Microbiology, Antimicrobial Susceptibility, and Antibiotic Treatment

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Introduction

Otitis media (OM) is caused by respiratory virus and/or bacterial infection of the middle ear space and the resulting host response to infection [1]. Acute otitis media (AOM) occurs most frequently as a consequence of viral upper respiratory tract infection (URTI) [2–4], which leads to eustachian tube inflammation/dysfunction, negative middle ear pressure, and movement of secretions containing the URTI-causative virus and pathogenic bacteria in the nasopharynx into the middle ear cleft. By using comprehensive and sensitive microbiologic testing, bacteria and/or viruses can be detected in the middle ear fluid (MEF) in up to 96 % of AOM cases (e.g., 66 % bacteria and viruses together, 27 % bacteria alone, and 4 % virus alone) [5]. Studies using less sensitive or less comprehensive microbiologic assays have yielded less positive results for bacteria and much less positive results for viruses [6–8].

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Microbiology

Virus

Epidemiologic studies have shown a strong relationship between viral upper respiratory infections (URIs) and AOM. Chonmaitree et al. reported that 63 % of 864 URI episodes of children less than 4 years of age in the USA were positive for respiratory viruses and adenovirus, coronavirus, and respiratory syncytial virus (RSV) frequently related to AOM [4].

In children with AOM in Japan, respiratory viruses were detected in 35 % of patients ($n = 1092$). RSV, influenza virus, and adenovirus were of the most common viruses [9]. Grieves et al. [10, 11] studied RSV pathogenesis in chinchillas to investigate how viral URI leads to AOM. After nasal RSV challenge, viral replication was seen from the site of inoculation to the pharyngeal orifice of the eustachian tube by 48 h, and the virus could be detected in the distal part of the eustachian tube after 5 days.

RSV and adenoviruses are still among the most important viruses associated with AOM. In a prospective, longitudinal study of children younger than 4 years in the USA, 63 % of 864 URI episodes were positive for respiratory viruses; rhinovirus and adenovirus were most frequently detected [4]. Of URI caused by a single virus, the rate of AOM complicating URI was highest in the episodes caused by adenovirus, coronavirus, and RSV.

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Molecular technologies have made it possible to detect new respiratory viruses related with AOM. Human metapneumoviruses (hMPV) were discovered a decade ago, and are now recognized as an important pathogen causing lower respiratory tract infection and URTIs in children. In a cohort of 1338 children with respiratory symptoms, hMPV was detected in 3.5 % of the children, and 41 % of infections were complicated by AOM [12]. The incidence of hMPV was highest in children younger than 2 years (7.6 %); 61 % of children younger than 3 years of age had hMPV infections complicated by AOM.

Human bocavirus (hBoV) was discovered in 2005; to date, the significance of hBoV in causing symptomatic illness is still controversial. hBoV occurs frequently in conjunction with other viruses and seems to persist for a long time in the respiratory tract. In asymptomatic children, hBoV has been detected from respiratory specimens at an alarmingly high rate (43–44 %) [13, 14]. In children with AOM, Beder et al. [15] have reported an hBoV detection rate of 6.3 % from nasopharyngeal secretions (NPS) and 2.7 % from MEF. The resolution time of AOM was longer, and the rate of fever was higher in children with hBoV. The virus has also been detected from 3 % of the MEFs from young children with otitis media with effusion (OME) [16]. The role of this virus in AOM and OME requires further investigation.

The new and old picornaviruses have also been studied in association with AOM. In young children with AOM, a new rhinovirus, human rhinovirus species C (HRV-C), was detected in almost half of the rhinovirus-positive NPS and MEF samples [17].

In a study of 495 children with AOM in Japan, Yano et al. [18] found 12 (2.4 %) cases with cytomegalovirus (CMV) infection; five of these cases (3–25 months of age) were primary CMV infection or reactivation documented by immunoglobulin M (IgM) serology [18]. Four of these five had CMV or viral nucleic acids in the MEF; two of five had no bacteria cultured from the MEF. The investigators suggested the role of CMV in AOM etiology. Similar findings have previously been reported. Because CMV is a rare cause of viral URI in young children, it is likely that the contribution of this virus to AOM is limited although possible.

