



Pathogens in the middle ear effusion of children with persistent otitis media: implications of drug resistance and complications

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Acute otitis media (AOM) is the most common disease for which pediatricians prescribe antimicrobial agents. Middle ear fluid were collected from 243 children with AOM that failed to respond to a previous course of antimicrobial therapy and who had then received myringotomy from September 1997 through August 1999. Bacterial cultures were done and antimicrobial susceptibilities were analyzed. *Streptococcus pneumoniae* (21.8%) was the most common causative organism, followed by *Haemophilus influenzae* (10.2%), *Staphylococcus aureus* (7%), and *Pseudomonas aeruginosa* (1.8%), while *Moraxella catarrhalis* (0.7%) and group A β -hemolytic streptococcus (0.2%) were rarely isolated. In patients whose condition failed to improve after a course of antibiotic treatment, drug resistance became a serious problem. Fourteen percent of the patients in this series had complications, which included recurrent AOM, persistent middle ear effusion necessitating ventilation tube insertion, hearing impairment, mastoiditis, meningitis, chronic otitis media, brain abscess, and sepsis. Possible risk factors such as young age, male sex, underlying diseases, and a culture of *S. pneumoniae* or *H. influenzae* were not significantly associated with an increased incidence of complications. More stringent diagnosis and the correct choice of antibiotic treatment combined with the introduction of potential virus and bacterial vaccines are promising ways to reduce the morbidity of AOM in children.

Key words: Acute otitis media, complication, drug resistance, myringotomy

Acute otitis media (AOM) is a common cause of physician visits in children [1]. The disease is defined as the rapid onset of signs and symptoms of acute infection within the middle ear [2]. The eustachian tube of younger children is shorter and more horizontal than in older children. Organisms from the nasopharynx can reach the middle ear more readily in younger children as a consequence. The peak age-specific attack rate occurs between 6 and 18 months of age. Other risk factors reported to be associated with AOM include male sex, genetic factors, gestational age younger than 33 weeks, birth weight less than 1500 gm, early onset of disease (younger than 6 months), use of a pacifier, prone sleeping position, not breast-fed, exposure to smoke, crowded living conditions, and immunodeficiency [2].

The microbiological causes of otitis media have been reported in many countries [3-6]. The 3 most

common bacterial pathogens in children with AOM are *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis* [7,8]. In our practice, however, *H. influenzae* and particularly *M. catarrhalis* infection seem to be less common than reported in Western countries. This study sought to determine the prevalence of various pathogens in middle ear fluid (MEF) and their antibiotic susceptibility patterns in children with persistent AOM.

Materials and Methods

Patients

Between September 1997 and August 1999, 326 myringotomies were performed on 243 children who has a diagnosis of AOM. The indications for myringotomy are as follows: (1) persistent symptoms of otalgia or signs of AOM on otoscopy after empirical antibiotic treatment; (2) concern about a resistant infection; (3) bulging ear drum with impending rupture; (4) bullous myringitis; or (5) presence of middle ear effusion in immunocompromised patients. Eighty-three patients received myringotomy in both ears. The age

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of the patients ranged from 3 months to 14 years and 5 months (mean, 3 years and 3 months). The underlying diseases and complications of these patients were reviewed from chart records.

Definition of acute otitis media

Acute otitis media was diagnosed by using an otoscope by an experienced otolaryngologist or pediatrician when children had otalgia or fever with tympanic membranes that were red, bulging, or full, and cloudy or purulent effusion was observed. Recurrent AOM was defined as 2 or more episodes of disease within a 2-year period from initial diagnosis.

Myringotomy

Myringotomy was performed by otolaryngologists after cleansing the external auditory canal with alcohol swab and removing cerumen and foreign bodies. An MEF sample was obtained by an aseptic cotton swab and put in the transport medium for the cultures and sensitivity determinations. The MEF sample was inoculated on sheep blood, chocolate agar plates, phenylethyl alcohol agar, eosin methylene blue agar, anaerobic blood plate, and kanamycin-vancomycin plate.

Antimicrobial susceptibility testing

The antimicrobial susceptibility test was performed by the disc diffusion method using the BBL Sensi-Disc antimicrobial susceptibility test discs (Becton-Dickinson, Cockeysville, MD, US) according to the manufacturer's instructions and in accordance with the criteria of the National Committee for Clinical Laboratory Standards [9].

