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109
Infective Endocarditis

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The proliferation of microorganisms on the endothelium of the heart results in infective endocarditis. The prototypic lesion at the site of infection, the *vegetation* (Fig. 109-1), is a mass of platelets, fibrin, microcolonies of microorganisms, and scant inflammatory cells. Infection most commonly involves heart valves (either native or prosthetic) but may also occur on the low-pressure side of the ventricular septum at the site of a defect, on the mural endocardium where it is damaged by aberrant jets of blood or foreign bodies, or on intracardiac devices themselves. The analogous process involving arteriovenous shunts, arterioarterial shunts (patent ductus arteriosus), or a coarctation of the aorta is called *infective endarteritis*.

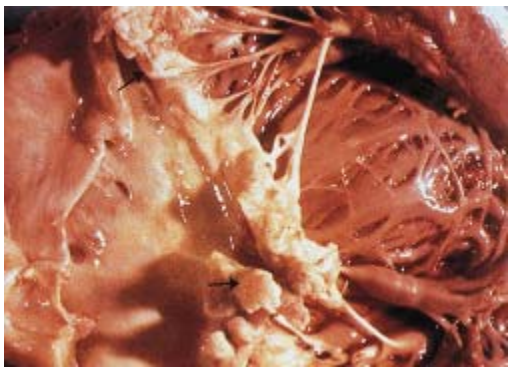

FIGURE 109-1 Vegetations (*arrows*) due to viridans streptococcal endocarditis involving the mitral valve.

Endocarditis may be classified according to the temporal evolution

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of disease, the site of infection, the cause of infection, or a predisposing risk factor such as injection drug use. While each classification criterion provides therapeutic and prognostic

insight, none is sufficient alone. The classification of endocarditis as acute and subacute was initially used to describe the illness and the time elapsed until death; presently it is applied to the features and progression of infection until diagnosis. *Acute endocarditis* is a hectically febrile illness, rapidly damages cardiac structures, hematogenously seeds extracardiac sites, and, if untreated, progresses to death within weeks. *Subacute endocarditis* follows an indolent course; causes structural cardiac damage only slowly, if at all; rarely causes metastatic infection; and is gradually progressive unless complicated by a major embolic event or ruptured mycotic aneurysm.

In developed countries, the incidence of endocarditis ranges from 1.5 to 6.2 cases per 100,000 population per year. In the late 1980s in a metropolitan area of the United States (Philadelphia), endocarditis occurred in 9.3 persons per 100,000 population per year. However, half of these cases arose as a consequence of injection drug use. The incidence of endocarditis is notably increased among the elderly. The cumulative rate of prosthetic valve endocarditis is 1.5 to 3.0% at 1 year after valve replacement and 3 to 6% at 5 years; the risk is greatest during the first 6 months after valve replacement.

ETIOLOGY

Many species of bacteria and fungi have been reported to cause sporadic episodes of endocarditis; nevertheless, a small number of bacterial species cause the majority of cases (Table 109-1). The causative microorganisms vary somewhat among the major clinical types of endocarditis, in part because of the different portals of entry. The oral cavity, skin, and upper respiratory tract are the respective primary portals for the viridans streptococci, staphylococci, and HACEK organisms (*Haemophilus*, *Actinobacillus*, *Cardiobacterium*, *Eikenella*, and *Kingella*) causing community-acquired native valve endocarditis. *Streptococcus bovis* originates from the gastrointestinal tract, where it is associated with polyps and colonic tumors, and enterococci enter the bloodstream from the genitourinary tract. Nosocomial native valve endocarditis is largely the consequence of bacteremia arising from intravascular catheters and less commonly from nosocomial wound and urinary tract infection. Endocarditis complicates 6 to 25% of episodes of catheter-associated *Staphylococcus aureus* bacteremia; the higher rates are detected by careful transesophageal echocardiography (TEE) screening (see “Echocardiography,” below).

TABLE 109-1 Organisms Causing Major Clinical Forms of Endocarditis

	Percent of Cases	
		Prosthetic Valve Endocarditis at Indicated Time of Onset

	Native Valve Endocarditis		(Months) after Valve Surgery			End
Organism	**Community-Acquired (n = 683)**	**Nosocomial (n = 82)**	**< 2 (n = 144)**	**2–12 (n = 31)**	**> 12 (n = 194)**	**Right-Sided (n = 346)**
Streptococci[a]	32	7	1	9	31	5
Pneumococci	1	—	—	—	—	—
Enterococci	8	16	8	12	11	2
Staphylococcus aureus	35	55	22	12	18	77
Coagulase-negative staphylococci	4	10	33	32	11	—
Fastidious gram-negative coccobacilli (HACEK group)[b]	3	—	—	—	6	—
Gram-negative bacilli	3	5	13	3	6	5
Candida spp.	1	4	8	12	1	—
Polymicrobial/miscellaneous	6	1	3	6	5	8
Diphtheroids	—	—	6	—	3	—
Culture-negative	5	2	5	6	8	3

[a] Includes viridans streptococci; *Streptococcus bovis*; other non–group A, groupable streptococci; and *Abiotrophi* variant, pyridoxal-requiring streptococci).

[b] Includes *Haemophilus* spp., *Actinobacillus actinomycetemcomitans*, *Cardiobacteriumhominis*, *Eikenella* spp., a

Note: Data are compiled from multiple studies.

Prosthetic valve endocarditis arising within 2 months of valve surgery is generally the result of intraoperative contamination of the prosthesis or a bacteremic postoperative complication. The nosocomial nature of these infections is reflected in their primary microbial causes: coagulase-negative staphylococci, *S. aureus*, facultative gram-negative bacilli, diphtheroids, and fungi. The portals of entry and organisms causing cases beginning >12 months after surgery are similar to those in community-acquired native valve endocarditis. Epidemiologic evidence suggests that prosthetic valve endocarditis due to coagulase-negative staphylococci that presents between 2 and 12 months after surgery is often nosocomial in origin but with a delayed onset. At least 85% of coagulase-negative staphylococci that cause prosthetic valve endocarditis within 12 months of surgery are methicillin-resistant; the rate of methicillin resistance decreases to 25% among coagulase-negative staphylococci causing prosthetic endocarditis that presents >1 year after valve surgery.

Transvenous pacemaker lead–and/or implanted defibrillator–associated endocarditis is usually a nosocomial infection. The majority of episodes occur within weeks of implantation or generator change and are caused by *S. aureus* or coagulase-negative staphylococci.

Endocarditis occurring among injection drug users, especially when infection involves the tricuspid valve, is commonly caused by *S. aureus* strains, many of which are methicillin-resistant. Left-sided valve infections in addicts have a more varied etiology and involve abnormal valves, often ones damaged by prior episodes of endocarditis. A number of these cases are caused by *Pseudomonas aeruginosa*

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and *Candida* species, and sporadic cases are due to unusual organisms such as *Bacillus*, *Lactobacillus*, and *Corynebacterium* species. Polymicrobial endocarditis occurs more frequently in injection drug users than in patients who do not inject drugs. The presence of HIV in this population does not significantly impact the causes of endocarditis.

