Crawford, Michael H.
Current Diagnosis & Treatment in Cardiology, 2nd Edition

29

Infective Endocarditis

Bruce K. Shively MD

ESSENTIALS OF DIAGNOSIS

- *Fever*
- *Blood cultures positive for bacteria or fungi*
- *Cardiac lesions on echocardiography*

General Considerations

Infective endocarditis is one of several infections in which endothelium is the initial site of infection. Healthy endothelium possesses an effective system of defense against both hemostasis and infection. Infection of the endothelium of blood vessels occurs only at sites markedly altered by disease or surgery, such as the severely atherosclerotic aorta or the suture lines of vascular grafts. By contrast, infection of the cardiac valve leaflet endothelium (endocardium) is not rare and occurs even in the absence of identifiable preexisting valve disease.

Pathophysiology & Etiology

A. CARDIAC INFECTION—VEGETATIONS

1. Precursor lesion and bacteremia—Valve infection probably begins when minor trauma, with or without accompanying valve disease, impairs the antihemostatic function of valve endocardium. Infection usually first appears along the coapting surface of the leaflets, suggesting a role for valve opening and closing. This hypothesis is supported by the observation that the ranking of valves in order of frequency of infection corresponds to the ranking of valves according to the force acting to close the valve (mitral > aortic > tricuspid > pulmonic).

This minor trauma may cause the formation of a microscopic thrombus on the leaflet surface. A small noninfected thrombus on the leaflet is called **nonbacterial thrombotic endocarditis (NBTE)**. The next step is infection of the fibrin matrix of the thrombus by blood-borne organisms, which appear briefly in blood under many circumstances, such as brushing one's teeth and during diagnostic procedures. When transient bacteremia

coincides with the presence of an NBTE lesion, organisms may adhere to the valve leaflet and begin to proliferate.

This theory for the pathogenesis of endocarditis is supported by observations regarding the circumstances under which endocarditis occurs and the particular organisms involved. Patients with endocarditis often tell of a preceding event that likely resulted in transient bacteremia. The common infecting agents are those that gain entry to the blood because they colonize body surfaces and are adapted for attachment and proliferation in the NBTE lesion (see Clinical Syndromes).

2. Growth of vegetations—Vegetations begin near the coaptation line of the leaflet on the side that contacts the opposite leaflet during valve closure. Mitral valve vegetations are typically attached within 1–2 cm of the leaflet tip on the left atrial side and prolapse into the left atrium during systole. Aortic valve vegetations usually occur on the left ventricular (LV) side of the mid or distal portions of the aortic cusps and prolapse into the LV outflow tract during diastole. A similar distribution of lesions occurs on the tricuspid and pulmonic valves.

Although the course of cardiac lesions in endocarditis varies, in a typical sequence of events (without treatment), the infection progresses by enlargement of the vegetation and extension of its region of attachment toward the base of the leaflet. Valve regurgitation almost always develops, as a result of either destruction of the leaflet tip or scarring and retraction of the leaflet. Erosion of the leaflet may lead to perforation (usually associated with clinically significant regurgitation). Weakening of the leaflet's spongiosum layer may result in a deformity called a leaflet aneurysm. Mitral or tricuspid chordal involvement may cause rupture and acute severe regurgitation. In rare cases (primarily in mitral bioprosthetic endocarditis; see Management of High-Risk Endocarditis) a large vegetation may cause hemodynamically significant valve obstruction.

P.459

3. Metastatic vegetations—These vegetations may form when the regurgitant jet of blood from an infected valve strikes an endocardial surface in the receiving chamber (wall or chordae), producing a small area of denuded endothelium. The thrombus that forms at this site also becomes infected, constituting a secondary vegetation. Such metastatic vegetations most often appear on the ventricular side of the anterior mitral leaflet where it is struck by a regurgitant jet from aortic valve endocarditis. Another common location is on the mitral chordae, also from aortic regurgitation. Metastatic lesions on the mural endocardium of the cardiac chambers can occur as well.

4. Abscess and fistula formation—Organisms eventually invade the valve annulus and adjacent myocardium. Abscess formation can take multiple forms and may occur with or without fistula formation. Aortic annular abscess is an infective mass that burrows into or around the outside of the annulus. The abscess may extend upward to the sinus of Valsalva or ascending aorta (a type of mycotic aneurysm). This extension may lead to a fistulous communication between the aorta and the left atrium or (rarely) the right atrium. In other patients, the abscess extends down through the fibrous trigone and forms a fistula to the LV outflow tract.

A band of fibrous tissue at the base of the anterior mitral leaflet (the intervalvular fibrosa)

separates the aortic annulus from the left atrial wall. Infection extending down from the posterior aortic annulus may produce an aneurysm in this area, which may in turn fistulize to the left atrium, aortic root, or into the pericardial space. Infection extending down from the anterior aortic annulus may invade the septal myocardium, causing a block in the conduction system.

When mitral valve infection extends to the base of the anterior leaflet, abscess formation involving the fibrous trigone may track upward and become fistulous. Infection from the posterior leaflet may extend to form a myocardial abscess in the LV posterior wall or a fistula around or through the mitral annulus between the left atrium and left ventricle. Infection may even penetrate through to the pericardial space, producing purulent pericarditis.

B. EXTRACARDIAC DISEASE

At any time during cardiac infection, extracardiac complications may supervene and dominate the clinical picture. Although these manifestations are emphasized in the medical literature, it should be kept in mind that many patients with endocarditis do not have them, especially at the time of presentation. The extracardiac disease in endocarditis results from the shedding of bacteria and fragments of infected thrombus from the valve vegetations.

1. Immune disease—The bacteremia accompanying endocarditis persists over long periods of time and represents a prolonged antigenic challenge to the immune system. Various antibodies and immune complexes appear in the blood—more so with longer duration of illness. Rheumatoid factors (anti-IgG or IgM antibody) and the antibodies yielding a false-positive Venereal Disease Research Laboratory (VDRL) test are rarely of interest for their diagnostic value. Other antibodies, such as those that form circulating immune complexes and activate complement, are of major importance because they cause microvascular damage, most frequently glomerulonephritis and vasculitic skin lesions.

2. Systemic and pulmonary emboli—The embolization of fragments of vegetation is a frequent and potentially catastrophic complication of endocarditis. The clinical consequences are highly variable and depend on many factors, including the size of the embolus, the site at which it lodges in the vasculature, the type and quantity of organisms carried, the point during treatment at which embolism occurs, and the host response. Small emboli are likely to present as metastatic infection; the most dreaded of these is brain abscess. Septic embolization may also lead to abscesses in the kidney, liver, bone, and (from the right heart) lung.

Large emboli present with signs and symptoms of major vascular obstruction. For endocarditis of the left heart, the most frequent and serious extracardiac complication is embolism to the brain. Strokes from this cause tend to be large, complicating subsequent management and often causing death. Emboli may also cause infarction of the spleen, liver, kidney, and the myocardium itself. Embolism to large arteries of the extremities is unusual and occurs primarily in fungal endocarditis.

3. Mycotic aneurysms—When infection of the arterial wall results in localized dilatation and progresses to abscess formation, mycotic aneurysms can occur. The cause is thought to be embolization of vegetation that does not obstruct blood flow enough to present

clinically as embolism. These lesions frequently occur at vessel branch points. The mycotic aneurysm may produce signs and symptoms many weeks after the diagnosis of endocarditis, and recognition may be difficult. Their effects are especially devastating in the central nervous system. Aneurysms may act as a protected site of infection and cause persistent fever or bacteremia despite appropriate antibiotic therapy. Alternatively, if antibiotic therapy has sterilized the aneurysm, it may present months or years later as unexplained hemorrhage.

C. CLINICAL SYNDROMES

Endocarditis can assume any of a wide variety of forms because of the many possible combinations of infecting

P.460

organisms, portals of entry, and host factors such as immunity and concomitant diseases. Although the list of organisms capable of causing endocarditis is very long (and the list of possible combinations of organisms and host factors is even longer), there are several common and distinctive clinical syndromes.

A distinction between the acute and subacute forms of endocarditis has been found to be of some clinical value. The differing characteristics of patients with these two forms are shown in Table 29-1. Many patients with endocarditis cannot be easily placed into one or the other of these two categories, however. Because the mean interval from the onset of infection to presentation is now short (10 days), many patients fail to develop the clinical syndrome originally ascribed to the subacute syndrome, but also do not meet the criteria for acute endocarditis.

Acute	Subacute
Symptom onset to diagnosis: 1 week	Symptom onset to diagnosis: 4 weeks
Acute malaise	Weight loss
Shaking chills	Fatigue
	Night sweats
Fever (may be high)	Low or no fever
Leukocytosis	Normal white cell count or leukopenia
Normal gamma globulins	Elevated gamma globulins
Rheumatoid factor +	Rheumatoid factor +

[a] Elevated erythrocyte sedimentation rate and anemia common to both syndromes.

Table 29-1. Characteristics of acute and subacute endocarditis.[a]

1. Viridans streptococcal endocarditis—The bacterial species classified as viridans streptococci account for approximately 30–40% of cases of endocarditis. These organisms can be divided into three groups: normal human oral flora (*Streptococcus mitis, S sanguis, S anginosus, S mutans, S salivarius,* and other nutritionally variant species), inhabitants of the lower gastrointestinal and genitourinary tracts (nonenterococcal group D organisms, of which *S bovis* is important), and *S pneumoniae,* or *pneumococcus,* which infrequently causes endocarditis—and causes a syndrome very different from the other viridans

streptococci. The first two groups of streptococci cause almost no other disease in humans, except for endocarditis. This predilection appears to stem from bacterial cell wall proteins that bind to fibronectin, platelets, laminin, and other components of blood clots.

