# An Altered Adolescent

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## Case

A healthy 17-year-old male was referred to the pediatric emergency department (ED) from his doctor's office for 1 day of fever and vomiting, incidentally noted to have right lower quadrant tenderness. He reported generalized weakness and nausea. He was afebrile with normal vital signs. Examination was significant for diffuse right-sided abdominal tenderness with guarding. His neurologic, cardiac, and pulmonary examinations were normal. Laboratory tests were remarkable for a left shift on complete blood count (92.8% granulocytes and 7.4 white blood cells). Ultrasound did not visualize the appendix. Intravenous fluids and ondansetron were administered with subsequent improvement in pain and vomiting. The patient was diagnosed with viral gastroenteritis and discharged home.

He returned to the ED later that evening again with fever and vomiting as well as altered mental status. He had become confused and disoriented at home; his parents reported that he could not remember how to flush the toilet or open a door. On arrival, he was afebrile but tachycardic to 115. He was anxious and ill appearing, confused and slow to answer questions. He complained of headache, right hand numbness, and nausea. He had no neck stiffness or neurologic deficits. The remainder of his examination was unremarkable. Complete blood count was significant for platelets of 78 (compared with 124 the day before), white blood cell count of 4.34 with 87.8% granulocytes. C-reactive protein was 290.7 mg/dL, procalcitonin 4.67 ng/dL, lactic acid 2.1 µmol/L, 2+ proteinuria. D-Dimer was 4.57 mg/L FEU and fibrinogen was 562 mg/dL. Coagulation studies were normal and urine drug screen was negative.

The patient received 2 intravenous 20 mL/kg saline boluses as well as metoclopramide and diphenhydramine for headache. Computed tomography scan of the head was normal. Vancomycin and ceftriaxone were given expeditiously prior to lumbar puncture due to concern for meningitis and sepsis. Cerebrospinal fluid (CSF) was remarkable for glucose of 48 mg/dL, protein of 109 mg/dL, white blood cell count of 87/mm$^3$, and, red blood cell count of 161/mm$^3$. CSF gram stain showed an intracellular gram-negative organism. Dexamethasone and cefepime were added due to concern for Neisseria meningitis.

During a 11-day hospital stay, 2 consecutive blood cultures grew *Staphylococcus aureus*. A new-onset murmur was noted, which was not present during his ED visit. Additionally, erythematous lesions appeared on the soles of his feet that were concerning for Janeway lesions (Figure 1). Transesophageal echo showed a bicuspid aortic valve with trace insufficiency and a 16 mm strand-shaped vegetation attached to the posterior aspect of the left ventricular outflow tract just inferior to the aortic valve, which moves back and forth between the aortic valve leaflets during the cardiac cycle (Figure 2). Although his mental status had returned to normal, magnetic resonance imaging of the brain demonstrated multiple areas of emboli (Figure 3). The CSF culture ultimately showed no growth, and the organism on initial gram stain had a "chewed up appearance" consistent with recent antibiotic administration. On hospital day 5 he underwent surgical removal of the vegetation, which was found to arise from an area of the ventricular septum below the aortic valve and adjacent to the mitral leaflet yet distinctly separate from both valve annuli. Postoperative echo showed no residual vegetation. He received 2 weeks total of cefepime and gentamycin and 8 weeks of oxacillin and recovered well.

## Final Diagnosis

Infective endocarditis with bacterial meningitis secondary to septic emboli.

## Discussion

Infective endocarditis is relatively uncommon in children but is associated with significant morbidity and mortality.[1] Infective endocarditis results from complex interplay between damaged endothelium, fibrin, platelets, and blood-borne pathogens. Injury to the endocardial surface

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is typically caused by turbulent blood flow in children with congenital heart disease or indwelling catheters in children without congenital heart disease. This injury results in the formation of a noninfected thrombus composed of fibrin, platelets, and occasional red blood cells. Finally, transient bacteremia or fungemia leads to the adherence of pathogens to the thrombus at the site of injury. Further platelet and fibrin deposition results in an infected vegetation with a protective sheath, which allows for rapid propagation of the organisms while also protecting them from the host's immune system. Secondary involvement of other organs is due to septic embolization or immune-mediated processes.[2]

