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HACEK ORGANISMS AND THEIR ROLE IN SUBACUTE INFECTIVE ENDOCARDITIS

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Abstract

Infective Endocarditis is most commonly caused by gram-positive organisms; however, a small subset of cases is attributed to fastidious gram-negative bacteria known as the HACEK group (Haemophilus spp., Aggregatibacter spp., Cardiobacterium hominis, Eikenella corrodens, and Kingella kingae). These organisms are part of the normal oropharyngeal flora and are characterized by slow growth and specific nutritional requirements, often leading to delayed or initially negative blood cultures. Although rare, HACEK organisms are clinically important causes of subacute infective endocarditis, typically affecting previously damaged heart valves or prosthetic valves. Patients often present with nonspecific symptoms such as prolonged fever, malaise, and new or changing heart murmurs, which can delay diagnosis. Advances in automated blood culture systems have improved detection rates, but prolonged incubation may still be required in some cases. Echocardiography remains essential for identifying valvular vegetations and confirming diagnosis. HACEK-associated endocarditis generally has a favorable prognosis when promptly treated with appropriate intravenous antibiotics, particularly third-generation cephalosporins. This review highlights the microbiological characteristics, clinical presentation, diagnostic challenges, and treatment strategies associated with HACEK group organisms as a rare but significant cause of infective endocarditis.

Keywords

Infective Endocarditis, HACEK group bacteria, fastidious gram-negative bacteria, subacute endocarditis, blood culture-negative endocarditis, oral flora, valvular vegetation, echocardiography, prosthetic valve endocarditis, third-generation cephalosporins, Haemophilus species, Aggregatibacter species, Cardiobacterium hominis, Eikenella corrodens, Kingella kingae.

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Infective endocarditis (IE) is caused by infection of the heart valve blood by fungi and bacteria (this bacteremia can cause septic symptoms) and their vegetative growth, which consists mainly of platelets, microorganisms and fibrins[1,3,4]. The superficial growth can cause embolism in many organs such as the kidneys, lungs, skin, brain, and central nervous system, leading to signs of divergence. If the patient with infective endocarditis does not receive adequate treatment, the disease can be lethal [1]. Diagnosis of IE is still difficult, although blood culturing methods, accurate diagnostic criteria and echocardiography have improved [2, 3]. Clinician may also notice possible illnesses such as stroke, heart failure, pulmonary embolism, meningitis, nephritis, collagenosis, pneumonia, or urinary tract infections due to the variety of symptoms in this disease.

IE is an infection to the heart valves and is an important differential diagnosis in patients presenting with unspecific systemic symptoms and signs of inflammation. IE mainly affects valves with previous pathology and can lead to heart failure and septic embolization. Despite HACEK group bacteria being well-known aetiology of IE and even mentioned in the diagnostic Duke criteria [3], knowledge of HACEK-related IE emanates mainly from smaller case series. The HACEK group of bacteria constitutes only 1–3% of all IE cases [2], but growth of HACEK bacteria in blood cultures implies a 40% probability of an IE diagnosis [4]. The most extensive study of IE due to HACEK is a multinational collaboration of centres (ICE) reporting cases of IE to a registry [5]. In that study, 77 cases of IE due to HACEK were reported, constituting 1.3% of all IE cases. Cases of IE caused by HACEK were compared to those caused by all other pathogens, and it was demonstrated that patients with IE due to HACEK were younger, had a higher risk of embolic stroke and had a lower risk of heart failure compared to patients with non-HACEK-related IE.

In a relatively recent publication, 16 cases of IE due to HACEK, reported to a Spanish registry, were compared to cases of streptococcal IE reported to the same registry. The groups had many similarities, but the prognosis was significantly more favourable for cases of IE caused by HACEK [7].Here we utilize a national registry of IE to describe cases of IE due to HACEK and compare these to cases of IE caused by other major bacterial pathogens.

Subacute infective endocarditis is a slowly progressive infection of the heart valves that typically develops over weeks to months. It most often affects previously damaged or abnormal valves. Clinically, patients present with prolonged low-grade fever, fatigue, malaise, weight loss, and new or changing heart murmurs.HACEK organisms normally reside in the oral cavity as commensals and may enter the bloodstream during dental procedures or in the

presence of gingival disease. Once in the bloodstream, they can adhere to damaged heart valves and form vegetations composed of fibrin, platelets, and microorganisms. These vegetations may progressively enlarge, leading to valvular destruction and serious complications[4,5].

One of the major complications of HACEK-related endocarditis is systemic embolization. Emboli can affect multiple organs, including the brain, kidneys, spleen, lungs, and skin, resulting in stroke, infarction, or organ dysfunction. Despite their clinical significance, HACEK organisms account for only about 1–3% of all cases of infective endocarditis.Diagnosis can be challenging because these organisms are slow-growing and may require prolonged incubation in blood cultures. In some cases, this may lead to delayed or initially negative culture results. Modern automated blood culture systems have improved detection, but extended incubation may still be necessary. Echocardiography remains essential for identifying valvular vegetations and confirming the diagnosis[3,5,6].

Treatment typically involves third-generation cephalosporins, particularly ceftriaxone, and most patients respond well to appropriate antibiotic therapy. Overall, although rare, HACEK organisms are clinically important causes of subacute infective endocarditis with generally favorable outcomes when diagnosed and treated promptly[2].

