Native-Valve Infective Endocarditis

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This Journal *feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the authors' clinical recommendations.*

A 72-year-old man with type 2 diabetes mellitus, stage 2 chronic kidney disease, and a history of mild aortic stenosis is admitted to the hospital with fever, dysuria, and urinary frequency. His temperature is 38.9°C, the pulse is regular at 110 beats per minute, and the blood pressure is 145/95 mm Hg. His lungs are clear; a grade 3/6 systolic ejection murmur is heard at the right upper sternal border. Laboratory tests are notable for a hemoglobin level of 12 g per deciliter, a white-cell count of 13,500 per cubic millimeter (with 80% polymorphonuclear cells), a serum glucose level of 340 mg per deciliter (18.7 mmol per liter), a serum creatinine level of 1.7 mg per deciliter (150 μmol per liter), and a urinalysis with 3+ protein, 20 to 50 white cells per high-power field, and 4+ glucose. Two blood cultures and a urine culture are positive for ampicillin-susceptible *Enterococcus faecalis.* How would you further evaluate and treat this patient?

THE CLINICAL PROBLEM

EPIDEMIOLOGIC, PATHOPHYSIOLOGICAL, AND CLINICAL FEATURES

NATIVE-VALVE INFECTIVE ENDOCARDITIS IS UNCOMMON, WITH AN INCIdence of approximately 2 to 10 cases per 100,000 person-years.[1,2] The presumed initiating event is injury to the valvular endothelium or endocardium. This injury exposes subendothelial collagen and other matrix molecules to which platelets and fibrin adhere and form a microthrombotic lesion called a sterile vegetation. Bacteria circulating in the bloodstream then bind to and colonize this lesion. In the absence of an effective host response, bacteria replicate in situ, stimulating further platelet and fibrin deposition to form an infected vegetation that is the hallmark of infective endocarditis (Fig. 1).

Vegetations create a protective microenvironment that is poorly accessible to neutrophils and host defense molecules. Vegetations are loaded with bacteria at very high densities (i.e., 10^9 to 10^{10} colony-forming units [CFU] per gram of vegetation) that promote high-grade bacteremia and further growth of the vegetation, which becomes friable and readily fragments into the circulation. These conditions (high bacterial densities, growing vegetation, and friability and fragmentation of the growing vegetation) drive the four mechanisms that are responsible for most of the clinical features of infective endocarditis and its complications: valvular destruction, paravalvular extension of infection, and heart failure; microvascular and large-vessel embolization; metastatic infection of target organs (e.g., the brain, kidneys, spleen, and lungs); and immunologic phenomena such as hypocomplementemic glomerulonephritis and false positive serologic findings of rheu-

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NATIVE-VALVE INFECTIVE ENDOCARDITIS

- The modified Duke criteria, which are based on findings on physical examination, echocardiography, microbiologic studies, and computed tomographic and magnetic resonance imaging of target organs, are sensitive and specific for the clinical diagnosis of infective endocarditis.
- Transesophageal echocardiography, which is more sensitive than transthoracic echocardiography (TTE) for identifying valvular vegetations and periannular complications of infective endocarditis, is indicated when TTE is negative or nondiagnostic.
- Beta-lactam antibiotics are recommended over vancomycin or daptomycin for treatment of infective endocarditis caused by methicillin-susceptible *Staphylococcus aureus*.
- In older patients with infective endocarditis caused by *Enterococcus faecalis*, especially those with underlying renal disease or those receiving other nephrotoxic agents, ampicillin plus ceftriaxone is preferred over aminoglycoside-containing regimens.
- Early surgery for uncontrolled infection, congestive heart failure caused by valvular dysfunction, or prevention of central nervous system embolization is associated with improved outcomes.
- A transition to an oral step-down regimen after an initial intravenous course of therapy may be considered in selected patients.
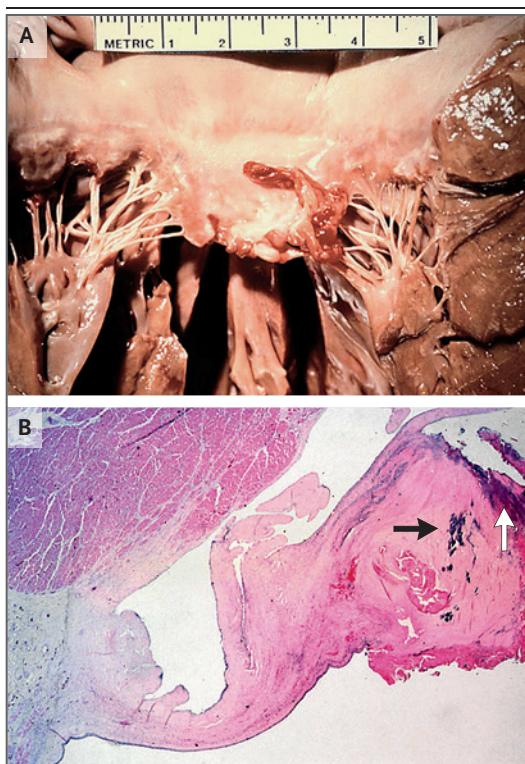
Figure 1. Mitral-Valve Vegetations in Infective Endocarditis.

