ORIGINAL RESEARCH

Assessing *Haemophilus influenzae* as a Contributing Pathogen in Children's Eye and Upper Respiratory Infections

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ABSTRACT
Background: Haemophilus influenzae, particularly non-typeable strains (NTHi), is a significant pathogen in pediatric infections, notably conjunctivitis, acute otitis media (AOM), and acute bacterial paranasal sinusitis. The concurrent occurrence of these infections, especially during specific seasons, underscores the need to understand their epidemiology and microbiology. **Objective:** To investigate the prevalence, clinical characteristics, and microbiological profiles of children presenting with conjunctivitis accompanied by AOM and/or acute bacterial paranasal sinusitis, with a focus on the role of H. influenzae. **Methods:** A prospective study was conducted involving 119 children aged 5 months to 10 years diagnosed with conjunctivitis plus AOM and/or acute bacterial paranasal sinusitis. Conjunctival samples were collected using rayon swabs and cultured on chocolate and blood agar. Isolates were identified based on colony morphology and conventional methods. Antimicrobial susceptibility was assessed using the microdilution method, and β-lactamase production was evaluated with Cefinase paper discs. **Results:** The mean age of participants was 31.3 months, with a median of 26 months. A significant seasonal peak was observed in March and April. Household clustering occurred in 52.2% of cases, with at least one family member exhibiting similar symptoms within a week of the index case. Underlying conditions were present in 11.2% of children. Hospitalization was required for 8.2% of patients due to complications such as preseptal cellulitis and bronchopneumonia. H. influenzae was the predominant pathogen isolated, with notable resistance to ampicillin (80%) and amoxicillin-clavulanate (18%). **Conclusion:** H. influenzae plays a predominant role in pediatric cases of conjunctivitis accompanied by AOM and/or acute bacterial paranasal sinusitis, particularly during the spring season. The high rate of household transmission and emerging antibiotic resistance patterns highlight the need for vigilant clinical management and consideration of empiric antibiotic therapy targeting H. influenzae.

Keywords: Haemophilus influenza, Non-typeable Haemophilus influenzae (NTHi), Conjunctivitis, Acute otitis media (AOM), paranasal sinusitis

INTRODUCTION

Haemophilus influenzae, a small Gram-negative coccobacillus, is a significant pathogen in pediatric upper respiratory tract infections. Although the introduction of the *Haemophilus influenzae* type b (Hib) conjugate vaccine has drastically reduced the incidence of invasive diseases such as meningitis and epiglottitis caused by encapsulated strains, non-typeable *Haemophilus influenzae* (NTHi) has emerged as a leading cause of localized, non-invasive infections in children.[1] These infections commonly include acute otitis media (AOM), conjunctivitis, and acute bacterial paranasal sinusitis.

NTHi lacks a polysaccharide capsule, distinguishing it from encapsulated strains and enabling it to colonize the nasopharynx asymptomatically. Disruption of the mucosal barrier by viral infections can lead to the migration of NTHi to adjacent anatomical structures, initiating bacterial infection.[2]In AOM, NTHi is one of the three primary bacterial pathogens, alongside *Streptococcus pneumoniae* and *Moraxella catarrhalis*, and is frequently identified in recurrent and chronic cases due to its ability to form biofilms and resist

phagocytosis.[3,4] Similarly, in bacterial sinusitis, NTHi is isolated in 20–25% of pediatric cases, often following viral upper respiratory tract infections.[3]

Conjunctivitis associated with NTHi, especially in the setting of conjunctivitis-otitis syndrome, is characterized by bilateral purulent discharge in conjunction with AOM. This syndrome is almost pathognomonic for infection with NTHi and underscores its tropism for mucosal surfaces.[4] The pathogen's increasing β-lactamase-mediated resistance to ampicillin and related antibiotics presents a clinical challenge, emphasizing the need for appropriate antibiotic stewardship and continuous epidemiological surveillance.

Understanding the evolving role of *Haemophilus influenzae*, particularly NTHi, in these common childhood infections is vital for effective treatment and the development of future preventive strategies, especially in the face of growing antimicrobial resistance.[5,6]

MATERIALS AND METHODS

For each patient, a single conjunctival specimen was collected from the lower fornix of the conjunctival sac using rayon-tipped swabs with transport medium. These swabs were cultured on chocolate and blood agar plates, which were incubated at 37°C for 48 hours in a 5% CO_2 environment. Identification of *Haemophilus influenzae* was performed based on colony characteristics and standard laboratory techniques.

