Review Articles

Medical Progress

Infective Endocarditis in Adults

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INFECTIVE endocarditis, a microbial infection of the endocardial surface of the heart, has been classified as "acute" or "subacute–chronic" on the basis of the tempo and severity of the clinical presentation and the progression of the untreated disease. The characteristic lesion, a vegetation, is composed of a collection of platelets, fibrin, microorganisms, and inflammatory cells. It most commonly involves heart valves but may also occur at the site of a septal defect, on the chordae tendineae, or on the mural endocardium.

This report will focus on progress made over the past decade in the diagnosis and management of endocarditis affecting native and prosthetic valves in adults. A discussion of antimicrobial prophylaxis against infective endocarditis is beyond the scope of this review, and readers are referred to the most recent guidelines for details (http://www.americanheart.org/Scientific/statements/1997/079701.html).[1]

EPIDEMIOLOGIC FEATURES AND PREDISPOSING FACTORS

Infective Endocarditis of Native Valves

The epidemiologic features of infective endocarditis in developed countries are changing as a result of increasing longevity, new predisposing factors, and an increase in nosocomial cases. In the United States and western Europe, the incidence of community-acquired native-valve endocarditis in most recent studies is 1.7 to 6.2 cases per 100,000 person-years.[2,3] Men are more often affected than women (mean male-to-female ratio, 1.7:1). As increased longevity has given rise to degenerative valvular disease, placement of prosthetic valves, and increased exposure to nosocomial bacteremia, the median age of patients has gradually increased; it was 30 to 40 years during the preantibiotic era and 47 to 69 years more recently.[3,4] Among patients with infective endocarditis associated with injection-drug use, there is a trend toward younger persons. The incidence of infective endocarditis in this group is estimated at 150 to 2000 per 100,000 person-years and can be higher among patients with known valvular heart disease.[5]

Other conditions associated with an increased incidence of infective endocarditis include poor dental hygiene, long-term hemodialysis, and diabetes mellitus.[6] Infection with the human immunodeficiency virus (HIV) may independently increase the risk of infective endocarditis.[7] However, among patients infected with HIV, infective endocarditis is usually associated with injection-drug use or long-term indwelling intravenous catheters. *Staphylococcus aureus* is the most frequent pathogen in these patients, and mortality is higher among those with advanced HIV disease.[8]

Mitral-valve prolapse is now the most common cardiovascular diagnosis predisposing patients to infective endocarditis; the frequency of mitral-valve prolapse in patients with infective endocarditis is more reflective of the high frequency of this lesion in the general population than of the small-to-moderate increase in the intrinsic rate of infection associated with this lesion. The incidence of infective endocarditis in persons with known mitral-valve prolapse is approximately 100 per 100,000 patient-years; the risk may be higher in men over 45 years of age.[9,10] Risk factors for infective endocarditis in patients with mitral-valve prolapse include the presence of mitral regurgitation or thickened mitral leaflets. In developing countries, rheumatic heart disease, which occurs primarily among the young, remains the most frequent underlying cardiac condition predisposing patients to infective endocarditis.[11,12]

Infective Endocarditis of Prosthetic Valves

Prosthetic-valve endocarditis accounts for 7 to 25 percent of cases of infective endocarditis in most developed countries. In metropolitan Philadelphia, for example, the frequency of infective endocarditis involving prosthetic valves was 0.94 per 100,000 patient-years.[2] Although mechanical heart valves are probably at higher risk for infection than are bioprostheses during the first three months after surgery, the rates of infection for the two valve types converge later and are similar at five years.[13-15] In 1985, Calderwood et al.[14] reported the cumulative risk of prosthetic-valve endocarditis as 3.1 percent at 12 months and 5.7 percent at 60 months after surgery. In more recent studies, this risk was approximately 1 percent at 12 months and 2 to 3 percent at 60 months.[16,17]

Cases with onset within two months after surgery are called early prosthetic-valve endocarditis and are usually acquired in the hospital. Cases that occur more

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than 12 months after surgery are called late prosthetic-valve endocarditis and are largely community-acquired. Cases occurring between 2 and 12 months after surgery are a mixture of hospital-acquired episodes caused by less virulent organisms and community-acquired episodes.[18]

Nosocomial Infective Endocarditis

In some series, 7 to 29 percent of all cases of endocarditis seen at tertiary care hospitals were nosocomial.[2,19] Infected intravascular devices give rise to at least half these cases.[19] Other sources of nosocomial infective endocarditis include genitourinary or gastrointestinal tract procedures or surgical-wound infection.

MICROBIOLOGIC FEATURES

In recent series, staphylococci, particularly *Staph. aureus,* have surpassed viridans streptococci as the most common cause of infective endocarditis (Table 1). In addition, coagulase-negative staphylococci, the most common pathogens in early prosthetic-valve endocarditis, have also been well documented as an occasional cause of native-valve endocarditis. One species of community-acquired coagulase-negative staphylococcus, *Staph. lugdunensis,* is commonly associated with valve destruction and the requirement for valve replacement.[20] The most common streptococci isolated from patients with endocarditis continue to be *Streptococcus sanguis, Strep. bovis, Strep. mutans,* and *Strep. mitis.* Infective endocarditis caused by *Strep. bovis* is prevalent among the elderly and is associated with preexisting colonic lesions. Enterococci are frequently implicated in nosocomial bacteremias and infective endocarditis that is resistant to medical therapy. However, enterococcal endocarditis is much less common than enterococcal bacteremia; the frequency of infective endocarditis is less than 10 percent among patients with enterococcal bacteremia.[19,21] Polymicrobial infective endocarditis, although still uncommon, is encountered most often in association with injection-drug use.