From 5 to 15% of patients with endocarditis have negative blood cultures; in one-third to one-half of these cases, cultures are negative because of prior antibiotic exposure. The remainder of these patients are infected by fastidious organisms, such as pyridoxal-requiring streptococci (now designated *Abiotrophia* species), the gram-negative coccobacillary HACEK organisms, *Bartonella henselae*, or *Bartonella quintana*. Some fastidious organisms that cause endocarditis have characteristic epidemiologic settings (e.g., *Coxiella burnetii* in Europe, *Brucella* species in the Middle East). *Tropheryma*

whipplei causes an indolent, culture-negative, afebrile form of endocarditis.

PATHOGENESIS

Unless it is injured, the normal endothelium is resistant to infection by most bacteria and to thrombus formation. Endothelial injury (e.g., at the site of impact of high-velocity jets or on the low-pressure side of a cardiac structural lesion) causes aberrant flow and allows either direct infection by virulent organisms or the development of an uninfected platelet-fibrin thrombus—a condition called *nonbacterial thrombotic endocarditis* (NBTE). The thrombus subsequently serves as a site of bacterial attachment during transient bacteremia. The cardiac lesions most commonly resulting in NBTE are mitral regurgitation, aortic stenosis, aortic regurgitation, ventricular septal defects, and complex congenital heart disease. These lesions result from rheumatic heart disease (particularly in the developing world, where rheumatic fever remains prevalent), mitral valve prolapse, degenerative heart disease, and congenital malformations. NBTE also arises as a result of a hypercoagulable state; this phenomenon gives rise to the clinical entity of *marantic endocarditis* (uninfected vegetations seen in patients with malignancy and chronic diseases) and to bland vegetations complicating systemic lupus erythematosus and the antiphospholipid antibody syndrome.

Organisms that cause endocarditis generally enter the bloodstream from mucosal surfaces, the skin, or sites of focal infection. Except for more virulent bacteria (e.g., *S. aureus*) that can adhere directly to intact endothelium or exposed subendothelial tissue, microorganisms in the blood adhere to thrombi. If resistant to the bactericidal activity of serum and the microbicidal peptides released by platelets, the organisms proliferate and induce a procoagulant state at the site by eliciting tissue factor from adherent monocytes or, in the case of *S. aureus*, from monocytes and from intact endothelium. Fibrin deposition, resulting from tissue factor initiation of the coagulation cascade, combines with platelet aggregation, stimulated by tissue factor and independently by proliferating microorganisms, to generate an infected vegetation. The organisms that commonly cause endocarditis bear surface components that facilitate adherence to injured endothelium and host proteins or, in the case of *S. aureus*, to intact endothelial cells or to thrombi. Fibronectin-binding proteins present on many gram-positive bacteria, clumping factor (a fibrinogen- and fibrin-binding surface protein) on *S. aureus*, and glucans on streptococci facilitate adherence. Fibronectin-binding proteins are required for *S. aureus* invasion of intact endothelium; thus these surface proteins may facilitate infection of previously normal valves. In the absence of host defenses, organisms enmeshed in the growing platelet-fibrin vegetation proliferate to form dense microcolonies. Organisms deep in vegetations are metabolically inactive (nongrowing) and relatively resistant to killing by antimicrobial agents. Proliferating surface organisms are shed into the bloodstream continuously, whereupon some are cleared by the reticuloendothelial system and others are redeposited on the vegetation and stimulate further vegetation growth.

The pathophysiologic consequences and clinical manifestations of endocarditis—other than constitutional symptoms, which are probably a result of cytokine production—arise from damage to intracardiac structures; embolization of vegetation fragments, leading to infection or infarction of remote tissues; hematogenous infection of sites during bacteremia;

and tissue injury due to the deposition of circulating immune complexes or immune responses to deposited bacterial antigens.

CLINICAL MANIFESTATIONS

The clinical syndrome of infective endocarditis is highly variable and spans a continuum between acute and subacute presentations. Native valve endocarditis (whether acquired in the community or nosocomially), prosthetic valve endocarditis, and endocarditis due to injection drug use share clinical and laboratory manifestations (Table 109-2). Although the relationship is not absolute, the causative microorganism is primarily responsible for the temporal course of endocarditis. β-Hemolytic streptococci, *S. aureus*, and pneumococci typically result in an acute course, although *S. aureus* occasionally causes subacute disease. Endocarditis caused by *Staphylococcus lugdunensis* (a coagulase-negative species) or by enterococci may present acutely. Subacute endocarditis is typically caused by viridans streptococci, enterococci, coagulase-negative staphylococci, and the HACEK group. Endocarditis caused by *Bartonella* species and the agent of Q fever, *C. burnetii*, is exceptionally indolent.

TABLE 109-2 Clinical and Laboratory Features of Infective Endocarditis

Feature	***Frequency, %***
Fever	80–90
Chills and sweats	40–75
Anorexia, weight loss, malaise	25–50
Myalgias, arthralgias	15–30
Back pain	7–15
Heart murmur	80–85
New/worsened regurgitant murmur	10–40

Arterial emboli	20–50
Splenomegaly	15–50
Clubbing	10–20
Neurologic manifestations	20–40
Peripheral manifestations (Osler's nodes, subungual hemorrhages, Janeway lesions, Roth's spots)	2–15
Petechiae	10–40
Laboratory manifestations	
Anemia	70–90
Leukocytosis	20–30
Microscopic hematuria	30–50
Elevated erythrocyte sedimentation rate	>90
Rheumatoid factor	50
Circulating immune complexes	65–100
Decreased serum complement	5–40

The clinical features of endocarditis are nonspecific. However, these symptoms in a febrile patient with valvular abnormalities or a behavior pattern (injection drug use) that predisposes to endocarditis suggest the diagnosis, as do bacteremia with organisms that frequently cause endocarditis, otherwise-unexplained arterial emboli, and progressive cardiac valvular incompetence. In patients with subacute presentations, fever is typically low-grade and rarely exceeds 39.4°C (103°F); in contrast, temperatures between 39.4 and

40°C (103 and 104°F) are often noted in acute endocarditis. Fever may be blunted or absent in patients who are elderly or severely debilitated or who have marked cardiac or renal failure.

Cardiac Manifestations

Although heart murmurs are usually indicative of the predisposing cardiac pathology rather than of endocarditis, valvular damage and ruptured chordae may result in new regurgitant murmurs. In acute endocarditis involving a normal valve, murmurs are heard on presentation in only 30 to 45% of patients but ultimately are detected in 85%. Congestive heart failure develops in 30 to 40% of patients; it is usually a consequence of valvular dysfunction but occasionally is due to endocarditis-associated myocarditis or an intracardiac fistula. The temporal progression of heart failure is variable; failure due to aortic valve dysfunction progresses more rapidly than that due to mitral valve dysfunction. Extension of infection beyond valve leaflets into adjacent annular or myocardial tissue results in perivalvular abscesses, which in turn may cause fistulae (from the root of

the aorta into cardiac chambers or between cardiac chambers) with new murmurs. Abscesses may burrow from the aortic valve annulus through the epicardium, causing pericarditis. Extension of infection into paravalvular tissue adjacent to either the right or the noncoronary cusp of the aortic valve may interrupt the conduction system in the upper interventricular septum, leading to varying degrees of heart block. Although perivalvular abscesses arising from the mitral valve may potentially interrupt conduction pathways near the atrioventricular node or in the proximal bundle of His, such interruption occurs infrequently. Emboli to a coronary artery may result in myocardial infarction; nevertheless, embolic transmural infarcts are rare.

