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REVIEW

## HACEK endocarditis: a review

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### ABSTRACT

**Introduction:** The HACEK group, referring to *Haemophilus* spp., *Aggregatibacter actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella kingae*, is a rare cause of infective endocarditis (IE). It causes the majority of Gram-negative endocarditis cases and has an excellent prognosis and simple management if properly identified. However, delay in diagnosis and associated complications can render the infection fatal.

**Areas Covered:** Over the past few decades, there have been tremendous advancements in understanding the manifestations and progression of HACEK endocarditis (HE). This review tackles the epidemiology of HE, the microbiological characteristics of each organism in the HACEK group, the methods used to diagnose HE, the clinical manifestations, complications, and mortality of patients with HE, as well as the recommended treatment and preventive methods.

**Expert Commentary:** The lack of robust randomized controlled trials in diagnosis and treatment of HE makes it difficult to determine the optimal management of such infections. Nevertheless, advancements in culturing methods have shown progress in isolating and identifying these fastidious organisms. Positive blood cultures for any of the HACEK organisms in the setting of no definite focus of infection is highly suggestive of HE. In such cases, treatment with ceftriaxone or a fluoroquinolone, even without obtaining antibiotic susceptibilities, should be initiated. Moreover, the decision to proceed with surgical intervention should be individualized. As is the case for other IE, HE requires the collaboration of a multidisciplinary team consisting of the infectious disease specialist, cardiologist, cardiothoracic surgeon, and the microbiologist.

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## 1. Introduction

HACEK endocarditis (HE) is a relatively rare disease with an excellent prognosis and simple management if the organism is properly identified. However, delay in diagnosis and associated complications can render the infection fatal.

The 'HACEK' acronym represents the five species or organisms implicated in these infections, which include *Haemophilus* spp., *Aggregatibacter* spp., *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella kingae*. The HACEK organisms are grouped together due to their similar characteristics including predominance in the oropharyngeal microbiota, low virulence, similar infectious profile, and most importantly, implication in infective endocarditis (IE) [1]. They can also cause a variety of other infections including periodontal infections, bacteremias, otitis media, and abscesses [2,3].

Over the past few decades, there have been tremendous advancements in understanding the main etiologies and manifestations of IE. Yet the existing literature on HE remains scarce due to the low incidence of the disease, the absence of randomized trials, and the few systematic reviews and case reports. Consequently, until only recently, guidelines for HE therapy had been based on expert opinion. With the increasing knowledge on HE, identification and management of the infection have significantly improved. This review will tackle the epidemiology

of HE, the microbiological characteristics of each organism in this group, the methods used to diagnose HE, the clinical manifestations, complications, and mortality of patients with HE, as well as the recommended treatment and preventive methods.

## 2. Epidemiology

IE is a severe disease with high morbidity but a low incidence of 1.7–7.9 cases per 100,000 inhabitants [4]. Gram-positive bacteria, such as oral streptococci and staphylococci, remain the predominant etiologic agents of IE, accounting for over 80% of cases [5]. The reported incidence of Gram-negative endocarditis ranges from 1.3 to 10%, with HACEK microorganisms contributing to the majority of these cases [6]. The incidence of HE among reported cases of IE has varied between studies, ranging between 1.4% and 3% of IE cases [5,7,8].

HE is a rare disease, which has limited the ability to collect complete epidemiological data to understand its distribution. In the United States, few studies have been conducted to estimate the incidence of HACEK group endocarditis. A study performed at the Mayo Clinic between 1970 and 1993 suggests that the incidence of HE in Minnesota is 0.14 per 100,000 patient-years [9].

Internationally, several reviews have determined the prevalence of HE. A multinational cohort study found that the

prevalence of HE among patients diagnosed with IE was 0.5% in North America, 1.5% in South America, 0.5% in Australia and New Zealand, 1.2% in Europe, 1.8% in the Middle East and Asia, and 0.5% in Africa [7]. A review of IE in France between 1983 and 2001 revealed no cases of HE, while a study between 2001 and 2009 found 0.5% of IE cases to be caused by HACEK organisms [10]. A multicenter study in Argentina (EIRA-2) conducted between June 2001 and November 2002 found that 6.1% of surveyed episodes of IE were due to HACEK organisms [11].