Panel A shows the gross appearance of a large vegetation on a rheumatic mitral valve, as measured in centimeters. Panel B shows hematoxylin and eosin staining of a microscopic cross section of a mitral-valve vegetation. Bacteria (black arrow) are surrounded by fibrin and embedded within the vegetation, and inflammatory cells (white arrow) are present on the surface of the vegetation.

matoid factor, antineutrophil antibodies, or syphilis.

Cardiac conditions that predispose to infective endocarditis include congenital disease (e.g., ventricular septal defect and bicuspid aortic valve) and acquired valvular disease (e.g., degenerative valvular disease, aortic stenosis, and rheumatic heart disease). Rheumatic heart disease, the most common predisposing condition for infective endocarditis in developing countries, is uncommon in developed countries, where the most frequent predisposing cardiac conditions are degenerative valvular diseases, congenital valvular abnormalities, and intracardiac devices.[3,4] Noncardiac risk factors include poor dentition, intravenous drug use, hemodialysis, chronic liver disease, diabetes, compromised immunity, neoplastic disease, and indwelling intravascular devices.

Fever and heart murmur, the two signature features of infective endocarditis, are present in approximately 90% and 75% of patients, respectively.[1,3] Infective endocarditis may present acutely with a rapidly progressive course complicated by congestive heart failure, stroke, systemic or pulmonary embolization, severe sepsis or septic shock, or subacutely with nonspecific symptoms such as low-grade fever, malaise, chills, sweats, dyspnea, back pain, arthralgias, and weight loss over a period of weeks or sometimes months. Microembolic or immunologic phenomena such as splinter hemorrhage, conjunctival hemorrhage, Osler nodes (distal vasculitic lesions of the fingers and toes), Janeway lesions (vasculitic lesions of the palms and soles), and Roth spots (hemor-

Table 1. Modified Duke Criteria for the Clinical Diagnosis of Infective Endocarditis.*

Major clinical criteria

Positive blood culture

Typical microorganisms (*Staphylococcus aureus*, viridans streptococci, *Streptococcus gallolyticus,* HACEK [haemophilus species, aggregatibacter (formerly actinobacillus) species, cardiobacterium species, *Eikenella corrodens*, and kingella species], and community-acquired enterococci in the absence of a primary focus) consistent with infective endocarditis from two separate blood cultures

Microorganisms consistent with infective endocarditis from persistently positive blood cultures, defined as ≥2 positive cultures from blood samples drawn >12 hr apart or all of 3 or a majority of ≥4 separate cultures of blood (with first and last sample drawn at least 1 hr apart)

Single positive blood culture for *Coxiella burnetii* or phase I IgG antibody titer >1:800

Positive echocardiography

Vegetation (defined as an oscillating intracardiac mass on a valve or supporting structure), abscess, or new partial dehiscence of a prosthetic valve

New valvular regurgitation (an increase or change in preexisting murmur is not sufficient)

Minor clinical criteria

Presence of predisposing cardiac condition or intravenous drug use

Temperature ≥38.0°C (100.4°F)

Vascular phenomena such as systemic arterial emboli, septic pulmonary emboli, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, or Janeway lesions

Immunologic phenomena such as glomerulonephritis, Osler nodes, Roth spots, or rheumatoid factor

Positive blood cultures that do not meet major criteria, or serologic evidence of active infection with organism consistent with infective endocarditis

* Adapted from Li et al.[6] A definite diagnosis is based on two major criteria, five minor criteria, or one major criterion plus three minor criteria. Possible endocarditis is based on three minor criteria or one major criterion plus one minor criterion. If criteria for either definite or possible endocarditis are not met, the diagnosis of infective endocarditis is rejected.

rhagic retinal lesions) are present in 5 to 10% of patients.

MICROBIOLOGIC FEATURES

Worldwide, gram-positive bacteria account for approximately 80% of cases of native-valve infective endocarditis. These bacteria include *Staphylococcus aureus* in 35 to 40% of cases of native-valve infective endocarditis, streptococci in 30 to 40% (viridans streptococci in approximately 20% and *Streptococcus gallolyticus* [formerly *S. bovis*] and other streptococci in approximately 15%), and enterococci in 10%.[1,2,4] Coagulase-negative staphylococci, a common cause of prosthetic-valve infective endocarditis, are uncommon in native-valve infective endocarditis, except for *S. lugdunensis*, which resembles *S. aureus* clinically. HACEK species (haemophilus species, aggregatibacter [formerly actinobacillus] species, cardiobacterium species, *Eikenella corrodens*, and kingella species), fungi, polymicrobial infection, and, rarely, aerobic gram-negative bacilli are isolated in 5% of cases.

