HACEK endocarditis: state-of-the-art

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Abstract

The HACEK group of bacteria – *Haemophilus parainfluenzae*, *Aggregatibacter* spp. (*A. actinomycetemcomitans*, *A. aphrophilus*, *A. paraphrophilus*, and *A. segnis)*, *Cardiobacterium* spp. *(C. hominis*, *C. valvarum)*, *Eikenella corrodens*, and *Kingella* spp. (*K. kingae*, *K. denitrificans*) – are fastidious gram-negative bacteria, part of the normal microbiota of oral and upper respiratory tract in humans. Although their pathogenicity is limited, they are responsible for 1-3% of all infective endocarditis. HACEK endocarditis mostly affect patients with underlying heart disease or prosthetic valves, and are characterized by an insidious course, with a mean diagnosis delay of 1 month (*Haemophilus* spp.) to 3 months (*Aggregatibacter* and *Cardiobacterium* spp.). The advent of continuously monitored blood culture systems with enriched media has erased the need for extended incubation for the diagnosis of HACEK endocarditis. Medical treatment relies on third generation cephalosporin, with a favourable outcome in 80-90% of cases, with or without cardiac surgery.

Key words: Infective endocarditis; HACEK group; *Haemophilus parainfluenzae*; *Aggregatibacter* spp.; *Cardiobacterium* spp.; *Eikenella corrodens*; *Kingella* spp.

The HACEK group of bacteria includes *Haemophilus parainfluenzae*, *Aggregatibacter* spp. (*A. actinomycetemcomitans*, *A. aphrophilus*, and *A. segnis*), *Cardiobacterium* spp. (*C. hominis*, *C. valvarum*), *Eikenella corrodens*, and *Kingella* spp. (*K. kingae*, *K. denitrificans*). These fastidious gram-negative bacteria share several common characteristics (Table 1): i) they all require – or are stimulated by – the presence of CO_2, with optimal growth achieved only on enriched media (e.g., as those currently in use for continuously monitored automated blood culture systems) [1]; ii) they are part of the normal human microbiota, mostly oropharyngeal, but also urogenital for some of them; iii) they are associated with infective endocarditis (IE) [2]. This latter is particularly salient, given that most bacteria (>80%) associated with IE are gram-positive [3], and that bacteria from the HACEK group are very rarely encountered in infectious diseases other than IE in humans [4], with the exception of *Kingella kingae*, the main cause of septic arthritis in children below 2 years of age [5].

The HACEK group is responsible for 1.2-3% of all IE cases [1 2 6-9]. Interestingly, the proportion of IE caused by HACEK seems to be lower in North America (0.3%), than in other parts of the World (2%) [8]. The relative proportion of each etiologic agent within the HACEK group is as follows: *H. parainfluenzae* (27-36%), *A. actinomycetemcomitans* (20%), *A. aphrophilus* (12-16%), *A. segnis* (1%), *C. hominis* (13-27%), *C. valvarum* (1%), *E. corrodens* (4-5%), *K. kingae* (3-7%), and *K. denitrificans* (1%) [2 7]. The mean age of patients with HACEK endocarditis (43-48 years) is usually lower than that of patients suffering from non-HACEK IE [2 7 9]. Of importance, the delay between symptoms onset and diagnosis is particularly long (i.e. between 2 weeks and 6 months), which may be related to the clinical presentation of HACEK IE, usually subacute. Main predisposing factors are pre-existing heart disease (60%), and poor dentition/previous dental procedure (58%) while IE preferentially occurs in patients with native valves (65-80%) [2 7 9]. Aortic (30-49%), and mitral (45-50%) valves are most commonly involved [2 7 9]. Surgical cardiac replacement is performed in 40% patients, and the overall outcome is favourable in most cases (87-89%) [2 7].

Several recent microbiological evolutions are remarkable: i) the development of enriched blood cultures (BC) media and the implementation of automated BC systems, that has erased the need for extended incubation for the diagnosis of HACEK IE [10 11]; ii) easier and reliable identification from cultures thanks to the MALDI-TOF mass spectrometry technology regardless of the system used (Microflex LT [Bruker Daltonics] or Vitek MS [bioMérieux]), with species- and genus-level identification in 66-93% and 88-95% cases, respectively [12-15]; iii) rapid molecular-based detection directly from clinical specimens using home-made protocols or commercially-available kits [16 17]; and iv) recent clinical and laboratory standards institute (CLSI) recommendations for antimicrobial susceptibility testing of the HACEK group using the broth microdilution technique [CLSI M45-A2 2010].

