Acute otitis media in an era of increasing antimicrobial resistance and universal administration of pneumococcal conjugate vaccine

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The last decade has witnessed a shift in the epidemiology of acute otitis media (AOM) with an earlier onset of disease and a greater proportion of children with recurrent episodes before 1 year of age. In addition antimicrobial resistance to beta-lactams, macrolides and trimethoprim-sulfamethoxazole among otopathogens has increased significantly. Most recently universal administration of a seven valent pneumococcal conjugate vaccine has been endorsed by the American Academy of Pediatrics and the Advisory Committee on Immunization Practices. Earlier onset of disease and the decrease in antimicrobial susceptibility among pediatric respiratory bacterial pathogens is likely to increase the risk of failure among young children with AOM. A seven valent pneumococcal conjugate vaccine (PCV7) has demonstrated efficacy for prevention of serotype-specific pneumococcal otitis; however, increase in disease caused by nonvaccine serotypes and Haemophilus influenzae has been reported. With these events as the background, I have reviewed the strategies most likely to be successful for the treatment of AOM in 2002.

INTRODUCTION

Acute otitis media (AOM) has evolved from its association with suppurative complications such as mastoiditis and chronic otitis media in the preantibiotic era to an acute localized illness with frequent recurrences in a substantial number of infants as the major morbidity. Although in most children AOM is a self-limited illness, recent clinical trials consistently demonstrate an excess failure rate in children who receive only symptomatic therapy. Engelhart et al. observed a failure rate of 70% in children receiving myringotomy alone. Kaleida et al. reported a 2-fold increment in failures among children with temperatures ≥103°F when myringotomy and placebo were compared with antibiotics (23.5% vs. 11.5%). More recently Little et al. demonstrated that children treated with amoxicillin improved more quickly than those receiving only placebo.

One theme of the last decade has been the judicious use of antibiotics. Because the majority of episodes of AOM are self-limited either because they are culture negative (~30%) or the host is able to clear bacterial pathogens from the middle ear (~25% of episodes), some countries have responded to the overuse of antibiotics by adopting a strategy of initial symptomatic therapy in combination with frequent reevaluation in children with AOM older than 1 year of age. Van Zuijlen et al. reported on comparative rates of mastoiditis in Europe, Canada, Australia and the United States. Although disease was infrequent in all countries (<4.2 cases/100,000 child years) regardless of the treatment strategy used for AOM, the rate in countries with low prescription rates for AOM was twice the rate in countries with high prescription rates, confirming the benefit of antimicrobial therapy in prevention of suppurative complications.

Since 1990 epidemiologic studies of AOM have demonstrated increasing disease in the first year of life. During the same time period resistance to penicillin among isolates of Streptococcus pneumoniae has increased significantly. Most recently in the fall of 2000, the first pneumococcal vaccine that prevents invasive disease was licensed and recommended for universal administration to children <2 years of age in the United States. The impact of these events on the current treatment strategies for AOM warrants examination.

A DECADE OF CHANGE: 1990 TO 2000

Significant changes in the epidemiology, the microbiology and the risk for suppurative complications of
acute otitis media have been reported during the last decade. Howie et al., in the 1970s, first used the term “otitis-prone” to describe children who had six or more episodes of acute otitis media before age 6 years. They identified 57 (11.7%) such children in a cohort of 488 followed prospectively from birth. Teele et al. prospectively studied a cohort of children from birth to 7 years of life. Their studies identified the near universality of acute otitis media in children (83% by 3 years of age with at least one episode). Age at onset, family history and the absence of breast-feeding were identified as the major risk factors for recurrent otitis media. AOM was observed in only approximately 30% of infants before 6 months of age, and three or more episodes were documented in 17% of children before their first birthday. Block et al. recently reported on the epidemiology of AOM in a 1993 and 1994 birth cohort followed prospectively for the first 3 years of life. Sixty percent of children had their first episode by 6 months and 85% by 1 year of age; 31% of the children had more than three episodes before 12 months of age. These prospective cohort studies conducted over a 20-year period suggest an increasing incidence in young children and earlier onset of acute otitis media. The most likely reason for the observed change is the high rate of day-care attendance (62%) in the cohort study reported by Block and colleagues.