STRATEGIES AND EVIDENCE

EVALUATION AND DIAGNOSIS

The modified Duke criteria provide the framework for the diagnosis of infective endocarditis. A definite pathological diagnosis can be made if organisms are identified on histologic analysis or culture of the vegetation, intracardiac abscess, or peripheral embolus, or if evidence of a vegetation or intracardiac abscess is confirmed by histologic analysis showing active endocarditis.[5] A definite or possible clinical diagnosis of infective endocarditis is based on a combination of major and minor criteria that are rooted in microbiologic, echocardiographic, and clinical metrics (Table 1). The sensitivity of the modified Duke criteria for infective endocarditis is approximately 80% for definite cases and higher if possible cases are included.[6,7] These criteria have lower sensitivity in infections related to a prosthetic valve or cardiac device, endocarditis on the right side of the heart, and culture-negative infective endocarditis.[7,8] The negative predictive value is

Table 2. Diagnosis of Culture-Negative Endocarditis.*

Microorganism	Clinical and Epidemiologic Clues	Serologic Testing	Specific RT-PCR Assay†	Ribosomal RNA PCR Assay†‡
Bartonella henselae, B. quintana	Exposure to cats (*B. henselae*), homelessness (*B. quintana*), body lice (*B. quintana*), human immunodeficiency virus infection; most common cause of culture-negative endocarditis in the United States	Available	Available	Available
Brucella species	Consumption of unpasteurized dairy products, exposure to tissue or fluids from infected animals (cattle, goats, sheep, or dogs)	Available	—	Available
Coxiella burnetii	Contact with farm animals (cattle, goats, or sheep), abattoir exposure, laboratory exposure; common cause of culture-negative endocarditis in southern Europe and Middle East	Available	Available	Available
Fungi	Injection drug use, immunosuppression, prosthetic valve	Available	—	Available
Legionella species	Immunocompromised host, prosthetic valve	Available§	Available	Available
Mycoplasma species	Acute infection, prosthetic valve	Available¶	—	Available
Staphylococci, streptococci, enterococci, HACEK	Previous use of antibiotics	—	Available	Available
Tropheryma whipplei	Chronic systemic illness, arthralgias, weight loss, gastrointestinal symptoms, central nervous system involvement	—	Available‖	Available

* Dashes indicate that the test to detect the microorganism is not available or not applicable. HACEK denotes haemophilus species, aggregatibacter (formerly actinobacillus) species, cardiobacterium species, *Eikenella corrodens*, and kingella species; PCR polymerase chain reaction; and RT-PCR reverse-transcriptase PCR.
† The sensitivity is substantially higher if the RT-PCR or broad-range 16S or 18S RNA PCR assay is performed on a valvular vegetation or on abscess material rather than blood.
‡ Broad-range PCR assays target 16S and 18S ribosomal RNA genes.
§ Serologic tests and urinary antigen tests detect only the *Legionella pneumophila* serotype 1.
¶ Serologic tests are performed to detect only *Mycoplasma pneumoniae*.
‖ Biopsy of the involved extracardial tissue (e.g., small bowel and synovium, if present) is recommended.

approximately 90% when criteria are not met for either definite or possible infective endocarditis.

Blood cultures are the most important microbiologic tests for the diagnosis and treatment of infective endocarditis, and they fulfill a major Duke criterion. Antimicrobial therapy largely depends on the blood-culture isolate and its antimicrobial susceptibility. Approximately 90 to 95% of cases of native-valve infective endocarditis are blood culture–positive. To maximize recovery of a pathogen, three separate sets of blood cultures drawn 30 minutes apart are recommended before the initiation of antibiotics.[9,10] Blood culture–negative cases are most commonly caused by recent administration of antimicrobial agents or by organisms that grow poorly or not at all in standard blood culture media (e.g., bartonella species, *Coxiella burnetii*, *Tropheryma whipplei*, and legionella).[11]

Serologic and molecular testing for likely pathogens should be performed if blood cultures are negative; this testing is guided by epidemiologic clues (e.g., *C. burnetii* infection may be associated with exposure to farm animals, and *Bartonella quintana* infection may be associated with homelessness) (Table 2). Molecular diagnosis is based on nucleic acid amplification by polymerase chain reaction (PCR), either with specific primers for a particular species or genus, or with broad-range primers targeting the 16S ribosomal RNA (rRNA) gene for bacterial pathogens or the 18S rRNA gene for fungal pathogens. For PCR diagnostic tests, the reported sensitivities are 33 to 90% and the reported specificities are 77 to 100%.[11,12] Next-generation sequencing, which is expected to be more accurate than PCR-based methods, is anticipated in the coming years. The preferred specimen for molecular assays is an excised valve or vegetation. Plasma DNA amplification assays may as-

sist in microbiologic diagnosis in cases in which the pathogen is difficult to determine.

Echocardiography is an essential tool in the diagnosis and management of infective endocarditis.[13] The sensitivity for detection of vegetations in native-valve infective endocarditis is 50 to 60% with transthoracic echocardiography (TTE) and 90% or more with transesophageal echocardiography (TEE).[13-15] The specificities of both are approximately 95%. Because TTE is also less sensitive than TEE for detecting intracardiac complications (e.g., paravalvular abscess), TEE is preferred to rule out infective endocarditis in patients in whom this condition is suspected and to assess intracardiac complications.

Among newer forms of imaging,[16,17] the most widely studied is ^{18}F-fluorodeoxyglucose cardiac positron-emission tomography (PET) plus computed tomography (CT). PET-CT is most applicable to the diagnosis and evaluation of prosthetic-valve infective endocarditis; its role in native-valve infective endocarditis is poorly studied and unclear.

