Infective Endocarditis

Series Editor: A. Maziar Zafari, MD, PhD, FACC
Assistant Professor of Medicine, Division of Cardiology, Department of Medicine, Emory University School of Medicine, Atlanta, GA; Director, CCU, Atlanta Veterans Affairs Medical Center, Decatur, GA

Contributors: Safwat Gassis, MD
Cardiology Fellow, Division of Cardiology, Department of Medicine, Emory University School of Medicine, Atlanta, GA

Stamatios Lerakis, MD, FACC, FASE, FCCP
Assistant Professor of Medicine, Division of Cardiology, Department of Medicine, Emory University School of Medicine, Atlanta, GA; Co-Director, Echocardiography Lab, Grady Memorial Hospital, Atlanta, GA

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Cover Illustration by Stacey Caiazzo
I. INTRODUCTION

Infective endocarditis (IE) has been recognized as a separate clinical entity for more than 100 years. Despite advances in both the diagnosis and treatment of this challenging disease, the morbidity and mortality associated with IE remain high. IE is defined as the presence of an active infection on the endocardium that usually involves 1 or more valve surfaces. The infection is not necessarily confined to the endocardial surface but can involve other cardiac structures such as myocardium, chordae, pericardium, and walls of adjacent blood vessels as well as endovascular devices. Accurate and early diagnosis is crucial because prompt management can have profound consequences on clinical outcome. However, the diagnosis of endocarditis can be challenging as signs and symptoms may be subtle and vague. The evolution of diagnostic criteria, along with developments in laboratory tests and advances in imaging technology, has substantially enhanced the diagnosis and, equally important, has helped prevent prolonged and unnecessary medical or surgical therapy.

II. EPIDEMIOLOGY

An estimated 10,000 to 15,000 new cases of endocarditis are diagnosed annually in the United States.\(^1\) The true incidence of IE has been difficult to ascertain because the diagnostic criteria have changed throughout the past 3 decades. Nonetheless, over this time the incidence has been increasing, with survey estimates ranging from 1.7 to 6.2 cases per 100,000 persons annually.\(^2\) This increase is probably related to the growing numbers of elderly in the population and the occurrence of age-related degenerative valvular disease among them as well as to increases in the number of injection drug abusers, nosocomial infections with resistant organisms, immunocompromised hosts, and prosthetic implantations. Rheumatic heart disease (RHD) historically has been a significant predisposing factor for developing IE (and is still so in developing countries) but now is related to less than 20% of cases.\(^2\) A report evaluating endocarditis cases between 1938 and 1967 showed RHD to be present in 39% of cases, whereas a recent report showed an RHD rate of 6%.\(^3,4\)

There are a number of risk factors for developing IE. Structural heart disease accounts for approximately three quarters of IE cases.\(^2,3\) The most significant risk factor for right-sided IE is injection drug abuse, although left-sided IE is equally prevalent in this high-risk group. Breaks in colonized mucosal surfaces confers risk for IE with certain organisms. *Streptococcus bovis* IE, for example, is highly associated with presence of colonic lesions due to inflammatory bowel disease, polyps, or malignancy. Nosocomial IE frequently is related to indwelling vascular devices or focal infections (eg, respiratory tract or an infected surgical site). Although more than 100,000 heart valves are implanted in the United States annually, IE of prosthetic valves is infrequent, comprising only 7% of cases in one report.\(^5\) Prosthetic-valve endocarditis (PVE) within the first 2 months after implantation (early PVE) is usually caused by nosocomial staphylococcal infections, while PVE occurring more than 1 year after implantation (late PVE) is usually caused by the organisms that cause community-acquired native valve IE.\(^6\) PVE occurs in 1% to 4% of valve recipients in the first year after implantation, and this rate increases by 1% per year thereafter.\(^5\) The type of prosthetic valve does not appear to alter the risk of developing IE.

III. PATHOGENESIS AND MICROBIOLOGY

Damage to the endocardial lining in the heart must be present for an infection to establish a vegetative lesion on a valvular surface because the endothelial lining is normally highly resistant to infection.\(^7\) Damage to the endocardial surface can arise from many etiologies, either congenital or acquired, and damage frequently occurs as a result of abnormal blood jets from high to low pressure regions inside the heart (eg, valvular disease that creates areas of turbulent flow). Patients with ventricular septal defects develop vegetative lesions on the right ventricular side of the defect.\(^8\) Patients with aortic regurgitation who develop IE tend to form vegetative lesions on the chordae
or the body of the anterior mitral valve leaflet. Similarly, patients with mitral regurgitation can develop MacCalmum’s patches, which are vegetative lesions on the atrial wall opposite the mitral orifice. Marantic endocarditis is a rare finding in patients with systemic lupus and is characterized by sterile vegetative lesions on valve surfaces that may predispose these patients to IE.

