



# Diagnosis and management of infective endocarditis

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■ Advances in chemotherapy and surgery have significantly improved the outcome of infective endocarditis, but the disease remains a therapeutic challenge with an overall mortality of 20%. More cases of infective endocarditis seen today are associated with prosthetic heart valves, intravenous drug abuse, or complications of medical and surgical technology. Prosthetic valve endocarditis occurs in 1% to 4% of patients with prosthetic valves. Echocardiography is not a precise diagnostic test for endocarditis, but it helps detect a variety of cardiac lesions, including valvular incompetence, annular ring abscesses, and sometimes vegetations. Serum bactericidal titers are predictive of neither cure nor treatment failure. The principal indication for urgent surgical intervention is acute valvular dysfunction. Other considerations for surgery include evidence of myocardial invasion, infection by antibiotic-resistant organisms, and large vegetations. For patients at risk of infective endocarditis, antibiotic prophylaxis during invasive procedures is an accepted practice.

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**I**N the preantibiotic era, infective endocarditis was considered a fatal disease. With effective chemotherapy and surgical intervention, it is no longer always fatal. It remains a therapeutic challenge, however, with an overall mortality rate approaching 20%. Today, infective endocarditis may be associated with implantation of prosthetic heart valves or intravenous drug abuse. Furthermore, although advances in medical and surgical technology allow our patients to live longer, they also subject them to nosocomial bloodstream infections that may result in infective endocarditis. For example, in a patient with a

prosthetic heart valve, *Staphylococcus aureus* bacteremia may develop from the site where a vascular catheter enters the skin and progress to endocarditis.

This article reviews the currently accepted diagnostic criteria and treatment regimens for infective endocarditis, and presents an updated summary of the Cleveland Clinic experience with infective endocarditis patients.

## DIAGNOSIS

Sir William Osler, in a 1908 lecture to physicians, listed these characteristics of "chronic infectious endocarditis": remittent fever, an old valvular heart lesion, embolic features (spleen, eyes, brain, and limbs), skin lesions (purpura and nodules) and, lastly, progressive cardiac changes.<sup>1</sup> We have added little to Sir Osler's astute clinical observations. The most important laboratory finding is evidence of sustained bacteremia or

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fungemia. Many patients with infective endocarditis also have anemia or a positive serologic test for rheumatoid factor.

Strict criteria must be used to establish a diagnosis of infective endocarditis in order to validate various therapeutic approaches to the disease. The label "proven or definite endocarditis" is appropriate only when histologic confirmation has been obtained at surgery or postmortem examination. Criteria for a diagnosis of "probable endocarditis" include at least two positive blood cultures and three or more of the following: regurgitant heart murmur, embolic lesions, splenomegaly, prolonged fever, or an echocardiogram showing definite vegetations.

#### DISEASE COURSE

The pathogenesis of infective endocarditis has fascinated clinicians and pathologists alike.<sup>2</sup> The disease begins with endothelial trauma, such as might occur from regurgitant blood flow or high pressure gradients. Nonbacterial thrombotic endocarditis results, and this lesion provides a nesting place for bacteria. Some species of *Streptococcus* secrete an adherence factor, dextran, that stimulates attachment to damaged endothelial surfaces. Organisms become enmeshed in a network of fibrin, continue to proliferate, and perpetuate the process.

Depending on host factors and the virulence of the microorganism, the clinical presentation may be acute or subacute. Acute disease begins abruptly with hectic fever, soon followed by valve destruction and cardiac failure. Such patients may die quickly despite the initiation of aggressive medical and even surgical therapy. Although any microorganism, including viridans streptococci, may cause acute infective endocarditis, the most common is *S aureus*.

Fortunately, most patients with infective endocarditis have subacute or chronic disease with symptoms that last for weeks to months. The prognosis in these cases is usually favorable. The organisms most commonly implicated in subacute infective endocarditis are viridans streptococci.

#### PROSTHETIC VALVE ENDOCARDITIS

Prosthetic valve endocarditis (PVE) occurs in 1% to 4% of patients with prosthetic heart valves. Twenty years ago, early-onset PVE (within 2 months of surgery) was a dreaded complication with a reported mortality rate as high as 50%. Early-onset PVE most often resulted from intraoperative contamination with

nosocomial bacteria, especially *Staphylococcus epidermidis*, and inexperience with newer surgical techniques. With increasing surgical expertise and perioperative antibiotic prophylaxis, early-onset PVE has become less common. In our experience, it accounts for less than 10% of total cases of PVE.

