Infected Endocarditis: Prophylaxis, Diagnosis and Management

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By Davinder S. Jassal, MD; and John M. Embil, MD, FRCPC

Case

A 58-year-old male presented to a local hospital with a two-week history of malaise, anorexia, 7 kg weight loss, night sweats and low-grade fever. The relevant aspects of his physical examination at the time of presentation were: temperature 37.9°C orally, gingivitis, several decayed teeth and a heart murmur consistent with aortic insufficiency, which the patient believed had been there in the past. Hepatosplenomegaly was absent. A set of blood cultures was obtained and the patient was provided with a one-week course of amoxicillin for a presumed dental infection. He was asked to follow up with his dentist.

The blood culture yielded Streptococcus sanguis, which was felt to be a contaminant as it was an unusual microorganism to be recovered from the blood. The patient did not go to the dentist’s office, as he did not wish to have any dental extraction prior to his son’s upcoming wedding.
Infective endocarditis is a diagnostic and therapeutic challenge to most physicians, who are not likely to see more than a few cases in their career. Although rare, infective endocarditis is a serious condition that should not be overlooked, as it has a high morbidity and mortality rate if left untreated.

The diagnosis and treatment of infective endocarditis has changed dramatically over the past 30 years. The etiology, diagnosis and treatment of infective endocarditis, including the current American College of Cardiology/ American Heart Association (ACC/AHA) guidelines for its management and prophylaxis will be reviewed in this article.

Infective Endocarditis

Infective endocarditis is the term used to describe an infection of the endocardial surface of the heart. The infection can involve the heart valves, structural abnormalities, such as atrial or ventricular septal defects, arteriovenous shunts, arterioatrial shunts, as well as infections of the aorta (i.e., coarctations).1 Infective endocarditis is a more desirable term than “bacterial endocarditis,” because other micro-organisms, such as the chlamydia, rickettsiae, mycoplasmas and fungi, also may be responsible for this condition.1 In the past, the disease was classified as acute, subacute and chronic, based on the progression of untreated disease. The acute form was a malignant condition with a rapidly progressive course, with death occurring within six weeks. The subacute form resulted in death within six weeks to three months. The chronic form caused death after > 3 months of the condition.1 The presumption of this classification was that all causes of endocarditis were bacterial, however, they are not. It has been suggested that classification based upon the infecting microorganism, may be more helpful.1 It has taken a number of years and attempts to create a suitable case definition for infective endocarditis.2,3 Although earlier definitions were reasonably specific using pathological criteria, they lacked sensitivity.2,3 Subsequently, the Duke criteria for the clinical diagnosis of infective endocarditis were established in 1994, using major and minor criteria in a manner analogous to the Jones criteria for rheumatic heart disease (Table 1).4,5

Case Cont’d

The patient completed the course of amoxicillin with resolution of the fever. One month after his initial presentation to the emergency department, he presented with similar symptoms, in addition to marked fatigue, dyspnea and left flank pain. The physical examination was unchanged. A presumptive diagnosis of pyelonephritis was made, and a complete blood count, urine and blood cultures were obtained. The patient was empirically started on parenteral ampicillin and gentamicin and admitted to the observation unit of his local hospital. The fever resolved on this regimen and the blood cultures, once again, yielded S. sanguis. The urine culture was sterile.

Further laboratory evaluation of the S. sanguis revealed the minimal inhibitory concentration for penicillin was 0.02 µg/mL. The electrocardiogram was within normal limits and a transthoracic echocardiogram revealed a bicuspid aortic valve with several small vegetations and severe aortic regurgitation.