Following localized damage, a nidus rich in platelets and fibrin attaches to the endocardial lining, forming a focus of nonbacterial thrombotic endocarditis (NBTE). Although this platelet-fibrin nidus is initially sterile, it confers an ideal medium for adherence of bacteria or fungi. After a transient bacteremia, the microorganisms adhere to the fibrin-platelet nidus. As the NBTE becomes colonized with the microorganisms, the aggregate attracts more platelets and fibrin to be deposited on its surface. With time, the structure forms an enlarging vegetative lesion attached at its base to the damaged endocardium or valve surface. The vegetative lesion continually sheds microbes into the bloodstream, resulting in a persistent bacteremia or fungemia.

Only bacteria that possess mechanisms to adhere to platelet-fibrin aggregates are capable of producing IE. Organisms such as staphylococci, streptococci, enterococci, and pseudomonads produce extracellular matrices that facilitate this interaction and thus are common causes of IE. In contrast, organisms that do not adhere to valvular surfaces, such as Escherichia coli, rarely cause endocarditis. Known pathogens that cause IE include Legionella, Coxiella, Bartonella, and Brucella species, the HACEK group (Haemophilus, Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens, and Kingella kingae), and certain fungi.

Streptococci, followed by staphylococci, are the most common causes of bacterial endocarditis (Figure 1). *Staphylococcus aureus* is an extremely virulent organism due to its ability to adhere avidly to endocardial tissue and shield itself from host defenses by secretion of an extensive extracellular matrix. The infection is associated with significant valvular destruction, especially when left-sided heart structures are involved. Most strains of *S. aureus* have developed resistance to penicillins, and a substantial proportion also are resistant to β-lactamase-resistant antibiotics, such as nafcillin (the agent of choice against penicillin-susceptible strains). Moreover, moderate vancomycin resistance is emerging, too.

Viridans streptococci, commonly found in the oropharynx, cause between 30% and 65% of cases of IE. Enterococci, which commonly colonize the genitourinary and gastrointestinal tracts, cause approximately 10% to 20% of cases of IE. The 2 most common species are *Enterococcus faecalis* and *Enterococcus fecium*, both of which are frequently resistant to penicillins and are rapidly developing resistance to vancomycin and aminoglycosides. *Streptococcus agalactiae* (Group B strep) is associated with neonatal IE because the organism frequently colonizes the mother’s genitourinary tract. *Streptococcus pneumoniae*, in contrast, is a rare cause of IE but can cause a rapidly progressive and severe infection with significant morbidity and mortality. Coagulase-negative staphylococci (CNS) colonize the skin in most persons but are an infrequent cause of IE except in patients with abnormal valves, artificial endovascular devices, prosthetic valves, or indwelling catheters. The infection is usually indolent and in most cases causes minor valve destruction. It is recognized as the most common cause of early PVE. An exception to this group is *Staphylococcus lugdunensis*, a community-acquired organism that has recently been found to cause severe valve destruction, frequently requiring valve surgery.

### IV. Diagnosis

**CLINICAL FINDINGS AND ROUTINE WORKUP**

Acute endocarditis, which is frequently caused by *Staphylococcus aureus*, is typically associated with high fevers, severe illness, infectious embolization, valvular insufficiency, and heart failure. Subacute endocarditis,
however, is a more indolent process with less rapidly progressive symptoms; it is frequently associated with peripheral stigmata such as clubbing, immunologic vascular phenomena, or peripheral embolization. Prolonged infection results in immune-complex deposition in various organs. For example, it causes glomerulonephritis that is often manifested as micro- or macrohematuria. Some of the classic immune-mediated findings include Janeway lesions (hemorrhagic macules on the palms and soles), Osler’s nodes (painful nodules on the finger and toes), and Roth’s spots (retinal hemorrhage with central pallor). Embolization can present as splinter hemorrhages (red/brown, nonblanching, linear petechiae under the nail beds) or infective embolization of distal organs. These findings may not be present early in the disease, but rather vague symptoms, such as low-grade fever, weight loss, fatigue, night sweats, and anorexia, may predominate.

The most important step in the diagnosis of IE is acquiring adequate blood culture samples. At least 3 sets of blood cultures should be obtained with at least 1 hour between the first and last set. Ideally, all samples should be obtained prior to the initiation of antibiotics. If the patient’s condition allows, antimicrobial therapy should be withheld until the causative organism is identified because therapy is largely dictated by the microbiologic nature of the vegetative lesion and its antimicrobial sensitivity profile. Additional cultures can be obtained as dictated by the patient’s response to therapy or if the initial cultures are inconclusive.

All patients require a chest radiograph, which may define the source of infection or show evidence of embolization from right-sided IE. All patients should also have an electrocardiogram (ECG), which may show conduction abnormalities, raising suspicion for perivalvular extension of the infection. Other radiologic imaging is not recommended as part of the routine evaluation for IE unless indicated by the patient’s presentation.