Viridans streptococci usually grow slowly, and the patient typically presents with a febrile illness of at least 10 days' duration and modest intensity; many cases fit the clinical syndrome of subacute bacterial endocarditis. Although valve destruction may be extensive, it is gradual, and abscess formation in the heart or elsewhere is uncommon. Infection of a normal valve by viridans streptococci is probably unusual. The renal disease accompanying endocarditis caused by these or-ganisms is usually mild and rarely causes significant renal insufficiency. Viridans streptococcal endocarditis is therefore often treatable medically and has a relatively good prognosis if antibiotic treatment is begun before complications occur.

Endocarditis from *S bovis* is strongly associated with underlying colorectal disease, especially malignancy. Colonization of the gastrointestinal tract by this organism increases with age and with malignancy for reasons that are not well understood. After initial endocarditis treatment, a patient with this disease should undergo a barium enema and sigmoidoscopy. If these tests are negative, evaluation should be repeated in 6 months.

Extra vigilance for complications is needed when treating patients with endocarditis from certain other streptococci. *S anginosus* and *S milleri* tend to cause abscesses in the brain and other major organs, and nutritionally variant streptococci are associated with higher morbidity and mortality rates than are the other viridans organisms—again for reasons that are not understood.

Complications from viridans streptococcal endocarditis are almost never due to failure to sterilize vegetations. Nevertheless, the sensitivity of these organisms to penicillin is not uniform, and testing for resistance is essential for establishing an appropriate antibiotic regimen.

2. Staphylococcus aureus endocarditis—*Staphylococcus aureus* is a relatively common cause of endocarditis, accounting for approximately 25% of all cases. In hospitals serving a large population of intravenous drug users, this may be the most common cause of endocarditis. Although *S aureus* frequently enters the circulation from the skin or nares, a culprit lesion may not be apparent on examination of these areas. Fewer than one quarter of episodes of *S aureus* bacteremia in hospitalized patients are caused by endocarditis.

Unlike patients with streptococcal endocarditis, those with endocarditis from *S aureus* are likely to present soon after the onset of bacteremia, which generally produces a febrile illness with marked constitutional symptoms and often rigors. This picture is especially common in intravenous drug users. *S aureus* tends to cause valve destruction more rapidly than do other organisms;

P.461

approximately 30% of cases result in extensive left-heart valve involvement complicated by abscess or fistula formation or pericarditis. *S aureus* endocarditis of the aortic valve is the most common cause of aortic annular abscess, often signaled by the appearance of PR interval prolongation. Mitral annular and myocardial abscesses are also associated with this organism.

Central nervous system involvement is present in 20% or more of cases, as cerebral embolization, intracranial hemorrhage from mycotic aneurysm rupture, and microscopic or macroscopic brain abscesses. Other significant complications include septic arthritis, osteomyelitis, and major organ abscesses. Renal involvement, as indicated by an active urine sediment, is present in almost all cases, and frank renal impairment occurs in approximately 20%. The renal dysfunction caused by *S aureus* rarely progresses to dialysis or permanent renal failure.

S aureus is the most lethal of the organisms commonly causing endocarditis, with mortality rates of approximately 30% in non-intravenous-drug users and >50% in patients with prosthetic valves. Intravenous drug users have a much lower mortality rate (approximately 5%).

3. Enterococcal endocarditis—This form accounts for approximately 5–15% of cases of endocarditis—almost all from *Enterococcus faecalis.* Enterococcal endocarditis tends to occur in elderly men undergoing diagnostic manipulation or surgery involving areas colonized by this organism, such as the gastrointestinal and genitourinary tracts; in intravenous drug users; or in women following obstetrical procedures. Patients with enterococcal endocarditis may present with an acute or insidious syndrome, although the findings typical of subacute bacterial endocarditis are unusual.

Enterococcal endocarditis is especially difficult to treat due to antibiotic resistance (discussed later). It is markedly different from and far more serious than streptococcal endocarditis. Overall mortality is only slightly less than that for staphylococcal endocarditis, and the incidence of major complications and need for valve replacement is approximately 30–40%.

4. Endocarditis from gram-negative bacteria—Gram-negative bacteria rarely cause endocarditis, with the exception of three groups of organisms: *Pseudomonas aeruginosa,* the HACEK organisms (*Hemophilus* spp., *Actinobacillus, Cardiobacterium, Eikenella, Kingella*) and the enteric organisms (*Escherichia coli, Proteus, Klebsiella,* and *Serratia marcescens*). *Pseudomonas* and *Serratia* are occasional causes of endocarditis in intravenous drug users.

The HACEK organisms are relatively slow growing and usually cause a subacute clinical syndrome. Organisms such as *Hemophilus* and *Cardiobacterium* are thought to account for cases of culture-negative endocarditis. Despite the often mild symptoms and signs of endocarditis caused by these organisms, valve destruction may be extensive by the time of diagnosis. The HACEK organisms are associated with endocarditis that causes major vessel embolism from large vegetations. Enteric organisms tend to produce an acute clinical syndrome similar to that caused by *Pseudomonas.*

5. Fungal endocarditis—Fungal endocarditis is associated with settings of immune compromise and procedures that give the organism access to the bloodstream, such as surgery, IV catheter placement, and IV drug abuse. *Candida* species (especially *C albicans*), *Histoplasma capsulatum,* and *Aspergillus* account for approximately 80% of cases of fungal endocarditis. Other less common causative organisms include *Mucor* and *Cryptococcus.* Clinicians must recognize when patients are at risk for fungal endocarditis because the signs and symptoms of the disease often escape notice or lead to

misdiagnosis. Risk factors are listed in Table 29-2. In most patients with fungal endocarditis of a native valve, the infection is related to a fundamental immune system impairment. Fungal superinfection should be considered when a patient with bacterial endocarditis relapses either late in the antibiotic course or after completing treatment. This observation is especially true for bacterial infection of a prosthetic valve. *Candida* species infection is usually nosocomial, whereas histoplasmosis may be a community-acquired infection. Fungal endocarditis in intravenous drug users is almost always due to non-*albicans* species of *Candida.*

History of an implanted cardiac device (eg, prosthetic valve, pacemaker, AICD)
Indwelling vascular catheter and prolonged hospitalization
Prolonged treatment with broad-spectrum antibiotics
Immunosuppression (eg, steroid or cytotoxic drugs, radiation, malnutrition, untreated malignancy)
Intravenous drug use

AICD = automatic implantable cardioverter-defibrillator.

Table 29-2. Risk factors for fungal endocarditis.

The clinical syndrome of fungal endocarditis is more difficult to recognize than that of bacterial endocarditis. This may be due partly to the postsurgical state or multisystem disease common in these patients. It has also been suggested that fever and murmurs develop later in the course of fungal disease than in bacterial endocarditis and that leukocytosis and such peripheral manifestations as petechiae are less frequent. The development of symptoms is often insidious, extending over weeks or months. Cardiac involvement is generally limited to the development of vegetations; invasion of the

myocardium occurs with a lower frequency than in bacterial endocarditis. The vegetations usually lead to leaflet destruction and valve regurgitation; they may be large and may occasionally cause valve orifice obstruction. The most likely complication of fungal infective endocarditis is embolism, including occlusion of large peripheral arteries from embolization. Table 29-3 lists the approximate frequency of causative organisms in native valve endocarditis.

Table 29-3. Native valve endocarditis: Causative organisms.

Organism	% of cases
Viridans streptococci	60
S sanguis	12
S mitior	15
S mutans	6
S bovis	15
S milleri	2
Other	10
Enterococci	5
Staphylococcus aureus	25
S epidermidis	3
Fungi	1
Pseudomonas	2
Other gram-negative bacteria	3
Other	1

6. Prosthetic valve endocarditis—The risk of developing endocarditis is higher with prosthetic heart valves than with severely diseased native valves, approximately 0.5% per patient-year. Despite some overlap, there is a clear difference between the causes of disease that develops within 2 months of implantation and that occurring later (Table 29-4). The difference is probably due to infection occurring during surgery in early prosthetic endocarditis, with organisms from the skin of the patient and operating room personnel (*Staphylococcus epidermidis* and *aureus*) accounting for more than half the cases. The incidence of early prosthetic endocarditis has been greatly reduced by the routine use of prophylactic antibiotics for several days after operation. Prosthetic infection after 2 months usually involves the same mechanism as does native valve endocarditis, except that the causative organisms are those adapted to nonbiologic material.

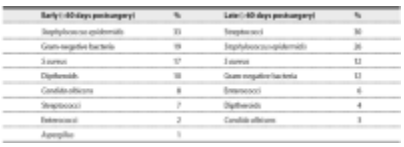


Table 29-4. Prosthetic valve endocarditis: Causative organisms.

Infection of a bioprosthesis involves primarily the sewing ring. Vegetations similar to those of native valve endocarditis can occur when the prosthesis is biologic, but infection more often begins in the area of attachment of the sewing ring to the annulus. Vegetations may form in this area, but—most important—early in the disease abscesses often form along the suture line, resulting in fistulization, paravalvular regurgitation, and partial or complete

detachment (dehiscence) of the prosthesis.

Infection of a mechanical prosthesis centers on the sewing ring. The inward growth of an infective mass from the ring frequently causes the occluder to become stuck in a partially open or closed position. The lesions caused by sewing ring infection of mechanical prostheses are otherwise similar to those of bioprostheses.

