

## Acute Otitis Media in Children: Current Epidemiology, Microbiology, Clinical Manifestations, and Treatment

Eugene Leibovitz, MD; David Greenberg, MD

An accurate differential diagnosis of AOM is essential for ensuring appropriate treatment, since overdiagnosis of disease is common and antibiotics are not indicated for otitis media with effusion. Although antibiotic therapy is required in only 20-30% of all AOM cases (high rate of spontaneous recovery), most of the patients are treated since this small proportion cannot be quickly and easily identified. The main determinant of the efficacy of antibiotics in AOM is the time that drug concentration at the site of infection exceeds the minimal inhibitory concentration for the pathogen. The major problems encountered in the antibiotic therapy of AOM are the tremendous increase in the resistance to antibiotics of its main pathogens and the lack of tight criteria in the selection of the appropriate antibiotic drugs for the treatment of this disease. The recently published Center for Disease Control and Prevention (CDC) guidelines for the treatment of AOM represent a major step forward in the rational approach to the management of this disease by establishing a clear hierarchy among the various therapeutic agents used in the treatment of simple and complicated AOM. A seven-valent pneumococcal conjugate vaccine recently licensed in the United States for universal immunization of infants <2 years has demonstrated efficacy for prevention of serotype-specific pneumococcal AOM. (*Chang Gung Med J* 2004;27:475-88)

**Key words:** acute otitis media, *Streptococcus pneumoniae*, *Haemophilus influenzae*, antibiotics, resistance, minimal inhibitory concentration.

Acute otitis media (AOM) is the most common bacterial infection in children and represents the main reason for antibiotic therapy and for tympanostomy tubes insertion in children in the United States.<sup>(1,2)</sup> AOM most commonly presents between the ages of 3 months and 3 years, with a peak incidence between 6 and 9 months.<sup>(3)</sup> By one year of age, at least 60% of children have experienced 1 episode and 17% have suffered at least 3 episodes of AOM. The risk for recurrence is related to the age of initial onset; 60% of the children who have had their first episode before the age of 6 months will experience at least two recurrences within the subsequent 2 years.<sup>(2,5)</sup> During the last 2 decades, the incidence of

AOM has increased in the United States, possibly as the result of the increased use of day care.<sup>(6)</sup> Children who attend day care centers experience more upper respiratory infections when compared with children cared in a family home.<sup>(7)</sup> Exposure to environmental tobacco smoke has been implicated as a risk factor for AOM as well as has male gender, a sibling history of recurrent AOM, early disease occurrence, and lack of breast feeding.<sup>(8,9)</sup> A seasonal variation has also been detected in the incidence of AOM, with peaks in the fall and winter, corresponding to a parallel increase in viral respiratory infections, a common trigger for AOM.<sup>(9)</sup> AOM is associated with a substantial economic burden that approaches \$3.8 bil-

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From the Pediatric Infectious Disease Unit, Soroka University Medical Center and the Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer-Sheva, Israel.

Received: Mar. 12, 2004; Accepted: May 21, 2004

Address for reprints: Dr. Eugene Leibovitz, The Pediatric Infectious Disease Unit, Soroka University Medical Center, P.O.B. 151, Beer-Sheva 84101, Israel Tel.: 972-8-6400606; Fax: 972-8-6232334; E-mail: eugenel@bgumail.bgu.ac.il

lion annually in the United States, mainly attributable to the cost of antibiotic therapy.<sup>(10)</sup>

The main bacterial causes of AOM are *Streptococcus pneumoniae*, non-typable *Haemophilus influenzae* and *Moraxella catarrhalis*.<sup>(11-14)</sup> Antibiotics are the standard of care for the treatment of AOM in the United States and many other countries all over the world.<sup>(6,15-18)</sup> Although antibiotic therapy is required in only 20-30% of all cases of AOM (high rate of spontaneous recovery), most of the patients are treated since this small proportion cannot be quickly and easily identified.<sup>(19)</sup> The main goal of antibiotic therapy is to eradicate the causative pathogens from the middle ear fluid (MEF).

