CASE REPORT

HACEK-induced endocarditis

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Dr Nancy Wassef,
nancy.wassef@gmail.com**SUMMARY**

A 61-year-old patient with diabetes had a bio-prosthetic aortic valve replacement 3 years before admission. He complained of lethargy, night sweats, decreased appetite and erratic blood glucose with no weight loss. He had splinter haemorrhage and a systolic ejection murmur at the aortic area. Chest and abdominal examination revealed no abnormality. The erythrocyte sedimentation rate and C reactive protein were raised. He had several sets of blood cultures and he was started on empirical vancomycin, rifampicin and gentamicin. Transthoracic echocardiography showed vegetation on the base of the anterior mitral leaflet, which was confirmed by a trans-oesophageal echocardiography. Blood culture was positive for *Haemophilus aphrophilus*, and he was started on ceftriaxone for 6 weeks instead of vancomycin and rifampicin and continued gentamicin for 2 weeks. Follow-up echocardiography showed no evidence of vegetations. The patient recovered completely and he was discharged home.

BACKGROUND

Haemophilus species, *Aggregatibacter* species, *Cardiobacterium Hominis*, *Eikenella Corrodens* and *Kingella* species (HACEK) organisms are found as part of the normal human oral flora. They are fastidious Gram-negative organisms that have been associated with various infectious processes, but most commonly are associated with cases of culture-negative endocarditis.¹

Based on large reviews, HACEK organisms are responsible for approximately 3% of cases of native valve infective endocarditis (IE).²

HACEK infections, although rare, can be extremely serious, but outcomes generally are successful if the organism is identified early and treated appropriately.³

CASE PRESENTATION

A 61-year-old patient with diabetes had a previous history of bicuspid aortic valve with stenosis, for which he had a bio-prosthetic aortic valve replacement 3 years before admission, as he refused taking warfarin. He presented with malaise and lethargy 1 week before admission. He had night sweats, decreased appetite and erratic blood glucose with no weight loss. He had no history of drug abuse or any recent travel. Physical examination revealed that he had a temperature of 38.1 °C with a regular pulse of 108 bpm, blood pressure of 120/80 mm Hg and no lymphadenopathy. He had splinter haemorrhage under the third right fingernail with no other lesions. On auscultation, he had a grade III/VI systolic ejection murmur at the aortic area with no propagation. Chest and abdominal

examination revealed no abnormality without splenomegaly.

INVESTIGATIONS

Blood investigations showed no leucocytosis with raised erythrocyte sedimentation rate and C reactive protein. Electrocardiogram showed a sinus tachycardia and the chest X-ray was normal. He had several sets of blood cultures during spikes of temperature and he was started on empirical vancomycin, rifampicin and gentamicin. He had a transthoracic echocardiography, which showed vegetation on the base of the anterior mitral leaflet, which was confirmed by a trans-oesophageal echocardiography. The bio-prosthetic aortic valve was well functioning, with no vegetations seen.

Seven out of eight bottles of blood culture were positive for *Haemophilus aphrophilus*, which was sensitive for ceftriaxone, amoxicillin and gentamicin.

TREATMENT

The patient was started on ceftriaxone instead of vancomycin and rifampicin and continued gentamicin for 2 weeks, after which gentamicin was stopped and he continued ceftriaxone for 6 weeks.

OUTCOME AND FOLLOW-UP

The patient improved and had no more bouts of fever or night sweats. The laboratory follow-up showed normalization of the CRP and a follow-up transthoracic echocardiography showed no evidence of the previously detected vegetation. The patient was discharged home and was followed up after 6 weeks with full recovery.

DISCUSSION

The HACEK group includes *Haemophilus* species, *Aggregatibacter actinomycetemcomitans* (formerly *Actinobacillus actinomycetemcomitans*), *Aggregatibacter aphrophilus* (formerly *Haemophilus aphrophilus* and *Haemophilus paraphrophilus*), *Cardiobacterium hominis*, *Eikenella corrodens* and *Kingella* species.⁴

These organisms commonly colonise the human oropharynx as normal, indigenous flora that could cause mouth infections. *Haemophilus* species have been isolated from brain abscesses, meningitis, endocarditis, otitis media, sinusitis, epiglottitis, hepatic abscesses, intra-abdominal infections, pneumonia, necrotising fasciitis, septic arthritis, osteomyelitis, postoperative surgical infections and urinary tract infections.^{5–6}

HACEK organisms are most often associated with infective endocarditis.^{7–9}

Patients may have a history of a preceding dental, urological or gastroenterological procedure.¹⁰ A

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history of intravenous drug use also should be considered because many drug users clean their needles or venous puncture sites with saliva. Among the HACEK organisms, *Eikenella corrodens* is the bacterium that has been most frequently associated with intravenous drug abuse.¹¹ A history of heart valve abnormalities or the presence of a prosthetic heart valve also predisposes to endocarditis.