Questions:

What is the diagnosis?
What are the warning signs?
Pathogenesis of Endocarditis

Several events must occur for infective endocarditis to manifest. An alteration in the valve surface to allow for the deposition of platelets and fibrin resulting in a sterile vegetation. Blood flow across the valve must be turbulent to allow for bacterial

### Table 1

The Duke Criteria for Diagnosis of Infective Endocarditis

<table>
<thead>
<tr>
<th>Major Criteria</th>
<th>1. <strong>Positive blood cultures for infective endocarditis:</strong></th>
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<tr>
<td></td>
<td>A. Two separate blood cultures yielding typical microorganisms for infective endocarditis, including viridans group streptococci, Streptococcus bovis, HACEK group or community-acquired Staphylococcus aureus or enterococci (without a primary focus); or</td>
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<td>B. Persistently positive blood cultures, with micro-organisms responsible for infective endocarditis, (unexplained); or</td>
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<td></td>
<td>C. Positive serology for Coxiella burnetti.</td>
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<td>2. <strong>Evidence of endocardial involvement:</strong></td>
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<td></td>
<td>A. New valvular regurgitation (worsening or changing of pre-existing murmur not sufficient); or</td>
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<td>B. Echocardiogram demonstrating any one of the following; Intracardiac vegetation, abscess, new dehiscence of a prosthetic valve (transesophageal echocardiogram) recommended in those who have prosthetic valves).</td>
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<table>
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<tr>
<th>Minor Criteria</th>
<th>1. Predisposition: predisposing heart condition or injection drug use.</th>
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<td>2. Fever: temperature &gt; 38 C.</td>
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<td>4. Immunological phenomena: glomerulonephritis, Osler's nodes, Roth's spots, and rheumatoid factor.</td>
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<td>5. Microbiological evidence: positive blood culture but does not meet major criteria as defined above.</td>
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<td></td>
<td>6. Serological evidence of active infection with organism consistent with infective endocarditis.</td>
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</table>

### Interpretation

**Definite:** Pathology or bacteriology of vegetations, or two major criteria or one major and three minor criteria, or five minor criteria.

**Possible:** One major or one minor criterion, or three minor criteria.

**Rejected:** Firm alternative diagnosis explaining evidence of infective endocarditis or resolution of infective endocarditis syndrome with antibiotic therapy for < four days or none of the above classifications applicable.

HACEK = Hemophilus spp (H parainfluenzae, H aphrophilus, H paraphrophilus), Actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens, Kingella kingae; TEE = Transesophageal echocardiography.

deposition on the altered surface. A transient bacteremia allows bacteria to colonize the vegetation, resulting in infective endocarditis. The transient bacteremia usually results from a dental, gastrointestinal, or genitourinary source. Not all cardiac lesions result in turbulent flow. Lesions with large surface areas, such as large ventricular septal defects, rarely result in bacterial endocarditis. Lesions, such as mitral valve prolapse with valvular regurgitation or mitral stenosis, however, result in significant turbulence. Although it is less common for infective endocarditis to occur in those with normal heart valves, it is certainly possible and typically seen in injection drug users, where *S. aureus* is the most likely pathogen. Infective endocarditis is more common in those with abnormal heart valves or prosthetic heart valves.

### Prosthetic valve endocarditis

often develops within the first two months after surgery, with *S. epidermidis* being the most frequent cause, followed by *S. aureus* and the gram-negative bacilli.

### The Culprits

*Streptococci* and *staphylococci* are responsible for causing 80% to 90% cases of infective endocarditis. The acute onset of infective endocarditis, which presents over days to weeks with marked clinical toxicity, is typically caused by *S. aureus*. The subacute form of endocarditis, which develops over weeks to months, is most frequently caused by the *streptococci*, *enterococci* and gram-negative bacteria, however, as noted above, other micro-organisms also may be responsible for the subacute presentation. It is important to remember that the pathogen depends on the presence of other factors, such as whether there is a native or prosthetic valve, a history of injection drug use and the use of antimicrobial therapy preceding the infection.

