CASE PRESENTATION

A 62-year-old functional but cachectic male, who was able to ambulate with a walker, presented to the emergency department (ED) with a temperature of 102.3 degrees F, and neck and low back pain. The patient reported having had subjective fever and chills at home starting 1 week prior to the hospital visit. He also reported generalized fatigue, occasional shortness of breath, and a 20-pound weight loss over 2 weeks. There were no reported changes in mental status. The patient did have a recent history of having had a left carotid sinus takedown with removal of the optic nerve in order to treat invasive aspergillosis infection of the left orbital apex 1 month previously. This infection had extended into the left sinuses and left optic nerve. During the surgery, which did have a good outcome with no immediate complications, a central line had been placed for venous access.

Investigation

The patient’s past medical history included coronary artery disease, a cerebrovascular accident in 1985 with no residual deficits, depression, non-insulin–dependent diabetes mellitus, chronic atrial fibrillation, and hypertension. Medications taken were glipizide, fosinopril, warfarin, and sertraline. On physical examination there were no meningeal signs. He denied chest pain or shortness of breath. The exam was remarkable for closed left eyelid, which the patient could not open, with no erythema, swelling, or drainage of the surrounding tissue. A healing left neck scar was evident with well-granulated suture sites. The patient also had a laceration extending from the left frontal to the left side of the scalp, with staples still in place; the wound was clean and dry. A Hickman catheter was attached at the right upper chest. The heart had a regularly irregular rhythm, with distant heart sounds and a 2/6 systolic ejection murmur, which was new by history. There was no clubbing, cyanosis, or edema in the lower extremities, and no Kernig or Brudzinski signs.

White blood cell count was slightly elevated to 11.2/mm3 with a normal differential. Hemoglobin and hematocrit were both decreased to 10 g/dL and 31.5%, respectively. Complete metabolic panel, including liver function tests and albumin, were within acceptable ranges.

Management and diagnosis

The patient was empirically started on ceftriaxone sodium and vancomycin, and a lumbar puncture was performed to rule out meningitis. Blood cultures were taken and a urinalysis was performed. After admission to the hospital, a two-dimensional echocardiography...
was done and revealed an ejection fraction of 45%. An abscess of perforation on the posterior leaflet of the mitral valve was also seen on echocardiography, and it was recognized that this could have represented a vegetation as well. In addition to severe mitral regurgitation, the test showed elevated right-sided pressures and mild mitral valve prolapse. A transesophageal echocardiogram (TEE) was scheduled, and when done confirmed severe mitral regurgitation, pulmonary vein flow reversal, a small vegetation and perforation of the posterior leaflet of the mitral valve, and a small patent foramen ovale.

Blood cultures initially showed gram-positive coci that subsequently grew *Staphylococcus aureus*, confirming the diagnosis of an endocarditis on the mitral valve, thought to be due to contamination by the Hickman catheter.

**GENERAL ASPECTS OF INFECTIVE ENDOCARDITIS**

Infective endocarditis (IE) is an infection of the endocardium of the heart involving significant disease processes of the valvular portions. Infection accumulates at a localized site of the endocardium that is damaged by a process such as a foreign body or jets of turbulent blood flow. Bacteria from various sources, such as the skin, gastrointestinal (GI), respiratory, or urinary tracts, enter and are carried through the bloodstream, eventually reaching this diminutive site of trauma, and lodging there. This area eventually forms a large, friable, and easily detachable vegetation that can form single or multiple foci at a particular heart valve. This vegetation is a tangled mass of bacteria, or fungi (rare, in immunocompromised patients), mixed with fibrin and aggregated platelets. A vegetation is typically localized near the lines of closure of the valvular leaflets, on one or more valves, and elicits an inflammatory reaction. Development of this on a valve can contribute to various complications and forms of pathology, including destruction of the heart valve itself.\(^1\)

Infective endocarditis affects only 2-6 people per 100,000 annually. Approximately 50% of cases are in patients over 50 years of age.\(^2\) Those 65 years of age or older are at nearly nine times higher risk than those who are younger, and the incidence is twice as high in men as in women. About 75% of cases in children and young adults are due to congenital cardiac defects.

