techniques. Perioperative antimicrobial prophylaxis should be administered intravenously within 1 hour before operation and repeated if the procedure is prolonged, in order to ensure maximal tissue drug levels during the entire procedure. Prophylaxis should be discontinued within 48 hours to reduce emergence of antimicrobial resistance and drug toxicity.[304–306] The standard perioperative prophylactic regimen is a first-generation cephalosporin (targeting *S. aureus* and CoNS), but it might be individualized on the basis of the local hospital susceptibility pattern and the patient's colonizing microbiota. The addition of vancomycin to cefazolin should be considered in certain situations: high prevalence of methicillin-resistant staphylococci in the hospital; patients with high risk for MRSA infection (elderly, diabetic); and patients with known MRSA colonization. It is also used in patients who cannot tolerate cephalosporins.[306,307] Some studies have suggested that preoperative screening for MRSA carriers and intranasal mupirocin may be effective in preventing postoperative MRSA surgical site infections.[308,309] The usefulness of preoperative chlorhexidine bathing is still unresolved.[310] Institutional infection-control practices should be updated regularly on the basis of new evidence and guidelines from national authorities. Early PVE usually starts in the sewing cuff–tissue interface, and impregnation of the prosthetic valve sewing cuffs with antimicrobial agents has been suggested as a preventive strategy.[311–314] In 1998 St. Jude Medical introduced prosthetic valves with silver-impregnated sewing cuffs (Silzone), designed to inhibit microbial attachment and colonization. But the product was withdrawn from the market when a significantly higher incidence of paravalvular leakage was noted in a large multicenter prospective randomized trial.[315] Increased risk of embolism during the early period was also observed in patients with Silzone valves in the mitral position.[316] It has been postulated that silver coating inhibited fibroblast growth, endothelialization of the prosthetic sewing ring, and healing, resulting in annular tissue necrosis, dehiscence, and paravalvular leakage.[316]

Late-onset PVE acquired in the community is usually caused by endogenous microbiota such as viridans-group streptococci and enterococci. Patients with prosthetic valves are considered to be a high-risk group.[317] Although there has been no randomized, placebo-controlled trial to define the efficacy and safety of antibiotic prophylaxis, there are recommendations for using it for dental procedures that involve manipulation of the gingival or periapical region of teeth or perforation of oral mucosa and during procedures on the respiratory tract, infected skin or skin structures, and musculoskeletal tissue.[317] Patients should undergo dental evaluation before valve surgery and be educated that good oral hygiene is important to prevent late-onset community-acquired PVE caused by oral pathogens. The proportion of late-onset PVE attributed to health care exposure is increasing; therefore, strict infection-control practices and careful evaluation of the need for central venous catheter use or continuation are important in its prevention.

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82 Infections of Nonvalvular Cardiovascular Devices

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SHORT VIEW SUMMARY

CARDIOVASCULAR IMPLANTABLE ELECTRONIC DEVICE (CIED) INFECTIONS

- The infection rate of CIED infection is rising disproportionate to the rate of implantation.
- Most early-onset (within 6 months of implantation) CIED pocket infections are caused by device contamination at the time of implantation, whereas hematogenous seeding is a frequent source of late-onset (after 6 months of implantation) CIED lead infections.
- Hematogenous seeding of CIED leads is rare with gram-negative bacteremia.
- Blood cultures should be obtained in all patients at initial presentation. If blood cultures are positive, then transesophageal echocardiography should be obtained to evaluate for lead infection or valvular endocarditis.
- Complete removal of the CIED system is necessary for eradication of device infection.
- A replacement device can be implanted once blood cultures are negative for 72 hours and perhaps earlier in cases in which admission blood cultures are negative. A 2-week delay in implantation is recommended for patients with valvular endocarditis.
- All patients should receive perioperative antibiotics for CIED placement/revision as primary prevention of CIED infection.

