TABLE 76.3 Pancreatic Infection Incidence and Mortality Rate in Controlled Trials with Antibiotics and Meta-analyses—cont'd

AUTHOR	ANTIBIOTIC	NO. OF PATIENTS	PANCREATIC INFECTION RATE (%) CONTROL/CASE	MORTALITY RATE (%) CONTROL/CASE	COMMENTS
Villatoro et al.[75]	Cochrane Review including RCTs comparing antibiotics with placebo in AP with CT-proven necrosis	294 (from 5 evaluable studies)			Findings: Significantly less mortality with therapy (6%) vs. controls (15.3%). No differences in rates of infected pancreatic necrosis, operative treatment, nonpancreatic infection, and fungal infection. Subgroup analysis of β-lactam treatment: Significantly less mortality (6.3% vs. 16.7%) than in controls, without significant differences in rates of operative treatment or nonpancreatic infections. No significant differences with quinolone plus imidazole treatment. β-Lactams associated with significantly decreased mortality and infected pancreatic necrosis
Rokke et al.[76]	Prospective RCT, imipenem (500 mg tid for 5–7 days) vs. no antibiotics	73 patients total: 36 received imipenem; 37 received no antibiotics	43/14[a]	11/8	Underpowered study (slow patient accrual). No differences in length of hospital stay, need of intensive care, need of acute interventions, need for surgery, or 30-day mortality rates. Authors conclude that "the study, although underpowered, supports the use of early prophylactic treatment with imipenem in order to reduce the rate of septic complications in patients with severe pancreatitis."
Dellinger et al.[77]	Multicenter, prospective, double-blind, placebo-controlled randomized study set in 32 centers within North America and Europe	100 clinically severe, confirmed necrotizing pancreatitis: 50 received meropenem (1g IV q8h); 50 received placebo within 5 days of symptom onset, for 7–21 days	12/18	18/20	No statistically significant difference between the treatment groups for pancreatic or peripancreatic infection, mortality, or requirement for surgical intervention
Jafri et al.[78]	Meta-analysis assessing the clinical outcome of patients with severe AP treated with prophylactic antibiotics compared with that of patients not treated with antibiotics	502 (from 8 studies)			Findings: No effect of antibiotics on mortality, rates of infected necrosis, or frequency of surgical intervention. Apparent benefit regarding nonpancreatic infections (RR, 0.60; 95% CI, 0.44–0.82), with a RR reduction of 40% (95% CI, 18% to 56%); absolute risk reduction of 15% (95% CI, 6% to 23%), and number needed to treat of 7 (95% CI, 4 to 17)
Villatoro et al.[80]	Cochrane Review including RCTs comparing antibiotics with placebo in AP with CT-proven necrosis	404 (from 7 evaluable studies)			Findings: No benefit of antibiotics in preventing infection of pancreatic necrosis or mortality, except when imipenem was considered on its own, in which case a significant decrease in pancreatic infection was found ($P = .02$; RR, 0.34; 95% CI, 0.13 to 0.84) without effect on mortality. "None of the studies included in this review were adequately powered. Further better-designed studies are needed if the use of antibiotic prophylaxis is to be recommended."
Xue et al.[79]	Imipenem-cilastatin 500 mg IV tid for 7–14 days	56	37/27.6	10.3/14.8	Incidence of operative necrosectomy, extrapancreatic infections, organ complications, and hospital courses were also not significantly different. A significantly increased incidence of fungal infection was observed in the study group (36.1% vs. 14.2%)
Wittau et al.[81]	Meta-analysis of 14 RCTs including 841 patients, comparing antibiotics vs. placebo				Findings: No significant differences in mortality, incidence of infected pancreatic necrosis, nonpancreatic infection, surgical intervention

[a] $P < .05$.

AP, Acute pancreatitis; *CI,* confidence interval; *CIP/MET,* ciprofloxacin/metronidazole; *CRP,* C-reactive protein; *CT,* computed tomography; *FNA,* fine-needle aspiration; *IV,* intravenous; *RCTs,* randomized controlled trials; *RR,* relative risk; *SDD,* selective decontamination of the digestive tract.

Modified from Tooulí J, Brooke-Smith M, Bassi C, et al. Guidelines for the management of acute pancreatitis. J Gastroenterol Hepatol. *2002;17(suppl):S15–S39.*

gram-positive infected necrosis between the SDD and the control groups. These issues may be related to the treatment with systemic cefotaxime, which protects from some of the more virulent gram-positive organisms but has relatively poor coverage against gram-negative organisms such as *Pseudomonas aeruginosa*. In fact, the most frequent gram-negative isolates in this study were *P. aeruginosa* and *E. coli* (13 patients each), whereas the most frequent gram-positive isolates were enterococci and *Staphylococcus epidermidis*.

Preemptive Systemic Antibiotic Therapy

Multiple groups have examined the efficacy of early treatment with systemic antibiotics in diminishing the risks of infection in AP. This literature generally describes an approach such as "prophylactic" antimicrobial therapy, but the strategy might be described more accurately as "early" or "preemptive" therapy, and these terms will be used preferentially here. Numerous animal pancreatitis studies have shown a benefit from early antibiotic administration, as reviewed by Ratschko and coworkers[7] and Sand and Nordback.[55] Among other aspects, the ability to administer antibiotics very early in the course of pancreatitis distinguishes these animal models from the treatment of human patients, who did not appear to benefit from antibiotic therapy in the initial prospective randomized studies from the 1970s. However, the human studies enrolled patients with mild disease who were at low risk for infection; among the aggregate of 199 patients in these studies, only 1 patient died. In addition, the treatment groups received monotherapy with ampicillin, which provides suboptimal activity against the relevant organisms and also penetrates poorly into pancreatic tissue and fluid.[7]

Several groups have evaluated antimicrobial penetration into pancreatic tissue. In human studies antibiotic levels in pancreatic tissue and fluid tend to correlate with the degree of inflammation; thus higher levels occur in patients with pancreatitis than in members of control groups.[7] In general, antimicrobials can be assigned to the following categories: (1) poor pancreatic penetration (aminoglycosides, first-generation cephalosporins, cefoxitin, and ampicillin); (2) variable pancreatic penetration, reaching minimal inhibitory concentrations (MICs) for some but not all relevant organisms (mezlocillin [not available in the United States], piperacillin, and cefotaxime); and (3) pancreatic penetration reaching MIC for most relevant organisms (fluoroquinolones, imipenem, ceftazidime, cefepime, metronidazole, clindamycin, chloramphenicol, doxycycline, and fluconazole).[60,61,62–64] One group developed an efficacy factor incorporating each drug's pancreatic penetration and activity against organisms typically associated with pancreatic infection, with a factor of 1.0 considered optimal.[61] The calculated factors were 0.98 for imipenem, 0.86 to 0.87 for fluoroquinolones, and 0.71 to 0.78 for piperacillin and third-generation cephalosporins. However, the relationship between antibiotic levels in pancreatic tissue or fluid and antibiotic efficacy in preventing or treating infections in necrotic pancreatic parenchyma or in the retroperitoneal fat outside the pancreas remains unclear.

Observational reports[13,65] have described single-institution experiences with lower rates of infected necrosis after introduction of early antibiotic therapy. One such report[65] describes a retrospective cohort review evaluating three groups of patients with necrotizing pancreatitis: 50 patients from 1982–89 receiving no early antibiotics, 55 patients from 1990–92 receiving variable antibiotic regimens at the discretion of their physicians, and 75 patients between 1993 and 1996 treated with imipenem until discharge or for up to 4 weeks, according to standard protocol, based on an APACHE score less than 6 and pancreatic necrosis (<15% of the gland), peripancreatic necrosis, or peripancreatic collection. The frequency of pancreatic infection was significantly lower among patients receiving preemptive antibiotics (76% in the earliest group vs. 45% in the middle group [$P = .003$] and 27% in the latest group [$P < .001$]). In addition, the difference in infection rates between the group of patients receiving nonprotocol antibiotics and the group receiving imipenem by protocol was statistically significant ($P = .04$). The mortality rates trended downward from 16% to 7% to 5% ($P = .11$). Mortality rates ranged from 19% to 40% for patients developing infection within the first 4 weeks, compared with 0% to 8% for those infected after 4 weeks. Time to infection, however, was the same across all groups. The authors conclude that early imipenem, or possibly ciprofloxacin, for a 4-week course should be the standard of care for patients with severe AP. Although this study has been invoked in support of routine administration of imipenem, the results are confounded by several factors. The middle group may have received antibiotics with an inadequate spectrum of coverage, later in the course of illness, or for an inadequate duration. Because the causative organisms were not reported, the importance of spectrum of coverage cannot be assessed. In addition, the longitudinal retrospective design of this study impairs understanding of the effects of non–antibiotic-related changes in detection and management of severe AP that may have influenced mortality rates. Of note, lower infection rates have not been associated with improved survival in retrospective studies.

Four initial randomized studies in the 1990s and early 2000s addressed the efficacy of systemic antibiotics in diminishing infection in AP, focusing on patients with severe disease and using broad-spectrum antibiotics with reasonable pancreatic penetration, as summarized in Table 76.3. The results of these studies, however, were not definitive because of problems in study design and sample size.

In one trial of 74 patients with necrotizing pancreatitis, early imipenem treatment reduced morbidity by decreasing the rates of tissue-confirmed pancreatic infection and nonpancreatic sepsis but did not influence time to onset of pancreatic sepsis, rate of multiorgan failure, need for surgery, or survival in comparison to patients receiving no early antibiotic treatment. Preemptive antibiotic therapy was especially effective for patients with mild-to-moderate pancreatic necrosis; no patient in the treated group with less than 50% necrosis developed septic complications versus 29% in the control group.[21]

In another trial[66] 60 patients with severe AP and necrosis were given no preemptive antibiotics or cefuroxime. The treated group suffered significantly fewer total infections, infections per patient, operations, and deaths (3% vs. 23%). However, the rate of culture-proven sepsis was not significantly different between groups, and only urinary tract infections were reduced significantly. The study has been criticized because of the large numbers of urinary tract infections and of *S. epidermidis* "infections" with questionable clinical significance. In addition, 67% of the treatment group patients changed antibiotics after a mean of 9.2 days, 3 because of strong clinical suspicion for (culture-negative) sepsis, and 17 for unstated reasons.[7] Finally, it is unclear whether the deaths were related to infection. The authors acknowledge that the reasons for mortality benefit from early cefuroxime treatment in this study are unclear because cefuroxime would not have been expected to alleviate most of the infections in the control group.[66]

A third group evaluated the effects of a 10-day course of IV ceftazidime, amikacin, and metronidazole in 23 patients with alcohol-induced severe AP. Infections occurred among 0% of patients in the treatment group versus 58% in the placebo group ($P = .03$). Mortality and multiple organ failure rates were not significantly different.[67]

The fourth study randomized 26 patients with pancreatic necrosis to early IV ofloxacin and metronidazole or no antibiotics. All patients underwent serial FNA; antibiotics were administered to the control patients who showed evidence of infection. There was no difference in the incidence or timing of infected necrosis. The mortality rate trended downward from 15% to 0% in the antibiotic-treated group.[68]

Thus, of the four initial randomized studies comparing routine early antibiotic treatment with no treatment in AP, three showed lower sepsis rates, two showed lower rates of pancreatic infection, and none showed any effect on the operation rate. Only one study[66] showed a statistically significant reduction in mortality rate associated with preemptive antibiotics; this particular study found no associated change in pancreatic infection rates. The inconsistencies among trials may arise from the relatively small numbers of patients, providing inadequate power to detect significant differences. Additional discrepancies might be related to the differences in patient populations and in nonantibiotic management among the various populations, such as rates, timing, and techniques of surgery; enteral nutrition; fluid resuscitation; and other factors.

Findings from meta-analyses of the published trials are summarized in Table 76.3.[69,70] The validity of meta-analysis for these studies is unclear because the enrollment criteria, antibiotic regimens, and methods of

diagnosing infections used in the trials are not uniform. Finally, one author points out that the absence of blinding in these studies may have encouraged clinicians to offer surgical débridement preferentially to control patients; such surgery might convert sterile necrosis to infected necrosis, which might increase mortality.[71]

A randomized, double-blinded, and placebo-controlled study was designed to demonstrate with a power of 90% that ciprofloxacin/metronidazole (CIP/MET) reduces the incidence of infected pancreatic necrosis from 40% to 20%.[72] After an interim analysis showed increased frequency of need for open antibiotic treatment in the placebo group, recruitment was stopped and results were reported: no differences in rates of infected pancreatic necrosis or mortality were found. The results of this study have been controversial because of the low rates of infected necrosis in both groups and the high rate of switch to open antibiotic treatment in the placebo group. The authors suggest that both of these issues are related to the close monitoring for signs of SIRS or progressive severe pancreatitis, which led to high switching rates and low rates of pancreatic infection. Brown[73] notes, "It will always be difficult to perform a randomized trial in subjects with severe AP in which the control group does not receive antibiotics" and comments further that the study was underpowered to detect the more meaningful end point of mortality.[73] Additional critiques include the relatively small number of patients with pancreatic necrosis and the substantial number of infections with coagulase-negative staphylococci, raising concern about whether these isolates are true pathogens versus contaminants.[74] Because mortality rates were similar in the two groups, the authors suggest that these data support the approach of antibiotic treatment "on demand" based on development of sepsis, SIRS, failure of two or more organ systems, proven pancreatic or extrapancreatic infection, and an increase in CRP along with evidence of pancreatic or extrapancreatic infection. The authors calculate that use of these criteria, rather than the preemptive antibiotic treatment given in the CIP/MET group, would have reduced antibiotic costs for this group by approximately 34%.[72]

A 2006 Cochrane Review of data from these five evaluable studies found no benefit of antibiotics in preventing infection of pancreatic necrosis or mortality, except for when imipenem was considered on its own, in which case a significant decrease in pancreatic infection but not mortality was found.[75]

A subsequent underpowered prospective randomized controlled trial (RCT)[76] measured outcomes in 73 patients with severe AP, of whom 36 received early imipenem (500 mg tid for 5–7 days) and 37 received no antibiotics. Imipenem treatment was associated with significant reduction in pancreatic infections (43% vs. 14%), but there were no differences in length of hospital stay, need of intensive care, need of acute interventions, need for surgery, or 30-day mortality. The authors conclude that "the study, although underpowered, supports the use of early prophylactic treatment with imipenem to reduce the rate of septic complications in patients with severe pancreatitis."