Noncardiac Manifestations

The classic nonsuppurative peripheral manifestations of subacute endocarditis are related to the duration of infection and, with early diagnosis and treatment, have become infrequent. In contrast, septic embolization mimicking some of these lesions (subungual hemorrhage, Osler's nodes) is common in patients with acute *S. aureus* endocarditis (Fig. 109-2). Musculoskeletal symptoms, including nonspecific inflammatory arthritis and back pain, usually remit promptly with treatment but must be distinguished from focal metastatic infection. Hematogenously seeded focal infection may involve any organ but most often is clinically evident in the skin, spleen, kidneys, skeletal system, and meninges. Arterial emboli are clinically apparent in up to 50% of patients. Vegetations >10 mm in diameter (as measured by echocardiography) and those located on the mitral valve are more likely to embolize than are smaller or nonmitral vegetations. Embolic events—often with infarction—involving the extremities, spleen, kidneys (Fig. 109-3), bowel, or brain are often noted at presentation. With antibiotic treatment, the frequency of embolic events decreases from 13 per 1000 patient-days during the initial week to 1.2 per 1000 patient-days after the third week. Emboli occurring late during or after effective therapy do not in themselves constitute evidence of failed antimicrobial treatment. Neurologic symptoms, most often resulting from embolic strokes, occur in up to 40% of patients. Other neurologic complications include aseptic or purulent meningitis, intracranial hemorrhage due to

hemorrhagic infarcts or ruptured mycotic aneurysms, seizures, and encephalopathy. (*Mycotic aneurysms* are focal dilations of arteries occurring at points in the artery wall that have been weakened by infection in the vasa vasorum or where septic emboli have lodged.) Microabscesses in brain and meninges occur commonly in *S. aureus* endocarditis; surgically drainable abscesses are infrequent.

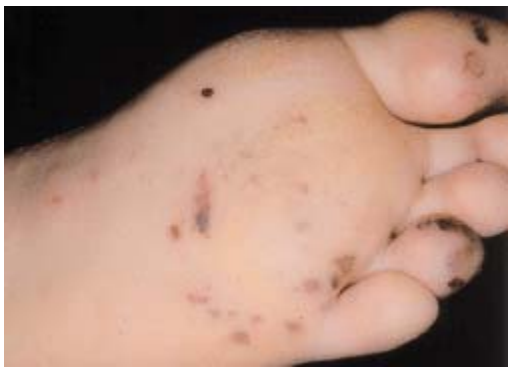

FIGURE 109-2 Septic emboli with hemorrhage and infarction due to acute *Staphylococcus aureus* endocarditis. *(Courtesy of L. Baden.)*

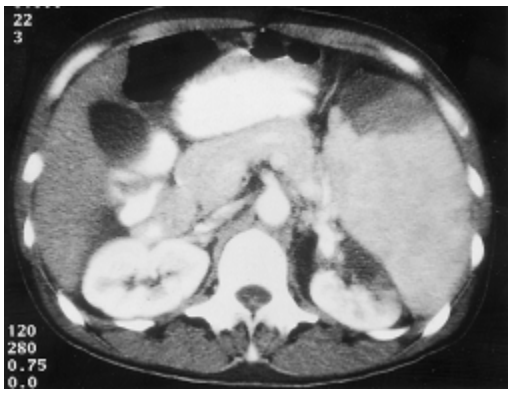

FIGURE 109-3 Computed tomography of the abdomen showing large embolic infarcts in the spleen and left kidney of a patient with *Bartonella* endocarditis.

Immune complex deposition on the glomerular basement membrane causes diffuse hypocomplementemic glomerulonephritis and renal dysfunction, which typically improve with effective antimicrobial therapy. Embolic renal infarcts cause flank pain and hematuria

but rarely cause renal dysfunction.

Manifestations of Specific Predisposing Conditions

In almost 50% of patients who have endocarditis associated with injection drug use, infection is limited to the tricuspid valve. These patients present with fever, faint or no murmur, and (in 75% of cases) prominent pulmonary findings, including cough, pleuritic chest pain, nodular pulmonary infiltrates, and occasionally pyopneumothorax. Infection involving valves on the left side of the heart presents with the typical clinical features of endocarditis.

Nosocomial endocarditis (defined as that which results from hospital care within the prior month and most commonly presenting as intravascular catheter–associated bacteremia), if not associated with a retained intracardiac device, has typical manifestations. Endocarditis associated with flow-directed pulmonary artery catheters is often cryptic, with symptoms masked by comorbid critical illness, and is commonly diagnosed at autopsy. Transvenous pacemaker lead–and/or implanted defibrillator–associated endocarditis commonly follows initial implantation or a generator unit change; may be associated with obvious or cryptic generator pocket infection; and results in fever, minimal murmur, and pulmonary symptoms similar to those encountered in addicts with tricuspid endocarditis.

Prosthetic valve endocarditis presents with typical clinical features. Cases arising within 60 days of valve surgery (early onset) lack peripheral vascular manifestations and may be obscured by comorbidity associated with recent surgery. In both early-onset and more delayed presentations, paravalvular infection is common and often results in partial valve dehiscence, regurgitant murmurs, congestive heart failure, or disruption of the conduction system.

DIAGNOSIS

The Duke Criteria

The diagnosis of infective endocarditis is established with certainty only when vegetations obtained at cardiac surgery, at autopsy, or from an artery (an embolus) are examined histologically and microbiologically. Nevertheless, a highly sensitive and specific diagnostic schema—known as the *Duke criteria*—has been developed on the basis of clinical, laboratory, and echocardiographic findings (Table 109-3). Documentation of two major criteria, of one major and three minor criteria, or of five minor criteria allows a clinical diagnosis of definite endocarditis. The diagnosis of endocarditis is rejected if an alternative diagnosis is established, if symptoms resolve and do not recur with ≤4 days of antibiotic therapy, or if surgery or autopsy after ≤4 days of antimicrobial therapy yields no histologic evidence of endocarditis. Illnesses not classified as definite endocarditis or rejected are considered cases of possible infective endocarditis when either one major and one minor criteria or three minor criteria are identified. Requiring the identification of clinical features of endocarditis

for classification as possible infective endocarditis increases the specificity of the schema

without significantly reducing its sensitivity.

TABLE 109-3 The Duke Criteria for the Clinical Diagnosis of Infective Endocarditis

MAJOR CRITERIA

1. Positive blood culture

   Typical microorganism for infective endocarditis from two separate blood cultures

   Viridans streptococci, *Streptococcus bovis*, HACEK group, *Staphylococcus aureus*, *or*

   Community-acquired enterococci in the absence of a primary focus, *or*

   Persistently positive blood culture, defined as recovery of a microorganism consistent with infective endocarditis from:

   Blood cultures drawn >12 h apart; *or*

   All of three or a majority of four or more separate blood cultures, with first and last drawn at least 1 h apart

   Single positive blood culture for *Coxiella burnetii* or phase I IgG antibody titer of >1:800

2. Evidence of endocardial involvement

   Positive echocardiogram

   Oscillating intracardiac mass on valve or supporting structures or in the path of regurgitant jets or in implanted material, in the absence of an alternative anatomic explanation, *or*

   Abscess, *or*

   New partial dehiscence of prosthetic valve, *or*

   New valvular regurgitation (increase or change in preexisting murmur not sufficient)

MINOR CRITERIA

1. Predisposition: predisposing heart condition or injection drug use
2. Fever ≥38.0°C (≥100.4°F)
3. Vascular phenomena: major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, Janeway lesions
4. Immunologic phenomena: glomerulonephritis, Osler's nodes, Roth's spots, rheumatoid factor
5. Microbiologic evidence: positive blood culture but not meeting major criterion as noted previously[a] or serologic evidence of active infection with organism consistent with infective endocarditis

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[a] Excluding single positive cultures for coagulase-negative staphylococci and diphtheroids, which are common culture contaminants, and organisms that do not cause endocarditis frequently, such as gram-negative bacilli.