To grow, HACEK organisms need an atmosphere enriched with carbon dioxide.^{5 12} They grow well on non-specific culture media rather than specialized agars like Mac-Conkey's agar, a growth medium for Gram-negative bacteria.⁵ Typically, HACEK organisms grow slowly and are subject to extended incubation periods of 7–21 days.⁷ With the advent of improved culture media and automated culture systems, prolonged incubation may no longer be necessary; a 3-day to 7-day incubation period may suffice.^{1 7}

Haemophilus (H) species include *aphrophilus*, *haemolyticus*, *parahaemolyticus*, *parainfluenzae*, *paraphrophilus* and *segnis*. *Haemophilus aphrophilus*, *Haemophilus paraphrophilus* and *Haemophilus segnis* recently were classified, along with *Actinobacillus* (A) *actinomycetemcomitans*, into the genus *Aggregatibacter*.¹³

The species *H aphrophilus* and *H paraphrophilus* have been reclassified as a single species *Aggregatibacter aphrophilus*.¹⁴ They are part of the normal flora found in the mouth and pharynx of humans.¹² Cases of endocarditis are overwhelmingly represented in the literature describing infections involving *H aphrophilus*. Rare cases of periodontal disease, brain abscess and vertebral osteomyelitis also have been reported.¹⁵

HACEK organisms are typically susceptible to third or fourth-generation cephalosporins, trimethoprim-sulfamethoxazole, aztreonam and fluoroquinolones, with most HACEK organisms being resistant to metronidazole, vancomycin, erythromycin and clindamycin. β -Lactamase production has recently been observed. HACEK infections, although rare, can be extremely serious, but outcomes generally are successful if the organism is identified early and treated appropriately.⁵

The treatment of a HACEK infection is based on the location of the infection, clinical severity and available susceptibility data. Owing to the increased frequency of β -lactamase-producing strains of HACEK infections, these organisms should be considered resistant to ampicillin.^{5 16} Local resistance patterns and isolate susceptibility should be considered, before an antibiotic therapy is selected.¹⁶

Although there have been no large trials evaluating the best therapy for HACEK endocarditis, the American Heart Association has published recommendations for the treatment of both native and prosthetic-valve endocarditis caused by HACEK organisms.^{3 16} Ceftriaxone or ampicillin/sulbactam is the therapy of choice for patients with HACEK endocarditis. Fluoroquinolones may be considered as alternative therapy. Regardless of the agent chosen, treatment should last 4–6 weeks, depending upon the type of valve involved.¹⁶ Although HACEK organisms have been associated with other infections, these are rare compared with endocarditis.

According to the British society for antimicrobial chemotherapy, HACEK endocarditis treatment should be with a β -lactamase-stable cephalosporin or amoxicillin if the isolate is susceptible.^{17 18} Gentamicin should only be added for the first 2 weeks of therapy. Ciprofloxacin can be considered an alternative agent and the native valve endocarditis should be treated for 4 weeks and prosthetic valve endocarditis should be treated for 6 weeks.¹⁷

Ciprofloxacin has been successfully used to treat HACEK IE and can be administered orally; it has therefore been included as an alternative agent for therapy.^{2 19}

H paraphrophilus (*Aggregatibacter paraphrophilus*) is associated with various types of abscesses. The total treatment duration with a third-generation cephalosporin is 6 weeks. Other cases of *H paraphrophilus* abscesses have been successfully treated with surgical drainage plus antibiotic therapy using combinations of cefotaxime, ciprofloxacin, meropenem, metronidazole, ceftriaxone, amoxicillin/clavulanic acid, gentamicin, flucloxacillin, piperacillin, ampicillin and penicillin G.^{20 21}

A actinomycetemcomitans is an oral bacterium known to be the major cause of periodontal disease, known as localised aggressive periodontitis, previously known as localised juvenile periodontitis.²² This disease affects only certain teeth (incisors and premolars) and causes rapid loss of the alveolar bone of the jaw leading to tooth loss.²³ This organism has been known to cause infective endocarditis, which should be suspected in patients with endocarditis and a history of periodontal disease.^{8 24} The organism is usually susceptible to cephalosporins, aminoglycosides, fluoroquinolones, trimethoprim-sulfamethoxazole and tetracycline.^{12 25} Resistance to ampicillin, penicillin G, vancomycin, erythromycin and clindamycin has been noted. Severe *A actinomycetemcomitans* periodontitis is usually treated with mechanical debridement and oral tetracycline.¹²

C hominis, a member of the HACEK group, is a rare cause of endocarditis.¹⁰ A recent review found that 77% of patients with *C hominis* endocarditis have been treated successfully with penicillin alone, ceftriaxone alone or penicillin plus an aminoglycoside.²⁶ It should be noted, however, that isolates with β -lactamase production have been reported.²⁷

Eikenella is a well-recognized cause of cellulitis resulting from human bites and clenched-fist injuries.²⁸ It typically is susceptible to penicillin G, ceftriaxone, amoxicillin/clavulanic acid, trimethoprim-sulfamethoxazole and fluoroquinolones.^{29 30} Carbapenems, tetracycline and chloramphenicol also may be considered for treatment. *Eikenella* is resistant to clindamycin, cephalixin, erythromycin and metronidazole.^{12 31} β -Lactamase production by *Eikenella* is uncommon but should be considered when antimicrobial therapy is being chosen.³⁰ Depending upon the location of the infection, surgical drainage may be more important than antibiotics alone for treatment, but coinfections with other organisms, especially streptococci, are common and antibiotic therapy may be necessary to cover other pathogens.^{29–31}

Kingella kingae a Gram-negative coccobacillus has been considered a rare cause of human infections. Most of the literature on invasive *K kingae* infection consists of single case reports or short series of patients with joint or bone infections or endocarditis.³² Successful treatment strategies for *K kingae* endocarditis include penicillin, ampicillin, gentamicin, tobramycin, ciprofloxacin and ceftriaxone.³ However, many of the isolates were resistant to clindamycin.³²

Learning points

- ▶ HACEK organisms are resistant to vancomycin, erythromycin, metronidazole and clindamycin and has β -lactamase production.^{3 5}
- ▶ A history of intravenous drug use also should be considered, because many drug users clean their needles or venous puncture sites with saliva.¹¹
- ▶ Endocarditis with *Actinobacillus actinomycetemcomitans* should be suspected in patients with endocarditis and a history of periodontal disease.⁸

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Competing interests None.

Patient consent Obtained.

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