In cases of native valve endocarditis, viridans group *streptococci* and *S. aureus* are the most common micro-organisms. In cases of prosthetic valve endocarditis, the timing of developing the infection post-operatively is noteworthy. In prosthetic valve endocarditis developing within the first two months after surgery, *S. epidermidis* is the most frequent cause, followed by *S. aureus* and the gram-negative bacilli. The micro-organism is most frequently introduced at the time of surgery. Late onset prosthetic valve endocarditis, occurring > 2 months after surgery, is caused by the same micro-organisms as early prosthetic valve endocarditis. The only significant difference is that the proportion of *streptococci* is increased with a decrease in the frequency of recovery of gram-negative bacilli. In patients presenting with prosthetic valve endocarditis, between the third and twelfth post-operative month, a nosocomial source for the infection is most frequently presumed. In individuals presenting with prosthetic valve endocarditis > 12 months after the surgery, these are most frequently community acquired infections. In those patients where an etiological organism is not identified from blood cultures, which occurs in 2% to 5% of cases, the HACEK group of bacteria (*Haemophilus aphrophilus*, *H. paraphrophilus*, *H. parainfluenzae*, *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens* and *Kingella kingae*) must be considered. These organisms should be considered along with fungi when large vegetations are noted on echocardiography. Other uncommon micro-organisms responsible for “culture-negative” endocarditis include *Coxiella burnetti*, *Bartonella spp*, *Brucella spp*, *Chlamydia spp*, and *Legionella spp*.

### What to Look For

Establishing the diagnosis of infective endocarditis may be challenging, as this condition may present...
with non-specific manifestations (i.e., fever, chills, weight loss, anorexia and night sweats) in those with subacute infective endocarditis. Fever may be absent in those who are debilitated, who have chronic renal or liver disease, who have received previous antimicrobial therapy, or in individuals where the infecting organism may be less virulent. The microorganisms recovered from the blood culture may provide clues as to the source of the microorganism and the possible method by which it reached the heart. The recovery of viridans group *streptococci* suggests an oral source and, therefore, a history of poor dentition or recent dental work and a thorough dental evaluation would be warranted. The recovery of *S. bovis* is strongly correlated with abnormalities of the gastrointestinal tract, specifically colonic carcinomas. Native valve *S. aureus* endocarditis would suggest the microorganism was possibly introduced percutaneously, either at the time of a surgery, or, alternatively, through injection drug use. The recovery of coagulase-negative *staphylococci* within 12 months of valve replacement surgery suggests the microorganism was introduced at the time of surgery. The same holds true for *S. aureus*, however, its recovery is less frequent than the coagulase-negative *staphylococci* during the same period.

The diagnosis of infective endocarditis begins with a careful history and physical examination. When endocarditis is suspected, special attention should be given to a history of prior endocarditis, conditions leading to abnormal heart valves, such as rheumatic fever, cardiac disease (i.e., mitral valve prolapse), conditions that may predispose to a source of bacteremia (i.e., injection drug use, recent dental work, respiratory, urogenital or gastrointestinal tract instrumentation).

Clinical suspicion of infective endocarditis may be raised by the presence of both systemic and cardiac manifestations. The presence of fever and systemic manifestations, such as Osler’s nodes (red tender nodules on the pulps of the fingers), Janeway lesions (non-tender erythematous maculopapular lesions on the hands), Roth spots (fusidal vasculitic lesions), petechiae, clubbing, splinter hemorrhages, and splenomegaly are frequent manifestations of infective endocarditis. The presence of a heart murmur, which is either new or has changed, herald the cardiac stigmata of endocarditis. New onset heart failure in those with native prosthetic heart valves, particularly when combined with a changing heart murmur, fever and other constitutional symptoms, is particularly worrisome for infective endocarditis. A thorough neurological examination should be performed to detect evidence of neurological injury secondary to systemic emboli, which may involve the middle cerebral artery in 15% to 20% of patients with native and prosthetic valve endocarditis.

**Diagnosing Endocarditis**

To establish the diagnosis of infective endocarditis, a combination of clinical, laboratory and echocardiographic findings are used. Ideally, all patients in whom the diagnosis of infective endocarditis is suspected, must have blood cultures obtained, in addition to baseline complete blood cell counts with differential, serum electrolytes, urinalysis (to evaluate for microscopic hematuria), erythrocyte sedimentation rate, C-reactive protein level and rheumatoid factor (Table 1). Standardized criteria for evaluating patients with infective endocarditis were proposed by the Duke University Group. These criteria integrate clinical laboratory and echocardiographic findings, therefore, stratifying patients into those who have a high, intermediate and low likelihood of having infective endocarditis (Table 1).