**Figure 1.** Janeway lesion.

The annual incidence of infective endocarditis in the United States is approximately 0.05 to 0.12 per 1000 pediatric hospital admissions.[3] Overall incidence is estimated at about 0.43 per 100 000 children.[4] This is lower than in adults, who have a reported incidence of about 15 per 100 0005.[5] Prior to the 1970s, as many as 50% of pediatric infective endocarditis cases occurred in the setting of underlying rheumatic heart disease. The prevalence of rheumatic heart disease has significantly declined in developing countries; it is now uncommon for infective endocarditis patients to have underlying rheumatic heart disease. Following the dramatic decrease in rheumatic heart disease, the incidence of pediatric infective endocarditis reached a nadir in the 1960s. Leading up to the 21st century, the incidence of infective endocarditis began to rise in children due to advances in cardiovascular surgery, improved survival in patients with congenital heart disease, and more frequent use of indwelling central venous catheters.[6] Congenital heart disease is now the most common underlying condition in pediatric endocarditis.[7] The cumulative incidence in children with underlying congenital heart disease is 6.1 per 1000.[3]

Cyanotic lesions such as tetralogy of Fallot, single ventricle defects, transposition of the great arteries, and tricuspid atresa are at highest risk for infective endocarditis, followed by endocardial cushion defects and left-sided lesions.[7,8] Bicuspid aortic valve is the most common congenital heart condition. Patients with bicuspid aortic valve endocarditis tend to be younger and with less comorbidities than those with tricuspid valves, and tend to be more commonly infected with *S aureus*.