New diagnostic approaches, including culture and microbiologic assessment of vegetations, have yielded a better understanding of blood-culture–negative infective endocarditis.[22] Only 5 to 7 percent of patients who have been given a diagnosis of infective endocarditis according to strict criteria and who have not recently received antibiotics will have sterile blood cultures. For example, blood cultures were negative in 88 of 620 cases (14 percent) of infective endocarditis documented in France during a one-year nationwide survey. In 42 of 88 cases, negative cultures were associated with the administration of antibiotics before blood was drawn for culture.[23] Suppression of bacteremia often persists longer than the antibiotic is present in blood. Such suppression can be countered in patients with subacute endocarditis by delaying empirical therapy and obtaining additional blood cultures.

The polymerase chain reaction can be used to identify unculturable organisms in excised vegetations or systemic emboli.[24] This approach has been used to diagnose infective endocarditis due to *Tropheryma whipplei* and bartonella species and is a promising tool for establishing a microbiologic diagnosis in se-

TABLE 1. MICROBIOLOGIC FEATURES OF NATIVE-VALVE AND PROSTHETIC-VALVE ENDOCARDITIS.

PATHOGEN	NATIVE-VALVE ENDOCARDITIS				PROSTHETIC-VALVE ENDOCARDITIS		
	NEONATES	2 MO–15 YR OF AGE	16–60 YR OF AGE	>60 YR OF AGE	EARLY (<60 DAYS AFTER PROCEDURE)	INTERMEDIATE (60 DAYS–12 MO AFTER PROCEDURE)	LATE (>12 MO AFTER PROCEDURE)
	approximate percentage of cases						
Streptococcus species	15–20	40–50	45–65	30–45	1	7–10	30–33
Staphylococcus aureus	40–50	22–27	30–40	25–30	20–24	10–15	15–20
Coagulase-negative staphylococci	8–12	4–7	4–8	3–5	30–35	30–35	10–12
Enterococcus species	<1	3–6	5–8	14–17	5–10	10–15	8–12
Gram-negative bacilli	8–12	4–6	4–10	5	10–15	2–4	4–7
Fungi	8–12	1–3	1–3	1–2	5–10	10–15	1
Culture-negative and HACEK organisms*	2–6	0–15	3–10	5	3–7	3–7	3–8
Diphtheroids	<1	<1	<1	<1	5–7	2–5	2–3
Polymicrobial	3–5	<1	1–2	1–3	2–4	4–7	3–7

*Patients whose blood cultures were rendered negative by prior antibiotic treatment are excluded. HACEK denotes haemophilus species (*Haemophilus parainfluenzae, H. aphrophilus,* and *H. paraphrophilus), Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens,* and *Kingella kingae.*

lected patients with blood-culture–negative infective endocarditis.[22,24-26]

When blood cultures from patients with suspected infective endocarditis remain sterile after 48 to 72 hours of incubation, the clinician must advise the laboratory of the suspected diagnosis. This will allow the laboratory, if the blood cultures remain negative after five to seven days, to intensify efforts to recover fastidious organisms and initiate serologic assessment of causation.[27] These efforts could include prolonged incubation and the plating of subcultures on more enriched mediums. Use of the lysis centrifugation system for blood cultures allows direct planting to special supportive mediums, with the potential to increase the speed of recovery of more fastidious organisms. In Table 2, we outline some of the most common causes of blood-culture–negative infective endocarditis and summarize approaches to diagnosis.

CLINICAL MANIFESTATIONS

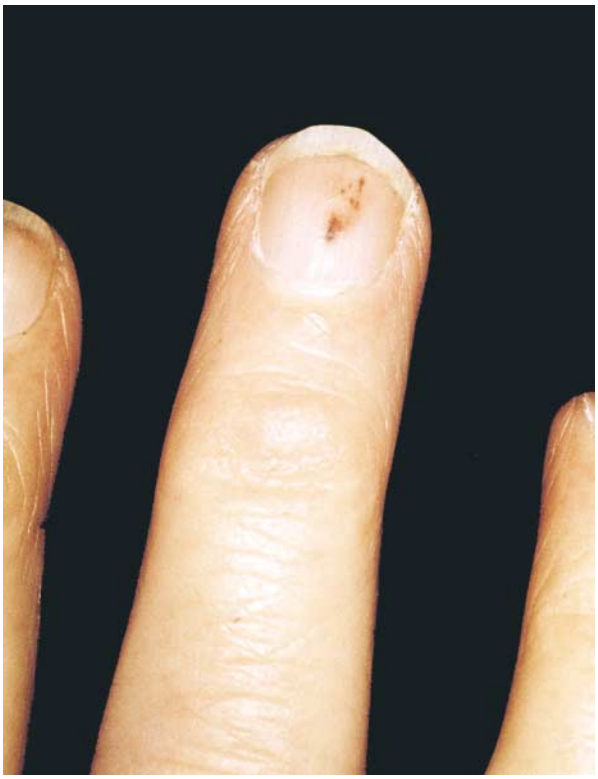
The presentation of infective endocarditis often includes extracardiac manifestations or findings that are associated with intracardiac extension of infection. Fever is the most common symptom and sign; however, it may be absent or minimal in patients with congestive heart failure, severe debility, chronic renal or liver failure, previous use of antimicrobial drugs, or infective endocarditis caused by less virulent organisms. Other common symptoms of subacute infective endocarditis include anorexia, weight loss, malaise, and night sweats. Most patients with infective endocarditis have a heart murmur (most commonly preexisting), and patients may have petechiae on the skin, conjunctivae, or oral mucosa, as well as splenomegaly and other peripheral manifestations (Fig. 1). Prosthetic-valve endocarditis may be manifested as an indolent illness with low-grade fever, or it can be an acute febrile and toxic illness. The high frequency of invasive infection in prosthetic-valve endocarditis results in higher rates of new or changing murmurs and of congestive heart failure. Unexplained fever in a patient with a prosthetic valve should prompt careful evaluation for prosthetic-valve endocarditis. Isolated right-sided infective endocarditis is not associated with peripheral emboli and other peripheral vascular phenomena; instead, pulmonary findings may predominate.