The distribution of HE organisms has varied between published reports. Studies vary in their reporting of the most common causative pathogens, with some citing *Haemophilus* spp. and others *Aggregatibacter* spp. [5,8,12]. *E. corrodens* seems to be the least common etiologic agent. In the review by Das et al. from the Mayo Clinic, the distribution of the HACEK organisms was as follows: 27% *Haemophilus parainfluenzae*, 27% *C. hominis*, 20% *Aggregatibacter actinomycetemcomitans*, 16% *Haemophilus aphrophilus*, 7% *K. kingae*, and 4% *E. corrodens* [9]. A large multinational cohort study found a similar distribution, with 36% *H. parainfluenzae*, 20% *A. actinomycetemcomitans*, 13% *C. hominis*, 5% *E. corrodens*, 4% other *Haemophilus* spp., and 3% *K. kingae* [7].

Studies have found no significant racial differences in the incidence of HE. In addition, there are not enough conclusive data to suggest a predominance of infection amongst a particular sex, although some reports have found a higher incidence among males [7].

Although the mean age of IE infection in the pre-antibiotic area was 35 years, there have been significant changes in the demographics of the IE patient population after the 1940s [13]. In recent years, reported mean age of IE patients ranges from 55 to over 60 years [7,13,14]. Additionally, some evidence suggest that patients with HE tend to be significantly younger than patients with non-HACEK IE [7]. In a large multinational cohort study conducted between June 2000 and September 2006, the median age of HE patients was 47.4 years, which is significantly lower than the median age of 60.5 years among non-HE endocarditis cases [7]. While the majority of HE have been reported in adults, *K. kingae* is more commonly found in children and young adults, with over 40% of cases reported in patients under the age of 20 [8].

The incidence of HE has been increasing, but this rise in reported cases must be considered in the context of an increased awareness among physicians and laboratory personnel, emerging literature, and epidemiological studies clarifying the main etiologies of blood culture negative endocarditis, as well as improved microbiological culture techniques [10,15].

### 3. HACEK microorganisms

The HACEK organisms are characterized by similar clinical manifestations, prognosis, and epidemiology. Common risk factors include dental procedures and underlying valvular disease. They all tend to occur in young and middle-aged adults, and they have a predilection for mitral valves. Yet, every HACEK infectious agent demonstrates some unique characteristics [8].

#### 3.1. *Haemophilus* species

*Haemophilus* spp. are aerobic, nonmotile, pleomorphic Gram-negative coccobacilli. They require X (hematin) and/or V

(nicotinamide adenine dinucleotide) factors for growth [6]. Previously, *Haemophilus* spp. were thought to cause up to 43% of all HE cases, and include *H. parainfluenzae*, *H. aphrophilus*, *H. paraphrophilus*, and *H. influenzae* [1]. However, recent modifications have introduced the genus *Aggregatibacter*, which includes some former *Haemophilus* and *Actinobacillus* species such as *Aggregatibacter aphrophilus* (previously *H. aphrophilus*), *Aggregatibacter paraphrophilus* (previously *H. paraphrophilus*), and *A. actinomycetemcomitans* (previously *Actinobacillus actinomycetemcomitans*) [12]. *H. aphrophilus*, now *A. aphrophilus*, was the second most common *Haemophilus* spp. involved in HE after *H. parainfluenzae*, accounting for 40% of cases [15,16]. This change in classification has impacted previous studies indicating that *Haemophilus* species are the most prevalent etiologic agents of HE.

*Haemophilus* organisms are frequently found in dental plaque and gingival scrapings [8]. Hence, the majority of cases of *Haemophilus* endocarditis are assumed to be secondary to oral disease, with other cases reported in the setting of otitis media or sinusitis. *H. parainfluenzae*, a pleomorphic coccobacillus and primary etiologic agent of the *Haemophilus* species, is characterized by its subacute course, large vegetations, and subsequent emboli [17]. *H. parainfluenzae* is more common among young and middle-aged adults, often presenting 1 month after a routine dental procedures [8]. The mitral valve is predominantly involved with this organism, while prosthetic valves are infected in over 10% of cases.