Two important differences distinguish prosthetic valve endocarditis from native valve infection. Prosthetic valve infection may be extensive without the

P.463

clinical signs, such as a murmur of regurgitation, heart failure, or embolism, usually seen in advanced native valve infection. When prosthetic valve dysfunction does occur (especially in a mechanical prosthesis), it tends to be abrupt and severe, as when the occluder becomes fixed in a half-open position. (Other differences are discussed later in this chapter.)

7. Endocarditis in the intravenous drug user—The patient usually presents with an intense febrile illness of several days' duration, starting within 24–48 h of the last injection. The mode of infection is a needle contaminated by skin flora, and an IV injection site may show an abscess or thrombophlebitis. The most likely causative organism is *S aureus,* which, overall, causes 70% of endocarditis in intravenous drug users, and which in this setting has a benign prognosis with only 2–5% mortality. Many other organisms can cause endocarditis in intravenous drug users, including gram-negative bacilli, especially *Pseudomonas aeruginosa, C albicans,* enterococci, and *Serratia marcescens;* as well as viridans streptococci. The prevalence of specific causative organisms varies widely in different urban areas. Endocarditis from these organisms tends to be less acute than that caused by *S aureus,* but only rarely is it truly subacute.

Infection of the tricuspid valve is almost unique to IV drug abusers and occurs in approximately 60% of cases of endocarditis in this population. Significant tricuspid regurgitation may not be clinically apparent. In as many as 40% of cases, the left heart valves alone are infected. Despite its proximity to the portal of entry in intravenous drug users, the pulmonic valve is rarely involved, probably because of the low pressure gradient and low wear and tear of this valve. Chest pain and dyspnea should prompt consideration of septic pulmonary emboli, which occur in 30% of tricuspid valve endocarditis. This complication usually presents as chest pain accompanied by scattered fluffy pulmonary infiltrates. On serial chest films, these lesions may appear migratory because of simultaneous resolution of older infiltrates and appearance of new ones. Infiltrates may also progress to cavitation.

8. Endocarditis and HIV—HIV infection and AIDS do not increase the risk of infective endocarditis. The increased frequency of endocarditis in patients with HIV is due to the prevalence of intravenous drug use in this population. HIV/AIDS patients appear to have an increased susceptibility to *Salmonella* endocarditis, a relatively antibiotic-responsive infection. Otherwise, the types of causative organisms seen is not altered by HIV status. The clinical syndrome and natural history of the disease in HIV patients is also unchanged, except that patients with advanced AIDS (CD4 count <200) tend to have a more fulminant course and increased mortality rates.

9. Nosocomial endocarditis—Hospital-acquired endocarditis is uncommon; overall approximately 5% of positive blood cultures in hospitalized patients are due to infective endocarditis (exceptions include strep viridans and nutritionally variant streptococci). Prosthetic valves are at far greater risk than native valves: 15–20% of patients with prosthetic valves who become bacteremic have or will develop endocarditis. Nosocomial endocarditis is marked by an increased likelihood of the presence of unusual or antibiotic-resistant organisms and an infected indwelling catheter as the likely portal of entry. Endocarditis occurs only rarely in postsurgical patients, usually after prolonged sepsis.

The usual causative organisms are coagulase-negative staph, *S aureus, Enterococcus,* and enteric gram-negative organisms, such as *Pseudomonas* and *Serratia.* Fungi, especially *Candida,* and fastidious organisms should also be suspected when endocarditis occurs in debilitated, leukopenic patients and those previously treated with long courses of antibiotics. Nosocomial endocarditis should be suspected when a hospitalized patient develops fever and positive blood cultures without an apparent source. Potential culprit catheters should be removed and cultured, followed by transesophageal echo-cardiography (TEE) if an additional risk factor for endocarditis exists. Examples of risk factors in this setting include a prosthetic valve, native valve disease predisposing to infection, or *S aureus* bacteremia. If the TEE is negative, and other sources of infection have been ruled out, a short (2-week) course of antibiotics is usually appropriate. Surveillance blood cultures during and after treatment, and a repeat TEE, should be considered if uncertainty regarding the response to treatment persists. In the case of exposure of a prosthetic valve to bacteremia, blood culture surveillance should be extended for at least 2 months.

10. Pacemaker endocarditis—Pacemaker endocarditis is infection of the lead or of parts of the heart in contact with the lead (tricuspid valve, right ventricular endocardium). Mortality is high, up to 25%, and the diagnosis is often missed due to the indolent nature of the infection. The vast majority of cases are due to contamination at the time of implant; hematogenous infection of a lead is rare. Most cases have evidence of present or prior infection at the implant site. The delay from the most recent pacemaker procedure to the diagnosis of endocarditis may be as long as 2 years or as little as 6 weeks. In addition to fever and positive blood cultures, infection causes septic pulmonary emboli in about a third of cases. Transesophageal echocardiography is the diagnostic test of choice, with a sensitivity of over 90%. Transthoracic echocardiography is often falsely negative.

Staphylococci are the usual infecting organisms, with *S epidermidis* accounting for 70% of cases and *S aureus*

for most of the rest. As with prosthetic valve endocarditis, early after implant, *S aureus* is the most likely culprit, whereas *S epidermidis* is more likely later. *Staphylococcus* species produce a slime-like “sleeve” along the lead that protects bacteria from host defense and antibiotics. Treatment requires removal of the lead, and usually the entire system. Lead removal can be accomplished percutaneously with reasonable safety if the mass(es) attached to the lead are small (<1 cm). Surgery is indicated if the lead is fixed, if a large mass (>1 cm) is present (with dislodgement likely to result in severe pulmonary embolism), or if tricuspid valve involvement is extensive. Lead removal is followed by 6 weeks of

antibiotic therapy. The pacemaker-dependent patient is given an epicardial lead; reimplant of a transvenous system can be considered after 2 months with negative surveillance blood cultures.

Clinical Findings

A. DIAGNOSTIC CRITERIA

In the current era, with the availability of sensitive blood culture techniques and transesophageal echocardiography, the clinician will rarely need to rely on a formal schema for the diagnosis of endocarditis. Prior to these technical advances, “major” criteria (fever, positive blood cultures) were combined with “minor” criteria (skin lesions, emboli, serologic abnormalities) to reach a probable diagnosis. This approach was useful because of the low sensitivity and specificity of each feature by itself. Now TEE and blood cultures independently have a diagnostic sensitivity of greater than 90%, and TEE has a specificity of greater than 90%. Diagnostic uncertainty may arise when the result of TEE is ambiguous or when adequate blood cultures are not obtained before starting antibiotics. In many such situations a diagnosis can be reached by gathering more data. For example, if the TEE fails to show endocarditis-specific valve disease and the patient is doing well, discontinuing antibiotics in order to repeat cultures should be considered. Many of the common features of endocarditis—fever, a cardiac murmur, and a set of positive blood cultures—occur frequently in other diseases and are occasionally absent in patients with endocarditis. Other diseases frequently mimicked by endocarditis include malignancy, autoimmune disease, and septicemia. In addition, patients with endocarditis may come to the physician because of a complication of endocarditis so dramatic as to distract attention from the underlying infection. Typical settings in which this error occurs include heart failure, stroke, and myocardial infarction.

The recognition of possible **prosthetic valve endocarditis** may be difficult because the signs of infection may be very subtle. In early prosthetic endocarditis, the symptoms and signs may be incorrectly ascribed to other diseases. Fever and bacteremia during the first few weeks after prosthetic implantation should be considered to indicate prosthetic valve endocarditis until proven otherwise. This is especially important because early prosthetic valve endocarditis appears to follow a more fulminant course than either late prosthetic or native valve endocarditis. These patients often have other potential causes of bacteremia, however, and an effort to prove infection from another site should be pursued vigorously. Transesophageal echocardiography probably has a sensitivity of approximately 80% for prosthetic valve endocarditis and should be performed whenever an alternative explanation for fever or bacteremia is not readily apparent. If the TEE is negative but bacteremia persists (especially if the organism is a frequent cause of prosthetic endocarditis), prosthetic infection should be presumptively treated. Fluoroscopy to rule out dehiscence has been replaced by TEE.

Fungal endocarditis is also often difficult to diagnose. Blood cultures are negative in approximately half of cases from *C albicans,* the majority of histoplasmosis cases, and almost all cases caused by *Aspergillus.* Histologic examination and culture should be performed whenever possible on specimens of embolic material, oropharyngeal lesions

(especially for histoplasmosis), skin lesions (for *Candida* species and *Aspergillus*), liver, bone marrow, and urine (for histoplasmosis). In addition, a careful eye examination should be performed in patients with suspected fungal endocarditis because of the high frequency of anterior uveitis and chorioretinitis.

Tricuspid valve endocarditis (as seen in IV drug users) produces a distinctive picture because of the frequent occurrence of septic pulmonary emboli. Scattered fluffy infiltrates seen on chest film are accompanied by pleuritic chest pain. Less often, the presentation may mimic pneumonia or include pleural effusion. The murmur of tricuspid regurgitation may be inaudible or soft because right-heart pressures are normally low, even when tricuspid infection is extensive. A loud holosystolic murmur at the left lower sternal border that increases with inspiration, *v* waves in jugular veins, and a pulsatile liver indicate the development of severe tricuspid regurgitation and pulmonary hypertension.

B. SYMPTOMS AND SIGNS

Constellations of certain symptoms should arouse suspicion of endocarditis. One combination of symptoms often seen is constitutional symptoms (eg, fatigue, malaise, headache, arthralgias or myalgias, nausea, anorexia, weight loss) and fever, which can range from mild feverish feelings and night sweats to shaking chills. When these symptoms are chronic or mild, other diagnoses are often considered, such as malignancy and autoimmune disease.