In addition to the laboratory investigations suggested above, an electrocardiogram is necessary to rule out conduction abnormalities and to establish a baseline, should a complication develop later in the management of the disease. If a new conduction abnormality develops, a thorough search for a myocardial abscess involving the valve rings (impinging upon the conduction system) must be undertaken. A chest radiograph may delineate the presence of congestive heart failure (CHF), and in the setting of right-sided endocarditis, septic pulmonary emboli and infiltrates with cavitation may be evident.
The most important laboratory investigation for establishing the diagnosis of infective endocarditis is the blood culture. Bacteremia is usually continuous and low grade. Blood cultures should be performed even if the patient has received, or is receiving, antimicrobial therapy at the time of presentation.\textsuperscript{1} Three sets of blood cultures, from separate sites, within the first 24 hours, is the usual method for establishing the bacteriological diagnosis.\textsuperscript{1,10} In patients who are hemodynamically unstable, three sets of blood cultures should be obtained in five- to 10-minute intervals, followed by empiric antimicrobial therapy.\textsuperscript{6} There is no additional diagnostic yield of obtaining more than three blood cultures, provided the patient was not previously treated with antibiotics.

Echocardiography serves two important roles in evaluating and managing patients with sus-
Endocarditis

Table 2 Cont’d

Antimicrobial Therapy for Infective Endocarditis Cont’d

Prosthetic Valve Endocarditis caused by the \textit{Staphylococcus}i

\textbf{Methicillin Susceptible}

- Cloxacillin 2 g IV q 4h for ≥ six weeks and rifampin 300 mg po 1 8 h for ≥ six weeks with gentamicin sulfate\(a\) 1 mg /kg IV/IM q 8 h for the first two weeks.

\textbf{Methicillin Resistant}

- Vancomycin 30 mg/kg per 24 IV in 2 equal divided doses q 12 h for six weeks (not to exceed 2 g/24 h) with rifampin 300 mg po q 8 h for six weeks with gentamicin sulfate\(a\) 1 mg/kg IV/IM q 8 h for the first two weeks.

Endocarditis caused by HACEK micro-organisms\(i\)

- Ceftriaxone sodium 2 g OD IV/IM for four weeks;\(k\) or

- Ampicillin sodium 12 g/24 h IV either continuously or q 4 h for four weeks with gentamicin sulfate 1 mg/kg IM/IV q 8 h.

\(a\) Gentamicin: When gentamicin is used, monitoring of drug levels as well as urea and creatinine is necessary.

\(b\) Vancomycin: Is an alternative in those who are penicillin allergic, if vancomycin is used, monitoring drug levels, as well as urea and creatinine, is necessary.

\(c\) Cefazolin may be substituted in those who are penicillin allergic (without immediate type hypersensitivity).

\(d\) If vancomycin is used, the addition of gentamicin is not necessary.

\(e\) The \textit{enterococci} are relatively resistant to penicillin, however, penicillin, ampicillin, or vancomycin in combination with aminoglycoside provide a synergistic bactericidal effect.

\(f\) Four weeks of therapy is recommended for those with symptoms or < three months duration, while six weeks of therapy is recommended for those with symptoms of > three months duration.

\(g\) In injection drug users with right-sided \textit{staphylococcal} endocarditis, a shorter treatment course may be successful.\(7\)

\(h\) Gentamicin used for synergy during the first three to five days of therapy may lead to a more rapid clearing of bacteremia, as well as decreasing damage to the heart valves and minimizing extra cardiac abscess formation.

\(i\) \textit{Staphylococcus: S. aureus} of coagulase negative \textit{staphylococci}, \textit{S. epidermidis} and other species. Complete identification and susceptibility testing must be undertaken to allow for selection of appropriate therapy.