The shift in onset of AOM and the increase in recurrent disease in young children have important implications for the treatment of AOM. Clinical and microbiologic failure is more often observed in children <18 months of age. Carlin identified 40 (14%) treatment failures in a cohort of 293 children; 97% were <18 months of age. Similarly Kaleida et al. observed that a greater proportion of “severely” symptomatic and “non-severe” otitis responded to antimicrobial therapy in children 2 years of age and older compared with infants <2 years of age. The likely explanation for these observations is the naivete of the immune system in infants, the relative horizontal nature of the Eustachian tube and possibly the difference in pharmacokinetics achieved with standard dosing of antimicrobial agents in young infants.

Studies of the microbiology of AOM continue to demonstrate S. pneumoniae, nontypable Haemophilus influenzae (NTHI) or Moraxella catarrhalis in 70% of cultures of middle ear fluid from symptomatic children. In a prospective study of children, these pathogens were identified in 26, 23 and 23% of episodes respectively from infants with AOM <2 years of age. Gehanno reviewed all middle ear samples collected over the 10-year period 1987–1997. NTHI (40%) and S. pneumoniae (31%) were the predominant pathogens; M. catarrhalis was isolated from only 8% of cases. In Finland, when M. catarrhalis was isolated it was most often from children <6 months of age. NTHI was more frequently recovered from children with recurrent disease (≥3 episodes) than from initial episodes. Group A Streptococcus, although rare in children <2 years of age, is recovered with some frequency from children >5 years of age with AOM.

Longitudinal surveillance of resistance to beta-lactams, macrolides and trimethoprim-sulamethoxazole among isolates of S. pneumoniae demonstrates decreasing susceptibility to specific agents, increasing prevalence of multidrug-resistant isolates and evolving mechanisms of resistance. Recent studies of antimicrobial susceptibility from the United States and Finland document the increase in isolates of S. pneumoniae with multi-drug resistant phenotype. In the United States isolates resistant to two classes of antimicrobial agents increased from 8.5% to 10.5% and those with three or more increased from 6.2% to 12.5% in the 4-year period of 1996 to 2000. In Finland in 2000, 40% of isolates with reduced susceptibility to penicillin demonstrated resistance to erythromycin, trimethoprim-sulamethoxazole and tetracycline as well. More than 50% of isolates with reduced susceptibility to penicillin contained one of two genetic markers for macrolide resistance (ribosomal methylase or macrolide efflux) and demonstrated reduced in vitro susceptibility to the macrolides.

Two studies have documented a reduction in episodes of otitis media and pneumococcal otitis media in children given a pneumococcal conjugate vaccine (PCV) at 2, 4 and 6 months followed by a booster at 12 to 15 months of age. In the first study, with the use of clinical endpoints an almost 8% reduction in episodes of AOM were observed in a cohort immunized with a seven valent pneumococcal conjugate vaccine (PCV7). In the Finnish Otitis Media study a reduction in acute otitis media caused by vaccine and vaccine-related serotypes as well as an overall reduction in pneumococcal otitis media was demonstrated with the use of microbiologic endpoints (Table 1). However, the sample size in this study was not large enough to demonstrate an overall reduction in all episodes of AOM as a modest increase in disease caused by nonvaccine serotypes of S. pneumoniae and a possible increase in NTHI disease blunted the overall effect.

The efficacy observed by Eskola for reduction in type specific AOM was not as large as that observed by Black for invasive pneumococcal diseases. Several reasons are likely to contribute to this observation. (1) The spectrum of serotypes isolated from the middle ear in children is broader than that observed for invasive pneumococcal diseases. Thus the vaccine would be expected to prevent a smaller proportion of total pneumococcal AOM. (2) Antibody concentrations in the middle ear are likely to be smaller than those in plasma and therefore may be less effective. This hypothesis is supported by the observation that disease
caused by serotype 19F was reduced only 25% in PCV recipients compared with controls. However, in a concurrent study with primary immunization with pneumococcal conjugate vaccine using outer membrane protein from *Neisseria meningitidis* and a booster with pneumococcal polysaccharide vaccine, higher serum concentrations of antibody against serotype 19F were observed, and increased efficacy against type 19F AOM was suggested. The PCVs are sufficiently immunogenic in young children that a reduction in nasopharyngeal colonization with vaccine and cross-reactive serotypes is observed in both immunized children and children living in the same household. However, an increase in colonization with nonvaccine serotypes is also observed. The increase in nasopharyngeal colonization with nonvaccine serotypes provides an understanding for the increase in episodes of AOM caused by nonvaccine serotypes observed in the Finnish study.

