THOMAS F. KEYS, MD
Department of Infectious Disease, Cleveland Clinic

Infective endocarditis: Prevention, diagnosis, treatment, referral

ABSTRACT

Infective endocarditis is a challenge to the primary care physician, who is not likely to see more than several cases a year. With proper diagnosis and treatment, the overall cure rate is over 80% and major complications such as congestive heart failure can be avoided. In some patients, even in some with acute infection, surgical intervention to restore cardiac function significantly improves the outcome. Guidelines for prophylaxis before various surgical procedures are presented.

KEY POINTS

Fever, regurgitant heart murmur, classic vascular skin lesions, and multiple positive blood cultures are virtually diagnostic.

Echocardiography can detect valve lesions associated with endocarditis and is used to follow up patients who have or develop valve dysfunction and may need surgery.

Nosocomial bacteremia and fungemia are newly appreciated risk factors for infective endocarditis.

Although antibiotic prophylaxis to prevent endocarditis remains unproven, it is accepted practice for patients at risk who are undergoing invasive procedures.

INFECTIVE ENDOCARDITIS is a challenge to busy primary care physicians or internists. Infectious disease specialists see cases with some regularity and so are familiar with the syndrome and the intricacies of the diagnosis and treatment. But other clinicians are unlikely to encounter more than one or two cases a year.

This review outlines the cardinal manifestations of infective endocarditis, guidelines for diagnosis, empiric and specific treatment, indications for surgery, and an approach to prophylaxis.

RISK FACTORS FOR INFECTIVE ENDOCARDITIS

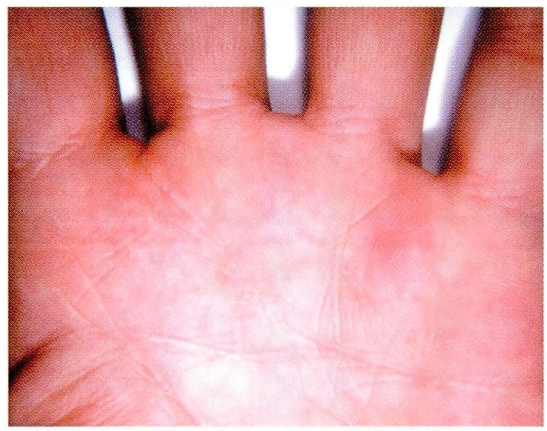
In general, a history of infective endocarditis, prosthetic valvular heart disease, or regurgitant heart murmur greatly increases the risk for infective endocarditis (TABLE 1).

Furthermore, 1% to 3% of patients who undergo valvular heart surgery contract endo-

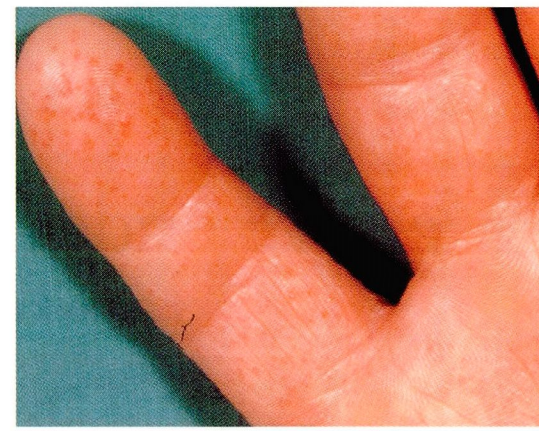
TABLE 1

Primary risk factors for infective endocarditis

History of infective endocarditis
Prosthetic valvular heart disease
Complex cyanotic heart disease
Surgically constructed pulmonary shunts
Acquired valvular heart disease
Hypertrophic cardiomyopathy
Mitral valve prolapse with regurgitation