Note: HACEK, *Haemophilus* spp., *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens*, *Kingella kingae*. Adapted from Li et al., with permission from the University of Chicago Press.

The roles of bacteremia and echocardiographic findings in the diagnosis of endocarditis are appropriately emphasized in the Duke criteria. That multiple blood cultures obtained over time are positive is consistent with the known continuous low-density nature of bacteremia characteristic of patients with endocarditis (≤100 organisms per milliliter). Among untreated endocarditis patients who ultimately have a positive blood culture, 95% of all blood cultures are positive, and in 98% of cases one of the initial two sets of cultures yields the microorganism. The diagnostic criteria attach significance to the species of organism isolated from blood cultures. To fulfill a major criterion, the isolation of an organism that causes both endocarditis and bacteremia in the absence of endocarditis (e.g., *S. aureus*, enterococci) must take place repeatedly (i.e., persistent bacteremia) and in the absence of a primary focus of infection. Organisms that rarely cause endocarditis but commonly contaminate blood cultures (e.g., diphtheroids, coagulase-negative species) must be isolated repeatedly if their isolation is to serve as a major criterion.

Blood Cultures

Isolation of the causative microorganism from blood cultures is critical not only for diagnosis but also for determination of antimicrobial susceptibility and planning of treatment. In the absence of prior antibiotic therapy, a total of three blood culture sets, ideally with the first separated from the last by at least 1 h, should be obtained from different venipuncture sites over 24 h. If the cultures remain negative after 48 to 72 h, two

or three additional blood cultures, including a lysis-centrifugation culture, should be obtained, and the laboratory should be asked to pursue fastidious microorganisms by prolonging incubation time and performing special subcultures. Empirical antimicrobial therapy should not be administered initially to hemodynamically stable patients with subacute endocarditis, especially those who have received antibiotics within the preceding 2 weeks; thus, if necessary, additional blood cultures can be obtained without the confounding effect of empirical treatment. Patients with acute endocarditis or with deteriorating hemodynamics that may require urgent surgery should be treated empirically immediately after the initial three sets of blood cultures are obtained.

Non-Blood-Culture Tests for the Etiologic Agent

Serologic tests can be used to identify some organisms causing endocarditis that are difficult to recover by blood culture: *Brucella*, *Bartonella*, *Legionella*, and *C. burnetii*. Pathogens can also be identified in vegetations by culture, by microscopic examination with special stains (i.e., the periodic acid–Schiff stain for *T. whipplei*), and by use of polymerase chain reaction to recover unique microbial DNA or 16S rRNA.

Echocardiography

Cardiac imaging with echocardiography allows anatomic confirmation of infective endocarditis, sizing of vegetations, detection of intracardiac complications, and assessment of cardiac function. A two-dimensional study with color flow and continuous as well as pulsed Doppler is optimal. Transthoracic echocardiography (TTE) is noninvasive and exceptionally specific; however, it cannot image vegetations <2 mm in diameter, and in 20% of patients it is technically inadequate because of emphysema or body habitus. Thus, TTE detects vegetations in only 65% of patients with definite clinical endocarditis (i.e., it has a sensitivity of 65%). Moreover, TTE is not adequate for evaluating prosthetic valves or detecting intracardiac complications. TEE is safe and significantly more sensitive than TTE. It detects vegetations in >90% of patients with definite endocarditis; nevertheless, false-negative studies are noted in 6 to 18% of endocarditis patients. TEE is the optimal method for the diagnosis of prosthetic endocarditis or the detection of myocardial abscess, valve perforation, or intracardiac fistulae.

Experts favor echocardiographic evaluation of all patients with a clinical diagnosis of endocarditis; however, the test should not be used to screen patients with otherwise-explained positive blood cultures or patients with unexplained fever. In patients with a low pretest likelihood of endocarditis (<5%), a high-quality TTE that is negative is sufficient to exclude endocarditis. For patients whose habitus makes them difficult to study with TTE and for those who may have prosthetic valve endocarditis or who are at high risk of intracardiac complications, TEE is the preferred imaging modality. For patients with a pretest probability of endocarditis ranging from 5 to 50%, initial evaluation by TEE—in lieu of a sequential strategy of TTE, which, if negative, will be followed by TEE—is cost-effective. A negative TEE when endocarditis is likely does not exclude the diagnosis but rather warrants repetition of the study in 7 to 10 days with optimal multiplanar technique.

Other Studies

Many laboratory studies that do not aid in diagnostic evaluation are nevertheless important in the management of patients with endocarditis; these studies include complete blood counts, creatinine measurement, chest radiography, and electrocardiography. The erythrocyte sedimentation rate, C-reactive protein level, circulating immune complex titer, and rheumatoid factor concentration are commonly increased in endocarditis (Table 109-2). Cardiac catheterization is useful primarily to assess coronary artery patency in older individuals who are to undergo surgery for endocarditis.

TREATMENT

ANTIMICROBIAL THERAPY

It is difficult to eradicate bacteria from the avascular vegetation in infective endocarditis because this site is relatively

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inaccessible to host defenses and because the bacteria are nongrowing and metabolically inactive. Since all bacteria in the vegetation must be killed, therapy for endocarditis must be bactericidal and must be given for prolonged periods. Antibiotics are generally given parenterally and must reach high serum concentrations that will, through passive diffusion, lead to effective concentrations in the depths of the vegetation. The choice of effective therapy requires precise knowledge of the susceptibility of the causative microorganisms. The initiation of treatment before a cause is defined must balance the need to establish a microbiologic diagnosis against the potential progression of disease or the need for urgent surgery (see “Blood Cultures,” above). The individual vulnerabilities of the patient should be weighed in the selection of therapy—e.g., simultaneous infection at other sites (such as meningitis), allergies, end-organ dysfunction, interactions with concomitant medications, and risks of adverse events.

Although given for several weeks longer, the regimens recommended for the treatment of endocarditis involving prosthetic valves (except for staphylococcal infections) are similar to those used to treat native valve infection (Table 109-4). Recommended doses and duration of therapy should be adhered to unless alterations are required by adverse events.