Haemophilus parainfluenzae

H. parainfluenzae is the most common cause of HACEK endocarditis, found in 28 (36%) of the 77 cases of HACEK endocarditis enrolled within the International Collaboration on Endocarditis (ICE) prospective cohort study during years 2000-2006 [7], and 12 out of 45 (27%) cases of HACEK IE reported from the Mayo Clinic in Rochester, during years 1970-1992 [2]. The association between *H. parainfluenzae* bacteremia and IE is strong, with a positive predictive value (PPV) for the diagnosis of IE estimated at 55% (10/18) [4].

Microbiology

H. parainfluenzae is a small, non-motile, non-spore-forming, non-acid-fast, pleomorphic gram-negative bacilli, which requires for growth V factor or nicotinamide (complexed as NAD or NADP), present in erythrocytes. Members of the *Pasteurellaceae* family, *Haemophilus* spp. are part of the normal upper and lower respiratory tract microbiota, *H. parainfluenzae* accounting for 75% of *Haemophilus* species in both oral cavity and pharynx. *H. parainfluenzae* has very rarely been associated with human infections and most case reports of non-IE infections were related to its primary reservoir, respiratory tract (e.g. sinusitis, bronchitis, otitis, exacerbation of chronic

obstructive pulmonary disease, pneumonia), although *H. parainfluenzae* brain abscess, surgical site infections, soft tissue infections, prosthetic joint infections, and hepatic and biliary tract infections have also been documented [18] . *H. parainfluenzae* may also be part of the genital tract microbiota, and documented cases of chorio-amniotitis, and neonatal sepsis have been reported.

A Canadian study of 37 clinical isolates of *H. parainfluenzae* originating from blood cultures, or abscess fluid, found susceptibility rates of 67.6% for penicillin, 97.3% for ampicillin, and 100% for amoxicillin-clavulanic acid, ceftriaxone, meropenem, and levofloxacin [19].

Characteristics of* H. parainfluenzae *endocarditis

A series of 26 cases of *H. parainfluenzae* endocarditis was reported in 1997, associated with a literature review of 26 additional cases [20]. Most patients (60% in the series) had underlying native valve disease, the remaining predisposing factors being prosthetic valve (12%), or previous infective endocarditis (10%). Of note, only one patient (2% of all cases of *Haemophilus* spp. endocarditis reported in this series) was an intravenous drug user (IVDU), while 38% of previously reported cases (15/40) occurred in IVDU. Portal of entry remained unknown in 75% of all cases. The mean duration from symptoms onset to diagnosis was quite long, at 34 days (range 2-330) in the series, and 37 days (range 5-365), for the cases previously reported. This diagnosis delay, possibly related to the insidious onset of symptoms and the subacute clinical course, may be one of the reason behind the high proportion of patients who present with symptomatic peripheral embolization (~50%), and large vegetation(s), > 10 mm in 42% of cases [20 21]. On the other hand, the proportion of patients with perivalvular abscess (7%), and heart failure (15-30%) is rather low as compared to usual figures in infective endocarditis, which may be related to the limited pathogenicity of these organisms. The mitral valve is most commonly affected in non-IVDU patients (71%), while the tricuspid valve is primarily involved in IVDU (45%). Data from two different cohorts suggested that *H. parainfluenzae* endocarditis was less likely to have an insidious onset than *A. actinomycetemcomitans* and *C. hominis* [2 7].

Despite the diagnosis delay, and the high proportion of patients with large vegetation(s), and/or

peripheral embolization, the overall prognosis of patients with *H. parainfluenzae* endocarditis is favourable in most cases: attributable mortality was estimated at 5% in the largest series reported to date [20], and 10% in the literature review. Surgical valvular replacement was performed in 40-70% of cases. Most patients have been treated with a β-lactam agent (mostly third-generation cephalosporin during recent years [7], in agreement with international guidelines [22]). However, the outcome of medically treated patients was also favourable in most cases in older series, when amoxicillin and ampicillin, usually combined with an aminoglycoside, were more commonly used [2 20].

Aggregatibacter spp.