### Clinical Presentation and Diagnosis

An accurate differential diagnosis of AOM is essential for ensuring appropriate treatment, since overdiagnosis of disease is common and antibiotics are not indicated for another diagnostic challenging entity, otitis media with effusion, which commonly follows AOM.<sup>(6,20)</sup> Children with AOM typically present with middle ear effusion and rapid onset of symptoms, including persistent severe ear pain, fever, nausea, vomiting, conductive hearing loss and, in young children, diarrhea. These generalized symptoms, however, may be similar to those encountered in upper respiratory infections. In otitis media with effusion, by contrast, children have only asymptomatic middle ear effusion. Children with AOM have otoscopic findings of middle ear inflammation, a bulging tympanic membrane that is opaque with pronounced erythema, and prominent vessels.<sup>(21-23)</sup> The Center for Disease Control and Prevention (CDC) recommend use of of specific diagnostic criteria in order to identify AOM, including 1) the presence of otorrhea of middle ear origin or 2) the presence of MEF and signs of acute local ear inflammation.<sup>(16,23,24)</sup> However, recent reports showed that compliance with recommended diagnostic criteria among community pediatricians is low.<sup>(23)</sup>

The pathogenesis of AOM is typically linked to inflammation and blockage of the eustachian tube.<sup>(25)</sup> The pathologic event in the development of AOM is a viral upper respiratory infection in which pathogens from nasopharynx reach the eustachian tube, causing inflammation, blockage, and negative middle ear pressure. If the eustachian tube remains

compromised, the pathogens proliferate in the middle ear causing AOM. Samples of middle ear secretions from children with AOM in which viruses were isolated revealed viral and bacterial coinfections in up to 65%.<sup>(26)</sup> Among the viruses recovered from the middle ear fluid, the respiratory syncytial virus is the most common, followed by parainfluenza virus, rhinovirus, influenza, enteroviruses and adenoviruses.<sup>(27)</sup> However, bacteria are by far the leading pathogens in AOM and only about 20% of the AOM cases are caused by viral infections alone.<sup>(27)</sup>

### Microbiology and Antimicrobial Resistance

In AOM, the main bacterial isolates are the same as those that typically infect the upper respiratory tract in children. In newborns, the causative pathogens are also those encountered in older age groups while the presence of gram-negative enteric bacilli in the MEF of neonates with AOM is extremely uncommon.<sup>(28)</sup> After the neonatal period, *S. pneumoniae* and non-typable *H. influenzae* occur in 40% or more of the infections.<sup>(6,11-14)</sup> *M. catarrhalis* is the third most common bacterial isolate in AOM (3 to 20%) while *Streptococcus pyogenes* is encountered in 1-5% of cases.

The antibiotic resistance is increasing among the bacterial pathogens causing AOM. The percentage of *S. pneumoniae* strains demonstrating resistance to penicillin and amoxicillin ranges between 30 and 70%.<sup>(29-32)</sup> The proportion of nonsusceptible *S. pneumoniae* isolated from the MEF of children with AOM nonresponsive to initial antibiotic therapy is even higher and may reach 80% or more of all isolates.<sup>(33)</sup> In a recently published multinational study on the prevalence of antimicrobial-resistant pathogens in MEF of children with AOM during 1994-1995, 30% of *S. pneumoniae* isolates were intermediately or fully resistant to penicillin, including 31% in Central and Eastern Europe, 52% in Israel and 21% in the United States.<sup>(14)</sup> In southern Israel, while 15% of *S. pneumoniae* strains isolated from the MEF of children with AOM were nonsusceptible to penicillin in 1992, their number rose to 58% in 1998 and 71% in 1999.<sup>(34-36)</sup> The resistance to macrolides rose from 3% to 10% and the resistance to trimethoprim-sulfamethoxazole (TMP-SMX) increased from 13% to over 50%. The resistance to three antibiotic classes (defined as multi-resistant *S.*

*pneumoniae*) rose from 1% only to 17%.<sup>(34-36)</sup> In some countries in the Asian-Pacific region, such as Taiwan and Korea, the resistance rates to penicillin and macrolide among pneumococci are extremely high.<sup>(37)</sup>