P.465

A high suspicion of endocarditis is warranted when this picture is associated with any symptom pointing to the circulatory system, such as complaints associated with left- or right-heart failure (dyspnea, orthopnea, cough, peripheral edema), vascular occlusion (stroke, systemic embolism), and chest pain (Table 29-5).

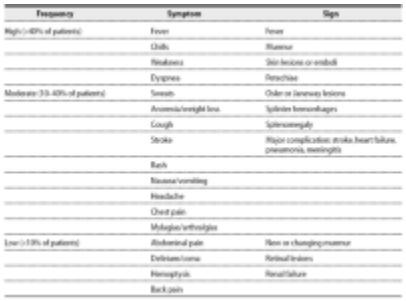


Table 29-5. Frequency of symptoms and signs in endocarditis.

C. PHYSICAL EXAMINATION

The physical examination is not essential for the diagnosis of endocarditis. Most of the physical findings caused by endocarditis are not specific for this diagnosis and should be

interpreted in the context of the overall examination and the patient's history. There are also no physical findings that, when absent, are useful for ruling out the diagnosis. A prominent murmur or skin lesion may arouse a clinical suspicion of endocarditis, but a murmur of valve regurgitation may be absent in patients with endocarditis. Vegetations may be present, but may cause only slight regurgitation.

The examination is absolutely essential, however, to the treatment of endocarditis patients. The initial examination assists the clinician in assessing the severity of the illness. During treatment (or observation for more definite evidence of endocarditis), serial physical examinations are vital for identifying important changes in the patient's status because physical findings may signal the need for surgery.

1. Fever—Fever is usually present when the patient comes to medical attention, although it may be intermittent or already resolved through inappropriate antibiotic treatment. It may be infrequently masked by severe comorbid conditions, such as alcoholic cirrhosis, leukopenia, or malnutrition. The diversity of endocarditis does not permit generalizations about the temporal pattern or degree of fever. Fever may be low grade (37.5–38.5°C) and accompanied by only malaise and anorexia, or it may be hectic with rigors, sweats, and temperature higher than 40°C. Recurrence of fever during treatment of endocarditis is a very important problem (see section on Failure of antibiotic therapy).

2. Cardiac examination—The cardiac examination in the patient with suspected or known endocarditis focuses on identifying which heart valves are infected, the hemodynamic severity of the resultant regurgitation (or

stenosis), and the adequacy of the patient's circulatory state.

At the time of initial evaluation of a patient with suspected endocarditis, the value of a detected murmur may be low because there may be no reliable information about the patient's prior cardiac condition. Systolic murmurs, for example, are common in the general population and very frequent in older or hospitalized patients; they are usually due to LV outflow or degenerative sclerosis of the aortic valve. Because endocarditis rarely causes valve stenosis, a systolic murmur related to endocarditis is almost always regurgitant.

Specific auscultatory features occasionally may be useful for determining how a valve has been damaged by infection. In mitral valve endocarditis, the examination may help identify which mitral leaflet has become partially flail. If the mitral regurgitant murmur radiates to the patient's back, the jet is likely to be directed posteriorly as a result of anterior leaflet prolapse into the left atrium. If the murmur radiates to the upper parasternal area (mimicking aortic stenosis), the posterior leaflet is likely to have lost its support.

It is essential that the examiner carefully note and document the cardiac findings as soon as the diagnosis of endocarditis is suspected. In addition to murmurs, the clinician should pay close attention to those aspects of the examination related to hemodynamic consequences of valvular dysfunction. Signs of pulmonary edema, dysfunction of either ventricle, and a low output state should be sought.

3. Skin and extremities—Assessment of the severity of extracardiac disease in endocarditis begins with a careful examination of the skin and peripheral circulation for

evidence of vasculitis and emboli. Although these findings are not specific for the diagnosis of endocarditis, in the context of probable endocarditis, they strongly support that diagnosis. Their appearance during antibiotic therapy may signal the need for a change in the treatment plan.

a. Petechiae—Examine the soft palate, buccal mucosa, conjunctiva, and the skin of the extremities for petechiae, which are often transient, appearing in crops and fading in 2–3 days.

b. Splinter hemorrhages—These brown streaks are 1–2 mm in length and found under the fingernails and toenails. Lesions in the proximal nail bed are moderately specific for endocarditis, whereas similar lesions under the distal nails are commonly found in healthy persons who work with their hands.

c. Roth spots—Vasculitis affecting small arteries of the retina may, on rare occasions, produce retinal infarction. The resulting funduscopic lesion, usually seen near the optic disc, is a pale retinal patch surrounded by a darker ring of hemorrhage.

d. Osler nodes—These painful indurated nodules are 2–15 mm in diameter and appear on the palms and soles and often involve the distal phalanges. They are usually multiple and, like petechiae, tend to occur in crops and fade over 2–3 days. Osler nodes are thought to be caused by either vasculitis or septic embolization.

e. Janeway lesions—These painless, flat red macules are similar in size and location to Osler nodes that usually persist longer than a few days. Their pathogenesis is uncertain but is suspected to be either vasculitis or septic embolization.

f. Blue-toes syndrome—Embolization of small vegetation fragments may cause ischemia in the distal arterial distribution of an upper or lower extremity. The affected finger or toe is tender, mottled, and cyanotic; over a period of days to weeks, the area becomes black and develops dry gangrene. Management is usually conservative (see 3. Embolism, later in this chapter). Acute arterial occlusive ischemia of a larger portion of an extremity raises the possibility of fungal endocarditis and is usually managed by embolectomy.

4. Neurologic examination—Cerebral embolization in endocarditis signals a poor prognosis and has a major impact on the overall management approach. The neurologic examination is an integral part of the evaluation of any patient with known or suspected endocarditis. During antibiotic treatment, symptoms that may be of neurologic origin justify careful repeat examination, often with CT.

5. Abdominal examination—Splenomegaly occurs in patients with endocarditis as part of generalized hyperplasia of the reticuloendothelial system. Its presence usually indicates endocarditis of at least 10 days' duration. Marked splenomegaly may be accompanied by abdominal pain from splenic infarction.

D. DIAGNOSTIC STUDIES

1. Detection of blood-borne infection—Bacteremia or fungemia invariably occurs at some point during endocarditis (a role for viruses is unproven). The presence of the organism in the blood is generally of low grade and continuous because of the vegetations in the

circulating bloodstream. Bacteremia may be intermittent or of variable intensity, however, especially if abscess formation has occurred or if the patient is under treatment.

The method of obtaining blood cultures depends on the severity of the patient's illness, as judged from the clinical syndrome and results of TEE. The preferred method in cases of suspected endocarditis is to obtain three to six sets of aerobic and anaerobic cultures, each from a separate venipuncture site, over a period of 24 h. This approach should be used if the suspicion of endocarditis is low, the patient appears well enough to

tolerate a 24-h delay of antibiotic therapy, or the TEE is negative or inconclusive.

Initiation of antibiotic therapy, however, should not be delayed if the suspicion of endocarditis is high and the patient is acutely ill, with a temperature more than 40°C, tachycardia, discomfort, or hypotension; the TEE is positive; or complications of endocarditis, such as embolism or congestive heart failure, have already occurred. Under these conditions, the cultures should be obtained over 1–2 h, followed immediately by antibiotic therapy.

Blood cultures have been found positive for an infecting organism in 70–95% of cases of endocarditis reported in studies since 1970. Proper technique and timing of blood cultures can improve the positive yield. Potential causes of negative blood cultures in patients with endocarditis are shown in Table 29-6. When blood cultures remain negative at 24–48 h in a patient with probable endocarditis, the most important concern is infection from unusual organisms, such as the fungi, HACEK organisms, *Coxiella burnetii* (Q fever), *Chlamydia psittaci, Bartonella* and abiotrophia species (nutritionally variant streptococci). The laboratory should be notified of the suspected diagnosis, and infectious disease consultation obtained.

Failure to obtain more than one set of blood cultures
Failure to hold blood cultures for longer than 1 week
Prior antibiotic prescription (normally within 2–3 days of culture)
Organism grows slowly in standard culture (eg, HACEK organisms, nutritionally variant streptococci)
Organism fails to grow in standard culture (eg, fungi, rickettsiae, Q fever, psittacosis, nutritionally variant streptococci)
Intermittent bacteremia or fungemia (rare)

Table 29-6. Causes of negative blood cultures in endocarditis.

If antibiotics have already been started for another diagnosis, modification of the blood culture technique can increase the positive yield. The importance of recovering the causative organism may warrant stopping all antibiotics. (The use of antibiotic removal devices or specialized media have not proven to be useful for increasing the yield from blood cultures in this situation.) Blood cultures then should be drawn according to the

routine outlined earlier, usually with an additional three blood cultures drawn over a second 24-h period. If the patient is acutely ill or the TEE demonstrates extensive infection, at least one set of blood cultures should be obtained promptly and empiric treatment begun (See section on Empiric antibiotic therapy).

If the suspicion of endocarditis remains moderate or high after the initial blood culture sets are drawn, empiric antibiotic therapy should also begin. The antibiotics should be changed according to the blood culture results as soon as these become available. If the initial blood cultures are negative after 24 h but endocarditis is still suspected, three more sets should be obtained and processed under the guidance of an infectious disease specialist. Hypertonic and nutritionally supplemented media are useful for detecting cell wall-deficient and nutritionally variant organisms, respectively. The lysis-centrifugation method of blood culture preparation also should be used in an attempt to detect fungi, and the microbiology laboratory should be notified to hold the cultures for 4 weeks. Serologic testing should be considered.

