The Journal of Laryngology & Otology (2011), ***125***, *928–933*.

doi:10.1017/S0022215111001587

MAIN ARTICLE

Otitis media with effusion in Lebanese children: prevalence and pathogen susceptibility

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Abstract

Objective: To determine the prevalence and resistance profile of bacterial pathogens present in the middle ear of children with otitis media with effusion, and to report beta-lactamase-negative, ampicillin-resistant bacteria for the first time in Lebanese children.

Method: We included 62 patients younger than 12 year (107 ears), who underwent myringotomy with tympanostomy tube placement for persistent otitis media with effusion. Bacteria were identified by Gram staining and biochemical tests, and antibiotic sensitivities tested by the disc diffusion method and via minimum inhibitory concentration (E-test).

Results: The commonest pathogen was *Haemophilus influenzae* (62 per cent), followed by *Streptococcus pneumoniae* (26 per cent). The *H influenzae* resistance profile was highest for amoxicillin (81.0 per cent) and lowest for cefotaxime (19.0 per cent). There was a high risk of developing *H influenzae* antibiotic resistance among children with a history of smoking exposure ($p = 0.001$), recurrent upper respiratory tract infection ($p = 0.001$) or previous antibiotic treatment ($p = 0.005$). Fifty-two per cent of *H influenzae* colonies were found to be beta-lactamase-negative and ampicillin-resistant.

Conclusion: In these children with persistent otitis media with effusion, *H influenzae* was the most prevalent bacteria. It showed a high incidence of resistance to the antibiotics most commonly prescribed to treat acute otitis media.

Key words: Otitis Media; Otitis Media With Effusion; Drug Resistance, Microbial; Beta Lactamase; Streptococcus Pneumoniae; Haemophilus Influenzae

Introduction

Otitis media with effusion is a common medical problem, and a leading cause of hearing impairment in children presenting to otolaryngology clinics. It is defined as the presence of fluid in the middle ear, without any signs or symptoms of acute ear infection.[1] Otitis media with effusion was previously thought to be a noninfectious disease secondary to eustachian tube dysfunction. However, several microbiological studies have now shown the presence of bacteria in the middle-ear fluid of patients with this condition.[1–5]

The inappropriate and excessive use of antibiotics in the treatment of acute otitis media and other respiratory tract infections has raised concern about an increased prevalence of pathogens resistant to commonly used paediatric antibiotics.[6]

Several studies in different countries have shown that *Streptococcus pneumoniae* and *Haemophilus influenzae* are among the most frequent causative organisms of acute otitis media, followed by *Moraxella catarrhalis*.[5,7,8] Furthermore, the bacteriology of acute otitis media has been shown to change over time.[9,10] *Streptococcus pneumoniae* used to be the most frequent bacteria associated with acute otitis media in the early twentieth century; however, nowadays *M catarrhalis* and *H influenzae* are becoming more frequent.[9]

In a 2001 study of acute otitis media, the three major pathogens found in 329 children aged two to 24 months were *S pneumoniae* (26 per cent), *M catarrhalis* (23 per cent) and *H influenzae* (23 per cent).[9] In addition, *M catarrhalis* infections were shown to peak at a very young age (six months), while *S pneumoniae* and *H influenzae* infections peaked at 12 and 20 months, respectively.[9]

Ruohola *et al.* found that new bacteria appeared in the middle ear more commonly during the follow-up period than at initial detection; on the first day of study, the above three common pathogens were detected in 89 per cent of 75 children.[10] *Moraxella catarrhalis* seemed to persist the longest in the middle ear.

Accepted for publication 19 January 2011 First published online 13 July 2011

In 1993, El-Shamy examined the bacteriological profile of otitis media in Egyptian children, and found that 50 per cent of all effusions yielded bacterial growth.[11] *Haemophilus influenzae* was the commonest isolated organism, followed by *M catarrhalis* and *S pneumoniae*.

In 2005, Barkai *et al.* raised concerns about antimicrobial drug resistance in *S pneumoniae* found in children with acute otitis media who were aged less than five years and lived in southern Israel.[12]

A 2007 review of persistent and recurrent acute otitis media occurring in 1077 children enrolled between 1995 and 2000 found that the most common cause of early recurrent acute infection in antibiotic-treated children was persistent *S pneumoniae* colonisation in the nasopharynx.[13] The author suggested that initial antibiotic treatment of acute otitis media should also target nasopharyngeal colonisation.

