23-Year-Old Man With Fever and a Sore Thumb

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A 23-year-old man presented to the emergency department with a 3-month history of recurrent objective fever and malaise. He was otherwise asymptomatic, reporting no chest pain, shortness of breath, abdominal pain, nausea, vomiting, or diarrhea. His medical history was notable only for a bicuspid aortic valve, and his only past surgery was a dental procedure 4 months before presentation. He was currently taking no medications but noted allergy to penicillin and cephalosporins, leading to type I hypersensitivity. His family history was remarkable only for hypertension and type 2 diabetes mellitus in his father. He did not use alcohol, tobacco, or illicit drugs and was a college student.

On physical examination, the patient was febrile (temperature, 38.2°C). His cardiovascular examination revealed an early grade 3/4 diastolic decrescendo murmur, loudest to auscultation in the third left intercostal space with radiation along the left sternal border. Carotid pulses were bounding with a rapid upstroke and collapse. His lung sounds were clear on auscultation bilaterally. Abdominal examination revealed a soft, nontender, nondistended abdomen with normal and active bowel sounds and no hepatosplenomegaly. His integument examination revealed a tender nodule on the right thumb.

Results of laboratory testing, including complete blood cell count and electrolyte panel, were all within normal limits, except for a leukocyte count of 24.6 × 10^9/L (reference range, 3.5-10.5 × 10^9/L). Electrocardiography revealed sinus tachycardia. Chest radiography documented no consolidation, but mildly increased interstitial markings with mild cephalization of the vasculature were noted, findings suggestive of mild pulmonary vascular redistribution and interstitial edema.

On initial blood stains and cultures, 4 of 4 specimens in 2 of 2 blood culture sets yielded gram-positive cocci in chains.

1. Which *one* of the following is the *most appropriate* empiric intravenous antibiotic treatment for the patient's bacteremia?

a. Ceftriaxone and gentamicin
b. Ampicillin and gentamicin
c. Gentamicin
d. Nafcillin
e. Vancomycin

Ceftriaxone in conjunction with an aminoglycoside such as gentamicin would not be a reasonable choice for bacteremia because of the possibility of enterococci.[1] Both ampicillin and nafcillin fail to cover certain gram-positive cocci, including the now common methicillin-resistant *Staphylococcus aureus* (MRSA). Ampicillin and gentamicin in combination is an appropriate empiric therapy when there is a low suspicion for MRSA and covers the most common pathogens. This is not the most appropriate treatment for our patient, who is allergic to penicillin-based antibiotics. Gentamicin is not sufficient as monotherapy. Intravenous vancomycin provides good monotherapy coverage for most gram-positive organisms and is compatible with our patient's allergies.

We initated empiric intravenous vancomycin, and after all blood cultures produced viridans streptococci, vancomycin therapy was continued. The combination of the patient's history, physical examination findings, and blood culture results sparked a concern for bacterial endocarditis.

2. To establish the diagnosis, which *one* of the following factors is *most relevant*?

a. Recent dental procedure
b. Predisposing valvular lesion
c. Leukocytosis
d. Age more than 35 years
e. Duration of symptoms

The Duke classification includes 2 major and 6 minor criteria that are used for the diagnosis of infective endocarditis.[2] Under these

See end of article for correct answers to questions.

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criteria, one of the following combinations is needed to establish a diagnosis of infective endocarditis: 2 major criteria, 1 major and 3 minor criteria, or 5 minor criteria. The major clinical criteria include persistently positive blood cultures and typical findings on echocardiography including vegetations or a new regurgitant murmur. Minor criteria include fever, structural heart disease, prosthetic heart valve, intravenous drug use, vascular phenomenon, immunologic phenomenon, and blood cultures not meeting major criteria. Our patient's dental procedure is a risk factor but not part of the Duke criteria. The predisposing valvular lesion, a bicuspid aortic valve, is included as a minor criterion. Leukocytosis, age, and duration of symptoms are also not part of the Duke criteria for infective endocarditis.

The diagnosis of infective endocarditis was established on the basis of Duke criteria, with our patient having 1 major (multiple positive blood cultures) and 3 minor (a predisposing valvular lesion, fever, and an Osler node) criteria.