ANTIMICROBIAL THERAPY

Recommendations for antimicrobial therapy for infective endocarditis (Table 3) are based almost entirely on observational studies rather than on randomized clinical trials. These recommendations rest on four basic principles: the ability of the regimen to kill the pathogen, the administration of a prolonged course of therapy (i.e., weeks rather than days), intensive dosing to ensure adequate drug exposure, and source control. In general, vancomycin plus ceftriaxone is a reasonable choice for empirical therapy to cover likely pathogens while cultures are pending in patients with native-valve infective endocarditis.

For susceptible strains, beta-lactam antibiotics are the cornerstone of definitive therapy. These agents are preferred over others unless the patient cannot take them without adverse effects or there is a documented immediate (type I) hypersensitivity reaction. Infective endocarditis that is caused by penicillin-nonsusceptible strains of viridans streptococci, *S. gallolyticus*, abiotrophia species, or granulicatella species can be treated with a combination of penicillin or ceftriaxone plus gentamicin; vancomycin monotherapy is an option, although there is less overall experience with this agent.

An antistaphylococcal penicillin (e.g., oxacillin) is the drug of choice for infective endocarditis that is caused by methicillin-susceptible strains of *S. aureus* (MSSA). Randomized, controlled trials have shown that combination therapy with an antistaphylococcal penicillin and either gentamicin or rifampin does not improve outcomes and is associated with adverse events; therefore, this combination is not recommended.[9,10,18,19] Cefazolin is a reasonable alternative for patients with MSSA who cannot receive penicillin without adverse effects.[9,20,21] One concern with cefazolin is that some strains have an "inoculum effect," which is defined as an increase in the broth dilution minimum inhibitory concentration (MIC) to 16 μg per milliliter or greater at an inoculum of 5×10^7 CFU per milliliter (100 times the standard inoculum of approximately 5×10^5 CFU per milliliter).[22] This inoculum effect, which is due at least in part to hydrolysis of cefazolin by staphylococcal penicillinase, may be associated with clinical failure.[23]

Daptomycin or vancomycin monotherapy is recommended for treatment of native-valve infective endocarditis caused by methicillin-resistant *S. aureus* (MRSA).[24,25] The benefit of combination therapy remains unproved. A randomized trial comparing vancomycin (or, in 8 patients, daptomycin) alone or in combination with an antistaphylococcal beta-lactam antibiotic (primarily flucloxacillin) for MRSA bacteremia in 363 patients (including 42 with infective endocarditis) showed no benefit of the combination for the primary composite outcome of mortality at 90 days, persistent bacteremia at day 5, microbiologic relapse, or microbiologic treatment failure.[26] The combination group had higher mortality at 90 days (despite more rapid clearance of blood cultures) and a significantly higher incidence of acute kidney injury. Anecdotal data suggest that combining a second agent (e.g., ceftaroline) with vancomycin or daptomycin may benefit patients who have persistent bacteremia or otherwise do not have a response.[27-29] However, the most beneficial combination is currently unknown.

Combination therapy is recommended for the treatment of enterococcal infective endocarditis. Penicillin or ampicillin in combination with low-dose, synergistic gentamicin has been the standard treatment for decades. The usefulness of this regimen is limited by gentamicin toxicity and an increasing incidence of high-level resistance to gentamicin that indicates a lack of

Table 3. Antimicrobial Regimens for Treatment of Native-Valve Infective Endocarditis.*