**BLOOD CULTURES**

The development of advanced culture, isolation, and diagnostic techniques coupled with a better understanding of the growth requirements of certain fastidious pathogens has helped researchers identify most of the organisms that cause IE. Members of the HACEK group, for example, may require blood cultures incubated for over 3 weeks before growth can be detected. It is important to notify the laboratory when endocarditis is suspected so that steps can be taken to support growth of fastidious or slow-growing organisms; such steps include prolonged incubation of the blood specimens, subculturing in enriched media, or incubation in carbon dioxide-enriched atmospheres. Culture-negative IE is usually the result of inability to isolate the culprit organism rather than true aseptic endocarditis; however, it is encountered in less than 6% of cases currently. The most common cause of culture-negative IE is administration of antimicrobials before all the blood culture specimens have been obtained. Polymerase chain reaction and serological techniques have aided in the diagnosis of fastidious organisms, such as *Bartonella* and *Chlamydia* species or *Coxiella burnetii* (causative agent of Q fever).

**DUKE CRITERIA**

To assist in the evaluation of IE, a number of criteria have been developed that incorporate clinical, laboratory, pathologic, and imaging modalities to determine the likelihood of infection. The 1981 von Reyn criteria relied mostly on pathologic specimens obtained at surgery or autopsy to define cases of definite endocarditis. Since many patients with IE are treated successfully without surgery, definite endocarditis was difficult to diagnose based on these criteria. The original Duke criteria for diagnosing IE incorporated echocardiography, clinical, and laboratory data and showed greater diagnostic yield. The criteria have been validated in numerous subsequent studies and have shown good sensitivity (72%–90%), specificity (77%–89%), and negative predictive value (> 98%) (Table 1). The original Duke criteria continue to be modified for better sensitivity and diagnostic yield. Bacteremia caused by the streptococci *Streptococcus viridans* and *S. bovis* or members of the HACEK group as well as community-acquired *Staphylococcus aureus* and enterococcal infections are given extra weight as these usually portend the presence of IE. Since IE is characterized by persistent bacteremia, the frequency of positive blood cultures is an important part of the diagnosis. Findings that carry diagnostic significance but are not specific were included in the minor criteria.

**ECHOCARDIOGRAPHY**

Echocardiography is an important tool for the diagnosis and treatment of IE. The presence of a vegetative lesion, prosthetic valve dehiscence, perianular abscess, or new valvular insufficiency are key features that can be identified by echocardiography. The decision of whether to use transthoracic (TTE) or transesophageal echocardiography (TEE) as the initial imaging modality depends on the pretest probability of the presence of IE. TTE is a noninvasive test that can be performed rapidly and thus often is performed initially. In patients with moderate to high suspicion for IE in whom suspicious lesions are found on TTE, TEE frequently is performed.
to better characterize a vegetative lesion and to screen for periannular complications. TEE also would be performed if the TTE was technically inadequate, which occurs in approximately 20% of patients. Because IE is a clinical diagnosis, TEE should always be considered, especially when adequate TTE shows no signs of IE but the suspicion remains high. Occasionally in patients with low pretest probability of IE, an adequately performed TTE may be sufficient to screen for vegetative lesions or valvular dysfunction.\(^\text{17}\) TTE has been shown to have a specificity of approximately 98% but a sensitivity of less than 60% for detecting vegetative lesions.\(^\text{18}\) TTE, however, can visualize right-sided lesions quite accurately because of the proximity of the transducer to the anteriorly located right heart structures. TTE is not recommended as a screening tool in every patient with a fever or positive blood culture when the probability is low. If there is moderate to high clinical suspicion, a TTE alone may not be sufficient to rule out IE or its complications, regardless of the quality of the study.

When the probability of IE is high (eg, *Staphylococcus aureus* bacteremia with recent injection drug abuse), it may be more cost-effective to proceed with TEE as the initial modality. The study is generally safe but is more invasive and carries a small risk of dental, pharyngeal, or esophageal injury as well sedation-related complications. TEE offers higher resolution images from a different perspective (viewing the heart from the posterior side), making it an ideal study for visualizing the left-sided structures. TEE is the modality of choice for suspected

### Table 1. Duke Criteria for Diagnosis of Infective Endocarditis (IE)

**Definite IE**

Pathologic criteria

1. Microorganism: demonstrated by culture or histologic examination of a vegetative lesion, a vegetative lesion that has embolized, or an intracardiac abscess specimen; or
2. Pathologic lesions: vegetative lesion or intracardiac abscess confirmed by histological examination showing active endocarditis

Clinical criteria

1. 2 major criteria; or
2. 1 major criterion and 3 minor criteria; or
3. 5 minor criteria

**Possible IE**

Findings consistent with IE that fall short of “definite” IE but not “rejected”

**Rejected**

1. Firm alternate diagnosis explaining manifestations of infective endocarditis; or
2. Resolution of infective endocarditis syndrome with antibiotic therapy ≤ 4 days or
3. No pathologic evidence of IE at surgery or autopsy, with antibiotic therapy for ≤ 4 days