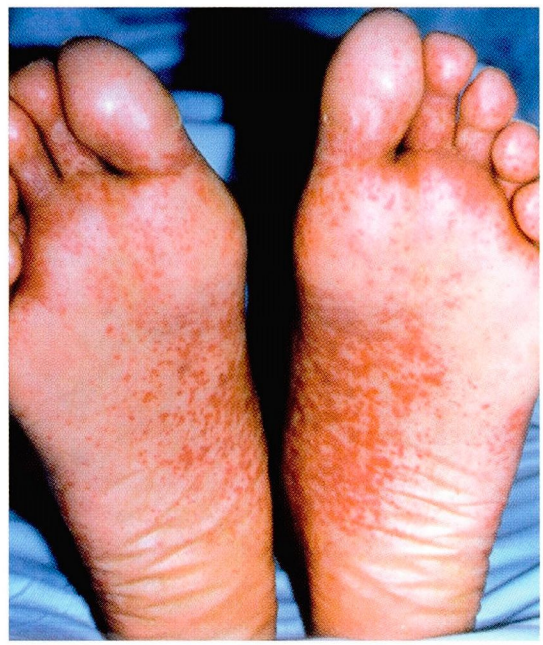


Raised red nodule on palm (*Pseudomonas aeruginosa*)

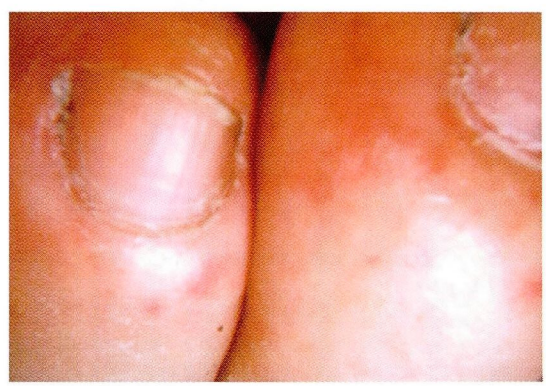


Fine raised rash on palm and fingers (*Actinobacillus actinomycetemcomitans*)

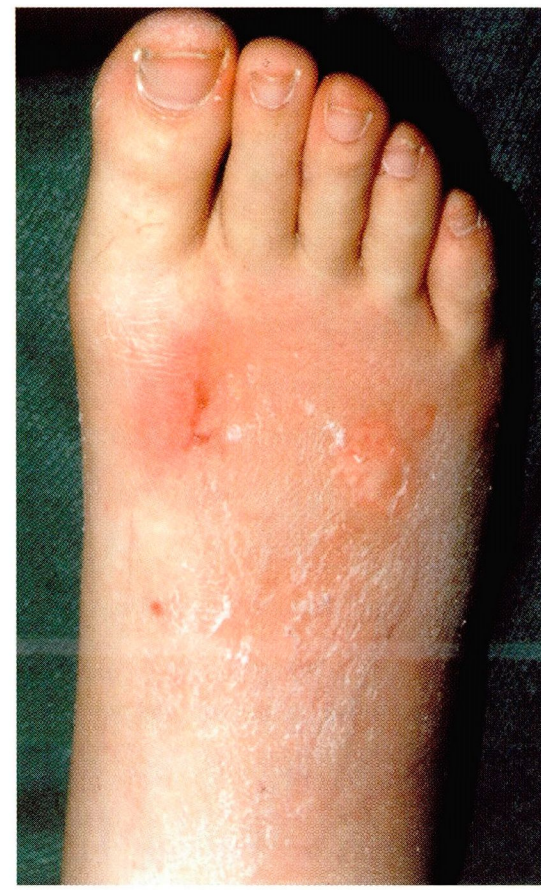
Look for lesions on the palms or soles, under the nail beds, in the subconjunctival sacs, or on the soft palate



Petechial rash on soles (*Viridans streptococci*)



"Flea-bitten" rash on toes (*Enterococcus faecalis*)



Embolic lesion on dorsum of foot (*Acinetobacter calcoaceticus*)

FIGURE 1. Vascular skin lesions associated with infective endocarditis

carditis within 60 days after the operation. Fortunately, the incidence is much lower now than in the days before standardized surgical techniques and antibiotic prophylaxis.

Today, nosocomial bacteremia is a growing concern in at-risk patients hospitalized for other medical and surgical problems. Sources of infection include surgical wounds, vascular catheters, and arteriovenous fistulae used for hemodialysis.[1] *Staphylococcus aureus*, often methicillin-resistant, may lead to endocarditis in up to 25% of cases.