Microorganism and Regimen	Dose and Duration of Treatment†	Comments
Viridans streptococci, *Streptococcus gallolyticus*		
Penicillin MIC ≤0.12 µg/ml		
Penicillin G	12 million–18 million units/day intravenously in 4–6 divided doses for 4 wk	
Ceftriaxone	2 g intravenously once daily for 4 wk	
Vancomycin	30 mg/kg/day intravenously in 2–3 divided doses for 4 wk	
Penicillin G plus gentamicin	Penicillin G (12 million–18 million units/day intravenously in 4–6 divided doses) plus gentamicin (3 mg/kg intravenously once daily) for 2 wk	Avoid gentamicin in patients with preexisting renal disease, in the elderly, and in patients at risk for nephrotoxicity or ototoxicity (i.e., in those receiving other potentially nephrotoxic or ototoxic drugs)
Ceftriaxone plus gentamicin	Ceftriaxone (2 g intravenously once daily) plus gentamicin (3 mg/kg intravenously once daily) for 2 wk	Avoid gentamicin in patients with preexisting renal disease, in the elderly, and in patients at risk for nephrotoxicity or ototoxicity (i.e., in those receiving other potentially nephrotoxic or ototoxic drugs)
Penicillin MIC >0.12 to <0.5 µg/ml		
Penicillin G plus gentamicin	Penicillin G (24 million units/day intravenously in 4–6 divided doses for 4 wk) plus gentamicin (3 mg/kg intravenously once daily for 2 wk)	
Ceftriaxone plus gentamicin	Ceftriaxone (2 g once daily for 4 wk) plus gentamicin (3 mg/kg intravenously once daily for 2 wk)	If the ceftriaxone MIC of the isolate is ≤0.5 µg/ml, ceftriaxone alone is an option
Vancomycin	30 mg/kg/day in 2–3 divided doses for 4 wk	
Abiotrophia defectiva, granulicatella species, viridans streptococci, *S. gallolyticus*, penicillin MIC ≥0.5 µg/ml		
Penicillin G plus gentamicin	Penicillin G (24 million units/day intravenously in 4–6 divided doses) plus gentamicin (3 mg/kg intravenously in 2–3 doses) for 4–6 wk	European Society of Cardiology guidelines[10] recommend penicillin or ceftriaxone for 6 wk plus gentamicin for ≥2 wk
Vancomycin	30 mg/kg/day in 2–3 divided doses for 4–6 wk	
Enterococci		
Ampicillin plus gentamicin	Ampicillin (12 g/day in 6 divided doses) plus gentamicin (3 mg/kg intravenously in 2–3 divided doses) for 4–6 wk	Not recommended for strains with high-level aminoglycoside resistance; limited data suggest that gentamicin can be discontinued after 2 wk
Penicillin G plus gentamicin	Penicillin G (24 million units/day intravenously in 4–6 doses) plus gentamicin (3 mg/kg intravenously in 2–3 divided doses) for 4–6 wk	Not recommended for strains with high-level aminoglycoside resistance; limited data suggest that gentamicin can be discontinued after 2 wk
Ampicillin plus ceftriaxone	Ampicillin (12 g/day in 6 divided doses) plus ceftriaxone (2 g every 12 hr) for 6 wk	Recommended for strains with high-level aminoglycoside resistance
Vancomycin plus gentamicin	Vancomycin (30 mg/kg/day in 2–3 divided doses) plus gentamicin (3 mg/kg/day in 2–3 divided doses) for 6 wk	Not recommended for strains with high-level aminoglycoside resistance; regimen of last resort because of toxicity
Methicillin-susceptible *Staphylococcus aureus*		Vancomycin or daptomycin is an option for patients who cannot receive beta-lactam antibiotics without adverse effects or with immediate hypersensitivity to beta-lactam antibiotics
Nafcillin or oxacillin	12 g/day intravenously in 6 divided doses for 6 wk	
Cefazolin	6 g/day intravenously in 3 divided doses for 6 wk	

Table 3. (Continued.)		
Microorganism and Regimen	Dose and Duration of Treatment†	Comments
Methicillin-resistant *S. aureus*		
Vancomycin	30–60 mg/kg/day intravenously in 2–4 divided doses for 6 wk	The target 24-hr area under the concentration curve is 400–600 $\mu g \times$ hr/ml
Daptomycin	10 mg/kg/day intravenously once daily for 6 wk	
HACEK		
Ceftriaxone	2 g intravenously once daily for 4 wk	
Ciprofloxacin	800 mg/day intravenously or 1500 mg orally in 2 divided doses for 4 wk	
Levofloxacin	750 mg intravenously or orally once daily for 4 wk	

* HACEK denotes haemophilus species, aggregatibacter (formerly actinobacillus) species, cardiobacterium species, *Eikenella corrodens*, and kingella species; and MIC minimum inhibitory concentration.
† The duration of therapy once blood cultures have converted to negative is shown.

synergy. Observational data suggest that a 6-week course of ampicillin plus ceftriaxone is an acceptable alternative for treatment of infective endocarditis caused by ampicillin-susceptible strains of *E. faecalis*.[9,10,20,30] If the ampicillin–gentamicin combination is used, the efficacy of combination therapy for 2 weeks followed by ampicillin alone for 4 to 6 weeks may be similar to that of the standard combination regimen for 4 to 6 weeks and is less toxic.[31,32]

SURGICAL MANAGEMENT

The three main indications for surgery in patients with native-valve infective endocarditis are heart failure due to valvular dysfunction or perforation, uncontrolled endocardial infection (e.g., paravalvular extension or persistent bacteremia), and prevention of systemic embolization, especially to the brain (Table 4). In a prospective cohort study involving patients with native-valve infective endocarditis, a multivariable analysis with adjustment for coexisting conditions showed that an indication for surgery without performance of the surgery was an independent predictor of death.[33] The appropriate timing of valve surgery is not well defined and is a highly individualized decision that is best made by an experienced multidisciplinary team.[34]

One small randomized, controlled trial compared early surgery during the initial hospitalization and within 48 hours after randomization (in 37 patients) with conventional treatment (in 39 patients) in patients with endocarditis on the left side of the heart, severe valvular regurgitation (without heart failure), and large vegetations

Table 4. Indications for Early Cardiac-Valve Surgery.
Heart failure
Refractory pulmonary edema or cardiogenic shock due to aortic-valve or mitral-valve dysfunction, obstruction, fistula, or shunt
Aortic-valve or mitral-valve regurgitation or dysfunction with poorly compensated hemodynamic function
Uncontrolled infection
Fungal pathogen
Multidrug-resistant pathogen
Blood cultures that are persistently positive for an antibiotic-susceptible pathogen in a patient receiving appropriate antimicrobial therapy for 6 or 7 days despite adequate source control of other foci of infection
Paravalvular complications (e.g., abscess)
Prevention of systemic embolization
Aortic-valve or mitral-valve vegetation >10 mm, especially when accompanied by ≥1 embolic events while the patient is receiving appropriate therapy

