Gram-negative endocarditis due to HACEK bacteria (Haemophilus species, Actinobacillus, Cardiobacterium, Eikenella and Kingella species) and non-HACEK organisms is an infrequent occurrence but is associated with significant morbidity and mortality. Traditionally, non-HACEK Gram-negative endocarditis has been associated with injection drug use. However, emerging data from more contemporary cohorts suggest changing epidemiology and risk factors for Gram-negative endocarditis, necessitating an updated review of this subject. Moreover, optimal management, including the need for surgical intervention, and strategies for the prevention of Gram-negative endocarditis need to be revisited.

**Keywords:** bacilli • endocarditis • Gram-negative • HACEK • management • recommendations

**Epidemiology**

**HACEK**

Gram-positive bacteria remain the predominant causative pathogens for bacterial endocarditis, accounting for nearly 80% of cases. The reported incidence of Gram-negative endocarditis ranges from 1.3 to 10%, with HACEK organisms comprising the bulk of cases [1]. Within the HACEK group, Haemophilus species (Haemophilus parainfluenzae, Haemophilus aphrophilus and Haemophilus paraphrophilus) are responsible for the majority of endocarditis cases, with Eikenella corrodens being the least common pathogen. **Figure 1** summarizes the relative distribution of endocarditis caused by various members of the HACEK group based on the review published by Das et al. [4].

**Non-HACEK**

Due to its infrequent occurrence, estimates of non-HACEK Gram-negative endocarditis prevalence are variable and depend on the study period. Historical association of non-HACEK Gram-negative endocarditis with intravenous drug use has limited the scope of earlier studies to certain populations and geographical areas, thus introducing a reporting bias. For instance, the earliest systematic review of Gram-negative endocarditis, conducted from 1945 to 1977, concentrated on intravenous drug users, reporting the prevalence of endocarditis in this population as 11–32%, with Gram-negative pathogens accounting for 13% of cases [5]. Similarly, an investigation by Cohen et al. reported 110 cases of Gram-negative endocarditis in intravenous drug users, with Pseudomonas and Serratia species accounting for nearly 80% of cases [5].

Such population selection bias also restricted earlier studies to large metropolitan cities, such as San Francisco (CA, USA), Cleveland (OH, USA), Detroit (MI, USA), Chicago (IL, USA) and New York (NY, USA). Interestingly, the
microbiology of endocarditis pathogens was associated with the profile of intravenous drugs used in different geographical locations. Levine et al. reported a higher prevalence of pseudomonal endocarditis in Detroit among patients injecting pentazocine and tripelennamine, whereas Serratia species were responsible for two-thirds of cases of Gram-negative endocarditis in San Francisco [5,6].

Recent data published by the International Collaboration on Endocarditis-Prospective Cohort Study (ICE-PCS) sheds new light on the contemporary epidemiology of Gram-negative endocarditis [3]. This cohort included cases from 61 centers in 28 countries between 2000 and 2005, presenting a unique opportunity to review the changing epidemiology of Gram-negative endocarditis. In their study, the reported incidence of non-HACEK Gram-negative endocarditis was near 2%, with the majority of cases caused by Escherichia coli (29%) and Pseudomonas (22%). Europe had the highest prevalence of non-HACEK Gram-negative endocarditis (53%, compared with 22% in North America). Other causative pathogens included Klebsiella (10%) and Serratia (8%) species. In another recent review, commonly reported pathogens for Gram-negative endocarditis included Salmonella, Enterobacter, Proteus, Providencia and Citrobacter species [1].