Viral–Bacterial Interactions

Pathogenesis of AOM involves complex interactions between viruses and bacteria; acute viral infection of the nasopharynx creates the environment that promotes the growth of pathogenic bacteria, which already colonize the nasopharynx and promote their adhesion to the epithelial cells and invasion into the middle ear.

Symptoms of viral URTIs usually last for a week, and viral shedding from the nasopharynx may last 3 weeks or longer. Studies of viral persistence in the nasopharynx, viral transmission, and asymptomatic infections have become more important in understanding the pathogenesis of URI and AOM. Viral infections from the upper respiratory tract usually induce major or minor damages of respiratory mucosa following the promotion of the growth of pathogenic bacteria in the nasopharynx, the enhancement of bacterial adhesion to the epithelial cells, and the eventual invasion into the middle ear causing AOM.

Ishizuka et al. reported that rhinovirus infecting cultured human airway epithelial cells stimulated *Streptococcus pneumoniae* adhesion to airway epithelial cells via increases in platelet-activating receptor (PAF-R) [19]. Increased adherence of *S. pneumoniae* may be one of the reasons that AOM or pneumonia develops after rhinovirus infections by inducing surface expression of PAF-R, a receptor for *S. pneumoniae* [20, 21]. In a mouse model, Sendai virus coinfection with *S. pneumoniae* and *Moraxella catarrhalis* increased the incidence rate, duration of AOM, and bacterial load [22].

In the human study, the detection of rhinovirus or adenovirus in the nasopharynx was positively associated with the presence of *Haemophilus influenzae* (aboriginal children) and *M. catarrhalis* (aboriginal and nonaboriginal children). However, adenovirus was negatively associated with *S. pneumoniae* in aboriginal children [23]. To-

mochika et al. reported from Japan that 31% of hospitalized children with RSV had AOM [24].

RSV nasal inoculation in chinchillas reduced the expression of the antimicrobial peptide chinchilla b-defensin 1 and increased the load of *H. influenzae* in the nasopharynx [25]. Infection of the airway with a respiratory virus downregulates the expression of b-defensin, which increases the nasopharyngeal colonization with *H. influenzae* and further promotes the development of AOM.

Bacteriology

The gold standard in determining the etiology of bacterial OM is the culture of MEF. In order to determine the OM bacteriology, the culture of MEF is recovered by tympanocentesis, drainage from tympanostomy tubes, or spontaneous otorrhea. These determinations are important to track changes in the distribution of pathogens that cause OM.

Bacteria are found in 50–90% of cases of AOM with or without otorrhea [26]. *S. pneumoniae*, nontypeable *H. influenzae* or *M. catarrhalis* are the leading causative pathogens responsible for AOM, and they frequently colonize in the nasopharynx [26]. *Streptococcus pyogenes* (group A β-hemolytic streptococci) accounts for less than 5% of AOM cases. The proportion of AOM cases with pathogenic bacteria isolated from the MEF varies depending on bacteriologic techniques, transport issues, and stringency of AOM definition. In series of reports from the USA and Europe from 1952–1981 and 1985–1992, the mean percentage of cases with bacterial pathogens isolated from the MEFs was 69 and 72%, respectively [26]. A large series from the University of Pittsburgh Otitis Media Study Group reported bacterial pathogens in 84% of the MEFs from 2807 cases of AOM [26]. Studies that applied more stringent otoscopic criteria and/or use of bedside specimen plating on solid agar in addition to liquid transport media have a reported rate of recovery of pathogenic bacteria from middle ear exudates ranging from 85 to 90% [27–29]. When using appropriate stringent diagnostic criteria, careful specimen handling, and sensitive microbiologic techniques, the vast majority of cases of AOM involve pathogenic bacteria either alone or in concert with viral pathogens.