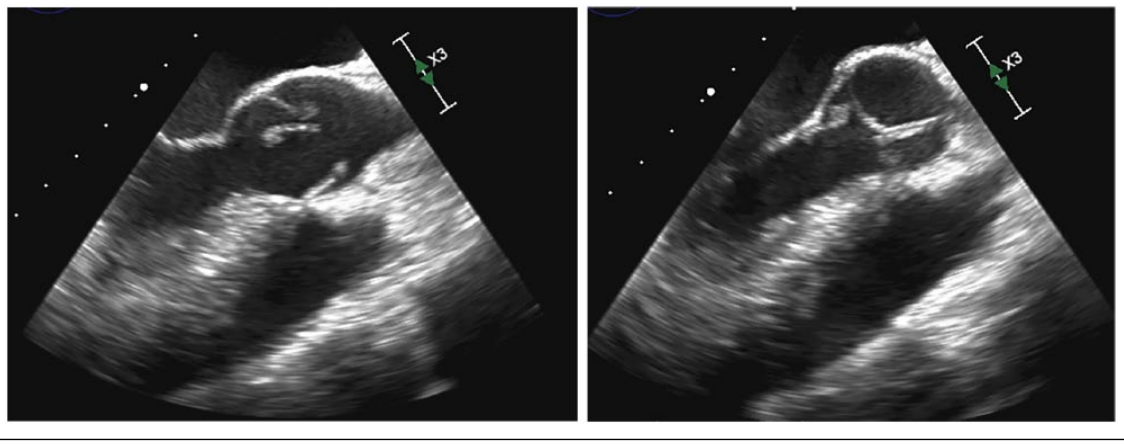


**Figure 2.** Echocardiogram showing vegetation strand along left ventricular outflow tract.

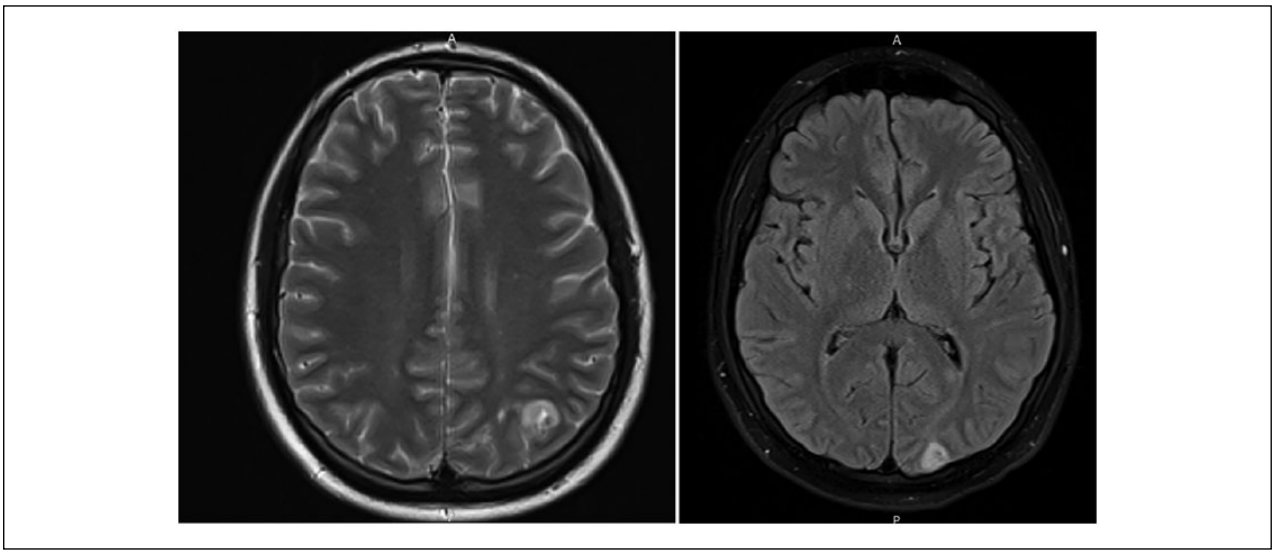

**Figure 3.** MRI showing left parietal and occipital areas of emboli with infarct.

In addition they tend to have more perivalvular complications and require surgery more often.[9]

The mortality risk of pediatric infective endocarditis varies from 5% to 10%,[10] compared with 20% overall mortality in adults.[11] Risk factors for mortality include congenital heart disease, prematurity, and *S aureus* infection. *Staphylococcus* species and viridans *Streptococcus* group are the most common pathogens seen in culture-positive pediatric infective endocarditis. *S aureus* accounted for approximately 36% to 57% of hospitalizations; it is the most common pathogen overall and in those without an underlying heart condition.[6] Viridans *Streptococcus* group is the most common pathogen in those with underlying heart conditions.[4] Staphylococcal infections are associated with worse outcomes than non-staphylococcal infective endocarditis; there is a significant increase in length of stay, acute kidney injury, and mortality.[6]

Diagnosis of infective endocarditis requires a high degree of clinical suspicion; its presentation is nonspecific and variable. Fever is present in more than 85% of cases, but the other signs and symptoms depend on the infective agent, the degree of cardiac damage, systemic involvement of other organs, and the time course of the disease. In addition to fever, patients may present with new onset or changing heart murmur, petechiae, hepatosplenomegaly, glomerulonephritis, or congestive heart failure. The traditional peripheral stigmata of infective endocarditis—Osler's nodes, Janeway's lesions, and splinter hemorrhages—has become rare due to improved early recognition and effective antibiotic treatment.[2]

Infective endocarditis is typically divided into acute and subacute presentations. Acute infective endocarditis generally presents with high fevers, toxic appearing patients, and rapid deterioration. *S aureus* is the most common causative organism in acute cases. Viridans group streptococci and other less virulent pathogens are typically seen in subacute infective endocarditis. The characteristic feature of subacute infective endocarditis is a protracted low-grade fever, which is generally accompanied by nonspecific symptoms such as weight loss, fatigue, diaphoresis, and arthralgias.[2]

The modified Duke criteria are used to make a definitive diagnosis of infective endocarditis in children. Diagnosis can be made based on either pathologic or clinical criteria. The pathologic criteria require a vegetation or intracardiac abscess and evidence of active infection, which is established by histology or cultures. The clinical criteria for diagnosis, divided into major and minor, are listed in Table 1. Definitive diagnosis of infective endocarditis is established with either 2 major criteria, 1 major and 3 minor criteria, or 5 minor criteria. All diagnoses made with the pathologic criteria are definite, but the clinical criteria allow the diagnosis of possible infective endocarditis, this is one of the modifications made to the original Duke criteria. Possible infective endocarditis is diagnosed when the patient fulfills 1 major and 1 minor clinical criteria or 3 minor clinical criteria.[2]