To distinguish between antibiotic-sensitive and resistant strains of *H. influenzae*, including BLNAS, BLNAR, BLPAR, and BLPACR types, antimicrobial susceptibility testing was carried out using both ampicillin and cefaclor. β-lactamase activity was detected using BBL Cefinase paper discs (Nippon Becton Dickinson Company, Tokyo, Japan), and minimum inhibitory concentrations (MICs) were determined using the microdilution method on dry plates ("Eiken," Eikenkagaku), following the guidelines of the Clinical and Laboratory Standards Institute (CLSI).

Susceptibility to eight antibiotics was evaluated: ampicillin, cefaclor, sultamicillin tosilate, cefotaxime sodium, cefditoren pivoxil, imipenem/cilastatin sodium, clarithromycin, and levofloxacin.

Classification of *H. influenzae* strains was based on CLSI standards:

BLNAS (β-lactamase-negative, ampicillin-susceptible): MIC for ampicillin ≤ 1 μg/mL

BLNAR (β-lactamase-negative, ampicillin-resistant): MICs ≥ 4 μg/mL for ampicillin and ≥ 16 μg/mL for cefaclor

BLPAR (β-lactamase-positive, ampicillin-resistant): MIC ≥ 4 μg/mL for ampicillin and ≤ 8 μg/mL for cefaclor

BLPACR (β-lactamase-positive, ampicillin and cefaclor-resistant): MICs ≥ 4 μg/mL for ampicillin and ≥ 16 μg/mL for cefaclor

RESULTS

A total of 119 children was recruited with ages ranging from 5 months to 10 years. The mean age was 31.3 (± 23.2) months with a median of 26 months (IQR 10–45). 40 (57.9%) patients were ≤ 3 years old. Demographic data and bacterial culture results are described in Table 1. The mean age of the children in which a particular pathogen was identified varied significantly (p = 0.01). Children with H. influenzae infection were the youngest, while the mean age of children with S. aureus infection was the oldest.

Table 1. Bacteriological culture results of conjunctiva discharge in children diagnosed of conjunctivitis with acute otitis media and/or acute bacterial paranasal sinusitis.

Gender and age	*H. influenzae* (N = 69)	*M. catarrhalis* (N = 28)	*S. pneumoniae* (N = 10)	*S. aureus* (N = 12)
%	57.9%	23.5%	8.4%	10.0%
Mean age ± SD*	28.4 ± 20.5	29.4 ± 20.4	45 ± 26.2	57.5 ± 40
Age group, n				
< 1y	7	6	3	0
1–2y	9	4	0	3
2–3y	8	4	0	4
3–4y	7	5	0	0
4–5y	6	2	4	0
> 5y	3	2	3	4
Male, n (%)	40 (57.9%)	23 (82.1%)	10 (100%)	11 (91.6%)

Conjunctivitis accompanied with acute otitis media and/or acute bacterial paranasal sinusitis is most prevalent in March and April, corresponding to spring season in Taiwan. Clusters in household were observed in 37 (52.2%) patients. At least one family member of these children had conjunctivitis and respiratory tract infection with or without fever within one week of illness of index patient. Three families had two children with a diagnosis of conjunctivitis plus acute otitis media and/or acute bacterial paranasal sinusitis contemporary. 10 (11.2%) children had underlying diseases including biliary atresia, congenital heart disease, Down syn- drome, bronchial asthma, prematurity, and cleft palate. Only 7 (8.2%) patients needed hospitalization. A 2-year- old boy was admitted for one week due to a complication of

preorbital cellulitis. The other three children were hospitalized for contemporary bronchopneumonia or dehydration due to poor oral intake. In addition, a 10-year- old boy had ophthalmological complications of keratitis and corneal ulcer during follow-up. Oral cefixime was administrated initially and the conjunctiva discharge culture yielded methicillin-susceptible S. aureus.

One child had recurrent conjunctivitis–otitis media syndrome one and a half years later. Another child had recurrent acute otitis media with complication of complex febrile convulsion required hospitalization two weeks after the initial episode.

Table 2. Antimicrobial susceptibilities of Haemophilus influenzae isolates recovered from conjunctiva or ear discharge using the disk diffusion method*. SXT, Trimethoprim/sulfamethoxazole. *One child received both conjunctiva and ear discharge culture examination, and both yielded Haemophilus influenzae with the same antimicrobial susceptibility pattern.