A larger multicenter, prospective, double-blind, placebo-controlled randomized study set in 32 centers within North America and Europe included 100 patients with clinically severe, confirmed necrotizing pancreatitis, of whom 50 received meropenem (1g IV q8h), and 50 received placebo within 5 days of the onset of symptoms for 7 to 21 days. In this study there were no differences in rates of pancreatic or peripancreatic infections, overall mortality, or need for surgical intervention.[77] Although there was a high percentage of patients in the placebo group (54%) who were treated with IV antibiotics, on average the antibiotic exposure was nearly 3 weeks after randomization. Howard[78] calculates that with the rates of "placebo group infection rate of 20% with a reduction to 10% using prophylactic antibiotic, accurate powering of a definitive study of prophylactic antibiotics patterned after [this] trial would now require the screening of approximately 8383 patients and randomization of 1006. Based on the disease frequency and heterogeneity, combined with the logistical problems found in the current study, this seems like an insurmountable task." He comments further that "the combined weight of these last two clinical trials will undoubtedly skew any future meta-analysis against routine prophylactic antibiotic use."[78]

A later RCT from China, published in 2009, included 276 patients with severe acute pancreatitis, of whom 56 had 30% or more necrosis and were randomized to IV imipenem within 72 hours of onset of symptoms for 7 to 14 days versus no antibiotic prophylaxis. There was no benefit for antibiotic prophylaxis in preventing infected pancreatic necrosis, mortality, or the incidence of operative necrosectomy. The rates of extrapancreatic infection, organ complications, and hospital course were also unchanged. However, the incidence of fungal infection was significantly higher in the study group (36% vs. 14%).[79]

As predicted, several subsequent meta-analyses of trials looking at benefits of antibiotic prophylaxis in severe AP have shown no effect of antibiotics on mortality, rates of infected necrosis, or frequency of surgical intervention. In one meta-analysis there was apparent benefit regarding nonpancreatic infections (RR, 0.60; 95% confidence interval [CI, 0.44 to 0.82), with a RR reduction of 40% (95% CI, 18% to 56%), absolute risk reduction of 15% (95% CI, 6% to 23%), and number needed to treat of 7 (95% CI, 4 to 17).[80] A 2011 meta-analysis of 14 RCTs including 841 patients found no significant differences in mortality, incidence of infected pancreatic necrosis, nonpancreatic infection, or surgical intervention.[81]

A 2015 meta-analysis of published RCTs of "early" administration of prophylactic antibiotics concluded that this was associated with a reduced incidence of infected pancreatic necrosis and with lower mortality.[82] "Early" refers to administration within 72 hours of onset of symptoms or within 48 hours after hospital admission. However, in addition to the difficulties with the design and interpretation of the individual RCTs in this study and the variability of antibiotic regimens/durations among them, an added limitation of this meta-analysis is that the RCTs compared the use and nonuse of antibiotics, not the timing of administration, making this study more strictly a sensitivity analysis of the RCTs rather than a meta-analysis per se. A 2010 Cochrane Review of seven randomized studies that included studies in which administration may have occurred after 72 hours of onset concluded that patients randomized to receive prophylactic antibiotics for acute necrotizing pancreatitis had no statistically significant reduction in infections.[83]

A meta-analysis that included both RCTs and cohort studies found no significant decrease in the incidence of infected pancreatic necrosis with the use of prophylactic antibiotics but did find a reduction in all-cause mortality.[84] However, this reduction in all-cause mortality was not observed when the cohort studies were excluded from the analysis.

Additional Data

One trial has addressed the selection of optimal antibiotic therapy by comparing a course of pefloxacin (not available in the United States) to treatment with imipenem in 56 patients. Infected necrosis and extrapancreatic infection rates were significantly lower in the imipenem group. Rates of death, all resulting from sepsis, did not differ significantly.[38]

Another trial addressed the timing of preemptive meropenem by comparing early treatment (started 1.07 ± 0.6 days after admission, group A) to treatment started after demonstration of pancreatic necrosis by CT (4.56 ± 1.2 days from admission, group B). Pancreatic infection rates were not significantly different between groups, but extrapancreatic infection occurred significantly less frequently in group A than in group B (16.6% vs. 44.8%). Need for surgery and length of hospitalization were also higher in group B. Mortality rates were similar in the two groups, but three of four patients with infected necrosis in group A, and only two of nine in group B, died. The authors conclude that early antibiotic treatment improves the prognosis of necrotizing AP by reducing the rate of septic complications.[85] Concerns about these conclusions include the lack of mortality difference between groups, the fact that organisms resistant to meropenem were responsible for all infections in the early antibiotic group patients, the use of TPN rather than enteral nutrition in this study, and the risks of *Clostridioides difficile* (formerly *Clostridium difficile*) associated with antibiotics.[86]

Review Article Recommendations

Between 1986 and the mid-2000s multiple groups made specific recommendations largely supporting use of carbapenem alone or quinolone plus metronidazole as first-choice preemptive antibiotic therapy, with third-generation cephalosporins or ureidopenicillins as alternative aerobic coverage and clindamycin as alternative anaerobic coverage. Most authors recognized that optimal duration of preemptive antimicrobial therapy

had not been studied, but some recommended 1 to 4 weeks, depending on the course of disease.[7]

In contrast, other investigators favored minimizing antimicrobial exposure. One group[87] recommended efforts to avoid imipenem and to limit the duration of empirical coverage to 14 days because of concerns about facilitating fungal superinfection. Another group[88] concluded that the risks of fungal infection warrant a policy of limiting treatment with broad-spectrum antibiotics to "as short a period as seems prudent (typically 5–7 days)." One review suggested an approach of "on-demand" antibiotics rather than uniform administration of antibiotics for all patients with severe AP with necrosis. Specifically, this group advocated limiting antibiotics to patients with extensive (rather than focal) necrosis and to patients who have undergone surgical procedures for extensive sterile necrosis because of the risks of gram-negative superinfection associated with surgical necrosectomy.[89]

Guidelines

On the basis of more recent studies, in 2013 several major guidelines (American College of Gastroenterology and International Association of Pancreatology) recommended avoiding preemptive antibiotic and antifungal use in AP.[90,91] Multiple other groups have also provided guidelines and recommendations recently, as summarized in Table 76.4.[92–96]

The only guidelines published since 2013 recommending prophylactic antibiotics routinely in severe AP are the Japanese guidelines from 2015,[92] in which authors cite in support of this recommendation the sensitivity analysis termed meta-analysis[82] looking at administration of antibiotics within 72 hours after onset of symptoms or 48 hours after admission.

The Italian Association for the Study of the Pancreas Guideline[93] raises the possibility of antibiotic prophylaxis for patients with pancreatic necrosis involving greater than 50% of the gland "on a case-to-case basis due to the high risk of infection" and favors carbapenem as first-line empirical treatment for patients with suspected infected pancreatic necrosis. No recent guidelines recommend routine antifungal prophylaxis or SDD.

Actual Practice

Despite multiple guidelines now recommending against use of prophylactic antibiotics in AP, substantial use of antibiotics continues in practice, both in mild AP and in more severe AP. In one 2016 study from the United Kingdom, 44% of patients with clinically mild AP received antibiotics.[97] In another 2016 study from Canada, 25.5% of non–intensive care unit (ICU) patients and 48.1% of ICU patients received prophylactic antibiotics.[98]

A 2016 review sums up the current understanding of the role of prophylactic antibiotics and its relationship to clinical practice as follows: "Although the development of infected pancreatic necrosis confers a significant risk of death, well-designed trials and meta-analyses have shown no benefit of prophylactic antibiotics. Prophylaxis with antibiotic therapy is not recommended for any type of acute pancreatitis unless infection is suspected or has been confirmed. Nonetheless, many patients continue to receive prophylactic antibiotics despite guidelines to the contrary."[99]

CONCLUSIONS

In general, mild-to-moderate AP is self-limited and rarely complicated by infection. Severe AP is associated with significant morbidity and mortality rates that may be related to pancreatic superinfection with GI microbiota. The management of such infections requires optimal diagnosis by way of thoughtful clinical assessment, imaging studies, and consideration of percutaneous aspiration of necrotic pancreatic material, as well as aggressive medical and surgical care, with current recommendations favoring efforts to postpone surgical intervention until the stage of WON (i.e., after 4 weeks) if possible. Enteral feeding prevents infection in AP. A consensus favoring early antibacterial treatment aimed at decreasing pancreatic infection risk for patients with severe AP emerged in the 1990s to 2000s with some support from the literature. However, small size and design flaws rendered these studies difficult to interpret. More recently, several larger studies with fewer design flaws have failed to show significant benefits from preemptive

TABLE 76.4 Recommendations From Review Articles and Guidelines Regarding Early Administration of Antibiotics in Patients with Acute Pancreatitis

AUTHORS	YEAR	INCLUSION CRITERIA	TIMING/DURATION
Tenner,[90] American College of Gastroenterology Guideline	2013	All pancreatitis	Routine use of prophylactic antibiotics in patients with AP is not recommended. Use of antibiotics in patients with sterile necrosis is not recommended.
Da Costa, Boerma, van Santvoort, et al.[96]	2013	All pancreatitis	Antibiotics are not indicated as part of initial management.
Yokoe et al.[92]	2015	Severe acute pancreatitis and necrotizing pancreatitis	Start within 72 h of onset or 48 h after admission, continue for no more than 2 weeks if there are no signs of infection.
Italian Association for the Study of the Pancreas[93]	2015	Severe acute pancreatitis	Routine prophylaxis with antibiotics/antifungals is not recommended in severe AP. In the case of pancreatic necrosis involving >50% of the gland, antibiotic prophylaxis might be considered on a case-by-case basis due to the high risk of infection. Among the different antibiotics used, a carbapenem-based prophylaxis has a trend toward efficacy. This class of antibiotics should be considered as a first line empirical treatment for patients with suspected infected pancreatic necrosis.
Greenberg et al.[94]	2016	Mild or severe AP	None unless patient is unstable with suspected sepsis and no source identified. "Treatment with broad-spectrum antibiotics on speculation may be indicated while an appropriate workup (bacterial and fungal cultures, CT) is carried out." Otherwise antibiotics should be prescribed only in patients with infected necrosis confirmed by FNA or if there is gas within a collection visualized on CT scan.
Janisch and Gardner[95]	2016	All pancreatitis	Prophylactic antibiotics are not recommended for use in AP and should not be administered in the first 24 hours of the episode unless there is clinical suspicion for concurrent extrapancreatic infection. Patients may present initially with sepsis, SIRS, and/or multiorgan failure. Treatment with antibiotics is appropriate if evaluation of the patient, via blood cultures and fine needle aspirations of pancreatic necrosis, reveals infection. However, if there is no obvious source of infection, antibiotics should be discontinued.

AP, Acute pancreatitis; *CT,* computed tomography, *FNA,* fine-needle aspiration; *SIRS,* systemic inflammatory response syndrome.

antibiotics, and these have led most experts to recommend against using antibiotics routinely for all patients with severe AP. The lack of benefit from preemptive antibiotics in these more recent studies may result in part from the fact that "modern care is associated with a reduction in the risk of necrosis becoming infected. This reduction would decrease the relative potential clinical impact of prophylactic antibiotics."[78] Residual enthusiasm for preemptive or prophylactic antibiotic treatment must be tempered also by concerns about selecting for increasingly resistant organisms, which have been associated with longer ICU stays and courses of antibiotics.[100]

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The complete reference list is available online at Expert Consult.

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77 Splenic Abscess

Lawrence C. Madoff

SHORT VIEW SUMMARY

Definition
- Abscesses comprise one or more focal collections induced by bacteria, mycobacteria, or fungi in the spleen.
- Predisposing conditions include immunosuppression, trauma, diabetes, hemoglobinopathy, Felty syndrome, intravenous drug use, and endocarditis.

Epidemiology
- Splenic abscesses are uncommon and have been reported only in small numbers in the medical literature.
- Splenic abscesses are present in 0.2% to 0.7% in general autopsy series.
- Splenic abscesses are a frequent finding in bacterial endocarditis and are present in up to one-third of patients at autopsy.
- There is a bimodal age distribution, with peaks in the third and sixth decades of life.

Microbiology
- Streptococci, staphylococci, salmonellae, and *Escherichia coli* are important causative agents, as well as fungi and mycobacteria increasingly.
- In specific geographic areas of Asia, *Klebsiella pneumoniae* and *Burkholderia pseudomallei* are important causative agents.
- Anaerobes are rare.

Clinical Findings and Diagnosis
- Fever is present with abdominal pain in the left upper quadrant but a paucity of specific symptoms and findings.
- Ultrasound, computed tomography, and magnetic resonance imaging are used for diagnosis.

Therapy
- Splenectomy has been the gold standard of treatment along with antibiotic treatment of underlying infection elsewhere.
- More recent emphasis has been on the use of percutaneous drainage with antibiotic treatment or, in some cases, antibiotic treatment alone in an attempt to reduce morbidity and preserve the spleen.

EPIDEMIOLOGY

The spleen is a highly vascular hematopoietic lymphoid organ that is part of the reticuloendothelial arm of the immune system. If the spleen is surgically removed, its absence is marked by heightened susceptibility to overwhelming infection by encapsulated bacteria and intraerythrocytic parasites (see Chapter 311). Abscesses of the spleen usually result from bacteremia, particularly in the setting of abnormalities caused by trauma, embolization, or hemoglobinopathy. Immunodeficiency such as that resulting from human immunodeficiency virus (HIV) infection is also a risk factor.[1] Occasionally splenic abscess results from extension of a contiguous focus of infection.

Splenic abscesses are relatively uncommon. For example, in one series of 540 intraabdominal abscesses, none were in the spleen.[2] Autopsy series have placed the incidence of splenic abscesses at 0.2% to 0.7%.[3,4] Only approximately 600 splenic abscesses had been reported in the literature as of 2008.[5] It has been suggested that the incidence may be increasing because of improved detection, increasing use of illicit intravenous drugs, and the increased number of immunocompromised individuals.[6–8] Splenic abscess has a bimodal age distribution, with peaks in the third and sixth decades of life.[8]

PATHOGENESIS

Bacteremic infection from a variety of sites is the most common cause of splenic abscess. Classically, infective endocarditis has been most strongly associated with splenic abscess, and in most series, endocarditis is identified as the leading cause.[9–12] In an autopsy series, 29% of patients with endocarditis between 1986 and 2008 were found to have splenic abscesses.[13] Other common sources of infection are the urinary tract, surgical wounds, and the gastrointestinal tract. Immunodeficiency has become a more important risk factor for the development of splenic abscess. In large reviews, 18% to 34% of patients were immunosuppressed (from disease, cancer chemotherapy, or steroid use) including 9% who were infected with HIV.[11,14,15] Trauma to the spleen, either iatrogenic or accidental, accounts for 7% to 30% of cases, with lower numbers in more recent studies, and contiguous spread of infection (e.g., from an adjacent intraabdominal process) continues to account for a small percentage of cases (2%–7%).[14] Other conditions associated with splenic abscess include splenic abnormalities such as Felty syndrome or amyloidosis, intravenous drug use, hemoglobinopathy, and diabetes mellitus.

Complications of splenic abscess can be life threatening and include perforation into the peritoneum, which occurred in 19 (6.6%) of 287 patients in one series.[14] Rupture into adjacent organs can occur, with resulting fistulas into the gastrointestinal tract, pleural space, or lung parenchyma. Overall mortality rates of 0% to 14% have been reported with appropriate therapy (see "Therapy"), although higher rates occur among immunocompromised patients, and mortality is strongly associated with signs of sepsis using several sepsis scoring systems.[16]

MICROBIOLOGY

Streptococci, staphylococci, salmonellae,[17] and *Escherichia coli* have been the major causative agents of splenic abscess for the past century (Table 77.1). However, with the increased number of immunocompromised patients, more recent series have shown greater numbers of fungal isolates including *Candida* spp., *Aspergillus* spp., and agents of mucormycosis. Mycobacteria have also become more common. Anaerobic bacteria remain a relatively infrequent cause of splenic abscess compared with other intraabdominal abscesses, despite improvements in culture techniques.

