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Aortic Valve Insufficiency in a 45-Year-Old Male

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Patient
45-year-old male.

Chief Complaint
Feeling under the weather, unable to go to work.

Past Medical History
Patient was referred from an outside hospital for evaluation of his aortic valve insufficiency. A transthoracic echocardiography study performed at an outside hospital within the previous week was not diagnostic for endocarditis and multiple blood cultures were negative. The patient has a history of ethanol abuse and poor dentition.

Family History
Unremarkable.

Physical Exam
Vital signs: temperature, 36.2°C; heart rate, 110 beats per minute; respiratory rate, 20 per minute; blood pressure 90/60 mm Hg. Skin: No rash. Extremities: No clubbing, cyanosis, edema. Pulmonary: Clear to auscultation bilaterally. Cardiac: Tachycardic with regular rhythm, 5/6 diastolic murmur (aortic area). Extremities: Unremarkable. Neuro: Alert and oriented, cranial nerves intact.

Principal Laboratory Findings (Table 1)

Results of Additional Diagnostic Procedures
Chest x-ray: Bilateral pleural effusions and diffuse interstitial prominence, consistent with interstitial edema. A transthoracic echocardiogram performed at admission identified severe aortic and mitral valve regurgitation. EKG: Normal.

Questions:

1. What are this patient's most striking clinical and laboratory findings?
2. How do you explain this patient's most striking clinical and laboratory findings?
3. What additional test(s) should be ordered on this patient and why?
4. What is this patient's most likely diagnosis?
5. How is this patient's condition typically treated?

Table 1_Principal Laboratory Findings

Test	Patient's Result	"Normal" Reference Interval
Hematology		
WBC Count	9.5	4.5-11.0 x10^9/L
RBC	3.51	4.50-5.90 x10^{12}/L
HCT	34.2	41.0-53.0%
MCV	93	80-100 fL
Platelets	170	150-440 x10^9/L
Chemistry		
Sodium	137	135-145 mmol/L
Potassium	3.4	3.5-5.0 mmol/L
Chloride	110	98-107 mmol/L
CO_2	21	22-30 mmol/L
BUN	6	7-21 mg/dL
Creatinine	0.7	0.8-1.4 mg/dL
TSH	3.36	0.46-4.68 microIU/ml

WBC, white blood cell; RBC, red blood cells; HCT, hematocrit; MCV, mean corpuscular volume; BUN, blood urea nitrogen; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; GGT, gamma-glutamyl transferase; CK, creatine kinase.

Possible Answers:

1. Significant clinical findings in this patient include tachycardia (HR>100), hypotension, 5/6 diastolic murmur, a history of prior and current dental disease, including tooth extractions on the day of admission, transesophageal echocardiogram with severe aortic and mitral valve regurgitation, pulmonary edema, and a normal EKG. Significant laboratory findings include multiple negative blood cultures (outside hospital), normocytic anemia, and a normal white cell count.

2. **Sinus tachycardia** (>100 beats/minute) in the absence of arrhythmia is a physiologic response to stress. Causes include fever, anxiety, exercise, thyrotoxicosis, hypoxemia, hypotension, congestive heart failure, or volume depletion. **Hypotension** can result from shock, a clinical syndrome characterized by hypoperfusion (and hypo-oxygenation) of organs. Shock has a variety of causes, generally categorized by hypovolemic shock (inadequate circulating volume, plasma volume loss, or excessive water and electrolyte loss), septic shock (infection), or neurogenic shock (drugs, spinal anesthesia). Lastly, cardiogenic shock can cause hypotension due to impaired contractility (mitral insufficiency, aortic insufficiency, dilated cardiomyopathy, acute myocardial infarction), decreased preload (right ventricular infarction, pulmonary embolism, pericardial tamponade), excessive afterload (malignant hypertension, aortic stenosis, hypertrophic cardiomyopathy). **Aortic regurgitation** (AR) results from aortic valve cusp thickening and shortening, which prevents complete closing during diastole. This results in a diastolic murmur, which represents