TABLE 109-4 Antibiotic Treatment for Infective Endocarditis Caused by Common Organisms[a]

Organism	*Drug, Dose, Duration*	*Comments*

Streptococci		
Penicillin-susceptible[b] streptococci, *S. bovis*	Penicillin G 2–3 million units IV q4h for 4 weeks	—
	Penicillin G 2–3 million units IV q4h *plus* gentamicin[c] 1 mg/kg IM or IV q8h, both for 2 weeks	Avoid penicillin plus gentamicin if risks of aminoglycoside toxicity are increased or case is complicated
	Ceftriaxone 2 g/d IV as single dose for 4 weeks	Can use ceftriaxone in patients with nonimmediate penicillin allergy
	Vancomycin[d] 15 mg/kg IV q12h for 4 weeks	Use vancomycin in patients with severe or immediate β-lactam allergy
Relatively penicillin-resistant[e] streptococci	Penicillin G 3 million units IV q4h for 4–6 weeks *plus* gentamicin[c] 1 mg/kg IV q8h for 2 weeks	Preferred for treatment of prosthetic valve endocarditis caused by penicillin-susceptible streptococci; continue penicillin for 6 weeks in this setting
Moderately penicillin-resistant[f] streptococci, pyridoxal-requiring streptococci (*Abiotrophia* spp.)	Penicillin G 3–4 million units IV q4h *plus* gentamicin[c] 1 mg/kg IV q8h, both for 4–6 weeks	—
Enterococci[g]	Penicillin G 3–4 million units IV q4h *plus* gentamicin[c] 1 mg/kg IV q8h, both for 4–6 weeks	Can use streptomycin 7.5 mg/kg q12h in lieu of gentamicin if there is not high-level resistance to streptomycin
	Ampicillin 2 g IV q4h *plus* gentamicin[c] 1 mg/kg IV q8h, both for 4–6 weeks	Do not use cephalosporins or carbapenems for treatment of enterococcal endocarditis
	Vancomycin[d] 15	Use vancomycin plus gentamicin for

	mg/kg IV q12h *plus* gentamicin[c] 1 mg/kg IV q8h, both for 4–6 weeks	penicillin-allergic patients or desensitize to penicillin
Staphylococci		
Methicillin-susceptible, infecting native valves (no foreign devices)	Nafcillin or oxacillin 2 g IV q4h for 4–6 weeks *plus* (optional) gentamicin[c] 1 mg/kg IM or IV q8h for 3–5 days	May use penicillin 3–4 million units q6h if isolate is penicillin-susceptible (does not produce β-lactamase)
	Cefazolin 2 g IV q8h for 4–6 weeks *plus* (optional) gentamicin[c] 1 mg/kg IM or IV q8h for 3–5 days	Can use cefazolin regimen for patients with nonimmediate penicillin allergy
	Vancomycin[d] 15 mg/kg IV q12h for 4–6 weeks	Use vancomycin for patients with immediate (urticarial) or severe penicillin allergy
Methicillin-resistant, infecting native valves (no foreign devices)	Vancomycin[d] 15 mg/kg IV q12h for 4–6 weeks	No role for routine use of rifampin
Methicillin-susceptible, infecting prosthetic valves	Nafcillin or oxacillin 2 g IV q4h for 6–8 weeks *plus* gentamicin[c] 1 mg/kg IM or IV q8h for 2 weeks *plus* rifampin[h] 300 mg PO q8h for 6–8 weeks	Use gentamicin during initial 2 weeks; determine susceptibility to gentamicin before initiating rifampin (see text); if patient is highly allergic to penicillin, use regimen for methicillin-resistant staphylococci; if β-lactam allergy is of the minor, nonimmediate type, can substitute cefazolin for oxacillin/nafcillin
Methicillin-resistant, infecting prosthetic valves	Vancomycin[d] 15 mg/kg IV q12h for 6–8 weeks *plus* gentamicin[c] 1 mg/kg IM or IV q8h for 2 weeks *plus* rifampin[h] 300 mg PO q8h for 6–8 weeks	Use gentamicin during initial 2 weeks; determine gentamicin susceptibility before initiating rifampin (see text)

HACEK organisms	Ceftriaxone 2 g/d IV as single dose for 4 weeks	May use another third-generation cephalosporin at comparable dosage
	Ampicillin 2 g IV q4h *plus* gentamicin[c] 1 mg/kg IM or IV q8h, both for 4 weeks	Determine ampicillin susceptibility; do not use ampicillin if β-lactamase is produced

[a] Doses are for adults with normal renal function. Doses of gentamicin, streptomycin, and vancomycin must be adjusted for reduced renal function. Ideal body weight is used to calculate doses per kilogram (men = 50 kg + 2.3 kg per inch over 5 feet; women = 45.5 kg + 2.3 kg per inch over 5 feet).

[b] MIC ≤ 0.1 μg/mL.

[c] Aminoglycosides should not be administered as single daily doses and should be introduced as part of the initial treatment. Target peak and trough serum concentrations of gentamicin 1 h after a 20- to 30-min infusion or IM injection are 3–5 μg/mL and ≤1 μg/mL, respectively; the target peak serum concentration of streptomycin (timing as with gentamicin) is 20–25 μg/mL.

[d] Desirable peak vancomycin level 1 h after completion of a 1-h infusion is30–45 μg/mL.

[e] MIC > 0.1 μg/mL and <0.5 μg/mL.

[f] MIC ≥ 0.5 μg/mL and <8.0 μg/mL.

[g] Antimicrobial susceptibility must be evaluated; see text.

[h] Rifampin increases warfarin and dicumarol requirements for anticoagulation.

Organism-Specific Therapies

STREPTOCOCCI

Although most strains of viridans streptococci and *S. bovis* that cause endocarditis are susceptible to penicillin [minimum inhibitory concentration (MIC) ≤0.1 μg/mL], recent reports indicate increasing penicillin resistance among viridans streptococci recovered from blood cultures. In the selection of optimal therapy, the penicillin MIC must be

determined (Table 109-4). The 2-week

penicillin/gentamicin regimen should not be used to treat complicated native valve infection or prosthetic valve endocarditis. Although small studies have suggested that a 2-week regimen of single daily doses of ceftriaxone (2 g IV) plus gentamicin (3 mg/kg) or netilmicin (4 mg/kg) is effective for penicillin-susceptible streptococcal endocarditis, the data are not sufficient to support routine use of this regimen. Penicillin/gentamicin is recommended for the treatment of endocarditis caused by group B streptococci.

ENTEROCOCCI

Enterococci are resistant to oxacillin, nafcillin, and the cephalosporins and are inhibited only by penicillin, ampicillin, teicoplanin (not available in the United States), and vancomycin. To kill enterococci requires the synergistic interaction of a cell wall–active antibiotic (penicillin, ampicillin, vancomycin, or teicoplanin) that is effective at achievable serum concentrations and an aminoglycoside (gentamicin or streptomycin) to which the isolate does not exhibit high-level resistance. An isolate's resistance to cell wall–active agents or ability to replicate in the presence of gentamicin at ≥500 μg/mL or streptomycin at 2000 μg/mL—a phenomenon called *high-level aminoglycoside resistance*—indicates that the ineffective antimicrobial cannot participate in the interaction to produce killing. High-level resistance to gentamicin predicts that tobramycin, netilmicin, amikacin, and kanamycin will also be ineffective. In fact, even when enterococci are not highly resistant to gentamicin, it is difficult to predict the ability of these other aminoglycosides to participate in synergistic killing; consequently, they should not in general be used to treat enterococcal endocarditis.