Clinical bacteriology has dramatically changed after the introduction of pneumococcal conjugate vaccine (PCV) [30]. The most commonly identified pathogen is *S. pneumonia,* which, prior to adoption of the 7-valent pneumococcal conjugate vaccine (PCV7), was isolated in approximately one third to half of all cases [30]. Block et al. studied changes of microbiology after the community-wide vaccination with PCV7 [31]. Comparing each cohort (1992–1998 vs. 2000–2003), the proportion of *S. pneumoniae* significantly decreased from 48 to 31%, and nontypable *H. influenzae* significantly increased from 41 to 56%. Post-PCV7, Gram-negative bacteria and beta-lactamase-producing organisms accounted for two thirds and one half of all AOM isolates, respectively. In terms of serotypic change in *S. pneumoniae,* vaccine efficacy of PCV7 against vaccine-serotype pneumococcal OM was about 60%. A later report [32] with data from 2007 to 2009, 6–8 years after the introduction of PCV7 in the USA, showed that PCV7 strains of *S. pneumoniae* virtually disappeared from the MEF of children with AOM who had been vaccinated. However, the frequency of isolation of non-PCV7 serotypes of *S. pneumoniae* from the MEF overall increased; this has made isolation of *S. pneumoniae* and *H. influenzae* of children with AOM nearly equal. In summary, the licensed 7-valent CRM197-PCV7 has modest beneficial effects in healthy infants with a low baseline risk of AOM. Administering PCV7 in high-risk infants, after early infancy and in older children with a history of AOM, appears to have no benefit in preventing further episodes.

Serotype 19A was a major cause of replacement disease following introduction of PCV7 [32–34]. Over the past decade, serotype 19A emerged as a major cause of acute OM, recurrent OM, and severe mastoiditis [32–34]. The increase in 19A was often attributed to introduction of PCV7. However, Dagan et al. [35] described the emergence of serotype 19A as a cause of OM prior to the introduction of PCV7 in Israel. Analysis of antibiotic administration patterns

suggests that antibiotic use may contribute to the emergence of certain lineages of *S. pneumoniae* [36, 37].

In 2010, a pneumococcal vaccine with 13 serotypes (1, 3, 4, 5, 6A , 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F) conjugated to diphtheria protein was licensed. PC-13V utilizes the same protein carrier as vaccine PC-7V, and was released in the United States by the FDA on the basis of immunogenicity and safety studies. Safety was evaluated by means of 13 controlled studies involving thousands of healthy children. It is still early to evaluate the true benefit of PVC 13, and numerous trials are under development. PC-13V is recommended for all children between 2 and 59 months of age and those between 5 and 6 years with risk factors for severe pneumococcal disease. The vaccine is applied in 4 doses at 2, 4, 6 and 12 months of age.

Currently, several RCTs with different (newly licensed, multivalent) PCVs administered during early infancy are ongoing to establish their effects on AOM. Results of these studies may provide a better understanding of the role of the newly licensed, multivalent PCVs in preventing AOM.

In a study of tympanocentesis over four respiratory tract illness seasons in a private practice, the percentage of *S. pneumoniae* initially decreased relative to *H. influenzae*. In 2005–2006 ($N=33$), 48% of bacteria were *S. pneumoniae*, and 42% were *H. influenzae*. For 2006–2007 ($N=37$), the percentages were equal at 41%. In 2007–2008 ($N=34$), 35% were *S. pneumoniae*, and 59% were *H. influenzae*. In 2008–2009 ($N=24$), the percentages were 54% and 38%, respectively, with an increase in intermediate and nonsusceptible *S. pneumoniae* [38]. Data on nasopharyngeal colonization from PCV7-immunized children with AOM have shown continued presence of *S. pneumoniae* colonization. Revai et al. [39] showed no difference in *S. pneumoniae* colonization rate among children with AOM who have been unimmunized, underimmunized, or fully immunized with PCV7. In a study during a viral URTI, including mostly PCV7-immunized children (6 months to 3 years of age), *S. pneumoniae* was detected in 45.5% of 968 nasopharyngeal swabs, *H. influenzae* was detected in 32.4%, and *M. catarrhalis* was detected in 63.1% [40]. Data show that nasopharyngeal colonization of children vaccinated with PCV7 increasingly is caused by *S. pneumoniae* serotypes not contained in the vaccine [41–44]. With the use of the recently licensed 13-valent pneumococcal conjugate vaccine (PCV13) [45], the patterns of nasopharyngeal colonization and infection with these common AOM bacterial pathogens will continue to evolve.