Intravenous drug addiction continues to be a risk factor for endocarditis. *S aureus* is the usual pathogen in these individuals, although gram-negative bacteria and fungi are also seen.

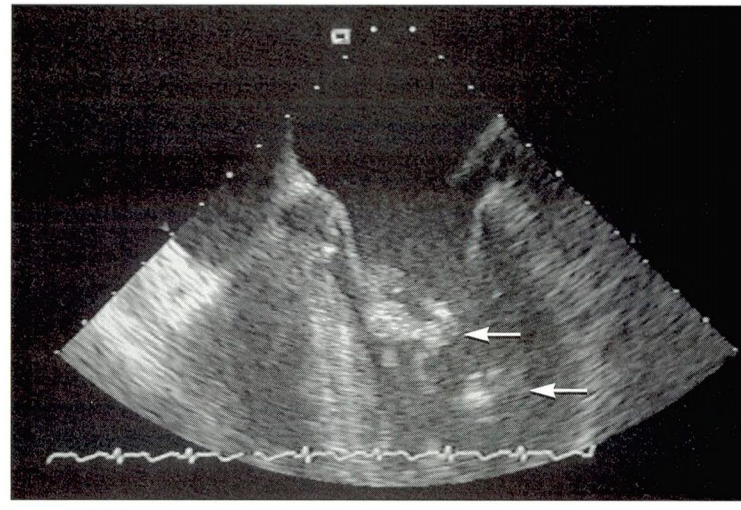


FIGURE 2. Transesophageal echocardiogram showing vegetations on anterior leaflet (top arrow) and papillary muscle (bottom arrow) of mitral valve.

DIAGNOSIS

Key clues

The key clinical clues to the diagnosis of infective endocarditis are fever, regurgitant heart murmur, and vascular skin lesions.[2] The skin lesions (**FIGURE 1**) are found especially on the palms or soles, under the nail beds ("splinter hemorrhages"), in the subconjunctival sacs, or on the soft palate.

Heart disease, weight loss, and splenomegaly are additional clues but are less specific since they are often associated with other disease processes.

Confirming the diagnosis

When fever, a regurgitant hear murmur, vascular skin lesions, weight loss, and splenomegaly are present in a patient who has risk factors for endocarditis, the clinician should consider the diagnosis and collect three blood cultures within 24 hours. Patients with sustained bacteremia due to typical organisms are likely to have endocarditis.[3] Transesophageal echocardiography can confirm the diagnosis by showing cardiac lesions compatible with vegetation or abscess (**FIGURE 2**).[4]

Negative blood cultures ("culture-negative endocarditis") or cultures that produce an organism not usually associated with endocarditis pose a diagnostic problem. Nevertheless, if the clinical picture suggests infective endocarditis and transesophageal echocardiography shows compatible lesions, the patient should be treated.

Pursuing 'culture-negative' endocarditis

A frequent cause of culture-negative endocarditis is suboptimal antibiotic therapy before the diagnosis is considered—eg, oral antibiotics prescribed for vague fever. Even minute concentrations of antibiotic in the blood may inhibit culture growth, especially streptococci that may be exquisitely susceptible to the penicillins. Ideally, one should wait at least 24 hours after the last dose of antibiotic before collecting blood cultures. In some cases, if necessary, two or more blood cultures beyond the usual two or three sets should be obtained, spaced several days apart.

Multiple positive blood cultures for typical organisms clinch the diagnosis

If these strategies fail, one should consider empiric therapy directed at the usual causes of endocarditis (eg, streptococci in patients with native heart valves, or staphylococci in patients with prosthetic heart valves). About 50% of patients will respond clinically to empiric therapy.

If a patient remains ill after 7 to 10 days of therapy, further diagnostic studies should be pursued. For example, the epidemiologic setting may suggest a diagnosis of Q-fever (due to *Coxiella burnetii*) or bartonellosis (due to *Bartonella henselae*).