The antibiotics tested against gram-positive bacteria were ampicillin, amoxicillin/clavulanate, chloramphenicol, clindamycin, cefmetazole, cephalothin, erythromycin, gentamicin, minocycline, oxacillin, penicillin, and trimethoprim/sulfamethoxazole, with or without cefuroxime. Oxacillin resistant staphylococci were also tested to determine response to vancomycin, fusidic acid, and teicoplanin. *H. influenzae* was tested with ampicillin, amoxicillin/clavulanate, chloramphenicol, cefotiam, cefmetazole, cephalothin, cefuroxime, gentamicin, penicillin, minocycline, and trimethoprim/sulfamethoxazole. Other gram-negative bacteria were tested with ampicillin, amoxicillin/clavulanate, chloramphenicol, cefotiam, cefmetazole, cephalothin, cefuroxime, cefoxitin, gentamicin, tobramycin, and trimethoprim/sulfamethoxazole; or additionally with amikacin, aztreonam, ceftazidime, cefepime, ciprofloxacin, cefotaxime, ceftriaxone, imipenem, netilmicin,

piperacillin/tazobactam, ticarcillin/clavulanate, flomoxef, and ceftizoxime.

Statistics

Potential risk factors for complications of AOM, which included age, sex, underlying diseases, and bacteriology, were assessed by using the chi-square method, Yates correction for continuity, and test of independence. A *p* value of less than 0.05 was considered statistically significant.

Results

Characteristics of persistent otitis media

A total of 243 patients were enrolled in this study. The median age of patients was 2 years and 7 months. Acute otitis media was most common in patients aged 1 to 2 years, followed by 2 to 3 years, and 0 to 1 year. It was uncommon in children older than 6 years to develop AOM (Fig. 1). Among the 243 children, 141 (58%) were boys and 102 (42%) were girls. No obvious seasonal variation was found. It seemed that severe AOM was most common during the period from February through April (76 patients), followed by November through January (65 patients).

Thirty-five patients had underlying diseases, of them 13 (37.1%) had asthma or allergic rhinitis, and 8 (22.9%) had congenital upper airway diseases, which included laryngomalacia and congenital tracheal stenosis. Half of the patients who had congenital upper airway diseases received a tracheostomy. Five patients had malignancies, which included leukemia and lymphoma. One patient had the congenital immunodeficiency syndrome, which was known as hypogammaglobulinemia.

Pathogens of middle ear fluid in acute otitis media

A total of 375 bacterial isolates were cultured from 326 ear fluid samples, of which 33.1% yielded coagulase-negative staphylococci (CNS), 21.8% *S. pneumoniae*,

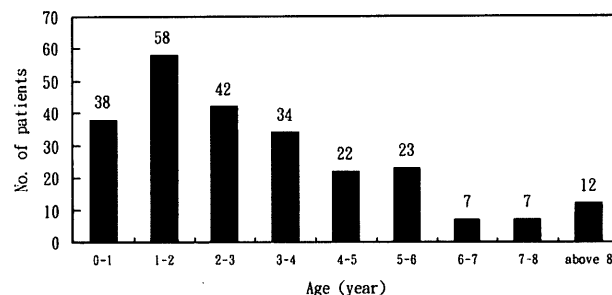


Fig. 1. Age distribution of patients with acute otitis media.

Table 1. Pathogens isolated from middle ear fluid (n = 441)

Microorganism	No. of isolates (%)
Coagulase-negative staphylococci	146 (33.1)
<i>Streptococcus pneumoniae</i>	96 (21.7)
<i>Haemophilus influenzae</i>	45 (10.2)
<i>Staphylococcus aureus</i>	31 (7.0)
Fungi	9 (2.0)
<i>Pseudomonas aeruginosa</i>	8 (1.8)
<i>Streptococcus</i> spp.	7 (1.6)
<i>Moraxella catarrhalis</i>	3 (0.7)
Others	30 (6.8)
No growth	66 (15.0)

10.2% *H. influenzae*, and 7% *S. aureus* (Table 1). Only 3 isolates of *M. catarrhalis* were found. Fungus constituted 2% of all cultured microorganisms. *Pseudomonas aeruginosa* accounted for 1.8% of the isolates, and other gram-negative rods accounted for another 2.5%. Only 1 group A β -hemolytic streptococcus was isolated. In 15% of samples, no pathogen was cultured. When CNS, diphtheroid organisms, and fungus were considered as having been isolated as a result of contamination, the rate of contamination of MEF cultures obtained by myringotomy was 38.9%.

Antimicrobial susceptibility pattern of pathogens

Of the 96 *S. pneumoniae* isolates, 92 (95.8%) were penicillin-resistant by the disc diffusion method. Only 2.1% of the *S. pneumoniae* isolates were sensitive to erythromycin. Chloramphenicol sensitivity was found in 62 (64.6%) isolates, and clindamycin sensitivity in 39 (40.6%) isolates. Trimethoprim/sulfamethoxazole sensitivity was found in 15 (15.6%) isolates. Of the 45 *H. influenzae* isolates, 40 (88.9%) were ampicillin-resistant. *H. influenzae* isolates were most sensitive to amoxicillin/clavulanate and cefuroxime, with sensitivities of 97.8% and 86.7%, respectively. *M. catarrhalis* was susceptible to all the tested antibiotics.