The three species *A. actinomycetemcomitans, A. aphrophilus*, and *A. segnis* are the second most common cause of HACEK endocarditis, found in 26 (34%) of the 77 cases of HACEK endocarditis enrolled within the ICE prospective cohort study [7], and 16 out of 45 (36%) cases of HACEK endocarditis reported from the Mayo Clinic [2]. The association between *Aggregatibacter spp.* bacteremia and endocarditis is strong, with a PPV for the diagnosis of IE estimated at 100% (22/22) for *A. paraphrophilus* and *A. actinomycetemcomitans*, and 55% (5/9) for *A. aphrophilus*, in a landmark New Zealand study [4].

Microbiology

Aggregatibacter spp. also belong to the *Pasteurellaceae* family and are facultatively anaerobic, non-motile, coccoid to rod-shaped, gram-negative bacteria. They are part of the normal microbiota of the human oral cavity, especially dental plaque. The genus *Aggregatibacter* was created in 2006, bringing together several former species of the *Actinobacillus* (*A. actinomycetemcomitans*) and *Haemophilus* (*H. aphrophilus*, *H. paraphrophilus*, and *H. segnis*) genera [23]. Note that the former species *H. paraphrophilus* corresponds now to V factor-dependent *H. aphrophilus* strains and is now classified within the species *A. aphrophilus* [23]. *A. actinomycetemcomitans* is particularly common in the gingival and supragingival crevices, and is a frequent cause of aggressive

periodontitis [24]. In addition, as inferred from its name, *A. actinomycetemcomitans* is commonly isolated concomitantly with members of the *Actinomycetes* group in abscess and wound specimens from actinomycotic lesions [25]. *A. paraphrophilus* is a normal inhabitant of the nasopharynx, oropharynx, mouth, lower gastro-intestinal tract, and vagina of mature women. Besides IE, *A. paraphrophilus* has mainly been documented from abscess (especially brain abscess), but also bone or joint infections, and endophtalmitis [18]. Likely underestimated due to misidentifications by conventional methods, *A. segnis* may also cause endocarditis as well as bacteremia and pyelonephritis [26 27].

A study of 11 clinical isolates of *A. aphrophilus* found susceptibility rates of 82% for penicillin, and 100% for ampicillin, amoxicillin-clavulanic acid, ceftriaxone, meropenem, and levofloxacin [19]. Of note, the only HACEK organism resistant to penicillin in the ICE-prospective cohort study was one isolate of *A. aphrophilus* [7].

Characteristics of* Aggregatibacter *spp. endocarditis

The first case of *A. actinomycetemcomitans* endocarditis was published in 1964, and a literature review of 102 cases of *A. actinomycetemcomitans* endocarditis published 40 years later found that: i) *A. actinomycetemcomitans* endocarditis mostly occurred in men (two thirds of all reported cases), with a mean age of 47 years; ii) risk factors mostly included underlying valve disease (75% of all cases, secondary to rheumatic heart disease in half of patients), and prosthetic valve (26%); iii) a dental disease was frequently associated (42%); iv) the disease was particularly insidious, with a mean diagnosis delay of 13 weeks after symptoms onset; v) the aortic valve was more commonly affected (51%), than the mitral valve (33%); vi) complications were not rare (63%), and mostly included emboli (30%), and heart failure (27%); vii) surgical valvular replacement was required in 25% of cases, and viii) the overall mortality rate was 18% [28]. When compared to other HACEK endocarditis within the ICE-prospective cohort study, *A. actinomycetemcomitans* endocarditis was more likely to occur on prosthetic valves (10/15, 67%), with a diagnosis delay > one month (8/15, 53%), and to be associated with Osler's nodes [7].

Other *Aggregatibacter* species are less common causes of endocarditis, and available data remain scarce: A review of 23 cases of *A. aphrophilus* endocarditis published in 1975 - then referred to as *Haemophilus aphrophilus* - was remarkable for the high mortality rate (48%) [29]. A review of 17 cases of *A. paraphrophilus* endocarditis published in 1995 - then referred to as *Haemophilus paraphrophilus* - was remarkable for the predominance of mitral valve endocarditis (16/17), while the mortality rate was in the usual range for IE, at 18% [30].

Cardiobacterium spp.