Due to the worldwide variation in the profile of middle-ear pathogens, the current study was conducted to evaluate the epidemiology and resistance profiles of bacteria implicated in otitis media with effusion in Lebanese children. The study also assessed the correlation between bacterial resistance profiles and other factors, such as smoking exposure at home and recurrent upper respiratory tract infection.

Materials and methods

This study was conducted prospectively in a single university hospital between January 2009 and April 2010. We enrolled 62 children (107 ears), who underwent myringotomy with tympanostomy tube placement for persistent otitis media with effusion.

The inclusion criteria were paediatric patients aged less than 13 years, who had otitis media with effusion diagnosed by pneumatic otoscopy, with resultant hearing impairment with or without language delay, and who had suffered at least six weeks' illness without any sign of resolution or improvement despite medical treatment (nasal steroids with or without reflux management).

The diagnostic criteria for otitis media with effusion included tympanic membrane opacification, colour change, decreased mobility and increased vascularity.

We excluded from the study any patients who presented with acute otitis media and other upper respiratory infections at the time of surgery, as well as those who had taken antibiotics within the past seven days prior to surgery.

The duration of otitis media with effusion was estimated based on the duration of hearing impairment noted by the parents, and also, more accurately, via follow up with pneumatic otoscopy. A detailed medical history was taken for each patient, focussing on relevant aspects such as age, sex, duration of hearing impairment, history of upper respiratory tract infection, smoking exposure at home and prior antibiotic use.

Surgery was performed under microscopy. After cleansing and antisepsis of the external auditory canal with 70 per cent alcohol, a myringotomy was made in the anteroinferior quadrant of the tympanic membrane.

The effusion was collected with a number five aspirator connected to a Polymed mucus extractor (POLY MEDICURE LTD, New Delhi, India), using aseptic technique. Effusion fluid was sent for direct culture no longer than 15 minutes after collection.

For direct culture, the effusion fluid was seeded onto plates containing sheep blood agar and chocolate agar (enriched with PolyViteX; BIOMERIEUX, France SA), and incubated in aerobic conditions under 5–10 per cent CO_2 for 48 hours at 37°C. The resultant bacteria were identified by Gram staining and biochemical testing.

After culture and identification of the different bacterial strains, sensitivity to commonly used antibiotics (including amoxicillin, amoxicillin–clavulanate, cefalotin and cefotaxime) was tested using the disc diffusion method, as recommended in 2008 by the Antibiogram Committee of the French Society of Microbiology. Pathogens with intermediate resistance were considered resistant to the relevant antibiotic. The sensitivity of *S pneumoniae* and *H influenzae* to amoxicillin and ceftriaxone was determined by assessing minimum inhibitory concentration, using the E-test. The Cefinase test (BIOMERIEUX, France SA) was used for *H influenzae* and *M catarrhalis* colonies to determine the capacity for beta-lactamase production. Strains of *H influenzae* were described as beta-lactamase-negative and ampicillin-resistant when beta-lactamase production was absent and the minimum amoxicillin inhibitory concentration was greater than 2 μg/ml.

Statistical analyses were performed using the Statistical Package for the Social Sciences software program (SPSS Inc, Chicago, Illinois, USA). The correlation between variables was evaluated using the chi-square test and Fisher's exact test. *P* values below 0.05 were considered to be statistically significant.

Results

A total of 62 children diagnosed with otitis media met the inclusion criteria. There were 40 boys (64.5 per cent) and 22 girls (35.5 per cent), with a mean ± standard deviation age of 4.21 ± 1.74 years. The majority were aged between three and five years (66 per cent). Around 61 per cent of the children had a history of smoking exposure, and 48.4 per cent had suffered recurrent upper respiratory tract infections. Amoxicillin–clavulanate was the commonest antibiotic used previously. Table I summarises patient characteristics.

