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Clinical characteristics of invasive *Haemophilus aphrophilus* infections

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Haemophilus aphrophilus, an oral fastidious Gram-negative commensal with low pathogenicity, is a member of the HACEK group (*H. aphrophilus*, *H. paraphrophilus*, *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella* spp.), and a rare cause of human infections. We reviewed the characteristics of 8 cases of *H. aphrophilus* infections diagnosed in our hospital from 1990-2003, and an additional 20 cases identified from the *MEDLINE* database, from 1990 to 2003. Their mean age was 47.4 years (range, 7-73 years), and 21 cases (75%) were male. The major manifestation was bone and joint infections (9 cases, 32%), including osteomyelitis, discitis, epidural abscess, spondylodiscitis, septic arthritis and prevertebral infection. Seven cases (25%) presented with infective endocarditis, involving native valves, and one underwent valvular replacement. Of note, 3 cases (10%) had ophthalmic infections (endophthalmitis in 2 cases and canaliculitis in 1), and 2 of them had previous ophthalmic procedures. Other manifestations included bacteremia, meningitis, brain abscess, cervical lymphadenitis, facial cellulitis, empyema, and purulent pericarditis and tamponade. All patients except 1 survived. Recent dental procedure was recalled by 11 cases (39%), and may be a predisposing factor for invasive *H. aphrophilus* infection. Appropriate antimicrobial therapy, such as a β-lactam/β-lactamase inhibitor, ceftriaxone or cefotaxime or a fluoroquinolone, can lead to a favorable clinical outcome.

Key words: Cephalosporins, fluoroquinolones, Haemophilus infections, signs and symptoms

Haemophilus aphrophilus was first reported by Khairat in 1940 and since then has been recognized as a cause of human infections [1]. *H. aphrophilus* is a component of normal oropharyngeal flora and a slowly growing, aerobic, non-motile, Gram-negative coccobacillus. It is oxidase-positive, catalase-negative, urease-negative, indole-negative, and can ferment glucose, sucrose, lactose, and maltose. *H. aphrophilus* was so named because of its preference for an atmosphere of carbon dioxide, "aphros" referring to the foam on wine vats [2,3]. This organism requires X factor (hemin) but not V factor (nicotinamide adenine dinucleotide) for growth and grows best in a carbon dioxide (CO_2)-enriched atmosphere, but also grows in moist air in the absence of CO_2 [4].

The presence of this organism in clinical specimens may remain undetected unless appropriate microbiologic methods are used. There is limited information on the clinical features of invasive *H. aphrophilus* infections from Taiwan. This retrospective study investigated the clinical spectrum, therapeutic effect of new antimicrobial agents, and prognosis in a series of patients with *H. aphrophilus* infections treated at the National Cheng Kung University Hospital (NCKUH). We also reviewed cases from the *MEDLINE* database.

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Materials and Methods

The medical records of patients with *H. aphrophilus* isolates from blood or other body sites treated from 1990 to 2003 at NCKUH, a university-affiliated medical center with approximately 1000 beds, including 67 intensive-care beds and serving a population of about two million in southern Taiwan, were reviewed. Data collected included demographic information, the site of culture, associated organisms, possible predisposing or associated conditions, antimicrobial therapy, and clinical outcome.

All clinical specimens were inoculated on to sheep blood agar plate (Trichistatin A II 5% SB; Becton Dickinson Microbiology Systems, Cockeysville, USA), chocolate agar (CHOC II; Becton Dickinson

Microbiology Systems), Columbia colistin-nalidixic acid agar (Becton Dickinson Microbiology Systems) and methylene blue agar (Becton Dickinson Microbiology Systems) and incubated under both 5% CO_2 and an atmosphere at 37°C. Those small Gram-negative bacilli growing only on blood and chocolate agar within 24 to 48 h were further analyzed using the VITEK NHI card (bioMérieux, Marcy l'Etoile, France) commercial identification system for final speciation.