**CLINICAL RELEVANCE OF ANTIBIOTIC RESISTANCE IN AOM**

The early clinical outcome (Days 3 to 5) of AOM correlates with eradication of bacterial pathogens in the middle ear. Lessons from experimental animal models, pharmacokinetic and pharmacodynamic evaluation of antibiotics and the results of “double tap” studies where tympanocentesis is performed at initiation of antimicrobial therapy and at 3 to 6 days later to determine the pathogen in the middle ear and its susceptibility demonstrate that isolates of otopathogens with decreased susceptibility are less likely to be eradicated from the middle ear. Recent studies by Dagan suggest that failure to sterilize the middle ear is also associated with poor clinical outcome at Days 12 to 14.

Dagan has demonstrated persistence of middle ear infection when the pharmacokinetic/pharmacodynamic (PK/PD) parameters necessary to achieve sterilization are not fulfilled. Beta-lactam and trimethoprim-sulfamethoxazole require the drug concentration in the middle ear to exceed the MIC for that specific pathogen for at least 40% of the dosing interval. Efficacy for azalides (azithromycin) and fluoroquinolones correlate with the ratio of area under the curve (AUC) to MIC. Although these principles are widely accepted, debate persists regarding whether intracellular or extracellular concentrations of antibiotics are most relevant. Table 2 identifies time over MIC or AUC/MIC ratio achieved for selected antimicrobials for susceptible and resistant (MIC ≥ 2 µg/ml for penicillin), pneumococci and beta-lactamase-negative and -positive isolates of NTHI. Increasing the dose of antibiotics administered has been one strategy suggested to overcome emerging resistance. However, it is necessary to understand the mechanism of resistance and the population distribution of MICs for a specific pathogen to predict whether such a strategy is likely to be successful. For example amoxicillin in standard dosage (13 mg/kg/dose three times daily) achieves peak middle ear concentrations of ~1 µg/ml. When amoxicillin is administered at 45 mg/kg/dose twice daily, the peak middle ear concentration increases to 5 µg/ml. For isolates of NTHI the MIC₉₀ increases from 0.5 µg/ml to ≥16 µg/ml in the presence of beta-lactamase production. Thus it is evident that increasing the dose of amoxicillin will not be successful for a beta-lactamase-producing nontypable *H. influenzae*. In contrast the MIC₉₀ for amoxicillin-resistant *S. pneumoniae* increases from 0.03 µg/ml to 2.0 µg/ml. Thus resistant isolates of *S. pneumoniae* are within the achievable PK/PD indices when higher doses of amoxicillin are administered. Table 2 summarizes the achievable time over MIC or AUC/MIC ratio for selected antimicrobial agents and predicts whether sterilization for resistant isolates is likely or unlikely.
The pathogenesis of AOM usually involves concurrent respiratory viral infection in the presence of nasopharyngeal colonization with potential otopathogens resulting in invasion of the middle ear space. Without vaccines that prevent upper respiratory viral infections, especially those caused by respiratory syncytial virus, influenza and parainfluenza and nasopharyngeal colonization with otopathogens, AOM is likely to continue as the most common bacterial infection in childhood. The shift in epidemiology to younger children with frequent episodes and the presence of otopathogens with resistance or reduced susceptibility to current antimicrobial agents has the potential to increase the proportion of children who fail to respond to antimicrobial therapy. Resistance among otopathogens varies by geography, age group and season. Introduction of PCV7 is likely to have some beneficial effect on the proportion of resistant S. pneumoniae isolates by decreasing carriage of vaccine and vaccine-related serotypes. In a 1996 to 1999 collection of pneumococcal isolates of S. pneumoniae obtained from middle ear culture, Joloba et al.\textsuperscript{29} found that amoxicillin resistance was identified in 6% and azithromycin resistance in 3% of 30 nonvaccine serotype isolates of S. pneumoniae compared with almost 23 and 54% of vaccine serotypes, respectively. Thus replacement of vaccine by nonvaccine serotypes will decrease the proportion of resistant isolates at least in the short term. Second, with the universal immunization of children <2 years of age with PCV7 for the prevention of invasive diseases, presumably fewer febrile children will receive presumptive antibiotic therapy and the selective pressure for the emergence of resistance will decrease.