**Definitions**

Major criteria

1. Blood culture positive for IE
   a. Typical microorganisms consistent with IE isolated from 2 separate blood cultures:
   2) Community-acquired *S. aureus* or enterococci, in the absence of a primary focus
   b. Microorganisms consistent with IE isolated from persistently positive blood cultures, defined as:
      1) At least 2 positive cultures of blood samples drawn > 12 hr apart; or
      2) All of 3 or a majority of ≥ 4 separate cultures (with first and last sample at least 1 hr apart)
2. Evidence of endocardial involvement
   a. Echocardiogram positive for IE defined as follows:
      1) Oscillating intracardiac mass on valve or supporting structures, or in the path of regurgitant jets, or on implanted material in the absence of an alternate anatomic explanation; or
      2) Abscess; or
   b. New valvular regurgitation (worsening of preexisting murmur not sufficient)

Minor criteria

1. Predisposing heart condition or injection drug use
2. Fever > 38°C
3. Vascular or immunologic phenomena: major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages or Janeway lesions
4. Microbiologic or echocardiographic evidence consistent with IE but not meeting major criteria

prosthetic mitral valve endocarditis, while TTE and TEE are complementary for suspected prosthetic aortic valve endocarditis. TEE offers higher sensitivity (86%–94%) and good specificity (88%–100%) for the detection and evaluation of vegetative lesions as well as superior detection rates of perivalvular complications of IE (76%–100% sensitivity, 94% specificity). With a negative TTE and TEE, the negative predictive value for endocarditis is 95%. In the presence of high clinical suspicion for IE, even a negative TEE cannot completely rule out IE, especially if the patient’s condition does not improve. In such cases, a repeat TEE 1 to 2 weeks later may be warranted.

V. COMPLICATIONS

The most common serious sequelae of IE are congestive heart failure (CHF) and central nervous system embolization with resultant infarction or hemorrhage. Vegetative lesions forming on valvular structures cause mostly valvular insufficiency and rarely stenosis. Acute valvular insufficiency of the aortic valve causes more severe CHF symptoms and rapidly progressive pulmonary edema than does mitral insufficiency. Valve perforation is a serious sequelae of IE that confers substantially increased mortality (25% versus 5% mortality in 1 study) and CHF requiring urgent surgery (70% versus 5%). A vegetative lesion also may cause destruction of valvular support structures, such as the annular ring or chordae. Rupture of the chordae can result in flail valve leaflets and acute CHF symptoms.

Infection extending to the perivalvular region can cause periannular abscesses in 10% to 40% of cases of native valve endocarditis. This complication makes the infection more difficult to treat and confers a worse prognosis. PVE frequently is associated with periannular invasion and valve dehiscence. Involvement of the conduction system can cause conduction delay or block. The infection also may extend into the myocardium, causing aneurysms or diverticula to form. Fistula formation involving adjacent structures can ensue, resulting in aortic-atrial or aortic-pericardial fistulae and subsequent tamponade.

Neurologic complications arise in 20% to 40% of patients with IE and are more frequent in patients with left-sided lesions and with *Staphylococcus aureus*, candidal, *Staphylococcus lugdunensis*, and HACEK group infection. Almost 65% of emboli involve the central nervous system. The risk of embolization in some studies has been attributed to the vegetative lesion size: in 1 series of 105 patients, vegetative lesions larger than 1 cm were more likely to embolize, but other studies have failed to show such correlation. Vegetative lesions on the mitral valve are more likely to cause systemic embolization than those on the aortic valve (25% versus 10% in 1 report). Duration of antimicrobial therapy, however, has been shown to decrease risk of embolization. The incidence of embolism was reduced from 13 per 1000 patient-days during the first week to 1.2 per 1000 after 2 weeks of therapy. Septic emboli to distant small blood vessels may result in microbial invasion of the arterial wall elements and formation of mycotic aneurysms. Vessel branching points are particularly susceptible due to increased turbulence at these sites. The clinical presentation of intracerebral mycotic aneurysms is variable—from localized headache or focal neurologic signs and symptoms if minor leakage occurs to fatal intracranial hemorrhage with rupture. The gold standard for evaluation is contrast angiography, which can usually detect a leaking aneurysm in time for surgical correction. Imaging with contrast computed tomography (CT) or magnetic resonance imaging is an appropriate alternative.

Vegetative lesions also may embolize to various organs, causing metastatic infections or end-organ infarction, such as mucocutaneous lesions, glomerulonephritis, meningitis, or encephalitis. Embolization to the spleen is a well-recognized complication that can cause splenic infarction in approximately 40% of IE cases. In a small subset, splenic infarcts may become secondarily infected and form splenic abscesses. These abscesses should be suspected in a patient with persistent fever or bacteremia despite prolonged antimicrobial therapy, especially when symptoms of diaphragmatic irritation are present (eg, pleurisy, abdominal or back tenderness, pleural effusion, shoulder pain, or intractable hiccups). Treatment often requires splenectomy to eradicate this persistent infection.

