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Original Article

Invasive *Haemophilus influenzae* disease in adults in Taiwan

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Background and Purpose: *Haemophilus influenzae* is an important cause of invasive infection in infants and children, but it has been considered an uncommon cause of invasive disease in adults. We conducted a retrospective survey of invasive *H. influenzae* disease in adults in order to better understand the characteristics of clinical presentation and microbiology.

Methods: Patients older than 18 years with *H. influenzae* isolated from normally sterile sites, between July 1999 and June 2002 in a teaching hospital for adult patients were retrospectively analyzed. Data on demographics, clinical presentation, serotype, antibiotic susceptibility, and beta-lactamase production of *H. influenzae* isolates were analyzed.

Results: Fifteen patients were enrolled. The infectious diagnosis of invasive diseases comprised: pneumonia (5 patients), empyema (2), pelvic inflammatory disease (2), peritonitis (2), periorbital cellulitis with abscess formation (2), endophthalmitis (1) and primary bacteremia (1). Most patients were elderly with underlying illness. Of ten *H. influenzae* isolates available for analysis, two were serotype b and eight were nontypeable. Beta-lactamase production and ampicillin resistance were found in 6 *H. influenzae* isolates (5 nontypeable, and 1 type b).

Conclusion: These data show *H. influenzae* disease in adults to be rare in Taiwan. Our limited number of cases suggest that nontypeable strains predominate in patients with invasive infection due to *H. influenzae*. Most patients had respiratory tract infections. Ampicillin resistance was found in more than one-half of *H. influenzae* isolates, and should be taken into consideration when antibiotics are prescribed on an empirical basis.

Key words: Bacteremia; Drug resistance, bacterial; *Haemophilus influenzae*; Morbidity; Treatment outcome

Introduction

Haemophilus influenzae is a Gram-negative coccobacillus, which is indigenous to humans and has no other known animal hosts. *H. influenzae* normally resides in the pharynx and less frequently in the conjunctiva and genital tract [1]. Some strains have polysaccharide capsules. The strains with capsules could be classified into 6 antigenically distinct types using antisera, namely types a to f [2]. Among them, *H. influenzae* type b (Hib) is virulent and most well known for causing pneumonia, empyema, meningitis, epiglottitis, septic arthritis, cellulitis, osteomyelitis, pericarditis, and bacteremia in young children.

Strains lacking polysaccharide capsules are referred to as nontypeable, because they are non-reactive to any of the 6 typing antisera. Nontypeable *H. influenzae* can occasionally induce acute bacterial otitis media, sinusitis, exacerbation of chronic obstructive pulmonary disease, conjunctivitis, tuboovarian infection, and non-bacteremic community-acquired pneumonia in adults. Encapsulated serotypes a and c-f are rarely recognized as pathogens.

The incidence of *H. influenzae* infection varies in different geographic areas, races and age groups. Invasive *H. influenzae* infection is caused mainly

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by type b strains and occurs mostly in children. The incidence of invasive *H. influenzae* infection in children is higher in western countries than in Taiwan [3]. The annual incidence of invasive *H. influenzae* disease in those aged 10 years and older has been lowered by initiation of an Hib vaccination program since 1991 in Alaska [4].

In adults, *H. influenzae* is not a common cause of invasive disease, with nontypeable strains the predominant cause of invasive disease [5-7]. The clinical data of invasive *H. influenzae* diseases in adults are sparse in Taiwan. We conducted a retrospective study to investigate the incidence, clinical characteristics, and antimicrobial resistance of invasive *H. influenzae* disease among adults in Taiwan.

Methods

Case identification

We collected cases from Taipei Veterans General Hospital, a teaching hospital with 2756 beds for adult patients and 145 beds for pediatric patients. There are approximately 10,000 outpatients per day and 100,000 inpatients are admitted per year. We retrieved cases from the microbiologic logbook of specimens sent for culture taken from patients between July 1999 and June 2002. Patients older than 18 years were included in this study, if *H. influenzae* was isolated from normally sterile sites. Their medical charts were reviewed and data concerning age, gender, underlying diseases, type of infection, treatment and outcome were collected and retrospectively analyzed.

Microbiologic study

Isolates were confirmed as *H. influenzae* by morphology of colonies on chocolate agar plate, Gram stain, an by the requirement of X and V factors for growth. *H. influenzae* isolates were preserved in trypticase soy broth with 5% sheep blood and 10% glycerol, in 1999, for research purposes. Respiratory isolates from adults between April 2001 and February 2002 were also investigated.

