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## Association of HACEK organisms-the oropharyngeal commensals in endocarditis

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### Abstract

HACEK organisms are the commensal organisms of oropharynx. Although, they cause wide spectrum of infections, infective endocarditis is the most notable among them. Historically, these organisms were considered to be difficult to culture and identify but the technological advancement in the recent years have made their identification easy. Infections with these organisms usually respond to ceftriaxone and various fluoroquinolones. The important strategies for prevention of HACEK endocarditis include maintenance of good oral hygiene and use of prophylactic antibiotics in high risk conditions before oral/dental procedures.

**Keywords:** Hacek, commensal, infective endocarditis, ceftriaxone, fluoroquinolones, prophylactic

### 1. Introduction

The acronym "HACEK" consists of a group of fastidious, slow-growing, Gram-negative bacteria whose growth requires an atmosphere of carbon dioxide<sup>[1, 2]</sup>. The HACEK group is based on the organisms' propensity to cause endocarditis, rather than on taxonomic relationships<sup>[3]</sup>. The members of this group include several *Haemophilus* species, *Aggregatibacter* (Formerly *Actinobacillus* species), *Cardiobacterium* species, *Eikenella corrodens*, and *Kingella kingae*.

Hacek bacteria are the commensals of the human oropharynx and have been found to be associated with various local infections in the mouth. They are well known to cause severe systemic infections- most often bacterial endocarditis, which can develop on either native or prosthetic valves<sup>[4]</sup>. They have also been implicated in soft-tissue abscess, brain abscess, endophthalmitis, parotitis, periodontitis, empyema and bacteremia without endocarditis, and osteomyelitis endometritis and urinary tract infection<sup>[5]</sup>.

### 2. Pathophysiology

Infective endocarditis refers to inflammation of the endocardial surface of the heart such as heart valves, mural endocardium or the endocardium that covers implanted material, such as prosthetic valves, pacemaker/defibrillator leads and catheters due to infectious agents.

Normal valvular endothelium is usually resistant to bacterial colonization upon intravascular challenge<sup>[6]</sup>. Thus, the development of infective endocarditis requires the simultaneous involvement of several independent factors<sup>[7]</sup>. The important ones are bacteremia with an organism capable of attaching to and colonizing valve tissue, alteration of the cardiac valve surface to produce a suitable site for bacterial attachment and colonization; and creation of the infected mass or vegetation by burying of the proliferating organism within a protective matrix of serum molecules (for example, fibrin) and platelet<sup>[7]</sup>.

#### a. Bacteremia

Introduction of bacteria into the bloodstream is an important factor for an infective endocarditis to occur. Entry of oropharyngeal commensal flora such as HACEK occurs into blood stream by surgical procedures such as tooth extractions or non-surgical procedures such as administration of local anesthesia, orthodontic band placement, periodontal probing, dental prophylaxis, scaling and root planing, and even after daily tooth brushing and flossing<sup>[8]</sup>.

#### b. Valvular damage

Damage to the valvular surface may occur due to a variety of factors, including turbulent

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blood flow related to primary valvular damage from specific systemic disease states (such as rheumatic carditis), mechanical injury by catheters or electrodes, or injury arising from repeated injections of solid particles in IDU.<sup>[7]</sup> The endothelial damage leads to the formation of fibrin-platelet deposits overlying interstitial oedema, a pathophysiological entity known as “nonbacterial thrombotic endocarditis” (NBTE)<sup>[6]</sup>.

### c. Bacterial colonization and formation of vegetation

When the bacteremia is established, adherence of the organism occurs to the fibrin-platelet matrices of NBTE. The bacteria multiply in the fibrin platelet matrices and form colonies. The mass of platelets, fibrin, microcolonies of microorganisms, and scant inflammatory cells is known as vegetation. Vegetation increase in its size by further cycles of platelet-fibrin deposition and bacterial proliferation<sup>[7]</sup>.

### d. Formation of emboli and immune complex

The vegetation may break down from the heart valve resulting in the formation of emboli. Circulating immune complexes have been found in high titres in almost all patients with IE<sup>[9]</sup>. Deposition of emboli and immune complex in various sites of body usually contribute to extra cardiac clinical presentation.

## 3. Epidemiology

Infective endocarditis is a relatively rare but life-threatening disease<sup>[7]</sup>. A systematic review of the global burden of infective endocarditis has indicated the crude incidence ranging from 1.5 to 11.6 cases per 100,000 person-years.<sup>[10]</sup> Even with best available therapy, mortality rate from infective endocarditis is approximately 25%<sup>[11]</sup>.

Approximately 0.8–6% of cases of infective endocarditis are attributable to HACEK organisms, most often *Aggregatibacter* species, *Haemophilus* species, and *Cardiobacterium hominis*<sup>[4]</sup>. Invasive infection is typically seen in patients with a history of cardiac valvular disease or prosthetic valves, often in the setting of a recent dental procedure or nasopharyngeal infection. The common valves affected are the aortic and mitral valves<sup>[4]</sup>.