The percentage of beta-lactamase-producing *H. influenzae* and *M. catarrhalis* strains has increased markedly in the last decade, leading to increased resistance to beta-lactam antibiotics. Currently, non-typeable *H. influenzae* is reported to be associated with 17-52% of cases of AOM and it is, in fact, more common or of same order of magnitude with *S. pneumoniae*.<sup>(14,38-40)</sup> In 1997, approximately 30% of the *H. influenzae* isolates examined in USA displayed resistance to amoxicillin, more than 90% of these by beta-lactamase production. Moreover, virtually all strains of *M. catarrhalis* were beta-lactamase positive.<sup>(41)</sup>

The emergence of multidrug-resistant strains, particularly of *S. pneumoniae*, complicates the management of AOM and increases the risk of treatment failure. Resistance among many bacterial species involved in the pathogenesis of AOM continues to increase, at least partially as a result of the inappropriate use of antibiotic therapy.<sup>(42)</sup>

### Nonresponsive Acute Otitis Media

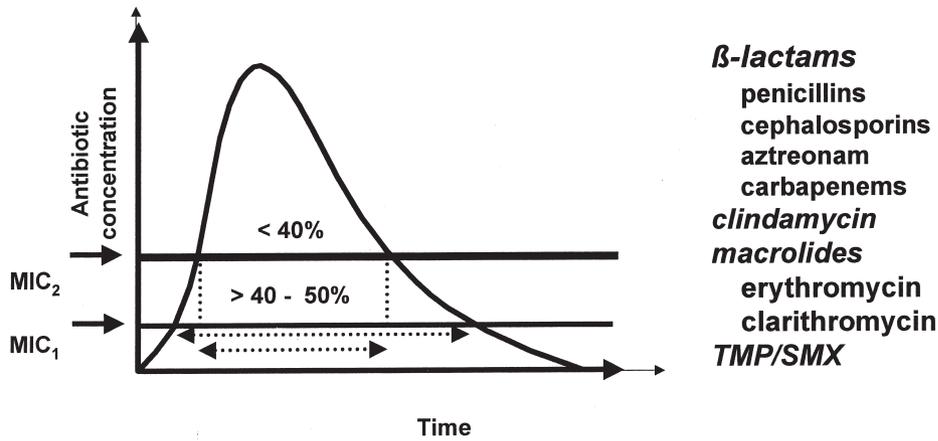
Non-responsive AOM is defined as persistence of both clinical and otoscopic findings of tympanic membrane inflammation after 48-72 hours of antibiotic therapy; it occurs in 10-20% of children initially treated with an antibiotic course. Contributory factors to the development of this entity are low age of patients (<2 years of age), mixed bacterial and viral infection, a history of recurrent episodes of AOM, previous courses of antibiotic therapy and day-care centers attendance. *S. pneumoniae*, and particularly the resistant strains, are found significantly more frequently in the MEF of children with non-responsive AOM and/or having recurrent episodes of AOM.<sup>(13,32,33,39,43,44)</sup> Recent studies demonstrated a high correlation between antibiotic-resistant *S. pneumoniae* strains and the treatment failure: only 14-21% *S. pneumoniae* isolated from patients with non-responsive AOM were susceptible to the antibiotic drug previously prescribed.<sup>(33,44)</sup> However, this trend was not evident for *H. influenzae* isolates: more than 77% of *H. influenzae* isolated from non-responsive AOM patients were susceptible to the previously adminis-