Viable *H. influenzae* isolates were subjected to susceptibility testing, serotyping, and beta-lactamase production testing. Susceptibility testing was performed by disk diffusion method with BBL Sensi-Disc™ antimicrobial susceptibility test disks (Becton, Dickson and Company, Sparks, MD, USA) on *Haemophilus* test medium supplemented with hematin, nicotinamide (Oxoid Limited, Hampshire, United Kingdom). Tested antibiotics included ampicillin, chloramphenicol, tetracycline, trimethoprim-sulfamethoxazole, cefuroxime, aztreonam, cefotaxime, ceftriaxone, ceftazidime and imipenem. Criteria for interpretation were those of the Clinical and Laboratory Standards Institute, USA [8]. We detected beta-lactamase activity with nitrocefin beta-lactamase disk (Remel Inc., Lenexa, KS, USA). Serotyping was performed by slide agglutination method with polyvalent and monovalent antisera (Difco Laboratories, Detroit, MI, USA). Non-agglutinable strain with polyvalent antisera were defined as nontypeable. Strains that reacted with *H. influenzae* antiserum type b were classified as type b strains.

Results

Fifteen adults with invasive *H. influenzae* infections were found from July 1999 to June 2002 (9 males and 6 females with a mean age of 65 years), comprising 7 cases of bacteremia, 2 of peritonitis, 2 of empyema, 2 of periorbital cellulitis with abscess formation, 1 of endophthalmitis, and 1 of lung abscess. Demographic, clinical and microbiological information of the included cases is summarized in Table 1.

Of seven cases of bacteremia, five (patients 9, 11, 12, 14 and 15; Table 1) were older than 60 years with at least a significant underlying disease, such as decompensated liver cirrhosis, hematological malignancy (1 multiple myeloma, 1 B-cell lymphoma), or chronic neurologic deficit with bedridden status (1 stroke, 1 senile dementia). Pneumonia was the primary site of infection in four of the five cases, and no primary focus could be identified in the other patient. Of five serotyped strains, two were found to be type b and three were nontypeable. Two of five patients died. One patient died of pneumonia with Hib bacteremia (patient 15). The other (patient 11) died of acute pancreatitis.

Two cases of *H. influenzae* bacteremia younger than 60 years (patients 1 and 4) were initially healthy females with pelvic inflammatory disease as the primary site of infection. Both survived after appropriate antibiotic treatment.

Three cases were found to involve the lower respiratory tract, 2 of empyema, and 1 of lung abscess. *H. influenzae* was isolated from abscess or pleural effusion. All had underlying pulmonary disease. A 26 year-old female (patient 5) had previous pulmonary tuberculosis with destroyed left lung. Two patients had lung cancer, and both died of a disease other than

Table 1. Summary of clinical data of adults with invasive infections caused by *Haemophilus influenzae*

Patient No.	Age (years)/ gender	Source of bacterial isolation	Serotype	beta-Lactamase	Community/ nosocomial acquisition	Diagnosis	Underlying disease and/or condition	Outcome
1	43/F	Blood	NA	NA	Community	Pelvic inflammatory disease	Ovarian tumor status post operation, uterine myoma	Survived
2	75/M	Vitreous aspirate	NA	NA	Nosocomial	Endophthalmitis	Cataract status post operation, diabetes mellitus, hypertension	Survived
3	57/F	CAPD fluid	NT	+	Nosocomial	CAPD peritonitis	Uremia	Survived
4	37/F	Blood	NA	NA	Community	Pelvic inflammatory disease	Asthma, hepatitis B virus carrier	Survived
5	26/F	Pleural effusion	NT	+	Community	Empyema and lung abscess	Old pulmonary tuberculosis with left destroyed lung	Survived
6	83/F	Eye swab ID	NT	+	Community	Orbital cellulitis with abscess	Nasolacrimal duct obstruction status post operation, diabetes mellitus, glaucoma	Survived
7	75/M	Ascites	NT	–	Community	Perforated peptic ulcer with peritonitis	Chronic obstructive pulmonary disease	Died
8	72/M	Pleural effusion	NA	NA	Community	Empyema	Lung cancer	Died
9	74/M	Blood	NT	–	Nosocomial	Primary bacteremia	Hepatitis B virus-related liver cirrhosis with esophageal varices, bronchiectasis	Survived
10	80/M	Lung mass aspirate	NT	+	Community	Obstructive pneumonitis	Lung cancer, coronary artery disease status post coronary artery bypass graft, intracranial hemorrhage, hypertension	Died
11	76/F	Blood	NT	–	Community	Pneumonia with respiratory failure	Multiple myeloma	Died
12	61/M	Blood	Type b	+	Community	Pneumonia	Chronic obstructive pulmonary disease, B-cell lymphoma status post chemotherapy	Survived
13	50/M	Pus from eye	NA	NA	Community	Orbital cellulitis with abscess	Ocular trauma	Survived
14	81/M	Blood	NT	+	Community	Pneumonia with respiratory failure	Previous stoke, diabetes mellitus, hypertension, colon tumor status post operation	Survived
15	84/M	Blood	Type b	–	Nosocomial	Pneumonia, acute respiratory distress syndrome	Hypertension, senile dementia with bedridden status	Died

Abbreviations: F = female; M = male; CAPD = continuous ambulatory peritoneal dialysis; ID = incision and drainage; NA = not available; NT = nontypeable; + = positive; – = negative

pulmonary infection, *Escherichia coli* bacteremia (patient 8) and intracranial hemorrhage (patient 10), respectively. Isolates were found in two of three patients and both were nontypeable.