VI. TREATMENT

ANTIMICROBIAL THERAPY AND INDICATIONS FOR SURGERY

Antibiotic susceptibility testing is crucial for adequate medical therapy because decisions regarding choice of drug, duration of therapy, and need for surgical intervention are often predicated on microbiologic data. The general principle of antimicrobial therapy is prolonged parenteral therapy to produce high serum concentrations; combination drug regimens are often used for synergistic effects. In native valve endocarditis caused by most penicillin-susceptible strains of streptococci, a penicillin or third-generation cephalosporin for 4 weeks is adequate. Organisms with relative resistance to...
Penicillin, enterococcal infections, or PVE require combined therapy with an aminoglycoside. Methicillin-susceptible strains of staphylococci can be treated with a β-lactamase-resistant penicillin, such as nafcillin, in combination with an aminoglycoside. Staphylococcal strains resistant to methicillin (eg, methicillin-resistant S. aureus) require treatment with vancomycin in addition to an aminoglycoside. PVE with staphylococci often requires a longer duration of therapy as well as a third agent, such as rifampin, for adequate synergistic coverage. PVE frequently involves perivalvular tissue, and combined medical and surgical treatment is needed in many cases. IE caused by members of the HACEK group can be treated with a 4-week course of ceftriaxone. Bartonella species also can be treated with an aminoglycoside and/or a fluoroquinolone; however, since the infection can be difficult to eradicate even with surgery, some centers advocate treatment with doxycycline for 3 to 4 years until antibody titers drop below 1:100. Recommendations for treatment of culture-negative endocarditis include vancomycin with an aminoglycoside (with or without a penicillin or third-generation cephalosporin) as well as amphotericin with or without flucytosine if fungal IE is suspected. Treatment of other less common causes of IE is guided by microbiologic data.

Indications for surgery are listed in Table 2 for native and prosthetic valve IE.

Anticoagulation does not appear to reduce the risk of embolization in patients with IE, and it may actually increase the risk of intracranial hemorrhage in these patients, especially if a mycotic aneurysm is present. Unless there is a strong preexisting indication for anticoagulation (eg, mechanical valve prosthesis), anticoagulation is not recommended.

**PROPHYLAXIS AND PREVENTION**

Invasive procedures involving penetration of the protective barrier of colonized mucosa increase the risk of developing IE and are the basis for antimicrobial prophylaxis. The risk of developing IE also varies with the patient’s preexisting cardiac condition. Table 3 lists the risk categories for patients with certain predisposing factors. In general, most dental procedures, especially those involving periodontal manipulation or deep cleaning, require prophylaxis. Additionally, many gastrointestinal, genitourinary, and respiratory tract procedures that involve penetration of the mucosa require prophylaxis. Some authorities recommend antibiotics in the high-risk group even if the mucosa of the gastrointestinal, genitourinary and respiratory tracts will not be penetrated during the procedure. Tables 4 and 5 summarize the recommended prophylaxis regimens.

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**VII. CASE PRESENTATIONS**

**PATIENT 1**

**Presentation**

A 61-year-old homeless man with a history of hypertension and mild renal insufficiency presents with a 3-month history of dyspnea on exertion. One week prior, he started taking antibiotics for possible bronchitis. He denies injection drug abuse or alcohol intake. He reports worsening symptoms of orthopnea and paroxysmal nocturnal dyspnea for the past 3 months. The patient appears unkempt. Blood pressure is 178/74 mm Hg, pulse is 98 bpm, breathing is 18 breaths/min, and temperature is 38°C. Neurologic examination is normal. He has 12 cm of jugular venous distention (JVD). Cardiac examination reveals a laterally displaced point of maximal impulse, mild precordial heave, normal S1, loud and split S2, present S3, and no S4. There is a 3/6 systolic ejection murmur at the apex and a decrescendo diastolic murmur at the lower left sternal border. Lung examination shows bibasilar rales. Abdominal examination is normal. He has moderate lower extremity pitting edema. There are no petechiae or other lesions on his skin.

- **What are the first steps in the evaluation of this patient?**
  
  A) Hospital admission, obtain 3 sets of blood cultures, TTE, empiric intravenous (IV) antibiotics until culture results are back, start warfarin to prevent embolization if a vegetative lesion is present
  
  B) Hospital admission, TEE, blood cultures, withhold antibiotics until culture results are back, start warfarin
  
  C) Immediate IV antibiotics after first set of blood cultures, initiate heparin for anticoagulation
  
  D) Hospital admission, TTE, 3 sets of blood cultures 1 hour apart, withhold antibiotics and repeat cultures in 2 to 4 days off antibiotics if initial sets are still negative and clinical status is stable, do not initiate anticoagulation

**Discussion**

The correct answer is D. This patient has clinical evidence of valvular heart disease with new or decompensated CHF that warrants inpatient assessment and treatment. The pretest probability is moderate for IE, and a TTE should be sought first as it is noninvasive and fast. Anticoagulation should be withheld unless the patient has a preexisting strong indication for anticoagulation, in
which case warfarin would be substituted for IV heparin. His bronchitis symptoms may have been the initial presentation of his CHF, and with the low-grade fever and cough, the diagnosis of IE is often obscured. In a patient who is clinically stable, withholding antibiotics until confirmation of the organism is advised. Clinical judgment is required to decide when to initiate antibiotics while waiting for culture results.