2. Serologic testing—Serologic testing can be helpful for identifying certain causes of endocarditis when blood cultures are negative. Histoplasmosis antigen is highly specific for systemic infection by this organism. Positive antibody titers for Q fever (*Coxiella burnetii*) or *Brucella* in a patient with culture-negative endocarditis identify these organisms as the cause. The usefulness of other serologic tests, such as that for *Candida albicans,* is highly dependent on the clinical situation.

Although not essential to the diagnosis of endocarditis, serologic testing is supportive and can be useful in certain situations. A positive rheumatoid factor, commonly found in patients with endocarditis of longer than 2 weeks' duration, and a false-positive VDRL, which is less frequent, signal the presence of high titers of antibodies (stimulated by the prolonged antigenemia occurring in endocarditis). These two laboratory abnormalities are not specific for endocarditis, however, and are found in other diseases that may imitate endocarditis, such as systemic lupus erythematosus. When blood cultures are positive but other evidence of endocarditis is lacking or equivocal, a positive rheumatoid factor or VDRL should prompt careful follow-up and retesting (eg, repeat TEE) for further evidence of endocarditis. Under some circumstances, these positive serologic tests may even warrant extension of antibiotic therapy to treat presumed endocarditis.

3. Echocardiography—

a. Transesophageal echocardiography—TEE should be performed within the first few hours after presentation of a patient with suspected endocarditis. With its detailed images of the heart valves and related structures, TEE is highly sensitive and specific for the diagnosis of endocarditis and is essential to defining the extent of disease. A positive TEE for a mass with the characteristics of a vegetation has a specificity of more than 90% for endocarditis (in the absence of a history of endocarditis, since it is difficult to distinguish between old and new vegetations). A negative TEE does

not rule out endocarditis, but it has a negative predictive accuracy of at least 90%. Because false-negative TEE studies can occur, however, a patient with a negative study but a high clinical suspicion of endocarditis should be either observed carefully or treated,

depending on the clinical severity of the illness. The TEE should be repeated if needed.

(1) Classification—Transesophageal echocardiographic studies in patients with suspected endocarditis may be classified according to the probability of the disease. A useful scheme is based on four categories: normal, possible, probable, and almost certain. In the **normal** category, no substrate for endocarditis or other abnormalities is present.

The TEE findings are classified as **possible endocarditis** in the presence of valve disease, such as a prosthetic heart valve, rheumatic or degenerative valvular sclerosis, or valve regurgitation likely to be pathologic, that predispose the patient to endocarditis—but without evidence of lesions. The classification of **probable endocarditis** is used when less specific lesions are found. Examples of such abnormalities include localized leaflet thickening or an nonmobile leaflet-related mass (especially if the lesion has the reflectance of soft rather than sclerotic tissue), mitral or aortic valve prolapse, chordal rupture, intracardiac thrombi, and paravalvular regurgitation in patients with prosthetic valves.

Patients with no history of endocarditis who have a lesion very strongly associated with infective endocarditis fall into the **almost-certain** category. In such cases, TEE shows an intracardiac mass with typical vegetation characteristics—a pedunculated mass attached near the leaflet tip and prolapsing during valve closure into the lower pressure chamber. Vegetations have soft-tissue reflectance (like myocardium) and vibratory or rotatory motion independent of the motion of the leaflet. Vegetations apparent on TEE vary in length from 1 or 2 mm to several centimeters.

Other lesions considered almost certain for endocarditis would be an abscess or fistula, a metastatic vegetation, and an aneurysm of the intervalvular fibrosa. An abscess appears on TEE as an echolucent space adjacent to a valve annulus or prosthetic sewing ring. The abscess often appears to be separated from adjacent structures by thin septa, and jets of blood flowing into the abscess during systole or diastole (depending on abscess location) may be shown by Doppler interrogation. The abscess is considered a fistula when there is communication with two or more adjacent cardiac chambers or blood vessels. Metastatic vegetations appear on echocardiography as vibratory or rotatory masses attached to an endocardial surface at a site with a regurgitant jet.

It should be noted that this classification scheme is appropriate for TEE only on patients with other reasons to suspect endocarditis (eg, unexplained fever, positive blood cultures) and no prior history of endocarditis.

(2) Diagnostic accuracy—Possible causes of a false-negative or false-positive TEE are shown in Table 29-7. Of particular importance is the possibility that a negative TEE may be due to endothelial infection in the vasculature rather than the heart. Because vascular infection is rare in the absence of prior vascular surgery, the diagnosis is usually suspected based on the patient's history. Nevertheless, the TEE examination in patients with suspected endocarditis routinely includes the thoracic aorta. Transesophageal echocardiography may identify severe atherosclerosis with mobile atheroma or thrombi. Although these abnormalities are not nearly as specific for infection as are intracardiac vegetations, the clinical picture may justify antibiotic treatment.

False-Positives
Myxomatous mitral valve disease
Papillary fibroelastomas
Partially flail leaflet
Healed vegetations
Mitral valve strands
Nodules of Arantii (aortic valve)
Lambl's excrescences (mitral valve)
False-Negatives
Aortic valve prosthesis
Mitral valve mechanical prosthesis (includes shadowing of acortic valve by a mitral prosthesis)
Calcified aortic root shadowing tricuspid or pulmonic valves
Mitral annular calcification
Aortic atheroma or aneurysm infection
Study done too early in disease course

Table 29-7. Causes of false-negative and false-positive results of transesophageal echocardiography.

In general, fewer than 10% of positive TEE are false- positives. By causing thickened, prolapsing leaflets and ruptured chordae, a myxomatous mitral valve can closely mimic endocarditis. A benign leaflet tumor, called a **papillary fibroelastoma,** may give the appearance of a vegetation. Several other abnormalities seen by TEE have lower specificity for the diagnosis of endocarditis than do typical vegetations; examples include paraaortic cavities (potentially representing either an abscess or an aneurysm of the sinus of Valsalva) and paraprosthetic regurgitation. Clinical context is often crucial to the interpretation of these findings. The paraneoplastic syndrome of myxomas may mimic endocarditis, although usually location and morphologic features of myxomas distinguish them from thrombi or vegetations. Intracardiac thrombi may be innocent bystanders in a patient with a clinical syndrome suggesting

P.469

endocarditis, or they may be secondarily infected.

Lambl's excrescences are thin, strand-like structures extending 1–10 mm from the mitral leaflet margins. Because they prolapse a few millimeters into the left atrium and exhibit hypermobility, Lambl's excrescences can be mistaken for small vegetations. Nodules of Arantii are similar extensions, not more than a few millimeters in length, from the center of the aortic cusp margin. When the aortic valve is closed, they may be seen by TEE prolapsing from the center of the valve.

In addition to detecting vegetations, TEE usually provides a detailed picture of the extent of cardiac infection; it is very accurate at assessing the exact size and location of vegetations. Several complicated forms of cardiac involvement are usually identifiable by TEE. Because many of these complex lesions require surgery, TEE should be performed as soon as possible in a patient with a moderate of high suspicion of endocarditis.

Blood cultures should be drawn either before or 15 min after TEE to avoid the transient bacteremia that infrequently occurs during the procedure. Prophylaxis for endocarditis is not indicated prior to TEE.

b. Transthoracic echocardiography—The initial diagnostic value of transthoracic echocardiography (TTE) is limited in patients with possible endocarditis because of its low sensitivity: a large number of false-negatives occur, particularly in patients with prosthetic valves. On the other hand, a positive TTE showing typical vegetations is at least 90%

specific for the diagnosis of endocarditis. Transthoracic echocardiography, however, cannot provide the detailed information regarding the anatomic extent of infection available from TEE.

Despite these limitations, TTE has a valuable ancillary role to play in patients with known endocarditis. It is well suited to assessing cardiac chamber dilatation, left and right ventricular dysfunction, and the patient's hemodynamic status. Presystolic closure of the mitral valve on TTE is a sign of elevated LV end-diastolic pressure and is an indication that the patient with aortic insufficiency should be considered for surgery. Similarly, right atrial and pulmonary artery pressures can be estimated by transthoracic Doppler examination. Additional Doppler data is essential to assessing the severity and hemodynamic sequelae of mitral regurgitation, including elevated left atrial pressure. Changes in the patient's clinical status during treatment often can be readily diagnosed by comparison of serial TTE studies. For these reasons it is advisable to perform transthoracic study at the same time as the initial TEE. One useful strategy is to discuss the results of TTE with the referring physician while the patient is still in the laboratory, and then proceed to TEE if appropriate.

4. Electrocardiography and chest radiography—The electrocardiograph (ECG) is occasionally useful in alerting the clinician to the severity of endocarditis. In patients with known or suspected aortic valve endocarditis, the PR interval should be followed closely for prolongation, an indication of aortic annular abscess formation. Less frequently, the ECG may show increased QRS voltage and a precordial strain pattern in patients developing either severe aortic or mitral regurgitation with marked LV enlargement. The chest radiograph is primarily useful in evaluating the patient with suspected endocarditis to assess the presence and severity of pulmonary edema and to detect septic pulmonary emboli in patients with possible right-heart endocarditis.

Management

A. INITIAL DECISIONS

Management of newly diagnosed endocarditis requires the physician to make two decisions promptly. The first is whether to initiate empiric antibiotic therapy based on available clinical information or to await the exact identity and antibiotic sensitivities of the infecting organism and then to select the optimal regimen. The second decision is whether valve surgery is indicated immediately or can be deferred to allow assessment of the patient's response to antibiotic therapy.