Infective endocarditis can have an impact on normal as well as diseased heart valves. The mitral valve is affected three times as often as the aortic valve.

**TYPES OF INFECTIVE ENDOCARDITIS AND THEIR ETIOLOGIES**

Infective endocarditis is usually community-acquired. There are two classifications of the disease based on severity and course, although a particular disease case can have overlap. These two categories are acute bacterial endocarditis (ABE) and subacute bacterial endocarditis (SBE).

In general, ABE is extremely virulent, mainly striking normal tricuspid or pulmonic valves and contributing to a more dire course and prognosis. Most cases are caused by *S. aureus* (about 50%) that is usually sensitive to methicillin (methicillin-sensitive *S. aureus* [MSSA]).\(^3\) It is often secondary to an infection originating somewhere else in the body.\(^1\) For instance, bacterial endocarditis typically occurs as a result of the introduction of a vascular catheter or due to intravenous drug abuse (IVDA). Symptoms may appear within 3-10 days, and illness is of such a severe degree that death can occur within days to weeks.\(^1,^4\) Gram-negative bacilli are also culprits in ABE.

The occurrence of IVDA as an etiological cause of IE is between 2% and 5% of cases of endocarditis per year. In addition to *S. aureus*, specific bacteria often involved include *Streptococcus faecalis*, *Pseudomonas*
*aeruginosa*, and *Candida* and *Bacillus* species. Intra-
venous drug abusers are susceptible to recurrent endo-
carditis as well. Interestingly, IE in HIV-infected
patients who are not drug abusers is not common.3

Subacute bacterial endocarditis typically impacts the
mitral valve. The primary organisms include the strep-
tococcus species (50-60%) of SBE cases. These include
*Streptococcus viridans* (over 50% of SBE cases), *Strepto-
coccus bovis* (25%), groups B and G streptococcus, and
*Streptococcus mutans* due to dental caries. The occur-
rence of SBE is regarded as being due to a chronic con-
dition, suggesting a predisposing valvular abnormality
or deformity such as congenital or rheumatic heart dis-
ease. Organisms tend to be of a less virulent type than
in ABE, and mortality may take more than 6 months
and up to 1 year to occur. Other causative agents of
SBE include: group D streptococci (enterococci from
the GI or genitourinary [GU] tracts), representing 15% of
cases; *Clostridium septicum* (related to GI malignan-
cies and polyps); rarely fungi (*Candida, Aspergillus*); and
the HACEK organisms (an acronym for *Haemophilus
aphrophilus*, *Actinobacillus actinomycetemcomitans*, Car-
diobacterium hominis, *Eikenella corrodens*, and *Kingella
ingae*; they account for 3% of SBE cases). This latter
group of gram-negative organisms are fastidious, grow-
ing slowly only in media enriched with carbon dioxide.
They commonly occur on prosthetic valves (less than
5% of patients with IE). It should be noted that at some
point nearly every type of bacterial species has been
found to have caused IE, including *Neisseria gonorr-
hoeae*, *Chlamydia*, and even *Propionibacterium acnes*.5
Symptoms, which are often nonspecific, tend to be low
grade, and may even be absent in the elderly.

Rheumatic fever as a predisposing cause of IE occurs
in the young. Because of effective treatment and mon-
itoring, the incidence of this as an etiology is decreas-
ing. Other factors associated with an increased risk for
endocarditis include congenital and valvular diseases.

These include a history of endocarditis, structural
defects such as an atrial septal defect, an ongoing shunt
of blood flow (as from the aorta to the pulmonary
artery), or the presence of a prosthetic valve. The intro-
duction of intravenous lines and catheters facilitate bac-
terial introduction into the bloodstream. Bicuspid aor-
tic valve and valvular stenosis due to degenerative
calcification are other risk factors. Use of contaminated
needles by IVDAs and the presence of some sexually
transmitted diseases can elevate risk as well.6

The overall mortality rate of IE is between 20% and
40%, even with the use of appropriate antibiotics, and
ranges between 2% and 20% for all types of IE when
considered together.7-9 The relapse rate is 14% or lower.