the backflow of blood through the incompletely closed aortic valve. Nearly 2/3 of patients with AR have a history of rheumatic disease, which is mainly associated with mitral valve defects.[1] Rheumatic disease less commonly causes isolated aortic valve disease. Other causes of aortic regurgitation include congenitial membrane subaortic stenosis (thickened valve leaflets), rheumatoid spondylitis, congenital bicuspid valves, prolapse secondary to ventricular septal defects, and congenital fenestrations of the aortic valve.[1] Primary aortic root disease resulting in the separation of the aortic valve leaflets can cause aortic regurgitation. Aortic root disease may manifest in Marfan's syndrome, idiopathic dilation of the aorta, syphilis, ankylosing spondylitis, and severe hypertension, which may develop into progressive AR. Acute aortic regurgitation can also result from infective endocarditis which can occur on valves previously damaged by rheumatic disease, congenitally deformed valves, and on occasion a normal aortic valve.[1] The most common causes of **pulmonary edema** include heart failure and volume overload. The functional consequence of pulmonary edema is the failure of gas exchange due to the excess fluid in the lungs.

3. Echocardiography should be performed in patients where the suspicion of endocarditis is high. Transesophageal echocardiogram (TEE) is able to anatomically confirm the presence of a vegetation and determine its size in >90% of patients with endocarditis. Transesophageal echocardiograms can also be used to assess for abscesses and determine cardiac function. Transesophageal echocardiogram has a higher sensitivity of detection cardiac valve vegetations than transthoracic echocardiography (TTE). The patient in the present case underwent both transthoracic and transesophageal echocardiography, both of which revealed a markedly thickened, bicuspid aortic valve. Moreover, large filamentous and highly mobile vegetations were noted on the two aortic cuspids and on the chordae of the medial papillary muscle just adjacent to the mitral valve (**Image 1**). The large aortic valve vegetation measured approximately 29 mm in length. The vegetation adjacent to the mitral valve was multilobular and measured approximately 20 mm in length. Significant aortic and mitral valve insufficiency was identified by Doppler mode. No abnormalities were identified on the right side of the heart. A cardiac MRI was additionally performed to evaluate the patient for abscess formation. There was no evidence of abscess formation by either echo or MRI. **Blood cultures** should be performed because identification of an organism is critical for both the diagnosis of endocarditis and selection of appropriate antibiotics.[2] In the absence of prior antibiotic treatment, 3 blood cultures should be collected from different venipuncture sites over 24 hours. If the cultures are negative, additional blood cultures should be performed after 48 to 72 hours and the laboratory notified that they should look for fastidious organisms by extending the incubation time.[1,2] Patients with deteriorating hemodynamics should be treated empirically for endocarditis. Peripheral blood cultures were collected from 2 sites on day 1 and the day after admission in the present case. Aerobic and anaerobic cultures were negative after 1 week. **Serological tests** can help determine the identification of organisms that are difficult to recover by blood culture. In the United States, serology testing for *Coxiella burneti* is used with some frequency, while additional testing for *Brucella* and *Bartonella* is used with more frequency in other parts of the world. **Studies to assist in the management** of endocarditis include CBC, creatinine, chest radiograph, EKG, and cardiac catherization in patients who undergo valve replacement to assess for coronary artery disease. The indications for surgery with endocarditis include heart failure, uncontrolled infection, significant valve dysfunction, artificial valve replacement, abscess formation, or recurrent emboli.[3] The decision to replace this patient's valve was based on his significant aortic and mitral valve dysfunction. The patient underwent cardiac catherization, which identified a 75% blockage in his left anterior descending coronary artery. A head CT with contrast was performed to identify possible septic emboli and was negative. **Direct examination** of pathogens can identify vegetations by microscopic examination, culture, special stains, and PCR identification. On day 5 of the patient's hospital stay, he underwent surgery to replace/repair his aortic and mitral valve in addition to coronary artery bypass surgery on his left anterior descending coronary artery. The aortic and mitral valves were sent to microbiology for direct examination and culture. The valves were minced, placed on slides, and Gram stained. Gram-positive cocci in chains were abundant throughout the specimens (**Image 2**). Both aortic and mitral valves were processed for histology (**Image 3**) and demonstrated fibrosis with focal areas of granulation tissue, fibrinopurulent exudates, and acute inflammation consistent with endocarditis. Tissue Gram stains showed sheets of gram-positive cocci when stained with a modified Brown and Brenn Gram stain. Aerobic and anaerobic cultures of the aortic and mitral valve were negative after 1 week as were cultures for fungus, *Legionella,* and *Actinomyces*.