#### 3.2. *Aggregatibacter* species

*A. actinomycetemcomitans* is a Gram-negative, nonmotile rod that grows in Tryptic soy broth and that represents 20% of HE cases [5]. It is part of the normal microbiota in the gingival sulci and may gain entry to the vascular compartment via spontaneous random bacteremias following oral hygiene procedures or mastication, dental infection, or less frequently during dental surgical procedures [18]. *A. actinomycetemcomitans* is thought to be transmissible among individuals, since family members of patients with localized juvenile periodontal disease harbor the organism at a higher frequency compared to the general population [8,18]. *A. actinomycetemcomitans* preferentially infects patients with underlying heart disease [6,19].

Other *Aggregatibacter* species include *A. aphrophilus* and *A. paraphrophilus*. *A. aphrophilus* is a fastidious Gram-negative organism normally presents in the oropharyngeal microbiota but does not cause odontogenic infections [20]. Previous valve injury is common among infected patients, and over 20% of infections affect prosthetic valves [8]. *A. paraphrophilus* organism inhabits the oropharyngeal and lower gastrointestinal tract microbiota, yet the portal of entry of the organism in reported cases of endocarditis remains unclear [16]. The highest incidence of *A. paraphrophilus* HE is among young or middle-aged adults, and preferentially infects males [16].

#### 3.3. *Cardiobacterium hominis*

*C. hominis* is a Gram-negative or Gram-variable pleomorphic rod with characteristic bulbous swelling at both ends [6]. It is found in the normal oral microbiota, with underlying oral infections or dental procedures in 44% of patients with endocarditis

[8]. *C. hominis* endocarditis is rare in children. Most cases involve the aortic valve, preferentially in the presence of pre-existing valvular abnormalities, or prosthetic valves [5].

### 3.4. *Eikenella corrodens*

*E. corrodens* is the least common etiologic agent of HE, responsible for an estimated 2–4% of cases [5]. *E. corrodens* is a Gram-negative pleomorphic rod. The growth of colonies corrodes the agar and produces a chlorine bleach odor [6]. This facultative anaerobe is found in dental and gingival scrapings and has been seen in odontogenic and periodontal infections, as well as human bite infections [5]. Salivary contamination of needles or puncture sites in intravenous drug users can cause tricuspid valve endocarditis with *E. corrodens* [5]. The infection is polymicrobial in 50% of these cases, usually associated with streptococcal organisms [8]. *E. corrodens* is an insidious infection that frequently involves the tricuspid valve [8].

### 3.5. *Kingella kingae*

*K. kingae* is a small Gram-negative coccobacillus found in the normal respiratory tract microbiota and accounts for 5–7% of HE [5]. Poor dental hygiene and oral surgery are among the factors associated with infection [8]. *K. kingae* infection most frequently occurs in very young children, with 40% of cases in patients under 20 years old [8]. *K. kingae* preferentially infects the mitral valve, involving native heart valves in 95% of infected children, while almost equally involving native and prosthetic valves in older patient populations [21]. *K. kingae* frequently infects children with congenital heart diseases (CHDs) such as tetralogy of Fallot and mitral prolapse [8]. *K. kingae* is thought to exploit mucosal impairment during viral infections, such as stomatitis, pharyngitis, or varicella-induced buccal ulcers, subsequently invading the bloodstream [8].

## 4. Clinical manifestations, complications, and mortality

Compared to non-HE, HACEK group endocarditis tends to be a subacute infection with a mean duration of about 13 weeks of symptoms before diagnosis [18]. Due to its subacute nature, HE patients are more prone to have a larger vegetation at diagnosis when compared to other IE patients [2].