3. Which *one* of the following is the *most appropriate* next diagnostic test?

a. Magnetic resonance imaging of the brain
b. Chest radiography
c. Transthoracic echocardiography (TTE)
d. Transesophageal echocardiography (TEE)
e. Cardiac computed tomography

Magnetic resonance imaging of the brain can identify cerebral septic emboli secondary to endocarditis but is not a first-line diagnostic test in a patient without neurologic examination findings. Chest radiography may reveal clues to endocarditis such as septic pulmonary emboli but is not the best diagnostic test. Transthoracic echocardiography is indicated when both clinical suspicion and initial patient risk are low. There was high clinical suspicion for infective endocarditis in our patient. Because TEE is useful in identifying vegetations and complications of infective endocarditis that could affect management, it is the most appropriate option at this point. Cardiac computed tomography is being evaluated in studies but is not currently recommended because of its cost and radiation exposure without a notable difference in efficacy compared with TEE, although it remains a useful diagnostic tool when TEE is contraindicated.[3]

Transesophageal echocardiography in our patient revealed mild left ventricular enlargement with an estimated left ventricular ejection fraction of 65%. Right ventricular size and function were normal. The left and right atria were normal in size. An aortic root abscess was present extending into the intervalvular fibrosa, with a communication between the periaortic abscess and the ascending aorta. There was no evidence of a communication into the right side of the heart. A bicuspid aortic valve (AV) had damaged AV cusps, and a large mobile vegetation involved both aortic cusps. There was perforation of the fused noncoronary/left cusp on the bicuspid AV. The mobile AV vegetation and/or torn cusp prolapsed into the left ventricular outflow tract producing severe AV regurgitation. Although the mitral valve was morphologically normal without stenosis, the base of the anterior mitral leaflet arose adjacent to the location of the abscess, producing mild mitral valve regurgitation. The tricuspid and pulmonic valves had no remarkable abnormalities.

4. In view of the findings thus far, which *one* of the following is the *most appropriate* next step?

a. Anticoagulation
b. Antibiotic therapy for 6 weeks
c. Heart failure education
d. Surgical evaluation
e. Repeated blood cultures

Anticoagulation has not shown a benefit in patients with native valve endocarditis. Antibiotic therapy is dependent on the causative organism and extent of disease. Antibiotic therapy is routinely continued for 6 weeks, but it is not the most appropriate next step. New-onset heart failure is an indication for surgical intervention, but heart failure education is not indicated in this patient. Current guidelines recommend early surgical intervention for heart failure, severe regurgitation, perivalvular abscess, difficult to treat pathogens, large vegetations, and septic emboli.[1,4] Blood cultures should be repeated 48 to 72 hours after antibiotics are begun to assess microbiological response to therapy but do not outweigh the need for early surgical evaluation.

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The cardiothoracic surgical team was consulted, and the patient underwent aortic root replacement with a homograft.

5. Which *one* of the following types of complications is *most* common in infective endocarditis?

a. Embolic
b. Neurologic
c. Cardiac
d. Musculoskeletal
e. Renal

Embolic complications are common in patients with infective endocarditis and can occur despite appropriate antibiotic therapy. Emboli can occlude or damage any blood vessel in the systemic or pulmonary circulation. Morbidity can include myocardial infarction, ischemic limbs, stroke, or blindness. Neurologic complications are diverse and include stroke, meningitis, or encephalitis in approximately 29% to 35% of patients.[5] Cardiac complications are the most common and occur in 30% to 50% of all patients, leading to heart failure, perivalvular abscess, pericarditis, and other complications. Musculoskeletal and renal complications are rare.

Our patient had no complications after surgery. He completed antibiotic therapy, and his postoperative blood culture results have remained negative.

DISCUSSION

In patients with recurrent fever and persistently positive blood cultures, a diagnosis of infective endocarditis should be suspected. First described by William Osler in 1885,[6] infective endocarditis has an incidence of 5.0 to 7.9 cases per 100,000 person-years.[7] Multiple risk factors exist including structural heart disease, prosthetic heart valves, and intravenous drug use. Other minor predisposing risk factors have been suggested, including hemodialysis, human immunodeficiency virus, and pregnancy.