Late-onset PVE, on the other hand, remains a significant problem. In this condition, which develops at least 2 months after implantation, the infection is usually caused by the same organisms that cause native valve endocarditis, and the cure rates are comparable.

#### REVIEW OF OUR EXPERIENCE

In 1987, we reported our 10-year experience with infective endocarditis in adults at The Cleveland Clinic Foundation.<sup>3</sup> Here, this study is reviewed in light of more current perspectives. Our series included 90 adult patients, 60 with native valve endocarditis (NVE) and 30 with prosthetic valve endocarditis. Excluded were patients who had received therapy at referring hospitals, patients with a history of intravenous drug abuse, and patients who were not followed for at least 3 months after discharge. Our patients' mean age was 52 years, and the series included three times as many men as women.

In patients with NVE, the most common underlying cardiac lesion was mitral valve prolapse, and the second most common was aortic sclerosis. Rheumatic valvular heart disease was a rare predisposing factor. Of patients with PVE, only two (6.6%) had early-onset disease. Nearly two thirds of NVE patients were symptomatic for more than 6 weeks, while only one quarter of PVE patients had symptoms of such duration. Fever, skin lesions, new regurgitant heart murmur, and splenomegaly occurred with equal frequency in both groups. Weight loss was more common in NVE patients, probably reflecting longer duration of illness before diagnosis. Two-dimensional echocardiography showed lesions compatible with vegetations in 42% of patients with NVE but in only 12% of patients with PVE.

Overall, 50 (83%) of 60 patients with NVE and 20 (71%) of 28 patients with late-onset PVE were cured (Table 1). In the NVE group, 46 patients received medical therapy alone, and 38 (83%) of them recovered. Of the 14 who received combined medical and surgical therapy, 12 (86%) recovered. Of the patients with late-onset PVE, 14 (82%) of 17 patients treated medically were cured, whereas 6 (55%) of 11 patients treated with combined medical and surgical therapy were cured. Both patients with early-onset PVE received combined medical and surgical therapy. One, who had infection due to

**TABLE 1**  
OUTCOME OF ENDOCARDITIS TREATMENT

Treatment	NVE		PVE	
	# Patients	Cures	# Patients	Cures
Medical therapy alone	46	38	17	14
Medical and surgical therapy	14	12	11	6
Total	60	50	28	20

NVE, native valve endocarditis; PVE, prosthetic valve endocarditis.

*Enterobacter cloacae*, died; the other, with infection due to *S epidermidis*, recovered.

Cure rates for infection due to *Streptococcus* species sensitive to penicillin (minimum inhibitory concentration [MIC] 0.1 µg/mL) and for *Enterococcus faecalis* (MIC >0.1 µg/mL) were 84% and 88%, respectively (Table 2). In 90% of cases of endocarditis caused by *S epidermidis* and 78% of cases caused by gram-negative bacilli, therapy was successful. Results of therapy were poor when infection was caused by *S aureus* (only one of six patients cured) or a fungus (only one of three patients cured).

### Echocardiography

Each patient in our study underwent conventional two-dimensional echocardiography. Based on a review of the echocardiographic findings, we concluded that this technology is not a sensitive diagnostic tool for infective endocarditis, especially in patients with prosthetic heart valves. Gentry and Khoshdel<sup>4</sup> recently reported a similar experience. They found that echocardiography has a sensitivity of 56% for native valve endocarditis and 33% for prosthetic valve endocarditis.

Since the report of our series, it has become evident that transesophageal echocardiography adds a new dimension and more sensitivity to the detection of vegetations. In studies by Mugge and colleagues<sup>5</sup> from West Germany, the detection rate for vegetations was 90% v 58% by standard transthoracic echocardiography. TEE allows more precise measurement of vegetations and is also useful for diagnosing ring abscesses and fistulae, which warrant surgical intervention.

### Serum bactericidal titer

In our experience, the serum bactericidal titer (SBT) results did not correlate with therapeutic outcome. Other factors, such as organism type and functional status of the patient, were more predictive of outcome than the SBT.