In addition, HE has been shown to occur at a younger age in patients without any comorbidities [7]. It is more likely to be acquired from the community and usually has a better prognosis than non-HACEK IE. It is associated with a significantly lower risk for congestive heart failure as compared to IE due to non-HACEK pathogens [7]. On the other hand, HE has a higher probability of vascular and immunological manifestations including strokes, due to increased embolization risk, and a higher prevalence among patients with prosthetic valves [7,22]. This increase in embolization risk can occur at any time of the HE infection but it is mostly seen at 2–4 weeks of starting antibiotic therapy [23]. Strokes lengthen, and might almost double, the hospital stay among HE patients by up to 20 days, with hemorrhagic strokes occurring more frequently than ischemic strokes [7]. Mitral valve vegetations carry the

highest risk of embolism, especially with the involvement of the anterior leaflet of the valve [22].

These observations have been deduced from a multicentered study done by the International Collaboration on Endocarditis Prospective Cohort Study (ICE-PCS) on patients with endocarditis from 28 countries. In this study, 1.4% of the 5591 enrolled patients with IE had HE [7]. It demonstrated that the in-hospital and 1-year mortality rates are lower among the HE group compared to the non-HACEK group; where the cumulative mortality rate was 6% in HE patients compared to 39% in non-HACEK IE patients ( $P = 0.001$ ) [7]. Moreover, many studies have reproduced the mortality rate of HE which ranges from 10% to 15% [5,24,25].

Among individual members of the HACEK group, there are no significant differences in the clinical presentation, except for the more acute course of *H. parainfluenzae* [18,26]. However, a study by Goldberg et al. showed that the mortality rate of IE caused by *Haemophilus* species reaches 35%, whereas that caused by *A. actinomycetemcomitans* is between 9% and 15% [5]. There are no clear data about the mortality rates of the HE cases caused by the three other organisms.

## 5. Diagnosis

### 5.1. Modified duke criteria and the role of echocardiography

HE follows the same modified Duke criteria for diagnosis as IE. A definite HE is diagnosed when two major criteria, one major and three minor criteria, or five minor criteria are present, while a possible HE is diagnosed when one major and one minor criteria or three minor criteria are met.

One of the two major criteria for diagnosing HE is the presence of a vegetation/new valvular regurgitation on echocardiography. Transthoracic echocardiography (TTE) is a fast and noninvasive method to diagnose IE with a high specificity (up to 98%). However, TTE has a sensitivity of 50% for prosthetic valve IE and of 70% for native valve IE [27]; TTE has an especially low sensitivity for detecting small vegetations, abscesses, or paravalvular complications, as well as when examining obese patients, patients with chronic obstructive pulmonary disease, or chest wall deformities, or patients with prosthetic valves. Hence, a negative TTE in a patient for whom a high suspicion of IE remains, should mandate the use of transesophageal echocardiography (TEE), which has a comparable specificity of around 90% and a negative predictive value of more than 92% [28]. In the setting of a pacemaker or a defibrillator, TEE is better at showing vegetations at the leads [29]. Repeat TTE/TEE is recommended in all cases of HE when treatment has been completed.

### 5.2. Blood cultures and other diagnostic measures

The HACEK organisms are classified within the culture-negative endocarditis group due to their historical difficulty to grow on routine blood culture media and their slow rate of growth. However, if exposed to carbon dioxide or an enriched blood culture media, the organisms are more easily detected [9].

Despite the traditional consensus that HACEK organisms are difficult to culture, it has been shown that they are isolated after a mean incubation period of only 3 days,

with a median of 3.4 days when using the automated blood culturing systems [30]. Moreover, extended incubation has not proven to be more efficacious in growing HACEK organisms [20]. This was addressed by a multicentered retrospective study done between 2003 and 2004 in three university hospitals, which included 407 blood cultures of patients with suspected Gram-negative endocarditis. None of these cultures grew HACEK or other organisms after a 10–14-day incubation [30]. Moreover, different methods have been used to culture these previously considered fastidious organisms, with varying times for incubation and laboratory procedures. It was suggested that the optimal growth and yield these bacteria obtain is by subculturing on 5–8% sheep blood and chocolate agar at 35–37°C in an aerobic 5–10% CO<sub>2</sub> containing atmosphere [8,31].