In HIV-infected patients, *Salmonella* spp. and *Mycobacterium tuberculosis* are common causes of splenic abscess, as are the opportunistic pathogens *Mycobacterium avium-intracellulare* complex, *Leishmania* spp., *Rhodococcus equi,* and *Pneumocystis jirovecii.* Sickle cell anemia has classically been associated with *Salmonella* infections of the spleen, but more recent series noted a predominance of staphylococcal infection associated with this condition.[8] Many other organisms have been described as causative agents of splenic abscess in case reports including *Bartonella henselae,*[18–20] *Streptobacillus moniliformis, Campylobacter*

TABLE 77.1 Organisms Cultured From Splenic Abscesses: Comparison of Five Time Periods

ORGANISM	% OF POSITIVE CULTURES				
	1900–1977 (*N* = 129)[a]	1977–1986 (*N* = 159)[b]	1987–1995 (*N* = 225)[c]	2000–2011 (*N* = 28)[d]	2012–2016 (*N* = 16)[e]
Aerobic bacteria					
Streptococcus spp.	21.7	6.9	10.2	7	25.0
Staphylococcus spp.	20.2	15.7	17.3	7	6.25
Salmonella spp.	10.9	10.7	16.1	7	6.25
Pseudomonas	0	1.3	6.3	3.5	
Escherichia coli	24.1[f]	10.7	12.5		6.25
Enterococcus spp.		6.3	3.9	7	6.25
Klebsiella		1.9	1.9	7	6.25
Proteus		1.3	3.1		
Other aerobes		8.2	7.1	10.7	
Anaerobic bacteria	5.4	17.6	7.1	7	
Mycobacteria					
Mycobacterium tuberculosis	0.8	0	5.5	3.5	6.25
Mycobacterium avium-intracellulare complex	0	0	1.9	3.5	6.25
Fungi	0.8	25.8	7.1	10.7	6.25
Sterile cultures	28.7	11.9	11.4	32.1	31.25
Bartonella henselae				3.5	

[a]Modified from Chun CH, Raff MJ, Contreras L, et al. Splenic abscess. *Medicine (Baltimore)*. 1980;59:50–65.
[b]Modified from Nelken N, Ignatius J, Skinner M, et al. Changing clinical spectrum of splenic abscess: a multicenter study and review of the literature. *Am J Surg*. 1987;154:27–34.
[c]Modified from Ooi LL, Leong SS. Splenic abscesses from 1987 to 1995. *Am J Surg*. 1997;174:87–93.
[d]Modified from Liu YH, Liu CP, Lee CM. Splenic abscesses at a tertiary medical center in Northern Taiwan. *J Microbiol Immunol Infect*. 2014;47:104–108.
[e]Modified from Lee MC, Lee CM. Splenic abscess: an uncommon entity with potentially life-threatening evolution. *Can J Infect Dis Med Microbiol*. 2018;2018:8610657.
[f]Total percentage for *E. coli, Enterococcus* spp., *Klebsiella, Proteus,* and other aerobes.

jejuni,[21] and *Nocardia* spp.[4] In a series from Thailand, the agent of melioidosis, *Burkholderia pseudomallei,* was the cause of splenic abscess in 24 of 41 cases from which a pathogen was isolated.[22] In a more recent series from Singapore, there was serologic evidence for melioidosis in 15 of 21 patients over a 10-year period, although 7 of these patients had negative blood cultures.[23] Of interest, nearly all the patients with melioidosis involving the spleen had diabetes mellitus (see Fig. 221.14 in Chapter 221). *Klebsiella pneumoniae* has become an increasingly common cause of community-acquired infection including splenic abscess in Taiwan and elsewhere in Asia.[10,20,24,25] In one series, *K. pneumoniae* was the most common cause of splenic abscess in a hospital in southern Taiwan.[24] Overall, blood cultures were positive in 24% to 60% of cases.[9,26] Splenic abscesses caused by enteric bacteria have been reported in patients with *Plasmodium vivax* infection, whose splenomegaly was otherwise attributed to malaria.[27,28] Occasionally aseptic abscesses have been described in the spleen, particularly in patients with inflammatory bowel disease.[29] Patients with these apparently noninfectious inflammatory lesions of unknown etiology present with fever and respond to treatment with corticosteroids but not to antibiotics. These aseptic abscesses are often accompanied by aseptic abscesses in other locations, but the spleen is the most frequent site.

CLINICAL MANIFESTATIONS

Fever may be the only manifestation of splenic abscess, and fever is present in 95% of cases. Another frequent finding is abdominal pain, which is either generalized or localized to the left upper quadrant and may radiate to the left chest or shoulder. Nausea, vomiting, anorexia, and weakness are often present. Abdominal tenderness is present in only half of the cases, most often in the left upper quadrant. Splenomegaly can be detected in a similar number of cases. Chest findings including dullness, rales, or both at the left base have been detected in many patients. Other findings that are less frequently present include splenic friction rubs, hepatomegaly, tenderness at the costovertebral angle, and ascites. The only laboratory abnormality that is frequently present is leukocytosis, which is seen in 60% to 80% of cases.

DIAGNOSIS

Because the symptoms and findings of splenic abscess are most frequently nonspecific, diagnosis depends on appropriate imaging studies. Plain radiographs are surprisingly sensitive, with abnormalities detected in 50% to 80% of chest radiographs and 25% of abdominal radiographs (e.g., basilar infiltrates, pleural effusion, elevated hemidiaphragm, shift of viscera, presence of gas)[26]; however, the findings are most often nonspecific. The use of radionuclide scans as described in earlier literature, primarily technetium 99m sulfur-colloid liver-spleen scans, has been largely supplanted by ultrasonography, computed tomography (CT), and magnetic resonance imaging (MRI).

Ultrasonography

The advantages of ultrasonography in the evaluation of splenic abscess include low cost, portability, and relatively high sensitivity, reportedly ranging from 75% to 93%.[8,14,26,30] It is therefore appropriate in the initial assessment of most suspected splenic abscesses. Ultrasonography typically demonstrates an area of decreased or absent echogenicity, sometimes with irregular areas of echodensity (debris) or a gas pattern within the lesion.[31] Splenomegaly can frequently be demonstrated. High-resolution (7.5 MHz) ultrasonography can detect microabscesses in patients infected with HIV that are missed with conventional ultrasonography.[1]

Computed Tomography

CT appears to be the most sensitive modality for the detection of splenic abscess, particularly if enhancement by intravenous contrast medium is used.[30] A sensitivity of greater than 90% has been seen in most series.[14] The abscess is seen as an area of low-density fluid or necrotic tissue within the relatively homogeneous spleen. Enhancement of the rim of the abscess cavity is seen in a few cases, so that splenic infarctions are difficult to distinguish from splenic abscesses on contrast-enhanced CT. Splenic infarction adjacent to intraabdominal abscesses elsewhere in the abdomen has been reported.[32]

Magnetic Resonance Imaging

There is far less experience with MRI for the detection of splenic abscesses, and its role in their management is not yet established. MRI is sensitive for the detection of other abdominal abscesses, and its sensitivity in the discovery of splenic abscesses is probably similar. Nonetheless, although MRI has been successfully coupled with drainage procedures, it appears to be more cumbersome and to offer fewer advantages than ultrasonography or CT.[33]

In a setting in which drainage may not be necessary, for example, in immunocompromised patients in whom pathogens other than pyogenic bacteria are more common, or if a noninfectious diagnosis such as malignancy or cyst is likely, fine-needle aspiration under the guidance of diagnostic imaging may be useful.[34,35] The sensitivity of this method is variable, and its role remains the subject of investigation.

THERAPY

Untreated splenic abscess has a high mortality rate.[8] Splenectomy has been the traditional modality for treatment and remains the gold standard against which other therapies must be assessed. Antibiotics play an important role in the treatment of associated endocarditis and sepsis, in stabilization of the patient for splenectomy or a drainage procedure, and in treatment of selected pathogens (e.g., mycobacteria, fungi), but they are rarely curative alone for splenic abscess caused by pyogenic bacteria. Broad-spectrum empirical antibiotic therapy should be initiated as soon as splenic abscess is suspected, pending surgical or percutaneous drainage. Antibiotics should include agents active against streptococci, staphylococci, and aerobic gram-negative rods. Vancomycin or oxacillin plus an aminoglycoside, a third-generation or fourth-generation cephalosporin, a fluoroquinolone, or a carbapenem would be reasonable empirical therapy. After blood or abscess culture results are obtained, antibiotic coverage can be narrowed accordingly. If splenectomy is a possibility, it is advisable to administer vaccinations for encapsulated bacterial pathogens as early as possible.

Experience with CT-guided and ultrasonography-guided percutaneous aspiration of splenic abscesses has grown in recent decades. These procedures have the advantage of lower initial morbidity and mortality than splenectomy and allow for preservation of the spleen. Success rates have ranged from 50% to 90% in several series.[8,14,36–42] In general, smaller (<3 to 4 cm), solitary, or unilocular abscesses have a higher rate of successful percutaneous drainage. In contrast, microabscesses; complex, phlegmonous, or multilocular processes; and abscesses with thick fluid tend to fare more poorly with this approach. Percutaneous drainage may be useful, at least initially, in patients who are unstable or who present an unacceptably high surgical risk. Failure to achieve effective drainage or failure of the patient's condition to improve is an indication for definitive surgery. Aspirated abscess fluid should be sent for Gram stain; bacterial, fungal, and mycobacterial culture; and other studies as clinically indicated.

The optimal duration of antibiotic therapy for splenic abscess has not been established in any clinical trial. For some patients, such as patients with bacterial endocarditis, the duration is dictated by the underlying condition. If splenectomy is performed and the focus of infection is eradicated, briefer durations may be possible. With percutaneous drainage, duration of therapy needs to be tailored to the clinical course, including resolution of the abscess as assessed by diagnostic imaging.

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78 Appendicitis

Costi D. Sifri and Lawrence C. Madoff

SHORT VIEW SUMMARY

Definition
- Appendicitis is acute inflammation of the vermiform appendix that is often related to obstruction and may be complicated by polymicrobial infection.
- Complications include perforation, peritonitis, and intraabdominal abscesses.

Epidemiology
- Acute appendicitis is a relatively common disease, often presenting in adolescence and early adulthood.
- Lifetime risk for appendicitis is 8.6% in men and 6.7% in women.
- More than 300,000 appendectomies are performed annually in the United States.

Biology
- The microbial community of the appendix resides in a mucus-rich biofilm that is continuously shed into the intestinal tract and may serve to repopulate the gut after acute diarrhea illness.

Microbiology
- The inflammation is usually polymicrobial, frequently involving aerobic and anaerobic gram-negative bacilli.
- The human appendiceal microbiome is a highly diverse community of organisms, with notable differences in taxonomic composition compared with other locations in the lower intestinal tract.
- Genomic analysis has shown that several taxa, including Fusobacteria, are enriched in the inflamed appendix.
- Infections by *Yersinia* spp., parasites, including *Entamoeba histolytica,* and viruses may mimic appendicitis (e.g., mesenteric adenitis) or cause obstruction leading to acute appendicitis.

Diagnosis
- Clinical diagnosis is enhanced by the use of imaging, especially computed tomography and ultrasonography.
- Diagnosis is more difficult in women of childbearing age in whom gynecologic processes may mimic appendicitis.

Therapy
- Surgical removal of the appendix, often performed laparoscopically, is curative.
- Adjunctive use of broad-spectrum antibiotics, such as piperacillin-tazobactam, ceftriaxone, and metronidazole, may be required.
- An "antibiotic first" strategy for acute uncomplicated appendicitis may be considered for carefully selected patients who have a strong preference for nonoperative treatment or who are poor surgical candidates.

In 1886 Fitz first described the natural course of acute inflammation of the appendix. In his seminal report he coined the term *appendicitis* and advocated early surgical intervention.[1] Today appendectomy is among the most common surgical emergencies of the abdomen; more than 330,000 nonincidental appendectomies are performed annually in the United States, accounting for 1 million inpatient hospital days.[2,3] With improvements in clinical assessment, antibiotic therapy, and surgical management, the overall mortality rate of acute appendicitis is less than 1%, although rates increase to 5% or more in the elderly.[3–5]

EPIDEMIOLOGY

The lifetime risk for appendicitis is 8.6% in men and 6.7% in women.[3] Although appendicitis is rare in infants, its incidence steadily increases through childhood and reaches a peak at 15 to 25 years of age for men and women.[3,5,6] The incidence of appendicitis declines through adulthood, and less than 25% of cases occur in individuals older than 45 years.[3] Men have slightly higher rates of appendicitis than women; the overall male-to-female rate ratio is 1.4:1.[3]

PATHOGENESIS

The appendix is a tube-shaped structure, usually 5 to 10 cm long in adults, which arises 2 to 3 cm below the terminal part of the ileum along the medial posterior wall of the cecum.[7] Once thought to be simply a vestigial remnant of evolution, recent studies suggest that the appendix may play an important role in the development and homeostasis of the intestinal microbiome and mucosal immune system.[8] Commensal bacteria reside in the appendix within a mucus-rich biofilm that is intermittently shed into the intestinal tract at a rate of approximately 3 mL per day. Given this, the appendix has been hypothesized to act as a microbial reservoir that can act to repopulate the intestinal tract when needed, for example, during recovery from acute diarrheal illnesses.[9,10] Microbe-host interactions between the resident microbiota and gut-associated lymphoid tissue of the appendix are also hypothesized to aid in the maturation of normal mucosal immune responses.[8,11]

Typically, the appendix lies in an ascending retrocecal position, but atypical positions, such as descending pelvic, transverse retrocecal, and ascending postileal, are common and can alter the typical clinical features of acute appendicitis.[7] Physical obstruction of the appendiceal lumen by fecaliths or other causes (e.g., foreign bodies, tumor, stricture, or parasites) has classically been thought to be the primary pathogenic mechanism of acute appendicitis.[12–16] Mucus accumulates within the obstructed appendiceal lumen, and intraluminal pressure increases, leading to compression of lymphatic and vascular drainage and causing ischemic damage of the mucosa, followed by microbial invasion and inflammation. Continued inflammation and ischemia, if left untreated, may lead to gangrene and eventual perforation. The pathologic hallmark of acute appendicitis is the presence of polymorphonuclear cells within the appendiceal wall, accompanied by other markers of inflammation, such as edema and vascular congestion.

In recent years, however, this classic model of pathogenesis of acute appendicitis has been called into question. In most modern case series fecaliths or other causes of obstruction are found in only a minority of cases.[17,18] The efficacy of medical rather than surgical treatment of acute appendicitis (see later) also suggests that physical obstruction may not be the primary pathogenic mechanism. This has led to the speculation that other inciting etiologies or cofactors, such as primary infectious agents, dietary fiber, genetic susceptibility, or hypersensitivity, lead to lymphoid hyperplasia and inflammation of the appendix.[18–21]

MICROBIOLOGY

Conventional cultures of inflamed or gangrenous appendices typically yield 10 to 14 different organisms, which generally reflect the colonic microbiota. A mixture of colonic anaerobic and facultative bacteria is usually recovered, predominantly *Escherichia coli, Bacteroides fragilis*

group, pigmented *Prevotella* spp., *Bilophila wadsworthia, Peptostreptococcus* spp., Enterobacteriaceae, and viridans streptococci, particularly the *Streptococcus anginosus* group.[22–24] *Pseudomonas aeruginosa* has also been found in a minority of cases (4%–15%) but is less frequently sensitive to routinely used antibiotics.[25,26]

Recently, culture-independent 16S ribosomal RNA gene sequencing-based studies have demonstrated that the microbial community of the appendix is remarkably diverse, consisting of more than a dozen phyla and hundreds of different species of bacteria.[27] Furthermore, these studies have shown that the appendiceal microbiome is distinct, with both quantitative and qualitative differences in composition compared with elsewhere in the digestive tract.[28] Although the diversity of bacteria in the healthy appendix is large, a relatively small number of taxa predominate, including those of the phyla Firmicutes, Proteobacteria, and Bacteroidetes.[27,28] A few taxa, including *Fusobacterium*, *Peptostreptococcus*, and *Parvimonas*—all typically considered to be oral commensal bacteria and occasional periodontal pathogens—are enriched in the inflamed appendix.[29,30] This has led some investigators to hypothesize that rather than being caused by physical obstruction of the appendiceal lumen, acute appendicitis may be the consequence of dysbiosis (microbial imbalance) of the appendix.[27,29]

In some instances intestinal pathogens have been associated with acute appendicitis. For example, *Yersinia enterocolitica* and *Yersinia pseudotuberculosis* are believed to have a causative role in some cases of acute appendicitis.[31–33] More common, however, nonplague *Yersinia* causes ileocecitis or mesenteric adenitis, which mimics acute appendicitis with fever, leukocytosis, and acute right lower quadrant pain.[34–36] Similarly, *Campylobacter* and nontyphoidal *Salmonella* can also cause ileocecitis and mesenteric adenitis.[35,37] Appendiceal or ileocecal tuberculosis, actinomycosis, and histoplasmosis are more likely to cause subacute or recurrent disease rather than classic acute appendicitis. Viral causes of mesenteric adenitis and, rarely, appendicitis include measles, Epstein-Barr virus, cytomegalovirus, and adenovirus.[38–41] Amebiasis may also cause appendicitis.[42] In many cases of mesenteric adenitis, an infectious cause is not identified but is probably present.[43] The disorder is usually discovered at the time of surgery for suspected appendicitis; mesenteric lymph nodes of the right iliac fossa are enlarged, the adjacent bowel is only mildly inflamed, and the appendix appears normal. Nevertheless, an appendectomy should be performed to avoid the need to differentiate a recurrent attack from true appendicitis in the future.