The onset of nosocomial infective endocarditis is usually acute, and signs of endocarditis are infrequent. The diagnosis of infective endocarditis is suggested by bacteremia persisting for days before treatment or

TABLE 2. LABORATORY DIAGNOSIS OF COMMON CAUSES OF CULTURE-NEGATIVE ENDOCARDITIS.*

ORGANISM	APPROACH
Abiotrophia species (previously classified as nutritionally variant streptococci)	Grow in thioglycolate medium of blood culture and as satellite colonies around *Staphylococcus aureus* on blood agar or on medium supplemented with pyridoxal hydrochloride or L-cysteine
Bartonella species (usually *Bartonella henselae* or *B. quintana*)	Serologic tests Lysis-centrifugation system for blood cultures PCR of valve or embolized vegetations[25,28,29]; special culture techniques available, but organisms are slow-growing and may require a month or more for isolation
Coxiella burnetii (Q fever)	Serologic tests PCR, Giemsa stain, or immunohistologic techniques on operative specimens
HACEK organisms	Blood cultures positive by day 7; occasionally require prolonged incubation and subculturing
Chlamydia species (usually *Chlamydia psittaci*)	Culture from blood has been described Serologic tests Direct staining of tissue with use of fluorescent monoclonal antibody
Tropheryma whipplei	Histologic examination (silver and PAS stains) of excised heart valve; PCR[26] or culture of vegetation[30]
Legionella species	Subculture from blood cultures, lysis-centrifugation pellet from blood cultures, or operative specimens on BCYE agar; direct detection on heart valves with fluorescent antibody Serologic tests
Brucella species (usually *Brucella melitensis* or *B. abortus*)	Serologic tests Prolonged incubation of standard or lysis-centrifugation blood cultures
Fungi	Regular blood cultures often positive for candida species; lysis-centrifugation system with specific fungal medium can increase yield; testing urine for *Histoplasma capsulatum* antigen or serum for *Cryptococcus neoformans* polysaccharide capsular antigen can be helpful Accessible lesions (such as emboli) should be cultured and examined histologically for fungi

*PCR denotes polymerase chain reaction; HACEK organisms haemophilus species (*Haemophilus parainfluenzae, H. aphrophilus,* and *H. paraphrophilus*), *Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens,* and *Kingella kingae;* PAS periodic acid–Schiff; and BCYE buffered charcoal yeast extract.



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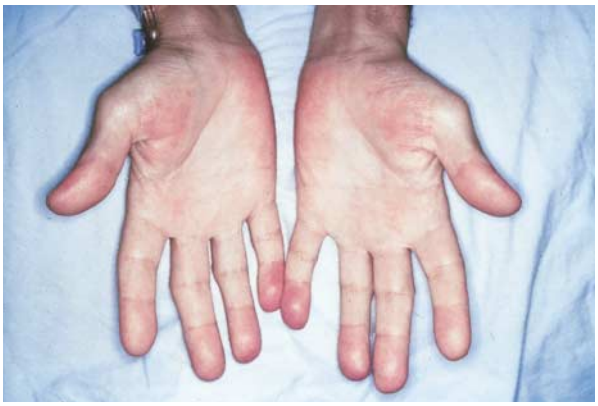

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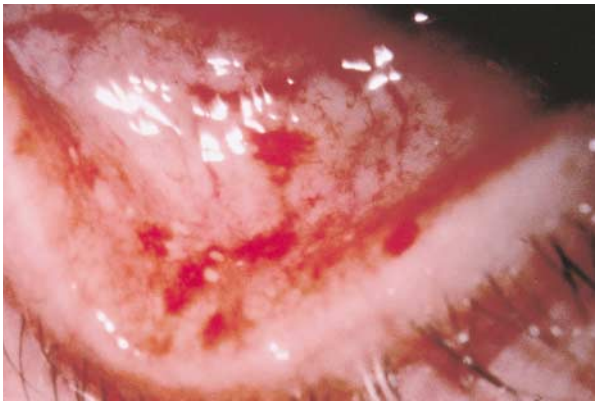

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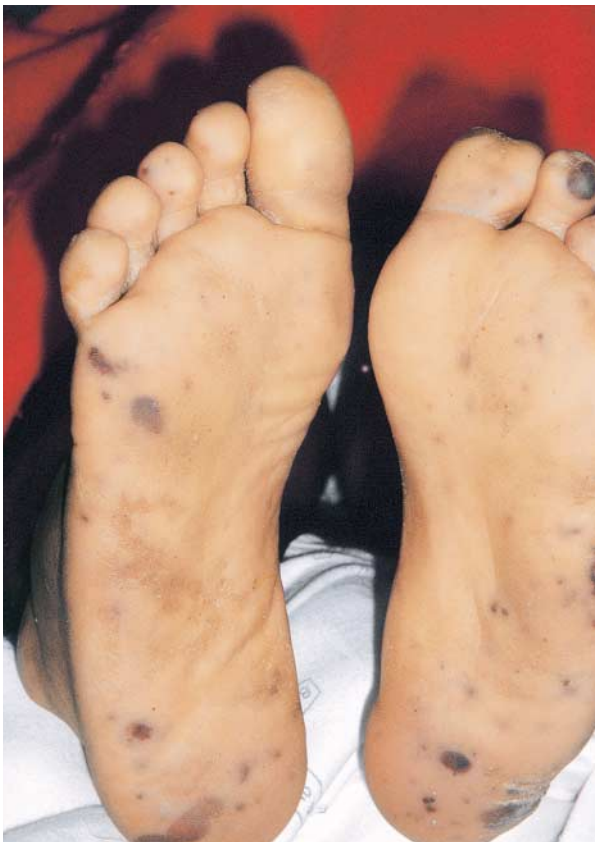

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Figure 1. Common Peripheral Manifestations of Infective Endocarditis.