**Risk factors**

**HACEK**

The HACEK organisms are grouped together due to their oropharyngeal inhabitancy, fastidious nature of pathogenesis and special media requirement for isolation [7]. These pathogens also share common risk factors for endocarditis, particularly poor dental hygiene and recent dental procedures, thus gaining entry to the vascular compartment at the time of local trauma or infection [4]. Another well-recognized predisposing factor for HACEK endocarditis includes pre-existing valvulopathy that facilitates bacterial adherence to the damaged endothelium. Owing to the nature of their pathogenesis, these risk factors for HACEK endocarditis have remained unchanged over several decades. Literature reviews from 1945 to 1977 illustrated similar risk factors including dental work, dental infection and upper respiratory tract infection as the predisposing event in the majority of HACEK endocarditis cases. Not surprisingly, the bulk of the patients also had degenerative heart disease [5]. Although the incidence of HACEK endocarditis is quite low, it remains an important concern, especially with changing demographic patterns. Increasing lifespan and a growing proportion of the elderly population is resulting in more degenerative valve diseases and placement of prosthetic heart valves, thus predisposing these patients to a higher likelihood of endocarditis [8].

**Non-HACEK**

Historically, endocarditis due to non-HACEK Gram-negative pathogens was regarded as a disease of intravenous drug users. Over the last decade, however, an increased incidence has been reported in prosthetic heart valve recipients and patients with cirrhosis [9]. A recent analysis by the ICE-PCS registry has shed more light on the changing profile of Gram-negative endocarditis, revealing that more than half of the patients with non-HACEK endocarditis (57%) had healthcare-associated infections whereas injection drug use was rare (4%). Furthermore, the study confirmed previous reports of a rising incidence of non-HACEK Gram-negative endocarditis in patients with implanted endovascular devices, including prosthetic heart valves, permanent pacemakers and implantable cardioverter-defibrillators [3]. Given these findings, one should be cognisant of non-HACEK endocarditis in non-intravenous drug users and in patients with endovascular devices.

Recent data also suggest that diminished host immune status may serve as an additional risk factor for endocarditis with this group of pathogens [10,11]. Although non-HACEK organisms account for the majority of Gram-negative bacteremias, hematogenous seeding of the cardiac valves with resultant endocarditis remains an infrequent event. This is probably due to their high sensitivity to serum bactericidal activity and low propensity to adhere to damaged endothelium. Exceptions to this general rule include Salmonella, possibly due to its ability to bind, invade and proliferate in the normal endothelium and lymphoid tissue, and Pseudomonas, with its capability to produce and survive in a biofilm [10]. The importance of host immune status in preventing Gram-negative bacterial endocarditis was highlighted in a study by Aubron et al. [10], who reported a higher incidence of Enterobacteriaceae endocarditis in immunocompromised patients (nearly 30% of all endocarditis cases).
Among the HACEK organisms, *Haemophilus* and *Actinobacillus* species usually run a subacute course with a higher rate of peripheral embolization (50%) and larger sized cardiac vegetation on echocardiography [7,15,16]. Infection with *Cardiobacterium hominis* is almost exclusively associated with endocarditis, especially in the setting of damaged cardiac valves. This organism is also notorious for an insidious course due to its markedly slower growth as compared with other HACEK pathogens. In fact, as part of the normal respiratory flora, it is usually overgrown by other organisms. The average duration of symptoms preceding diagnosis of *C. hominis* endocarditis is reported to be 138 days [1]. *Kingella*, responsible for 7% of HACEK endocarditis, is observed in all age groups, including children [7,17]. Unlike other HACEK pathogens, endocarditis caused by this organism can have a rapid progression. *E. corrodens*, best known for causing infections after human bites, is the least common cause of HACEK endocarditis. Interestingly, endocarditis caused by this pathogen has been associated with intravenous drug users who lick needles thus allowing oropharyngeal contamination [1,18].

**Non-HACEK**

Fever remains the most common finding and first symptom in non-HACEK Gram-negative endocarditis. However, the duration of symptoms and severity of disease may vary depending on the particular pathogen and comorbid conditions of the patient [10]. ICE-PCS investigators reported time from onset of symptoms to clinical diagnosis as greater than 1 month in 90% of the cases of non-HACEK Gram-negative endocarditis [5].