(>10 mm in diameter).[35] Early surgery significantly reduced the risk of the combined end point of in-hospital death or embolic events within 6 weeks after randomization, but this decreased risk was driven entirely by decreases in the risk of systemic embolism. This trial was limited in that patients had few underlying diseases, and patients with streptococcal infections and mitral-valve infective endocarditis were overrepresented. Two meta-analyses showed that early surgery, as compared with conventional therapy (i.e., medical therapy or late surgery at >20 days), was associated with a 40 to 60% reduction in death from any cause.[36,37] However, how best to identify patients who are most likely to benefit from early valve surgery remains unclear.

AREAS OF UNCERTAINTY

Modified Duke criteria for the clinical diagnosis of infective endocarditis are not based on the results of molecular diagnostic testing. As these methods improve in accuracy and become routinely available, their role in diagnosis will need to be taken into account.

Whether routine brain magnetic resonance imaging (MRI) and other advanced imaging techniques such as PET-CT improve the diagnosis, treatment, and outcomes in patients with native-valve infective endocarditis is unclear. MRI is more sensitive than CT for detecting central nervous system (CNS) lesions, and the presence of asymptomatic embolic lesions in patients with suspected infective endocarditis is a minor criterion in support of the diagnosis.[16,17,38] Routine brain MRI has been recommended to detect silent CNS emboli in patients who are candidates for valvular surgery,[34] although whether this improves outcomes is unknown.

Data from randomized, controlled trials to inform the benefits and risks of oral antimicrobial therapy for infective endocarditis are limited. The Partial Oral Treatment of Endocarditis (POET) trial[39] showed that in patients with infective endocarditis on the left side of the heart and whose condition had stabilized, treatment with oral antibiotics after an initial course of intravenous antibiotics was noninferior to standard intravenous antibiotic treatment at 6 months after the end of treatment; longer-term follow-up showed no deleterious outcomes with oral step-down therapy.[40] However, only 20% of the patients who underwent screening were enrolled, and few had *S. aureus* infection (none with MRSA). Additional data are needed to clarify the safety and efficacy of this approach in a variety of clinical settings.[41]

The timing of surgery in patients with infective endocarditis, criteria for delaying surgery, and predictors of surgical mortality and poor outcomes need to be better defined. Most guidelines recommend delaying valve surgery for at least 4 weeks in patients with large embolic CNS lesions or intracranial hemorrhage,[9,10,20] although earlier surgery may be safely performed in selected patients despite these conditions[42] and in patients with small embolic brain lesions (<2 cm in diameter), without hemorrhage or major neurologic deficits. Several scoring systems have been proposed to predict surgical mortality and postoperative complications in patients with infective endocarditis[43]; however, limitations, including small sample sizes, reliance on retrospective data, changes in surgical practice over time (which may span decades), and lack of large-scale, external validation make it difficult to assess the accuracy of these systems.

GUIDELINES

The American Heart Association, the European Society of Cardiology, the Japanese Society of Cardiology, and the American Association for Thoracic Surgery[9,10,20,34] have each published guidelines on the diagnosis and management of infective endocarditis. These guidelines are generally concordant in their recommendations, with relatively minor differences with respect to antimicrobial therapy, forms of imaging, and indications for and timing of surgery. The recommendations presented here are in general agreement with these guidelines.

CONCLUSIONS AND RECOMMENDATIONS

The patient described in the vignette has community-acquired enterococcal pyelonephritis with bacteremia. On purely clinical grounds, the presence of bacteremia plus a murmur in a febrile patient is strongly suggestive of underlying infective endocarditis. At presentation, this patient probably satisfies three minor Duke criteria for possible endocarditis: fever; two positive blood cultures for *E. faecalis*, but with a primary focus of pyelonephritis (hence, this is not a major criterion); and aortic stenosis, a predisposing cardiac condition.

Additional blood cultures should be obtained, which if positive would meet a major criterion for the diagnosis of infective endocarditis — persistently positive blood cultures. Echocardiography should be performed immediately to document the nature of the valvular lesion and the presence of vegetations or complications of infective endocarditis. Although TEE is much more sensitive than TTE for detecting valvular vegetations and paravalvular complications, we would start with TTE, since it is noninvasive, can be readily performed, and provides better information on myocardial function (e.g., the ejection

fraction). If TTE is negative or nondiagnostic, then TEE is indicated given the strong suspicion for infective endocarditis. If TEE is nondiagnostic and suspicion for infective endocarditis remains high, then it should be repeated several days later.

We would engage a multidisciplinary team in care, including specialists in cardiology, cardiovascular surgery, and infectious diseases. Combination antimicrobial therapy for treatment of presumed enterococcal infective endocarditis should be administered promptly. Although susceptibility of the isolate to gentamicin should be confirmed, this patient's age, diabetes, and chronic kidney disease place him at high risk for acute kidney injury from gentamicin, and we would favor initial treatment with ampicillin and ceftriaxone. Blood cultures should be obtained to confirm clearance of bacteremia with therapy, and the patient should be carefully evaluated for any indications for immediate valve surgery. Antimicrobial therapy should be continued 6 weeks after blood cultures convert to negative. Consideration also should be given to screening colonoscopy, since some data suggest that, similar to infective endocarditis caused by *S. gallolyticus*, enterococcal infective endocarditis may be associated with colonic neoplasm,[44,45] although further study is needed.