Splinter hemorrhages (Panel A) are normally seen under the fingernails or toenails. They are usually linear and red for the first two to three days and brownish thereafter. Panel B shows conjunctival petechiae. Osler's nodes (Panel C) are tender, subcutaneous nodules, often in the pulp of the digits or the thenar eminence. Janeway's lesions (Panel D) are nontender erythematous, hemorrhagic, or pustular lesions, often on the palms or soles.

for 72 hours or more after the removal of an infected catheter and the initiation of treatment, especially in patients with an abnormal or prosthetic heart valve.[31] Among patients with prosthetic valves, nosocomial bacteremia or candidemia from sources other than valves carries risks of subsequent prosthetic-valve endocarditis of approximately 16 percent and 11 percent, respectively.[32,33]

DIAGNOSIS

The diagnosis of infective endocarditis requires the integration of clinical, laboratory, and echocardiographic data. Nonspecific laboratory abnormalities may be present, including anemia, leukocytosis, abnormal urinalysis results, and an elevated erythrocyte sedimentation rate and C-reactive protein level.

Patients with suspected infective endocarditis should have electrocardiography performed on admission (and repeated during their course as appropriate). New atrioventricular, fascicular, or bundle-branch block, particularly in the setting of aortic-valve endocarditis, suggests perivalvular invasion, and such patients may need cardiac monitoring until they are stable. New atrioventricular block carries a moderately high positive predictive value for the formation of a myocardial abscess, but the sensitivity is low.[34-36]

The Duke Criteria

In 1994, a group at Duke University proposed standardized criteria for assessing patients with suspected infective endocarditis.[37] These criteria integrated factors predisposing patients to the development of infective endocarditis, the blood-culture isolate and persistence of bacteremia, and echocardiographic findings with other clinical and laboratory information. The usefulness of these Duke criteria in assessing patients with potential infective endocarditis has been validated in several subsequent studies.[38-43] The specificity of the initially proposed criteria (the ability to reject the diagnosis correctly) was high (0.99, with a 95 percent confidence interval of 0.97 to 1.0),[43] and the negative predictive value was greater than 92 percent.[44] Also, a retrospective study of 410 patients with diagnosed endocarditis found that the Duke criteria had good (72 to 90 percent) agreement with clinical assessment by infectious-disease experts.[41] Most discrepancies occurred when the experts rejected cases categorized as possible endocarditis according to the Duke criteria. Misclassification of culture-negative cases, the increasing role of transesophageal echocardiography, the relative risk of endocarditis in *Staph. aureus* bacteremia, and the overly broad categorization of cases as "possible" were problems with the original criteria. A modified version of the Duke criteria has recently been proposed[45] (Table 3).

Echocardiography

Transthoracic echocardiography is rapid and noninvasive and has excellent specificity for vegetations (98 percent).[48] However, transthoracic echocardiography may be inadequate in up to 20 percent of adult patients because of obesity, chronic obstructive pulmonary disease, or chest-wall deformities; the overall sensitivity for vegetations may be less than 60 to 70 percent.[48,49] Transesophageal echocardiography is more costly and invasive but increases the sensitivity for detecting vegetations to 75 to 95 percent while maintaining specificity of 85 to 98 percent.[49-51] Transesophageal echocardiography is particularly useful in patients with prosthetic valves and for the evaluation of myocardial invasion.[50] A negative transesophageal echocardiogram has a negative predictive value for infective endocarditis of over 92 percent.[44,52]

Recent guidelines suggest that among patients with suspected infective endocarditis, transthoracic echocardiography should be used in the evaluation of those with native valves who are good candidates for imaging.[53] In fact, the appropriate use of echocardiography depends on the prior probability of infective endocarditis.[54] If this probability is less than 4 percent, a negative transthoracic echocardiogram is cost effective and clinically satisfactory in ruling out infective endocarditis.[51] For patients whose prior probability of infective endocarditis is 4 to 60 percent, initial use of transesophageal echocardiography is more cost-effective and diagnostically efficient than initial use of transthoracic echocardiography, which, if negative, is followed by transesophageal echocardiography. This category of intermediate prior probability includes patients with unexplained bacteremia with a gram-positive coccus, those with catheter-associated *Staph. aureus* bacteremia, and those admitted with fever or bacteremia in the setting of recent injection-drug use.[51]

Clinical diagnosis of perivalvular extension of infective endocarditis is imprecise.[55] Persistent bacteremia or fever, recurrent emboli, heart block, congestive heart failure, or a new pathologic murmur in a patient with infective endocarditis may suggest such extension. Transesophageal echocardiography is more sensitive than transthoracic echocardiography for defining perivalvular extension of infective endocarditis and the presence of a myocardial abscess.[49,50,53,55-57] Transesophageal echocardiography with spectral and color-flow Doppler techniques can also demonstrate the distinctive flow patterns of fistulas, pseudoaneurysms, or unruptured abscess cavities and is more sensitive than transthoracic echocardiography for identifying valve perforations.[58]

Patients with *Staph. aureus* Bacteremia

The prevalence of endocarditis among patients with *Staph. aureus* bacteremia is variable. In a study that included 103 patients with fever and *Staph. aureus* bacteremia, all of whom underwent both transthoracic and transesophageal echocardiography, infective endocarditis was diagnosed in 25 percent of all patients (and in 23 percent of the 69 patients with in-