Fungal endocarditis. At least 50% of patients with fungal endocarditis have negative blood cultures. Consider it in patients who have undergone prolonged antibiotic therapy, parenteral nutrition through central

TABLE 2

Empiric antibiotic therapy for endocarditis in adults with normal renal function

CLINICAL SETTING	LIKELY PATHOGENS	ANTIBIOTIC REGIMEN*
Patient has native valve		
Not acutely ill	*Viridans* streptococci HACEK organisms†	Ampicillin 2 g every 4 hours, plus Gentamicin 1.5 mg/kg every 12 hours
Acutely ill	*Staphylococcus aureus* *Streptococcus pneumoniae*	Vancomycin 1.0 g every 12 hours, plus Gentamicin 1.5 mg/kg every 12 hours
Intravenous drug abuser	*Staphylococcus aureus* *Pseudomonas aeruginosa*	Vancomycin 1.0 g every 12 hours, plus Gentamicin 3.0 mg/kg every 12 hours
Patient has prosthetic valve		
Onset within 60 days	*Staphylococcus epidermidis* *Staphylococcus aureus*	Vancomycin 1.0 g every 12 hours, plus Gentamicin 1.5 mg/kg every 12 hours
Onset after 60 days	*Viridans* streptococci *Staphylococcus epidermidis* *Staphylococcus aureus*	Ampicillin‡ 2 g every 4 hours, plus Vancomycin 1.0 g every 12 hours, plus Gentamicin 1.5 mg/kg every 12 hours

*All doses given intravenously
†*Haemophilus* sp, *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens*, *Kingella* sp
‡Vancomycin may be substituted for ampicillin in patients allergic to penicillin

MODIFIED FROM THE AMERICAN HEART ASSOCIATION AND INFECTIOUS DISEASE SOCIETY OF AMERICA RECOMMENDATIONS, REFERENCE 8

Start empiric intravenous antibiotics against the likely pathogen

TABLE 3

Antibiotic therapy for infective endocarditis due to streptococci and enterococci in adults with normal renal function

ORGANISM TYPE	ANTIBIOTIC REGIMEN*
Penicillin-sensitive streptococcus (penicillin MIC† < 0.1 µg/mL)	Penicillin G‡ 18 million units daily for 4 weeks, or Ceftriaxone 2.0 g every 24 hours for 4 weeks
Penicillin-insensitive streptococcus (penicillin MIC > 0.1 and ≤ 0.5 µg/mL)	Penicillin G‡ 18 million units daily for 4 weeks, plus Gentamicin 1.5 mg/kg every 12 hours for 2 weeks
***Enterococcus* species or streptococcus (penicillin MIC > 0.5 µg/mL)**	Penicillin G‡ 30 million units daily for 4–6 weeks, plus either Gentamicin 1.5 mg/kg every 12 hours for 4–6 weeks (if gentamicin MIC is < 500 µg/mL), or Streptomycin 7.5 mg/kg every 12 hours for 4–6 weeks (if streptomycin MIC is < 2,000 µg/mL)
Vancomycin-resistant *enterococcus* (vancomycin MIC > 8 µg/mL)	Quinupristin-dalfopristin 7.5 mg/kg every 8 hours for 6 weeks

*All doses given intravenously
†Minimal inhibitory concentration of the isolate to an antibiotic
‡Vancomycin 1.0 g intravenously every 12 hours can be substituted if the patient is allergic to penicillin

MODIFIED FROM THE AMERICAN HEART ASSOCIATION AND INFECTIOUS DISEASE SOCIETY OF AMERICA RECOMMENDATIONS, REFERENCE 8

TABLE 4

Antibiotic therapy for infective endocarditis due to staphylococci and HACEK group organisms in adults with normal renal function