In addition, it has been established that using the BacT/Alert system in culturing blood has a sensitivity reaching 99% in identifying an organism in the first 5 days [32]. This was also reiterated in the European IE guidelines in 2009, where prolonged incubation was only recommended if IE diagnosis is still strongly considered in the setting of negative cultures after 72 h [33]. Furthermore, data from 11 American hospitals with hundreds of thousands of seeded vials showed that prolonged incubation has no value in diagnosing culture-negative endocarditis [10]. Despite these studies, the American Heart Association (AHA) maintains that cultures which are initially negative be retained for greater than 2 weeks in all patients with suspected IE [23].

Recently, matrix-assisted laser desorption ionization–time of flight mass spectrometry (MALDI-TOF MS) has been very successful in identifying HACEK organisms with high sensitivity reaching 98%. It has also been demonstrated that MALDI-TOF MS allows for an earlier identification of species comprising the HACEK group [34].

Although polymerase chain reaction (PCR) has a high sensitivity and specificity in detecting different microorganisms (reaching 96% and 100%, respectively), it is still not available for the HACEK group [22,35]. Similarly, the HACEK group does not show a monophyletic based on 16s rRNA amplification and the test is not useful in identifying a specific bacterial etiology [8].

Positive blood cultures for any bacteria of the HACEK group are highly suggestive of IE if no other focus of infection is identified. This is true even in the absence of any of the IE clinical findings [22]. Once the HACEK organism grows on a blood culture, gradient tests, such as *E*-test, are used to determine the susceptibility of the organism to different antibiotics [36].

## 6. Treatment

Most of the literature on HE derive from case reports and reviews of treatment strategies. In general, HE has an excellent prognosis if identified and treated early, emphasizing the importance of clear guidelines for diagnosis and treatment strategies. Several factors determine treatment options and duration such as prosthetic versus native valve endocarditis (NVE), the resistance profile of the bacterial strain, and the patient comorbidities.

Medical treatment alone, or along with adjunctive surgical intervention, can cure up to 87% of patients with HE [8].

However, antibiotic therapy alone is usually sufficient to treat most cases of HE.

### 6.1. Antibiotic treatment

In the past, combination therapy with penicillin or ampicillin and an aminoglycoside such as gentamicin was the treatment of choice for HE. However, the rise of  $\beta$ -lactamase producing organisms has changed the therapeutic strategy. The decision of which drug to use should be based on susceptibility data of the organism, if available. However, the nature of these fastidious organisms can make susceptibility testing difficult and impractical in certain settings. In these cases, therapy is chosen empirically based on published guidelines [3].

Both the AHA and the European Society of Cardiology (ESC) IE guidelines recommend considering the organisms ampicillin-resistant due to the difficulty to demonstrate susceptibility and the high likelihood of resistance among HACEK microorganisms. Thus, broad-spectrum cephalosporins or fluoroquinolones are considered the first line of treatment for HE [22,27]. Despite previous practices, ampicillin should not be used for patients with HE unless the organism is proven to be susceptible, and gentamicin is no longer recommended due to its nephrotoxic risks [23].

The standard treatment for HE is monotherapy with intravenous ceftriaxone at 2 g daily. The regimen should be given for 4 weeks in NVE and for 6 weeks in prosthetic valve endocarditis [22,27]. Ampicillin–sulbactam (intravenously at 12 g daily divided in four doses) is a less well-validated alternative. If the HACEK organisms are not  $\beta$ -lactamase producers, ampicillin (intravenously at 12 g daily in four or six divided doses) and gentamicin (3 mg/kg/day in two or three divided doses) for 4–6 weeks is an alternative option [27].

Alternative, yet infrequently used options in cases of  $\beta$ -lactam allergy are fluoroquinolones such as ciprofloxacin, levofloxacin, or moxifloxacin [23,27].