Key clinical signs and symptoms are helpful for diagnosis. The Duke criteria, most recently modified in 2000, uses clinical and pathologic factors divided into major and minor criteria to define endocarditis as definite, possible, or unlikely.[2] Under these criteria, one of the following combinations is needed to establish a diagnosis of infective endocarditis: 2 major criteria, 1 major and 3 minor criteria, or 5 minor criteria. The major clinical criteria include persistently positive blood cultures and typical findings on echocardiography including vegetations or a new regurgitant murmur. Minor criteria include fever, structural heart disease, prosthetic heart valve, intravenous drug use, vascular phenomenon, immunologic phenomenon, and blood cultures not meeting major criteria.

In addition to a comprehensive clinical examination, appropriate imaging plays a key role in diagnosis. There is strong evidence that TTE or TEE should be performed in patients with suspected native or prosthetic valve endocarditis.[8] Whether the first diagnostic test should be TTE or TEE remains controversial. One study of 134 patients reported that TTE evidence of normal morphology and function is 96% consistent with normal findings on TEE.[9] In addition to detecting vegetations, TTE can detect abnormalities suggestive of infective endocarditis such as valvular dysfunction, valve perforation, abscess, or fistula. However, when clinical suspicion is high, proceeding first with TEE is recommended because it has a higher sensitivity for vegetation detection, and it is the first-line diagnostic test for detection of complications and for preoperative evaluation of abnormalities that would affect surgical management.[10] Other cardiac studies including electrocardiography and chest radiography can be helpful but do not yield findings pathognomonic for endocarditis. Electrocardiographic changes may provide evidence of myocardial ischemia or infarction, new conduction delay, or heart block.

Persistently positive blood cultures along with clinical examination findings are pathognomonic for infective endocarditis until another etiology is found. A microbial source is best confirmed when blood cultures are performed on 2 separate sources and before the initiation of antibiotic therapy. Persistently positive blood cultures are defined as positive culture results from specimens drawn 12 hours apart. Multiple microorganisms have been shown as the causative agent of infective endocarditis. The most common causes are staphylococci and streptococci species, with *S aureus* the most common cause followed by viridans group streptococci.[11] Most epidemiological studies of infective endocarditis have been

completed in large tertiary centers, and their findings may not reflect the most common causative microorganisms in more rural areas. This epidemiological variation is reflected in a study conducted in Olmsted County, Minnesota, in which viridans group streptococci was the most common cause of infective endocarditis followed by *S aureus*.[7]

Antibiotic therapy has drastically changed the mortality from infective endocarditis. The causative organism isolated from blood cultures is critical and guides antimicrobial therapy. If patients are not acutely ill, empiric antibiotic therapy should be avoided until the causative organism is identified. If the patient is acutely ill, obtaining 2 sets of blood cultures 30 to 60 minutes apart before starting antibiotic therapy is preferred if possible. Empiric therapy with a third- or fourth-generation cephalosporin and an aminoglycoside, such as ceftriaxone and gentamicin, should be initiated to cover the most likely organisms including methicillin-sensitive staphylococci and streptococci.[8] If MRSA is suspected, monotherapy with vancomycin should be initiated. Blood cultures should be repeated 48 to 72 hours after antibiotics are begun to assess microbiological response to therapy. Duration of therapy in patients with native valve endocarditis ranges from 2 to 6 weeks, whereas patients with prosthetic valve endocarditis require 6 weeks of therapy.[8] Two-week therapeutic regimens have been shown to be effective in a small number of carefully selected patients with right-sided methicillin-sensitive staphylococcus endocarditis and in selected patients with endocarditis due to penicillin and high-level aminoglycoside-susceptible viridans streptococci.[12] Completing antibiotic therapy as an outpatient has become a reasonable option for some patients who are hemodynamically stable, adherent, and capable of managing the technical aspects of intravenous therapy and have access to regular monitoring.[1]

The 2006 American College of Cardiology—American Heart Association guidelines recommend surgery in patients with heart failure, severe regurgitation, perivalvular abscess, difficult to treat pathogens, large vegetations, and septic emboli.[8] The timing of surgery has been evolving over the years. A recent randomized trial comparing early valve surgery with conventional treatment in patients with infective endocarditis revealed that early surgery performed within 48 hours after diagnosis reduced death from any cause and embolic events.[4] Surgery for prosthetic valve endocarditis is guided by the same principles, although more patients require surgical intervention.