Investigators have attempted to predict the type of AOM pathogenic bacteria on the basis of clinical severity, but the results have not been promising. *S. pyogenes* has been shown to occur more commonly in older children [46] and cause a greater degree of inflammation of the middle ear and tympanic membrane (TM), a greater frequency of spontaneous rupture of the TM, and more frequent progression to acute mastoiditis compared with other bacterial pathogens [46–48]. As for clinical findings in cases with *S. pneumoniae* and nontypeable *H. influenzae*, some studies suggest that signs and symptoms of AOM caused by *S. pneumoniae* may be more severe (fever, severe earache, bulging TM) than those caused by other pathogens [29, 49, 50]. These findings were refuted by results of the studies that found AOM caused by nontypeable *H. influenzae* to be associated with bilateral AOM and more severe inflammation of the TM [51, 52]. Leibovitz et al. [53] concluded, in a study of 372 children with AOM caused by *H. influenzae* ($N=138$), *S. pneumoniae* ($N=64$), and mixed *H. influenzae* and *S. pneumoniae* ($N=64$), that clinical/otologic scores could not discriminate among various bacterial etiologies of AOM. However, there were significantly different clinical/otologic scores between bacterial culture-negative and culture-positive cases. A study of middle ear exudates of 82 cases of bullous myringitis has shown a 97% bacteria-positive rate, primarily *S. pneumoniae*. In contrast to the previous belief, *Mycoplasma* sp. is rarely the causative agent in this condition [54]. Accurate prediction of the bacterial cause of AOM on the basis of clinical presentation, without bacterial culture of the middle ear exudates, is not possible, but specific

etiologies may be predicted in some situations. Published evidence has suggested that AOM associated with conjunctivitis (otitis-conjunctivitis syndrome) is more likely caused by nontypeable *H. influenzae* than by other bacteria [55–57].

M. catarrhalis is derived from the upper respiratory tract [58]. High rate of spontaneous clinical resolution occurs in children with AOM attributable to *M. catarrhalis* [59, 60]. AOM attributable to *M. catarrhalis* rarely progresses to acute mastoiditis or intracranial infections [61, 62].

Substantial geographic variability is observed in the proportion of OM caused by *M. catarrhalis*. For example, the rate of *M.catarrhalis* in Israel is low, whereas in Finland this microorganism is the most common bacterial cause of recurrent OM in children with tympanostomy tubes [63, 64]. As the distribution of pathogens changes with widespread use of PCVs, the relative proportion of OM due to *M. catarrhalis* is increasing in some studies [65, 66].

Polymicrobial Interactions

A murine model of nasal colonization and AOM to study relationships among various combinations of bacterial OM pathogens (*S. pneumoniae*, *H. influenzae*, and *M. catarrhalis*) and Sendai virus, which is the murine equivalent of human parainfluenza virus has been reported by Krishnamurthy et al. [22]. As expected, viral infection significantly increased the incidence of acute OM. Coinfections with *S. pneumoniae* and *M. catarrhalis* increased the incidence and duration of pneumococcal OM compared with *S. pneumoniae* alone and *S. pneumoniae* and *H. influenzae* together.