CLINICAL MANIFESTATIONS

The clinical manifestations of acute appendicitis are distinctive and, in many cases, diagnostic. Appendicitis classically starts as colicky, visceral periumbilical pain that evolves for the next 6 to 24 hours to localized, somatic right lower quadrant abdominal pain after inflammation extends to the parietal peritoneum. If the inflamed appendix lies in the anterior position, tenderness is often maximal at or near the McBurney point, which lies two to three fingerbreadths above the right anterior superior iliac spine on a line with the umbilicus. If the appendix lies in a position relatively hidden from the parietal peritoneum, pain may remain poorly localized, and migration to the right lower quadrant may be delayed or absent.[44] Pelvic appendices can cause pelvic or left lower quadrant pain. Third-trimester pregnancy or intestinal malrotation may shift pain to the right upper quadrant. Pain is often accompanied by mild fever, anorexia, nausea, and vomiting.

Guarding is usually seen on examination of the abdomen. Rebound tenderness in the right lower quadrant with palpation of the left lower quadrant, known as the Rovsing sign, may be elicited. Other maneuvers that support the diagnosis of appendicitis include pain with active extension of the right hip, termed the *psoas sign,* and pain with internal rotation of the right hip, termed the *obturator sign.* High fever or a sudden reduction in pain suggests perforation, whereas abdominal rigidity suggests diffuse peritonitis. A palpable right lower quadrant mass may indicate a phlegmon or walled-off periappendiceal abscess[4,45] or, alternatively, a cecal carcinoma.[46] Most instances of perforation occur as the result of delays in seeking medical care.[47]

Acute appendicitis in the elderly can present as subtle and muted clinical signs.[48,49] Pain may be generalized and of longer duration. This may result in delay of surgery and overall poorer outcome.

DIAGNOSIS

The diagnosis of acute appendicitis primarily is suggested by the history and physical examination findings. Acute onset of abdominal pain migrating over several hours to the right lower quadrant, with guarding and tenderness over the McBurney point, is most predictive of acute appendicitis; a history of previous pain, long duration of symptoms, and lack of migration to the right lower quadrant argue against it.[4,50] The serum concentration of β-human chorionic gonadotropin should be measured in all women of reproductive age to rule out a uterine or ectopic pregnancy. Most patients have a mild leukocytosis and elevated C-reactive protein value. If inflammation extends to the ureter or bladder, sterile pyuria may be noted on urinalysis. Elevation in procalcitonin levels has not been found to add diagnostic value to leukocyte counts or to the C-reactive protein level but may suggest complicated appendicitis.[51] Acute salpingitis with a tubo-ovarian abscess or impaction of a stone in the right ureter can be confused with acute appendicitis.

The appendix is found to be normal in 8% to 25% of patients who undergo emergency appendectomy.[3,5,52–54] This "negative appendectomy rate" is significantly higher in women of childbearing age, young children, and elderly individuals.[53,55,56] Conversely, 20% of all cases of appendicitis are initially missed on presentation.[57–59] In an effort to improve diagnostic accuracy, scoring systems based on clinical findings and laboratory data have been developed to assist in the diagnosis of acute appendicitis.[60] In practice, however, these systems lack sufficient power to discriminate reproducibly acute appendicitis from other causes of pain in the right lower quadrant (Table 78.1).[61]

Observation, laparoscopy, and imaging are additional methods used to improve the diagnostic accuracy of acute appendicitis. If the clinical presentation is ambiguous, observation and reassessment can distinguish cases of evolving appendicitis from other causes of abdominal pain without increasing the risk for perforation.[62] Diagnostic laparoscopy is particularly effective in women of childbearing age, in whom gynecologic causes of abdominal pain are common.[63,64] Diagnostic imaging, by ultrasonography, computed tomography (CT), or magnetic resonance imaging (MRI), has been shown to be very effective in diagnosing acute appendicitis. Ultrasonography is rapid and noninvasive, requires no contrast material, uses no ionizing radiation, and is excellent at visualizing gynecologic abnormalities. As such, it has proved to be particularly useful in the evaluation of young women, pregnant women, and children with suspected appendicitis.[65–68] Ultrasonography fails to visualize the appendix in 10% of cases[69] and is not as accurate as CT in diagnosing an abscess or phlegmon.[67]

TABLE 78.1 Causes of Right Lower Quadrant Pain

- Gastrointestinal
  - Appendicitis
  - Crohn ileitis/cecitis
  - Cecal diverticulitis
  - Meckel diverticulitis
  - Mesenteric lymphadenitis
  - Bacterial *(Yersinia, Campylobacter, Salmonella)* ileocolitis
  - Amebic colitis
  - Tuberculous colitis
  - Ileocecal actinomycosis
  - Biliary colic
  - Epiploic appendagitis
  - Typhlitis (neutropenic cecitis)
- Urinary tract
  - Pyelonephritis
  - Renal colic
- Neoplastic
  - Cecal adenocarcinoma
  - Carcinoid
  - Lymphoma
  - Metastasis
- Gynecologic
  - Ovarian cyst
  - Ectopic pregnancy
  - Endometriosis
  - Cervicitis
  - Uterine leiomyoma
  - Tubo-ovarian abscess
  - Pelvic actinomycosis
- Nonspecific abdominal pain

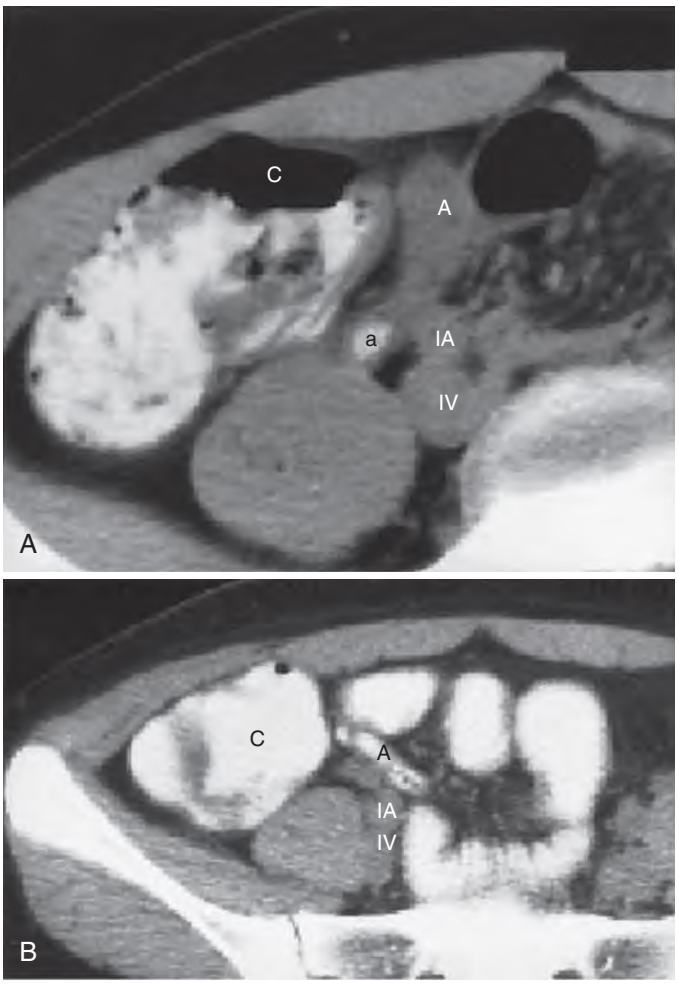

FIG. 78.1 Appendicitis. (A) Computed tomography (CT) scan of a 17-year-old boy with appendicitis. Axial image shows an inflamed, unopacified appendix *(A),* 15 mm in diameter, with proximal appendicolith *(a).* Also shown, and also in part B, are the cecum *(C),* common iliac artery *(IA),* and common iliac vein *(IV).* (B) CT scan of a 21-year-old woman with appendicitis. Axial image shows a tubular, opacified normal appendix *(A). (From Rao PM, Rhea JT, Novelline RA, et al. Effect of computed tomography of the appendix on treatment of patients and use of hospital resources.* N Engl J Med. *1998;338:141–146. Copyright © 1998 Massachusetts Medical Society. All rights reserved.)*

CT, particularly focused helical appendiceal CT, has a reported sensitivity of 94% to 99% and a specificity of 95% to 98% in patients with suspected appendicitis (Fig. 78.1).[70–72] CT can avoid delays before necessary appendectomy, diagnose other pathologic conditions such as right-sided diverticulitis, reduce negative appendectomy rates, and prevent unnecessary hospital admissions.[70,72] The addition of enteral contrast to intravenous contrast does not improve the sensitivity of CT for the diagnosis of acute appendicitis.[73] Low-dose CT, which reduces exposure to ionizing radiation, has been found to be noninferior to standard-dose CT.[74] Use of CT to improve the diagnostic accuracy of suspected appendicitis has been less consistent, however, in clinical practice.[75,76]

MRI can also aid in the diagnosis of appendicitis. Using rapid unenhanced imaging protocols, MRI has a diagnostic accuracy for acute appendicitis that is better than ultrasound and comparable to CT (sensitivity, 96%–97%; specificity 95%–99%).[77–79] Like ultrasound, MRI offers the advantages of avoiding exposure to ionizing radiation and radiographic contrast media and therefore may be particularly attractive in certain populations, such as pregnant women and persons with contrast allergies.[80,81]

Many experts recommended a graded approach to the evaluation of possible acute appendicitis, where factors such as history, examination, patient characteristics (e.g., age, pregnancy status), and clinical risk scores are used to determine diagnostic and management strategies.[45,82,83] An example of one algorithm is presented in Fig. 78.2.[82]

THERAPY

The primary treatment of appendicitis is surgery. Preoperative treatment includes fluid resuscitation and parenteral use of antibiotics. In cases of uncomplicated acute appendicitis, routine perioperative antibiotic prophylaxis for gastrointestinal surgery usually suffices (see Chapter 313).[84–86] In cases of appendicitis with rupture, gangrene, abscesses, or secondary peritonitis, an antibiotic regimen that provides broad coverage for facultative and anaerobic colonic flora should be used: piperacillin-tazobactam, ceftriaxone plus metronidazole, imipenem-cilastatin (see Chapter 74).[85,86] Acute appendicitis, either without rupture or with perforation and secondary peritonitis, requires prompt surgical intervention. There is no clear consensus regarding the optimal operative approach (open vs. laparoscopic) in patients with suspected appendicitis. Laparoscopic appendectomy offers the advantage of allowing for further diagnostic evaluation if a normal appendix is found.[64] In addition, a Cochrane Database systematic review of more than 50 studies suggested that patients have fewer wound infections, less postoperative pain, shorter hospital stays, and quicker returns to normal activity after laparoscopic appendectomy than after open appendectomy.[87] A population-based study from Taiwan of more than 65,000 patients showed a lower readmission rate and shorter hospital stay for laparoscopic versus open appendectomy.[88] Laparoscopic appendectomies are associated, however, with more frequent intraabdominal abscesses, longer operative times, and higher operative and total hospital costs.[87,88] In many cases surgery for acute, uncomplicated appendicitis can be safely deferred for a short period of time (overnight).[87]

There is even less consensus on the optimal postoperative treatment of perforated appendicitis, including the duration of antibiotic therapy, use of parenteral versus oral agents, and duration of hospitalization.[89,90] Patients generally are treated with intravenously administered antibiotics for 4 to 7 days until fever resolves, the white blood cell count normalizes, and bowel function returns.[85,86] However, recent data from an observational study comparing 3 days versus 5 days of antibiotics after appendectomy for complicated appendicitis suggests that 3 days may be sufficient.[91] Institutional clinical practice pathways have been shown to reduce infectious complications and the cost of care.[92,93]

In cases of appendicitis complicated by a contained perforation or phlegmon, antibiotic therapy and percutaneous drainage of the periappendiceal abscess, if present, can be performed. If these maneuvers produce a favorable response, interval appendectomy can be performed 6 to 8 weeks later after inflammation subsides.[86,94,95] Historically, untreated appendicitis was a major cause of portal vein thrombophlebitis (pylephlebitis) and pyogenic liver abscess (see Chapter 75), but these complications are rare in the antibiotic era.[96]

Recently, the need for an appendectomy in all cases of uncomplicated appendicitis has been called into question.[97,98] In fact, "antibiotic first" therapy has recently been advanced as an alternative approach for the management of clinically suspected appendicitis in young men with equivocal imaging, as long as they are observed in the hospital for at least 48 hours and show clinical improvement within 24 hours.[85] It has been known for decades that some individuals with a clinical diagnosis of appendicitis and lacking access to immediate surgical care, such as personnel on submarines, may fully recover spontaneously or with antibiotic treatment alone.[99] More recent studies have confirmed that radiographically proven appendicitis can resolve with conservative therapy.[100,101] If routine, a predominantly nonsurgical approach to the treatment of appendicitis would avoid complications of surgery and lead to substantial health care cost savings. Several more recent studies suggest that medical treatment of appendicitis can be successful, at least in certain patient populations.[101–108] Recurrent appendicitis has been reported to occur in 5% to 38% of all patients, however, of which 4% to 100% progress to perforation or secondary peritonitis.[101–105] Other prospective studies have shown antibiotic therapy alone to be inferior to surgery.[109,110] Systematic reviews and meta-analyses have come to conflicting conclusions, and editorials have weighed in on both sides.[111–117] The most appropriate study design by which to compare antibiotics to