**Course and Further Workup**

TTE evaluation findings are suspicious but not diagnostic of ascending aortic dissection. There is a mobile 1-cm mass on the ventricular side of the right coronary cusp of the aortic valve. Moderately severe aortic insufficiency is also present. The patient’s ejection fraction is reduced to 35%. Three sets of blood cultures are drawn. The patient continues to have low-grade fever to 38.1°C, but his CHF symptoms improve with diuretics and afterload reduction.

- **What is the next step in evaluation?**
  A) TEE, start IV antibiotics when cultures are positive or if there is any clinical deterioration or evidence of embolization
  B) Refer for aortic angiography and start IV antibiotics and routine heart failure medications

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**Table 2. Recommendations for Surgery for Native Valve and Prosthetic Valve Endocarditis**

<table>
<thead>
<tr>
<th>Indication</th>
<th>Class*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Native valve endocarditis</strong></td>
<td></td>
</tr>
<tr>
<td>Acute aortic regurgitation (AR) or mitral regurgitation with heart failure</td>
<td>I</td>
</tr>
<tr>
<td>Acute AR with tachycardia and early closure of the mitral valve</td>
<td>I</td>
</tr>
<tr>
<td>Fungal endocarditis</td>
<td>I</td>
</tr>
<tr>
<td>Evidence of annular or aortic abscess, sinus or aortic true or false aneurysm</td>
<td>I</td>
</tr>
<tr>
<td>Evidence of valve dysfunction and persistent infection after a prolonged period (7–10 days) of appropriate antibiotic therapy as indicated by presence of fever, leukocytosis, and bacteremia, provided that there are no noncardiac causes for infection</td>
<td>I</td>
</tr>
<tr>
<td>Recurrent emboli after appropriate antibiotic therapy</td>
<td>IIa</td>
</tr>
<tr>
<td>Infection with gram-negative organisms or organisms with a poor response to antibiotics in patients with evidence of valve dysfunction</td>
<td>IIa</td>
</tr>
<tr>
<td>Mobile vegetative lesions &gt; 10 mm</td>
<td>IIIb</td>
</tr>
<tr>
<td>Early infections of the mitral valve that can likely be repaired</td>
<td>III</td>
</tr>
<tr>
<td>Persistent fever and leukocytosis with negative blood cultures</td>
<td>III</td>
</tr>
<tr>
<td><strong>Prosthetic valve endocarditis</strong></td>
<td></td>
</tr>
<tr>
<td>Early prosthetic valve endocarditis (within first 2 months of surgery)</td>
<td>I</td>
</tr>
<tr>
<td>Heart failure with prosthetic valve dysfunction</td>
<td>I</td>
</tr>
<tr>
<td>Fungal endocarditis</td>
<td>I</td>
</tr>
<tr>
<td>Staphylococcal endocarditis not responding to antibiotic therapy</td>
<td>I</td>
</tr>
<tr>
<td>Evidence of paravalvular leak, annular or aortic abscess, sinus aortic true or false aneurysm, fistula formation, or new-onset conduction disturbance</td>
<td>I</td>
</tr>
<tr>
<td>Infection with gram-negative organisms with a poor response to antibiotics</td>
<td>I</td>
</tr>
<tr>
<td>Persistent bacteremia after a prolonged course (7 to 10 days) of appropriate antibiotic therapy without noncardiac causes for bacteremia</td>
<td>IIa</td>
</tr>
<tr>
<td>Recurrent peripheral embolus despite therapy</td>
<td>IIa</td>
</tr>
<tr>
<td>Vegetative lesion of any size on or near the prosthesis</td>
<td>IIb</td>
</tr>
</tbody>
</table>

*Class refers to strength of evidence as outlined by the American College of Cardiology/American Heart Association guidelines.

C) Contrast CT to evaluate dissection, start broad spectrum IV antibiotics
D) TEE, start oral antibiotics as dictated by culture results

Discussion

The correct answer is A. TEE is needed to further evaluate for a vegetative lesion, perivalvular complications, surgically constructed systemic-pulmonary shunts or conduits.

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**Table 3. Recommendations for Endocarditis Prophylaxis**