One hundred and seven ears were tested for bacterial growth, resulting in positive bacterial cultures for 32 per cent ($n = 34$) of the tested ears. The most common cultured pathogen was *H influenzae* ($n = 21$, 62 per cent), followed by *S pneumoniae* ($n = 9$, 26 per cent) and moraxella species ($n = 4$, 12 per cent).

https://doi.org/10.1017/S0022215111001587 Published online by Cambridge University Press

TABLE I
PATIENT CHARACTERISTICS

Parameter	Value
Age (mean ± SD)	4.21 ± 1.74
Gender	
– Female	22 (35.5)
– Male	40 (64.5)
Smoking exposure	38 (60.7)
Recurrent URTI	30 (48.4)
Prev antibiotic use*	
– None	38 (60.7)
– Amoxicillin	2 (3.7)
– Amoxicillin–clavulanate	18 (29)
Positive culture†	
– Overall	34 (32)
– *H influenzae*	21 (61.8)
– *S pneumoniae*	9 (26.5)
– *M catarrhalis*	4 (11.8)

Data represent patient numbers (percentages) unless otherwise specified. *Per patient. †Per tested ear. SD = standard deviation; URTI = upper respiratory tract infection; prev = previous

Of those patients who had both ears tested, cultures were bilaterally positive in the majority.

Haemophilus influenzae had the greatest resistance profile to antibiotics commonly prescribed for acute otitis media; resistance findings were: amoxicillin, 81.0 per cent; amoxicillin–clavulanate, 52.4 per cent; cefalotin, 61.9 per cent; and cefotaxime, 19.0 per cent ($p = 0.001$) (Figure 1). The streptococcal resistance profile was low, with 11.11 per cent resistance to amoxicillin, to amoxicillin–clavulanate and to cefotaxime. Moraxella pathogens were sensitive to the latter two antibiotics, but showed 50 per cent resistance to amoxicillin. Fifty-two per cent of *H influenzae* strains were both beta-lactamase-negative and ampicillin-resistant, i.e. all strains had a negative Cefinase test, no evidence of beta-lactamase secretion, and a minimum amoxicillin inhibitory concentration of more than 2 μg/ml.

The mean duration of otitis media with effusion before surgery was four months. Assessment of the correlation between culture results and otitis media with effusion duration indicated that bacterial culture was more likely to be positive for otitis media with effusion

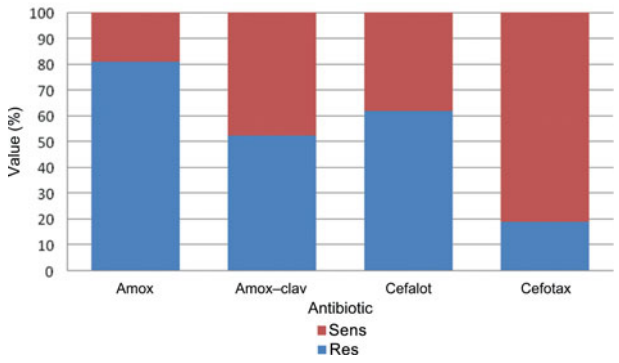

FIG. 1

Haemophilus influenzae sensitivity (sens) and resistance (res) profiles for beta-lactam antibiotics. Amox = amoxicillin; clav = clavulanate; cefalot = cefalotin; cefotax = cefotaxime

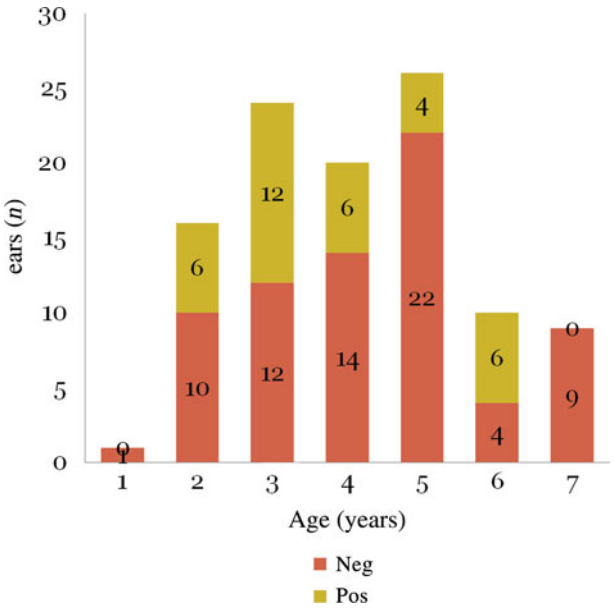

FIG. 2

Prevalence of culture-negative (neg) and culture-positive (pos) effusions, by patient age.