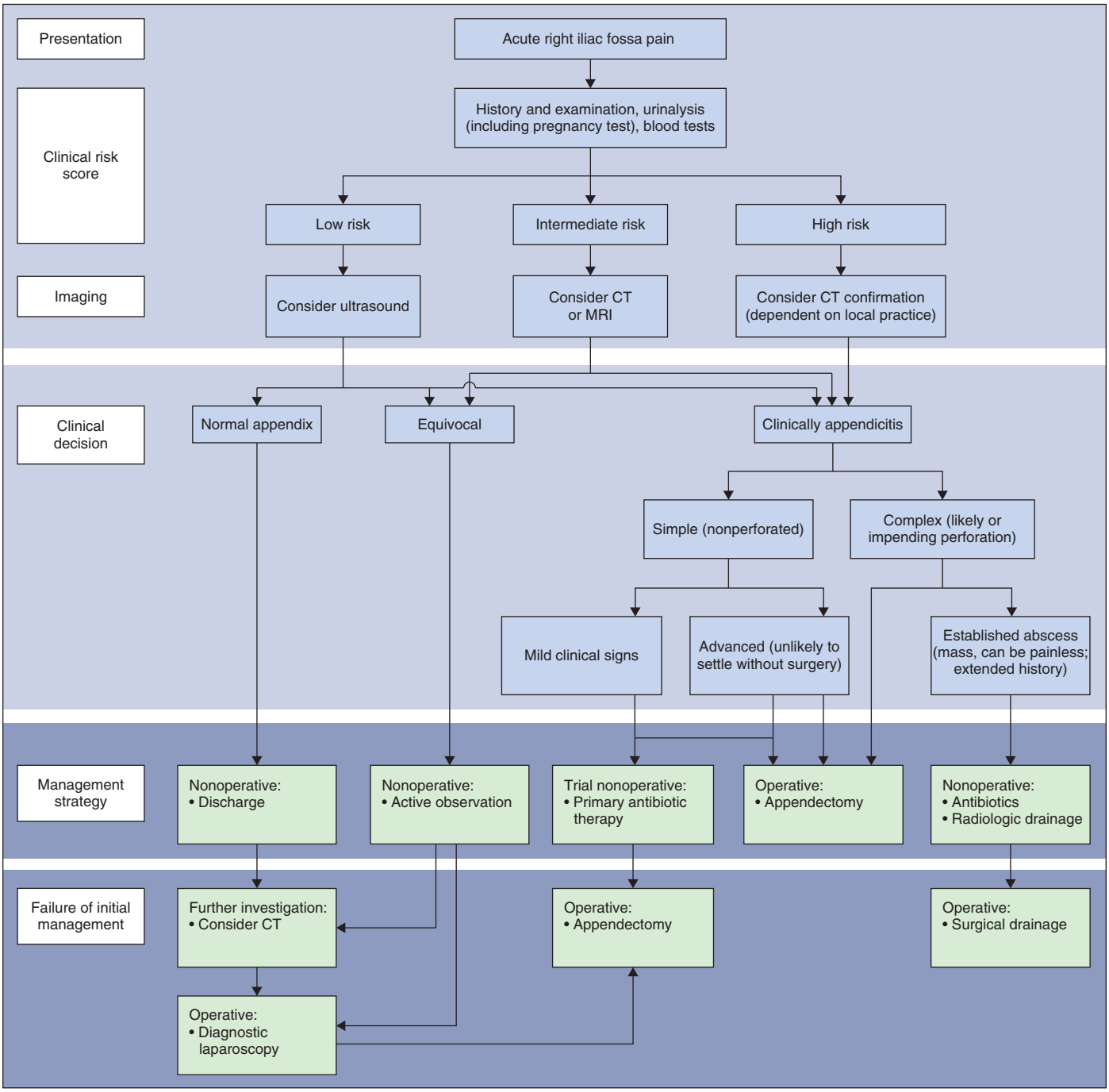

FIG. 78.2 Flowchart of guidance for a stratified approach to preoperative management of suspected appendicitis. *CT,* Computed tomography; *MRI,* magnetic resonance imaging. *(From Bhangu A, Søreide K, Di Saverio S, et al. Acute appendicitis: modern understanding of pathogenesis, diagnosis, and management.* Lancet. *2015;386:1278–1287.)*

surgery is also a matter of debate, and a recent editorial[118] and letter[119] have emphasized that future studies should use well-defined clinical criteria to judge risks and benefits. Conservative therapy may delay the diagnosis of other pathologic processes, such as appendiceal tumors. Unless large prospective randomized trials with appropriate follow-up demonstrate equivalent efficacy of a nonoperative approach to the treatment of acute appendicitis, surgery will likely remain the standard approach except in carefully selected patients.[85]

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The complete reference list is available online at Expert Consult.

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79 Diverticulitis and Neutropenic Enterocolitis

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SHORT VIEW SUMMARY

Definition
- Diverticulitis is inflammation and infection of the bowel wall, leading to microperforation of colonic diverticula.
- Neutropenic enterocolitis (typhlitis) is characterized by abdominal pain and fever during periods of neutropenia resulting from mucosal inflammation, degeneration, and microbial invasion.

Epidemiology
- Diverticulitis occurs in 10% to 25% of all individuals with diverticulosis, which has a prevalence of 30% to 40% in Western society.
- Diverticulitis leads to 150,000 hospital admissions and 24,000 elective operations annually in the United States.
- The incidence of neutropenic enterocolitis is unknown but has been estimated to be 5% in hospitalized neutropenic adults with cancer.
- Bacteremia or fungemia occurs in 14% to 44% of patients with neutropenic enterocolitis.

Microbiology
- Acute diverticulitis is a polymicrobial infection caused by endogenous anaerobic and facultative bacteria, including *Bacteroides* spp., *Peptostreptococcus* spp., Enterobacteriaceae, viridans-group streptococci, and enterococci.
- *Pseudomonas aeruginosa,* Enterobacteriaceae, *Bacteroides fragilis,* viridans-group streptococci, enterococci, and *Candida* spp. are common causes of bloodstream infections in patients with neutropenic enterocolitis.

Diagnosis
- Radiographic imaging (computed tomography and ultrasonography) is essential for the evaluation of suspected diverticulitis and neutropenic enterocolitis.
- More than half of patients with clinically suspected diverticulitis are diagnosed with an alternative condition after diagnostic imaging.
- Radiographic findings of diverticulitis include pericolic fat stranding, diverticula, bowel wall thickening, and phlegmon or abscess formation.
- Neutropenic enterocolitis can be defined as bowel wall thickening, usually of the cecum, greater than 4 mm, with neutropenia, fever, and abdominal pain.

Therapy
- Acute uncomplicated diverticulitis can be safely treated in select outpatients with a short course of oral antibiotics. However, the necessity of antibiotic therapy for the treatment of uncomplicated diverticulitis is controversial.
- Complicated diverticulitis or patients with comorbidities or other predictors of worse outcomes should be hospitalized.
- Percutaneous drainage of large abscesses (>5 cm in diameter) can be temporizing in acutely ill patients.
- Management of neutropenic enterocolitis includes bowel rest, intravenous fluids, nutritional support, and broad-spectrum parenteral antibiotics that cover enteric facultative and anaerobic flora, *P. aeruginosa,* and perhaps yeast.
- Surgery may be required for patients with diverticulitis or neutropenic enterocolitis with intraperitoneal perforation, uncontrolled sepsis, persistent gastrointestinal bleeding, or obstruction, or for those who fail to respond to medical therapy.

Prevention
- High dietary fiber and physical activity may be associated with reduced symptomatic diverticular disease.
- Prolonged nonsteroidal antiinflammatory drug use appears to be a risk factor for diverticular disease.

DIVERTICULITIS

Most colonic diverticula are pseudodiverticula that occur when the mucosa and submucosa herniate through the muscularis propria. These saccular herniations develop in areas of relative structural weakness of the colonic wall, where small nutrient arteries supplying the colonic mucosa, the *vasa recta,* penetrate the circular muscle layer. In the West, the sigmoid and descending colons are most commonly affected. In Asia, colonic diverticula are predominantly right sided, involve all layers of the colonic wall, and likely represent a distinct clinical condition. *Diverticulitis,* defined as inflammation and infection of the bowel wall associated with diverticula, is the most frequent complication of this disorder.

Epidemiology

Only 4% to 25% of patients with diverticulosis manifest clinical disease, making its true prevalence difficult to measure.[1,2] Although the disorder occurs worldwide, diverticulosis is particularly prominent in Western society, where the prevalence has been estimated to be 30% to 40%.[3,4] In the United States alone, there were over 150,000 hospital admissions for acute diverticulitis and an estimated 24,000 elective operations for diverticulitis in 2005, based on hospital discharge records.[5] By contrast, the prevalence of diverticulosis in rural Asia and Africa is estimated to be much less than 1%.[6] Increased prevalence is observed in populations that become westernized, presumably because of dietary changes or other environmental factors.[7–9] The prevalence of diverticulosis increases with age in the West, affecting 50% of those older than 70 years of age and up to two-thirds of individuals by 85 years of age.[1,6,10] The complications of diverticulosis, including diverticulitis, also increase with age,[10] although some studies suggest that diverticulitis may recur more often or be more malignant in patients who are younger than 40 years of age.[2,11–13] Diverticulitis appears to be increasing in the United States, but it is not clear if this reflects demographic shifts, changes in diet, improved recognition resulting from increased use of computed tomography (CT), or other factors.[5]

The most extensively studied risk factor for the development of diverticular disease is low dietary fiber intake. Diets with reduced dietary fiber are associated with more colonic diverticulosis[6] and with symptomatic diverticular disease.[14,15] Other risk factors for the development of diverticulitis are less well understood. Use of corticosteroids, nonsteroidal antiinflammatory drugs, or opiates may be positively associated with diverticulitis, perforation, or both.[16–18] Lack of physical activity and obesity also appear to be independent risk factors for symptomatic disease.[12,19,20] By contrast, vigorous physical activity independent of body mass may reduce symptomatic diverticular disease.[21] Contrary to popular belief, popcorn, corn, and nuts do not appear to increase the incidence of diverticular disease. In fact, nuts and popcorn consumption were

shown to be protective in one study.[22] Tobacco, alcohol, and caffeine consumption also do not appear to increase diverticular disease.[23]

Pathogenesis

The formation of diverticula is thought to be caused by a combination of increased intraluminal pressure and weakening of the bowel wall.[24] High dietary fiber intake increases stool volume and reduces bowel transit time, leading to decreased intracolonic pressures. For over a century, the pathogenesis of diverticulitis has been thought to be very similar to that of acute appendicitis: a fecalith obstructs the neck of the diverticulum,[25] causing mucus accumulation, bacterial overgrowth, perforation, and inflammation of the bowel wall and adjacent tissues. Recent speculation has turned to whether changes in the intestinal microbiota—a consequence of a low-dietary-fiber Western diet—alters mucosal immune homeostasis, leading to low-grade chronic inflammation, particularly in chronic diverticular disease.[26,27,28,29] Microperforation may remain well localized, leading to limited colonic wall inflammation and the formation of a small peridiverticular phlegmon or abscess. Macroperforation results in larger abscesses; if not confined, its complications include distant abscesses, extension to other organs, spreading peritonitis, large inflammatory masses, and fistula formation.[10,24] Less commonly, gross fecal contamination can occur with free rupture of an unobstructed and uninflamed diverticulum into the peritoneal cavity. Rupture of a localized peridiverticular abscess into the peritoneal cavity does not result in gross fecal contamination, presumably because the diverticular neck is obstructed by a fecalith or inflammation.[24]

Microbiology

Like most other cases of secondary peritonitis, acute diverticulitis is a polymicrobial infection caused by a variety of endogenous anaerobic and facultative bacteria. Commonly isolated organisms include *Bacteroides* spp., *Peptostreptococcus* spp., Enterobacteriaceae, viridans streptococci, and enterococci.[30,31]

Clinical Manifestations

The clinical manifestations of uncomplicated diverticulitis resemble those of appendicitis but with findings typically on the left side of the abdomen. Diverticulitis often starts with visceral hypogastric pain that evolves to somatic pain that is localized, in the case of sigmoid disease, to the left lower quadrant. In contrast to acute appendicitis, the pain is often recurrent and is present for several days before presentation.[32] Fever, nausea and vomiting, changes in bowel habits, and urinary symptoms often accompany the pain. Leukocytosis is common but not invariably present (69%–93% of cases).[33] Urinalysis may reveal sterile pyuria if inflammation extends to the urinary system. Trace blood may be present in the stool, but hematochezia is uncommon and should raise suspicion for an alternative diagnosis. Low-grade fever is common in uncomplicated disease, and the physical examination typically reveals abdominal tenderness, guarding, and rebound tenderness in the left lower quadrant, the suprapubic area, or both; bowel sounds may be hypoactive or normal. A palpable abdominal mass may be caused by an inflammatory process but may also be indicative of cancer. High fever and abdominal rigidity suggest generalized peritonitis after perforation. Hyperactive bowel sounds suggest obstruction. Fistulization of the bladder or ureter with the colon may lead to pneumaturia and fecaluria[34]; passage of feces and flatus through the vagina occurs with fistula formation with the vagina or uterus.[35] Recurrent diverticulitis can lead to stricture and obstruction. Pyogenic liver abscess and pylephlebitis are rare complications.[36]

Diagnosis

Although the diagnosis of acute diverticulitis can be made on the basis of the clinical evaluation,[10,33] more than half of patients with clinically suspected diverticulitis are found to have alternative conditions.[37] For this reason, diagnostic studies are performed in most cases of suspected diverticulitis,[18,38] and they are particularly important in the patient with an atypical presentation, a suspected complication, severe illness, or clinical deterioration.[10,33] Imaging modalities include CT and ultrasonography.

CT is now considered to be the diagnostic procedure of choice for patients with suspected acute diverticulitis.[10,24,33,39] Tomographic evidence of diverticulitis includes pericolic fat stranding (98%), diverticula (84%), bowel wall thickening (70%), and phlegmon or abscess formation (35%).[40] CT also offers the opportunity for therapeutic intervention: CT-guided percutaneous drainage can be temporizing in acutely ill patients with large abscesses (>5 cm in diameter), permitting curative surgery on an elective basis.[10,24,41,42] Immediate surgery is indicated, however, if the abscess cavity contains gross fecal material. Abdominal CT for suspected diverticulitis has traditionally used oral, rectal, and, if not contraindicated, intravenous contrast. Helical CT using colonic contrast alone has been shown to be highly effective in the evaluation of patients with left lower quadrant pain. Similar to appendiceal CT, "diverticular CT" has been shown to have high sensitivity (97%), specificity (100%), and overall diagnostic accuracy (99%) in the prospective evaluation of suspected diverticulitis.[37] CT findings include arrowhead-shaped collections of contrast and presence of an inflamed diverticulum.

Magnetic resonance imaging (MRI) has also been utilized in diagnosis of diverticulitis with high sensitivity (86%–94%) and specificity (88%–92%), and with findings similar to those seen with CT.[43,44] MRI has the advantage of absence of radiation exposure, which may be a consideration if repeated examinations are necessary. However, the inability to drain abscesses percutaneously is a disadvantage of using MRI alone. Comparative studies of CT and MRI would be helpful to further guide their use in this setting.

Acute diverticulitis can also be confirmed by ultrasonography, which is capable of delineating inflamed colonic segments, phlegmons, and abscesses.[45] When performed by experienced operators, the diagnostic accuracy of ultrasonography rivals that of CT.[46] In practice, however, ultrasonography is used less frequently than CT for the evaluation of left lower quadrant pain, in contrast to right abdominal pain. The use of a contrast enema to diagnose acute diverticulitis has largely been supplanted by CT and ultrasound; when used, water-soluble contrast should be used in the event of unrecognized macroperforation. Double-contrast enemas should be avoided, because insufflation of air could dislodge an obstructing fecalith and cause perforation.[24] Given the risk of perforation, endoscopy is also avoided in the initial evaluation of patients with suspected acute diverticulitis. On occasion, limited sigmoidoscopy with minimal air insufflation is performed in ambiguous cases to exclude other diagnoses, such as inflammatory bowel disease, carcinoma, or ischemic colitis.[10,24] A complete colonic evaluation should be performed 6 to 8 weeks after resolution of an episode of acute diverticulitis to rule out coexisting lesions, including colon cancer.