Patients with *E. coli* endocarditis tend to be older with more debilitating illnesses. Understandably, mortality associated with non-HACEK Gram-negative endocarditis is also higher as confirmed by several studies [3,13,19]. In the majority of these patients, presumed sources of acquisition include the genitourinary tract and non-oral gastrointestinal (GI) tract [3,19]. Consequently, persistent bacteremia in elderly patients with urinary tract and/or GI Gram-negative pathogens should raise the possibility of non-HACEK endocarditis.

Owing to its pathogenesis and virulence factors, pseudomonal endocarditis affects native as well as prosthetic valves. Although previous studies reported a predominance of right heart involvement, a higher incidence of left-sided endocarditis was noted at the beginning of 1980, perhaps pointing to evolution of demographic characteristics and risk factors associated with pseudomonal endocarditis [20]. When affecting the left side, the disease has an acute course with a mean duration of illness from onset to diagnosis reported as 15 days, and a significantly higher rate of complications including peripheral embolization (40%), congestive heart failure, valve-ring abscesses, splenic abscesses and neurological sequelae (53% in older studies) [20]. As expected, mortality is high, ranging from 69% in earlier published series to 10% in more contemporary cohorts with improved medical and surgical therapies [20–22]. Although earlier studies had noted a mortality benefit with surgical intervention, Reyes et al. reported no significant difference in outcome between medical treatment alone versus combined medical-surgical intervention between the 1969–1975 and 2006–2008 time periods [21]. This

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**Clinical presentation**

**HACEK**

Due to the fastidious nature of the organisms and nonspecific symptoms, diagnosis of HACEK endocarditis may be delayed for several weeks. Symptoms may include fever, night sweats, anorexia, back pain and weight loss, with or without peripheral stigmata of infective endocarditis [1]. However, fever may be absent in elderly and immunocompromised patients [8]. The second major obstacle in making an early and accurate diagnosis of HACEK endocarditis is the requirement of special culture media and laboratory techniques for isolation. Historically, a longer incubation period was required for isolating HACEK organisms due to their slower growth. However, recent utilization of modern laboratory techniques has increased the yield of HACEK organisms with a standard 5–7 days of incubation, thereby potentially diminishing the requirement for prolonged incubation [14]. A high index of suspicion and consultation with microbiology laboratory staff may increase the likelihood of isolating HACEK organisms in suspected cases. Growth characteristics of HACEK organisms are summarized in Table 1.  

Owing to frequent delay in diagnosis, HACEK organisms are also associated with a high rate of peripheral embolization, with reported rates ranging from 30 to 40% [4,7]. Of these, cerebral emboli and mycotic aneurysms are particularly concerning. Mycotic aneurysms may be clinically silent until they rupture. A CT or MRI scan of the head should be considered, especially if surgery is being planned. Cardiac surgery requires intra-operative heparinization and predisposes to risk of hemorrhagic transformation if clinically silent ischemic infarcts are present.

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could perhaps be explained by introduction of fourth-generation cephalosporins, such as cefepime, with enhanced potency and higher affinity against Gram-negative pathogens [21]. Salmonella species remain a rare cause of non-HACEK endocarditis (0.2–0.4%). However, when present, they are very destructive, with an increasing rate of valve-ring abscess, valve perforations, cusp rupture and peripheral embolization. Mortality associated with Salmonella aortitis and endocarditis remains high (40–45%), especially in infants, adults older than 50 years and patients with comorbid condition [11]. Because infection caused by Salmonella can take different forms (ranging from febrile illness and gastroenteritis to bacteremia and endovascular infections), diagnosis of Salmonella endocarditis remains hindered, requiring a high level of suspicion. Another factor is the relative inadequacy of transthoracic echocardiography for diagnosing bacterial endocarditis [11]. Due to the aggressive nature of this disease, patients suspected of Salmonella bacteremia should undergo further investigation to delineate underlying endovascular infection in the appropriate clinical setting, especially known cardiac valvulopathy and vascular aneurysms.