Eighty percent of cases are due to infection with streptococci or staphylococci. *S. viridans* and *S. aureus* are the organisms that primarily infect native
valves. *Staphylococcus epidermidis* IE typically occurs
in patients with a valvular prosthesis.

*Enterococcus faecalis* causes anywhere between 5% and 20% of all IE cases, and approximately 90% of
cases specifically due to enterococcal infection.10,11 It
occurs mostly in older men over 60 years of age. The
primary sources of infection are the GU and the GI
systems (GI source includes 3-27% of cases, including
diseases, procedures, and surgery of the biliary tract or
large bowel; colon cancer and polyps may predispose
to IE’s occurrence). Treatment regimens include
administration of ampicillin; imipenem and van-
comycin may also be added.12 The relapse rate follow-
ing standard therapy ranges between 0% and 14%.10

The HACEK organisms are a recognized but
unusual cause of IE. Along with fever and a new or
changing heart murmur, splenomegaly is also a com-
mon symptom of infection with this group of bacte-
rria13 (Table I14). They typically colonize the orophar-
ynx and spread to the vascular system after trauma (ie,
dental work) or local infection (ie, poor dentition).
Studies have shown that heart valve endocarditis, whether native or prosthetic, due to HACEK organisms is associated with a favorable prognosis. The HACEK organisms are susceptible to beta-lactam antibiotics. Usual treatment regimens include ampicillin combined with an aminoglycoside, or a third-generation cephalosporin alone. Antibiotic treatment is ineffective if the causative agent of the endocarditis is fungal. Surgery is then necessary, typically done after a regimen of amphotericin B has been initiated.

EVALUATION OF INFECTIVE ENDOCARDITIS

Signs of IE include Roth’s spots (white lesions with a rim of hemorrhage in the eye fundus) and Osler’s nodes (tender skin lesions in the pads of the fingers). Janeway lesions (nontender macules of hemorrhagic lesions on the palms and soles) are usually seen in ABE. The digits may also be clubbed. Symptoms are nonspecific and encompass the patient having fever, fatigue, and malaise—all to a worse degree in ABE than in SBE. Aspects of heart failure may be evident, and there may be a new heart murmur on auscultation due to the turbulent blood flow around the vegetation, indicating a larger and/or fragmenting focus of infection (Table I).

The diagnostic work-up of IE includes obtaining at least three blood cultures from different sites before empiric antibiotic therapy is initiated. Quantitative susceptibility testing is then done to determine the responsible organism, and the antibiotic regimen is then adjusted accordingly for specific coverage. Five to ten percent of all patients diagnosed with IE are culture-negative. This is usually due to a patient having received a sufficient amount of antibiotic treatment prior to evaluation (usually within 1-2 weeks) to eradicate enough of the offending organism that it cannot be grown in culture, despite the patient not having received a full course of the recommended medication regimen nor having available bacterial sensitivities. Culture-negative endocarditis may also be due to the infecting organism being a fungus or one of the HACEK bacteria, which require special media to grow on. An electrocardiogram (EKG) may reveal P-R prolongation due to the infection extending into the conducting system of the heart. The two-dimensional echocardiography may detect the vegetation and turbulent flow of blood through the chambers of the heart, but it is only 55% sensitive. In addition, a false-pos-