Therapy

A trial of outpatient therapy is indicated for acute, uncomplicated diverticulitis or for a well-localized, small (≤5 cm in diameter) peridiverticular abscess, provided the patient can tolerate oral hydration. Outpatient treatment may also include a limited (e.g., 7- to 10-day) course of an oral broad-spectrum antibiotic agent or regimen active against facultative and anaerobic colonic microbiota.[10,24] Antibiotic regimens recommended by the Surgical Infection Society are shown in Table 79.1. Success rates of 94% to 97% have been reported for patients treated in this manner.[47,48,49,50] In one retrospective study, predictors of failure of outpatient therapy included free fluid on tomographic imaging and female sex.[49] A systematic review supported the use of outpatient management in mild or uncomplicated diverticulitis.[51] However, the necessity of treating acute uncomplicated diverticulitis with antibiotics has recently been challenged. Several retrospective case-control series and one open, multicenter, randomized controlled trial of hospitalized patients with CT-proven uncomplicated diverticulitis failed to demonstrate that antibiotics prevented complications, sped recovery, or reduced recurrent diverticular disease.[52–54] A Cochrane review also supported the view that antibiotics may not be necessary in this setting, though it calls for more high-quality trials.[50] Guidelines from the American Gastroenterological Association Institute suggest that "antibiotics should be used selectively, rather than routinely, in patients with acute uncomplicated diverticulitis."[55] Probiotics, mesalamine (5-aminosalicylic acid), and nonabsorbable antibiotics, such as rifaximin, are examples of therapies under investigation that target the potential roles of intestinal dysbiosis and chronic low-grade inflammation in diverticular disease pathogenesis.[27,56–58] If the patient is unable to tolerate oral hydration,

TABLE 79.1 Agents and Regimens That May Be Used for the Initial Treatment of Diverticulitis

	COMMUNITY-ACQUIRED INFECTION IN ADULTS	
REGIMEN	**Mild-to-Moderate Severity[a]**	**High Risk or Severity: Severe Physiologic Disturbance, Advanced Age, or Immunocompromised State[a]**
Single agent	Ertapenem Moxifloxacin	Imipenem-cilastatin Meropenem Doripenem Piperacillin-tazobactam
Combination	Ceftriaxone + metronidazole Cefotaxime + metronidazole Ciprofloxacin + metronidazole Levofloxacin + metronidazole	Cefepime + metronidazole Aztreonam + metronidazole + vancomycin

[a]Because of increasing resistance of *Escherichia coli* to fluoroquinolones, local population susceptibility profiles and, if available, isolate susceptibility should be reviewed.
Modified from Manzuski JE, Tessier JM, Addison MK, et al. The Surgical Infection Society revised guidelines on the management of intra-abdominal infection. Surg Infect. *2017;18:1–76.*

requires narcotic analgesics, or fails to improve despite appropriate outpatient therapy, admission to the hospital for nasogastric tube placement, bowel rest, and parenteral antibiotics is indicated. Elderly patients and those with compromised immune systems or other comorbidities also should be hospitalized. Parenteral antibiotics should be started for the treatment of secondary peritonitis, as shown in Table 79.1 (see Chapter 74).[59] Failure to respond to medical therapy within 48 to 72 hours should prompt repeat investigation for complications, consideration of alternative diagnoses, and surgical evaluation.[10,24]

Conservative medical therapy is successful in 70% to 80% of patients hospitalized with acute diverticulitis.[24,33] Indications for emergency colonic resection include uncontrolled sepsis, generalized peritonitis, acute clinical deterioration, persistent obstruction, and failure to respond to medical therapy. Under these circumstances, a two-stage operation, such as the Hartmann procedure, is usually performed.[33,60] The Hartmann procedure entails resection of the diseased colon, end colostomy, and closure of the distal loop or creation of a mucous fistula; colonic continuity can be restored several months later by elective anastomosis.[60] An alternative two-stage operation is primary resection of the diseased segment of colon with immediate anastomosis after intraoperative colonic lavage and proximal fecal diversion, followed later by elective stoma closure.[61]

Elective colonic resection is usually performed in cases of fistula formation or recurrent attacks of diverticulitis or for complicated diverticulitis brought under control with conservative therapy.[24,33] In these cases, a one-stage procedure with primary resection and anastomosis can be performed, with lower morbidity and mortality and a shorter hospital length of stay than a two-stage procedure. Elective surgery should also be considered for patients at high risk for complications of recurrent diverticulitis, including those with immunosuppressive conditions (e.g., organ transplantation, chronic corticosteroid therapy, renal failure)[62,63,64,65] and perhaps those younger than 40 years,[11] although these considerations are controversial.[66–68] Laparoscopic sigmoidectomy is an alternative to laparotomy in cases of mild-to-moderate disease.[69,70] Retrospective studies have reported that a one-stage procedure, combined with intraoperative colonic lavage but no protective diverting colostomy, may be feasible even in the moderate- to high-risk patient with colonic perforation.[71,72] Peritoneal lavage without sigmoidectomy has also emerged as a treatment for perforated diverticulitis. To date, three randomized trials have compared laparoscopic lavage to the Hartmann procedure, which involves sigmoid resection and end colostomy. In three trials, laparoscopic lavage was not found to be superior to the Hartmann procedure, with one trial demonstrating increased morbidity in the laparoscopic lavage group.[73–75] In one trial, laparoscopic lavage reduced the need for reoperation and had a safety profile similar to that of the Hartmann procedure.[76] The disparate findings in these trials may have been due to differences in primary outcome variables.[77] However, more recent guidelines no longer advocate laparoscopic lavage for perforated diverticulitis.[78]

The classic three-stage procedure, consisting of drainage and proximal diverting colostomy, interval resection of diseased bowel with primary anastomosis, and stoma closure, has largely been abandoned because failure to eliminate the source of peritoneal infection resulted in higher mortality rates compared with the two-stage procedure.[60]

NEUTROPENIC ENTEROCOLITIS (TYPHLITIS)

Neutropenic enterocolitis is also referred to as typhlitis, from the Greek *typhi* or "blind," referring to the blind-ended cecum. It is a life-threatening complication of myelosuppressive chemotherapy administered for the treatment of hematologic and, less commonly, solid-tissue malignancies.[79–83] It is also rarely seen in individuals with human immunodeficiency virus infection[84] and in those with neutropenia caused by aplastic anemia, drug-induced agranulocytosis, cyclic neutropenia, or acute leukemia before the initiation of chemotherapy.[81,85–87] Although estimates vary greatly between studies, the incidence rate of neutropenic enterocolitis has been estimated to be approximately 5% for neutropenic adults hospitalized with hematologic or solid malignancies or with aplastic anemia.[79,88]

Pathogenesis

The pathologic characteristic of neutropenic enterocolitis is marked thickening and edema of the bowel wall, typically involving the cecum and often extending to the ascending colon, terminal ileum, or both.[85] Although the cecum is most commonly involved, other segments of the large or small bowel may also be affected.[89] Examination of the bowel wall reveals discrete or coalesced mucosal ulceration, intramural thrombocytopenic hemorrhage, and degeneration of the muscularis mucosa. Histologic specimens demonstrate mononuclear infiltrates and a variety of invading bacteria and fungi. The pathogenesis is multifactorial and incompletely understood. Cytotoxic chemotherapy and irradiation lead to activation of nuclear factor kappa B, production of proinflammatory cytokines, epithelial cell apoptosis, and increased mucosal permeability.[79,90] Rarely, ulceration and necrosis resulting from direct leukemic infiltration of the intestinal tract can occur.[91] The combination of neutropenia, mucosal injury, and possibly ischemia resulting from cecal distention allows gut flora to opportunistically invade the bowel wall. In the setting of impaired host immunity, these organisms proliferate and cause local destruction by elaboration of exotoxins.[92] Complications include sepsis resulting from translocation of the resident microflora and endotoxins across the injured mucosal barrier, uncontrolled hemorrhage, and perforation.

Clinical Manifestations

Clinical manifestations are variable and depend on the extent of disease. Patients typically present with fever, nausea, vomiting, abdominal pain and tenderness, and diarrhea that is often bloody. Given the prominence of cecal involvement, neutropenic enterocolitis can mimic acute appendicitis, with localization of abdominal pain and tenderness to the right lower quadrant.[93] Right lower abdominal pain is absent in 40% to 55% of cases, however,[94,95] and corticosteroid therapy may mask the symptoms of abdominal pain altogether.[85] Abdominal distention may be present in up to two-thirds of patients, but paralytic ileus is uncommon.[79] Severe stomatitis and pharyngitis may be present and are markers

of diffuse mucosal injury. Rapid progression to the development of an acute abdomen is not uncommon. Symptoms typically develop after 7 to 14 days of neutropenia (absolute neutrophil count, <500/mm^3). In a study of patients with newly diagnosed acute myeloid leukemia treated with cytarabine and idarubicin, 26% developed neutropenic enterocolitis at a median of 17 days after starting chemotherapy.[96] Alternative diagnoses, in addition to acute appendicitis, include chemotherapy-induced mucositis, pseudomembranous colitis, graft-versus-host disease, chronic mucormycosis or aspergillosis, intussusception, ischemic colitis, bowel obstruction, Ogilvie syndrome (colonic pseudo-obstruction), ileus, acute cholecystitis, acute pancreatitis, cytomegalovirus enterocolitis, and herpes zoster.[79,97]

Diagnosis

Ultrasonography and CT have largely supplanted plain radiography of the abdomen in the evaluation of suspected neutropenic enterocolitis.[82,97] Proposed diagnostic criteria for acute neutropenic enterocolitis include bowel wall thickening of greater than 4 mm, fever, and abdominal pain.[88] The degree of bowel wall thickening, as measured by ultrasonography or CT, correlates with severity of disease: patients with bowel wall thickness greater than 10 mm had a 60% mortality rate compared with 4% for those with a thickness of less than 10 mm.[98]

Diagnostic tests for *Clostridioides difficile* (formerly *Clostridium difficile*) should be performed, and blood and stool cultures should be obtained. Bacteremia or fungemia occurs in 14% to 44% of patients, most commonly with *Pseudomonas aeruginosa,* Enterobacteriaceae, *Bacteroides fragilis,* viridans-group streptococci, enterococci, and *Candida* spp.[81,82,95,99,100] Patients with *Clostridium septicum* bacteremia may have a more fulminant, lethal course,[86,101] and this infection may represent a different syndrome.[102]

Therapy

The management of neutropenic enterocolitis has evolved over the last several decades. Although a number of early studies reported mortality rates greater than 50% and advocated early surgical intervention,[103,104] recent studies have reported mortality rates of less than 20% with conservative medical therapy.[81,82,95,99,100] Management includes bowel rest, decompression, intravenous fluids, nutritional support, and broad-spectrum parenteral antibiotics. The antimicrobial regimen should cover enteric facultative and anaerobic flora, *P. aeruginosa,* and perhaps yeast. Examples include cefepime or ceftazidime with metronidazole, piperacillin-tazobactam, or meropenem, all with the possible addition of an antifungal agent with activity against *Candida,* especially if there is a lack of response at 72 hours.[59,83,88,105] The regimen should also effectively treat *C. difficile* if it has not been excluded as a possible cause. The indications for immediate surgical intervention include persistent gastrointestinal bleeding despite resolution of hematologic and clotting abnormalities, free intraperitoneal perforation, and clinical deterioration, suggesting uncontrolled sepsis.[100]

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The complete reference list is available online at Expert Consult.

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G Cardiovascular Infections

80 Endocarditis and Intravascular Infections

Thomas L. Holland, Arnold S. Bayer, and Vance G. Fowler, Jr.

SHORT VIEW SUMMARY

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

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

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

Diagnosis
- Results of blood cultures remain the cornerstone of diagnosis of endocarditis.
- Clinical evaluation alone is insufficient to exclude the possibility of endocarditis.
- Echocardiography, particularly transesophageal echocardiography, has greatly improved the clinician's ability to identify endocarditis.
- Diagnostic schema, such as the modified Duke criteria, are useful in establishing the presence of endocarditis.

Therapy
- Cardiac surgery is required in up to half of patients with endocarditis and improves patient outcome.
- Cardiac surgery is especially important in patients with endocarditis who have heart failure, paravalvular abscess, recurrent embolic events, or ongoing sepsis or who are infected with highly resistant or fungal pathogens.
- Although the timing of cardiac surgery, particularly after embolic events involving the central nervous system, remains controversial, emerging evidence supports the benefit of early valve replacement surgery for endocarditis.
- Antibiotic therapy involves extended courses of antibiotics. Treatment is highly pathogen specific and is summarized in Table 80.7. Guidelines for treatment of IE were updated in 2015.[1]
- Addition of adjunctive low-dose, short-course gentamicin to standard antibiotic treatment of *S. aureus* native valve IE has been shown to confer high risk for nephrotoxicity without significant improvement in clinical outcomes and is not encouraged.
- Several observational studies support the use of high-dose ceftriaxone in combination with ampicillin for the treatment of ampicillin-susceptible, aminoglycoside-resistant enterococcal endocarditis or for patients with underlying renal disease.

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

INFECTIVE ENDOCARDITIS

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

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

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

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

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

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

These questions are discussed in detail in the following sections.

Epidemiology

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

Age

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

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

Health Care–Associated Infective Endocarditis

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

Pattern of Valvular Involvement

The heart valve involved by the infection varies considerably with the proportion of acute cases reported in each series. The distribution ranges from 28% to 45% of cases for the mitral valve alone, 5% to 36% for the aortic valve alone, and 0% to 35% for the aortic and mitral valves combined. The tricuspid valve rarely is involved (0%–6% of cases), and the pulmonary valve even less often (<1%).[7,18] Involvement of the aortic valve alone is increasing in frequency and correlates with the increase in acute cases; the incidence was 5% in 1938 and increased to 38% by 2000.[7]

Predisposing Factors

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

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

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

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

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

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

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

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

Pathogenesis and Pathophysiology

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

Nonbacterial Thrombotic Endocarditis

Luschka, in 1852, first suggested that IE resulted when septic coronary emboli lodged in the vessels of the cardiac valve.[46] This hypothesis was discarded, because cardiac valves are poorly vascularized.[43,47,48] It now is clear that the initial colonization occurs on the damaged endothelial surface of the valve. In experimental animals, it is almost impossible to produce IE with intravenous injections of bacteria unless the valvular surface is first perturbed. If a polyethylene catheter is passed across the aortic valve of a rat or rabbit, IE is produced with intravenously injected bacteria or fungi.[49,50] Microscopic examination of this early lesion shows the organisms intimately adherent to fibrin-platelet deposits overlying interstitial edema and mild cellular distortion that have formed in areas of valvular trauma.[51] Scanning electron micrographs of the damaged valvular surface confirm the adhesion of microorganisms to these areas of fibrin-platelet deposition early in the disease course.[52] The organisms are covered rapidly by fibrin.[53]

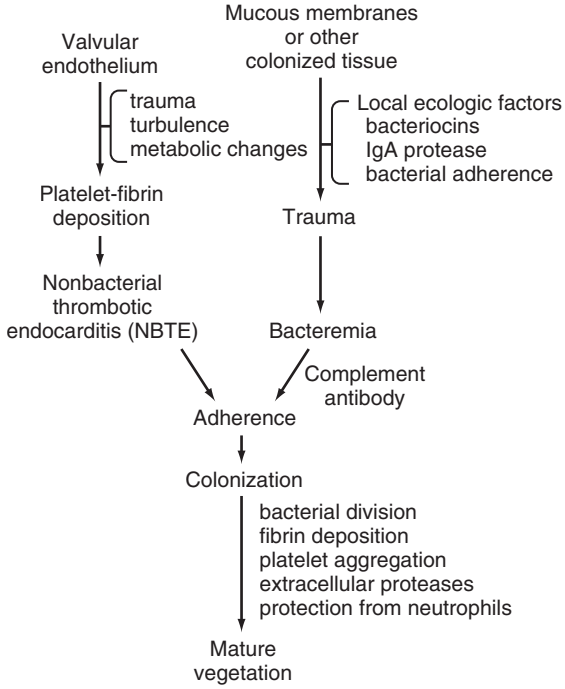

FIG. 80.1 Proposed scheme for the pathogenesis of infective endocarditis. *IgA,* Immunoglobulin A.

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

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

patients with solid tumors undergoing prospective echocardiographic screening.[56] Valvular lesions were most common among patients with carcinoma of the pancreas or lung or lymphoma.