REFERENCES

1. Cahill TJ, Prendergast BD. Infective endocarditis. Lancet 2016;387:882-93.
2. Bin Abdulhak AA, Baddour LM, Erwin PJ, et al. Global and regional burden of infective endocarditis, 1990-2010: a systematic review of the literature. Glob Heart 2014;9:131-43.
3. Murdoch DR, Corey GR, Hoen B, et al. Clinical presentation, etiology, and outcome of infective endocarditis in the 21st century: the International Collaboration on Endocarditis-Prospective Cohort Study. Arch Intern Med 2009;169:463-73.
4. Ambrosioni J, Hernandez-Meneses M, Téllez A, et al. The changing epidemiology of infective endocarditis in the twenty-first century. Curr Infect Dis Rep 2017;19:21.
5. Pettersson GB, Hussain ST, Shrestha NK, et al. Infective endocarditis: an atlas of disease progression for describing, staging, coding, and understanding the pathology. J Thorac Cardiovasc Surg 2014; 147(4):1142-1149.e2.
6. Li JS, Sexton DJ, Mick N, et al. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. Clin Infect Dis 2000;30:633-8.
7. Habib G, Derumeaux G, Avierinos JF, et al. Value and limitations of the Duke criteria for the diagnosis of infective endocarditis. J Am Coll Cardiol 1999;33: 2023-9.
8. Prendergast BD. Diagnostic criteria and problems in infective endocarditis. Heart 2004;90:611-3.
9. Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis in adults: diagnosis, antimicrobial therapy, and management of complications: a scientific statement for healthcare professionals from the American Heart Association. Circulation 2015;132:1435-86.
10. Habib G, Lancellotti P, Antunes MJ, et al. 2015 ESC Guidelines for the management of infective endocarditis: the Task Force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC) — endorsed by: European Association for Cardio-Thoracic Surgery (EACTS), the European Association of Nuclear Medicine (EANM). Eur Heart J 2015;36:3075-128.
11. Fournier P-E, Gouriet F, Casalta J-P, et al. Blood culture-negative endocarditis: improving the diagnostic yield using new diagnostic tools. Medicine (Baltimore) 2017;96(47):e8392.
12. Liesman RM, Pritt BS, Maleszewski JJ, Patel R. Laboratory diagnosis of infective endocarditis. J Clin Microbiol 2017;55: 2599-608.
13. Afonso L, Kottam A, Reddy V, Penumetcha A. Echocardiography in infective endocarditis: state of the art. Curr Cardiol Rep 2017;19:127.
14. Habib G, Badano L, Tribouilloy C, et al. Recommendations for the practice of echocardiography in infective endocarditis. Eur J Echocardiogr 2010;11:202-19.
15. Bai AD, Steinberg M, Showler A, et al. Diagnostic accuracy of transthoracic echocardiography for infective endocarditis findings using transesophageal echocardiography as the reference standard: a meta-analysis. J Am Soc Echocardiogr 2017;30(7):639-646.e8.
16. Gomes A, Glaudemans AWJM, Touw DJ, et al. Diagnostic value of imaging in infective endocarditis: a systematic review. Lancet Infect Dis 2017;17(1):e1-e14.
17. Wong D, Rubinshtein R, Keynan Y. Alternative cardiac imaging modalities to echocardiography for the diagnosis of infective endocarditis. Am J Cardiol 2016; 118:1410-8.
18. Cosgrove SE, Vigliani GA, Fowler VG Jr, et al. Initial low-dose gentamicin for *Staphylococcus aureus* bacteremia and endocarditis is nephrotoxic. Clin Infect Dis 2009;48:713-21.
19. Thwaites GE, Scarborough M, Szubert A, et al. Adjunctive rifampicin for *Staphylococcus aureus* bacteraemia (ARREST): a multicentre, randomised, double-blind, placebo-controlled trial. Lancet 2018;391: 668-78.
20. Nakatani S, Ohara T, Ashihara K, et al. JCS 2017 guideline on prevention and treatment of infective endocarditis. Circ J 2019;83:1767-809.
21. Weis S, Kesselmeier M, Davis JS, et al. Cefazolin versus anti-staphylococcal penicillins for the treatment of patients with *Staphylococcus aureus* bacteraemia. Clin Microbiol Infect 2019;25:818-27.
22. Nannini EC, Stryjewski ME, Singh KV, et al. Inoculum effect with cefazolin among clinical isolates of methicillin-susceptible Staphylococcus aureus: frequency and possible cause of cefazolin treatment failure. Antimicrob Agents Chemother 2009; 53:3437-41.
23. Miller WR, Seas C, Carvajal LP, et al. The cefazolin inoculum effect is associated with increased mortality in methicillin-susceptible *Staphylococcus aureus* bacteremia. Open Forum Infect Dis 2018;5(6): ofy123.
24. Fowler VG Jr, Boucher HW, Corey GR, et al. Daptomycin versus standard therapy for bacteremia and endocarditis caused by *Staphylococcus aureus*. N Engl J Med 2006; 355:653-65.
25. Holland TL, Arnold C, Fowler VG Jr. Clinical management of *Staphylococcus aureus* bacteremia: a review. JAMA 2014; 312:1330-41.
26. Tong SYC, Lye DC, Yahav D, et al. Effect of vancomycin or daptomycin with vs without an antistaphylococcal β-lactam on mortality, bacteremia, relapse, or treatment failure in patients with MRSA bacteremia: a randomized clinical trial. JAMA 2020; 323:527-37.
27. Geriak M, Haddad F, Rizvi K, et al.