Complications that lead to severe morbidity and mortality can occur in patients with infective endocarditis, with cardiac complications being the most common. Cardiac complications occur in 30% to 50% of all patients with infective endocarditis and include heart failure, perivalvular abscess, and pericarditis. Neurologic complications can be silent or symptomatic and include stroke, meningitis, encephalitis, hemorrhage, brain abscess, and seizure.[5] Embolic phenomena are a common complication of left-sided endocarditis and can affect any blood vessel in the body and lead to end-organ damage. Musculoskeletal complications are rare and include septic arthritis and vertebral osteomyelitis. Renal complications are also rare and include renal infarction due to emboli or renal abscess. Mortality rates vary considerably among studies. Higher in-hospital mortality in patients with prosthetic valve endocarditis has been associated with certain characteristics including older age, health care—associated infection, *S aureus* infection, and complications including heart failure, stroke, intracardiac abscess, and persistent bacteremia. Age, staphylococci infection, and a contraindication to surgery have been shown to predict 6-month mortality.

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REFERENCES

1. Baddour LM, Wilson WR, Bayer AS, et al; Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease; Council on Cardiovascular Disease in the Young; Councils on Clinical Cardiology, Stroke, and Cardiovascular Surgery and Anesthesia; American Heart Association; Infectious Diseases Society of America. Infective endocarditis: diagnosis, antimicrobial therapy, and management of complications: a statement for healthcare professionals from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, and the Councils on Clinical Cardiology, Stroke, and Cardiovascular Surgery and Anesthesia, American Heart Association: endorsed by the Infectious Diseases Society of America [published corrections appear in *Circulation*. 2005; 112(15):2373; *Circulation*. 2007;115(15):e408; *Circulation*. 2007;

116(21):e547; and *Circulation*. 2008;118(12):e497]. *Circulation*. 2005;111(23):e394-e434.
2. Li JS, Sexton DJ, Mick N, et al. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. *Clin Infect Dis*. 2000;30(4):633-638.
3. Feuchtner GM, Stolzmann P, Dichtl W, et al. Multislice computed tomography in infective endocarditis: comparison with transesophageal echocardiography and intraoperative findings. *J Am Coll Cardiol*. 2009;53(5):436-444.
4. Kang DH, Kim YJ, Kim SH, et al. Early surgery versus conventional treatment for infective endocarditis. *N Engl J Med*. 2012;366(26):2466-2473.
5. Jones HR Jr, Siekert RG. Neurological manifestations of infective endocarditis: review of clinical and therapeutic challenges. *Brain*. 1989;112(pt 5):1295-1315.
6. Levy DM. Centenary of William Osler's 1885 Gulstonian lectures and their place in the history of bacterial endocarditis. *J R Soc Med*. 1985;78(12):1039-1046.
7. Correa de Sa DD, Tleyjeh IM, Anavekar NS, et al. Epidemiological trends of infective endocarditis: a population-based study in Olmsted County, Minnesota [published correction appears in *Mayo Clin Proc*. 2010;85(8):772]. *Mayo Clin Proc*. 2010;85(5):422-426.
8. Bonow RO, Carabello BA, Chatterjee K, et al. ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to revise the 1998 guidelines for the management of patients with valvular heart disease); developed in collaboration with the Society of Cardiovascular Anesthesiologists; endorsed by the Society for Cardiovascular Angiography and Interventions and the Society of Thoracic Surgeons. *J Am Coll Cardiol*. 2006;48(3):e1-e148.
9. Irani WN, Grayburn PA, Afridi I. A negative transthoracic echocardiogram obviates the need for transesophageal echocardiography in patients with suspected native valve active infective endocarditis. *Am J Cardiol*. 1996;78(1):101-103.
10. Shively BK, Gurule FT, Roldan CA, Leggett JH, Schiller NB. Diagnostic value of transesophageal compared with transthoracic echocardiography in infective endocarditis. *J Am Coll Cardiol*. 1991;18(2):391-397.
11. Selton-Suty C, Célard M, Le Moing V, et al; AEPEI Study Group. Preeminence of *Staphylococcus aureus* in infective endocarditis: a 1-year population-based survey. *Clin Infect Dis*. 2012;54(9):1230-1239.
12. Francioli P, Ruch W, Stamboulian D. Treatment of streptococcal endocarditis with a single daily dose of ceftriaxone and netilmicin for 14 days: a prospective multicenter study. *Clin Infect Dis*. 1995;21(6):1406-1410.

CORRECT ANSWERS: 1. e. 2. b. 3. d. 4. d. 5. c