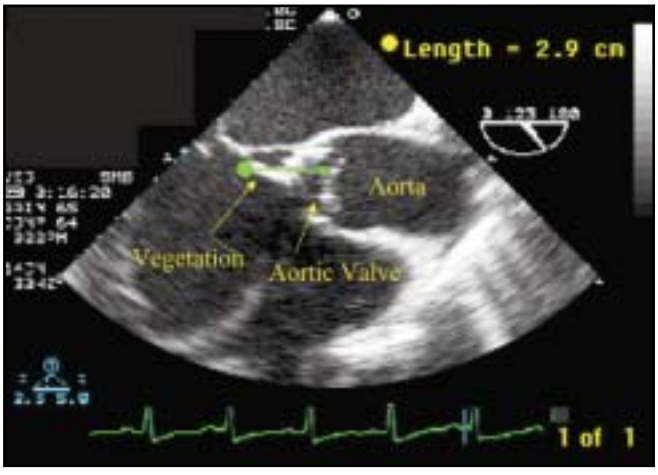

Image 1_Trans-esophageal echocardiographic study of the patient described in this study. Vegetation (Green Line) on the aortic valve was present and floating freely upon trans-esophageal echocardiography in this patient upon presentation.

Molecular detection. Currently few laboratories have the capability to detect bacteria other than *Chlamydia trachomatis* and *Neisseria gonorrhoeae* by molecular means. However this is a potentially powerful alternative to diagnosing infections from internal body sites such as cardiac vegetations in a patient with culture negative endocarditis.[4-11] In this approach, primers with a broad range are used to amplify specific regions of the 16S rRNA gene. The resulting amplicons are then sequenced and the obtained sequence is matched with known sequences for specific organisms. If the obtained sequence matches a known organism sequence, the patient is considered infected by this organism.

4. ***Most likely diagnosis:*** *Infective endocarditis due to viridins streptococci.*

The **Duke Criteria** are used to diagnose infective endocarditis using both clinical and laboratory findings (**Table 2**).[12] Infective