Clinical data on daptomycin plus ceftaroline versus standard of care monotherapy in the treatment of methicillin-resistant *Staphylococcus aureus* bacteremia. Antimicrob Agents Chemother 2019;63(5):e02483-18.

28. Gritsenko D, Fedorenko M, Ruhe JJ, Altshuler J. Combination therapy with vancomycin and ceftaroline for refractory methicillin-resistant *Staphylococcus aureus* bacteremia: a case series. Clin Ther 2017; 39:212-8.

29. Holubar M, Meng L, Deresinski S. Bacteremia due to methicillin-resistant *Staphylococcus aureus*: new therapeutic approaches. Infect Dis Clin North Am 2016; 30:491-507.

30. Fernández-Hidalgo N, Almirante B, Gavaldà J, et al. Ampicillin plus ceftriaxone is as effective as ampicillin plus gentamicin for treating *enterococcus faecalis* infective endocarditis. Clin Infect Dis 2013; 56:1261-8.

31. Dahl A, Rasmussen RV, Bundgaard H, et al. *Enterococcus faecalis* infective endocarditis: a pilot study of the relationship between duration of gentamicin treatment and outcome. Circulation 2013;127:1810-7.

32. Olaison L, Schadewitz K. Enterococcal endocarditis in Sweden, 1995-1999: can shorter therapy with aminoglycosides be used? Clin Infect Dis 2002;34:159-66.

33. Habib G, Erba PA, Iung B, et al. Clinical presentation, aetiology and outcome of infective endocarditis: results of the ESC-EORP EURO-ENDO (European infective endocarditis) registry: a prospective cohort study. Eur Heart J 2019;40:3222-32.

34. AATS Surgical Treatment of Infective Endocarditis Consensus Guidelines Writing Committee. 2016 The American Association for Thoracic Surgery (AATS) consensus guidelines: surgical treatment of infective endocarditis: executive summary. J Thorac Cardiovasc Surg 2017;153(6): 1241-1258.e29.

35. Kang D-H, Kim Y-J, Kim S-H, et al. Early surgery versus conventional treatment for infective endocarditis. N Engl J Med 2012;366:2466-73.

36. Anantha Narayanan M, Mahfood Haddad T, Kalil AC, et al. Early versus late surgical intervention or medical management for infective endocarditis: a systematic review and meta-analysis. Heart 2016;102:950-7.

37. Liang F, Song B, Liu R, Yang L, Tang H, Li Y. Optimal timing for early surgery in infective endocarditis: a meta-analysis. Interact Cardiovasc Thorac Surg 2016;22: 336-45.

38. Beganovic M, Luther MK, Rice LB, Arias CA, Rybak MJ, LaPlante KL. A review of combination antimicrobial therapy for *Enterococcus faecalis* bloodstream infections and infective endocarditis. Clin Infect Dis 2018;67:303-9.

39. Iversen K, Ihlemann N, Gill SU, et al. Partial oral versus intravenous antibiotic treatment of endocarditis. N Engl J Med 2019;380:415-24.

40. Bundgaard H, Ihlemann N, Gill SU, et al. Long-term outcomes of partial oral treatment of endocarditis. N Engl J Med 2019;380:1373-4.

41. Spellberg B, Chambers HF, Musher DM, Walsh TL, Bayer AS. Evaluation of a paradigm shift from intravenous antibiotics to oral step-down therapy for the treatment of infective endocarditis: a narrative review. JAMA Intern Med 2020 March 30 (Epub ahead of print).

42. Venn RA, Ning M, Vlahakes GJ, Wasfy JH. Surgical timing in infective endocarditis complicated by intracranial hemorrhage. Am Heart J 2019;216:102-12.

43. Gatti G, Sponga S, Peghin M, et al. Risk scores and surgery for infective endocarditis: in search of a good predictive score. Scand Cardiovasc J 2019;53:117-24.

44. Escolà-Vergé L, Peghin M, Givone F, et al. Prevalence of colorectal disease in *Enterococcus faecalis*: results of an observational multicenter study. Rev Esp Cardiol (Engl Ed) 2019 August 20 (Epub ahead of print).

45. Pericàs JM, Corredoira J, Moreno A, et al. Relationship between *Enterococcus faecalis* infective endocarditis and colorectal neoplasm: preliminary results from a cohort of 154 patients. Rev Esp Cardiol (Engl Ed) 2017;70:451-8.

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