SETTING AND PATHOGEN	ANTIBIOTIC REGIMEN*
Patient with native valve	
Methicillin-susceptible *Staphylococcus aureus* or *S epidermidis*	Oxacillin† 2.0 g every 4 hours for 6 weeks
Methicillin-resistant *S aureus* or or *S epidermidis*	Vancomycin 1.0 g every 12 hours for 6 weeks
HACEK group organisms‡	Ceftriaxone 2.0 g every 24 hours for 4 weeks
Patient with prosthetic valve	
Methicillin-susceptible *S aureus* or *S epidermidis*	Oxacillin† 2.0 g every 4 hours for 6 weeks, plus Rifampin 300 mg by mouth every 8 hours for 6 weeks, plus Gentamicin 1.5 mg/kg every 12 hours for 2 weeks
Methicillin-resistant *S aureus* or *S epidermidis*	Vancomycin 1.0 g every 12 hours for 6 weeks, plus Rifampin 300 mg by mouth every 8 hours for 6 weeks, plus Gentamicin 1.5 mg/kg every 12 hours for 2 weeks
HACEK group organisms‡	Ceftriaxone 2.0 g every 24 hours for 6 weeks

*All doses intravenously unless otherwise stated
†Vancomycin 1.0 g intravenously every 12 hours may be substituted if the patient is allergic to penicillin
‡HACEK group includes *Haemophilus parainfluenzae, Haemophilus aphrophilus, Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens* and *Kingella kingae*

MODIFIED FROM THE AMERICAN HEART ASSOCIATION AND INFECTIOUS DISEASE SOCIETY OF AMERICA RECOMMENDATIONS, REFERENCE 8

vascular catheters, or immunosuppressive therapy. Fungi such as *Candida* and *Aspergillus* can produce large valvular vegetations. Surgical intervention with debridement and valve replacement is usually required. The diagnosis may only be established by stains, smears, and cultures of resected valves or other embolic lesions found during surgery.

MEDICAL MANAGEMENT OF INFECTIVE ENDOCARDITIS

Before the advent of antibiotics, death was the near-universal outcome for patients with infective endocarditis. Today, with appropriate antibiotic and surgical therapy, the death rate is 15% to 20%.[5]

Empiric therapy

Once a working diagnosis of infective endocarditis is established, begin aggressive intravenous antibiotic therapy directed at a likely pathogen (TABLE 2).

Targeting streptococci and enterococci

Most patients with native valve or late-onset prosthetic valve endocarditis have infection due to streptococcal species. Therapy (TABLE 3) is guided by the minimal inhibitory concentration (MIC) of the isolate to penicillin. Patients with an isolate MIC equal to or less than 0.1 µg/mL should receive intravenous penicillin or ceftriaxone alone for 4 weeks. Ceftriaxone is as effective as penicillin and more convenient for the stable patient, as it may be continued at home.[6] Patients with an MIC from 0.1 to 0.5 µg/mL should receive intravenous penicillin with gentamicin for 6 weeks. Higher doses of penicillin are recommended when the MIC is greater than 0.5 µg/mL, or the organism is an enterococcus.

Anti-streptococcal therapy is guided by the MIC

Vancomycin-resistant enterococci are a growing concern. One study[7] reported success with quinupristin-dalfopristin plus doxycycline and rifampin, but at present, options are limited and treatment is often unsuccessful.

Prosthetic valve endocarditis needs more aggressive treatment than native valve endocarditis