While neurological sequelae (seizures, stroke, hemorrhage, brain abscess, diffuse vasculitis, or meningitis) may occur in up to 30% of pediatric cases of infective endocarditis, bacterial meningitis is a rare initial presentation in children. Mohapatra et al[12] described a case in which a previously healthy, unimmunized 10-month-old girl who presented in sepsis with meningeal signs and a new-onset murmur. She was later confirmed to

**Table 1.** Major and Minor Criteria[a].

| Major Criteria |
|---|
| *Two positive blood cultures with typical organisms* |
| Typical microorganism for infective endocarditis from 2 separate blood cultures: viridans streptococci, *Staphylococcus aureus*, *Streptococcus bovis*, HACEK group (*Haemophilus* spp, *Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella* spp, and *Kingella kingae*) *or* |
| Community-acquired enterococci, in the absence of a primary focus |
| *Persistent bacteremia* |
| Persistently positive blood culture, defined as recovery of a microorganism consistent with infective endocarditis from blood cultures drawn more than 12 hours apart *or* |
| Persistently positive blood culture, defined as recovery of a microorganism consistent with infective endocarditis from all of 3 or a majority of 4 or more separate blood cultures, with first and last drawn at least 1 hour apart |
| *Single positive blood culture for Coxiella burnetti or phase I antibody titer $>1:800$* |
| *Evidence of endocardial involvement on echocardiogram* |
| Positive findings: oscillating intracardiac mass, on valve or supporting structures, or in the path of regurgitant jets, or on implanted material, in the absence of an alternative anatomic explanation or myocardial abscess or new partial dehiscence of prosthetic valve |
| *New valvular regurgitation (increase or change in preexisting murmur not sufficient)* |
| **Minor Criteria** |
| Predisposing heart condition or intravenous drug use |
| Fever $\geq$38.0°C (100.4°F) |
| Vascular phenomena: major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhage, Janeway lesions |
| Immunologic phenomena: glomerulonephritis, Osler's nodes, Roth spots, rheumatoid factor |
| Positive blood culture not meeting major criterion as noted previously (excluding single positive cultures for coagulase-negative staphylococci and organisms that do not cause endocarditis) or serologic evidence of active infection with organism consistent with infective endocarditis |

[a]Adapted from Baltimore et al.[2]

have *Streptococcus* pneumonia meningitis and endocarditis when a mitral valve vegetation was found on follow-up echocardiogram.

Angstwurm et al[13] also performed an extensive literature review of published infective endocarditis case series from 1967 to 2000. In these studies, the frequency of meningitis in patients with infective endocarditis varies from 0% to 20%; the mean frequency is 3.5%, median 6.8%. Meningitis was noted at presentation in 57 of a possible 3712 cases. Lucas et al[14] performed a prospective nationwide cohort study of adults with community-acquired bacterial meningitis in the Netherlands from 2006 to 2012. Endocarditis was identified in 24 of 1025 episodes (2%) of bacterial meningitis. Three patients were diagnosed with meningitis and endocarditis when initially admitted, but 21 of the 24 (87.5%) endocarditis cases were not identified until the patient was already hospitalized.[14]

## Conclusion

In our patient, his previously undiagnosed bicuspid aortic valve with regurgitation in combination with transient staphylococcal bacteremia likely led to vegetation growth on the ventricular wall, which subsequently embolized and seeded his meninges, creating septic emboli containing multiple organisms. The gram-negative intracellular rod seen on CSF gram stain was likely from one of these emboli. Bacterial endocarditis is relatively rare in healthy children and adolescents with no known congenital heart disease and presentation can be variable and non-specific.[15] It should be considered in any patient with bacterial meningitis with unusual blood or CSF culture isolates.

### Author Contributions

This case was presented and written up by MM and JK. JK performed the literature review and discussion which MM edited and approved.

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