TABLE 3. MODIFIED DUKE CRITERIA FOR THE DIAGNOSIS OF INFECTIVE ENDOCARDITIS.*

CRITERIA	COMMENTS
Major criteria	
Microbiologic	
Typical microorganism isolated from two separate blood cultures: viridans streptococci, *Streptococcus bovis,* HACEK group, *Staphylococcus aureus,* or community-acquired enterococcal bacteremia without a primary focus	In patients with possible infective endocarditis, at least two sets of cultures of blood collected by separate venipunctures should be obtained within the first 1 to 2 hours of presentation. Patients with cardiovascular collapse should have three cultures of blood obtained at 5-to-10-minute intervals and thereafter receive empirical antibiotic therapy
or	
Microorganism consistent with infective endocarditis isolated from persistently positive blood cultures	
or	
Single positive blood culture for *Coxiella burnetii* or phase I IgG antibody titer to *C. burnetii* >1:800	*C. burnetii* is not readily cultivated in most clinical microbiology laboratories
Evidence of endocardial involvement	
New valvular regurgitation (increase or change in preexisting murmur not sufficient)	
or	
Positive echocardiogram (transesophageal echocardiogram recommended in patients who have a prosthetic valve, who are rated as having at least possible infective endocarditis by clinical criteria, or who have complicated infective endocarditis)	Three echocardiographic findings qualify as major criteria: a discrete, echogenic, oscillating intracardiac mass located at a site of endocardial injury; a periannular abscess; and a new dehiscence of a prosthetic valve
Minor criteria	
Predisposition to infective endocarditis that includes certain cardiac conditions and injection-drug use	Cardiac abnormalities that are associated with infective endocarditis are classified into three groups: High-risk conditions: previous infective endocarditis,[46,47] aortic-valve disease, rheumatic heart disease, prosthetic heart valve, coarctation of the aorta, and complex cyanotic congenital heart diseases Moderate-risk conditions: mitral-valve prolapse with valvular regurgitation or leaflet thickening, isolated mitral stenosis, tricuspid-valve disease, pulmonary stenosis, and hypertrophic cardiomyopathy Low- or no-risk conditions: secundum atrial septal defect, ischemic heart disease, previous coronary-artery bypass graft surgery, and mitral-valve prolapse with thin leaflets in the absence of regurgitation
Fever	Temperature >38°C (100.4°F)
Vascular phenomena	Petechiae and splinter hemorrhages are excluded None of the peripheral lesions are pathognomonic for infective endocarditis
Immunologic phenomena	Presence of rheumatoid factor, glomerulonephritis, Osler's nodes, or Roth spots
Microbiologic findings	Positive blood cultures that do not meet the major criteria Serologic evidence of active infection; single isolates of coagulase-negative staphylococci and organisms that very rarely cause infective endocarditis are excluded from this category.

*Criteria are adapted from Li et al.[45] Cases are defined clinically as definite if they fulfill two major criteria, one major criterion plus three minor criteria, or five minor criteria; they are defined as possible if they fulfill one major and one minor criterion, or three minor criteria. HACEK denotes haemophilus species (*Haemophilus parainfluenzae, H. aphrophilus,* and *H. paraphrophilus*), *Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens,* and *Kingella kingae.*

travenous-catheter–associated infection).[59] Among another 262 patients with *Staph. aureus* bacteremia, 34 (13 percent) were found to have definite infective endocarditis, and the frequency of infective endocarditis was similar whether or not bacteremia was associated with an intravascular catheter.[45] Factors associated with an increased probability of infective endocarditis in patients with *Staph. aureus* bacteremia include community acquisition, absence of a primary focus, presence of metastatic sequelae, and fever or bacteremia persisting for more than three days after the removal of the catheter. Although these risk factors are useful clinical aids, recent studies suggest that the use of transesophageal echocardiography to determine the appropriate duration of therapy in patients with uncomplicated, intravascular-catheter–associated *Staph. aureus* bacteremia may be a more cost-effective approach than an empirical choice of either two or four weeks of therapy.[51,59-63]

COMPLICATIONS

Cardiac Complications

Congestive heart failure and neurologic events have the greatest influence on the prognosis of infective endocarditis. The usual cause of congestive heart failure in patients with infective endocarditis is infection-induced valvular damage. Rarely, embolism of fragments of vegetations can cause acute myocardial infarction and subsequent congestive heart failure. Aortic-valve infection is more frequently associated with congestive heart failure than is mitral-valve infection.

Extension of infective endocarditis beyond the valve annulus predicts higher mortality, the more frequent development of congestive heart failure, and the need for cardiac surgery. Extension of infection into the septum may lead to atrioventricular, fascicular, or bundle-branch block. Erosion of a mycotic aneurysm of the sinus of Valsalva can cause pericarditis, hemopericardium and tamponade, or fistulas to the right or left ventricle. Pericarditis can also occur as a complication of myocardial infarction due to coronary-artery embolization.

Neurologic Complications

Up to 65 percent of embolic events in infective endocarditis involve the central nervous system, and neurologic complications develop in 20 to 40 percent of all patients with infective endocarditis.[61,64,65] A stroke syndrome in a patient with fever and underlying valvular heart disease suggests the possibility of infective endocarditis. The rate of embolic events in patients with infective endocarditis decreases rapidly after the initiation of effective antibiotic therapy, from 13 per 1000 patient-days during the first week of therapy to fewer than 1.2 per 1000 patient-days after two weeks of therapy.[65-67]

Mycotic aneurysms result from septic embolization of vegetations to the arterial vasa vasorum or the intraluminal space, with subsequent spread of infection through the intima and vessel wall. Arterial branching points favor the impaction of emboli and are the most common sites of mycotic aneurysms. The clinical presentation of patients with intracranial mycotic aneurysms is quite variable. Some intracranial aneurysms leak slowly before rupture and produce headache and mild meningeal irritation, whereas in other patients, there are no clinically recognized premonitory findings before sudden intracranial hemorrhage.

Imaging procedures to detect intracranial mycotic aneurysms may be useful in patients with localized or severe headaches, meningitis with negative cultures, or focal neurologic signs. Contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) may provide useful initial information; these techniques have approximately 90 to 95 percent sensitivity for intracerebral bleeding and may identify the location of an aneurysm.[27] Magnetic resonance angiography is a promising new technique for the detection of intracranial mycotic aneurysms, but its sensitivity for aneurysms smaller than 5 mm is inferior to that of conventional four-vessel cerebral angiography,[27,68] which remains the standard for evaluation.