**TABLE I**

<table>
<thead>
<tr>
<th>Manifestations</th>
<th>Percentage of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical</strong></td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>80-90</td>
</tr>
<tr>
<td>Murmur</td>
<td>80-85</td>
</tr>
<tr>
<td>Chills and sweats</td>
<td>40-75</td>
</tr>
<tr>
<td>Anorexia, weight loss, malaise</td>
<td>25-50</td>
</tr>
<tr>
<td>Arterial emboli</td>
<td>20-40</td>
</tr>
<tr>
<td>Neurologic manifestations</td>
<td>20-40</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>15-50</td>
</tr>
<tr>
<td>Arthralgia or myalgia</td>
<td>15-30</td>
</tr>
<tr>
<td>New or worsened regurgitant murmur</td>
<td>10-40</td>
</tr>
<tr>
<td>Petechiae</td>
<td>10-40</td>
</tr>
<tr>
<td>Clubbing of fingertips</td>
<td>10-20</td>
</tr>
<tr>
<td>Back pain</td>
<td>7-15</td>
</tr>
<tr>
<td>Peripheral manifestations (Osler’s nodes, subungal hemorrhages, Janeway lesions, Roth’s spots)</td>
<td>2-15</td>
</tr>
<tr>
<td><strong>Laboratory</strong></td>
<td></td>
</tr>
<tr>
<td>Elevated erythrocyte sedimentation rate</td>
<td>&gt; 90</td>
</tr>
<tr>
<td>Anemia</td>
<td>70-90</td>
</tr>
<tr>
<td>Circulating immune complexes</td>
<td>65-100</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>50-65</td>
</tr>
<tr>
<td>Rheumatoid factor</td>
<td>50</td>
</tr>
<tr>
<td>Microscopic hematuria</td>
<td>30-50</td>
</tr>
<tr>
<td>Leukocytosis</td>
<td>20-30</td>
</tr>
<tr>
<td>Decreased serum complement level</td>
<td>5-40</td>
</tr>
</tbody>
</table>

This table was reprinted from an article originally published in *Federal Practitioner* 2001;18(11):46-54. © 2001 by Federal Practitioner, Quadrant HealthCom Inc. It appears here with the permission of Quadrant HealthCom Inc. No part of this table may be reproduced without the prior written permission of Quadrant HealthCom Inc.
itive reading may occur due to an atrial myxoma, myxomatous valvular degeneration, or chordae tendineae rupture. The gold standard diagnostic test is the TEE, which is able to detect over 90% of vegetations. It is also 95% sensitive for the occurrence of abscesses.

**DETERMINATION OF THE SEVERITY OF INFECTIVE ENDOCARDITIS**

The Duke criteria utilize various aspects of a clinical work-up to diagnose endocarditis and include two major and six minor criteria, designating three diagnostic categories for the presence of IE: definite, possible, and rejected. Definitive IE is present if: both major criteria are present, one major and three minor criteria are present, five minor criteria are present, or if there is confirmation of microorganisms in vegetations, emboli, or abscesses. The criteria are listed in Table II.

People at moderate or high risk for developing endocarditis (ie, those already with valvular disease) should be prophylactically treated with antibiotics prior to certain surgical and dental procedures. This preemptive strategy is intended to reduce the bacterial load that could enter the circulation as a result of manipulation of such invasive instrumentation in the body; a process that may lead to focal bacterial accumulation on a heart valve or damaged site, thereby facilitating the development of endocarditis. Common at-risk procedures range from dental cleanings to endoscopic interventions of the GI, GU, and respiratory tracts (Table III). Getting a tattoo and body piercing may also need to be treated prophylactically if certain risk factors exist.

Prophylactic treatment includes administering amoxicillin 2 g by mouth 1 hour before a procedure, or an intramuscular (IM) or IV dose of penicillin 30 minutes prior to the procedure. Gentamicin may be added in high-risk patients, such as those with a prosthetic valve or a pulmonary-systemic shunt contributing to cyanotic heart disease. Patients at moderate risk include those with a history of rheumatic heart disease, mitral valve prolapse, or hypertrophic cardiomyopathy. A macrolide such as azithromycin may be given if the patient is already on a monthly penicillin regimen to reduce the risk from a penicillin-resistant bacteria. Erythromycin, vancomycin, or clindamycin may be used in patients with a penicillin allergy. Recent recommendations do not suggest giving antibiotics after a procedure, unless the patient is at high risk and is undergoing a GI or GU procedure.

