

CLINICAL CASE OF THE MONTH

A 54 Year-Old Woman With Fever and Chills of Four-Days Duration

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CASE REPORT

A 54 year-old woman with diabetes mellitus type two and end-stage renal disease on hemodialysis presented to the emergency department with a four day history of generalized malaise, fever, and chills. Her symptoms were also associated with occasional dyspnea without a cough. She reported intermittent chronic diarrhea with hemodialysis which was currently unchanged. On the day of admission, she could not tolerate hemodialysis due to her symptoms. Over the past year she admitted to night sweats and a 40 pound weight loss. She denied having palpitations, chest pain, hemoptysis, lymph node swelling, sick contacts, or recent travel. The remainder of the review of systems was negative.

The patient's additional medical history included an ischemic stroke without residual deficits, hyperlipidemia, hypertension, glaucoma, chronic obstructive pulmonary disease, treated latent tuberculosis, previous blood transfusions, and vitamin D deficiency. The patient smoked a couple of cigarettes daily for 40 years, but denied current alcohol or illicit drug use.

Upon physical examination, the patient's vital signs included a temperature of 97.7°Fahrenheit (although she had intermittent elevated temperatures throughout her hospital stay), pulse of 69 beats per minute, blood pressure of 136/70 mmHg, oxygen saturation of 99% on BiPAP, and a respiratory rate of 19 breaths per minute. She was 5 foot 4 inches and 139 pounds with a BMI of 24 kg/m².

Her physical exam revealed a III/VI holosystolic murmur heard best at the apex that was not previously documented. She also had abdominal distension without guarding or rebound, multiple dental caries, and no skin lesions. Her A-V fistula was without evidence of infection and demonstrated a thrill. Significant laboratory studies included an elevated leukocyte count of 18,400/mm³ without a bandemia. Blood cultures were drawn and she was started on broad spectrum antibiotics. Her cultures were positive for Gram-negative bacilli one day after admission.

A transthoracic echocardiography (Figure 1) showed a 12x9 mm vegetation on the posterior mitral valve leaflet with a normal ejection fraction and mild mitral regurgitation, which was confirmed by transesophageal echocardiography.

Her antibiotics were changed to ceftriaxone alone once the blood cultures resulted as positive for *Aggregatibacter aphrophilus* (Figure 2), a HACEK organism. This organism was also noted on peripheral blood smear.

With her poor dentition as a possible source of infection, she underwent dental extraction during her admission. The patient improved clinically and was discharged home to complete a six week course of ceftriaxone. Follow-up echocardiography showed a less mobile vegetation on the mitral valve.

Surgical intervention was deferred by the cardiothoracic surgeons to medical treatment at the initial admission. However, one day after completion of her six-week antibiotic regimen, she returned to the emergency department with shortness of breath. She was found to have severe mitral regurgitation secondary to localized thickening of the lateral scallop of the posterior mitral valve leaflet with a perforation. She required a mitral valve repair and also underwent coronary artery bypass graft with coronary endarterectomy due to coronary artery stenosis that was noted on angiography. She was discharged on post-operative day ten in stable condition.



Figure 1: Echocardiogram showing 12x9mm vegetation on posterior mitral valve leaflet.

EPIDEMIOLOGY

There is an incidence of 10,000-15,000 new cases of infective endocarditis each year in the United States.¹ These are most commonly caused by Gram-positive bacteria such as *Staphylococcus* and *Streptococcus* species.² Rare causes of infective endocarditis are Gram-negative organisms, including the HACEK group: *Haemophilus* species, *Aggregatibacter* (previously *Actinobacillus*) species, *Cardiobacterium hominus*, *Eikenella corrodens*, and *Kingella* species.³

Although HACEK organisms are documented to comprise up to 3% of all infective endocarditis cases, 60% of individuals with HACEK bacteremia are found to have endocarditis as well.^{4,5} The various positive predictive values of the occurrence of endocarditis differ among the HACEK species, as does the course of disease.⁶ For instance, infective endocarditis with *Haemophilus* and *Aggregatibacter* species typically evolves soon after infection with a more likely possibility of complications. *Cardiobacterium hominis*-associated infections typically pursue a more gradual course and causes endocarditis mostly in damaged cardiac valves. *Eikenella corrodens* is notorious for causing infection after oropharyngeal contamination (i.e., human bites). Infections caused by *Kingella* species can progress quickly.