In summary, endocarditis with non-HACEK Gram-negative bacilli should be a consideration in patients with history of injection drug use or bacteremia in the setting of pre-existing valvulopathy, cardiovascular implantable electronic devices (pacemakers and defibrillators) and prosthetic heart valves or vascular grafts. Furthermore, elderly patients with several comorbid conditions, immunocompromised status, and recent GI and/or genitourinary infection with persistent bacteremia also merit further investigation for non-HACEK endocarditis. Peripheral vascular or immunologic phenomena are present in only a third of the cases. Consequently, a lack of peripheral manifestations should not dissuade clinicians from consideration of bacterial endocarditis in the above scenario.

Role of echocardiography

Transthoracic echocardiogram has a low sensitivity for detection of smaller vegetations, perivalvular extension of endocarditis and myocardial abscesses, especially in patients who are obese, have chronic obstructive pulmonary disease or chest wall deformities, and those with prosthetic heart valves [8]. Consequently,
transesophageal echocardiography (TEE) should be performed in all cases of suspected Gram-negative bacterial endocarditis and resultant complications. Intracardiac abscesses were reported in 25% of the patients with non-HACEK Gram-negative endocarditis in the ICE-PCS registry, while paravalvular complications were noted in 31% of cases [3]. TEE also provides better visualization of vegetations attached to pacemaker or defibrillator leads in cases of device-related Gram-negative endocarditis [23].

Management

HACEK

Historically, β-lactam antibiotics such as penicillin or ampicillin, with or without the addition of an aminoglycoside, were considered the drugs of choice for HACEK endocarditis. However, more recent data suggest an increasing frequency of β-lactamase-producing pathogens in the HACEK group [9,24]. Current practice guidelines from the American Heart Association (AHA) recommend empiric treatment with a third-generation cephalosporin (e.g., ceftriaxone 2 g intravenously or intramuscularly every 24 h) or ampicillin–sulbactam (12 g every 24 h in four equally divided doses) as the first line of therapy for HACEK endocarditis [9]. The recommended duration of therapy is 4 weeks. Alternative treatment options include the use of fluoroquinolones (e.g., ciprofloxacin 500 mg orally every 12 h or 400 mg intravenously every 12 h) in patients who are allergic to or unable to tolerate cephalosporins and ampicillin. However, AHA guidelines caution that use of fluoroquinolones should be avoided in patients younger than 18 years of age.

Non-HACEK

Cardiac surgery has traditionally been recommended as a cornerstone of therapy for non-HACEK, especially *Pseudomonas* endocarditis because of the high mortality associated with conservative medical management. However, in a more contemporary cohort of non-HACEK endocarditis reported by ICE-PCS investigators [3], the mortality rate did not statistically differ between patients who received medical therapy alone compared with those receiving combined medical and surgical intervention. In their study, in-hospital mortality rate remained high (24%) despite higher rates of cardiac surgery (51%). Most patients (63%) received combined antibiotic therapy with a β-lactam plus an aminoglycoside and/or fluoroquinolone, while 38% received monomicrobial treatment. Once again, there was no difference in outcome among patients receiving single as opposed to combination antibiotic therapy with aminoglycosides [3]. However, one major limitation of this investigation was the lack of follow-up and outcome data after hospital discharge.

We recommend a thorough evaluation of patients with non-HACEK Gram-negative endocarditis to assess the necessity of surgical intervention. Decision to treat medically versus combined medical and surgical treatment should be individualized and made on a case-by-case basis. Patients with TEE evidence of valve perforation, chordae tendineae rupture, intra-cardiac abscesses or paravalvular extension of infection should be promptly referred for surgical evaluation. In addition, traditionally described indications for valve surgery such as worsening heart failure, persistently positive blood cultures and isolation of multidrug-resistant Gram-negative bacteria may be additional considerations for cardiac surgery. Whether the large size of the vegetation (>1 cm) or location (anterior mitral leaflet) alone are indications for valve replacement surgery in bacterial endocarditis remains a subject of debate. Recurrent embolization during appropriate antimicrobial therapy also warrants surgical consultation.