**COMPLICATIONS OF INFECTIVE ENDOCARDITIS**

A common complication of endocarditis is heart failure. It may present as the sudden worsening of left ventricular function, which may lead to cardiogenic shock. The mechanism of action varies and includes: valve leaflet perforation, chordae tendineae rupture, and valve orifice occlusion by the vegetation itself. Because of a nonfunctional leaky mitral valve, blood may flow backward into the lungs, causing congestive heart failure. Mortality is 13-44%. The degree of heart failure is regarded as the most important prognostic factor in IE outcome.

Another complication of IE is embolization, which can occur in anywhere between 2% and 70% of cases. This occurs when a fragment of the vegetation breaks away from the source and enters the systemic or pulmonary circulation. These emboli often travel to the brain (resulting in possible ischemic stroke, or less serious central nervous system [CNS] sequelae such as headaches or confusion), eye, spleen, and GI system. Portions of the vegetation on the heart valve may break off, embolizing into the bloodstream and initiating bacteremia and/or septicemia. They may separate from the tricuspid valve and seed the lungs, initiating the formation of cavitary abscesses or infiltrates on chest x-ray, as well as seeding to the spleen (causing left
upper quadrant pain). Emboli may also reach the kidney and cause renal failure with an antecedent focal glomerulonephritis. This usually occurs in patients with right-sided endocarditis and negative blood cultures.\textsuperscript{17} Uremia and hematuria may occur due to damage to the glomeruli. Continuous shedding of septic emboli from the vegetation into the bloodstream may occur, with clearance of the bacteria by the reticuloendothelial system (ie, liver, spleen).\textsuperscript{18}

Other complications include valvular destruction, abscess formation, myocardial infarctions, arrhythmias (including atrial fibrillation), suppurative pericarditis, perforation and/or ulceration of the valve cusps with or without erosions, as well as arterial aneurysms. This latter occurrence (also called a mycotic aneurysm) has an associated increase in the risk of hemorrhage when anticoagulants are used. The CNS effects can involve transient ischemic attacks, altered mental status, visual disturbances, neuropathy, and seizures secondary to emboli. Arthritis or spondylodiskitis (involvement of intervertebral disks) are extremely rare complications of IE.\textsuperscript{19}

**TREATMENT OF INFECTIVE ENDOCARDITIS**

Early diagnosis and treatment have a significant impact on reducing mortality for patients with IE, especially the elderly. Overall prognosis and eventual outcome depends on timely initiation of therapy and diagnosis, type of organism, its virulence, its susceptibility to the antimicrobial regimen, the size and friability of the vegetation, and the extent of valvular
recommended due to the toxic effects of ototoxicity. Nephrotoxicity and neurotoxicity may also occur as side effects, and great care must be taken in administering an aminoglycoside to elderly patients. Their levels, as well as those of vancomycin, need to be monitored regularly. Like gentamicin, vancomycin can damage cranial nerve eight, leading to ototoxicity. Vancomycin is the treatment of choice for patients with IE due to *S. epidermidis*. The gold standard regimen for the HACEK organisms is a third-generation cephalosporin, such as ceftriaxone. Vegetations seen on twodimensional echocardiography may take up to 3 years after clinical resolution to dissipate to the point that they are no longer detectable.

During most of the treatment time, the antibiotics are given intravenously. Additional blood cultures are taken to confirm that the antibiotic regimen is effective. If severe valvular damage has occurred, cardiovascular surgeons tend to wait for the course of treatment to be completed in order to clear any underlying bacteremia before performing a valve repair. However, if it appears that the antibiotics are not working due to persistent infection, or the patient’s overall condition is deteriorating rapidly, surgery may need to be undertaken sooner than intended in order to replace the affected valve. For instance, mortality rates are high in elderly patients with infections of the aortic valve, and surgery is often required expeditiously (Table IV).