All the isolated strains of *P. aeruginosa* were sensitive to ceftazidime, ciprofloxacin, and imipenem. More than 75% of *P. aeruginosa* strains were sensitive to gentamicin, netilmicin, amikacin, piperacillin/tazobactam, and ticarcillin/clavulanate (Table 2).

Complications of acute otitis media

Thirty-four (14%) patients had complications of otitis media, which included recurrent AOM (64.7%), persistent middle ear effusion necessitating a ventilation tube insertion (26.5%), sequelae of hearing impairment (11.8%), mastoiditis (8.8%), meningitis (8.8%), chronic otitis media (5.9%), brain abscess (2.9%), and sepsis (2.9%). Half of these patients required hospitalization to treat the complications. The median age of AOM patients with complications was 2 years and 5 months. One boy died of pneumococcal meningitis. One of the patients with mastoiditis had simultaneous subosteal abscess. During the 2-year study period, 25 patients had at least 2 episodes of AOM. Eight of these patients underwent insertion of a ventilation tube during the study period. A 2-year-old boy had 4 episodes of myringotomy during the study period, and finally developed chronic otitis media. The time interval from the first episode of AOM to disease recurrence ranged from 1 to 15 months. More than half of the patients had a recurrence of AOM within 3 months of initial development of disease. Hearing tests were not conducted in every patient during acute episode because of the young age of the patients. According to the records, 12 patients developed mild to severe hearing impairment.

Complications were not statistically associated with younger age, male sex, underlying disease, or the isolation of *S. pneumoniae* or *H. influenzae*.

Discussion

Almost all of the patients in this series had persistent AOM and did not respond to 1 or more courses of

Table 2. Antimicrobial susceptibility of major pathogens isolated from patients with acute otitis media

Microorganism	Susceptible rate (%)										
	E	PCN	SXT	CC	C	MI	CP	CXM	AMC	AM	
<i>S. pneumoniae</i>	2.1	4.2	15.6	40.6	64.6	61.5	–	–	–	–	
<i>H. influenzae</i>	–	–	8.9	–	48.9	77.8	48.9	86.7	97.8	11.1	
<i>P. aeruginosa</i>	IPM	TZP	TIM	GM	NET	AN	CIP	NN	FEP	ATM	CAZ
	100	87.5	75	75	75	87.5	100	62.5	75	87.5	100

Abbreviations: AM = ampicillin; AMC = amoxicillin/clavulanate; AN = amikacin; ATM = aztreonam; C = chloramphenicol; CAZ = ceftazidime; CC = clindamycin; CIP = ciprofloxacin; CP = cephalothin; CXM = cefuroxime; E = erythromycin; FEP = cefepime; GM = gentamicin; IPM = imipenem; MI = minocycline; NET = netilmicin; NN = tobramycin; PCN = penicillin; SXT = trimethoprim/sulfamethoxazole; TIM = ticarcillin/clavulanate; TZP = piperacillin/tazobactam

antimicrobial therapy. This finding suggests a high prevalence of highly resistant strains of bacteria in MEF in the Mackay Memorial Hospital.

The peak age-specific incidence of AOM is reported to be in the first 2 years of life, typically between 6 and 18 months [10]. Numerous studies have reported that boys are at higher risk of AOM than girls, but several other studies found no male-female disparity [7]. The incidence of AOM is highest during the winter months and lowest in the summer, which parallels the incidence of viral upper respiratory tract infection [11-14]. Viral infection of the upper respiratory epithelium causes dysfunction of the eustachian tube, alteration of the host's immune defense, and an increase in bacterial colonization or adherence [13]. If coinfection of bacteria and virus in the middle ear develops, inflammation is enhanced and prolonged, and bacterial clearance from the middle ear is delayed [11]. Respiratory syncytial virus is one of the most common viruses associated with AOM, followed by parainfluenza virus, influenza virus, enterovirus, and adenovirus [11,13].

The epidemiological findings of isolates from MEF and those of 3 other studies were compared [3,7,8]. *S. pneumoniae* and *H. influenzae* were the most common organisms in MEF. By examining samples obtained by myringotomy, CNS was found to constitute 38.9% of the positive isolates in this study compared to 19.6% in the study of Calhoun *et al* [3]. The proportion of CNS seemed to be even lower in studies that used tympanocentesis and did not exclude CNS in the analysis. Because myringotomy was used in this study to collect specimens, the chance for a specimen to be contaminated with pathogens of the external ear canal was high. The failure rate of bacterial eradication was about 50% in those who failed clinically. *M. catarrhalis* and group A β -hemolytic streptococcus are easily eradicated by treatments using first-line antibiotics. Almost every patient in this series had received antibiotics before myringotomy, which might explain the low isolation rate of *M. catarrhalis* and group A β -hemolytic streptococcus. Isolation of *S. aureus* might have been resulted from contamination from the external auditory canal. Though *S. aureus* is generally considered to be an important pathogen in chronic otitis media, its role in AOM is not clear [4,5]. Virus, *Chlamydia pneumoniae*, and *Mycoplasma pneumoniae* are possible pathogens in MEF without any isolated bacteria [15].