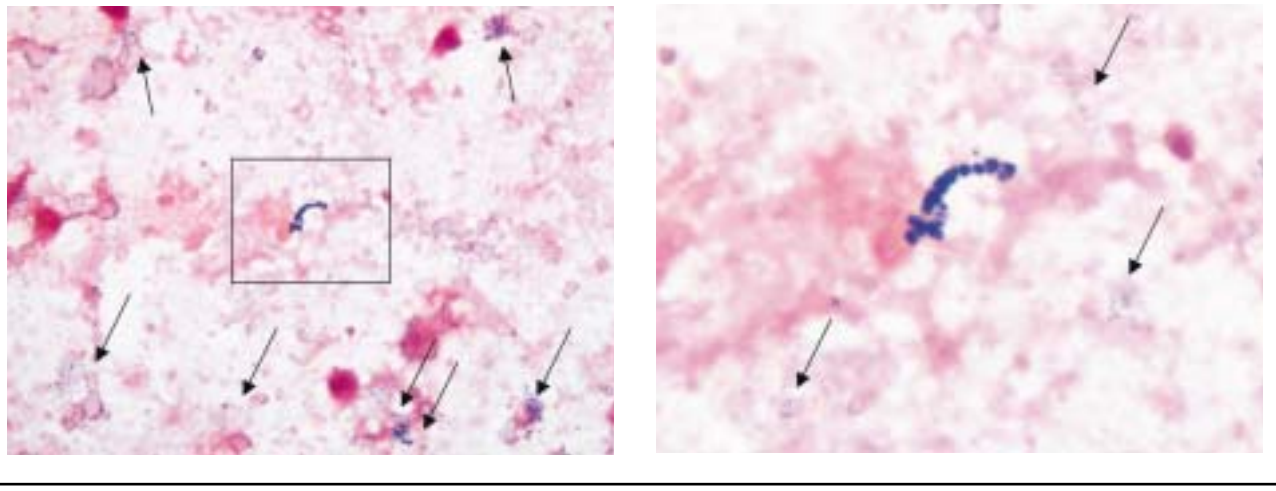

Image 2_Mitral valve biopsy Gram stain seen at 400x (left) and 100x (right) demonstrates gram-positive cocci in chains. Distributed throughout the biopsy preparation, gram-positive cocci that stain poorly are present (arrows) and may represent the results of pre-surgical antibiotic therapy.

endocarditis can be diagnosed in 4 ways. The diagnosis can be made if there is positive valve culture or histology. In the present case, gram-positive cocci in chains were identified from the valves removed during surgery, which confirms the diagnosis of infective endocarditis. A patient can also be diagnosed if they have 2 major criteria: 1) typical organism present; 2) positive echo for vegetations; 3) abscess/valve dehiscence OR 5 of 6 minor criteria: 1) valvular heart disease; 2) fever; 3) vasculitis; 4) skin lesions; 5) suggestive echo; 6) positive blood culture. Lastly, the diagnosis of infective endocarditis can be made if 1 major and 3 minor criteria are met. The presence of gram-positive cocci in chains in the present case is suggestive of *Streptococcus* and *Enterococcus* spp., both of which have been implicated in infective endocarditis (**Table 3**). In native valve infective endocarditis, 45% to 65% are caused by *Streptococcus* species, while 5% to 8% are caused by *Enterococcus* species.[2] Of the *Streptococcus* spp. implicated in