Clearly, enterococci causing endocarditis must be tested for high-level resistance to streptomycin and gentamicin, β-lactamase production, and susceptibility to penicillin and ampicillin (MIC ≤ 16 μg/mL) and to vancomycin (MIC ≤ 8 μg/mL). If the isolate produces β-lactamase, ampicillin/sulbactam or vancomycin can be used as the cell wall–active component; if the penicillin/ampicillin MIC is >16 μg/mL, vancomycin can be considered; and if the vancomycin MIC is >8 μg/mL, penicillin or ampicillin may be considered. Based on the absence of high-level resistance, gentamicin or streptomycin should be used as the aminoglycoside. If there is high-level resistance to both these drugs, no aminoglycoside should be given; instead, an 8- to 12-week course of a single cell wall–active agent is suggested. If single-drug therapy fails or the isolate is resistant to all of the commonly used agents, surgical treatment is advised. The role of newer agents potentially active against multidrug-resistant enterococci (quinupristin/dalfopristin, linezolid, and daptomycin) in the treatment of endocarditis has not been established. Although the dose of gentamicin used to achieve bactericidal synergy in treating enterococcal endocarditis is smaller than that used in standard therapy, nephrotoxicity is not uncommon during treatment with recommended regimens for 4 to 6 weeks. Regimens wherein gentamicin treatment has been truncated at 2 to 3 weeks because of nephrotoxicity have been curative. Thus, discontinuation of gentamicin is recommended when progressive nephrotoxicity develops in patients with enterococcal endocarditis who have responded satisfactorily to therapy.

STAPHYLOCOCCI

The regimens used to treat staphylococcal endocarditis are not based upon coagulase

production but rather upon the presence or absence of a prosthetic valve or foreign device, the native valve(s) involved, and the resistance of the isolate to penicillin and methicillin. Penicillinase is produced by 95% of staphylococci; thus, all isolates should be considered penicillin-resistant until shown not to produce this enzyme. The addition of gentamicin (if the isolate is susceptible) to a β-lactam antibiotic to enhance therapy for native mitral or aortic valve endocarditis is optional. Its addition hastens eradication of bacteremia but does not improve survival rates. If added, gentamicin should be limited to the initial 3 to 5 days of therapy to avoid nephrotoxicity. Gentamicin generally is not added to the vancomycin regimen in this setting.

Methicillin-susceptible *S. aureus* endocarditis that is uncomplicated and limited to the tricuspid or pulmonic valve—a condition occurring almost exclusively in injection drug users—can often be treated with a 2-week course that combines oxacillin or nafcillin (but not vancomycin) with gentamicin. Prolonged fevers (≥5 days) during therapy suggest that these patients should receive standard therapy.

Staphylococcal prosthetic valve endocarditis is treated for 6 to 8 weeks with a multidrug regimen. Rifampin is an essential component because it kills staphylococci that are adherent to foreign material. Two other agents (selected on the basis of susceptibility testing) are combined with rifampin to prevent in vivo emergence of resistance. Because many staphylococci, particularly methicillin-resistant *S. aureus* and *S. epidermidis*, are resistant to gentamicin, the utility of gentamicin should be established before rifampin treatment is begun. If the isolate is resistant to gentamicin, another aminoglycoside or a fluoroquinolone (chosen in light of susceptibility results) should be substituted.

OTHER ORGANISMS

Endocarditis caused by *Streptococcus pneumoniae*, with a penicillin MIC ≤ 1.0 can be treated with intravenous penicillin (4 million units every 4 h), ceftriaxone (2 g/d as a single dose), or cefotaxime (at a comparable dosage). Infection caused by strains with a penicillin MIC ≥ 2.0 should be treated with vancomycin. Until the strain's susceptibility to penicillin is established, therapy should consist of vancomycin plus ceftriaxone, especially if concurrent meningitis is suspected. *P. aeruginosa* endocarditis is treated with an antipseudomonal penicillin (ticarcillin or piperacillin) and high doses of tobramycin (8 mg/kg per day in three divided doses). Endocarditis caused by Enterobacteriaceae is treated with a potent β-lactam antibiotic plus an aminoglycoside. Corynebacterial endocarditis is treated with penicillin plus an aminoglycoside (if the organism is susceptible to the aminoglycoside) or with vancomycin, which is highly bactericidal for most strains. Therapy for *Candida* endocarditis consists of amphotericin B plus flucytosine and early surgery; long-term (if not indefinite) suppression with fluconazole is used increasingly.

Empirical Therapy

In designing and executing therapy without culture data (i.e., before culture results are known or when cultures are negative), clinical and epidemiologic clues to etiology must be weighed, and both the pathogens associated with the specific endocarditis syndrome and the hazards of suboptimal therapy must be considered. Thus, empirical therapy for acute endocarditis in an injection drug user should cover methicillin-resistant *S. aureus* and gram-negative bacilli. The initiation of treatment with vancomycin plus gentamicin

immediately after blood is obtained for cultures covers these as well as many other potential causes. In treating culture-negative episodes, marantic endocarditis must be excluded and fastidious organisms sought serologically. In the absence of confounding prior antibiotic therapy, it is unlikely that *S. aureus*, coagulase-negative staphylococcal, or enterococcal infection will present with negative blood cultures. Thus, in this situation, these organisms are not the determinants of therapy for subacute endocarditis. Blood culture–negative subacute native valve endocarditis is treated with ceftriaxone plus gentamicin; these two antimicrobials plus vancomycin should be used if prosthetic valves are involved.

Outpatient Antimicrobial Therapy

Fully compliant patients who have sterile blood cultures, are afebrile during therapy, and have no clinical or echocardiographic findings that suggest an impending complication may complete therapy as outpatients. Careful follow-up and a stable home setting are necessary, as are predictable intravenous access and selection of antimicrobials that are stable in solution.

Monitoring Antimicrobial Therapy

The serum bactericidal titer—the highest dilution of the patient's serum during therapy that kills 99.9% of the standard inoculum of the infecting organism—is no longer recommended for assessment of patients receiving standard regimens. However, in the treatment of endocarditis caused by unusual organisms, this measurement, although not standardized and difficult to interpret, may provide a patient-specific assessment of in vivo antibiotic effect. Serum concentrations of aminoglycosides and vancomycin should be monitored.

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Antibiotic toxicities, including allergic reactions, occur in 25 to 40% of patients and commonly arise during the third week of therapy. Blood tests to detect antibiotic-specific potential end-organ toxicity should be performed periodically.

In most patients, effective antibiotic therapy results in subjective improvement and resolution of fever within 5 to 7 days. Blood cultures should be repeated daily until sterile, rechecked if there is recrudescent fever, and performed again 4 to 6 weeks after therapy to document cure. Blood cultures become sterile within 2 days after the start of appropriate therapy when infection is caused by viridans streptococci, enterococci, or HACEK organisms. In *S. aureus* endocarditis, β-lactam therapy results in sterile cultures in 3 to 5 days, whereas positive cultures may persist for 7 to 9 days with vancomycin treatment. When fever persists for 7 days in spite of appropriate antibiotic therapy, patients should be evaluated for paravalvular abscess and for extracardiac abscesses (spleen, kidney) or complications (embolic events). Recrudescent fever raises the question of these complications but also of drug reactions or complications of hospitalization. Serologic abnormalities (e.g., erythrocyte sedimentation rate, rheumatoid factor) resolve slowly and do not reflect response to treatment. Vegetations become smaller with effective therapy, but at 3 months after cure half are unchanged and 25% are slightly larger.

SURGICAL TREATMENT

Intracardiac and central nervous system complications of endocarditis are important

causes of the morbidity and mortality associated with this infection. In some cases, effective treatment for these complications requires surgery. Most of the clinical indications for surgical treatment of endocarditis are not absolute (Table 109-5). The risks and benefits as well as the timing of surgical treatment must therefore be individualized (Table 109-6).