tered antibiotic, according to NCCLS established breakpoints.<sup>(33)</sup>

The etiology of recurrent AOM episodes and the relationship between the original pathogens and those isolated from MEF at AOM relapse were addressed in two recent studies. Leibovitz et al.<sup>(45)</sup> reported that most (71%) recurrent AOM episodes occurred during the first 2 weeks of follow-up after the successful completion (bacterial eradication and clinical improvement or cure at end of therapy) of the antibiotic therapy for the initial AOM episodes. Furthermore, most (72%) recurrent AOM episodes were found to represent new infections and *H. influenzae* was very likely to cause true bacteriologic AOM relapses 14 days or later after completion of therapy. Leibovitz et al.<sup>(46)</sup> reported recently that early recurrent AOM with *S. pneumoniae* was more common in patients in whom this pathogen was present in the nasopharynx of patients at the end of successful therapy for the initial AOM episode compared with those without *S. pneumoniae*. The authors used antibiotic susceptibility studies, serotyping and pulsed field gel electrophoresis in order to compare the nasopharyngeal pneumococcal isolates with those recovered from MEF at recurrence and found that most early recurrent pneumococcal AOM episodes were caused by isolates present in the nasopharynx at the end of therapy for the original AOM episode.

### Pharmacokinetic and Pharmacodynamic Principles

Most of the drugs used for the treatment of AOM belong to the  $\beta$ -lactam and macrolide classes, acting against the AOM pathogens by a time-dependent "killing" mechanism.<sup>(47,48)</sup> The major determinant of their efficacy is the time that drug concentration at the site of infection exceeds the minimal inhibitory concentration (MIC) for the pathogen (Fig. 1). Animal studies have shown that bacterial killing of both Gram-negative and Gram-positive organisms occurs when serum concentrations of ceftriaxone, cefotaxime and ceftazidime exceed the MIC values for 40-50% of the dosing interval.<sup>(49)</sup> An effective dosing regimen for AOM would also require that drug concentration in MEF exceeds the MIC values for the causative pathogens for at least 40-50% of the dosing interval. As a matter of fact, for most peni-



**Fig. 1** Relation of the drug concentration at the site of infection to MIC of the drug to the pathogen. A  $\beta$ -lactam drug (no. 2) that achieves concentration above MIC for <40% of the dosing interval is predicted to have a high rate of failure. Drug no.1, administered against the same organism, will show a high rate of eradication, since its concentration above MIC exceeds 40-50% of the dosing interval.

cillin intermediately-resistant *S. pneumoniae* strains, the only  $\beta$ -lactam drug that exceeds the MIC<sub>90</sub> for an acceptable period of time is amoxicillin, while cefuroxime axetil, cefprozil and cefpodoxime will reach MEF levels above MIC<sub>50</sub> for at least 40% of the dosing interval. For penicillin highly-resistant *S. pneumoniae* strains, only amoxicillin (50 mg/kg/day and particularly 80-90 mg/kg/day dosages) and intramuscular ceftriaxone reach MEF concentrations above MIC values for most of the dosing interval.<sup>(47,48,50)</sup>

The azalides (azithromycin), quinolone and aminoglycoside classes act against AOM pathogens by a "concentration killing mechanism", meaning that bacterial killing is not especially dependent on time above MIC values, but mainly on the ratio between the peak MEF concentration and the MIC of the pathogen, or the ratio AUC (area under the concentration curve)/MIC.<sup>(47-50)</sup> The pharmacokinetic/pharmacodynamic calculations for azithromycin must take into account the extracellular concentrations rather than the total drug MEF concentrations.<sup>(51)</sup> Indeed, this drug rapidly reaches high intracellular concentrations at the expense of low extracellular ones, while the concentrations required for bacterial eradication are the extracellular fluid concentrations, since AOM pathogens such as *S. pneumoniae*, *H. influenzae* or *M. catarrhalis* are mainly extracellular organisms.

#### Clinical Characteristics of AOM Caused by Different Organisms

Previous clinical data suggest that *S. pneumoniae* is more virulent than *H. influenzae* or *M. catarrhalis*, persisting in the MEF of inappropriately treated AOM patients and causing more sequelae and complications than the other 2 pathogens.<sup>(19,52,53)</sup> AOM caused by *S. pneumoniae* was found to be associated with higher fever and more redness of the tympanic membrane than AOM caused by *H. influenzae* or *M. catarrhalis*.<sup>(54)</sup> Furthermore, peripheral white blood cell counts, serum cytokine concentrations and MEF white blood cell counts were significantly higher in AOM caused by *S. pneumoniae* than in AOM caused by *H. influenzae* or *M. catarrhalis*.<sup>(55-57)</sup> However, no differences could be found in the magnitude of the inflammatory process, as measured by the concentrations of various cytokines (TNF- $\alpha$ , IL-1, IL-6 and IL-8) released in the MEF, between AOM caused by *S. pneumoniae*, *H. influenzae*, *M. catarrhalis* or mixed *S. pneumoniae* and *H. influenzae* infections.<sup>(58-61)</sup>