There were two cases of peritonitis. One, a 57-year-old female (patient 3) had uremia under continuous ambulatory peritoneal dialysis. She recovered after intraperitoneal antibiotic treatment. The other (patient 7), a case of chronic obstructive pulmonary disease, was admitted due to perforated peptic ulcer, and later, died of polymicrobial bacteremia. The two *H. influenzae* isolates obtained from ascites were nontypeable strains.

There were three patients with ophthalmic infections caused by *H. influenzae*. One case, an elderly diabetic male, received cataract operation. Two days

later, endophthalmitis of right eye occurred and led to loss of vision. The other two cases had periorbital cellulitis complicated with abscess formation secondary to nasolacrimal duct obstruction, and were cured after surgical drainage and oral antibiotic treatment. Only one isolate was found and was a nontypeable strain.

Only ten of the fifteen *H. influenzae* isolates survived preservation, and only two were Hib strains. Beta-lactamase was detected in six isolates which showed ampicillin resistance (1 Hib and 5 nontypeable isolates). Four isolates were resistant to tetracycline or chloramphenicol. Two isolates were not susceptible to trimethoprim-sulfamethoxazole (1 resistant, 1 intermediate). Antibiotic therapy is summarized in Table 2.

We also investigated the serotypes and susceptibility tests of *H. influenzae* isolated from respiratory tracts of adults. In total, 87 isolates were available, and all were nontypeable. Beta-lactamase production was detected in 48 isolates (55.1%). Fifty isolates (57.5%) were not susceptible to ampicillin (39 resistant, 11 intermediate), 40 (46.0%) were resistant to trimethoprim-sulfamethoxazole, 32 (36.8%) were not susceptible to tetracycline (30 resistant, 2 intermediate), and 26 (30.0%) not susceptible to chloramphenicol.

Discussion

This study was performed at a teaching medical center in Taipei, a veterans general hospital, and therefore most patients were elderly. The mean age of our patients was 65 years. We did not include cases of pneumonia, unless accompanied by *H. influenzae* bacteremia. We also did not include cases of otitis media, sinusitis, or other respiratory tract infection caused by *H. influenzae,* which are rarely associated with bacteremia. Thus, our report on documented invasive diseases represented only a fraction of all *H. influenzae* diseases occurring in adults. According to the national notifiable surveillance system of Taiwan Centers for Disease Control, annual case numbers of invasive Hib diseases in adults (aged >18 years) were 17 persons in 2000, 9 in 2001, 9 in 2002, 4 in 2003, and 4 in 2004, respectively [9], suggesting a gradual decline in cases. Our hospital-based population may not represent the general population. However, the epidemiologic data of invasive *H. influenzae* infections in Taiwan is scanty. From the limited number of cases in our study, invasive *H. influenzae* infection could be regarded as a rare disease in adults in Taiwan.

Our study and studies in western countries [5-7] revealed that nontypeable strains predominated in *H. influenzae* isolates causing invasive diseases among adults. Since Hib vaccine is not routinely inoculated in children in Taiwan, and would be indicated only in scheduled splenectomized adults, more surveillance may be necessary to evaluate the relationship between Hib vaccination and the declining incidence of invasive diseases due to nontypeable *H. influenzae* in adults.

Most patients were elderly, and the common clinical presentation of invasive *H. influenzae* diseases was lower respiratory tract infection (pneumonia), a result consistent with previous reports [7,10-13]. In addition, underlying disease was found in 71-90% of adults with invasive *H. influenzae* infection [7,11, 12,14]. Cellulitis is predominantly seen in young children and caused by Hib. The clinical features are fever and a raised, warm, tender area of distinctive blue hue, most often located on one cheek or in the periorbital region. The skin lesion may progress rapidly over a few hours [1]. Two of our patients had periorbital cellulitis with nasolacrimal duct abnormality. The location of cellulitis was similar to that of children, but one viable isolate from our study was nontypeable. The dominant strains seemed to differ in children and adults. Nontypeable *H. influenzae* is a well documented cause of tuboovarian or chronic salpingitis [1]. Invasive genital infection caused by *H. influenzae* also occurred in our study, as pelvic inflammatory disease, but preservation of the isolates failed and serotyping could not be performed.