TABLE 109-5 Indications for Cardiac Surgical Intervention in Patients with Endocarditis

Surgery required for optimal outcome
Moderate to severe congestive heart failure due to valve dysfunction
Partially dehisced unstable prosthetic valve
Persistent bacteremia despite optimal antimicrobial therapy
Lack of effective microbicidal therapy (e.g., fungal or *Brucella* endocarditis)
S. aureus prosthetic valve endocarditis with an intracardiac complication
Relapse of prosthetic valve endocarditis after optimal antimicrobial therapy
Surgery to be strongly considered for improved outcome[a]
Perivalvular extension of infection
Poorly responsive *S. aureus* endocarditis involving the aortic or mitral valve
Large (>10-mm diameter) hypermobile vegetations with increased risk of embolism
Persistent unexplained fever (≥10 days) in culture-negative native valve endocarditis
Poorly responsive or relapsed endocarditis due to highly antibiotic-resistant enterococci or gram-negative bacilli

[a] Surgery must be carefully considered; findings are often combined with other indications to prompt surgery.

TABLE 109-6 Timing of Cardiac Surgical Intervention in Patients with Endocarditis

	Indication for Surgical Intervention	
Timing	***Strong Supporting Evidence***	***Conflicting Evidence, but Majority of Opinions Favor Surgery***
Emergent (same day)	Acute aortic regurgitation plus preclosure of mitral valve	
	Sinus of Valsalva abscess ruptured into right heart	
	Rupture into pericardial sac	
Urgent (within 1–2 days)	Valve obstruction by vegetation Unstable (dehisced) prosthesis Acute aortic or mitral regurgitation with heart failure (New York Heart Association class III or IV) Septal perforation Perivalvular extension of infection with/without new electrocardiographic conduction system changes Lack of effective antibiotic therapy	Major embolus plus persisting large vegetation (>10 mm in diameter)
Elective (earlier usually preferred)	Progressive paravalvular prosthetic regurgitation Valve dysfunction plus persisting infection after ≥7–10 days of antimicrobial therapy Fungal (mold) endocarditis	Staphylococcal PVE Early PVE (≤2 months after valve surgery) Fungal endocarditis (*Candida* spp.) Antibiotic-resistant

		organisms

Abbreviation: PVE, prosthetic valve endocarditis.

Source: Adapted from I Olaison, G Pettersson: Infect Dis Clin North Am 16:453, 2002.

Intracardiac Surgical Indications

Most surgical interventions are warranted by intracardiac findings, often detected by echocardiography. Because of the highly invasive nature of prosthetic valve endocarditis, as many as 40% of affected patients merit surgical treatment. In many patients, coincident rather than single intracardiac events necessitate surgery.

CONGESTIVE HEART FAILURE

Moderate to severe refractory congestive heart failure caused by new or worsening valve dysfunction is the major indication for cardiac surgical treatment of endocarditis. Of patients with moderate to severe heart failure due to valve dysfunction who are treated medically, 60 to 90% die within 6 months. In the setting of similar hemodynamic dysfunction, surgical treatment is associated with mortality rates of 20 to 40% with native valve endocarditis and 35 to 55% with prosthetic valve infection. Surgery may be required to relieve functional stenosis due to large vegetations or to restore competence to damaged regurgitant valves.

PERIVALVULAR INFECTION

This complication, which occurs in 10 to 15% of native valve and 45 to 60% of prosthetic valve infections, is suggested by persistent unexplained fever during appropriate therapy, new electrocardiographic conduction disturbances, and pericarditis. Extension can occur from any valve but is most common with aortic valve infection. TEE with color Doppler is the test of choice to detect perivalvular abscesses (sensitivity ≥ 85%). Although occasional perivalvular infections are cured medically, surgery is warranted when fever persists, fistulae develop, prostheses are dehisced and unstable, and invasive infection relapses after appropriate treatment. Cardiac rhythm must be monitored since high-grade heart block may require insertion of a pacemaker.

UNCONTROLLED INFECTION

Continued positive blood cultures or otherwise-unexplained persistent fevers (in patients with either blood culture–positive or–negative endocarditis) despite optimal antibiotic therapy may reflect uncontrolled infection and warrant surgery. Surgical treatment is also advised for endocarditis caused by those organisms against which clinical experience indicates that effective antimicrobial

therapy is lacking. This category includes infections caused by yeasts, fungi, *P. aeruginosa*, other highly resistant gram-negative bacilli, *Brucella* species, and probably *C. burnetii*.

S. AUREUS ENDOCARDITIS

Mortality rates for *S. aureus* prosthetic valve endocarditis exceed 70% with medical treatment but are reduced to 25% with surgical treatment. In patients with intracardiac complications associated with *S. aureus* prosthetic valve infection, surgical treatment reduces mortality by twentyfold. Surgical treatment should be considered for patients with *S. aureus* native aortic or mitral valve infection who have TTE-demonstrable vegetations and remain septic during the initial week of therapy. Isolated tricuspid valve endocarditis, even with persistent fever, rarely requires surgery.

PREVENTION OF SYSTEMIC EMBOLI

Mortality and persisting morbidity due to emboli are largely limited to patients suffering occlusion of cerebral or coronary arteries. Echocardiographic determination of vegetation size and anatomy, although predictive of patients at high risk of systemic emboli, does not identify those patients in whom the benefits of surgery to prevent emboli clearly exceed the risks of the surgical procedure and an implanted prosthetic valve. Net benefits favoring surgery are most likely when the risk of embolism is high and other surgical benefits can be achieved simultaneously—e.g., repair of a moderately dysfunctional valve or debridement of a paravalvular abscess. Reduced overall risks of surgical intervention (e.g., use of vegetation resection and valve repair to avoid insertion of a prosthesis) make the benefit-to-risk ratio more favorable and this intervention more attractive.

Timing of Cardiac Surgery

In general, when indications for surgical treatment of infective endocarditis are identified, surgery should not be delayed simply to permit additional antibiotic therapy, since this course of action increases the risk of death (Table 109-6). Delay is justified only when infection is controlled and congestive heart failure is fully compensated with medical therapy. Recrudescent endocarditis involving a prosthetic valve follows surgery in 2% of patients with culture-positive native valve endocarditis and in 6 to 15% of patients with active prosthetic valve endocarditis. These risks are more acceptable than the high mortality rates that result when surgery is inappropriately delayed or not performed.

Among patients who have experienced a neurologic complication of endocarditis, further neurologic deterioration can occur as a consequence of cardiac surgery. The risk of significant neurologic exacerbation is related to the interval between the complication and surgery. Where feasible, cardiac surgery should be delayed for 2 to 3 weeks after a nonhemorrhagic embolic stroke and for 4 weeks after a

hemorrhagic embolic stroke. A ruptured mycotic aneurysm should be clipped and cerebral edema allowed to resolve prior to cardiac surgery.

Extracardiac Complications

Splenic abscess develops in 3 to 5% of patients with endocarditis. Effective therapy requires either computed tomography–guided percutaneous drainage or splenectomy.

Mycotic aneurysms occur in 2 to 15% of endocarditis patients; half of these cases involve the cerebral arteries and present as headaches, focal neurologic symptoms, or hemorrhage. Cerebral aneurysms should be monitored by angiography. Some will resolve with effective antimicrobial therapy, but those that persist, enlarge, or leak should be treated surgically if possible. Extracerebral aneurysms present as local pain, a mass, local ischemia, or bleeding; generally these aneurysms are treated by resection.