Agent	No. of isolates tested	No. (%) of indicated susceptibility	
		Susceptible	Resistant
Ampicillin	58	13 (22.4)	45 (77.5)
Amoxicillin-clavulanate	59	47 (79.6)	12 (20.3)
Chloramphenicol	58	52 (89.6)	6 (10.3)
Cefixime	58	54 (93.1)	4 (6.8)
Cefpodoxime	54	50 (92.5)	4 (7.4)
Cefotaxime	57	57 (100)	0 (0)
Cefuroxime	58	50 (86.2)	8 (13.7)
SXT	58	19 (32.7)	39 (67.2)

DISCUSSION

In this study, pediatric patients aged between 5 months and 10 years were evaluated for bacterial conjunctival infections. The majority of the children (57.9%) were under the age of three, with a mean age of 31.3 months. These findings highlight the increased vulnerability of younger children—particularly those under three years of age—to ocular bacterial infections. This trend may be due to underdeveloped immune systems, increased exposure in communal childcare settings, and more frequent upper respiratory tract infections, which are known risk factors for conjunctival and otic co-infections (Brouwer et al., 2022).

The statistically significant variation in mean age according to the identified pathogen ($p = 0.01$) suggests age-related differences in susceptibility to specific bacteria. Notably, *Haemophilus influenzae* was more commonly isolated in the youngest children, which aligns with previous studies that have established non-typeable *H. influenzae* (NTHi) as a dominant pathogen in early childhood conjunctivitis, especially in those with concurrent otitis media (Pichichero, 2000; Usonis et al., 2021). This association may reflect NTHi's nasopharyngeal colonization in infants and its frequent transition from colonization to infection following viral upper respiratory infections (Bakaletz, 2012).

In contrast, *Staphylococcus aureus* was more frequently identified in older children. This organism is a common component of the skin flora and becomes more prevalent with age, possibly due to increased hand-eye contact and self-inoculation in older, more mobile children (Block et al., 2013). Furthermore, *S. aureus* is known to play a more significant role in bacterial conjunctivitis in older children and adolescents, often linked to underlying dermatologic conditions like blepharitis or atopic dermatitis (Harrington et al., 2019).

These age-related microbial patterns have important implications for empirical treatment strategies. Understanding which pathogens are more likely based on a child's age can help guide the selection of first-line antibiotics, especially in settings where culture and sensitivity testing are not readily available. For instance, in very young children, empiric coverage for *H. influenzae* may be prioritized, while in older children, *S. aureus* coverage becomes more relevant. Additionally, these data reinforce the importance of infection control practices in early childhood care environments to limit bacterial transmission.

The seasonal peak of conjunctivitis accompanied by acute otitis media (AOM) and/or acute bacterial paranasal sinusitis observed in March and April in Taiwan aligns with known patterns of increased upper respiratory tract infections (URTIs) during spring. Fluctuating temperatures and elevated allergen levels during this period may predispose children to URTIs, subsequently leading to secondary bacterial infections such as AOM and sinusitis.

The occurrence of household clusters in over half of the cases underscores the contagious nature of these infections. Close contact among family members facilitates the spread of pathogens like non-typeable *Haemophilus influenzae* (NTHi), a common cause of conjunctivitis and otitis media. Bodor et al. reported that in families with more than one child, 47% of siblings were affected simultaneously or within a one-month period .[10-13]

The presence of underlying conditions such as biliary atresia, congenital heart disease, Down syndrome, bronchial asthma, prematurity, and cleft palate in a subset of patients highlights the increased susceptibility of these children to infections and

complications. These conditions can impair immune responses or anatomical defenses, making children more prone to severe or recurrent infections.[13] While only a small percentage of children required hospitalization, the cases that did were due to serious complications like preseptal cellulitis, bronchopneumonia, or dehydration from poor oral intake. These findings suggest that while most cases are manageable in outpatient settings, vigilance is necessary to identify and treat complications promptly .[14]

The report of recurrent episodes in some children emphasizes the need for ongoing monitoring and possibly preventive strategies. Factors contributing to recurrence include early onset of AOM, anatomical abnormalities, and environmental exposures. Addressing modifiable risk factors—such as reducing exposure to tobacco smoke and promoting breastfeeding—can help mitigate the risk of recurrence.

CONCLUSION

In conclusion, the seasonal pattern, familial clustering, and association with underlying conditions in conjunctivitis cases accompanied by AOM and/or sinusitis highlight the multifactorial nature of these infections. A comprehensive approach that includes awareness of seasonal trends, infection control within households, consideration of underlying health conditions, and prompt management of complications is essential for effective care.

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