A principal problem with the SBT has been the lack of

**TABLE 2**  
OUTCOME ACCORDING TO CAUSATIVE ORGANISM

Organism	NVE		PVE		Total	
	# Patients	Cures	# Patients	Cures	# Patients	Cures
<i>Streptococcus</i> species*	39	32	11	10	50	42
<i>Enterococcus faecalis</i>	6	6	2	1	8	7
<i>Staphylococcus aureus</i>	4	1	2	0	6	1
<i>Staphylococcus epidermidis</i>	5	5	5	4	10	9
Gram-negative bacilli	4	4	5	3	9	7
Yeasts	0	—	3	1	3	1
Other	2	2	2	2	4	4
Total	60	50	30	21	90	71

\*Penicillin-sensitive, MIC to penicillin ≤0.1 µg/mL

NVE, native valve endocarditis; PVE, prosthetic valve endocarditis

standard methodology for performing the test. In 1985 Weinstein and colleagues<sup>6</sup> reported on a standardized SBT as a prognostic indicator of infective endocarditis. In their study, a peak SBT =1:64 correlated with cure, but lower titers did not correlate with treatment failure. Concerns about reliability and reproducibility of the SBT were recently addressed by MacLowry.<sup>7</sup> We no longer perform the SBT routinely to monitor antibiotic therapy in our patients with infective endocarditis.

### TREATMENT

#### Indications for surgery

Aggressive surgical therapy is the most important advance in the treatment of infective endocarditis since antibiotics became available. Surgery during acute infection does not increase hospital mortality; on the contrary, restoration of a failing pump is likely to lead to a favorable outcome. Valve failure causing moderate to severe congestive heart failure (New York Heart Association Class 3 or 4) is the prime indication for surgery.<sup>8</sup> Other relative indications are myocardial invasion (manifested by hectic fever and conduction disturbances), large vegetations (especially from fungi and gram-negative bacteria), and infection with organisms that are insensitive or resistant to antimicrobial agents (*S aureus*, *Pseudomonas aeruginosa*, yeasts, and molds).

#### Antibiotic therapy

Selection of antibiotic and duration of therapy depend on the causative organism, susceptibility studies,

**TABLE 3**  
GUIDELINES FOR ANTIBIOTIC THERAPY

Organism	Regimen
Penicillin-sensitive (MIC $\leq 0.1$ $\mu\text{g/mL}$ ) <i>Streptococcus</i> species <i>Enterococcus faecalis</i>	Penicillin G, 5 million units IV q6h, plus gentamicin, 80 mg IV q12h, for 2 wk; penicillin-allergic patient: vancomycin, 1 g IV q12h, or cefazolin, 1 g IV q8h, for 4 wk
Methicillin-sensitive (MIC $\leq 8$ $\mu\text{g/mL}$ ) <i>Staphylococcus aureus</i> (MSSA)	Penicillin G, 5 million units IV q6h, plus gentamicin, 80 mg IV q8h, for 4 wk; penicillin-allergic patient: vancomycin, 1 g IV q12h, plus gentamicin, 80 mg IV q8h, for 4 wk
Methicillin-resistant (MIC $> 8$ $\mu\text{g/mL}$ ) <i>Staphylococcus aureus</i>	Oxacillin, 2 g IV q4h, for 6 wk; gentamicin, 80 mg q8h, may be added for first 3-5 d; penicillin-allergic patient: vancomycin, 1 g IV q12h, for 6 wk; gentamicin, 80 mg q8h, may be added for first 3-5 d
Methicillin-sensitive (MIC $\leq 8$ $\mu\text{g/mL}$ ) <i>Staphylococcus epidermidis</i>	Vancomycin, 1 g IV q12h, for 6 wk; gentamicin, 80 mg q8h, may be added for first 3-5 d
Methicillin-resistant (MIC $> 8$ $\mu\text{g/mL}$ ) <i>Staphylococcus epidermidis</i>	Oxacillin, 2 g IV q4h, plus rifampin, 300 mg po q12h, for 6 wk; gentamicin, 80 mg IV q8h, is added for first 2 wk of therapy; penicillin-allergic patient: vancomycin, 1 g IV q12h, plus rifampin, 300 mg po q12h, for 6 wk; gentamicin, 80 mg IV, is added for the first 2 wk
Vancomycin, 1 g IV q12h, plus rifampin, 300 mg po q12h, for 6 wk; gentamicin, 80 mg IV q8h, is added for the first 2 wk	
<i>Haemophilus</i> species, <i>Actinobacillus actinomycetemcomitans</i> , <i>Cardiobacterium hominis</i> <i>Eikenella corrodens</i> , <i>Kingella kingae</i>	Ampicillin, 2 g IV q4h, for 3 wk