OUTCOME

The outcome of infective endocarditis is affected by a variety of factors, some of which are interrelated. Factors with an adverse impact include older age, severe comorbid conditions, delayed diagnosis, involvement of prosthetic valves or the aortic valve, an invasive (*S. aureus*) or antibiotic-resistant (*P. aeruginosa*, yeast) pathogen, intracardiac complications, and major neurologic complications. Death and poor outcome often are related not to failure of antibiotic therapy but rather to the interactions of comorbidities and endocarditis-related end-organ complications. The overall survival rate for patients with native valve endocarditis caused by viridans streptococci, HACEK organisms, or enterococci (susceptible to synergistic therapy) ranges from 85 to 90%. For *S. aureus* native valve endocarditis in patients who do not inject drugs, survival rates are 55 to 70%, whereas 85 to 90% of injection drug users survive this infection. Prosthetic valve endocarditis beginning within 2 months of valve replacement results in mortality rates of 40 to 50%, whereas rates are only 10 to 20% in later-onset cases.

PREVENTION

Antibiotics have been administered in conjunction with selected procedures considered to entail a risk for bacteremia and endocarditis. The benefits of antibiotic prophylaxis are not established and in fact may be modest: only 50% of patients with native valve endocarditis know that they have a valve lesion predisposing to infection, most endocarditis cases do not follow a procedure, and 35% of cases are caused by organisms not targeted by prophylaxis. Dental treatments, the procedures most widely accepted as predisposing to endocarditis, are no more frequent during the 3 months preceding this diagnosis than in uninfected matched controls. Nevertheless, an expert committee of the American Heart Association, along with similar advisory groups in other developed countries, has identified procedures that may precipitate bacteremia with organisms that cause endocarditis (Table 109-7), patients who should receive prophylaxis based on the relative risk for developing endocarditis and the severity of subsequent infection (Table 109-8), patients who are at low risk and do not require prophylaxis (Table 109-9), and regimens that may be used for prophylaxis (Table 109-10). Except for an isolated secundum atrial septal defect and a totally corrected patent ductus arteriosus, ventricular septal defect, or pulmonary stenosis, patients with congenital heart defects continue to experience high rates of endocarditis despite total surgical correction of the defect. In vulnerable patients, maintaining good dental hygiene and aggressively treating local infections may reduce the risk of endocarditis.

TABLE 109-7 Procedures for which Endocarditis Prophylaxis Is Advised in Patients at High or Moderate Risk for Endocarditis[a]

Dental procedures
Extractions
Periodontal procedures, cleaning causing gingival bleeding
Implant placement, reimplantation of avulsed teeth
Endodontic instrumentation (root canal) or surgery beyond the apex
Subgingival placement of antibiotic fibers or strips
Placement of orthodontic bands but not brackets
Intraligamentary injections (anesthetic)
Respiratory procedures
Operations involving the mucosa
Bronchoscopy with rigid bronchoscope
Gastrointestinal procedures[b]
Esophageal: Sclerotherapy of varices, stricture dilation
Biliary tract: Endoscopic retrograde cholangiography with biliary obstruction, biliary tract surgery
Intestinal tract: Surgery involving the mucosa
Genitourinary procedures
Urethral dilation, prostate or urethral surgery
Cystoscopy

[a] Prophylaxis is optional for high-risk patients undergoing bronchoscopy or gastrointestinal endoscopy with/without biopsy, vaginal delivery, vaginal hysterectomy, or transesophageal echocardiography.

[b] Prophylaxis is recommended for high-risk patients and optional for moderate-risk group (see Table 109-8).

Source: Adapted from AS Dajani et al: JAMA 277:1794, 1997; with permission.

TABLE 109-8 Cardiac Lesions for which Endocarditis Prophylaxis Is Advised

High Risk	*Moderate Risk*
Prosthetic heart valves	Congenital cardiac malformations (other than high-/low-risk lesions), ventricular septal defect, bicuspid aortic valve
Prior bacterial endocarditis	Acquired aortic and mitral valve dysfunction
Complex cyanotic congenital heart disease; other complex congenital lesions after correction (see text)	Hypertrophic cardiomyopathy (asymmetric septal hypertrophy)
Patent ductus arteriosus	Mitral valve prolapse with valvular regurgitation and/or thickened leaflets
Coarctation of the aorta	
Surgically constructed systemic-pulmonary shunts	

TABLE 109-9 Cardiac Conditions That Are Considered to Pose a Low Risk of Endocarditis and for which Antibiotic Prophylaxis Is Not Recommended

Isolated secundum ASD

Surgically repaired ASD, VSD, PDA (without residual defect, >6 months after repair)

Prior coronary artery bypass graft

Mitral valve prolapse without regurgitation or thickened leaflets

Physiologic or functional murmur

Prior Kawasaki disease or acute rheumatic fever without valve dysfunction

Cardiac pacemakers or implanted defibrillators

Abbreviations: ASD, atrial septal defect; VSD, ventricular septal defect; PDA, patent ductus arteriosus.

Source: Adapted from AS Dajani et al: JAMA 277:1794, 1997; with permission.

TABLE 109-10 Antibiotic Regimens for Prophylaxis of Endocarditis in Adults at Moderate or High Risk[a]

I. Oral cavity, respiratory tract, or esophageal procedures[b]

A. Standard regimen

1. Amoxicillin 2.0 g PO 1 h before procedure

B. Inability to take oral medication

1. Ampicillin 2.0 g IV or IM within 30 min of procedure

C. Penicillin allergy

1. Clarithromycin 500 mg PO 1 h before procedure
2. Cephalexin[c] or cefadroxil[c] 2.0 g PO 1 h before procedure
3. Clindamycin 600 mg PO 1 h before procedure or IV 30 min before procedure

D. Penicillin allergy, inability to take oral medication

1. Cefazolin[c] 1.0 g IV or IM 30 min before procedure

II. Genitourinary and gastrointestinal tract[d] procedures

A. High-risk patients

1. Ampicillin 2.0 g IV or IM *plus* gentamicin 1.5 mg/kg (not to exceed 120 mg) IV or IM within 30 min of procedure; repeat ampicillin 1.0 g IV or IM or amoxicillin 1.0 g PO 6 h later

B. High-risk, penicillin-allergic patients

1. Vancomycin 1.0 g IV over 1–2 h *plus* gentamicin 1.5 mg/kg (not to exceed 120 mg) IV or IM within 30 min before procedure; no second dose recommended

C. Moderate-risk patients

1. Amoxicillin 2.0 g PO 1 h before procedure or ampicillin 2.0 g IV or IM within 30 min before procedure

D. Moderate-risk, penicillin-allergic patients

1. Vancomycin 1.0 g IV infused over 1–2 h and completed within 30 min of procedure

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[a] Dosing for children: for amoxicillin, ampicillin, cephalexin, or cefadroxil, use 50 mg/kg PO; cefazolin, 25 mg/kg IV; clindamycin, 20 mg/kg PO, 25 mg/kg IV; clarithromycin, 15 mg/kg PO; gentamicin, 1.5 mg/kg IV or IM; and vancomycin, 20 mg/kg IV.

[b] For patients at high risk (Table 109-8), administer a half-dose 6 h after the initial dose.

[c] Do not use cephalosporins in patients with immediate hypersensitivity (urticaria, angioedema, anaphylaxis) to penicillin.

[d] Excludes esophageal procedures.

Source: Adapted from AS Dajani et al: JAMA 277:1794, 1997; with permission.

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