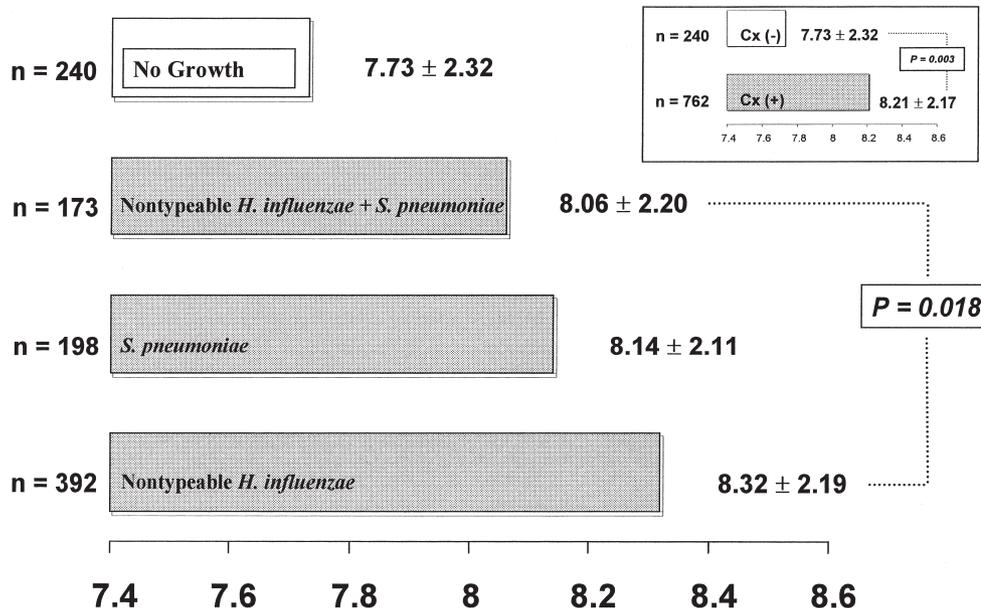
Various combinations of symptoms and signs diagnostic of AOM were used in order to characterize the clinical picture as function of the disease etiology and different clinical scores were composed while looking for a rapid and noninvasive etiologic diagnosis. A clinical score consisting of 9 non-spe-

cific and 4 specific symptoms clinical score (including fever, ear ache, irritability and poor feeding) in children with AOM was not discriminative between AOM cases caused by bacteria, viruses or mixed bacterial and viral etiology.<sup>(62)</sup> However, a bulging ear was significantly more likely to be diagnosed in children with bacterial or bacterial+viral AOM and patients infected with *S. pneumoniae* were more likely to present with fever and a bulging tympanic membrane. A 5-parameters (fever, irritability, ear tugging and tympanic membrane redness and bulging) clinical/otological severity score was used by Leibovitz et al.<sup>(63)</sup> to determine the severity of disease and the impact of various pathogens in 372 children with AOM. The use of this score could not discriminate between the various bacterial AOM etiologies and AOM caused by *H. influenzae* was not found to be a milder disease than that caused by *S. pneumoniae*. In an analysis of the clinical/otological picture of 1,003 children with AOM, Satran et al.<sup>(64)</sup> used a 4-parameter (fever, irritability and tympanic membrane redness and bulging) clinical/otological

score to determine the clinical characteristics of AOM according to specific etiologies, at diagnosis and also during antibiotic therapy. The authors found that the clinical score was significantly higher in culture-positive than in culture-negative patients, but was not helpful in differentiating between AOM caused by *S. pneumoniae*, *H. influenzae* or mixed infection with these 2 pathogens (Fig. 2).