The resistance rate of ampicillin in invasive isolates and respiratory isolates was high. In a surveillance study of antibiotic resistance in Taiwan, beta-lactamase production was found in 50-60% of *H. influenzae* [15]. Thus, *H. influenzae* resistance should be taken into consideration when determining antibiotic treatment. Unusually, five isolates were resistant to aztreonam, four to ceftazidime, one to cefotaxime, and one to imipenem by disk diffusion methods. However, the results were not confirmed by minimal inhibitory concentration test.

In conclusion, invasive *H. influenzae* infection in adults in Taiwan could be regarded as a rare disease. Nontypeable strains predominated and the common presentation was lower respiratory tract infection in adults. A high rate of ampicillin resistance was found, and should be taken into consideration when choosing antibiotic treatment.

Table 2. Antibiotic susceptibility profile of *Haemophilus influenzae* isolates and antibiotic treatment

Patient no.	AM	ATM	CTX	CAZ	CRO	CH	TE	SXT	CXM	IMP	Treatment
1	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Cefuroxime 1500 mg IV q8h, clindamycin 600 mg IV q8h and gentamicin 60 mg q8h for 6 days, then cefalexin 500 mg oral qid and clindamycin 150 mg oral qid for 7 days
2	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Intravitreous vancomycin, ceftazidime, aztreonam, with topical 5% vancomycin, 5% ceftazidime ophthalmic solution
3	R	S	S	S	S	S	R	I	S	S	Intraperitoneal vancomycin, tobramycin[a]
4	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Cefazolin 1g IV q6h, and sisomicin 50 mg IV q8h for 3 days, then ofloxacin 400 mg oral bid for 3 days
5	R	S	S	S	S	R	R	S	S	S	Clindamycin 600 mg IV q8h, and gentamicin 80 mg IV q12h for 5 days, then cefuroxime 1500 mg IV q8h
6	R	S	S	S	S	R	S	S	S	S	Cefazolin 1g IV q8h, and gentamicin 60 mg IV q12h for 9 days with topical cefazolin, gentamicin ophthalmic solution, then trimethoprim-sulfamethoxazole (80 mg/400 mg) 2 tablets for 12 days, then amoxicillin-clavulanate (250 mg/125 mg) 1 tablet for 1 day. Incision and drainage
7	S	S	S	S	S	S	S	S	S	S	Aztreonam 1 g IV q8h, and clindamycin 600 mg IV q8h for 1 day
8	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Cefuroxime 750 mg IV q6h for 6 days, then cefuroxime 1500 mg IV q6h, and netromycin 150 mg IV q12h for 10 days
9	S	S	S	S	S	S	S	S	S	S	Cefuroxime 1500 mg IV q8h for 14 days
10	R	S	S	S	S	R	R	R	S	S	Cefuroxime 1500 mg IV q8h and netilmicin 150 mg IV q12h for 7 days, with roxithromycin 300 mg oral bid for 5 days
11	S	S	S	S	S	S	S	S	S	S	Ampicillin-sulbactam 1500 mg IV q6h and gentamicin 60 mg IV q12h for 2 days, then penicillin 3 mega units IV q6h, pefloxacin 400 mg IV q12h and metronidazole 500 mg IV q6h for 5 days, then cefotaxime 2 g for 28 days
12	R	S	S	S	S	R	R	S	S	S	Ceftazidime 2 g IV q8h and clindamycin 600 mg IV q8h for 6 days, with amikacin 375 mg IV q12h for 2 days, then ofloxacin 200 mg oral tid
13	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Cefalexin 500 mg oral qid with topical 0.25% chloramphenicol ophthalmic solution, incision and drainage
14	R	S	S	S	S	S	S	S	S	S	Cefoperazone 2 g IV q8h and fosfomycin 2 g q12h for 6 days, penicillin 3 mega units IV q6h, and ciprofloxacin 400 mg IV q12h for 3 days, cefmetazole 1 g IV q6h for 4 days, then ceftazidime 2 g IV q8h for 6 days
15	S	S	S	S	S	S	S	S	S	S	Aztreonam 1 g IV q6h, clindamycin 600 mg IV q8h for 7 days

Abbreviations: AM = ampicillin; ATM = aztreonam; CTX = cefotaxime; CAZ = ceftazidime; CRO = ceftriaxone; CH = chloramphenicol; TE = tetracycline; SXT = trimethoprim-sulfamethoxazole; CXM = cefuroxime; IMP = imipenem; NA = not available; R = resistant; S = susceptible; I = intermediate; IV = intravenous; q8h = every 8 h; qid = four times a day; q6h = every 6 h; bid = two times a day; q12h = every 12 h; tid = three times a day

[a]Dosage, duration of treatment missing in chart.

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