The current approach to otitis media continues to be identification of children at high risk for disease caused by resistant otopathogens.\textsuperscript{30} High risk features for AOM caused by resistant otopathogens include recent antibiotic therapy, especially those currently failing therapy or having just completed therapy, disease in late winter, a community with a high prevalence of antibiotic resistance, age <2 years and day care. The specific treatment of the previous episode should also be considered. Leibovitz et al.\textsuperscript{31} demonstrated that children either currently taking or recently completing amoxicillin therapy are likely to have disease caused by a beta-lactamase-producing NTHI as a cause of or relapse. Dagan et al.\textsuperscript{32} observed that disease caused by a resistant S. pneumoniae might emerge during the course of successful treatment of AOM caused by a susceptible pathogen.

The CDC’s working group recommendation for the treatment of AOM would appear to remain appropriate until changes in the prevalence of resistant isolates in the community have been documented.\textsuperscript{30} These recommendations are based on clinical studies demonstrating efficacy for both high dose Augmentin (80 to 90/kg/day for 10 days) and ceftriaxone (50 mg/kg/day for 3 days) for disease caused by beta-lactamase-producing NTHI or drug-resistant S. pneumoniae.\textsuperscript{24, 33} In addition the CDC recommendation includes cefuroxime to which cefoxime and cefdinir can be added. The PK/PD profile of these three cephalosporins suggests good activity against all NTHI and against susceptible and many penicillin-intermediate isolates of S. pneumoniae.\textsuperscript{34} However, none of the three is likely to sterilize the middle ear when penicillin-resistant isolates (MIC ≥ 2.0 µg/ml) are present.

Azithromycin is likely to be effective for children at low risk for disease caused by a resistant otopathogen. Its activity against H. influenzae is insufficient to demonstrate rapid sterilization of the middle ear; however, animal studies suggest a reduction in the density of middle ear disease.\textsuperscript{35} The precise clinical significance of this observation requires further clarification.

Continued evolution of the resistant mechanisms in pediatric respiratory pathogens is a challenge to the medical community. Emerging resistance of S. pneumoniae to fluoroquinolones has been reported.\textsuperscript{36} At the same time initial data on the PK/PD in children and

### TABLE 2. Time above MIC or AUC\textsubscript{24}:MIC ratio for selected antimicrobial agents and otopathogens\textsuperscript{a,b, 22, 26}

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Staphylococcus pneumoniae (%)</th>
<th>Haemophilus influenzae</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pen-S</td>
<td>Pen-R</td>
</tr>
<tr>
<td>Amoxicillin (45 mg/kg/day)</td>
<td>85</td>
<td>40</td>
</tr>
<tr>
<td>Amoxicillin (90 mg/kg/day)</td>
<td>85</td>
<td>60</td>
</tr>
<tr>
<td>Amoxicillin/clavulanate (90 mg/kg/day)</td>
<td>85</td>
<td>60</td>
</tr>
<tr>
<td>Ceftriaxone (50 mg/kg/day)</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Cefuroxime (30 mg/kg/day)</td>
<td>60</td>
<td>30</td>
</tr>
<tr>
<td>Cefprozil (30 mg/kg/day)</td>
<td>80</td>
<td>20</td>
</tr>
<tr>
<td>Cefixime (8 mg/kg/day)</td>
<td>80</td>
<td>0</td>
</tr>
<tr>
<td>Azithromycin\textsuperscript{b} (10 mg/kg on Day 1; 5 mg/kg on Days 2–5)</td>
<td>50</td>
<td>&lt;1\textsuperscript{b}</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Efficacy is associated with ≥40% time over AUC for beta-lactams or AUC:MIC ≥25 for azithromycin.

\textsuperscript{b} AUC\textsubscript{24}:MIC (area under the curve is a measure of antibiotic concentrations in plasma during a 24-h period), approximate value.

\textsuperscript{‡} For isolates resistant to both penicillin and erythromycin.

BI (−), beta-lactamase-negative; BI (+), beta-lactamase-producing.
eradication of middle ear otopathogens by gatifloxacin was presented at the 41st Interscience Conference on Antimicrobial Agents and Chemotherapy. \textsuperscript{37, 38} Advanced generation macrolides (ketolides) are in development. These agents are active against azithromycin-resistant isolates of pneumococci, suggesting that in the near future additional antimicrobial agents effective against the currently evolving otopathogens will be available. For the long term, effective vaccines that target respiratory viruses and at least the two major bacterial otopathogens will be necessary to reduce the burden of middle ear disease in children.

REFERENCES