Cardiobacterium spp. are the third most common agents responsible for HACEK endocarditis, found in 11 (14%) of the 77 cases of HACEK endocarditis enrolled within the ICE prospective cohort study [7], and 12 out of 45 (27%) cases of HACEK endocarditis reported from the Mayo Clinic [2]. Although *C. hominis* is by far the most common *Cardiobacterium* species involved, a few cases of *C. valvarum* endocarditis have been reported since it was first identified in a patient with bicuspid aortitis and ruptured mycotic cerebral aneurysm, in 2004 [31]. The association between *C. hominis* bacteremia and endocarditis is strong, with a PPV for the diagnosis of endocarditis estimated at 88% (7/8) in one study [4], and 94% (32/34), or 95% (60/63) in two large literature reviews [32 33].

Microbiology

Cardiobacterium spp. belong to the *Cardiobacteriaceae* family and consist of facultatively anaerobic, non-motile, gram-negative rods. After gram staining, they appear as pairs, short chains, teardrop forms, rosettes, or clusters – sometimes with bulbous ends. The normal habitat of these species is the human oral cavity and nasopharynx. *Cardiobacterium* spp. have also been isolated from the genital tract of asymptomatic women. These organisms are of low virulence, and their pathogenic effect is mostly limited to IE in humans. Inocula as great as 10^9 microorganisms injected into various mice, rabbits, hamsters, guinea pigs, and pigeons, failed to produce any evidence of infection [33]. Note that one case of prosthetic valve endocarditis was reported following upper

gastrointestinal endoscopy [34].

Although most clinical isolates of *Cardiobacterium* spp. investigated to date were susceptible to penicillin and ampicillin, rare reports of β-lactamase-producing *C. hominis* strains causing endocarditis [35 36], have led to the recommendation that third-generation cephalosporins must be considered as the first-line antibacterial treatment of *Cardiobacterium* spp. endocarditis.

***Characteristics of Cardiobacterium* spp. endocarditis**

In 2005 and 2006, two large reviews of 63 and 67 cases of *C. hominis* endocarditis were reported [32 37]. The main characteristics of *C. hominis* endocarditis are as follows: i) patients mean age was 50.2 ± 15 years (range, 17-82), with a male-to-female sex ratio of ~2; ii) most common risk factors were underlying valve disease (61%, mostly congenital heart disease and rheumatic fever), and prosthetic valve (28%); iii) *C. hominis* endocarditis may be even more insidious than other HACEK endocarditis, with a mean diagnosis delay of 138 ± 128 days according to Malani et al. [32], and 169 days according to Wormser et al. [33]; iv) the aortic valve is most commonly affected (52%), followed by the mitral valve (44%); v) main complications were heart failure (40%), and central nervous system emboli (21%); vi) valve replacement was required in 27 cases (45%), and the outcome was favourable in most cases (93% overall; 94% for the subgroup of patients with prosthetic valve endocarditis) [32]. Limited data on *C. valvarum* endocarditis would suggest that large vegetations and extensive valvular destruction are common [38].

Eikenella corrodens

The genus *Eikenella*, within the family *Neisseriaceae*, includes the unique species *E. corrodens*. It is a facultatively anaerobic, non-motile, straight gram-negative small rod with rounded ends. It is a normal inhabitant of oral cavities of humans and some mammals from which it can be transmitted via saliva (bites, syringes). The prevalence carriage is higher among people under 20 years of age, and in those with periodontal disease.

Its association with endocarditis is rather weak, as i) this bacteria was responsible for only ~5% of

all HACEK endocarditis reported from the Mayo clinic [2], and in the ICE-prospective cohort study [7]; ii) the PPV of *E. corrodens* bacteremia for the diagnosis of endocarditis is the lowest among all HACEK bacteria (none of 11 consecutive cases of *E. corrodens* bacteremia was related to endocarditis in one study) [4]; iii) *E. corrodens* is involved in a broad spectrum of infectious diseases, including localized infections of the head and neck, upper or lower tract respiratory infections, subcutaneous abscesses, cellulitis, and osteomyelitis [39]. Interestingly, these latter have been especially reported following clenched fist injuries or human bites, due to the traumatic inoculation of *E. corrodens* originating from the oral microbiota [40]. In addition, IVDU is a risk factor for skin and skin structure or endovascular *E. corrodens* infections, due to the use of saliva for skin cleansing or dissolution of narcotics in some settings [41]. Endocarditis represented only 2% of all invasive infections due to *E. corrodens* in one study [39].