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

Hemodynamic Factors

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

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

Transient Bacteremia

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

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

TABLE 80.1 Incidence of Bacteremia After Various Procedures

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

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

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

Microorganism–Nonbacterial Thrombotic Endocarditis Interaction

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

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

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

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

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

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

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

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

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

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

Viridans-Group Streptococcal Interactions With Platelets

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

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

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

Adhesion to Nonbacterial Thrombotic Endocarditis by Other Organisms

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

Pathogenesis of *Staphylococcus aureus* Infective Endocarditis

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

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

Effect of Antibiotics on Development of Infective Endocarditis

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

Platelets and the Pathogenesis of Infective Endocarditis

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

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

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

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

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

Microbial resistance to the microbicidal activity of PMPs may contribute to the pathogenesis of IE. This hypothesis was supported by a reduction in vegetation weight and bacterial concentration in rabbits with experimental aortic valve *S. aureus* endocarditis after treatment with aspirin.[160] In addition, three studies in experimental IE confirmed the importance of the relationship of PMP resistance and the pathogenesis of IE. In experimental viridans streptococcal IE and *S. aureus* IE, PMP-resistant strains exhibited an enhanced capacity to persist at sites of valvular damage.[161,162] In addition, *S. aureus* strains exhibiting the PMP resistance phenotype in vitro were able to proliferate within the vegetation and hematogenously seeded extracardiac foci (kidneys, spleen) to a significantly greater extent than their isogenic counterparts, which were PMP susceptible in vitro.[163,164]

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

Interactions Between Bacteria and the Growing Vegetation

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

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

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

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

Immunopathologic Factors

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

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

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

One relatively unexplored area of pathogenesis of IE is dietary impacts on susceptibility to this infection. It is known that diet, and specifically dietary metals, can modify the risk of infection. However, for example, the mechanisms by which manganese (Mn), a common dietary supplement, alters infection remain undefined. The Skaar laboratory[198] has reported that dietary Mn levels can dictate the outcome of experimental *S. aureus* cardiac infections. Mice fed a high-Mn diet displayed increased Mn levels, with preferential localization in and around cardiac abscesses. Although the canonical mammalian Mn-sequestering protein calprotectin surrounded such lesions, it was not released into the abscess nidus and did not limit Mn within cardiac abscesses. Consequently, excess Mn was bioavailable to the organism in the depths of these lesions. Bioavailable Mn is used by *S. aureus* to detoxify reactive oxygen species and protect the organism from neutrophil killing. Therefore a single dietary modification (i.e., Mn restriction) may be able to help amplify host antistaphylococcal defenses in patients at risk for *S. aureus* IE. Of interest, companies are focusing vaccine efforts to include components designed to raise antibodies against the *S. aureus* Mn receptor.[199]

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

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

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

Pathologic Changes

Heart

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

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

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

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

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

Kidney

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

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

1. Bacteria are rarely, if ever, seen in the lesions.
2. Glomerulonephritis can occur with right-sided IE.
3. Glomerulonephritis is rare in acute IE, even though large, friable vegetations result in widespread metastatic abscess formation.
4. Immunofluorescent staining with antiimmunoglobulin antibody reveals the typical lumpy-bumpy distribution seen in other forms of immune complex nephritis.
5. In diffuse glomerulonephritis, subepithelial electron-dense deposits are seen with electron microscopy and IgG, IgM, IgA, or complement is shown in these deposits with immunofluorescence.
6. Specific antibacterial antibody can be eluted from the lesions.[211]
7. Anti–glomerular basement membrane antibody has been found in a single case of IE with nephritis.
8. The glomerulonephritis often is accompanied by hypocomplementemia, with a positive result on serum assay for rheumatoid factor.
9. All of these abnormalities usually resolve with successful antimicrobial therapy as the concentration of circulating immune complexes declines.

Mycotic Aneurysms

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

Central Nervous System

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

Spleen

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

Lung

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

Skin

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

Eye

Roth spots consist microscopically of lymphocytes surrounded by edema and hemorrhage in the nerve fiber layer of the retina (Fig. 80.4).[234]

Clinical Manifestations

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

The symptoms and signs of IE (Table 80.3) can be protean, and essentially any organ system may be involved. Four processes contribute to the clinical picture[46]: (1) the infectious process on the valve, including the local intracardiac complications; (2) bland or septic embolization to virtually any organ; (3) constant bacteremia, often with metastatic foci of infection; and (4) circulating immune complexes and other immunopathologic factors.[41–44,46] As a result, the clinical presentation of patients with IE is highly variable and the differential diagnosis often is broad. Because of its many manifestations, the diagnosis of IE may be delayed; occasionally, it is not clinically suspected and is identified only at postmortem examination.[236–238] In a recent postmortem study of IE cases, in 38.2% IE was not diagnosed until autopsy. Important to note, Fernández Guerrero and colleagues found no significant difference in rates of "clinically occult" IE diagnoses before (1970–1985) and after (1986–2008) the availability of echocardiography at their institution (35% vs. 42.8%, respectively).[239] Fever is common but may be absent (5% of cases), especially in the setting of CHF, renal failure, a terminal disease, older age,[240,241] or previous antibiotic therapy. The fever pattern is usually remittent, and the patient's temperature rarely exceeds 40°C (104°F), except in acute IE. Persistent fever during antimicrobial therapy for IE is

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

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

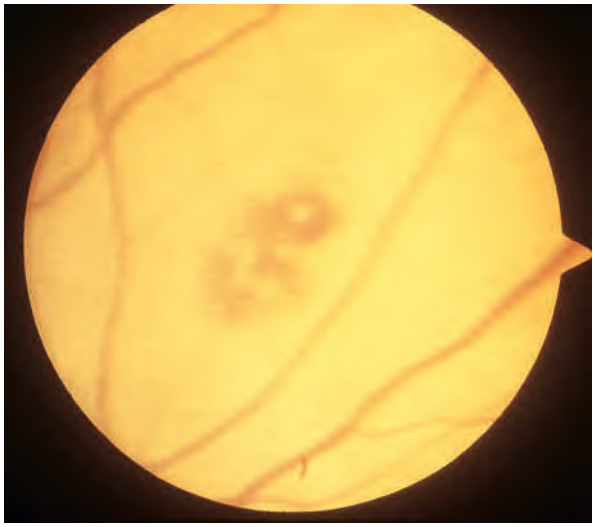

FIG. 80.4 Retina from a patient with viridans streptococcal endocarditis showing Roth spots. *(From Sande MA, Strausbaugh LJ. Infective endocarditis. In: Hook EW, Mandell GL, Gwaltney JM Jr, et al, eds.* Current Concepts of Infectious Diseases. *New York: Wiley Press; 1977.)*

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

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

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

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

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

Cardiac Murmurs

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

Peripheral Manifestations of Infective Endocarditis

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

Splenomegaly

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

Musculoskeletal Manifestations

Musculoskeletal manifestations are common in IE. In a review of 192 cases,[249] 44% of patients had musculoskeletal symptoms. These symptoms usually occurred early in the disease and were the only initial complaint in 15% of cases. They included proximal oligoarticular or monarticular arthralgias (38%), lower-extremity monarticular or oligoarticular arthritis (31%), low back pain (23%), and diffuse myalgias (19%). The back pain may be severe, limiting movement, and may be the initial complaint in 5% to 10% of cases.[29] These findings may mimic those of rheumatic disease, resulting in a diagnostic delay.

Embolic Events

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

Neurologic Manifestations

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

Renal Manifestations

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

Infective Endocarditis in Drug Addicts

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

Of patients with tricuspid valve infection, 30% have pleuritic chest pain; pulmonary findings may dominate the clinical picture, and the chest radiograph shows abnormalities (e.g., infiltrates, effusion) in 75% to 85% of the cases.[261] Radiographic evidence of septic pulmonary emboli is eventually present in 87% of cases.[262] Signs of tricuspid insufficiency (gallop rhythm, systolic regurgitant murmur louder with inspiration, large V waves, or a pulsatile liver) are present in only one-third of cases. Most of these patients are 20 to 40 years old (80%), and men predominate in a ratio of 4:1 to 6:1. Almost two-thirds of these patients have extravalvular sites of infection, which are helpful in the diagnosis.[261–263] The course of acute staphylococcal IE in an addict tends to be less severe than in nonaddicts,[261] although this may not be true in AIDS patients. HIV-seropositive patients acquire IE by one of two mechanisms: through injection drug abuse or as a complication of long-term central venous catheterization for administration of medications (e.g., for cytomegalovirus [CMV] retinitis). In either situation, *S. aureus* is the most common etiologic organism. IE is more common among injection drug users with advanced HIV immunosuppression ($CD4^+$ count, <200 cells/mm^3), even after accounting for injection drug use behaviors.[264] Conversely, among HIV-infected persons who do not practice injection drug use, IE is rare despite the increasing number of HIV-infected patients worldwide.[220] In the absence of injection drug abuse, HIV-seropositive patients develop left-sided and right-sided IE with equal frequency.[265] In contrast, in the setting of injection drug abuse, HIV-seropositive patients develop predominantly right-sided IE. The IE-related morbidity and mortality rates in HIV-seropositive patients who do not have an AIDS-defining illness or criteria are similar to the rates in HIV-seronegative counterparts.[265]

Laboratory Findings

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

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

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

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

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

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

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

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

Special Diagnostic Tests

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

Supplementation of media with vitamin B_6 or with cysteine may assist in the recovery of *Abiotrophia* and *Granulicatella* spp. The lysis-centrifugation blood culture technique assists in the detection of staphylococci[284] and fungi, but *Abiotrophia* and *Granulicatella* spp. do not survive this procedure, and yields of pneumococci and anaerobes are decreased.[285] Routine use of this technique is not indicated, but it may be helpful in suspected culture-negative cases of IE. Because of improvements in blood culture media and automated blood culture incubation systems, extended incubation times of blood cultures are no longer necessary to recover HACEK organisms (see later discussion).[280,286] Special efforts to neutralize or inactivate antimicrobial agents present in blood, such as the addition of penicillinase or of antibiotic-removal resins, do not substantially enhance the yield of positive blood cultures in IE, and they increase the incidence of laboratory contamination of the blood culture. These maneuvers are not recommended routinely.[285]

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

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

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

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

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

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

Echocardiography

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

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

Positive findings on the echocardiogram in a patient with IE should serve as adjunctive evidence, together with clinical parameters, in favor of surgical intervention. In one analysis from the Mayo Clinic,[316] emboli were not statistically more common in patients with left-sided native valve IE and echocardiographically documented vegetations within 72 hours after beginning antimicrobial therapy than in patients without vegetations visualized by transthoracic techniques. The occurrence of emboli was correlated positively with the infecting microorganism, being more common in IE due to viridans streptococci than in IE due to *S. aureus.* Most studies have suggested that mitral valve vegetations (particularly vegetations attached to the anterior leaflet), regardless of size, are associated with higher rates of embolization (25%) than are aortic valve vegetations (10%). This association implicates the mechanical effects of abrupt mitral valve leaflet excursions, occurring twice per heartbeat, in enhancing the embolic potential of vegetations.[317] Visualization of vegetations by echocardiography is not sufficient to prompt early surgery.[318] Serial echocardiograms often reveal the persistence of vegetations after successful therapy, but sequential studies may be useful in the timing of surgical intervention. Although the finding is still controversial, larger vegetation size has been associated with an increased risk for cerebral emboli. One large meta-analysis incorporating data from 10 studies involving 738 patients showed that large vegetation size (>1 cm) was associated independently with an increased risk for stroke.[319] Short-term changes in vegetation size during therapy do not correlate well with clinical outcome.[320]

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

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

Transesophageal Echocardiography

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

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

these complications,[335] but clinical experience with this modality is limited.

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

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

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

Cardiac Catheterization

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

Diagnostic Criteria

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

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

Definite Infective Endocarditis

Pathologic Criteria

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

Clinical Criteria (See Below for Definitions)

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

Possible Infective Endocarditis

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

Rejected

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

Major Criteria

Blood Culture Positive for Infective Endocarditis

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

Evidence of Endocardial Involvement

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

Minor Criteria

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

[a]Excludes single positive cultures for coagulase-negative staphylococci and organisms that do not cause endocarditis.

HACEK, Haemophilus, Aggregatibacter (formerly *Actinobacillus*), *Cardiobacterium, Eikenella, Kingella*; *IgG,* immunoglobulin G; *TEE,* transesophageal echocardiography; *TTE,* transthoracic echocardiography.

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

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

Etiologic Agents

Streptococci

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

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

The streptococci most commonly isolated from cases of IE are *S. sanguinis, Streptococcus bovis* (we will continue to use this name here, although the human strains have been reclassified as *Streptococcus gallolyticus*), *S. mutans,* and *S. mitior.*[81] In a series of 317 cases of streptococcal IE, the breakdown was as follows: α-hemolytic, 45%; nonhemolytic, non–group D, 21%; group D, 25%; pyogenic (groups A, B, C, G), 5%; miscellaneous, 3%; and aerococci, 1.3%. The α-hemolytic strains included *S. sanguinis* (16.4% of all cases of IE), non–dextran-producing *S. mitior* (13.2%), dextran-positive *S. mitior* (7.3%), and an unclassified group (7.9%). Some isolates of *S. sanguinis,* formerly called *Streptococcus* SBE, are in Lancefield group H; however, most are nontypeable. *S. mutans* (14.2%), *S. anginosus* (5.4%), and *S. salivarius* (1.3%) are the nonhemolytic, non–group D strains. Group D organisms include the enterococci (8%) and *S. bovis* (17%). In another analysis,[352] viridans streptococci caused 58% of cases of IE at The New York Hospital from 1970 to 1978. The various responsible species were as follows: *S. mitior,* 31%; *S. bovis,* 27%; *S. sanguinis,* 24%; *S. mutans,* 7%; vitamin B_6–dependent *S. mitior,* 5%; *S. anginosus,* 4%; and others, 2%—all of which were slightly different from the species reported from the United Kingdom. By contrast, group D streptococci constituted 25% of all cases of IE within six regions of France representing 16 million inhabitants.[353] Among 1242 consecutive episodes of IE from 1996 to 2013 in three Spanish centers, 294 were streptococcal, of which 47 were *S. bovis* (3.8%), 134 viridans-group streptococci (10.8%), and 113 enterococcal (9.1%).[354]

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

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

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

TABLE 80.5 Etiologic Agents in 1779 Patients With Definite Infective Endocarditis

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

HACEK, Haemophilus, Aggregatibacter (formerly *Actinobacillus*), *Cardiobacterium, Eikenella, Kingella.*
Data from Fowler VG Jr, Miro JM, Hoen B, et al. Staphylococcus aureus *endocarditis throughout the world: a consequence of medical progress. The International Collaboration on Endocarditis Prospective Cohort Study.* JAMA. *2005;293:3012.*

Enterococci

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

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

Streptococcus pneumoniae

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

Abiotrophia and *Granulicatella* spp. can cause difficulties in isolation and were implicated in 1.5% of all IE cases at one Spanish medical center over a 15-year period.[377] The organisms do not grow on subculture unless L-cysteine or pyridoxal vitamin B_6 is provided. IE due to nutritionally deficient streptococci is almost always indolent in onset and associated with preexisting heart disease.[378] Therapy is difficult, because systemic embolization, relapse, and death are common (occurring in 17%–27% of cases). A closely related species, *S. mitis,* although not nutritionally deficient, also causes serious infections, including IE, in adults[379] and has emerged as an important causative agent of IE among drug addicts in some areas (e.g., New York City[380]).

β-Hemolytic Streptococci

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

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

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

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

Gemella

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

Aerococci

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

Staphylococci

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

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

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

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

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

Coagulase-Negative Staphylococci

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

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

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

Gram-Negative Bacilli

Gram-negative aerobic bacilli now cause approximately 2% of cases of IE. Among more than 2700 patients with definite endocarditis prospectively enrolled into ICE-PCS from 60 centers in 28 countries, 49 patients (1.8%) had endocarditis due to non-HACEK gram-negative bacilli.[430] Traditionally, injection drug use has been regarded as the primary risk factor for enteric gram-negative bacterial endocarditis[413,431–436] and injection drug users remain a high-risk population in specific locations.[437] However, experience from the large, contemporary, and multinational ICE-PCS demonstrated that health care contact, and not injection drug use, was the most common risk factor for enteric gram-negative IE. In this definitive study, more than half of the patients with IE due to non-HACEK gram-negative bacilli had health care–associated infection, whereas injection drug use was rare (4%). Prosthetic valves and implanted endovascular devices were frequently associated with non-HACEK gram-negative bacillary IE. Patients with cirrhosis[438] also seem to be at an increased risk for the development of gram-negative bacillary IE.