Systemic Emboli and Splenic Abscess

Systemic embolism is a frequent complication of infective endocarditis and most commonly involves the spleen, the kidney, the liver, and the iliac or mesenteric arteries. Splenic abscess may develop from bacteremic seeding of a previously infarcted area or direct seeding of the spleen by an infected embolus. Splenic abscess can be a cause of prolonged fever and may cause diaphragmatic irritation with pleuritic or left shoulder pain; abdominal pain and splenomegaly may be absent. Abdominal CT and MRI appear to be the best tests for the diagnosis of splenic lesions, each with a sensitivity and specificity of 90 to 95 percent.[27,69]

Prolonged Fever

Fever associated with infective endocarditis often resolves within two to three days after the start of appropriate antimicrobial treatment in patients with less virulent pathogens, and defervescence occurs in 90 percent of patients by the end of the second week of treatment. The most common causes of persistent fever (more than 14 days) are the extension of infection beyond the valve (often with myocardial abscess), focal metastatic infection, drug hypersensitivity (particularly if the fever resolves and then recurs), or a nosocomial infection or other complication of hospitalization, such as pulmonary embolism.[70]

TREATMENT

Choice of Antimicrobial Agents

Treatment of the most common causes of infective endocarditis is summarized in Table 4. Prolonged parenteral administration of a bactericidal antimicrobial agent or combination of agents is currently recommended.[27,71,72] Treatment is usually begun in the hospital, but it is often completed on an outpatient basis once the fever has resolved and follow-up blood cultures are negative, as long as indications for cardiac surgery are not present.

The optimal therapy for infective endocarditis resulting from less common causes is still not adequately defined. Aminoglycosides and fluoroquinolones are bactericidal for bartonella species. However, most patients with reported cases of infective endocarditis due to bartonella species have been treated with a beta-lactam antibiotic and an aminoglycoside.[25] Most patients with infective endocarditis due to bartonella have also required valve-replacement surgery for cure. Doxycycline with a second antimicrobial agent, often given for three to four years until IgG antibody titers drop below 1:400, has been the recommended treatment for infective endocarditis due to Q fever. A prospective study among 35 patients with Q fever infective endocarditis suggested that the combination of doxycycline and hydroxychloroquine (median duration, 26 months) was associated with a lower rate of relapse than was therapy with doxycycline and a fluoroquinolone for a median of 60 months.[78,79] Eradication of Q fever infective endocarditis usually requires valve-replacement surgery, although relapse of infection on the replaced valve may occur.

In the absence of clinical clues to a specific cause, therapy for culture-negative native-valve endocarditis should be individualized and generally includes pen-

TABLE 4. USUAL ANTIMICROBIAL THERAPY FOR COMMON CAUSES OF INFECTIVE ENDOCARDITIS.*

PATHOGEN	NATIVE-VALVE ENDOCARDITIS		PROSTHETIC-VALVE ENDOCARDITIS	
	ANTIMICROBIAL THERAPY	COMMENTS	ANTIMICROBIAL THERAPY	COMMENTS
Penicillin-susceptible viridans streptococci, *Streptococcus bovis,* and other streptococci with MIC of penicillin ≤0.1 μg/ml	Penicillin G or ceftriaxone for 4 wk†	A 2-wk regimen of penicillin G (or ceftriaxone) and gentamicin can be used in some cases,[73,74] but it is not recommended for patients with myocardial abscess, extracardiac foci of infection, or prosthetic-valve endocarditis.	Penicillin G for 6 wk and gentamicin for 2 wk†	Shorter duration of treatment with an aminoglycoside (2 wk) is usually appropriate for prosthetic-valve endocarditis due to penicillin-susceptible viridans streptococci, *S. bovis,* or other streptococci with MIC of penicillin ≤0.1 μg/ml.
Relatively penicillin-resistant streptococci (MIC of penicillin >0.1 to 0.5 μg/ml)	Penicillin G for 4 wk and gentamicin for 2 wk†		Penicillin G for 6 wk and gentamicin for 4 wk†	
Streptococcus species with MIC of penicillin >0.5 μg/ml, enterococcus species, or abiotrophia species	Penicillin G (or ampicillin) and gentamicin for 4–6 wk†	6 wk of therapy is recommended for patients with symptoms lasting longer than 3 mo, myocardial abscess, or selected other complications.	Penicillin G (or ampicillin) and gentamicin for 6 wk†	
Methicillin-susceptible staphylococci	Nafcillin or oxacillin for 4–6 wk, with or without addition of gentamicin for the first 3–5 days of therapy‡	In the few patients infected with a penicillin-susceptible staphylococcus, penicillin G may be used instead of nafcillin or oxacillin.	Nafcillin or oxacillin with rifampin for 6 wk and gentamicin for 2 wk‡	It may be prudent to delay initiation of rifampin for 1 or 2 days, until therapy with two other effective antistaphylococcal drugs has been initiated.
Methicillin-resistant staphylococci	Vancomycin, with or without addition of gentamicin, for the first 3–5 days of therapy		Vancomycin with rifampin for 6 wk and gentamicin for 2 wk	If the staphylococcus is resistant to gentamicin, an alternative third agent should be chosen on the basis of in vitro susceptibility testing.
Right-sided staphylococcal native-valve endocarditis in selected patients	Nafcillin or oxacillin with gentamicin for 2 wk	This 2-wk regimen has been studied for infections due to an oxacillin- and aminoglycoside-susceptible isolate. Exclusions to short-course therapy include any cardiac or extracardiac complications associated with infective endocarditis, persistence of fever for 7 days or more, and infection with HIV. Patients with vegetations greater than 1–2 cm according to echocardiography should probably be excluded from short-course therapy.[75-77]		
HACEK organisms	Ceftriaxone for 4 wk	Ampicillin and gentamicin for 4 wk is an alternative regimen, but some isolates may produce beta-lactamase, thereby reducing the efficacy of this regimen.	Ceftriaxone for 6 wk	Ampicillin and gentamicin for 6 wk is an alternative regimen, but some isolates may produce beta-lactamase, thereby reducing the efficacy of this regimen.

*Data are from Bayer et al.,[27] Working Party of the British Society for Antimicrobial Chemotherapy,[71] and Wilson et al.[72] MIC denotes minimal inhibitory concentration; HACEK organisms, haemophilus species (*Haemophilus parainfluenzae, H. aphrophilus,* and *H. paraphrophilus), Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens,* and *Kingella kingae;* and HIV, human immunodeficiency virus.