LEFT VENTRICULAR ASSIST DEVICE (LVAD) INFECTIONS

- Besides being a bridge to transplantation, LVADs are increasingly being used as destination therapy for patients with end-stage heart failure who are not transplantation candidates.
- Driveline exit site infections are the most common type of LVAD-specific infections, followed by LVAD-related bloodstream infection and endocarditis.
- *Staphylococcus aureus* and coagulase-negative staphylococci are responsible for the majority of LVAD-specific infections.
- Most LVAD infections are managed with antimicrobial therapy alone because device removal is not an option in most cases.
- Suppressive antibiotics are used lifelong or until the infected LVAD is removed.
- Immobilizing the driveline at the skin exit site to prevent repeated skin trauma reduces the risk of local device infections.

PROSTHETIC VASCULAR GRAFT INFECTIONS (PVGIs)

- Staphylococcal species are the predominant pathogens in PVGIs.
- Computed tomographic (CT) scanning is the best tool in the diagnostic evaluation of graft infection. CT findings of perigraft fluid accumulation, fat stranding or gas bubbles, lack of a fat plane between graft and bowel, and anastomotic aneurysms are all suggestive of graft infection.
- Surgical management of an infected graft includes complete excision of infected graft material, débridement of all infected and devitalized tissues, and revascularization of distal tissues.
- If complete excision of an infected graft is not feasible, patients should be prescribed lifelong oral suppressive antibiotics after an initial 4-week course of parenteral antimicrobial therapy.

The rapid evolution of technology, coupled with an aging population with multiple comorbid conditions, has led to the development of several new implantable devices that help to improve or sustain life. However, despite improvements in device manufacturing and availability of experienced operators implanting these devices, infection has remained a major complication of implantable cardiovascular devices. Risk of infection varies greatly (Table 82.1) and depends on the type and size of device, site of implantation, surgical technique used for device implantation, and host factors. Infections that complicate nonvalvular cardiovascular devices are addressed in this chapter. Intravascular catheter-related infections are reviewed elsewhere (see Chapter 300).

CARDIOVASCULAR IMPLANTABLE ELECTRONIC DEVICES

Permanent pacemaker (PPM), implantable cardioverter-defibrillator (ICD), and cardiac resynchronization therapy (CRT) devices are the three most commonly used cardiovascular implantable electronic devices (CIEDs). Sternotomy or thoracotomy was required for epicardial lead placement for the first generation of CIEDs. In contrast, most devices today are implanted percutaneously using transvenous leads. This change has led to a marked reduction in implantation-related morbidity and avoidance of potentially life-threatening infectious complications of major cardiothoracic surgical interventions. However, infection remains a major complication of CIED implantation and is associated with significant morbidity, mortality, and financial cost.[1,2,3]

Epidemiology of Cardiovascular Implantable Electronic Device Infections

Reported rates of CIED infection have ranged from 0.13% to 19.9%.[4,5] Over the past 2 decades, the rate of CIED implantation has rapidly increased in the United States. In a survey of Nationwide Inpatient Sample (NIS) discharge records from 1993–2008,[3] the incidence of CIED implantation increased an average of 4.7% annually during the study period. Although the rate of CIED infection remained stable until 2004, it increased significantly from 1.53% in 2004 to 2.41% in 2008. This increase in the rate of device infections coincided with an increase in the number of comorbidities in device recipients. Moreover, this infection rate resulted in significant increases in in-hospital mortality and cost of care.[6] In a separate analysis of a Medicare population,[2] patients with CIED infection remained at higher risk of death, even after hospital discharge, compared with device recipients without infection.

Pathogenesis of Cardiovascular Implantable Electronic Device Infections

Microbial contamination of a device generator or leads with skin microbiota at the time of implantation is the most likely mechanism for most early-onset (within 6 months of device implantation) CIED infections.[7] This likely explains the preponderance of staphylococci as causative pathogens. Colonization and subsequent infection of CIED is facilitated by an ability of these organisms to adhere to device surfaces and produce biofilm.[8–10] This interferes with the host immune system's