Host competition may also affect the selection of virulence characteristics in *S. pneumoniae* [67]. A combination of theoretical models and in vivo nasopharyngeal colonization experiments was used to demonstrate that competition with *H. influenzae* may select for more virulent strains of *S. pneumoniae*.

Taken as a whole, the studies indicated that the specific combination of colonizing bacteria and respiratory viruses can alter the incidence and duration of OM, and pneumococci have several methods to compete with co-colonizing and coinfecting species.

Implications of Bacterial Vaccine Efforts for Practice

The recurrent nature of acute otitis media continues to be burdensome to children and families, especially those who suffer from frequent recurrences and in disadvantaged populations where disease progresses to chronic suppurative otitis media with associated impacts on hearing loss and educational potential. PC-7V has reduced the burden of vaccine-serotype disease as well as shifted the pneumococcal serotypes carried in the nasopharynx toward those with lower disease-causing potential. Antibiotic resistance remains a challenge to successful therapy with ceftriaxone-resistant pneumococci present in the community and increasing emergence of b-lactamase–negative, amoxicillin-resistant NTHi identified globally. The next-generation PC-13V has been introduced, and early data suggest efficacy against invasive pneumococcal disease and carriage of SP19A, the multidrug resistance isolate that has been associated with both treatment failure in AOM 90 and the increasing number of cases of pneumococcal mastoiditis. Promising data on an 11-valent pneumococcal polysaccharide conjugate vaccine with protein D as a carrier was published in 2006, but additional confirmation of efficacy against NTHi otitis media with the licensed formulation, PHiD-CV (a 10-valent conjugate), is pending data future studies. For NTHI specifically, a number of candidate protein antigens have had progress to human trials since 2007, remains to be demonstrated. Multiple candidates have demonstrated the necessary requirements for candidate vaccine antigens: conservation among isolates, surface exposure, immunogenicity in animals, and protection in animal models of disease or specifically experimental otitis media. Further research of the role of each antigen in the pathogenesis of disease, to elicit response in the youngest infants is likely to

be productive and permit more antigens to move into clinical trials.

Bacterial Susceptibility to Antibiotics

Selection of antibiotic to treat AOM is based on the suspected type of bacteria and antibiotic susceptibility pattern, although clinical pharmacology and clinical and microbiologic results and predicted compliance with the drug are also taken into account. Early studies of AOM patients show that 19% of children with *S. pneumoniae* and 48% with *H. influenzae* cultured on initial tympanocentesis who were not treated with antibiotic cleared the bacteria at the time of a second tympanocentesis 2–7 days later [68]. Approximately 75% of children infected with *M. catarrhalis* experienced bacteriologic cure even after treatment with amoxicillin, an antibiotic to which it is not susceptible [59, 60].

Antibiotic susceptibility of major AOM bacterial pathogens continues to change, but data on middle ear pathogens have become scanty because tympanocentesis is not generally performed in studies of children with uncomplicated AOM. Most available data come from cases of persistent or recurrent AOM. Current US data from a number of centers indicate that approximately 83 and 87% of isolates of *S. pneumoniae* from all age groups are susceptible to regular (40 mg/kg/day) and high-dose (80–90 mg/kg/day divided twice daily) amoxicillin, respectively [69–73]. Pediatric isolates are smaller in number and include mostly ear isolates collected from recurrent and persistent AOM cases with a high percentage of multidrug-resistant *S. pneumoniae*, most frequently nonvaccine serotypes that have recently increased in frequency and importance [37].

The definitions of resistance are the minimum inhibitory concentration (MIC) breakpoints set by the Clinical and Laboratory Standards Institute (CLSI). CLSI has established a new approach to penicillin breakpoints [74], and this approach is needed to guide appropriate treatment because it takes into account whether penicillin is given orally or parenterally, and whether the patient has meningitis. The revised penicillin breakpoints are for infections other than meningitis. Currently, the studies of AOM use the new oral penicillin breakpoints and define all isolates with a penicillin MIC of $\leq$2.0 μg/mL as penicillin nonsusceptible *S. pneumoniae* (PNSP), or use an MIC of 4.0 μg/mL to define penicillin-intermediately resistant *S. pneumoniae* (PISP), and $\geq$8.0 μg/mL to define penicillin-resistant *S. pneumoniae* (PRSP).