The clinical diagnosis of osteoarticular infections was made by the growth of *H. aphrophilus* from cultures of blood or abscess, in the presence of relevant clinical symptoms and signs, radiologic images or surgical findings. Cases of infective endocarditis were categorized as definitive or possible according to the Duke criteria [5]. Those isolates obtained from the oral cavity and ophthalmic area in patients with clinical symptoms of infection were also included.

In the English literature, cases of infections due to *H. aphrophilus* were identified by a computerized search of the *MEDLINE* database from 1990 to 2003, using the search term "*Haemophilus aphrophilus*". The references of the obtained manuscripts were then examined to identify additional reports. Only those cases that were detailed sufficiently to be individually analyzed were included.

Results

A total of 28 cases of *H. aphrophilus* infection were included in this study, 8 from NCKUH and 20 from the *MEDLINE* database. The clinical characteristics of these 28 cases are listed in Tables 1-4 and include osteoarticular infections, infective endocarditis, ophthalmic infections and other infections [6-25]. There were 21 males (75%) and 7 females (25%) with a mean age of 47.4 years, ranging from 7 to 73 years. All except 1 cirrhotic case were initially healthy adults.

Clinical features

Fever (17/28) was the most common symptom of invasive *H. aphrophilus* infections. Nine cases (32%) had osteoarticular infections, which was the major disease entity, including osteomyelitis, epidural abscess,

Table 1. Clinical characteristics of osteoarticular infections caused by *Haemophilus aphrophilus*

Case no.	Age (years)/ gender	Underling illness or predisposing factors	Culture	Diagnosis	Symptoms	Antimicrobial therapy (duration)	Surgery	Outcome
1 [PR]	70/F	No	Blood	Vertebral osteomyelitis (C6-7)	Neck pain	iv ceftriaxone (2 weeks), then aztreonam (5 weeks)	Yes	Recovery
2 [PR]	69/M	Dental procedure	Pus of mandible	Mandibular osteomyelitis	Fever, chills, toothache	iv clindamycin (10 days) and gentamicin (3 days)	Yes	Recovery
3 [6]	40/M	No	Blood	Vertebral osteomyelitis (T11-12)	Fever, back pain	iv ciprofloxacin (3 weeks), then oral amoxicillin-clavulanic acid (5 weeks)	Yes	Recovery
4 [7]	53/M	Dental procedure	Discal pus	Discitis and vertebral osteomyelitis (L4-5)	Backache	iv ciprofloxacin (NM)	Yes	Recovery
5 [8]	73/F	Liver cirrhosis	Blood	Vertebral osteomyelitis (L4-5), spinal epidural abscess (L1 to sacrum)	Fever, back pain	iv cefotaxime (3 weeks), then ciprofloxacin (2 weeks), followed by oral ciprofloxacin (8 weeks)	No	Recovery
6 [9]	36/F	Dental procedure	Incisional biopsy of bone	Humeral osteomyelitis	Bone pain	iv cefazolin (4 weeks)	Yes	Recovery
7 [10]	35/M	Dental procedure	Discovertebral abscess	Spondylodiscitis (L4-5)	Fever, back pain	iv ceftriaxone (3 weeks), then oral ciprofloxacin (6 weeks)	No	Recovery
8 [11]	56/M	No	Synovial fluid	Septic arthritis, right knee	Fever, joint pain	iv ceftriaxone (2 weeks)	No	Recovery
9 [12]	53/M	Dental procedure	Blood	Septicemia with prevertebral infection (C-spine)	Neck pain	iv amoxicillin (3 weeks) and ciprofloxacin (3 weeks), followed by oral ciprofloxacin (2 weeks)	Yes	Recovery

Abbreviations: PR = present report; F = female; M = male; iv = intravenous; NM = not mentioned

Table 2. Clinical characteristics of infective endocarditis caused by *Haemophilus aphrophilus*