<table>
<thead>
<tr>
<th>Indication</th>
<th>Class*</th>
</tr>
</thead>
<tbody>
<tr>
<td>High risk</td>
<td>I</td>
</tr>
<tr>
<td>Prosthetic heart valves, including bioprosthetic homograft and allograft valves</td>
<td></td>
</tr>
<tr>
<td>Previous bacterial endocarditis</td>
<td></td>
</tr>
<tr>
<td>Complex cyanotic congenital heart disease (eg, single ventricle states, transposition of the great arteries, tetralogy of Fallot)</td>
<td></td>
</tr>
<tr>
<td>Surgically constructed systemic-pulmonary shunts or conduits</td>
<td></td>
</tr>
<tr>
<td>Moderate risk</td>
<td>II</td>
</tr>
<tr>
<td>Most other congenital cardiac malformations (other than above or below)</td>
<td></td>
</tr>
<tr>
<td>Acquired valvular dysfunction (eg, rheumatic heart disease)</td>
<td></td>
</tr>
<tr>
<td>Hypertrophic cardiomyopathy</td>
<td></td>
</tr>
<tr>
<td>MVP with auscultatory evidence of valvular regurgitation and/or thickened leaflets</td>
<td></td>
</tr>
<tr>
<td>Low or negligible risk†</td>
<td>III</td>
</tr>
<tr>
<td>Isolated secundum atrial septal defect</td>
<td></td>
</tr>
<tr>
<td>Surgical repair of atrial septal defect, ventricular septal defect, or patent ductus arteriosus (without residual &gt; 6 months)</td>
<td></td>
</tr>
<tr>
<td>Previous coronary artery bypass graft surgery</td>
<td></td>
</tr>
<tr>
<td>MVP without valvular regurgitation</td>
<td></td>
</tr>
<tr>
<td>Physiological, functional, or innocent heart murmurs</td>
<td></td>
</tr>
<tr>
<td>Previous Kawasaki disease without valvular dysfunction</td>
<td></td>
</tr>
<tr>
<td>Cardiac pacemakers and implanted defibrillators</td>
<td></td>
</tr>
</tbody>
</table>

**Table 4. Endocarditis Prophylaxis Regimens for Dental, Oral, Respiratory, or Esophageal Procedures in Adults**

<table>
<thead>
<tr>
<th>Situation</th>
<th>Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard general prophylaxis</td>
<td>Amoxicillin 2 g orally 1 hr before procedure</td>
</tr>
<tr>
<td>Unable to take oral medication</td>
<td>Ampicillin 2 g IM/IV 30 min before procedure</td>
</tr>
<tr>
<td>Penicillin allergic</td>
<td>Clindamycin 600 mg orally 1 hr before procedure</td>
</tr>
<tr>
<td>Penicillin allergic and unable to take oral medications</td>
<td>Cephalexin* or cefadroxil* 2 g orally 1 hr before procedure</td>
</tr>
<tr>
<td>Penicillin allergic</td>
<td>Azithromycin or clarithromycin 500 mg orally 1 hr before procedure</td>
</tr>
<tr>
<td>Penicillin OR cefazolin* 600 mg IV 30 min before procedure</td>
<td></td>
</tr>
</tbody>
</table>

**Table 5. Endocarditis Prophylaxis Regimens for Genitourinary/Gastrointestinal (Excluding Esophageal) Procedures**

<table>
<thead>
<tr>
<th>Situation</th>
<th>Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-risk</td>
<td>Ampicillin 2 g IM/IV plus gentamicin 1.5 mg/kg IV (max 120 mg) within 30 min of start of procedure. 6 hr later; ampicillin 1 g IM/IV or amoxicillin 1g orally</td>
</tr>
<tr>
<td>High-risk, allergic to penicillin</td>
<td>Vancomycin 1 g IV over 1–2 hr plus gentamicin 1.5 mg/kg IV/IM (max 120 mg) within 30 min of start of procedure</td>
</tr>
<tr>
<td>Moderate-risk</td>
<td>Amoxicillin 2 g orally 1 hr before procedure or ampicillin 2 g IV/IM within 30 min of start of procedure</td>
</tr>
<tr>
<td>Moderate-risk, allergic to penicillin</td>
<td>Vancomycin 1 g IV over 1–2 hr within 30 min of start of procedure</td>
</tr>
</tbody>
</table>


**MVP = mitral valve prolapse.**

*Class refers to strength of evidence as outlined by the American College of Cardiology/American Heart Association guidelines.

†Endocarditis prophylaxis not recommended.

IM = intramuscularly; IV = intravenous.
and valve integrity. TEE also would evaluate for aortic dissection in this case. The choice of antibiotic is dictated by culture and sensitivity profile results. The antibiotic should be started as soon as the diagnosis is made because risk of embolization is inversely related to duration of therapy.

**Patient Course**

The third set of blood cultures grows *Staphylococcus aureus* that is sensitive to methicillin. TEE confirms severe aortic regurgitation and a 1.5-cm aortic valve vegetative lesion on the aortic side of the right coronary cusp (Figure 2). No evidence of dissection, perivalvular extension, or abscess is found. He has intermittent low-grade temperatures and notes occasional left flank pain.

- **The most appropriate next step is:**
  A) Start vancomycin and aminoglycoside combination therapy for 4-week course; if CHF symptoms worsen, refer for valve surgery
  B) Start nafcillin and aminoglycoside combination therapy and surgical evaluation for valve replacement surgery after abdominal imaging
  C) Because the patient has a sensitive organism and is nontoxic appearing, an oral antibiotic regimen (a penicillin) can be started with close outpatient follow-up.
  D) Start vancomycin and rifampin combination therapy and repeat TEE at regular intervals to confirm resolution of vegetative lesion

**Discussion**

The correct answer is B. The patient has an organism known to cause IE and that is associated with high incidence of CHF, relapse, and mortality if treated with medical therapy alone. Presence of a vegetative lesion of the same or smaller size after successful medical treatment is found in about 60% of patients and does not confer a worse prognosis. Although repeat echocardiography can aid in assessing embolic risk or decision about surgery in some cases (if vegetative lesion size has increased), this patient already has indications for surgery and repeat imaging is of little benefit. Evaluation for metastatic infections is important when clinically suspected because they should be treated before valve surgery to reduce risk of relapse. In patient 1, abdominal CT showed no renal, hepatic, or splenic infarctions or abscesses, which are frequent complications of IE.