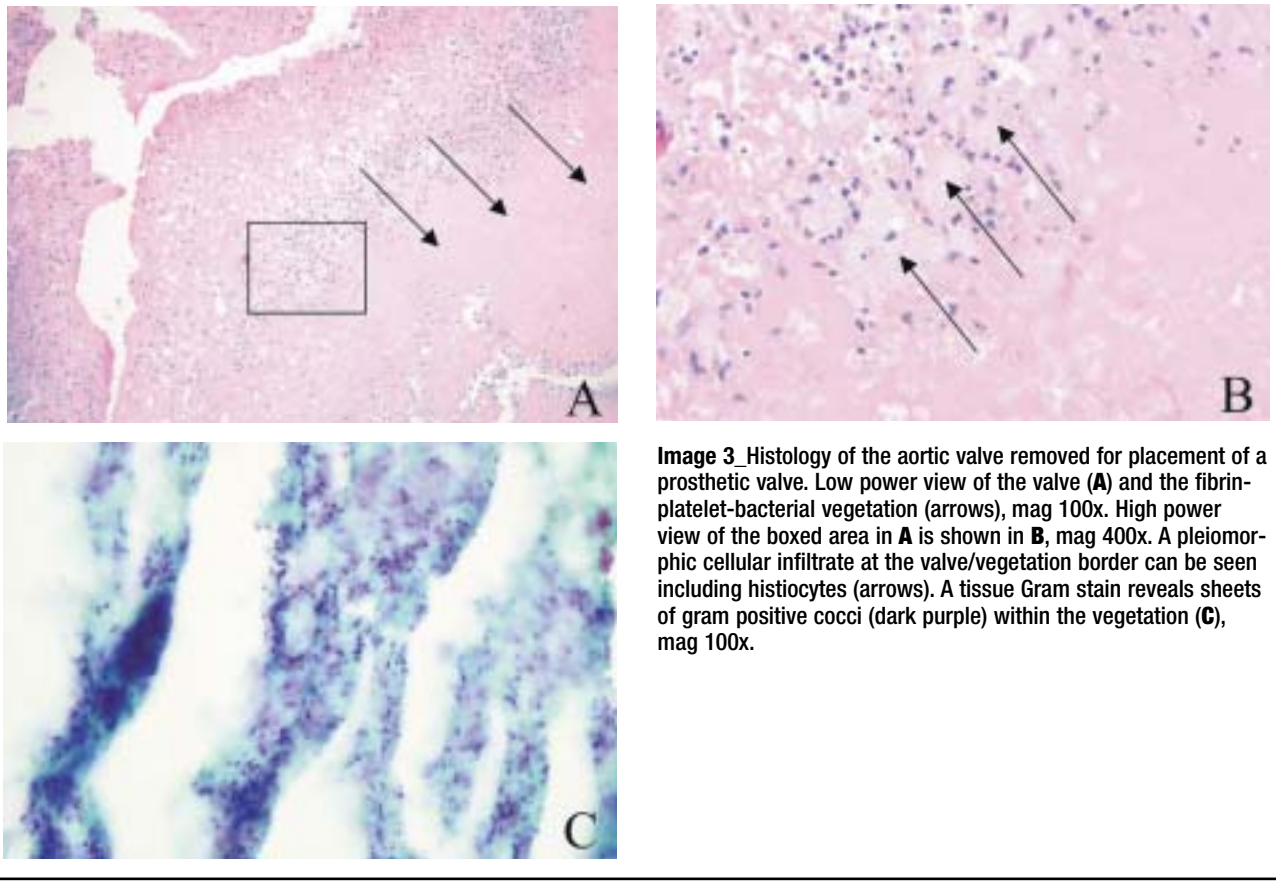

Image 3_Histology of the aortic valve removed for placement of a prosthetic valve. Low power view of the valve (**A**) and the fibrin-platelet-bacterial vegetation (arrows), mag 100x. High power view of the boxed area in **A** is shown in **B**, mag 400x. A pleiomorphic cellular infiltrate at the valve/vegetation border can be seen including histiocytes (arrows). A tissue Gram stain reveals sheets of gram positive cocci (dark purple) within the vegetation (**C**), mag 100x.

Table 2_Diagnostic (Duke) Criteria of Infective Endocarditis

1. Positive valve culture or histology	OR
2. 2 major criteria:	
a. Typical organism	
b. Positive echocardiography for vegetations	
c. Abscess or valve dehiscence	OR
3. 5 of 6 minor criteria:	
a. Valvular heart disease or IV drug abuse	
b. Fever greater than 38°C	
c. Vasculitis	
d. Skin lesions	
e. Suggestive echocardiography (but not definitive)	
f. Positive blood culture	OR
4. 1 major and 3 minor criteria	

Adapted from: Durack DT, et al., Am J Med, *1994;96:200-209.*

Table 3_Etiologic Agents Found in Native-Valve Infective Endocarditis

Pathogen	Native Valve Patient age 16-60 years old	Prosthetic Valve <60 days (60 days -12 months) after procedure
Streptococcus spp.	45-65%	1 (7-10)%
Staphylococcus aureus	30-40%	20-24 (10-15)%
Coag-neg staphylococci	4-8%	30-35 (30-35)%
Enterococcus	5-8%	5-10 (10-15)%
Gram-neg bacilli	4-10%	10-15 (2-4)%
Fungi	1-3%	5-10 (10-15)%
Culture neg/HACEK* organisms	3-10%	3-7 (3-7)%
Diptheroids	<1%	5-7 (2-5)%
Polymicrobial	1-2%	2-4 (4-7)%

Adapted from: Mylonakis et al., N Engl J Med. *2001;345(18):1318.*
**HACEK: Haemophilus* spp., *Actinobacillus actinomycetemcomitans, Cardiobacterium hominus, Eikinella la corrodens, Kingella kingae.*

endocarditis, 75% are due to viridans group streptococcus, 20% to *Streptococcus bovis*, and the remaining 5% are due to other *Streptococcus* spp. Viridans group streptococcus are found mainly in the oral cavity, where trauma to the tissues can precipitate bacteremia. The severity of periodontal disease and the intensity of the trauma play a role in the magnitude and frequency of bacteremia. *Enterococcus* bacteremia, on the other hand, is associated with examination and instrumentation of the gastrointestinal and genitourinary tract.[13] The patient in the current study had 2 negative aerobic and anaerobic blood cultures in addition to a negative aortic valve biopsy culture plated both aerobically and anaerobically. Therefore, the history of poor dentition in this patient, along with the gram-positive cocci in chains detected in the vegetation itself, leads to the likely conclusion that this patient had viridans streptococcus endocarditis.