cases of shorter duration (i.e. zero to two months (28.6 per cent culture positivity) and three to six months (20 per cent)), compared with those which had persisted for six months or more (0 per cent) ($p < 0.001$).

In addition, cultures were more likely to be positive in patients younger than four years of age, compared with older patients (culture positivity rates were 40 per cent for two-year-olds, 50 per cent for three-year-olds, 28.6 per cent for four-year-olds and 15.4 per cent for five-year-olds) ($p = 0.015$).

We found a high risk of developing *H influenzae* antibiotic resistance among children with a history of exposure to smoking ($p = 0.001$), recurrent upper respiratory tract infections ($p = 0.001$) and previous antibiotic treatment ($p = 0.005$). In *H influenzae* cases with exposure to smoking, 88.9, 55.6 and 66.7 per cent showed resistance to amoxicillin, amoxicillin–clavulanate and cefalotin, respectively. Similar findings were observed for children with a history of recurrent upper respiratory tract infection (Table II).

Children with a mean age of 4 ± 1.5 years were at high risk of developing *H influenzae* resistance to amoxicillin, compared with those with a mean age of 2.5 ± 0.6 years ($p = 0.006$). No statistically significant correlation was observed between age and the development of resistance to other antibiotics.

Discussion

The bacterial types and prevalences identified in our cases of otitis media with effusion were similar to those reported in the world literature (i.e. 20–60 per cent).[2–5] A higher incidence of positive culture was found to correlate with younger age (less than four years) and shorter duration of otitis media with effusion (six months or less). These findings are in keeping with

https://doi.org/10.1017/S0022215111001587 Published online by Cambridge University Press

TABLE II
CORRELATION BETWEEN *H INFLUENZAE* ANTIBIOTIC RESISTANCE AND PATIENT CHARACTERISTICS

Characteristic	ears (*n*)	Antibiotic resistance (ears (*n* (%)))				*p*
		Amox	Amox–clav	Cefalot	Cefotax	
Smoking exp?						
– Yes	18	16 (88.9)	10 (55.6)	12 (66.7)	4 (22.2)	0.001
– No	3	1 (33.3)	1 (33.3)	1 (33.3)	0	
Rec URTI?						
– Yes	17	15 (88.2)	11 (64.7)	11 (64.7)	4 (23.5)	0.001
– No	4	2 (50)	0	2 (50)	0	
Prev Ab Rx?						
– Yes	11	11 (100)	9 (81.8)	9 (81.8)	4 (36.4)	0.005
– No	10	0	2 (20)	4 (40)	0	

amox = amoxicillin; clav = clavulanate; cefalot = cefalotin; cefotax = cefotaxime; exp = exposure; rec URTI = recurrent upper respiratory tract infections; prev Ab Rx = previous antibiotic therapy

the definition of otitis media with effusion as the persistence of fluid in the middle ear after resolution of acute otitis media, rather than eustachian tube dysfunction. Otitis media with effusion had previously been regarded as a strictly inflammatory process with a sterile effusion, until Senturia and colleagues' 1958 report of bacteria in otitis media with effusion redefined previously accepted concepts.[14]

Our study findings are in agreement with other reports regarding the high prevalence, within otitis media with effusion fluid, of *H influenzae* followed by *S pneumoniae* and *M catarrhalis*, albeit with slightly varying proportions.[5–11,17–21] These minor differences from other studies may be attributed to varying inclusion criteria, sample sizes, microbiological methodology and geographical areas. Two similar Lebanese studies investigating the bacterial aetiology of paediatric otitis media with effusion have found that *H influenzae* was the most prevalent bacteria.[15,16]

Our patients' low incidence of *S pneumoniae* within otitis media effusion fluid may be due to the increased prevalence of vaccination against *S pneumoniae* strains. Furthermore, our patients' low incidence of moraxella strains was similar to incidences reported in other studies, and may be related to the high sensitivity and decreased resistance of this fragile organism to most commonly used antibiotics.