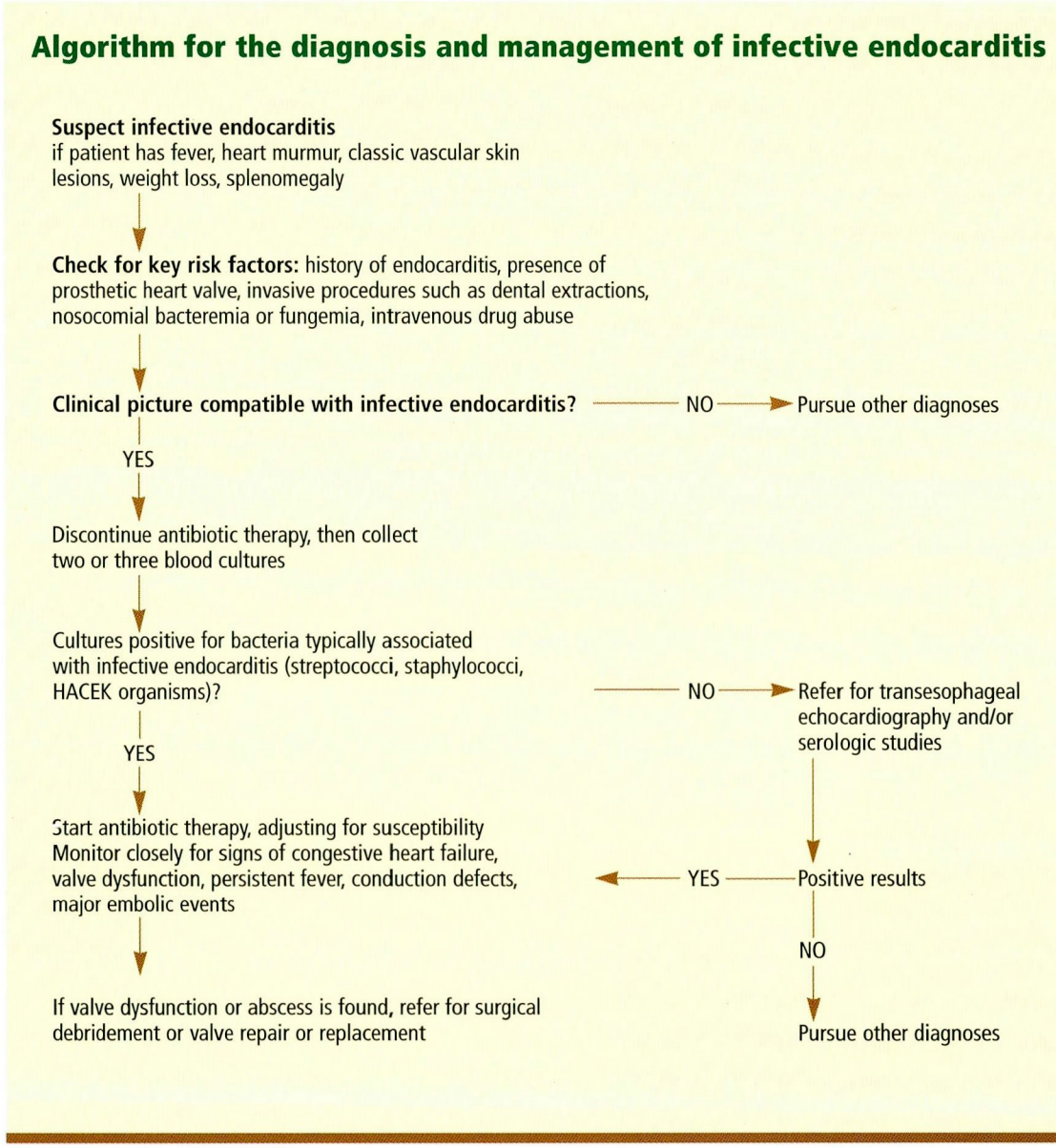


FIGURE 3

Targeting staphylococci

TABLE 4 lists recommended therapies for staphylococci and the HACEK group of fastidious gram-negative bacteria[8] (*Haemophilus* sp, *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens*, *Kingella* sp). Note that therapy for prosthetic valve endocarditis must be more intensive and prolonged because relapse and failure rates are higher than in patients with native valve endocarditis. **FIGURE 3** provides an algorithm for the overall management of infective endocarditis.

TERTIARY CARE REFERRAL AND SURGICAL MANAGEMENT

Guidelines for referral

While most patients with infective endocarditis respond to antibiotic therapy and have a smooth course with a favorable outcome, some require more intensive evaluation and treatment beyond antibiotics. For example, in patients with congestive heart failure, the heart failure may or may not be associated with valvular or cardiac dysfunction due to endocarditis, and serial transesophageal

TABLE 5

Antibiotic prophylaxis for invasive procedures

PROCEDURE	PROPHYLACTIC REGIMEN
Oral, respiratory, esophageal Dental extraction Periodontal procedures Dental implants Prophylactic cleaning Tonsillectomy, adenoidectomy Rigid bronchoscopy Esophageal dilation Sclerotherapy	Amoxicillin* 2 g by mouth 1 hour before the procedure, or 2 g intramuscularly or intravenously 1/2 hour before the procedure
Gastrointestinal, genitourinary Endoscopic retrograde cholangiopancreatography for biliary obstruction Biliary tract surgery Operations on intestinal mucosa Prostate surgery Cystoscopy Urethral dilation	Ampicillin* 2 g intramuscularly or intravenously, plus Gentamicin 1.5 mg/kg intramuscularly or intravenously 1/2 hour before the procedure