A study of 17 clinical isolates of *E. corrodens* found susceptibility rates of 94% for penicillin and ampicillin, and 100% for ampicillin-sulbactam, amoxicillin-clavulanic acid, ceftriaxone, meropenem, and levofloxacin [19].

Kingella spp.

Kingella spp. are also members of the *Neisseriaceae* family and consist of facultatively anaerobic, non-motile, short gram-negative rods with tapered ends. Occasionnally, they may be resistant to decolorization and appear as gram-positive bacteria. They are part of the normal microbiota of upper respiratory and genitourinary tracts in humans. Within the genus, *K. kingae* is the main species responsible for invasive diseases, although cases of *K. denitrificans* endocarditis have been reported [7]. *K. kingae* colonizes the oropharynx - but not the nasopharynx - of approximately 10% of children aged from 6 months to 4 years [5], and may be transmitted via respiratory droplets between family members and other close contacts

As for *E. corrodens*, its association with endocarditis is rather weak, as i) this bacteria was responsible for 7% of HACEK endocarditis diagnosed during years 1970-1993 at the Mayo clinic

[2], and 5% in the ICE-prospective cohort study (2000-2006) [7]; ii) the PPV of *K. kingae* bacteremia for the diagnosis of endocarditis was estimated at 42% (8/19) [4]. The situation is strikingly different for young children (i.e., under four years of age), who are much more prone to *Kingella* spp. invasive diseases [5]: *K. kingae* is the most common cause of septic arthritis in this population, which may be related to a potent repeats-in toxin system (RTX), that exhibits a wide range of cytotoxic activity and is particularly deleterious for macrophages, leucocytes, and synovial cells [42]. A study of 143 consecutive patients with *K. kingae* infections diagnosed in southern Israel during years 1988-2013 found that septic arthritis, osteomyelitis or tenosynovitis were most commonly involved (55%), followed by occult bacteremia (39%). Only two patients (1% of all invasive *K. kingae* infections) were diagnosed with endocarditis [42].

However, given the very low incidence of infective endocarditis in children, a literature review found that *K. kingae* was the most common cause of HACEK endocarditis in this population, at the same level as *H. parainfluenzae* (36% of all HACEK endocarditis). Children with *K. kingae* endocarditis had underlying heart disease in 62% of cases (mostly congenital), and 12/13 initially survived (92%), although two had neurological sequels (hemiplegia), and one died during cardiac surgery three months later [43]. Outbreaks of invasive infections due to *K. kingae* have been reported in children communities, with severe manifestations - including endocarditis and meningitis - and high prevalence of colonization, suggesting that some isolates may present with enhanced colonization fitness, increased transmissibility, and high virulence [44].

Expert commentary

Although HACEK endocarditis has been first reported more than 50 years ago, and remains a rare clinical entity, totalling around 1-3% of all infective endocarditis [7 21 45-47], this state-of-the-art paper is justified by the new findings gathered over the last decade in the fields of taxonomy, clinical presentation, diagnosis, and treatment:

- Firstly, taxonomic revisions in the genera *Haemophilus* and *Actinobacillus* have resulted in the

description of the genus *Aggregatibacter* in 2006 which, by chance, did not change the acronym 'HACEK', but introduced some movement within some letters: While the '*H*' initially referred to *H. parainfluenzae*, *H. aphrophilus*, and *H. paraphrophilus*, these two latter are now combined within a unique *Aggregatibacter* species, *A. aphrophilus*. In addition, *A. actinomycetemcomitans* was reclassified within the *Aggregatibacter* genus, which also comprises *A. segnis* (formerly *Haemophilus segnis*). Hence, the HACEK group now refers to *H. parainfluenzae*, *Aggregatibacter* spp. (*A. actinomycetemcomitans, A. aphrophilus,* and *A. segnis)*, *Cardiobacterium* spp. *(C. hominis, C. valvarum)*, *Eikenella corrodens*, and *Kingella* spp (*K. kingae, K. denitrificans*) [18].