Several studies, in different countries, have shown that *S pneumoniae* and *H influenzae* are among the most frequent causative organisms for acute otitis media, and that bacterial resistance varies considerably over time and geographical region, as summarised in Table III.[5–7,9] The streptococcal resistance profile to penicillin was low in our study; this could be related to the increased prevalence of vaccination against these bacterial strains in Lebanon. The *H influenzae* strains isolated from otitis media with effusion cases showed a high incidence of resistance to two of the

TABLE III
REPORTS OF OME BACTERIAL PREVALENCE AND ANTIBIOTIC RESISTANCE

Study		Bacteria (strains (%))		
Author	Year	*H influenzae*	*S pneumoniae*	Other
Bacterial prevalence				
Current study	2011	62	26	12*
El-Shamy[11]	1993	36.5		
Li *et al.*[7]	2001	10.2	21.8	0.7*
Pereira *et al.*[5]	2004	39.1	12.5	10.2*
Kilpi *et al.*[9]	2001	23	26	23*
Martinez *et al.*[8]	2007	17.2	37.5	
Antibiotics resistance prevalence				
Current study	2011	81, amox 52.4, amox–clav 61.9, cefalot 19.0, cefotax	11.11, amox 11.11, amox–clav 11.11, cefotax	50, amox*
Mills *et al.*[17]	1985	36, pen	25, trimeth	81, pen†
Lim *et al.*[18]	1980	48, amp 61, pen		50, pen ‡
Rodriguez *et al.*[19]	1995	62, pen	21, pen	98, amp*
Rosenblut *et al.*[20]	2006		22, pen (intermed)	
Dagan *et al.*[21]	1996		40, pen (intermed)	
Pereira *et al.*[5]	2004	23, pen	62.5, pen	98, pen*

**M catarrhalis*; †*S aureus*; ‡all bacteria. OME = otitis media with effusion; amox = amoxicillin; clav = clavulanate; cefalot = cefalotin; cefotax = cefotaxime; pen = penicillin; trimeth = trimethoprim; intermed = intermediate

https://doi.org/10.1017/S0022215111001587 Published online by Cambridge University Press

most commonly prescribed antibiotics used in the treatment of paediatric upper respiratory tract infections (i.e. amoxicillin and amoxicillin–clavulanate).

This is the first study to report beta-lactamase-negative, ampicillin-resistant *H influenzae* strains in Lebanon; these strains constituted approximately half of the *H influenzae* strains cultured in our study. This finding could be due to the overuse of antibiotics in Lebanon, where antibiotics are available without a prescription. Hamamoto *et al.* reported in 2005 that long-term exposure to antibiotics may significantly influence the bacterial genome of *S pneumoniae* isolated from middle-ear effusions.[22]

Many authors have noted that levels of antibiotic resistance are increasing markedly among bacterial pathogens which are common causes of paediatric acute otitis media, such as *S pneumoniae* and *H influenzae*.[17–19,22–28]

Haemophilus influenzae resistance to ampicillin emerged in the early 1970s, and levels of resistance have increased steadily since that time.[23] In *H influenzae*, resistance to ampicillin and other beta-lactam antibiotics is generally limited either to production of a beta-lactamase or, in the case of beta-lactamase-negative, ampicillin-resistant strains, to the presence of altered penicillin binding proteins with lowered affinity for beta-lactams.[24,25] A very small proportion of strains possess both mechanisms, and are referred to as beta-lactamase-positive, amoxicillin–clavulanate-resistant strains. Our results for beta-lactamase-negative, ampicillin-resistant *H influenzae* strains are similar to findings from Japan, where almost 40 per cent of *H influenzae* isolates have been reported to be beta-lactamase-negative and ampicillin-resistant.[25–27] It is important to note that our definition of beta-lactamase-negative, ampicillin-resistant *H influenzae* was taken from another study, and that there is currently no consensus on this definition.[27]