\(j\) The duration of therapy for native valve endocarditis is four weeks, and six weeks for prosthetic valve endocarditis.

\(k\) Other third-generation cephalosporins may be substituted.


pected infective endocarditis. The first involves assisting in the diagnosis of the condition through imaging vegetations, as it is one of the major criteria as stipulated by the Duke Criteria (Table 1). Additionally, echocardiography is useful in detecting and characterizing the hemodynamic consequences of infection. The sensitivity for detection of vegetations by transthoracic echocardiogram (TTE) is 60% and increases to 95% using transesophageal echocardiography (TEE).\(16\) According to the American College of Cardiology/American Heart Association (ACC/AHA) guidelines in 1998, a TTE is used initially in individuals with native heart valves, whereas TEE should be used as the primary diagnostic imaging of choice in patients with prosthetic valves.\(16\)
Treatment

Optimal therapy for infective endocarditis includes the use of culture-directed parenteral bactericidal agents over a prolonged period (typically six weeks) to effectively eradicate the causative microorganisms. The duration of therapy varies according to the microorganism that is isolated.

The following factors influence the type and duration of therapy for infective endocarditis:

- Micro-organism and antimicrobial susceptibility;
- Native versus prosthetic valve;
- Right-sided versus left-sided endocarditis;
- Drug allergy history; and
- Patient compliance and social factors.

Table 2 illustrates the preferred treatment regimens for the more common causative microorganisms, as summarized in the ACC/AHA statement. Anticoagulant therapy has not been shown to prevent systemic embolization, and may lead to an increased risk of intracerebral hemorrhage. In patients with native-valve endocarditis, anticoagulation should be used only if there is a clear indication independent of infective endocarditis. Meanwhile, in those with involvement of a prosthetic heart valve, anticoagulation should be continued in accordance to their pre-existing anticoagulation regimen. If central nervous system embolization with hemorrhage has occurred, it may be prudent to temporarily discontinue the anticoagulant therapy.

When is Surgery Indicated?

Abbreviated courses of treatment have been proposed for those with right-sided endocarditis caused by S. aureus. This is particularly helpful in the management of injection drug users whose compliance with prolonged hospitalizations may be suboptimal and who may not be ideal candidates for home parenteral antimicrobial therapy programs. Appropriate timing of surgical intervention for infective endocarditis remains a sub-

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**Table 3**

**Indications for Endocarditis**

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<thead>
<tr>
<th>Low risk cardiac conditions not requiring endocarditis prophylaxis</th>
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<tr>
<td>• Cardiac pacemaker or implantable defibrillator</td>
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<tr>
<td>• Previous rheumatic fever or Kawasaki disease without valvular dysfunction</td>
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<tr>
<td>• Isolated mitral valve prolapse without mitral regurgitation</td>
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<tr>
<td>• Patent ductus arteriosus</td>
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<tr>
<td>• Surgically repaired ventricular septal defect</td>
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<tr>
<td>• Atrial septal defect</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Moderate/high risk cardiac conditions requiring endocarditis prophylaxis</th>
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</thead>
<tbody>
<tr>
<td>• Prosthetic heart valves</td>
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<tr>
<td>• Prior history of infective endocarditis</td>
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<tr>
<td>• Surgically constructed systemic or pulmonary conduit</td>
</tr>
<tr>
<td>• Hypertrophic cardiomyopathy</td>
</tr>
<tr>
<td>• Mitral valve prolapse with regurgitation and/or valve thickening</td>
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<tr>
<td>• Cyanotic congenital heart defects</td>
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</table>

ject of intense debate. Surgery, and the timing thereof, is dependent upon the cardiac and systemic complications caused by the infection, the micro-organism’s virulence and the response to antimicrobial therapy. Some authors believe that patients who demonstrate any cardiovascular compromise should proceed to surgery regardless of the duration of antimicrobial therapy. Infective endocarditis may cause a number of cardiac and extracardiac complications, including:

- Valve abscess;
- Valvular incompetence;
- CHF; and
- Embolic stroke and systemic embolization.