- Secondly, the advent of continuously monitored automated blood culture systems with enriched media have changed the paradigm that the diagnosis of HACEK bloodstream infections would require extended incubation of blood cultures: Indeed, various studies have found that >99% of the HACEK responsible for endocarditis will be recovered within the standard 5-day incubation protocol [48]: Baron et al. analysed data from 1995-1997 at the Standford University Medical Hospital during which time a special endocarditis blood culture protocol with extended incubation (up to 6 weeks) was implemented following physician requests in 215 patients: The 24 HACEK bacteria identified during that time (out of ~14,000 routine blood cultures), were all recovered within the standard 5-day incubation protocol [11]. Similar findings have been found with different blood culture systems [10 11 48-50]. The advent of matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF) may allow dramatic improvement in the identification of HACEK bacteria once blood cultures return positive, in terms of accuracy, and delay [14 18].

- Thirdly, a systematic study on the association between HACEK bacteremia and the probability of endocarditis [4], found striking heterogeneity within the HACEK group: Indeed, the positive predictive value of positive blood culture(s) for the diagnosis of endocarditis ranged from 0% with *E. corrodens* bacteremia, to 100% for *A. actinomycetemcomitans*.

- Fourthly, a large multi-national, prospective cohort of 5,591 patients with definite infective endocarditis, found that the 77 cases of HACEK endocarditis (1.4% of the whole cohort), were

significantly younger (median age, 47 *vs.* 61 years, P<0.001), had more vascular/immunologic manifestations (32% *vs.* 20%, P<0.008), and stroke (25% *vs.* 17%, P=0.05), but lower risk of heart failure (15% *vs.* 30%, P=0.004), in-hospital mortality (4% *vs.* 18%, P<0.001), and one-year mortality (6% *vs.* 20%, P=0.01) [7]. Importantly, the favourable outcome of both medically and surgically treated HACEK endocarditis on prosthetic valve demonstrates that these organisms are not a stand-alone indication for surgical valvular replacement (i.e. usual criteria for surgical treatment should apply, mostly heart failure, embolism risk, and medical treatment failure [22 51]).

- Fifthly, β-lactamase–producing strains of HACEK may be emerging [19 52], and difficulty in performing antimicrobial susceptibility testing as a result of failure of growth *in vitro* have led endocarditis experts to recommend that, '*unless growth is adequate for in vitro screening, then HACEK microorganisms should be considered ampicillin resistant, and penicillin and ampicillin should not be used to treat patients with IE in these cases*' [22]. However, when reliable drug-susceptibility testing demonstrate that amoxicillin or ampicillin are effective *in vitro*, in the absence of β-lactamase production, one of these agent may be used instead of third generation cephalosporin [51], as their narrower spectrum would imply a lower risk of drug-resistant bacteria selection, and a more limited impact on microbiota - hence a lower risk of *Clostridium difficile* colitis. The use of aminoglycoside is not recommended for HACEK endocarditis. Ciprofloxacin is the main alternative in patients who cannot tolerate β-lactam agents. The recommended duration of treatment is 4 weeks for native valve endocarditis, and six weeks for prosthetic valve endocarditis.

Five-year view

The field of HACEK endocarditis will probably experience limited development over the next 5 years. There is no reason why it would evolve as an emerging disease, given the very low and steady proportion of infective endocarditis that were related to these pathogens since the first descriptions of HACEK endocarditis more than 50 years ago. In addition, the changing profile of infective endocarditis since the early 2000's mostly favours the emergence of staphylococci

endocarditis, as a consequence of medical progress. Current systems for blood cultures have resolved the need for extended incubation of blood culture bottles for the diagnosis of HACEK endocarditis, and the advent of new tools for rapid identification of bacteria (e.g. MALDI-TOF) have brought additional progress in the field, so that no dramatic improvement is expected to have any significant impact on the diagnosis of HACEK endocarditis over the next five years. Finally, current recommendations for treatment will probably not dramatically change as well, given the 100% susceptibility rate of HACEK bacteria to the first-line regimen currently recommended (third generation cephalosporin), and the favourable outcome in most cases, with the use of current criteria for surgical valvular replacement.