and whether the patient is allergic to penicillin. Often, combined therapy with two or more antibiotics is recommended. For example, penicillin and gentamicin remain the cornerstone of therapy for streptococcal endocarditis.<sup>9</sup> This combination kills bacteria, even those relatively penicillin-sensitive, more effectively than penicillin alone. When endocarditis is caused by gram-negative bacteria, appropriate therapy depends on prior clinical experience as well as in vitro susceptibility studies.<sup>10</sup> Specific guidelines for antibiotic therapy for infective endocarditis are presented in *Table 3*.

### Culture-negative endocarditis

Because of improved technology in the microbiology laboratory and an increased awareness of other diseases that can masquerade as infective endocarditis, true culture-negative infective endocarditis accounts for less than 5% of cases today. The most common reason for negative blood cultures is prior antibiotic treatment that suppresses bacteremia. Usually, however, waiting several days before drawing blood for more cultures allows recovery of the offending pathogen.

If cultures remain negative, noninfective causes such as myxoma, rheumatic valvulitis, nonbacterial verrucous endocarditis, marantic endocarditis, or carcinoid syndrome should be considered.<sup>11</sup> If these diagnoses can

be excluded, empiric therapy for “culture-negative” infective endocarditis is appropriate. For patients with native heart valves, ampicillin plus gentamicin is a reasonable choice; for those with prosthetic heart valves, vancomycin should be added to the regimen or substituted for ampicillin.

### ANTIBIOTIC PROPHYLAXIS

The need for and the adequacy of antibiotic prophylaxis for infective endocarditis continue to be debated.<sup>12,13</sup> It is sobering to note that Bayliss and colleagues<sup>14</sup> found a dental portal in fewer than 20% of 582 well-studied cases of infective endocarditis. In nearly two thirds of patients, no portal was determined. However, at present, prophylaxis seems indicated for dental procedures, especially dental surgery; instrumentation of an infected urinary tract; invasive gastrointestinal procedures, such as endoscopy with biopsy and sclerotherapy; and rigid bronchoscopy.

The patient with a prosthetic heart valve, history of infective endocarditis, aortic regurgitation, or ventricular septal defect deserves maximal prophylaxis. Ampicillin, 1 g to 2 g (IM or IV), with gentamicin, 80 mg (IM or IV), should be given 30 minutes before the procedure. For the penicillin-allergic patient, van-

comycin, 1 g IV administered over a 60-minute period, is substituted for ampicillin.

Patients who appear to be at somewhat lower risk for endocarditis include those with mitral valve insufficiency, including mitral valve prolapse<sup>15</sup>; bicuspid aortic valvular heart disease; asymmetric septal hypertrophy; and tricuspid insufficiency. For these patients, amoxicillin prophylaxis has been used successfully in the United Kingdom.<sup>16,17</sup> It is less costly than the more traditional regimens and is probably equally effective. The dosage is amoxicillin, 3 g by mouth 30 minutes before the procedure and 1.5 g 4 hours later. If the patient is allergic to penicillin, erythromycin, 1 g before the procedure and 0.5 g 6 hours after, is substituted for amoxicillin.

During cardiopulmonary bypass surgery, the operative wound may become colonized with coagulase-negative staphylococci and other skin flora. Perioperative antibiotic prophylaxis is prescribed to prevent wound infections and early-onset prosthetic valve endocarditis. Surgeons at most

medical centers begin to administer a first- or second-generation cephalosporin intravenously immediately before surgery and continue it for 48 hours postoperatively. In hospitals where methicillin-resistant *S epidermidis* is a frequent cause of early-onset prosthetic valve endocarditis, vancomycin is substituted for the cephalosporin.

#### COMMENT

Since our 1987 report, transesophageal echocardiography has been shown to be of significant value in the management of patients with infective endocarditis. Not only does TEE seem indicated for patients with congestive heart failure who may benefit from surgical intervention, but also for those with infections caused by *S aureus*, where the prognosis is poor. Serial TEE studies in these patients may detect subtle changes before heart failure is clinically apparent, and so prompt earlier surgical intervention than occurred previously.

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