Prevention

For the last few decades, antimicrobial prophylaxis before invasive dental procedures was considered a crux of preventing bacterial endocarditis from oropharyngeal organisms, in particular the viridian group streptococci and HACEK organisms, in a variety of cardiac valvulopathies. However, these recommendations were based on small, uncontrolled studies and personal anecdotes. With more contemporary and better designed population-based studies, the routine use of antibiotic prophylaxis before dental procedures has come under question. A recent study by Lockhart et al. demonstrated a higher incidence of bacteremia from daily tooth brushing than after ‘periodic’ dental procedures [25]. Others have also demonstrated frequent bacteremias from activities of daily life such as chewing food, urinating, defecating and tooth brushing. Based on these data, the AHA revised their guidelines for endocarditis prophylaxis in a statement published in 2008 [26]. Revised practice guidelines place greater emphasis on optimal oral hygiene over prophylactic antibiotics for dental procedure. Use of antimicrobial prophylaxis is now reserved for certain high-risk situations that include presence of prosthetic heart valves, previous history of infective endocarditis, uncorrected or recently corrected congenital cardiac defects and development of cardiac valvulopathy after cardiac transplantation. However, no clinical data or guidelines are available for prevention of non-HACEK Gram-negative bacilli endocarditis during GI or genitourinary procedures.

Expert commentary & five-year view

This article illustrates that, although epidemiology and management of HACEK group endocarditis has remained relatively unchanged over time, fundamental changes are needed in our understanding of non-HACEK Gram-negative endocarditis. First, healthcare contact now represents a primary risk factor for acquisition of Gram-negative endocarditis due to these organisms. Historically, non-HACEK Gram-negative endocarditis has remained an infrequent diagnosis and one postulate for this relative rarity is extreme serum sensitivity of Gram-negative pathogens to complement-mediated bactericidal activity which, in turn, reduces the possibility of bacteremia from distant sources to persist long enough to colonize the endocardium. However, with the growing size of the elderly population with degenerative valve diseases, an increased rate of immunosuppression and a rising incidence of prosthetic valve implantsation, we anticipate an increase in incidence of non-HACEK Gram-negative bacterial endocarditis in the future.

Second, while surgery was considered the cornerstone of therapy for non-HACEK Gram-negative endocarditis in earlier reported series, recent data from the ICE-PCS study challenge the conventional practice of routinely referring these patients for surgical intervention [3]. It is quite possible that a subset of patients who do not have cardiac complications on TEE (such as valve
perforation, dehiscence, severe regurgitation, intracardiac abscess or paravalvular extension of infection) may be managed conservatively with antimicrobial therapy alone. These patients should be monitored carefully as surgery may be needed if bacteremia does not clear or if they develop syndromic heart failure that would require surgical intervention. Unfortunately, the ICE-PCS study did not provide long-term follow-up after discharge from hospital. Therefore, it is conceivable that some of these patients may develop valvular dysfunction or symptomatic heart failure as a late complication and require surgical intervention.

Third, the benefit of dual antibacterial therapy for non-HACEK Gram-negative endocarditis must be re-examined. Combination antibiotic therapy for severe Gram-negative infections, especially *Pseudomonas* bacteremia and endocarditis, has been a longstanding paradigm in infectious diseases for several reasons: to have synergistic action based on each agent’s distinct mechanism of action; to amplify the extent and rapidity of killing; and to prevent emergence of resistance to one of the agents used in combination. A combination of cell-wall active agents (such as β-lactams) and low-dose aminoglycosides has been historically used to achieve rapid killing of Gram-negative bacteria, especially *Pseudomonas* bloodstream infection. Once again, data from the ICE-PCS study did not demonstrate an advantage of combination antibacterial therapy for non-HACEK Gram-negative endocarditis over treatment with a single effective agent. However, caution must be exercised to avoid overinterpretation of their data. The ICE-PCS study was a prospective observational study and was not designed or powered to show a superiority of combination antibiotic therapy over monotherapy. Moreover, several other factors such as presence or absence of cardiac and metastatic complications, surgical versus conservative medical therapy, antimicrobial susceptibility profile of the causative Gram-negative pathogen and comorbid conditions of the host, influence the outcome of endocarditis in these cases. We believe that combination antimicrobial therapy should be used in the earlier phase of treatment while awaiting antimicrobial susceptibility testing of the causative pathogens. However, once the bloodstream clears the pathogen and drug susceptibility data are available, completing the treatment course with a single drug may be adequate. Ideally, these management issues should be examined in large, well-controlled and randomized prospective clinical trials. However, considering the rarity of non-HACEK Gram-negative endocarditis, such trials are unlikely to be performed in the near future and therapy must be guided by expert opinion and consultation with infectious diseases specialists for individual cases.