The incidence of infective endocarditis continues to rise with a yearly incidence of around 15,000 to 20,000 new cases in the United States.[14] The incidence of community-acquired infective endocarditis (IE) on native-valves in the United States and western Europe is approximately 1.7 to 6.2 cases per 100,000 people per year.[2] Men are affected almost twice as much as women (1.7:1), and the median age is 47 to 69 years.[2] When endocarditis is associated with intravenous drug use, the incidence is approximately 150 to 2000 per 100,000 people per year.[2] Multiple conditions pre-dispose people to infective endocarditis including diabetes mellitus, hemodialysis (long-term), and poor dental hygiene.[2] The most common cardiovascular disease associated with infectious endocarditis is mitral valve prolapse (100 per 100,000 person with IE per year).[2] Rheumatic heart disease, as a result of group A streptococcus infection in the young, is the most common pre-disposing factor leading to infective endocarditis in the world.[2]

Endothelial cells in the vasculature are resistant to bacteria and thrombus formation unless they are injured. Endothelial cell injury may result in turbulent flow that can be conducive to either infection or the development of platelet-fibrin thrombus (non-bacterial thrombotic enodcarditis).[1] The formation of a thrombus can also serve as a place where bacteria can attach during episodes of bacteremia. Organisms found in endocarditis (**Table 3**) enter the blood from skin, mucosal surfaces, or discrete infections. Most bacteria adhere directly to thrombi except more virulent bacteria such as *S. aureus,* which can adhere to the endothelial cells/sub-endothelium directly.[1] The proliferating organisms at the valve site induce tissue factor (TF) which is released from monocytes and/or endothelial cells, initiating the coagulation cascade, leading to fibrin deposition at the site. This leads to the formation of "vegetation," which is comprised of inflammatory cells, bacteria, fibrin, and platelets. Adherence of organisms is achieved by receptors that bind fibronectin in many gram-positive bacteria, a fibrinogen/fibrin binding protein on *S. aureus* (clumping factor), and glucan binding protein on streptococci.[1] *Streptococcus mutans* has additionally been shown to be able to bind and activate plasminogen, which could be part of the pathogenesis by which extracellular matrix molecules are degraded.[15] Organisms deep in the vegetation are metabolically active and resistant to antibiotics. The organisms are continuously released into the circulation and cleared by the immune system or re-colonize the vegetation. Endocarditis may arise as a result of vegetation embolization on the heart valve, damage to cardiac structures, and tissue injury due to circulating immune complexes. Embolized vegetation can lead to infection and/or infarction to distant sites such as the extremities and brain.

Patients with infective endocarditis have non-specific cardiac and non-cardiac symptoms. Heart murmurs represent cardiac pathology, specifically valvular damage. Significant regurgitant murmurs can lead to heart failure. The patient in the present study had a significant diastolic murmur as a result of his aortic and mitral valve insufficiency. Thirty to forty percent of patients have a murmur upon presentation and congestive heart failure occurs in as many people as well.[1] If the infection extends into the adjacent myocardial tissues, form abscesses, and extend through the epicardium, pericarditis can occur. Abscesses adjacent to the aortic valve can lead to disruption of the conductive system and heart block. Emboli can break off and end up in the coronary arteries resulting in myocardial infarction, although this is rare.[16] Hematogenous spread of infection can lead to focal infection in the skin, kidneys, meninges, and muscle. Arterial emboli are apparent in nearly 50% of patients clinically, particularly in patients with vegetations that are >10 mm in diameter.[17] Antibiotic treatment decreases embolic event rates that are 13/1,000 patient days in the first week to 1.2/1,000 patient days in the 3rd week.[17] Mimicking the more severe embolic lesions are Janeway lesions (under fingernails) and Osler's nodes seen in *S. aureus* endocarditis. Systemic emboli occur in 22% to 50% of endocarditis cases.[18] Of these, 60% to 70% involve the central nervous system, which result in severe and potentially lethal manifestations.[18]