†Vancomycin therapy is indicated for patients with confirmed immediate hypersensitivity reactions to beta-lactam antibiotics.

‡For patients who have infective endocarditis due to methicillin-susceptible staphylococci and who are allergic to penicillins, a first-generation cephalosporin or vancomycin can be substituted for nafcillin or oxacillin. Cephalosporins should be avoided in patients with confirmed immediate-type hypersensitivity reactions to beta-lactam antibiotics.

icillin, ampicillin, ceftriaxone, or vancomycin, often in combination with an aminoglycoside. Therapy for culture-negative prosthetic-valve endocarditis within the initial 12 months after valve replacement often includes at least vancomycin and gentamicin. For patients with prosthetic-valve endocarditis that begins 12 months or more after valve surgery, ceftriaxone or cefotaxime could be added to cover for so-called HACEK organisms (haemophilus species [*Haemophilus parainfluenzae, H. aphrophilus,* and *H. paraphrophilus*], *Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens,* and *Kingella kingae*). If fever due to infective endocarditis persists after empirical therapy, valve-replacement surgery for

débridement and to obtain material for microbiologic and pathological evaluation may be considered.

Antimicrobial-Susceptibility Testing

Determination of the minimal inhibitory concentration (MIC) of penicillin is necessary to define optimal therapy for streptococcal infection (Table 4). Susceptibility of staphylococci should be determined for oxacillin (or methicillin), vancomycin, rifampin, and gentamicin (or an alternative aminoglycoside). Strains of staphylococci that are resistant to oxacillin (or methicillin) are cross-resistant to all beta-lactam antibiotics, regardless of the results of in vitro antimicrobial-susceptibility testing.

Optimal therapy for enterococcal infective endocarditis requires a synergistic bactericidal combination of a cell-wall–active antimicrobial agent to which the organism is susceptible (penicillin, ampicillin, or vancomycin), plus an aminoglycoside. Susceptibility testing of enterococci from patients with infective endocarditis should include determination of the MICs of penicillin (or ampicillin) and vancomycin and evaluation for the presence of high-level resistance to gentamicin and streptomycin.[80] Optimal synergistic antimicrobial therapy is not available for strains of enterococci with high-level resistance to both gentamicin and streptomycin; therapy for infective endocarditis due to such organisms (or to organisms highly resistant to penicillin or ampicillin and resistant to vancomycin) should be developed in consultation with an infectious-disease specialist.

Because of the frequency of adverse events in patients treated for infective endocarditis and the associated need to revise therapy, the causative organism should ideally be retained until cure has been ensured. In addition, to ensure the optimal therapeutic regimen, organisms recovered from surgical specimens or blood cultures at relapse should be studied for antimicrobial susceptibility.

Anticoagulant Therapy

Anticoagulant therapy has not been shown to prevent embolization in infective endocarditis and may increase the risk of intracerebral hemorrhage. Anticoagulant therapy for native-valve endocarditis is restricted to patients with a clear indication separate from infective endocarditis; in the presence of intracranial hemorrhage or mycotic aneurysm, anticoagulant therapy should be suspended until the complications have resolved. In general, patients with infective endocarditis involving a prosthetic heart valve that requires maintenance anticoagulation are cautiously given continued anticoagulant therapy during treatment of prosthetic-valve endocarditis. However, in the presence of central nervous system emboli with hemorrhage, temporary discontinuation of anticoagulant therapy is appropriate.

Patients with *Staph. aureus* prosthetic-valve endocarditis who are receiving anticoagulant therapy are particularly susceptible to central nervous system hemorrhage[61]; indirect evidence from uncontrolled studies in a limited number of patients suggests that anticoagulant therapy should generally be suspended in such patients during the acute phase of the illness.[81] If cardiac surgery for infective endocarditis is planned, warfarin may be discontinued and replaced with heparin to allow more rapid reversal of anticoagulation at the time of surgery. The role (if any) of aspirin in the prevention of embolism in infective endocarditis is still under evaluation.[82]

Surgical Therapy

Several studies suggest that combined medical and surgical therapy for infective endocarditis can decrease mortality among patients who have congestive heart failure, perivalvular invasive disease, or uncontrolled infection despite maximal antimicrobial therapy; congestive heart failure is the strongest indication for surgery in infective endocarditis. For example, medically treated patients with moderate-to-severe congestive heart failure due to endocarditis-related valvular dysfunction have a mortality rate of 56 to 86 percent, as compared with 11 to 35 percent among patients treated with combined medical and surgical therapy.[83-86] The hemodynamic status of the patient at the time of valve-replacement surgery is the principal determinant of operative mortality[87,88]; the optimal time to perform surgery is before severe hemodynamic disability or spread of the infection to perivalvular tissue has occurred.[89] Serial echocardiograms may be helpful to monitor the need for valve-replacement surgery. In some patients, the presence of metastatic infection may need to be assessed before valve-replacement surgery so as to avoid relapse of infection on the prosthetic valve that is seeded from these sites.

Medical therapy for infective endocarditis caused by some microorganisms is usually unsuccessful, and surgical therapy is generally advised. These pathogens include *Pseudomonas aeruginosa,* brucella species, *Coxiella burnetii,* candida species,[90,91] other fungi, and probably enterococci for which there is no synergistic bactericidal regimen. Also, uncontrolled sepsis in spite of maximal antimicrobial therapy due to any pathogen is usually an indication for surgery.

Infective endocarditis involving a prosthetic valve is another common indication for surgical evaluation. Patients with prosthetic-valve endocarditis who can be treated with antimicrobial agents alone are usually characterized by late onset of infection (more than 12 months after implantation of a prosthesis); infection by viridans streptococcus, HACEK organisms, or enterococci; and no evidence of perivalvular extension of infection. Although the rate of recurrent prosthetic-valve endocarditis after surgery for active infective endocarditis was up to 7 percent over a mean follow-up period of six years,[92] there is no compelling

evidence that delaying surgery in patients with progressive infection or hemodynamic deterioration improves outcome.