### 6.2. Antimicrobial susceptibility

Antimicrobial susceptibility testing for a significant proportion of HACEK isolates may not be possible using recommended methods due to the fastidious nature of the organisms [3]. Thus, recommendations of susceptibility testing may not be optimal in the treatment of HE. A study examining the antimicrobial susceptibilities of 241 HACEK isolates in Ontario, Canada confirmed the difficult susceptibility testing and the high resistance among HACEK microorganisms [3]. Resistance was highest in *Aggregatibacter* and *Haemophilus* spp., usually to more than one antimicrobial agent. Ceftriaxone was active against all isolates, as the most effective cephalosporin when compared to cefixime, cefepime, cefuroxime, and cefaclor. Such findings confirm the use of broad-spectrum cephalosporins and fluoroquinolones as the optimal first-line therapy for HE.

### 6.3. Surgical treatment

There are no specific recommendations for the surgical treatment of HE. However, one advantage of surgical intervention is to harvest valve tissue, which can be used for

microbiological documentation [10]. Besides valve culture, histopathology of valves showing microorganisms or neutrophil infiltration as signs of active endocarditis is a very useful tool, and PCR of the valves may also be helpful [37,38]. Although HACEK group is not considered among the difficult-to-treat or highly resistant organisms, surgical intervention is warranted in the presence of heart failure, paravalvular extension, persistence of the infection despite appropriate antimicrobial treatment, and/or for the prevention of embolic events. These indications for surgery apply to native, as well as prosthetic, valve HE [22,27,39]. After surgical intervention, if operative tissue cultures are negative, antibiotic therapy should be continued to complete the preoperative course, starting from the first negative blood culture after HE diagnosis. However, in case of positive operative tissue cultures, a full course of antibiotics should be given according to the susceptibility profile of the operative cultures starting from the time of surgery [22,27].

A newly published retrospective study by Lee et al. demonstrated that surgical mitral valve repair with lifting annuloplasty strip in 27 patients with an acute IE, including HE in 15% of cases, has a 5-year survival rate of 96.3%. This study also showed a significant decrease in left ventricular end-diastolic dimensions with no/minimal regurgitation up to a median follow-up of 54 months post operation [40].

## 7. Prevention and recommendations for prophylaxis

Previously, prophylaxis before invasive dental procedures was a standard recommendation for preventing bacterial endocarditis from oropharyngeal organisms, particularly HACEK organisms and viridans group streptococci. However, this recommendation was revoked by the AHA in 2007 after population-based data revealed that only a small number of cases of IE are prevented by administering prophylactic antibiotics for dental procedures [41]. Increasing evidence and clinical trials continue to challenge and update recommended prophylactic strategies.

The use of antimicrobial prophylaxis is now recommended in specific high-risk situations, such as the presence of a prosthetic heart valve, previous history of IE, uncorrected or recently corrected CHD, and development of cardiac valvulopathy after cardiac transplantation [6,27]. For patients in these high-risk populations, prophylaxis is indicated before dental procedures that involve manipulation of gingival tissue or periapical region of the teeth, or perforation of the oral mucosa such as scaling and root canal procedures [27,41]. The use of antibiotic prophylaxis is not recommended for local anesthetic injections in noninfected tissues, treatment of superficial caries, removal of sutures, dental X-rays, placement or adjustment of removable prosthodontic or orthodontic appliances or braces, or trauma to the lip and mucosa [27].

The main target of antibiotic prophylaxis in these populations is oral streptococci, although HACEK organisms are also included. According to the ESC 2015 guidelines, the main regimens recommended for prophylaxis are amoxicillin or ampicillin, 2 g orally or intravenously in adults and 50 mg/kg orally or intravenously in children. If the patient is allergic to penicillin or ampicillin, clindamycin can be given at 600 mg for

adults and 20 mg/kg in children. The antibiotics are given as a single dose 30–60 min prior to the dental procedure [27].