Case no.	Age/ gender	Predisposing factors	Positive culture specimen	Involved cardiac structure	Symptoms	Antimicrobial therapy (duration)	Surgery	Outcome
10 [PR]	66/M	Dental procedure	Blood	Native mitral valve	Fever, chills	iv ceftriaxone (2 weeks), then iv ofloxacin (4 weeks)	No	Recovery
11 [13]	26/M	Valvular heart disease	Blood	Native aortic valve and anterior mitral leaflet	Fever	Penicillin, gentamicin, chloramphenicol (NM)	No	Recovery
12 [14]	7/M	Dental procedure Congenital heart disease	Blood	Native tricuspid and mitral valves	Fever	iv ampicillin (9 weeks) and gentamicin (8 weeks)	No	Recovery
13 [15]	43/M	Dental procedure	Blood	Left ventricle thrombus	Fever	iv and oral ciprofloxacin (6 weeks)	No	Recover
14 [16]	25/M	Dental procedure, valvular heart disease, tongue piercing	Blood	Native aortic valve	Fever	iv ceftriaxone and gentamicin (6 weeks)	No	Loss of follow-up
15 [17]	62/M	Valvular heart disease	Blood	Native aortic valve	Fever	Levofloxacin (NM)	No	Recovery
16 [18]	21/M	No	Blood	Native aortic valve	Fever, chills	iv flucloxacillin and gentamicin (NM)	Yes	Recovery

Abbreviations: PR = present report; M = male; iv = intravenous; NM = not mentioned

spondylodiscitis, septic arthritis and prevertebral infection.

Focal pain was the most common complaint in patients with osteoarticular infections. Cultures of blood were positive in 4 of 9 cases (44.9%). Of the 6 cases with osteomyelitis, spinal vertebrae were the main affected sites, noted in 4 cases. Infective endocarditis was found in 7 cases (21%), involving native valves (aortic valves in 3 cases, aortic and mitral valves in 1, aortic and tricuspid valves in 1, and mitral valve in 1), and left ventricle thrombus (1 case) [Table 2]. All had fever at initial presentation. Ophthalmic infections (endophthalmitis in 2 cases and canaliculitis 1 case) developed in 3 patients who presented with ophthalmic discomfort without fever (Table 3).

Predisposing factors

Recent dental procedure was traced in 11 cases (39%), including 5 of 9 cases with osteoarticular infections, 4 of 7 with infective endocarditis, 1 with brain abscess, and 1 with facial cellulitis. Underlying cardiac valvular disease was presented in 4 cases of infective endocarditis (Table 2). Previous ophthalmic procedures had been performed in 2 of 3 patients with ophthalmic infection.

Antimicrobial susceptibility

Antimicrobial susceptibility results determined by agar-disk diffusion, broth dilution, agar dilution or E-test method, were available for 20 isolates. 17 isolates of *H. aphrophilus* were susceptible to ampicillin, 14 to third-generation cephalosporin, and 13 to fluoroquinolone.

Treatment

Treatment was by antimicrobial therapy alone in 13 patients, and surgical intervention in addition to antimicrobial therapy was given in 15 patients. Initial empiric therapy varied among patients. Amoxicillin or ampicillin with or without a β-lactamase inhibitor was used in 6 patients, a first-generation cephalosporin (cefazolin or cephalothin) in 4 patients, a third-generation cephalosporin (cefotaxime or ceftriaxone) in 9 patients, and a fluoroquinolone (ciprofloxacin, ofloxacin or levofloxacin) in 4 patients.

All 9 patients with osteoarticular infection received antimicrobial therapy, such as amoxicillin, cefazolin, ceftriaxone, ciprofloxacin or gentamicin. Six patients with osteoarticular infection underwent surgical interventions and all were cured. The mean duration of treatment was 6.6 weeks (range, 2-13 weeks). Infective endocarditis was present in 6 patients, 1 of whom required valvular replacement in addition to antimicrobial therapy. Of the 3 patients with ophthalmic infections, 2 with endophthalmitis were treated with antibiotics and surgical manipulations, and the visual acuity of both eyes improved. The other patient with

Table 3. Clinical characteristics of ophthalmic infections caused by *Haemophilus aphrophilus*