The patient described in this case had his aortic valve replaced, which places him in another risk category of infective endocarditis. While prosthetic valve endocarditis presents the same way as native valve endocarditis does, the symptoms can be overlooked as morbidity associated with the surgery to replace the valve. The types of infections that occur during this time are significantly different from native valve infections and should be treated appropriately. Specifically, the most common infection within the first year is coag-negative staphylococcus.[2] The patient was started on coumadin on post-operative day #2 in order to reduce emboli formation in the new prosthetic aortic valve. He was released several days later with an INR of 2.9 (goal 2 to 3).

5. Left untreated, patients with infective endocarditis are at high risk for death. Therefore, it is important to institute therapy as quickly as possible. Bacterial vegetation is avascular and the bacteria are not proliferating, which makes eradication with antibiotics extremely difficult. Since complete eradication is necessary for therapy, antimicrobial therapy has to be bactericidal and long term.[1] In the present case, the aortic valve was replaced, the mitral valve repaired, and the vegetations removed. However, prolonged antibiotic therapy based on the presumed organisms needed to be given. Most viridans streptococcus species are susceptible to penicillin. However, recent studies have identified an increase in resistance to penicillin.[19,20]

Native valve therapies. If the viridans streptococci are penicillin susceptible (MIC <0.1 μg/mL), penicillin G or ceftriaxone is recommended.[2] Gentamicin can be given concomitantly in some cases, but is not recommended in patients with abscesses, extracardial foci, or prosthetic valve endocarditis.[2] In streptococcus species with a penicillin MIC >0.5 and enterococcus species, penicillin G (or ampicillin) with gentamicin for 4 to 6 weeks should be given.[2] In these patients, 6 weeks of antibiotic therapy is recommended if the symptoms have been longer than 3 months or if other complications such as myocardial abscess are present.[2] In native valve endocarditis where the culture is negative, antibiotics generally given include penicillin, ampicillin, ceftriaxone, or vancomyin in combination with an aminoglycoside.[2] The patient described is the present case was treated with vancomycin and tobramycin to be continued for 6 weeks in accordance with these previous studies. Both peak and trough drug levels were to be followed weekly to ensure that adequate drug levels were being achieved.

Prognosis. Mortality and morbidity are generally related to the patient's other diseases and endocarditis-related organ damage and not antibiotic failure.[1] Survival for patients with native valve endocarditis caused by viridans streptococci, HACEK organisms, or enterococci range from 85% to 90%.[1] A high rate of mortality (40% to 50%) is seen in prosthetic valve replacement if it occurs within the first 60 days.[1] Mortality is lower (10% to 20%) for later onset prosthetic valve infection.[1]

Prevention. Prophylactic antibiotics should be given to patients at risk for endocarditis undergoing procedures that have a high probability of inducing bacteremia (dental procedures likely to cause bleeding, tonsillectomy/adenoidectomy, surgery on infected tissues, surgery of airways/GI/GU tracts). The evidence for the benefit of antibiotic prophylaxis is modest and unproven.[21,22] It has been estimated that patients requiring penicillin are 5 times more likely to die from anaphylaxis than infective endocarditis.[22] Only one-half of patients with native valve endocarditis are diagnosed following a procedure.[1] However, maintaining dental hygiene is important for patients at risk for infective endcarditis.[1] In fact, poor dental health itself is a significant risk factor for the development of endocarditis. Since the patient in this study had an ongoing history of dental disease, and his endocarditis source was likely from his oral flora, it is important that the patient resolves his dental problems. The rate of relapse in native valve penicillin-susceptible viridans streptococci is less than 2%; the relapse rate for enterococci is 8% to 20%.[2] These facts emphasize the need to resolve his dental problems, which also place him at a greater risk for relapse with his prosthetic valve. LM

Keyword

Infective endocarditis, viridins streptococcus, *Enterococcus*

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