The indications for surgery in infective endocarditis (native valve and/or prosthetic valve) recently have been reviewed by the AHA/ACC task force and are as follows:

- Acute mitral or aortic regurgitation with intractable CHF;
- More than one significant systemic embolic event;
- Hemodynamically significant valvular dysfunction demonstrated by echocardiography;
- Ineffective antimicrobial therapy (i.e., in fungal endocarditis or Q-fever);
- Mycotic aneurysms;
- Perivalvular or endocardial abscesses;
- Ongoing systemic infection, despite a prolonged period of antimicrobial therapy (seven to 10 days); and
- Early prosthetic valve endocarditis (less than two months after surgery) or prosthetic valve endocarditis with antibiotic-resistant pathogens.

**Other Diagnoses**

When patients with presumed endocarditis are not improving with empiric antimicrobial therapy, an alternative diagnosis should be sought. Medical conditions that may mimic infective endocarditis include atrial myxoma, systemic lupus erythematosus with marantic endocarditis, acute rheumatic fever and carcinoid syndrome.

**Who Needs Prophylaxis?**

Although it is possible to treat both native and prosthetic valve endocarditis, the mortality for both of these conditions remains high resulting from either hemodynamic compromise or central nervous system embolization. It is, therefore, critical to prevent bacterial endocarditis from occurring. Despite the absence of randomized controlled clinical trials evaluating the utility of prophylaxis for preventing bacterial endocarditis, many recommendations have been based on the consensus of expert opinions in the field. Endocarditis prophylaxis is not recommended for individuals with low-risk cardiac conditions as listed in Table 3. Moderate to high-risk cardiac conditions for which antimicrobial prophylaxis is indicated prior to invasive dental or surgical procedures are listed in Table 3.

The antimicrobial regimen suggested for infective endocarditis prophylaxis depends on the clinical procedure to be performed, as the microflora varies in different regions of the body. The prophylaxis should be given before procedures in which bacteremias are likely with organisms that cause endocarditis. For dental, oral or upper respiratory tract procedures, amoxicillin 2 g orally, given one hour prior to the procedure is the antibiotic of choice. In individuals allergic to penicillin, alternatives include oral clindamycin 600 mg, cephalexin 2 g, or azithromycin 500 mg one hour prior to the procedure. For genitourinary or gastrointestinal procedures, ampicillin 2 g parenterally and gentamicin 1.5 mg/kg (not to exceed 120 mg), 30 minutes prior to the procedure, followed by either oral amoxicillin 1 g or parenteral (intramuscular, intravenous), ampicillin 1 g, six hours later. Vancomycin (1 g IV) may be used as an alternative in the event of a penicillin allergy.

**Summary**

Infective endocarditis continues to be a condition associated with high morbidity and mortality. With prompt diagnosis and treatment the cure rate approaches 80%, averting major complications, such as CHF and embolic strokes. The goal, howev-
Endocarditis

er, is to prevent bacterial endocarditis from occurring initially. Prophylaxis is essential for the prevention of bacterial endocarditis and its role cannot be overemphasized. If the patient becomes hemodynamically unstable or demonstrates any of the manifestations noted in the “When Is Surgery Indicated?” section, it may be prudent to seek consultation with a cardiovascular surgeon.

Discussion of Case

The patient in the case history was diagnosed with endocarditis. He was discharged home on once-daily parenteral ceftriaxone 2 g to complete a four-week course of therapy. The decayed teeth were extracted and he underwent aortic valve replacement at the end of the parenteral antibiotic course. He remains well four years later. Prior to any dental work, he takes oral amoxicillin 2 g, one hour before the procedure.

The unusual micro-organisms initially recovered in the blood culture should have served as a warning sign that a more malignant process than gingivitis was occurring. The patient’s initial therapy for the gingivitis likely led to a transient arrest and later relapse.

References


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