Case no.	Age/ gender	Predisposing factors	Positive culture specimen	Diagnosis	Symptoms	Antimicrobial therapy	Surgery	Residual visual acuity
17 [PR]	62/F	No	Discharge of canthus	Canaliculitis	Swelling of the lower canaliculi in the left eye	Topical antibiotics	No	Recovery
18 [19]	51/M	Cataract extraction	Conjunctiva and vitreous fluid	Endophthalmitis	Red painful right eye associated with decreased visual acuity	iv cefazolin and gentamicin, topical antibiotics, intravitreal and subconjunctival gentamicin injection	Yes	Improved
19 [20]	56/F	Primary trabeculectomy	Bleb swab	Endophthalmitis	Pain, redness and reduced vision in the left eye	iv cefazolin and gentamicin, topical antibiotics, subcutaneous injections of cefazolin and tobramycin	Yes	Improved

Abbreviations: PR = present report; F = female; M = male; iv = intravenous

canaliculitis was treated with topical antibiotics and his visual acuity was not influenced by the event. Excluding a case without information on clinical outcome, the overall mortality rate in this study was 3.7% (1/27).

Discussion

H. aphrophilus, a fastidious Gram-negative coccobacillus, is part of the normal oropharyngeal flora. This organism was first described in 1940 when it was reported as a fatal case of infective endocarditis, and has mainly been associated with endocarditis since that time. Bieger et al reviewed 90 cases of *H. aphrophilus* infections in 1978 [26], and found that endocarditis (46 cases) accounted for half of all cases. However, in our series, the major clinical entity of *H. aphrophilus* infection was osteoarticular infection (9/28), a clinical spectrum not frequently associated with *H. aphrophilus*. Among the 9 cases of *H. aphrophilus* with osteoarticular infections, only 1 case had underlying liver cirrhosis, with the other cases being initially healthy adults. The affected bony structure was mainly spinal vertebrae (4 cases), which was in accordance with a previous report [10].

In cases of endocarditis, previous dental procedures were noted in 4 patients and underlying heart disease in 4. Previous reports demonstrated that 21-33% of cases of *H. aphrophilus* infective endocarditis were related to dental diseases [4,26]. Dental procedures prior to *H. aphrophilus* infection are associated with development of infective endocarditis.

Approximately 3 decades ago, the recommended antimicrobial therapy for *H. aphrophilus* infective endocarditis was a penicillin derivative combined with an aminoglycoside [26,27]. However, 4 of our cases (cases 4, 5, 10 and 15) were treated with a fluoroquinolone because of intolerance to or a poor clinical response with ceftriaxone or cefotaxime therapy. Ciprofloxacin and other new fluoroquinolones have potent activity against *Haemophilus* spp. [28,29], and fluoroquinolone therapy has been increasingly reported for *H. aphrophilus* infections since 1992 [6-8,12,15,17,21]. Because of the emergence of β-lactamase-producing strains, the use of a third-generation cephalosporin for 4-6 weeks has been recommended for *Haemophilus* endocarditis [17]. Antimicrobial regimens such as ceftriaxone or a fluoroquinolone resulted in a favorable prognosis in patients with *Haemophilus* endocarditis compatible with the excellent in vitro antibacterial activity of these antimicrobial agents against *H. aphrophilus* [15-17]. Therefore, ceftriaxone or fluoroquinolones are effective alternatives for penicillin-allergic individuals with *H. aphrophilus* infection.

However, clinical failure of cefotaxime treatment and antimicrobial resistance of *H. aphrophilus* to ampicillin, cefuroxime, cefotaxime, and ceftazidime have been reported in a β-lactamase-negative strain [7]. The possible mechanisms of β-lactam resistance, such as changes in penicillin-binding proteins or outer membrane permeability, were not characterized in this strain.