Relapse of prosthetic-valve endocarditis after appropriate medical therapy should lead to careful echocardiographic assessment for perivalvular extension of infection or for metastatic foci of infection, such as splenic abscess or osteomyelitis. Some patients with relapsed prosthetic-valve endocarditis may respond to a second course of antimicrobial therapy, but many such patients will require combined medical and surgical therapy for cure. More patients with *Staph. aureus* prosthetic-valve endocarditis survive with medical and surgical therapy than with medical therapy alone (relative risk of death, 0.18), suggesting that *Staph. aureus* prosthetic-valve endocarditis alone may be an indication for valve-replacement surgery.[93]

Some authorities recommend surgery if there have been two episodes of embolization or one episode with residual large vegetations. However, there are no data from prospective, controlled trials to support a firm recommendation. The development of embolic neurologic complications during infective endocarditis is associated with an increase in mortality by a factor of two to four. Large vegetations on the mitral valve, especially on the anterior leaflet, are associated with a higher risk of embolism than vegetations of similar size elsewhere. An increase in the size of vegetations that is detected by echocardiography during the course of therapy may identify a subgroup of patients with a higher rate of complications. However, there is no size or location threshold that suitably predicts increased mortality associated with embolization in such a way that the risk-to-benefit ratio of surgery for the prevention of embolization can be calculated. Also, the persistence of vegetations, as determined by echocardiography, is common after successful medical treatment of infective endocarditis and is not necessarily associated with late complications.[94] The characteristics of the vegetations alone rarely justify surgical intervention; rather, data on vegetations should be weighed in the context of the overall clinical picture to assess the benefits of surgery. Because the frequency of emboli decreases rapidly with effective antimicrobial therapy, the benefit of surgery in preventing further emboli is greatest if it is performed early in the course of infective endocarditis.

Because of the potential for postoperative neurologic deterioration or death, a recent neurologic complication of infective endocarditis has been considered a relative contraindication to valve-replacement surgery. A retrospective study of 181 patients with cerebral complications who underwent surgery for infective endocarditis found that the proportion of patients who had postoperative neurologic deterioration (including death) depended on the interval between the preceding cerebral event and cardiac surgery. Among those who had had nonhemorrhagic cerebral infarcts 7 days or less before surgery, neurologic deterioration occurred in 44 percent; among those undergoing surgery 8 to 14 days after the central nervous system event, only 16.7 percent had neurologic deterioration. The risk of a worsening neurologic deficit after cardiac surgery fell to 2.3 percent when the operation was performed four weeks or more after the central nervous system event. However, the risk of a worsening central nervous system deficit after cardiac surgery persisted for up to four weeks after intracerebral hemorrhage.[64] In contrast, other studies have suggested that valve-replacement surgery can be undertaken with minimal risk of neurologic deterioration in patients who have left-sided endocarditis without central nervous system hemorrhage.[95,96] A conservative approach is to delay valve-replacement surgery, if feasible, for two to three weeks after an embolic infarct in the central nervous system and for at least a month after intracerebral hemorrhage.[64,97,98]

The duration of antimicrobial therapy after valve-replacement surgery for active infective endocarditis has not been assessed in carefully controlled trials, but it should depend on the length of preoperative therapy, the presence of perivalvular extension of infection, and the microbiologic and pathological findings at surgery. The duration of combined preoperative and postoperative therapy for patients undergoing surgery should be at least as long as that recommended in Table 4. In patients with a positive intraoperative culture, a myocardial abscess, or a positive Gram's stain for organisms on a prosthesis removed from a patient with prosthetic-valve endocarditis, a full course of postoperative therapy is a reasonable, conservative approach.

MORTALITY AND RELAPSE

The mortality rate among patients with infective endocarditis varies according to the following factors: the causative microorganism (4 to 16 percent mortality for viridans streptococci and *Strep. bovis,* 15 to 25 percent for enterococci, 25 to 47 percent for *Staph. aureus,* 5 to 37 percent for Q fever, and more than 50 percent for *P. aeruginosa,* Enterobacteriaceae, or fungi); the presence of complications or coexisting conditions (for example, congestive heart failure, neurologic events, renal failure, or severe immunosuppression due to HIV infection); the development of perivalvular extension or a myocardial abscess; and the use of combined medical and surgical therapy in appropriate patients. The overall mortality rates for both native-valve and prosthetic-valve endocarditis remain as high as 20 to 25 percent, with death resulting primarily from central nervous system embolic events and hemodynamic deterioration. The mortality rate for right-sided endocarditis in injection-drug users is generally lower, approximately 10 percent.[76]

Relapse of infective endocarditis usually occurs

within two months of the discontinuation of antimicrobial therapy. The relapse rate for patients with native-valve endocarditis caused by penicillin-susceptible viridans streptococcus who have been treated with one of the recommended courses of therapy is generally less than 2 percent. The relapse rate for patients with enterococcal native-valve endocarditis after standard therapy is 8 to 20 percent. Among patients with infective endocarditis caused by *Staph. aureus,* Enterobacteriaceae, or fungi, treatment failure often occurs during the primary course of therapy. A positive culture at the time of valve-replacement surgery, particularly in patients with staphylococcal endocarditis, is a risk factor for subsequent relapse.[99] The relapse rate in prosthetic-valve endocarditis is approximately 10 to 15 percent, and relapse of infection may be an indication for combined medical and surgical therapy.

CONCLUSIONS

Over the past decade, substantial improvements have been made in the diagnosis and management of infective endocarditis. Treatment of this infection requires a multidisciplinary approach among health care providers from a variety of backgrounds. The same multidisciplinary approach should be used to guide the design of new clinical-research studies. Such studies should increasingly use, as much as feasible, a prospective, randomized, double-blind, multicenter design that will provide definitive answers to several of the remaining questions about this complex infection.

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