Both decisions depend on the extent of cardiac infection (usually characterized by TEE), the severity of the patient's symptoms and signs of infection, the patient's circulatory status, the seriousness of extracardiac complications, and the available data about the organism.

Once initial treatment is underway, the physician must maintain a high level of vigilance for evidence of an inadequate response to treatment or the development of complications that will require additional medical or surgical intervention.

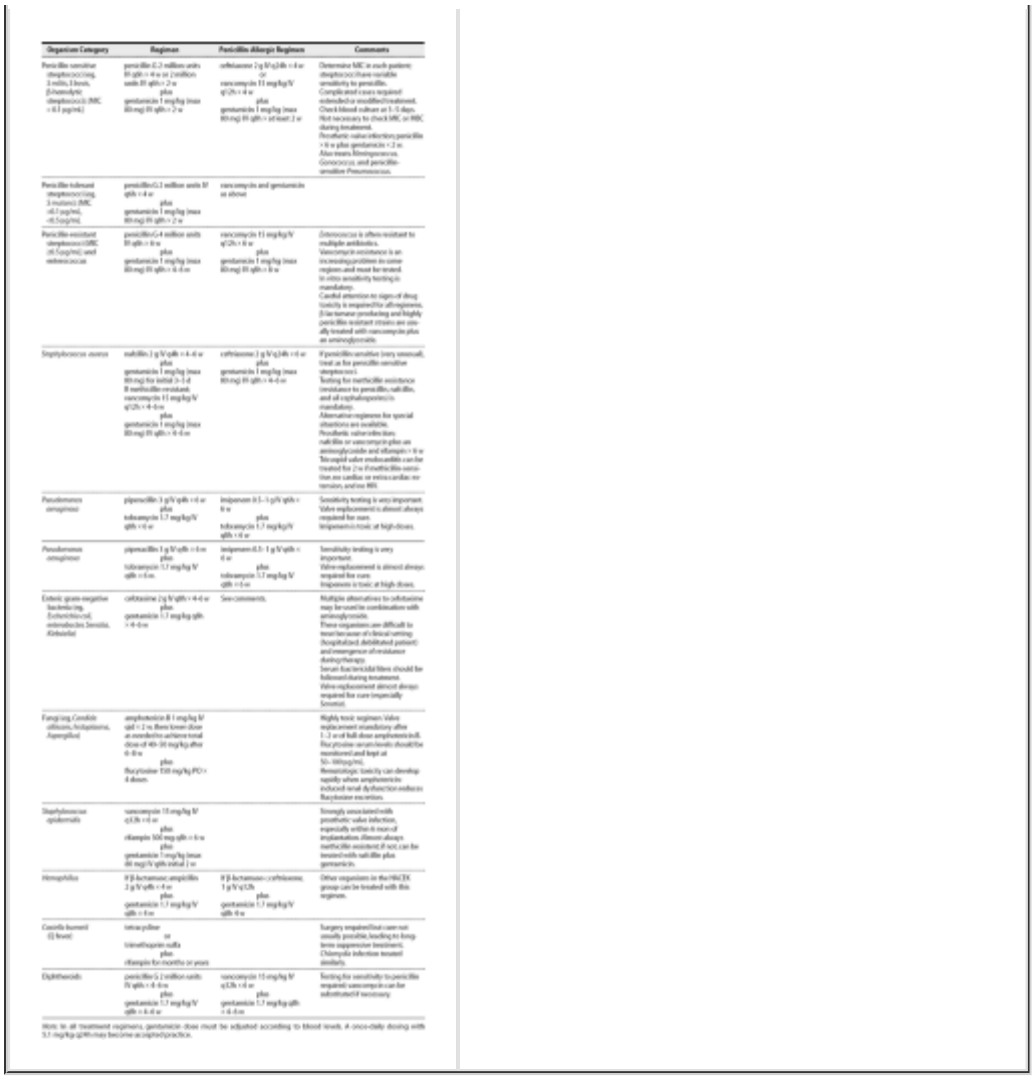
B. ANTIBIOTIC THERAPY

The goal of antibiotic therapy is to sterilize vegetations. For most causative organisms, this is an achievable goal and will cure the patient if cardiac abscess and metastatic infection to other organs have not occurred. Vegetations, however, provide proliferating organisms with an environment that is protected against both the patient's immune system and antibiotics. Organisms grow under the surface of the vegetation where phagocytes cannot penetrate, and bacterial metabolism is slowed within the nutrient-poor vegetation, contributing to antibiotic resistance. For these reasons, antibiotic treatment is directed toward achieving bactericidal concentrations of drug within the vegetation over an extended period. It must be noted that certain important aspects of antibiotic dosing, especially in seriously ill patients, are beyond the scope of this text, and infectious disease consultation is advised.

1. Principles of antibiotic therapy—

a. In vitro sensitivity testing—For organisms with variable antibiotic sensitivity (eg, streptococci), the choice of drug and the dosage depend on in vitro sensitivity testing of the strain infecting the patient. An organism's sensitivity to an antibiotic is quantified by the minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC). The MIC is defined as the minimum concentration of antibiotic that prevents proliferation of the organism in a standardized culture system. The MBC is the minimum concentration that kills 99.9% of the bacteria at 24 h in a similarly standardized system. These tests are widely used to guide treatment of endocarditis, as in the characterization of penicillin sensitivity of the multiple species of streptococci and staphylococci (Table 29-8).

Table 29-8. Antibiotic treatment of endocarditis.



MIC and MBC data are also used to identify organisms with antibiotic tolerance, which is defined as an MBC more than ten times higher than the MIC. In such cases, although the infecting organism is susceptible to the antibiotic, the rate of killing is not increased at higher antibiotic concentrations, as would be expected. The tolerance of *Enterococcus* for penicillin, for example, probably explains the substantial failure rate of medical therapy in diseases caused by this organism despite the use of a high-dose multidrug regimen. In all patients with enterococcal endocarditis, the organism's MIC for penicillin and vancomycin should guide the choice of which antibiotic to pair with an aminoglycoside. Resistance to gentamicin and streptomycin should be determined as well. *Staphylococcus aureus* is among the other potentially tolerant organisms that may require an alteration in the antibiotic regimen. Methicillin resistance, if present, requires pairing of vancomycin with an aminoglycoside.

b. Drug combinations—Combinations of drugs with additive, or synergistic, killing power are used frequently for treating endocarditis. A frequent combination (see Table 29-8) is a β-lactam antibiotic (the penicillins and cephalosporins) with an aminoglycoside. This combination is synergistic because the β-lactam drug damages the bacterial cell wall,

which allows more rapid penetration of the aminoglycoside into the cell.

c. Parenteral treatment—Antibiotic treatment must be given parenterally to ensure high and consistent serum drug levels and compliance. Outpatient IV drug therapy can be undertaken only under specific conditions (See Section 3. Outpatient Treatment), and oral therapy is almost never sufficient.

d. Prolonged treatment—The duration of antibiotic administration is almost always for a month or more. Prolonged exposure of the patient to antibiotics can lead to frequent side effects and serious toxicity (monitoring antibiotic therapy is discussed in the following section).

2. Empiric antibiotic therapy—Empiric antibiotic therapy is the initiation of antibiotics for the purpose of treating endocarditis without identifying the causative organism. Ideally, empiric therapy is needed only briefly until culture and sensitivity data are available. It requires treating the patient for the worst-case organism and can subject the patient to the additional risk of receiving multiple antibiotics over a prolonged period. This approach should be avoided whenever the patient's clinical status allows waiting for blood culture results, and the physician should make every effort to draw blood cultures consistent with a tolerable delay in the initiation of appropriate therapy.

Empiric therapy may be necessary if the patient presents with the syndrome of acute endocarditis (see Table 29-1), appears with symptoms of significant toxicity, or shows signs of septic shock; if the patient presents with signs and symptoms of left-heart failure and is likely to need surgery in the near future; or if the patient's echocardiogram (preferably TEE) shows evidence of extensive cardiac involvement. Although data on the prognostic implications of specific TEE findings are still incomplete, extensive involvement probably includes a vegetation longer than 2–3 cm, valve dysfunction likely to be hemodynamically significant, more than one infected valve, leaflet perforation, annular abscess, and pericarditis. A history of endocarditis must be ruled out. The choice of antibiotic for empiric therapy may be guided by considering the most likely infecting organisms based on the patient's presentation. Table 29-9 shows a four-category scheme for the selection of empiric therapy.

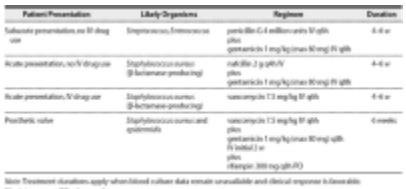


Table 29-9. Empiric treatment for endocarditis.

3. Outpatient treatment—Outpatient parenteral antibiotic therapy, now widely used, can provide an excellent outcome. Careful patient selection and management are mandatory. The first 2 weeks of treatment should almost always be as an inpatient because complications are most likely during this time. If the patient has a low-virulence organism, if valve involvement is limited to vegetations attached to leaflets and vegetations are not large (<15 cm), and the first 2 weeks have been uncomplicated, then outpatient treatment should be considered. Endocarditis due to strep viridans and the HACEK group can be treated as an outpatient. At present, it is less certain that infection with *S aureus,* especially of the aortic valve, can be safely treated this way, due to the frequency of abscess and subvalve extension.

In addition to a specialized team of nurses managing the infusion and assessing the patient daily, a physician experienced in the treatment of endocarditis should be available for a same-day visit in the event of evidence of complications (discussed further under Section C. Management of Complications). The patient should live close to a hospital and have drug levels, blood cultures,

P.471

P.472

P.473

and other blood work monitored as with an inpatient.