RISK FACTOR

Although HACEK organisms are a rare cause of infective endocarditis, the high mortality rate requires a strong clinical suspicion. Risk factors for HACEK endocarditis can vary and include some of the same factors associated with other sources of infective endocarditis. These factors can include age greater than 60 years, intravenous drug use, valvular disease, prosthetic valves, pacemakers, congenital heart disease, chronic hemodialysis, HIV

infection, and upper respiratory tract infection.^{3,7,8} Poor dentition and recent dental procedures are significant predisposing risk factors for infections with HACEK organisms owing to their presence in the normal oropharyngeal flora.³ More recent data has not been able to prove that HACEK endocarditis affects a predominant sex.⁹

CLINICAL PRESENTATION

HACEK organisms are commonly found in the oropharynx as part of the normal flora, although they are capable of causing significant disease such as periodontal infections, endocarditis, bacteremia, pneumonia, peritonitis, urinary tract infections, osteomyelitis, and wound infections. In HACEK endocarditis, fever is common and may be associated with anorexia, weight loss, fatigue, back pain, arthralgias, myalgias, pleuritic chest pain, nausea, vomiting, emboli, and night sweats.⁶ These symptoms may progress over weeks. In immunocompromised and elderly patients, however, fever may not be present.¹⁰

On physical exam, HACEK-associated infective endocarditis may present as a new murmur or change in a heart murmur. The type of murmur will depend on the involved valve. Cutaneous lesions are more common in sub-acute presentations of infective endocarditis and include findings such as clubbing, splinter hemorrhages, Osler's nodes, and Janeway lesions. Additional symptoms can result from septic embolization to the central nervous system, kidney, heart, mesentery, and lung.¹¹

DIAGNOSIS

The diagnosis of infective endocarditis may utilize the Modified Duke Criteria which takes into account a patient's history, physical exam, blood culture results, and imaging.¹² These criteria distinguish definite, possible, and rejected diagnoses of infective endocarditis based on major and minor criteria. Major criteria consist of growth of organisms that typically cause infective endocarditis. Examples of these micro-organisms are *Staphylococcus aureus*, viridans streptococci, and HACEK organisms amongst others, from two separate blood cultures. Alternatively, *Coxiella burnetii* endocarditis infections only require a single positive blood culture. Evidence of endocardial involvement with a positive echocardiogram for infective endocarditis (i.e., an intracardiac mass, abscess, or new dehiscence of prosthetic valve), or new/worsening valvular regurgitation are additional major criteria. There are several minor criteria that contribute to the diagnosis of infective endocarditis. Having an existing heart condition and intravenous drug use are predisposing factors included in the minor criteria. Vascular phenomena, major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, and Janeway lesions are included as well. Additionally, immunologic phenomena that include glomerulonephritis, Osler's nodes, Roth spots and rheumatoid factor are also included as minor criteria. A fever above 38.0°C (100.4°F) and microbial evidence not included in the major criteria are also minor criteria.^{12,13}



Figure 2: *A. aphrophilus* culture on chocolate agar.

Diagnosis of definite infective endocarditis must meet one of the following: 1) two major criteria, 2) one major with three minor criteria, or 3) five minor criteria. Possible infective endocarditis must meet one of the following: 1) one major criteria with one minor criteria, or 2) three minor criteria. A diagnosis of infective endocarditis is rejected if one of the following occur: 1) there is a differential diagnosis that accounts for the signs and symptoms of infective endocarditis, 2) resolution of symptoms with antibiotic therapy for less than or equal to four days, 3) no pathological evidence at surgery or autopsy with antibiotic therapy for less than or equal to four days, or 4) if it does not meet the criteria as listed above.^{12,13}

The diagnosis of HACEK-associated bacteremia leading to infective endocarditis had previously been easily overlooked because these organisms are fastidious and difficult to isolate.¹³ These organisms required prolonged incubation of enriched culture media and increased carbon dioxide tension to enhance growth. The average incubation period necessary to notice growth is three to five days, but there have been cases of incubation requiring up to thirty days.¹⁴ In the setting of negative blood cultures with a clinical picture of endocarditis, HACEK endocarditis is a consideration and blood cultures can be retained for at least two weeks.¹³ With the advancement of modern microbiologic technology, growth detection without prolonged incubation is enhanced.¹⁵

TREATMENT

HACEK-associated endocarditis has a documented mortality rate of up to 15%.³ Historically, the drugs of choice for treatment are beta-lactam antibiotics, and the organisms are typically susceptible to third-generation cephalosporins like ceftriaxone.¹³ The American Heart Association suggests the following treatment options: 1) ceftriaxone 2 g per 24 hour IV or IM in one dose for four weeks, or 2) ampicillin-sulbactam 12 g per 24 hour IV in four equally divided doses for four weeks. These possible regimens extended to six weeks in patients with prosthetic valve-associated HACEK endocarditis. Fluoroquinolones, such as ciprofloxacin, levofloxacin, and moxifloxacin, are used if the patient has a beta-lactam allergy. Ciprofloxacin 1000 mg per per 24 hour PO or 800 mg per 24 hour IV in two equally divided doses for four weeks is recommended.¹³

Medical management is initially instituted unless certain criteria are met requiring surgical intervention. Echocardiography is a key study in determining a need for surgical intervention. Evidence of refractory congestive heart failure, persistent or increase in size of the vegetation after therapy, at least one embolic episode, regional complications such as myocardial abscess, perianular extension of infection, valvular dysfunction, valvular perforation, or valvular rupture, or failed medical management would all be potential indications for surgery.^{13,16}

Prognosis is dependent on various factors including increased age and valvular abnormalities. However, most patients with HACEK-associated infective endocarditis have an excellent prognosis with appropriate therapy.³

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