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

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

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

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

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

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

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

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

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

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

Other Gram-Negative Bacteria

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

Gram-Positive Bacilli

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

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

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

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

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

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

Anaerobic Bacteria

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

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

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

Other Bacteria

Coxiella burnetii

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

Chlamydia psittaci

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

Tropheryma whipplei

T. whipplei is the causative agent of Whipple disease. Although its precise ecologic niche is unclear, there is increasing evidence to suggest that *T. whipplei* may be a component of the microbiota of the human respiratory tract, especially in patients with HIV. *T. whipplei* is an occasional cause of IE and has been cultivated from human valvular tissue.[491] In a review of 35 reported cases of Whipple IE, CHF, fever, and preceding valvular abnormalities all were less common in patients with Whipple IE than in patients with IE due to other pathogens.[295]

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

Brucella species

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

Unusual Bacterial Causes of Infective Endocarditis

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

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

Fungi

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

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

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

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

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

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

Viruses

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

Culture-Negative Endocarditis

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

TABLE 80.6 Causes of Culture-Negative Endocarditis

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

HACEK, Haemophilus, Aggregatibacter (formerly *Actinobacillus*), *Cardiobacterium, Eikenella, Kingella*; *IE,* infective endocarditis; *PCR,* polymerase chain reaction.

Polymicrobial Endocarditis

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

Etiology of Infective Endocarditis in Injection Drug Users

The organisms responsible for IE in injection drug users require separate consideration, because the distribution differs from that in other patients with IE. The frequencies of the etiologic agents isolated before 1977 in seven major series were as follows: *S. aureus,* 38%; *P. aeruginosa,* 14.2%; *Candida* spp., 13.8%; enterococci, 8.2%; viridans streptococci, 6%; *S. epidermidis,* 1.7%; gram-negative aerobic bacilli, 1.7% to 15%; other bacteria, 2.2%; mixed infections, 1.3%; and culture negative, 12.9%. In addition, there was an unexplained geographic variation in the causal agents of IE associated with injection drug use. *S. aureus* predominated in New York City, Chicago, Cincinnati, and Washington, DC; *P. aeruginosa* IE was traditionally encountered in Detroit and has recently resurfaced there,[437] but MRSA still predominates. A 1990 compilation from Detroit indicated the distribution of causative agents in addicts with IE (n = 74) as follows: *S. aureus,* 60.8%; streptococci, 16.2%; *P. aeruginosa,* 13.5%; polymicrobial, 8.1%; and *Corynebacterium* JK, 1.4%.[519]

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

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

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

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

THERAPY FOR INFECTIVE ENDOCARDITIS

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

Information on antimicrobial concentration in vegetations, either in experimental models or in humans with IE, is sparse. Experiments involving a single dose of a radiolabeled antimicrobial agent with autoradiographic analysis of drug dispersion within vegetations of animals with experimental IE revealed three patterns[526]: (1) concentration at the periphery of the vegetation without diffusion into the core (e.g., teicoplanin); (2) progressive diffusion, but with a high gradient from periphery to core (e.g., ceftriaxone); or (3) homogeneous diffusion throughout the vegetation (e.g., several fluoroquinolones). The predictive value of these observations with regard to therapeutic efficacy is unknown. The suboptimal clinical efficacy of teicoplanin in several clinical trials treating intravascular *S. aureus* infections may relate to the maldistribution of this agent within vegetations.[527] Analysis of pharmacodynamic variables (e.g., concentration-dependent bactericidal activity, postantibiotic effect) also may assist in the rational selection of regimens for the treatment of IE.[526] Studies in animals have confirmed that when vegetation formation is inhibited with anticoagulants, the organisms are eradicated more rapidly with penicillin treatment than in control animals with larger vegetations.[175] Enzymatic modification of the glycocalyx in the vegetations of experimental streptococcal IE by in vivo dextranase administration facilitated the bactericidal activity of penicillin by more rapid sterilization of the lesion.[528] In contrast, tissue-type plasminogen activator produced a concentration-dependent lysis of fibrin clots or vegetations infected with *S. epidermidis* or *S. sanguinis* but did not enhance antimicrobial activity in in vitro models.[529,530] Several studies in experimental IE have confirmed the utility of aspirin in reducing the size of vegetations and the microbial densities within aortic vegetations.[531,532] In addition, one clinical study in patients with established IE suggested that aspirin could mitigate the growth of vegetative lesions (as monitored echocardiographically) and prevent cerebral emboli.[533]

General Principles

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

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

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

Patients with left-sided IE should be managed at least initially in facilities with access to cardiothoracic surgery. Although persistent or recurrent fever despite appropriate antimicrobial therapy may be due to pulmonary or systemic emboli or drug hypersensitivity, the most common cause is extensive valve ring or adjacent structure infection or metastatic infection.[539] Approximately one-third of patients with left-sided IE require surgery during the acute stages of infection for either valve replacement or metastatic infection.[347] Close monitoring of and early surgical consultation for patients with IE, particularly those with signs of heart failure or persistent fever, are essential. The critical role of early cardiac surgery in many cases of IE has been clearly reiterated by a large, well-designed propensity study[540] and one randomized trial.[541] However, this latter study has been criticized for study design issues that limited generalizability, including infrequency of *S. aureus* IE and a relatively young and healthy patient population.

Tests Useful for Antimicrobial Treatment Monitoring

Management of IE demands careful consideration of the choice, dose, and duration of antimicrobial therapy. The following laboratory tests can help the physician to monitor treatment and can aid in rational therapeutic decisions. In every case of bacterial IE, the etiologic agent must be isolated in pure culture and the minimal inhibitory concentration (MIC) and minimal bactericidal concentration (MBC) must be determined for the usual antibiotics used (see later discussion). Standard disk sensitivity testing is unreliable in the context of treating IE, and results may be misleading without the quantitative information provided from the MIC and MBC.

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

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

Antimicrobial Therapy

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

TABLE 80.7 Summary of Treatment Options for Endocarditis

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

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

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

[a]Dosages assume normal renal function. For patients with renal insufficiency, adjustments must be made for all antibiotics except nafcillin, rifampin, and ceftriaxone. Gentamicin doses should be adjusted to achieve a peak serum concentration of approximately 3 μg/mL 30 minutes after dosing and a trough gentamicin level of <1 μg/mL.
[b]Primarily relevant to left-sided IE.
[c]Enterococci must undergo antimicrobial susceptibility testing. These recommendations are for enterococci susceptible to penicillin, gentamicin, and vancomycin except as indicated.
[d]Ampicillin, 12 g/day, can be used instead of penicillin.
[e]The need to add an aminoglycoside has not been demonstrated for penicillin-resistant streptococci.
[f]Limited data exist.
FDA, US Food and Drug Administration; *HACEK, Haemophilus, Aggregatibacter* (formerly *Actinobacillus*), *Cardiobacterium, Eikenella, Kingella*; *IE,* infective endocarditis; *MIC,* minimal inhibitory concentration.
Modified from Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis: diagnosis, antimicrobial therapy, and management of complications: a scientific statement for healthcare professionals from the American Heart Association. Circulation. *2015;132:1435.*

Penicillin-Sensitive Streptococcal Endocarditis

Most strains of viridans streptococci, "other" streptococci (including *S. pyogenes*), and nonenterococcal group D streptococci (primarily *S. bovis*) are exquisitely sensitive to penicillins, with an MIC of less than 0.12 μg/mL. Of viridans streptococci, 15% to 20% are "resistant" to this arbitrary concentration of penicillin.[352,377] In addition, approximately 15% of the strains of *S. mutans* show a low MIC for penicillin (<0.1 μg/mL), but the MBC is considerably higher (1.25–50 μg/mL).[356] These organisms probably should be considered "penicillin tolerant" and should be treated accordingly. Although results depend on the in vitro methodology employed,[544] studies beginning in the 1980s suggested that tolerance to penicillin among viridans streptococci was more prevalent than previous reports had indicated.[545] Of viridans streptococci cultured from gingiva and blood after dental procedures, 19% were tolerant,[546] especially among *S. mutans* (27%) and *S. mitior* (20%) isolates. Almost identical figures were reported among blood culture isolates of viridans streptococci,[547] with tolerance defined as a penicillin MBC-to-MIC ratio exceeding 10:1. Almost all strains of nutritionally dependent streptococci were tolerant to penicillin.[548,549] The influence of the tolerance phenomenon on the response to penicillin therapy in experimental IE is not known; two studies yielded conflicting results.[550,551] Data on human infections with tolerant strains and the therapeutic results are unavailable. Except for *Abiotrophia* and *Granulicatella* spp., we do not believe that the demonstration of tolerance by an isolate of viridans streptococci influences therapeutic decisions.

With broth dilution susceptibility tests, the usual MBC determinations for the so-called penicillin-sensitive streptococci are as follows: penicillin, 0.1 to 1 μg/mL; cephalothin, 0.15 to 1.25 μg/mL; vancomycin, 0.15 to 0.4 μg/mL; streptomycin, 6.25 to 50 μg/mL; and gentamicin, 1.56 to 3.12 μg/mL.[552,553] *S. bovis* is 10 to 5000 times more susceptible to penicillin than the other group D species (enterococci). They also are relatively susceptible to oxacillin, methicillin, and lincomycin, whereas the enterococci are resistant.[360] Most streptococci in this group show synergism in vitro between penicillin or vancomycin and streptomycin, gentamicin, or kanamycin (see later discussion).[554,555] The first strains of viridans streptococci with high-level streptomycin resistance (MIC ≥1000 μg/mL) were reported in 1982 from Paris. Although these strains are rare (2%–8% of isolates in some locales),[556] the documentation of aminoglycoside-modifying enzymes and the lack of penicillin-streptomycin synergy in vitro and in experimental animal models[556,557] are alarming. These penicillin-susceptible strains may be killed synergistically by penicillin-gentamicin combinations. Significant antibiotic antagonism was shown with the combination of clindamycin and gentamicin for *S. mutans* IE. The in vitro synergism between penicillin and aminoglycosides was found to correlate with a more rapid rate of eradication of bacteria from cardiac vegetations in vivo in the rabbit endocarditis model[558,559] for the common viridans streptococci. All of these studies have been summarized in reviews.[560–562] Low-level penicillin resistance (defined in this study as MIC 0.2–2 μg/mL) was found in 31% of viridans streptococci in Madrid in 1988 and 1989, and an additional 17% of strains showed high-level resistance.[563] Perhaps most important, streptomycin and cefotaxime resistance also was found to be "common."[22] The authors suggested a vancomycin-gentamicin regimen for IE due to viridans streptococci in Spain.

The combination of penicillin and streptomycin was used in more than 200 historical cases at The New York Hospital–Cornell Medical Center without a documented relapse.[554] This clinical experience has been confirmed elsewhere, but the overall reported relapse rate is 1.4%.[561] This regimen is as follows: aqueous penicillin G, 10 million to 20 million units given intravenously daily, or procaine penicillin G, 1.2 million units given intramuscularly every 6 hours, for 4 weeks, combined with streptomycin, 0.5 g intramuscularly every 12 hours for the first 2 weeks. Studies by Wilson and colleagues at the Mayo Clinic[564,565] showed that a 2-week course of intramuscular procaine penicillin (1.2 million units every 6 hours) and streptomycin (0.5 g every 12 hours) cured at least 99% of patients with penicillin-sensitive streptococcal IE. These results were similar to those obtained with therapy consisting of β-lactams alone for a total of 4 weeks[566,567] but significantly better than results obtained with penicillin alone for 2 weeks. The latter regimen was associated with a 50% relapse rate if low doses of penicillin were used and improved to 17% with higher penicillin dosages. The 2-week penicillin-streptomycin regimen has been the most cost-effective and the preferred therapy among these three regimens in uncomplicated penicillin-sensitive (MIC ≤0.12 μg/mL) streptococcal IE in young patients. However, since the advent of ceftriaxone-based regimens (featuring 2 weeks of ceftriaxone plus an aminoglycoside), many clinicians have opted for this approach (see later discussion).[568,569] Four weeks of penicillin (or ceftriaxone; see later discussion) alone is recommended for patients with impaired renal function and for those who are particularly susceptible to the low risk for streptomycin-induced ototoxicity (i.e., the elderly). The Cornell regimen (4 weeks of penicillin with an initial 2 weeks of streptomycin) has been recommended for patients with a complicated course, a history of disease exceeding 3 months' duration, or prosthetic valve IE caused by these sensitive strains and when susceptibility testing reveals the rare penicillin-resistant streptococci.[570] The preferred regimen for IE due to penicillin-tolerant streptococci is not established.

Most of the published clinical data with β-lactam–aminoglycoside regimens for the treatment of viridans streptococcal IE involve the use of penicillin or ampicillin plus either streptomycin or gentamicin. On the basis of extensive in vitro and animal data and for a variety of other reasons, however, the American Heart Association has deemed gentamicin preferable to streptomycin in this context.[237] First, gentamicin currently is more widely available and is used more often clinically than streptomycin in viridans streptococcal IE. Second, gentamicin (but not streptomycin) serum level determinations are performed routinely in most hospital laboratories. Because in vitro synergy against most viridans streptococci with penicillin or ampicillin in combination with gentamicin occurs at low gentamicin concentrations (1–3 μg/mL), most authorities recommend using gentamicin at a total daily dose of no more than 3 mg/kg/day (IM or IV), split into either a twice-daily (every 12 hours) or a thrice-daily (every 8 hours) dosage regimen. However, one study using ceftriaxone plus gentamicin given as a once-daily dose reported excellent efficacy against penicillin-susceptible streptococcal IE with no increases in aminoglycoside-associated nephrotoxicity.[569] Despite the apparent safety of once-daily aminoglycoside dosing in this study and in clinical trials involving patients with other infectious disorders,[571] the total number of patients receiving such regimens for 2 weeks or longer has been relatively limited. As with any patients receiving aminoglycosides, appropriate clinical and blood level monitoring to mitigate ototoxicity and nephrotoxicity should be used. Nomograms for prudent monitoring and adjustment of aminoglycoside doses when once-daily regimens are used have been published.[570]

We believe that gentamicin, at a total daily dose of 3 mg/kg, should be substituted for streptomycin in the aforementioned regimens when combination therapy is deemed advisable. In addition, a penicillin-gentamicin regimen is indicated for viridans streptococcal IE if high-level streptomycin resistance is present[556,557] and for strains that are relatively resistant to penicillin (MIC >0.12 μg/mL and ≤0.5 μg/mL).[334] Infections caused by strains with a penicillin MIC greater than 0.5 μg/mL should be treated as for enterococcal IE (see later discussion). Because of the enhanced rate of bacterial killing in animal models[572,573] and the high relapse rate of about 17%,[574] we also believe that the Cornell regimen (using gentamicin as the preferred aminoglycoside) should be employed for all patients with IE due to *Abiotrophia* and *Granulicatella* spp. Although temafloxacin plus tobramycin was as effective as penicillin plus tobramycin against experimental IE caused by *G. adiacens* in rabbits,[575] quinolones are best avoided for IE due to streptococci pending further data.

In a penicillin-allergic patient for whom a cephalosporin is deemed safe, several regimens are acceptable for IE caused by penicillin-susceptible viridans streptococci: (1) cefazolin, 2 g IM or IV every 8 hours for 4 weeks, combined with streptomycin, 0.5 g IM or IV every 12 hours; or (2) gentamicin, administered IM or IV in two or three daily doses for a total of no more than 3 mg/kg daily, for the initial 2 weeks; or (3) ceftriaxone alone, 2 g IV or IM given daily for 4 weeks. This last regimen has been proven efficacious against penicillin-sensitive streptococcal IE.[576,577] In one uncontrolled trial in Europe, 55 of 59 patients completed treatment with 4 months to 5 years of follow-up; treatment was completely