4. Monitoring antibiotic therapy—

a. Drug levels—Monitoring the levels and effects of antibiotics is important in managing endocarditis because the patient's prolonged exposure to high doses of antibiotics increases the frequency of adverse drug effects. The use of aminoglycosides requires monitoring of serum levels at peak (1–2 h after infusion is started) and trough (immediately before the next dose). A peak level for gentamicin or tobramycin of less than 5 μg/mL is associated with treatment failure for many organisms and may warrant adjustment of the dose or the dosing interval. At a trough level of more than 2 μg/mL, gentamicin carries an increased risk of nephrotoxicity, and the dose should be reduced. Monitoring these levels assumes even greater importance in the setting of renal insufficiency, especially if renal function is changing. Although vancomycin and flucytosine levels should always be monitored for the same reasons, levels for β-lactam antibiotics are available but rarely needed.

b. Serum bactericidal titers—The efficacy of the antibiotic therapy can be estimated by testing the killing power of the patient's serum. (The serum bactericidal titer is defined as the greatest dilution of serum that kills an inoculum of the organism in a standardized system.) In general, a titer of 1:8 or greater is associated with cure; however, serum bactericidal titers provide no significant additional benefit over the use of standardized antibiotic regimens for most organisms. They are occasionally useful in assessing the adequacy of treatment against unusual organisms or when an unconventional antibiotic regimen must be used.

c. Adverse effects—The most frequent adverse effects are a pruritic maculopapular rash and low-grade fever seen with β-lactam antibiotics. The rash may signify delayed hypersensitivity and may be accompanied by hepatic or renal dysfunction. Liver function

tests (aspartate aminotransferase and alkaline phosphatase) and creatinine should be checked in this situation. If these tests are abnormal, substitution of another drug is required. If not, it is preferable to continue the antibiotic and treat the symptoms. Patients on β-lactam antibiotics should have a routine complete blood count every 3 or 4 days during therapy to detect anemia, thrombocytopenia, and leukopenia. The sodium content of β-lactam antibiotics may require diuretic therapy in patients with heart failure.

Patients on aminoglycosides should have the serum creatinine checked routinely at 3–4-day intervals. Equally useful for detection of renal dysfunction is the periodic examination of urine for white cell or granular casts. Ototoxicity is an idiosyncratic reaction unrelated to aminoglycoside levels that occurs in 10–20% of cases.

Diarrhea may occur during antibiotic therapy; this is usually due to overgrowth of gut organisms competing with those sensitive to the antibiotic (eg, *Clostridium difficile* colitis).

C. MANAGEMENT OF COMPLICATIONS

1. Failure of antibiotic therapy—Changes in the cardiac examination during antibiotic treatment are particularly

important in detecting failure of medical therapy. Changes in a regurgitant murmur almost always indicate valve dysfunction, and the appearance of a new murmur may signal metastatic infection of another valve. Such new findings almost always warrant repeat echocardiography (usually TEE) and blood cultures. There may also be an increase in the resting sinus rate and the appearance of heart failure.

Failure of antibiotic therapy is usually heralded by persistent or recurrent fever. Persistent fever is that which continues more than a week during antibiotic treatment. Recurrent fever develops after an afebrile period of several days and occurs at least a week after initiation of antibiotics. Persistent infection is only one cause of fever in this setting; others include hypersensitivity to antibiotics and other drugs, phlebitis, silent emboli (especially pulmonary and splenic), intercurrent urinary or upper respiratory tract infection, or simply a delayed response to antibiotic therapy. Blood cultures should be obtained and efforts made to rule out these possibilities. If blood cultures are negative, and the patient shows no other evidence of deterioration, watchful waiting is appropriate.

Positive blood cultures after more than 1 week of antibiotic therapy strongly suggest persistent infection. The cause may be either antibiotic resistance or a protected site of infection. The site may be an intracardiac annular or myocardial abscess or an extracardiac site of metastatic infection, septic embolization, or mycotic aneurysm. Repeat TEE is strongly indicated. Careful comparison to the studies obtained at the time of initial diagnosis may detect intracardiac suppurative complications; there is a sensitivity range of 80–90%. If the TEE is positive, urgent surgery is indicated. If it is negative, a careful history and physical examination coupled with CT or a technetium, gallium, or indium scan will often reveal an infective focus.

2. Worsening valve dysfunction and heart failure—At any time during the course of endocarditis, heart failure signs and symptoms may appear as a result of worsening regurgitation and failure of ventricular compensatory mechanisms. In fact, heart failure may

appear despite effective antibiotic therapy—and even after bacteriologic cure. The onset of heart failure may be insidious and difficult to recognize, or it may be abrupt and catastrophic. Frequent appraisal of the patient's status by history and physical examination is the best way to ensure early detection of heart failure. Any change in the patient's regurgitant murmur during antibiotic therapy usually signifies progression of valvular dysfunction and the likely need for surgery. A persistent tachycardia or slowly increasing heart rate is a useful sign of impending heart failure prior to the appearance of the typical signs such as rales, S_3, and pulmonary vascular redistribution on chest x-ray film. In patients with aortic valve endocarditis, the appearance of a widened pulse pressure usually indicates increased valve regurgitation.

Serial TTE or TEE is useful in confirming a suspected change in the patient's hemodynamic status; it may even identify the cause. Worsening of the mitral regurgitant lesion is suggested by an increase in size of the color-flow Doppler jet or an increase in the radius of the flow convergence region on the LV side of the regurgitant orifice. A rise in transmitral early filling velocity (E wave) and a fall in forward systolic pulmonary venous flow (S wave) may indicate a rise in mean left atrial pressure.

In the case of aortic regurgitation, jet enlargement over time is also a useful indicator of worsening regurgitation. Additional indications of severe aortic regurgitation include closure of the mitral valve on M-mode echocardiography prior to the onset of the QRS and shortening of the pressure half-time of the aortic insufficiency velocity, both from a rapid rise of LV pressure to a high level in late diastole. For either mitral or aortic regurgitation, the presence or development of a hyperdynamic left ventricle (increased ejection fraction, stroke volume, or both) and progressive LV dilatation on two-dimensional echocardiography are useful indirect indications of an excessive regurgitant burden. The appearance of pulmonary or right atrial hypertension, as estimated from tricuspid jet velocity and inferior vena caval dynamics, is another sign of hemodynamic decompensation. Transesophageal echocardiography has the additional major advantage of being able to detect the intracardiac complications accounting for the change in the patient's hemodynamic status.

If heart failure is mild, surgery should be deferred while diuretics, digoxin, and afterload-reducing drugs are given to optimize the patient's hemodynamic status. If the patient responds readily to therapy, surgery might be optional. In most cases, however, surgery should be undertaken as soon as feasible because it is almost certain that valve repair or replacement will be required eventually (for the hemodynamic lesion, if not for infection), and the patient's surgical risk is lowest at this early stage. One clear exception to surgery for mild heart failure is sodium overload (related to antibiotic therapy) and suspected valve dysfunction not confirmed by echocardiography.

If heart failure is moderate or severe, valve surgery should be undertaken immediately while drug therapy is used to stabilize the patient. Because of the difficulty in predicting the rate of progression of valve dysfunction, delaying surgery for hemodynamic optimization is ill-advised. Rapid development of heart failure may signal the occurrence of a major intracardiac complication, such as leaflet perforation, chordal rupture, or fistula formation. Preoperative or intraoperative TEE is usually helpful in guiding surgical planning in this setting.

3. Embolism—Embolism most often occurs early in the course of antibiotic therapy but can occur at any time, even after biologic cure. Suspected cerebral embolism should be evaluated immediately by CT; if necessary, cerebral angiography should be performed in order to rule out an intracranial mycotic aneurysm. Nonhemorrhagic infarcts may warrant measures to reduce cerebral edema.

If the patient is already on anticoagulant therapy prior to development of endocarditis, anticoagulation is usually continued. After cerebral embolism in a patient with endocarditis, however, anticoagulation therapy is usually discontinued (if possible) for 7–14 days to reduce the likelihood of massive intracerebral bleeding. If stroke occurs in mechanical prosthetic valve endocarditis, the balance of risks and benefits of continuing anticoagulation is unknown. In patients with stroke from endocarditis, serial neurologic examinations and (if a change is suspected) repeated CT scans are indicated to permit early detection of brain abscess.

Because no clinically useful means (including echo-cardiography) has been found to identify patients at high risk for embolism, valve surgery in endocarditis is not indicated to prevent embolism. Even the probability of embolism recurring after one episode is not necessarily high enough to warrant surgery for prevention. On the other hand, surgery may be advised if the patient has had more than one episode and has a persistent vegetation.

Peripheral embolization is managed conservatively and without anticoagulation whenever possible. Vascular surgery to restore the circulation may be indicated if major organ embolization becomes life-threatening. Embolectomy is generally indicated in culture-negative endocarditis in order to make an causative diagnosis; likely organisms include *Aspergillus, Candida,* and the HACEK group. Embolectomy is necessary, strictly for treatment, in fungal endocarditis in order to remove as much infection as possible from the circulation.

4. Mycotic aneurysm—A complaint of severe headache or visual disturbance (especially homonymous hemianopsia) in a patient with endocarditis should prompt an urgent CT scan for the possibility of an expanding intracranial mycotic aneurysm. This catastrophic complication may also present as a subarachnoid or intracerebral hemorrhage, usually massive. If the scan is negative, cerebral angiography is often necessary to confirm or rule out the diagnosis. Treatment is surgical removal as soon as the patient's condition will allow.