High-dose amoxicillin will yield MEF levels that exceed the MIC of all *S. pneumoniae* serotypes that are intermediately (penicillin MIC 4.0 μg/mL) and, many but not all, highly resistant serotypes (penicillin MIC$\geq$8.0 μg/mL) for a longer period of the dosing interval and has been shown to improve bacteriologic and clinical efficacy compared with the regular dose [75, 76]. Hoberman et al. [77] reported superior efficacy of high-dose amoxicillin/clavulanate in eradication of *S. pneumoniae* (96%) from the middle ear at days 4 to 6 of therapy compared with azithromycin.

The antibiotic susceptibility pattern for *S. pneumoniae* is expected to continue to evolve with the use of PCV13, a conjugate vaccine containing 13 serotypes of *S. pneumoniae* [78–80]. Widespread use of PCV13 could potentially reduce diseases caused by multidrug-resistant pneumococcal serotypes and diminish the need for the use of higher dose of amoxicillin or amoxicillin/clavulanate for AOM. Some *H. influenzae* isolates produce β-lactamase enzyme, causing the isolate to become resistant to penicillins. Current data from different studies with non-AOM sources and geographic locations that may not be comparable show that 58–82% of *H. influenzae* isolates are susceptible to regular and high-dose amoxicillin [42, 70, 71, 81]. These data represented a significant decrease in β-lactamase-producing *H. influenzae*, compared with data reported in the 2004 AOM guideline.

Nationwide data suggest that 100% of *M. catarrhalis* derived from the upper respiratory tract are β-lactamase-positive but remain susceptible to amoxicillin-clavulanate [81]. However, the high rate of spontaneous clinical resolution occurring in children with AOM attributable to *M.*

catarrhalis treated with amoxicillin reduces the concern for the first-line coverage for this microorganism [59, 60]. AOM attributable to *M. catarrhalis* rarely progresses to acute mastoiditis or intracranial infections [62, 82, 83].

Antibiotic Therapy

High-dose amoxicillin is recommended as the first-line treatment in most patients, although there are a number of medications that are clinically effective [1]. The justification for the use of amoxicillin relates to its effectiveness against common AOM bacterial pathogens as well as its safety, low cost, acceptable taste, and narrow microbiologic spectrum [59, 75]. In children who have taken amoxicillin in the previous 30 days, those with concurrent conjunctivitis, or those or whom coverage for β-lactamase-positive *H. influenzae* and *M. catarrhalis* is desired, therapy should be initiated with high-dose amoxicillin/clavulanate (90 mg/kg/day of amoxicillin, with 6.4 mg/kg/day of clavulanate, a ratio of amoxicillin to clavulanate of 14:1, given in two divided doses, which is less likely to cause diarrhea than other amoxicillin/clavulanate preparations) [84].

Alternative initial antibiotics include cefdinir (14 mg/kg per day in one or two doses), cefuroxime (30 mg/kg per day in two divided doses), cefpodoxime (10 mg/kg per day in two divided doses), or ceftriaxone (50 mg/kg, administered intramuscularly). It is important to note that alternative antibiotics vary in their efficacy against AOM pathogens. For example, recent US data on in vitro susceptibility of *S. pneumoniae* to cefdinir and cefuroxime are 70–80%, compared with 84–92% amoxicillin efficacy [69–72]. In vitro efficacy of cefdinir and cefuroxime against *H. influenzae* is approximately 98%, compared with 58% efficacy of amoxicillin and nearly 100% efficacy of amoxicillin/clavulanate [81]. A multicenter double tympanocentesis open-label study of cefdinir in recurrent AOM attributable to *H. influenzae* showed eradication of the organism in 72% of patients [85].