Surgery in patients with overt CHF or hemodynamic compromise should not be delayed until completion of the antibiotic course as these 2 factors carry the highest mortality risk. The major indication for delaying surgery is a cerebral event (embolic stroke or intracranial hemorrhage). Studies have shown that waiting 2 to 3 weeks after an embolic stroke and 4 weeks for hemorrhagic stroke is optimal to reduce postoperative neurologic impairment. The most important risk factor for relapse is a positive culture from a surgical specimen with organisms such as *Staphylococcus aureus*, Enterobacteriaceae, *Bartonella* species, or fungi. A complete antibiotic regimen is warranted even if no perivalvular complications are present, especially in staphylococcal IE.

**PATIENT 2**

**Presentation**

A 37-year-old woman with renal failure from complications of systemic lupus who has required hemodialysis for the past 2 months is admitted to the hospital because...
of fever, worsening shortness of breath, and productive cough. The patient notes unintentional weight loss and night sweats for 4 weeks prior to her hospitalization. On day 5, the patient becomes acutely ill and short of breath with minimal exertion. Blood pressure is 150/70 mm Hg, pulse is 115 bpm, respirations are 28 breaths/min, and temperature is 39.4°C. She has no focal neurologic deficits. JVD is 8 cm with a prominent V-wave. Her dialysis catheter site appears clean. Cardiac examination reveals tachycardia, a loud S2, and a 3/6 systolic murmur at the left lower sternal border. Lung examination reveals scattered rhonchi and evidence of consolidation at the right lower lung field. She has no peripheral stigmata of embolization but shows +1 lower extremity edema. White blood cell count is 16,000/mm³, and her chemistry profile reflects her renal failure but is otherwise unremarkable. A chest radiograph reveals lung opacity in the right lower lobe abutting the pleura. A ventilation/perfusion scans shows moderate probability for pulmonary embolism (PE).

- What is the most appropriate next step in diagnosis?
  A) Repeat blood cultures, withhold antibiotics until an organism is obtained, perform TTE
  B) Repeat blood cultures, start broad spectrum empiric antibiotics, perform TTE
  C) Start anticoagulation for suspected PE since fever, leukocytosis, and respiratory symptoms are likely from an embolism and infection is unlikely because the catheter was recently replaced and cultures are negative
  D) Perform urgent TEE, start empiric antibiotics, remove catheter

Discussion

The correct answer is B. In an acutely ill patient with signs of sepsis, it is not prudent to withhold antibiotics pending culture results. A broad antibiotic regimen was initiated after initial blood and catheter tip cultures were obtained to cover nosocomial and catheter related organisms. This patient had developed either an embolism from a clot or mass on her dialysis catheter or septic PE from right-sided endocarditis with secondary pneumonia. The persistence of signs of infection despite removal of the catheter 5 days earlier raises suspicion of endocarditis. A TTE as the initial modality is warranted to view right-sided structures and evaluate for valvular abnormality. TEE in this patient may worsen her already compromised respiratory status. Anticoagulation is not recommended for IE without a preexisting indication for anticoagulation as it increases likelihood of embolization and intracranial bleeding.

Patient Course

The patient is started on broad spectrum antibiotics. A TTE reveals moderate to severe tricuspid valve regurgitation and a possible tricuspid mass (Figure 3). TEE performed after the patient’s respiratory condition improved also shows a large mobile mass in the high right atrium extending from the superior vena cava (Figure 4). Blood cultures grow CNS. A chest CT reveals multiple areas of consolidation in both lung fields with cavitations.

- What is the most appropriate next step in management?
  A) Surgical resection of the remaining vegetative lesions
B) At least 6 weeks IV antibiotic regimen that includes IV vancomycin, follow-up TTE to examine for any progression of tricuspid regurgitation or right-sided heart failure
C) Tricuspid valve replacement and a 6-week course of vancomycin

Case Resolution

The correct answer is B. The patient is treated with antibiotics and followed for signs of right-sided heart failure. She continues to improve and a follow-up TEE evaluation 2 weeks later shows a marked decrease in the size of the vegetative lesions. Her lower extremity edema resolves 2 weeks later. A follow-up TTE 3 months after treatment shows improvement of the tricuspid regurgitation and no evidence of right ventricular failure. Coagulase-negative staphylococcus infections typically cause indolent infections and are often treated nonsurgically. Given that the infection improved with antibiotics and there was no further evidence for worsening heart failure or embolization, nonsurgical management was appropriate in this situation.

REFERENCES


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