The most notable trend in the bacteriology of AOM is a rise in drug-resistant *S. pneumoniae*, β -lactamase-producing *H. influenzae*, and *M. catarrhalis* [15]. South Korea has the highest reported prevalence of penicillin-

resistant *S. pneumoniae* (PRSP) in the world, with a resistance rate of 77% during 1991 to 1993. Taiwan is another area that has a high prevalence of PRSP [16]. In the Mackay Memorial Hospital, the rate of PRSP was less than 10% between 1990 and 1991, which has been increased to 20% in 1992 and remained at 45% during 1994 and 1995 [17]. From 1996 through 1997, *S. pneumoniae* isolates from throughout Taiwan were analyzed, and 56.4% were found to be non-susceptible to penicillin [18]. In this study, the prevalence of PRSP in MEF of children who had been treated with antibiotics was 95.8%. Block *et al* [19] reported a 5- to 15-fold increase in the incidence of PRSP from children who had AOM recently treated. Potential factors associated with the development of resistant strains include frequent and inappropriate use of antibiotics for viral infections, selection of antibiotics, inadequate antimicrobial coverage, and non-compliance with therapy. Long-term use of subtherapeutic doses and inadequate duration of treatment can also increase the risk of developing drug-resistant strains [15].

Oral amoxicillin and intramuscular ceftriaxone provide MEF concentrations above the minimum inhibitory concentration (MIC) of penicillin-intermediate and resistant *S. pneumoniae* for most of the dosing interval [20]. A higher dosage of amoxicillin (80-90 mg/kg/d) can result in high MEF concentrations, and may be sufficient to eliminate many strains that are non-susceptible to penicillin [1,20-23]. Cefaclor, cefibuten, and cefixime may be ineffective against intermediate-resistant *S. pneumoniae* [20,21]. Cefuroxime, cefpodoxime, and cefprozil displayed some activities against moderately resistant *S. pneumoniae*, but were not active against highly penicillin-resistant *S. pneumoniae* [1]. Only 2.1% of the *S. pneumoniae* strains isolated in this study were sensitive to erythromycin, whereas 59.4% were susceptible to clindamycin. A previous study found that 48% of cases of AOM caused by *H. influenzae* and 75% of cases caused by *M. catarrhalis* cleared spontaneously without antimicrobial agents [24]. β -lactamase-producing strains account for up to 40% of *H. influenzae* and 90% of *M. catarrhalis* isolates [20]. In Taiwan, the rate of β -lactamase production of *H. influenzae* was 58.1%, of which 33.8% was resistant to trimethoprim/sulfamethoxazole, and 0.3% to cefuroxime [26]. In this study, 88.9% of *H. influenzae* in MEF was resistant to ampicillin, 2.2% to amoxicillin/clavulanate, 13.3% to cefuroxime, and 81.1% to trimethoprim/sulfamethoxazole. Amoxicillin/clavulanate, cefpodoxime, cefuroxime, and cefixime have relatively high stability to the β -lactamase-producing strains of *H. influenzae* and *M. catarrhalis* [21]. If the

conditions of patients who had AOM caused by *H. influenzae* fail to improve clinically, amoxicillin/clavulanate, cefuroxime, cefpodoxime, cefixime, 1-day regimen of intramuscular ceftriaxone, or myringotomy may be effective.

Complications of AOM, although develop infrequently, include mastoiditis, bacteremia, meningitis, and auditory sequelae [20]. The most common complication of AOM is auditory sequelae. Nine of the patients in this series required ventilation tube placement because of persistent middle effusion. Sequelae of hearing loss were documented in only a few patients in this study. The number of patients with hearing loss was lower than expected. Age below 2 years, male sex, underlying disease, and a causative pathogen of *S. pneumoniae* or *H. influenzae* were not significantly associated with a greater chance of AOM complications in this study.

Excluding the contaminants, *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis* accounted for 79.6% of all isolates from MEF of children with persistent AOM in this study. The presence of drug-resistant strains is an important problem, especially in children whose conditions did not improve in previous antimicrobial therapy. More stringent diagnostic criteria and more judicious use of antibiotics are important in decreasing the rate of drug-resistance. By introducing conjugate *H. influenzae* type b vaccine, pneumococcal vaccine, and influenza vaccine [27,28], the ratio of complication and sequelae of AOM may be decreased.

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