In summary, invasive infections caused by *H. aphrophilus*, though rarely encountered, can develop in initially healthy individuals, especially those with a history of recent dental or ophthalmic procedures. In addition to infective endocarditis, osteoarticular infection is another common manifestation of

Table 4. Clinical characteristics of other infections caused by *Haemophilus aphrophilus*

Case no.	Age/ gender	Predisposing factors	Positive culture specimen	Diagnosis	Symptoms	Antimicrobial therapy (duration)	Surgery	Outcome
20 [PR]	26/M	No	Pleural effusion	Empyema	Fever, left pleuritic chest pain and dyspnea	iv + oral amoxicillin-clavulanate (10 days)	Yes	Recovery
21 [PR]	35/M	Dental procedure	Pus	Facial cellulitis	Right facial swelling and painful sensation	Oral amoxicillin (10 days)	Yes	Recovery
22 [PR]	58/F	Valvular heart disease	Blood	Bacteremia	Fever, chills	iv cephalothin (1 day) then oral amoxicillin-clavulanate (3 days)	No	Recovery
23 [PR]	56/M	Mitral valve prolapse and regurgitation	Blood	Bacteremia	Fever	iv ampicillin-sulbactam (3 weeks)	No	Recovery
24 [21]	72/M	No	Blood	Bacteremia	Fever	iv ciprofloxacin, chloramphenicol, ceftriaxone, and oral doxycycline	No	Death
25 [22]	7/F	No	Pus	Cervical lymphadenitis	Tender vesicle on the postauricular area of neck	iv ampicillin-sulbactam (2 days) then iv amoxicillin-clavulanate (14 days)	Yes	Recovery
26 [23]	62/M	Gingivitis, dental caries	Blood, pericardial effusion	Purulent pericarditis and tamponade	Fever, chest pain	iv ceftriaxone (NM), then by oral ciprofloxacin (6 weeks)	Yes	Recovery
27 [24]	47/M	No	Cerebrospinal fluid	Meningitis	Fever, headache	iv cefotaxime (20 days)	No	Recovery
28 [25]	61/M	Dental procedure	Pus	Brain abscess	Left side weakness	iv ceftriaxone (6 weeks)	Yes	Recovery

Abbreviations: PR = present report; M = male; F = female; iv = intravenous; NM = not mentioned

H. aphrophilus infections. Appropriate antimicrobial therapy, such as amoxicillin or ampicillin with a β-lactamase inhibitor, ceftriaxone or cefotaxime, or a fluoroquinolone, can lead to a favorable clinical outcome in patients with *H. aphrophilus* infections.

References

1. Khairat O. Endocarditis due to a new species of *Haemophilus*. J Pathol Bacteriol 1940;50:497-505.
2. Speller DC, Prout BJ, Saunders CF. Subacute bacterial endocarditis caused by a micro-organism resembling *Haemophilus aphrophilus*. J Pathol Bacteriol 1968;95:191-8.
3. Yamashita J, Bone FJ, Hitchcock E. Brain abscess due to *Haemophilus aphrophilus*: case report. J Neurol Neurosurg Psychiatry 1972;35:909-11.
4. Page MI, King EO. Infection due to *Actinobacillus actinomycetemcomitans* and *Haemophilus aphrophilus*. N Engl J Med 1966;275:181-8.
5. Durack DT, Lukes AS, Bright DK. New criteria for diagnosis of infective endocarditis: Utilization of specific echocardiographic findings. Am J Med 1994;96:200-9.
6. Bejuk D, Kuzman I, Soldo I, Kuzmanovic N, Popovic-Uroic T. Vertebral osteomyelitis caused by *Haemophilus aphrophilus*. Eur J Clin Microbiol Infect Dis 1993;12:643-4.
7. O'Driscoll JC, Keene GS, Weinbren MJ, Johnson AP, Palepou MF, George RC. *Haemophilus aphrophilus* discitis and vertebral osteomyelitis. Scand J Infect Dis 1995;27:291-3.
8. Hung CC, Hsueh PR, Chen YC, Fang CT, Chang SC, Luh KT, et al. *Haemophilus aphrophilus* bacteraemia complicated with vertebral osteomyelitis and spinal epidural abscess in a patient with liver cirrhosis. J Infect 1997;35:304-8.
9. Dewire P, McGrath BE, Brass C. *Haemophilus aphrophilus* osteomyelitis after dental prophylaxis. A case report. Clin Orthop 1999;363:196-202.
10. Colson P, La Scola B, Champsaur P. Vertebral infections caused by *Haemophilus aphrophilus*: case report and review. Clin Microbiol Infect 2001;7:107-13.
11. Merino D, Saavedra J, Pujol E, Vega D, Colchero J, Boto A, et al. *Haemophilus aphrophilus* as a rare cause of arthritis. Clin Infect Dis 1994;19:320-2.
12. Poullis A, Gould SR, Lim AG. It could only happen to a doctor—*Haemophilus aphrophilus* septicaemia complicated by a prevertebral infection after dental work. Postgrad Med J 2001;77:261-2.