### Financial & competing interests disclosure
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.

No writing assistance was utilized in the production of this manuscript.

### Key issues
- Healthcare contact is an emerging risk factor for non-HACEK Gram-negative endocarditis. Injection drug use is a relatively infrequent cause of endocarditis in this group of patients in more contemporary cohorts.
- All patients with suspected Gram-negative endocarditis should undergo transesophageal echocardiography (TEE) to confirm the diagnosis and assess for cardiac complications such as intracardiac abscesses and paravalvular extension of infection.
- Transthoracic echocardiogram has low sensitivity and, if negative, should be followed by TEE to exclude endocarditis.
- Not all cases of non-HACEK Gram-negative bacterial endocarditis necessarily require surgical intervention. Indications for surgical intervention in patients with Gram-negative endocarditis are similar to those with endocarditis due to *Staphylococcus aureus*.
- Combination antibacterial therapy does not necessarily result in better outcomes in patients with non-HACEK, especially *Pseudomonas*, endocarditis.
- Patients with native or prosthetic valve HACEK endocarditis can be managed with a single agent administered intravenously for 4 weeks.
- Good oral hygiene is considered the mainstay of preventing HACEK endocarditis from a dental source and routine use of antimicrobial prophylaxis is not recommended.
- Antimicrobial prophylaxis for prevention of HACEK bacterial endocarditis before invasive dental procedures should be reserved for selected high-risk patients with prosthetic heart valves, previous history of endocarditis, uncorrected congenital heart defects and those who develop valvulopathy after cardiac transplant.
- All patients with Gram-negative bacterial endocarditis should be managed in consultation with an infectious diseases specialist.

### References
Papers of special note have been highlighted as:

• of interest


• Data from an International Collaboration on Infective Endocarditis Prospective Cohort Study (ICE-PCS). Authors report that non-HACEK Gram-negative endocarditis is no longer a disease of injection drug users and that most cases in contemporary practice are associated with healthcare contact. A significant proportion of these patients had implanted endovascular devices. Mortality remained high, despite a high rate of surgical intervention.
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2. Authors report Mayo Clinic experience related to HACEK endocarditis. Results support the proposed pathogenesis of HACEK endocarditis and the oropharyngeal origin of bacteremia in the majority of cases. Survival remained high despite a long delay (several weeks) between symptom onset and diagnosis of endocarditis in a significant proportion of cases.


5. Multiple valve involvement was most common in patients with *Pseudomonas* endocarditis.


10. Authors report 42 cases of Gram-negative endocarditis from Slovakia. Mortality in this group of patients was comparable to endocarditis caused by Gram-positive organisms.


13. Elderly patients frequently present with atypical findings and a high index of suspicion is necessary to make an accurate diagnosis of endocarditis in this patient population.


16. Contrary to commonly held belief, most HACEK organisms can be recovered from blood cultures after a standard 5-day incubation period. Specialized methods are more important than extended incubation for recovery of these fastidious pathogens.


21. Authors report 42 cases of Gram-negative endocarditis from Slovakia. Mortality in this group of patients was comparable to endocarditis caused by Gram-positive organisms.