For penicillin-allergic children, recent data suggest that cross-reactivity among penicillins and cephalosporins is lower than historically reported [86–89]. The previously cited rate of cross-sensitivity to cephalosporins among penicillin-allergic patients (approximately 10%) is likely an overestimate. The rate was based on data collected and reviewed during the 1960s and 1970s. A study analyzing pooled data of 23 studies, including 2400 patients with reported history of penicillin allergy and 39,000 with no penicillin-allergic history concluded that many patients who present with a history of penicillin allergy do not have an immunologic reaction to penicillin [88]. The chemical structure of the cephalosporin determines the risk of cross-reactivity between specific agents [87, 90]. The degree of cross-reactivity is higher between penicillins and first-generation cephalosporins but is negligible with the second-and third-generation cephalosporins. Because of the differences in the chemical structures, cefdinir, cefuroxime, cefpodoxime, and ceftriaxone are highly unlikely to be associated with cross-reactivity with penicillin [87]. Despite this, the Joint Task Force on Practice Parameters; American Academy of Allergy, Asthma and Immunology; American College of Allergy, Asthma and Immunology; and Joint Council of Allergy, Asthma and Immunology [91] stated that "cephalosporin treatment of patients with a history of penicillin allergy, selecting out those with severe reaction histories, show a reaction rate of 0.1%." They recommend cephalosporin in cases without severe and/or recent penicillin-allergy reaction history when skin test is not available.

Macrolides, such as erythromycin and azithromycin, have limited efficacy against both *H. influenzae* and *S. pneumoniae* [69–72]. Clindamycin lacks efficacy against *H. influenzae*. Clindamycin alone (30–40 mg/kg per day in three divided doses) may be used for suspected PRSP; however, the drug will likely not be effective for the multidrug-resistant serotypes [69, 81, 88].

In the patient who is persistently vomiting or cannot otherwise tolerate oral medication, even when the taste is masked, ceftriaxone (50 mg/kg, administered intramuscularly in one or two sites in the anterior thigh, or intravenously) has been demonstrated to be effective for the initial or repeat antibiotic treatment of AOM [92, 93].

Although a single injection of ceftriaxone is approved by the US Food and Drug Administration (FDA) for the treatment of AOM, results of a double tympanocentesis study (before and 3 days after single-dose ceftriaxone) by Leibovitz et al. [93] suggest that more than one ceftriaxone dose may be required to prevent recurrence of the middle ear infection within 5–7 days after the initial dose.

Initial Antibiotic Treatment Failure

When antibiotics are prescribed for AOM, clinical improvement should be noted within 48–72 h. During the 24 h after the diagnosis of AOM, the child's symptoms may worsen slightly. In the next 24 h, the patient's symptoms should begin to improve. If initially febrile, the temperature should decline within 48–72 h. Irritability and fussiness should lessen or disappear, and sleeping and drinking patterns should normalize [94, 95]. If the patient is not improved by 48–72 h, another disease or concomitant viral infection may be present, or the causative bacteria may be resistant to the chosen therapy.

Some children with AOM and persistent symptoms after 48–72 h of initial antibacterial treatment may have combined bacterial and viral infection, which would explain the persistence of ongoing symptoms despite appropriate antibiotic therapy [96, 97]. Literature is conflicting on the correlation between clinical and bacteriologic outcomes. Some studies report good correlation ranging from 86 to 91 % [98, 99], suggesting continued presence of bacteria in the middle ear in a high proportion of cases with persistent symptoms. Others report that MEF from children with AOM in whom symptoms are persistent is sterile in 42–49 % of cases [100, 101]. A change in antibiotic may not be required in some children with mild persistent symptoms.

In children with persistent, severe symptoms of AOM and unimproved otologic findings after initial treatment, the clinician may consider changing the antibiotic. If the child was initially treated with amoxicillin and failed to improve, amoxicillin/clavulanate should be used. Patients who were given amoxicillin/clavulanate or oral third-generation cephalosporins may receive intramuscular ceftriaxone (50 mg/kg). In the treatment of AOM unresponsive to initial antibiotics, a 3-day course of ceftriaxone has been shown to be better than a 1-day regimen [93].