5. Myocardial infarction—Chest pain in the course of infective endocarditis is most likely due to myocardial infarction, pericarditis, or septic pulmonary embolization. Myocardial infarction during infective endocarditis is almost always caused by coronary embolization, although it may occasionally complicate purulent pericarditis or myocardial abscess. In the latter setting, inflammatory thrombosis of the artery probably occurs. Treatment is noninterventional. Anticoagulation is probably not indicated because its benefits for reducing myocardial ischemia in this setting are unknown and the risks of potential cerebral embolization are significant.

6. Pericarditis—The possibility of purulent pericarditis complicating infective endocarditis should be evaluated by TTE. If pericardial fluid is seen, prompt pericardiocentesis is

needed. A transudate may be present; in this infrequent case management can be conservative. Usually a purulent exudate will be found, necessitating surgical drainage or pericardiectomy. Most important, purulent pericarditis may signal the presence of an intracardiac abscess. Transesophageal echocardiography is indicated, and if an abscess is found, surgical drainage and valve surgery should be performed. Fortunately, the treatment of these related problems can be performed in a single operation. If an underlying myocardial abscess is not found, a pericardial window may be sufficient therapy. Continued observation is indicated because of the risk of subsequent additional cardiac or pericardial suppurative complications.

D. MANAGEMENT OF HIGH-RISK ENDOCARDITIS

1. Prosthetic valve endocarditis—Far higher morbidity and mortality rates are associated with prosthetic valve endocarditis than with native valve endocarditis. Infection of a prosthesis by fungi carries a mortality rate of more than 90%, whereas prosthetic infection from streptococci has a mortality rate of approximately 30%. In addition, the mortality rate from prosthetic valve endocarditis early after implantation is around twice that of late infection (after 2 months). Survival is improved by early operation in most cases, when the patient's surgical risk is acceptable. Surgical replacement is necessary in 85% of cases of biologic valve endocarditis and in almost all cases of mechanical prosthetic infection. Indications for surgery in prosthetic valve endocarditis are summarized in Table 29-10.

Mechanical prosthesis (almost all cases)
Bioprosthesis if:
New paravalvular regurgitation or fistula
Sewing-ring abscess or dehiscence
Infection from *Staphylococcus epidermidis* or *aureus*, *Enterococcus*, gram-negative bacteria, fungi
Blood cultures still positive after 1 week of antibiotics
Embolism or other major complication

Table 29-10. Indications for surgery in prosthetic valve endocarditis.

Medical treatment can be attempted in mechanical valve endocarditis when the surgical risk is high and the only evidence of valve involvement (using TEE) is a vegetation in the area of the sewing ring. In such cases, frequent serial TEE may be useful to follow valve function and the response of the infected mass to treatment. Initial medical treatment of bioprosthetic endocarditis may be attempted when infection is due to a low-risk organism (such as *Streptococcus*) and involvement is limited to a vegetation on the either the prosthetic leaflets or sewing ring (see Table 29-9). Repeated TEE is very useful if the patient fails to respond to antibiotics. Blood cultures should be obtained every 4–7 days during treatment and weekly for a month following apparently successful treatment.

2. Fungal endocarditis—Overall mortality rates for fungal endocarditis are more than 80%; they are especially high in cases caused by *Aspergillus* and *Candida* species. Treatment requires the close collaboration of the primary physician, cardiologist, surgeon, and infectious disease specialist. Treatment is almost always a combination of valve replacement and a full course of amphotericin B (see Table 29-8). Late relapses are common and require prolonged surveillance for years following successful completion of antibiotic therapy. In addition to serologic tests and blood cultures, TEE is useful in monitoring the patient during and after treatment.

3. Endocarditis from gram-negative bacteria—*Pseudomonas* endocarditis carries a mortality rate of almost 80% because of the frequent inability to sterilize vegetations by medical treatment. Among the causes for this inability is the frequent emergence of antibiotic-resistant bacterial strains during therapy. Surgery is usually performed as soon as possible after the diagnosis of *Pseudomonas* endocarditis of the left-sided valves. Surgery is also frequently indicated in endocarditis caused by the HACEK organisms, but here the reason is extensive valvular destruction by the time of diagnosis. In contrast to *Pseudomonas,* infection from HACEK organisms is readily cured by antibiotics. The treatment of endocarditis from enteric gram-negative bacteria is similar to that for *Pseudomonas* in that antibiotic therapy may fail, leading to a need for valve replacement. In vitro antibiotic sensitivity testing is crucial to antibiotic therapy of gram-negative bacteria.

E. SURGERY

The indications for valve replacement or repair during infective endocarditis (discussed in the preceding section) are summarized in Table 29-11. The indications and timing of valve surgery are guided by several important principles. Surgical morbidity and mortality rates are much higher if the patient is in even mild heart failure, is hypotensive, or has a low cardiac output when sent to the operating room. Similarly, uncontrolled infection, with its attendant systemic stress and peripheral dilatation, confers a higher surgical risk. In the absence of these factors, surgical risk generally is low despite active infective endocarditis. Surgery should not be delayed with the intention of prolonging preoperative antibiotic therapy. It has never been shown that either the risk of reinfection of the new prosthetic valve or surgical complications are reduced by longer preoperative antibiotic treatment.

Absolute Indications
Intracardiac abscess or fistula
Left heart failure from severe regurgitation or (rarely) obstruction
Endocarditis caused by fungi and resistant gram-negative organisms
Relative Indications
Mild heart failure in otherwise uncomplicated case
Recurrent embolization with persistant vegetation
Purulent pericarditis
Bacteremia despite optimal antibiotic therapy
Recurrent life-threatening septic pulmonary emboli
Severe tricuspid regurgitation with a low output state

Table 29-11. Indications for valve surgery in native valve endocarditis.

The anatomic location and extent of valve involvement and other factors may allow valve debridement and repair rather than replacement. The advantages of valve repair are that future anticoagulation is not needed, and subsequent valve replacement carries a lower risk. The disadvantages of valve repair are the greater possibility of residual infected tissue and significant valve regurgitation. Valve repair is not considered in the presence of abscess or fistula near the valve or when significant leaflet erosion has occurred. As part of a repair, however, leaflet perforation can be patched and chordal support reconstructed. In general, valve repair is feasible when excision of the infected leaflet with a 2-mm margin of normal tissue will still leave enough normal leaflet to preserve valvular competence. Preoperative or intraoperative TEE is usually indicated for surgical planning and guidance.

F. FOLLOW-UP AFTER ENDOCARDITIS

Long-term survival of the patient following an episode of endocarditis is much lower than that of the general population. Overall survival following native valve endocarditis is approximately 80% at 5 years and 50% at 10 years. Survival is considerably lower after prosthetic valve endocarditis. The patient remains at risk for three consequences of the disease: relapse of the original infection, noninfective sequelae of the infection, and recurrent endocarditis.

Failure to eradicate infection completely is usually apparent within 15 days after antibiotics are discontinued,

although relapse has been reported up to 6 months after apparently successful treatment. Relapse rates tend to be low with viridans streptococci (<5%), intermediate with enterococci (8–20%) and high with *Pseudomonas* and fungi (>20%). Relapse of *Staphylococcus aureus* endocarditis is not frequent (5%) but should prompt a search for an extracardiac source. Treatment of a relapse includes a reassessment of the extent of cardiac infection, and surgery warrants careful consideration. If antibiotic therapy is given a trial, the patient should be carefully monitored during therapy to determine the need for surgery.

After successful treatment of infection, the patient remains at risk for the development of heart failure, stroke, and rupture of a mycotic aneurysm. If the patient had moderate or severe valve regurgitation or an episode of heart failure prior to hospital discharge, the probability of late heart failure is greatly increased. The risk of embolic stroke is very low after the first 4 weeks of antibiotic treatment but may persist for an unknown length of time. Rupture of a mycotic aneurysm after treatment is also rare but should be considered when a patient with stroke has a history of prior endocarditis.

Although estimates vary, recurrent endocarditis, defined as a repeat episode after more than 6 months, occurs in approximately 5–8% of cases. Controversy exists regarding the tendency for the infecting organism and the involved valve to be similar to those of the original episode. The recurrent episode probably carries a higher mortality rate than does the original one. Risk factors for recurrent endocarditis include intravenous drug use, congenital heart disease, rheumatic and myxomatous disease, and (in one study)

periodontitis.

References

Andrews MM, von Reyn CF: Patient selection criteria and management guidelines for outpatient parenteral antibiotic therapy for native valve infective endocarditis. Clin Infect Dis 2001;33:203.

Barnes PD, Crook DWM: Culture-negative endocarditis [Review]. J Infection 1997;35:209.

Bayer AS et al: Diagnosis and management of infective endocarditis and its complications. Circulation 1998;98:2936.

Dajani AS et al: Prevention of bacterial endocarditis. Circulation 1997;96:358.

Fang G et al: Prosthetic valve endocarditis resulting from nosocomial bacteremia. Ann Intern Med 1993:119:560.

Fowler VG et al: Role of echocardiography in evaluation of patients with staphylococcus aureus bacteremia, experience in 103 patients. J Am Coll Cardiol 1997;30:1072.

Klug D et al: Systemic infection related to endocarditis on pacemaker leads. Circulation 1997;95:2098.

Li JS et al: Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. Clin Infect Dis 2000;30: 633.

Mylonkis E, Calderwood SB et al: Infective endocarditis in adults. [Review] N Engl J Med 2001;345(18):1318.

Wilson WR et al: Antibiotic treatment of adults with infective endocarditis due to streptococci, enterococci, staphylococci, and HACEK microorganisms. JAMA 1995;274:1706.