HACEK group bacteria causing Infective Endocarditis typically present with a subacute clinical course. The disease develops gradually, and symptoms may evolve over weeks or even months.Patients commonly present with prolonged low-grade fever, along with nonspecific systemic symptoms such as fatigue, malaise, loss of appetite, and weight loss. Because these symptoms are not specific, the condition is often initially misdiagnosed as other infections.As the heart valves become involved, patients may develop a new or changing heart murmur due to valvular damage. With progression of the disease, some patients may develop signs of heart failure, including dyspnea, peripheral edema, and orthopnea.[3,8]

A key feature of HACEK-related endocarditis is systemic embolization. Vegetations may dislodge and travel through the bloodstream, leading to complications in multiple organs:

- Brain: stroke or neurological deficits
- Kidneys: hematuria or renal infarction
- Spleen: left upper quadrant pain or splenic infarction
- Lungs: pulmonary embolism (especially in right-sided endocarditis)
- Skin: petechiae, purpura, Osler nodes, and Janeway lesions

Some patients may also show peripheral signs of endocarditis, such as petechiae, Osler nodes (painful fingertip lesions), and Janeway lesions (painless lesions on palms and soles).

Due to its slow and insidious onset, diagnosis is often delayed, increasing the risk of complications. However, when diagnosed early and treated appropriately, HACEK endocarditis generally has a better prognosis compared to many other forms of bacterial endocarditis.

Blood culture is a key diagnostic tool; however, HACEK organisms are fastidious and slow-growing Gram-negative bacteria, which may lead to delayed growth in standard culture systems. Because of their slow growth, prolonged incubation periods (up to several days) are often required. In some cases, automated blood culture systems improve detection, but cultures may still initially appear negative, contributing to the concept of culture-negative or delayed-positive endocarditis.Echocardiography plays a central role in diagnosis. Both transthoracic echocardiography (TTE) and transesophageal echocardiography (TEE) are used to identify valvular vegetations, abscess formation, and valvular dysfunction. TEE is more sensitive, especially in detecting small vegetations or prosthetic valve involvement. The presence of vegetations strongly supports the diagnosis of infective endocarditis.The diagnosis is formally established using the Modified Duke Criteria, which classify findings into major and minor criteria[7,8,10].

Major criteria include positive blood cultures for typical organisms causing infective endocarditis, including persistent bacteremia with HACEK organisms, as well as evidence of endocardial involvement on echocardiography such as vegetations, abscesses, or new valvular regurgitation[6,8].

Minor criteria include fever, vascular phenomena such as emboli or septic infarcts, immunological phenomena such as Osler nodes or glomerulonephritis, predisposing heart conditions or intravenous drug use, and microbiological evidence that does not meet major criteria.A diagnosis of definite infective endocarditis is made when there are either two major criteria, or one major criterion combined with three minor criteria, or five minor criteria[9].

HACEK organisms are an uncommon but clinically important cause of Infective Endocarditis, accounting for approximately 1–3% of all cases. Despite their low frequency, they are significant due to their diagnostic challenges and their association with systemic complications such as embolic events.In terms of prognosis, HACEK-related infective endocarditis generally has a more favorable outcome compared to infections caused by other major bacterial pathogens, particularly *Staphylococcus aureus*. With appropriate and timely antibiotic therapy,

most patients respond well, and mortality rates are relatively lower, often reported around 10% or less in modern studies. However, delayed diagnosis due to slow-growing organisms can increase the risk of complications, including embolic stroke and valvular destruction[8,10].

When compared with other causative agents of infective endocarditis, HACEK organisms differ in several important aspects. *Staphylococcus aureus* infections typically present as acute and highly aggressive disease with rapid valve destruction and higher mortality. In contrast, HACEK infections usually follow a subacute course with slower progression. *Streptococcus viridans* endocarditis shares some similarities with HACEK in terms of subacute presentation, but HACEK organisms are more challenging to detect due to their fastidious growth requirements in blood cultures. Additionally, while embolic complications can occur in both, HACEK infections have been associated with a relatively higher risk of embolic stroke in some studies.Overall, although rare, HACEK organisms represent a distinct group of pathogens in infective endocarditis with characteristic subacute presentation, diagnostic difficulties, and generally favorable prognosis when compared to more virulent organisms such as *Staphylococcus aureus[4,6,8]*

Conclusion:HACEK organisms are rare but clinically important etiological agents of Infective Endocarditis, accounting for a small proportion of all cases. Despite their low incidence, they represent a significant diagnostic and therapeutic challenge due to their fastidious growth characteristics and the resulting delay in blood culture detection.Clinically, HACEK-related endocarditis typically follows a subacute course with nonspecific systemic symptoms, making early recognition difficult. Echocardiography and the Modified Duke Criteria remain essential tools for timely diagnosis, while prolonged blood culture incubation is often required for microbiological confirmation.Overall, although HACEK organisms are less aggressive compared to pathogens such as *Staphylococcus aureus*, they are still associated with serious complications, particularly systemic embolization. With early diagnosis and appropriate antibiotic therapy, the prognosis is generally favorable, highlighting the importance of clinical suspicion and prompt management.

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