183e Infections Due to the HACEK Group and Miscellaneous Gram-Negative Bacteria

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THE HACEK GROUP

HACEK organisms are a group of fastidious, slow-growing, gram-negative bacteria whose growth requires an atmosphere of carbon dioxide. Species belonging to this group include several *Haemophilus* species, *Aggregatibacter* (formerly *Actinobacillus*) species, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella kingae*. HACEK bacteria normally reside in the oral cavity and have been associated with local infections in the mouth. They are also known to cause severe systemic infections—most often bacterial endocarditis, which can develop on either native or prosthetic valves (Chap. 155).

In large series, 0.8–6% of cases of infective endocarditis are attributable to HACEK organisms, most often *Aggregatibacter* species, *Haemophilus* species, and *C. hominis.* Invasive infection typically occurs in patients with a history of cardiac valvular disease, often in the setting of a recent dental procedure or nasopharyngeal infection. The aortic and mitral valves are most commonly affected. Compared with non-HACEK endocarditis, HACEK endocarditis occurs in younger patients and is more frequently associated with embolic, vascular, and immunologic manifestations but less commonly associated with congestive heart failure. The clinical course of HACEK endocarditis tends to be subacute, particularly with *Aggregatibacter* or *Cardiobacterium*. However, *K. kingae* endocarditis may have a more aggressive presentation. Systemic embolization is common. The overall prevalence of major emboli associated with HACEK endocarditis ranges from 28% to 71% in different series. On echocardiography, valvular vegetations are seen in up to 85% of patients. *Aggregatibacter* and *Haemophilus* species cause mitral valve vegetations most often; *Cardiobacterium* is associated with aortic valve vegetations. The microbiology laboratory should be alerted when a HACEK organism is being considered; however, most cultures that ultimately yield a HACEK organism become positive within the first week, especially with improved culture systems such as BACTEC. In addition, polymerase chain reaction (PCR) techniques (e.g., of cardiac valves) and other tools, such as matrix-assisted laser desorption ionization–time of flight (MALDI-TOF) mass spectrometry performed directly on agar colonies, are facilitating the diagnosis of HACEK infections. Because of the organisms' slow growth, antimicrobial testing may be difficult, and β-lactamase production may not be detected. Resistance is most commonly noted in *Haemophilus* and *Aggregatibacter* species. E-test methodology may increase the accuracy of susceptibility testing. The overall prognosis in HACEK endocarditis is excellent and significantly better than that in endocarditis caused by non-HACEK pathogens.

***Haemophilus* Species** *Haemophilus parainfluenzae* is the most common species isolated from cases of HACEK endocarditis. Of patients with HACEK endocarditis due to *Haemophilus* species, 60% have been ill for <2 months before presentation, and 19–50% develop congestive heart failure. Mortality rates as high as 30–50% were reported in older series; however, more recent studies have documented mortality rates of <5%. *H. parainfluenzae* has been isolated from other infections, such as meningitis; brain, dental, pelvic, and liver abscess; pneumonia; urinary tract infection; and septicemia.

***Aggregatibacter* Species** The species of *Aggregatibacter* that most frequently cause infective endocarditis are *A. actinomycetemcomitans*, *A.* (formerly *Haemophilus*) *aphrophilus*, and *A. paraphrophilus*. *Aggregatibacter* is associated with prosthetic valve endocarditis more often than are *Haemophilus* species. *A. actinomycetemcomitans* can be isolated from soft tissue infections and abscesses in association with *Actinomyces israelii*. Typically, patients who develop endocarditis with *Aggregatibacter* have periodontal disease or have recently undergone dental procedures in the setting of underlying cardiac valvular damage. The disease is insidious; patients may be sick for several months before diagnosis. Frequent complications include embolic phenomena, congestive heart failure, and renal failure. *A. actinomycetemcomitans* has been isolated from patients with brain abscess, meningitis, endophthalmitis, parotitis, osteomyelitis, urinary tract infection, pneumonia, and empyema, among other infections, while *A. aphrophilus* is often associated with bone and joint infection.

Cardiobacterium hominis *C. hominis* primarily causes endocarditis in patients with underlying valvular heart disease or with prosthetic valves. This organism most frequently affects the aortic valve. Many patients have signs and symptoms of long-standing infection before diagnosis, with evidence of arterial embolization, vasculitis, cerebrovascular accidents, immune complex glomerulonephritis, or arthritis at presentation. Embolization, mycotic aneurysms, and congestive heart failure are common complications. A second species, *C. valvarum*, has now been described in association with endocarditis.

Eikenella corrodens *E. corrodens* is most frequently recovered from sites of infection in conjunction with other bacterial species. Clinical sources of *E. corrodens* include sites of human bite wounds (clenched-fist injuries), endocarditis, soft tissue infections, osteomyelitis, head and neck infections, respiratory infections, chorioamnionitis, gynecologic infections associated with intrauterine devices, meningitis, brain abscesses, and visceral abscesses. This organism is the least common cause of HACEK endocarditis.

Kingella kingae Because of improved microbiologic methodology and molecular methods such as real-time PCR, the isolation of *K. kingae* is increasingly common. Inoculation of clinical specimens (e.g., synovial fluid) into aerobic blood culture bottles enhances recovery of this organism. More than half of cases of *K. kingae* infection are bone and joint infections; the majority of the remaining infections are infective endocarditis and bacteremia. PCR studies of joint fluid can identify *K. kingae* in culture-negative cases. Some studies now demonstrate that *K. kingae* has surpassed *Staphylococcus aureus* as the leading cause of septic arthritis in children. Invasive *K. kingae* infections with bacteremia are associated with upper respiratory tract infections and stomatitis in 80% of cases. Rates of oropharyngeal colonization with *K. kingae* are highest in the first 3 years of life (detected in ~10% of children), coinciding with an increased incidence of skeletal infections due to this organism. *K. kingae* bacteremia can present with a petechial rash similar to that seen in *Neisseria meningitidis* sepsis.

Infective endocarditis, unlike other infections with *K. kingae*, occurs in older children and adults. The majority of patients have preexisting valvular disease. There is a high incidence of complications, including arterial emboli, cerebrovascular accidents, tricuspid insufficiency, and congestive heart failure with cardiovascular collapse.

TREATMENT HACEK ENDOCARDITIS

(Table 183e-1) Ceftriaxone (2 g/d) is first-line therapy for HACEK endocarditis. Data on the use of levofloxacin (500–750 mg/d) for HACEK endocarditis remain limited, but this drug can be considered an alternative for treatment of patients intolerant of β-lactam therapy. Of note, *Eikenella* is resistant to clindamycin, metronidazole, and aminoglycosides.

Native-valve endocarditis should be treated for 4 weeks with antibiotics, whereas prosthetic-valve endocarditis requires 6 weeks of therapy. The cure rates for HACEK prosthetic-valve endocarditis appear to be high. Unlike prosthetic-valve endocarditis caused by other gram-negative organisms, HACEK endocarditis is often cured with antibiotic treatment alone—i.e., without surgical intervention.