Key issues

- Following 2006 taxonomy changes, HACEK now refers to *Haemophilus parainfluenzae*, *Aggregatibacter* spp. (*A. actinomycetemcomitans, A. aphrophilus, A. paraphrophilus*, and *A. segnis)*, *Cardiobacterium* spp. *(C. hominis, C. valvarum)*, *Eikenella corrodens*, and *Kingella* spp. (*K. kingae, K. denitrificans)*
- The HACEK bacteria are an heterogeneous group of fastidious, gram-negative bacilli, part of the normal upper respiratory tract microbiota in humans, with limited pathogenicity - except endocarditis - for most of them
- HACEK are responsible for 1-3% of all infective endocarditis, and mostly occurs in patients with underlying valve disease
- As compared to other infective endocarditis, HACEK endocarditis are characterized by an insidious course – hence a prolonged delay before symptoms onset, and diagnosis, in most cases
- As for any other infective endocarditis, the diagnosis of HACEK endocarditis relies mainly on sampling an adequate volume of blood for cultures before any antibacterial treatment.
- Continuously monitored automated blood culture systems with enriched media routinely used in industrialized countries identifies ~100% of HACEK endocarditis within 5 days of incubation
- Unless growth is adequate for *in vitro* screening, HACEK microorganisms should be considered ampicillin resistant, and a third generation cephalosporin should be preferred for the treatment of HACEK endocarditis. Ciprofloxacin is the main alternative for patients with severe intolerance to all β-lactams
- No combination of antimicrobials is necessary; treatment duration should be 4 weeks for native valve endocarditis, and 6 weeks for prosthetic valve endocarditis

Declaration of interest

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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Table 1. Characteristic features of HACEK organisms causing endocarditis

Organism	**Microbiology** (family, gram)	**Pathogenicity in Humans**	**Epidemiology of endocarditis**	**Characteristics of endocarditis**	**Outcome**
Haemophilus parainfluenzae	*Pasteurellaceae* pleomorphic gram-negative coccobacilli	55% of patients with positive BC have endocarditis Other infections rare: respiratory tract, brain abscess, soft tissue, prosthetic joint, biliary tract, neonatal sepsis	27-36% of all HACEK endocarditis Risk factors: underlying heart disease (60%), prosthetic valve (12%), IVDU	Moderately insidious (mean duration of symptoms before diagnosis, 35 days) Mostly mitral valve (71%)	Cardiac surgery, 40-70% Mortality, 5-10%
***Aggregatibacter* spp.** *A. actinomycetemcomitans* *A. aphrophilus* *A. paraphrophilus* *A. segnis*	*Pasteurellaceae* pleomorphic gram-negative coccobacilli	100% of patients with positive BC for *A. actinomycetemcomitans* and *A. paraphrophilus* have endocarditis Other infections rare: abscesses, association with *Actinomycetes*, endophtalmitis, bone and joint	34-36% of all HACEK endocarditis Risk factors: underlying heart disease (75%), prosthetic valve (26%) Dental disease (42%)	*A. actinomycetemcomitans* Very insidious (mean duration of symptoms before diagnosis, 100 days) Mostly aortic (51%), or mitral valve (33%)	Cardiac surgery, 25% Mortality, 18%
***Cardiobacterium* spp.** *C. hominis* *C. valvarum*	*Cardiobacteriaceae* pleomorphic gram-negative or gram-variable bacilli	88-95% of patients with positive BC for *Cardiobacterium hominis* have endocarditis Very low virulence in animals No other infection	14-27% of all HACEK endocarditis Risk factors: underlying heart disease (61%), prosthetic valve (28%)	The most insidious (mean duration of symptoms before diagnosis, 138-169 days) Mostly aortic (52%), or mitral valve (44%)	Cardiac surgery, 45% Mortality, 7%
Eikenella corrodens	*Neisseriaceae* pleomorphic gram-negative bacilli	0/11 patients with positive BC for *E. corrodens* had endocarditis in one study *E. corrodens* is involved in a broad spectrum of infectious diseases: i) in IVDU (soft tissue, endovascular); ii) traumatic inoculation (human bites, clenched fist injuries)	~5% of all HACEK endocarditis	Limited data (no series)	Limited data (no series)
***Kingella* spp.** *K. kingae* *K. denitrificans*	*Neisseriaceae* small gram-negative coccobacilli	8/19 patients (42%) with positive BC for *K. kingae* had endocarditis in one study First cause of septic arthritis in children < 2 years of age, and a common cause of occult bacteremia in this population	5-7% of all HACEK endocarditis 36% of all HACEK endocarditis in children (underlying heart disease, 62%)	Limited data (no series)	Cardiac surgery, 23% Mortality, 8%

HACEK microorganisms: *Haemophilus parainfluenzae*, *Aggregatibacter* spp., *Cardiobacterium* spp., *Eikenella corrodens*, and *Kingella* spp.
BC: blood cultures; IVDU: intravenous drug use