Few studies have evaluated the antimicrobial susceptibility patterns of common bacterial pathogens found in cases of paediatric otitis media with effusion. Over the past two decades, findings from such studies have shown that levels of resistance to penicillin and/or ampicillin are much higher in *H influenzae* than *S pneumoniae*, as summarised in Table III.[17–19] In 2006, Rosenblüt *et al.* showed that *S pneumoniae* resistance to penicillin did not extend to amoxicillin; strains with intermediate and high levels of resistance to penicillin were more common (22 and 4.5 per cent, respectively) than strains with intermediate and high levels of resistance to amoxicillin (18 and 0.5 per cent, respectively).[20] On the other hand, Dagan and colleagues' 1996 study found that 40 per cent of *S pneumoniae* isolates were intermediately penicillin-resistant, and that acute otitis media caused by such penicillin-resistant *S pneumoniae* strains responded inadequately to oral cephalosporins, mainly cefaclor.[21]

Eradication of *S pneumoniae* colonisation of the pharynx, using several different antibiotic classes including but not limited to macrolides, could spread azithromycin-nonsusceptible *S pneumoniae*.[29] A 1998 review paper suggested the introduction of new antibiotic treatments for acute otitis media, due to increased *H influenzae* and *M catarrhalis* resistance to commonly used antibiotics.[30]

The range of pathogens responsible for acute otitis media has changed over recent decades. This situation has given rise to recent guidelines and studies highlighting the benefit of pneumococcal conjugate vaccines in reducing the overall disease burden of severe and recurrent acute otitis media, as well as the importance of appropriate antibiotic usage to avoid recurrence of infection and the development of bacterial antibiotic resistance.[6,31,32]

A recent systematic review of acute otitis media has shown that the microbiology of acute otitis media has changed following the introduction of the PCV7 heptavalent pneumococcal conjugate vaccine. Prior to the introduction of this vaccine, the prevalence of *S pneumoniae* and *H influenzae* varied from 33 to 48 per cent and from 41 to 43 per cent, respectively. Following introduction of the vaccine, prevalence of *S pneumonia* decreased to 23–31 per cent while prevalence of *H influenza* increased to 56–57 per cent.[32]

- **Beta-lactamase-negative, ampicillin-resistant *Haemophilus influenzae* strains are present in Lebanese children with otitis media with effusion (OME)**
- **This study found a high prevalence of *H influenzae* strains resistant to commonly used antibiotics**
- **Antibiotic resistance correlated with previous recurrent upper respiratory tract infections and smoking exposure**
- **Greater public awareness of these influences is needed, given the high local prevalence of smoking and probable antibiotics overuse**
- **It is important to constantly monitor OME bacteria antibiotic resistance, to enable appropriate guidance of patient treatment**

The development of new diagnostic technology could help improve clinical and microbial diagnosis of acute otitis media.[31] Myringotomy with aspiration and tympanostomy tube insertion can include the collection of material for microbiological monitoring of otitis media. This could help define local antibiotic resistance trends, and identify populations at higher risk of infections caused by resistant pathogens.

Our study findings indicate that pathogens such as *H influenzae* and *M catarrhalis* are clinically important in acute otitis media, and that therapy should be directed against these pathogens, in addition to *S pneumoniae*.

https://doi.org/10.1017/S0022215111001587 Published online by Cambridge University Press

Conclusion

Our study established a microbiological profile of bacterial organisms associated with otitis media with effusion, and their antibiotic resistance patterns. There was a high prevalence of *H influenzae* strains resistant to commonly used antibiotics.

The presence of bacterial antibiotic resistance correlated with recurrent previous upper respiratory tract infections and smoking exposure, emphasising the need to improve public awareness in this regard.

In addition, we identified a high prevalence of beta-lactamase-negative, ampicillin-resistant *H influenzae* strains, a finding which may have important clinical implications.

Overall, we suggest that ongoing evaluation of the resistance patterns of bacteria implicated in otitis media with effusion would provide physicians with better information, facilitating appropriate treatment of such cases.

Acknowledgement

The authors would like to acknowledge Dr Issam Saliba for his critical review of this paper.

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Dr S C Nasser takes responsibility for the integrity of the content of the paper
Competing interests: None declared