Antibiotic prophylaxis is not recommended for patients at intermediate risk of IE, which include patients with any other form of native valve disease such as bicuspid aortic valve, mitral valve prolapse, and calcific aortic stenosis. Nevertheless, while antimicrobial prophylaxis is restricted to high-risk populations, other preventative measures should be applied to all patients with cardiac disease. The ESC guidelines propose nonspecific preventative measures such as strict dental and cutaneous hygiene, biannual dental follow-up, disinfection of wounds, curative antibiotics for any focal bacterial infection, no self-medication with antibiotics, and the limited use of infusion catheters and invasive procedures [27].

## 8. Expert commentary

Although HACEK organisms contribute to the majority of Gram-negative IE [6], the lack of randomized controlled trials in diagnosing and treating HE makes it difficult to optimally manage such infections. Nevertheless, culturing methods have shown progress in isolating these fastidious organisms using the MALDI-TOF MS. Positive blood cultures for any of the HACEK organisms in the setting of no definite focus of infection is highly suggestive of HE. In such cases, treatment with ceftriaxone or a fluoroquinolone, even without obtaining antibiotic susceptibilities, should be initiated, due to the difficulty in performing susceptibility testing. Moreover, the decision to proceed with adjunctive surgical intervention should be individualized. As is the case for other IE, HE requires the collaboration of a multidisciplinary team consisting of the infectious disease specialist, cardiologist, cardiothoracic surgeon, and the microbiologist.

## 9. Five-year view

With the advances in culturing and isolating fastidious organisms, new culturing techniques might further shorten the duration for growing HACEK organisms, allowing for earlier intervention and fewer complications and mortality. This will positively affect the treatment of such organisms by allowing early administration of narrow-spectrum directed therapy, which is particularly important in an era of high resistance. The value of non-culture-based techniques, such as PCR amplification, will unfold in the coming years. Molecular techniques are highly sensitive but their specificity may be questionable. When minute amounts of bacterial DNA are recovered, their clinical significance is not always understood. In addition, unless resistance genes are also amplified, molecular techniques would not provide antimicrobial susceptibility data. Although echocardiography remains pivotal in diagnosing HE, we await more data in support of newer imaging techniques such as cardiac MRI and nuclear imaging, particularly in the detection of small vegetations, mural abscesses, and prosthetic valve complications.

## 10. Key issues

- HACEK Endocarditis (HE) is a relatively rare disease with an excellent prognosis and simple management if the organism is properly and readily identified.

- The incidence of HE among infective endocarditis (IE) cases ranges between 1.4–3%, but the distribution of HE organisms varies between published reports with recent reclassifications of the *Haemophilus* and *Aggregatibacter* species.
- Compared to non-HE, HE tends to have a sub-acute presentation and to be acquired from the community. It usually infects younger patients without comorbidities, and although associated with an increased risk of stroke, it tends to have a better prognosis.
- The diagnosis of HE relies on the modified Duke criteria for IE, and the etiologic organism is identified using advanced culturing techniques such as BacT/Alert system or MALDI-TOF mass spectrometry.
- The first line of antimicrobial therapy for HE, based on American Heart Association (AHA) and European Society of Cardiology (ESC) guidelines, includes monotherapy with a broad-spectrum cephalosporin or a fluoroquinolone for 4 weeks in native valve endocarditis, and for 6 weeks in prosthetic valve endocarditis.
- Ampicillin is a less-validated alternative for treatment of HE due to rising antimicrobial resistance, especially among the *Aggregatibacter* and *Haemophilus* species, while ceftriaxone remains effective on all isolates.
- The indications for surgical treatment are not specific to HE, and these include heart failure, para-valvular extension, persistence of infection despite antimicrobial therapy, and/or prevention of embolic events.
- The widespread IE prophylaxis recommendations before invasive dental procedures were revoked by AHA in 2007, and antimicrobial prophylaxis is currently only recommended in specific high-risk situations, such as the presence of prosthetic heart valves, a previous history of IE, and uncorrected or recently corrected congenital heart disease.
- The management of HE should be individualized to the patient and etiologic organism, and involves rapid identification of the organism, establishing the diagnosis of IE, and administration of appropriate antimicrobial therapy.

## Declaration of interests

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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• of interest

•• of considerable interest

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