The clinical course of HACEK endocarditis is generally subacute, particularly with *Aggregatibacter* or *Cardiobacterium*. However, *K. kingae* and *H parainfluenzae* how more aggressive presentation<sup>[4, 5]</sup>. A large multi-center study has highlighted that HACEK endocarditis compared with non-HACEK endocarditis occurs in younger patients and is more frequently associated with embolic, vascular, and immunologic manifestations but a lower prevalence of congestive heart failure and death<sup>[12]</sup>. The overall prevalence of major emboli associated with HACEK endocarditis ranges from 28 to 71% in different series<sup>[4]</sup>. On echocardiography, valvular vegetations is reported in up to 85% of patients<sup>[4]</sup>. *Aggregatibacter* and *Haemophilus* species cause mitral valve vegetations most often whereas *Cardiobacterium* is associated with aortic valve vegetations.<sup>[4]</sup> Mortality rates associated with HACEK endocarditis range from 10%-40% and may vary by organism<sup>[5]</sup>.

The other important epidemiological features of HACEK members are as follows<sup>[4]</sup>.

### *Haemophilus* species

Among the various species of *Haemophilus*, *Haemophilus parainfluenzae* is the most common *Haemophilus* species isolated from cases of HACEK endocarditis.

### *Aggregatibacter* species

- They are the most common cause of HACEK endocarditis. Of the various species of *Aggregatibacter*, the most frequently involved are the *A. actinomycetemcomitans*, *A. (Formerly haemophilus) aphrophilus*, and *A. paraphrophilus*.
- The patients who develop *Aggregatibacter* endocarditis typically have periodontal disease or have recently undergone dental procedures in the setting of underlying cardiac valvular damage. The disease has insidious nature and patients may be sick for several months before diagnosis.

### *Cardiobacterium* SPECIES

*C. hominis* is the most frequently involved *Cardiobacterium* species in endocarditis. It causes endocarditis primarily in patients with underlying valvular heart disease or with prosthetic valves.

### *Eikenella corrodens*

This organism is the least common cause of HACEK endocarditis. It 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 etc.

### *Kingella kingae*

Infective endocarditis with *K. kingae*, unlike other infections, is seen in older children and adults. Most of the patients have preexisting valvular disease. *K. kingae* bacteremia can present with a petechial rash similar to that seen in *Neisseria meningitidis* sepsis.

## 4. Identification

When a HACEK organism is being considered, the microbiology laboratory should be alerted<sup>[4]</sup>. Previously, HACEK organisms were reported in endocarditis from which no pathogen could be isolated (so called “culture-negative endocarditis”). This was due to their slow growth in old blood culture formulations and resulted in recommendations for extended incubation (>5 days) when the presence of these organisms was suspected<sup>[3]</sup>. In the recent years, most cultures that yield a HACEK organism become positive within the first week, especially with improved culture systems such as BACTEC<sup>[13]</sup>. It is not yet clear whether prolonged incubation increases laboratory recovery of clinically significant HACEK isolates<sup>[4]</sup>. Polymerase chain reaction (PCR) techniques, such as gene amplification of 16S rRNA, and matrix-assisted laser desorption ionization–time of flight (MALDI-TOF) mass spectrometry performed directly on agar colonies, are very useful for the accuracy and speed of diagnosis of HACEK infections<sup>[3, 4]</sup>.

HACEK organisms can be recovered on routinely used non-selective media such as chocolate agar and blood agar. But, they grow better in the former than the latter. They do not grow on selective media designed for enterics such as MacConkey agar. Automated systems can also be used for their identification but performance may be suboptimal.<sup>[14]</sup>

## 5. Susceptibility testing and treatment

Though standard guidelines are available for susceptibility testing of HACEK organisms, the testing would be difficult due to their failure of growth in broth-dilution panels 60% of the time<sup>[3]</sup>. Since these organisms commonly produce beta lactamases, routine testing of their beta lactamase production

is recommended using chromogenic substrates [3].

Since resistance of HACEK organisms to cephalosporin is rare, ceftriaxone has been recommended by current Infectious Diseases Society of American (IDSA) guidelines on endocarditis for treatment of their infections [15].

The HACEK group is usually susceptible in vitro to fluoroquinolones [15]. Considering their susceptibility data, a fluoroquinolone (ciprofloxacin, levofloxacin, or moxifloxacin) may be considered as an alternative agent in patients who cannot tolerate ceftriaxone (or other third- or fourth-generation cephalosporins) therapy. In addition, a combination of ampicillin and sulbactam may be considered a treatment option, although HACEK resistance to this agent in vitro has been reported [16].

In both native-valve and prosthetic-valve HACEK endocarditis, the overall prognosis is excellent and is significantly better than that in endocarditis caused by non-HACEK pathogens [4].

## 6. Prevention

The risk of endocarditis due to HACEK organisms could be reduced by maintaining good dental hygiene [5]. Guidelines are available for infective endocarditis (IE) prophylaxis prior to dental procedures [17]. The current recommendations support the use of prophylactic antibiotics only for high-risk patients. Antibiotic prophylaxis should be considered before oral/dental procedures in patients with high-risk cardiac conditions [17]. The high-risk conditions include the following:

- Prosthetic valves,
- Previous bacterial endocarditis,
- Complex cyanotic congenital heart disease,
- Surgically constructed systemic pulmonary shunts or conduits and
- Valvulopathy in cardiac transplantation recipients.

## 7. Conclusion

An association of HACEK group of organisms in endocarditis has been clearly evident. On suspicion of these organisms, clinical microbiology laboratory should be alerted and recent or updated technical strategies should be employed for their identification. These organisms respond well to the available antimicrobials. Prevention of endocarditis associated with them is mainly done by administration of antibiotic prophylaxis in the high risk patients before oral/dental procedures.

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