*Substitute clindamycin 600 mg by mouth or intravenously if patient is allergic to penicillin

ADAPTED FROM THE AMERICAN HEART ASSOCIATION RECOMMENDATIONS, REFERENCE 11

echocardiographic studies are needed to assess valve function during medical therapy. Such patients are best managed at a tertiary medical center with expertise in cardiology and cardiothoracic surgery, where special technology and appropriate surgery are readily available.

Surgical intervention

Surgical intervention must be available immediately when medical management fails. In the past, surgeons were reluctant to operate on patients with active infection, but we know now that restoration of cardiac function by surgery clearly improves outcome. The persistence of fever beyond several days of therapy or the development and evolution of first-degree atrioventricular block on the electrocardiogram might indicate an annular or myocardial abscess, which will also likely require surgery.[9] Even after antibiotic therapy has been completed, patients are at risk for mechanical valve dysfunction, and a significant number require corrective surgery sometime in the near future.

Neurologic complications of endocarditis

While major neurologic complications from endocarditis are rare, they are associated with significant morbidity and mortality. This is especially true when the organism is *S aureus*. Embolic strokes and encephalopathy are usually seen during the initial presentation of the illness. Brain abscesses and mycotic aneurysms are more worrisome but, fortunately, are even rarer. Mycotic aneurysms in the cerebral circulation are usually peripheral and small and resolve with antibiotic treatment. Aneurysms that are more central may bleed into the subarachnoid space or ventricles, and neurosurgical intervention is usually required. Large brain abscesses may need to be drained surgically.

In general, anticoagulation therapy should be discontinued because of the increased risk of intracranial bleeding from such neurologic complications. However, this decision depends on the type of valve, cardiac rhythm, and prior valve-related embolic events.

Surgery restores cardiac function and improves outcome

PROPHYLAXIS GUIDELINES FOR INFECTIVE ENDOCARDITIS

The need for antibiotic prophylaxis

Although antibiotic prophylaxis to prevent endocarditis has become standard practice before a number of surgical and dental procedures, there is little published evidence to suggest that it really works. A controversial case-control study[10] of dental and cardiac risk factors in 273 patients concluded that dental treatment does not seem to increase the risk for infective endocarditis and that "few cases of infective endocarditis would be preventable with antibiotic prophylaxis, even with 100% effectiveness assumed," and it called for a reconsideration of current prophylaxis policies.[10] However, the study did confirm that cardiac valvular abnormalities are clearly associated with risk for endocarditis. These abnormalities include mitral valve prolapse, congenital heart disease, rheumatic valvular heart disease, previous cardiac surgery, and a history of infective endocarditis. A known cardiac murmur was associated with a sixfold increase in risk.

We have little evidence that antibiotic prophylaxis really works

Guidelines for prophylaxis have been recently updated by the American Heart Association.[11] Diseases associated with risk for endocarditis are listed in TABLE 1, and prophylactic regimens for dental and other invasive procedures are described in TABLE 5.

Patients who undergo cardiac valve surgery should receive perioperative antibiotic prophylaxis with a first-generation or second-generation cephalosporin. For surgical centers with a high prevalence of methicillin-resistant staphylococci, vancomycin should be used instead. The antibiotic infusion must be given shortly before the skin incision, preferably within 30 minutes. The antibiotic should not be continued longer than 24 hours after the operation. Some surgeons give a preoperative dose and another dose during surgery if the operation is longer than 4 hours, and no more is given afterward.

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ADDRESS: *Thomas F. Keys, MD, Department of Infectious Disease, Cleveland Clinic Foundation, 9500 Euclid Avenue, S32, Cleveland, Ohio 44195-5066, e-mail keyst@ccf.org.*