Although trimethoprim/sulfamethoxazole and erythromycin/sulfisoxazole had been useful as therapy for patients with AOM, pneumococcal surveillance studies have indicated that resistance to these two combination agents is substantial [69, 72, 102]. Therefore, when patients fail to improve while receiving amoxicillin, neither trimethoprimsulfamethoxazole [103] nor erythromycin/sulfisoxazole is appropriate therapy.

Tympanocentesis with culture of MEF should be considered for bacteriologic diagnosis and susceptibility testing when a series of antibiotic drugs have failed to improve the clinical condition. If tympanocentesis is not available, a course of clindamycin may be used, with or without an antibiotic that covers nontypeable *H. influenzae* and *M. catarrhalis*, such as cefdinir, cefixime, or cefuroxime.

Because *S. pneumoniae* serotype 19A is usually multidrug-resistant and may not be responsive to clindamycin [37, 72], newer antibiotics that are not approved by the FDA for treatment of AOM, such as levofloxacin or linezolid, may be indicated [104−106]. Levofloxacin is a quinolone antibiotic that is not approved by the FDA for use in children. Linezolid is effective against resistant Gram-positive bacteria. It is not approved by the FDA for AOM treatment and is expensive. In children with repeated treatment failures, every effort should be made for bacteriologic diagnosis by tympanocentesis with Gram stain, culture, and antibiotic susceptibility testing of the organism(s) present. The clinician may consider consulting with pediatric medical subspecialists, such as an otolaryngologist for possible tympanocentesis, drainage, and culture and an infectious disease expert, before use of unconventional drugs such as levofloxacin or linezolid.

When tympanocentesis is not available, a possible way to obtain information on the middle ear pathogens and their antimicrobial susceptibility is to obtain a nasopharyngeal specimen for bacte-

rial culture. Almost all middle ear pathogens derive from the pathogens colonizing the nasopharynx, but not all nasopharyngeal pathogens enter the middle ear to cause AOM. The positive predictive value of nasopharyngeal culture during AOM (likelihood that bacteria cultured from the nasopharynx is the middle ear pathogen) ranges from 22 to 44% for *S. pneumoniae*, 50–71% for nontypeable *H. influenzae*, and 17–19% for *M catarrhalis*. The negative predictive value (likelihood that bacteria not found in the nasopharynx are not AOM pathogens) ranges from 95 to 99% for all three bacteria [107, 108]. Therefore, if nasopharyngeal culture is negative for specific bacteria, that organism is likely not the AOM pathogen. A negative culture for *S. pneumoniae*, for example, will help eliminate the concern for multidrug-resistant bacteria and the need for unconventional therapies, such as levofloxacin or linezolid. On the other hand, if *S. pneumoniae* is cultured from the nasopharynx, the antimicrobial susceptibility pattern can help guide treatment.

Duration of Therapy

The optimal duration of therapy for patients with AOM is uncertain; the usual 10-day course of therapy was derived from the duration of treatment of streptococcal pharyngotonsillitis. Several studies favor standard 10-day therapy over shorter courses for children younger than 2 years [84, 109–113]. Thus, for children younger than 2 years and children with severe symptoms, a standard 10-day course is recommended. A 7-day course of oral antibiotic appears to be equally effective in children 2–5 years of age with mild or moderate AOM. For children 6 years and older with mild to moderate symptoms, a 5–7-day course is adequate treatment.

Conclusion

The impact of AOM on child health far exceeds the discomfort and suffering associated with individual episodes of disease. AOM is among the largest drivers of antibiotic use in children. Providing support for prevention of the disease is an important strategy for reducing antibiotic prescribing and subsequently the emergence of resistance. AOM and its treatment, and its complications, have a significant economic cost for the society.

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