### Indications for Endocarditis Prophylaxis

#### Required Procedures
- Dental extractions
- Teeth cleaning
- Tonsillectomy
- Adenoidectomy
- Esophageal sclerotherapy
- Dilation of esophageal stricture
- Endoscopic retrograde cholangiography
- Biliary tract surgery
- Prostate surgery
- Cystoscopy
- Urethral dilation
- Patients with a prosthetic valve
- Prior history of infective endocarditis
- Cardiac defects: ventricular septal defect, coarctation of aorta
- Mitral stenosis
- Aortic regurgitation
- Arteriovenous malformations

#### Optional Procedures for High-Risk Patients
- Gastrointestinal endoscopy
- Sigmoidoscopy
- Transesophageal echocardiography
- Bronchoscopy
- Vaginal delivery

### Other Medical Aspects of Endocarditis

As stated earlier, 90-95% of IE cases return with positive blood cultures. The other 10% are diagnosed as
having culture-negative endocarditis. Blood cultures are negative often because the patient has previously received inadequate treatments of an antibiotic. This definition also applies if a suspected organism is slow-growing or fastidious, requires special culture media to incubate, or is difficult to cultivate. This includes fungi and nutritionally deficient streptococci. The differential for culture-negative endocarditis should also include atrial myxoma, multiple pulmonary emboli, acute rheumatic fever, and nonbacterial thrombotic or marantic endocarditis.21 Depending on the clinical situation, a standard or modified treatment regimen can be instituted. Some cases of culture-negative endocarditis are confirmed only at autopsy or with valve replacement.

Endocarditis complicates between 1% and 5% of valve replacements. Studies have shown that mortality rates for IE affecting prosthetic valves within two months of valve replacement are between 40% and 50%; they are 10-20% in cases with a later onset. Patients can acquire IE after valve replacement has been done for various reasons, such as repair of mitral regurgitation unassociated with endocarditis. Infective endocarditis status after such surgeries is considered either early or late, depending on when the infection occurs and if bacteremia is sustained. Early disease occurs within 2 months of surgery and is typically due to *S. aureus*, *S. epidermidis*, gram-negative bacilli, *Candida* species, and other opportunistic infections.4 Late disease occurs more than 2 months after surgery; infecting organisms during this period involve the same groups as those that infect native valves. After placement of a prosthetic valve, the most common etiologic species causing bacterial endocarditis are coagulase-negative staphylococci, which also frequently cause false-positive blood cultures arising from skin flora.22

Other less common types of endocarditis include: (1) the noninfective, verrucous endocarditis in patients with systemic lupus erythematosus (SLE), referred to as Libman-Sacks endocarditis,23 and (2) nonbacterial (thrombotic) endocarditis, seen in both old and young patients with metastatic cancers, renal failure, or an ongoing septic process.6 The vegetations are sterile and not associated with inflammation. This entity is regarded as being clinically insignificant, rarely leading to compromised cardiac function or systemic sequelae. Of note is the fact that in verrucous endocarditis, vegetations can occur on either side of the affected leaflets, a quality different from the other forms of endocarditis where formation of the vegetation occurs on the side of the valve from which the flow of blood is moving (ie, right atrium to right ventricle). Both of these mentioned clinical entities may be caused by hypercoagulable states or injury to endothelium.

### OUTCOME OF THE CASE PATIENT

The patient had been followed previously by the ear, nose, and throat (ENT) service, ophthalmology, and neurosurgery, and all of these services were alerted to his hospitalization. The cardiothoracic surgery team was consulted to evaluate the patient for a mitral valve replacement. Their immediate recommendations included continuing infection treatment and maximizing the angiotensin-converting enzyme (ACE) inhibitor. A peripherally inserted
A central catheter line was placed to deliver outpatient oxacillin 2 g every 4 hours for a 4-week course, at which time the cardiothoracic team scheduled a re-evaluation. A treatment course of voriconazole was continued for the invasive aspergillosis.

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