13. Lalitha MK, Pandian R, Nair U, Krishnaswami S. Infective endocarditis with *Haemophilus aphrophilus*. Indian J Pathol Microbiol 1991;34:64-6.
14. Webb CH, Hogg GM. *Haemophilus aphrophilus* endocarditis. Br J Clin Pract 1990;44:329-31.
15. Dawson SJ, White LA. Treatment of *Haemophilus aphrophilus* endocarditis with ciprofloxacin. J Infect 1992;24:317-20.
16. Akhondi H, Rahimi AR. *Haemophilus aphrophilus* endocarditis after tongue piercing. Emerg Infect Dis 2002;8:850-1.
17. Almeda FQ, Tenorio AR, Barkatullah S, Parrillo JE, Simon DM. Infective endocarditis due to *Haemophilus aphrophilus* treated with levofloxacin. Am J Med 2002;113:702-4.
18. Groeneveld JH, Puylaert JB. Images in clinical medicine. Septic peripheral embolization from *Haemophilus aphrophilus* endocarditis. N Engl J Med 2002;347:816.
19. Alvarez O, Morales J, McCartney DL, May DR, Allison K. *Haemophilus aphrophilus* endophthalmitis associated with a filtering bleb. Arch Ophthalmol 1991;109:618-20.
20. Macken PL, Boyd SR, Campbell I, Chang D, Rootman DS, Trope GE. *Haemophilus aphrophilus* bleb infection after a mitomycin trabeculectomy. Aust N Z J Ophthalmol 1995;23: 323-5
21. Aldova E, Marova J, Stafova J, Kudrna L, Urbaskova P, Karpenkova H, et al. *Haemophilus aphrophilus* isolated from blood. Zentralbl Bakteriol 1990;273:539-44.
22. White DR, Mukherji SK, Mangum ME, Hamrick HJ. Recurrent cervical lymphadenitis caused by *Haemophilus aphrophilus*. Clin Infect Dis 2000;30:627-9.
23. Gill CJ, Mularski RA. *Haemophilus aphrophilus* purulent pericarditis and tamponade. Infect Med 2003;20:31-3.
24. Adeyemi-Doro FA, Hui AC, Ho FN, Ip M. *Haemophilus aphrophilus* meningitis complicated by hydrocephalus in an immunocompetent adult. Infection 1998;26:405-7.
25. Kao PT, Tseng HK, Su SC, Lee CM. *Haemophilus aphrophilus* brain abscess: a case report. J Microbiol Immunol Infect 2002; 35:184-6.
26. Bieger RC, Brewer NS, Washington JA 2nd. *Haemophilus aphrophilus*: a microbiologic and clinical review and report of 42 cases. Medicine (Baltimore)1978;57:345-55.
27. Elster SK, Mattes LM, Meyers BR, Jurado RA. *Hemophilus aphrophilus* endocarditis: review of 23 cases. Am J Cardiol 1975;35:72-9.
28. Wilson WR, Karchmer AW, Dajani AS, Taubert KA, Bayer A, Kaye D, et al. Antibiotic treatment of adults with infective endocarditis due to streptococci, enterococci, staphylococci, and HACEK microorganisms. JAMA 1995;274:1706-13.
29. Wollschlager CM, Raoof S, Khan FA, Guarneri JJ, LaBombardi V, Afzal Q. Controlled, comparative study of ciprofloxacin versus ampicillin in treatment of bacterial respiratory tract infections. Am J Med 1987;82(4A):164-8.