### Treatment of Acute Otitis Media

Antibiotics are considered today as the standard of care for the treatment of AOM in the US and many other countries of the world.<sup>(65)</sup> However, classical AOM antibiotic studies comparing various antibiotics drugs on the basis of symptomatic relief only, were generally performed on small numbers of patients and failed to discern major differences between those drugs in the treatment of AOM. Those studies were most probably affected by the so-called "Polyanna phenomenon" as described by Marchant et al.<sup>(66)</sup> who showed that, due to the high rate of



**Fig. 2** Mean clinical score by culture status at enrollment. The clinical score was based on the temperature measured at enrollment, irritability as reported by parents and bulging and redness of the tympanic membrane as documented by an otolaryngologist unaware of the microbiological findings. For each of these 4 parameters the clinical score could be 0 (normal), 1 (mild), 2 (moderate) or 3 (severe). Maximal severity clinical score was 12.

spontaneous recovery in AOM, drugs with poor antibacterial activity may appear as effective as highly efficacious drugs. Therefore, significant differences in the bacteriologic efficacy will be associated with much smaller differences in clinical outcome and such a clinical difference may be reached in antibiotic studies looking for clinical outcome only by increasing the number of recruited patients to hundreds or even thousands in each comparative study arm. In addition, the "classical" studies suffered from various methodologic problems, such as lack of tight enrollment criteria (unselective inclusion of children with otitis media with effusion associated with a nonspecific intercurrent illness) and by inclusion of a considerable number of children >2 years old who generally were shown to have a milder form of the disease.

An appropriate demonstration of bacteriologic eradication of AOM pathogens can be obtained only by performing randomized comparative antibiotic trials in which a tympanocentesis with MEF culture is performed before antibiotic administration and also during the course of therapy, generally at days 4-6 after initiation of therapy. This method, introduced by Howie and Ploussard 30 years ago<sup>(52,53,67,68)</sup> and named "in vivo sensitivity test", has the advantage of being able, following the enrollment of relatively few patients, to unequivocally discriminate between the efficacy of different drugs used in the treatment of AOM. The same authors demonstrated already more than 3 decades ago major differences in the persistence of different AOM pathogens in the MEF of patients receiving placebo therapy: when a second tympanocentesis was performed on day 2-7, *S. pneumoniae* persisted in 89% of the patients while *H. influenzae* was found in only 52% of cases, suggesting a different spontaneous eradication rate for the different pathogens of AOM.<sup>(67)</sup>

### **Antibiotics Indicated for the Treatment of AOM**

The Centers for Disease Control and the American Academy of Pediatrics published the "Principles of Judicious Use of Antimicrobial Agents for Pediatric Upper Respiratory Infections" in 1998.<sup>(6,16,18)</sup> These recommendations emphasized the importance of distinguishing AOM from otitis media with effusion and prescribing antibiotics only for the

former, minimizing the use of the antibiotics and discerning between first and second-line antibiotics in the treatment of simple uncomplicated AOM vs. nonresponsive/recurrent AOM. Some investigators advocate withholding antibiotic treatment for AOM completely or delaying treatment for 2 days after symptom onset.<sup>(69-71)</sup> Generally, antimicrobial therapy in children with AOM is most beneficial when the antibiotic selection is guided by previous information on the pathogens causing the disease and their susceptibility patterns; when bacterial eradication is used to evaluate treatment outcome; and when the clinical outcome of antibiotic therapy is assessed at 2 or 3 days after completion of therapy, instead of 7 to 14 days.<sup>(16,18)</sup> In addition, young children-under the age of 2 years tend to benefit more from antibiotic treatment than older children.<sup>(20)</sup> It should also be noted that middle ear effusion in AOM may persist for weeks, or even months, after antibiotic therapy has been completed and therefore, in otherwise asymptomatic children with AOM, further antimicrobial therapy is unnecessary.<sup>(72,73)</sup> Short antibiotic courses have been proven to be inferior particularly in the treatment of AOM in children <2 years of age and in those with nonresponsive or recurrent episodes of AOM.<sup>(74)</sup>

Recently accumulated evidence based on double-tympanocentesis studies showed a clear relationship between the MIC values for AOM pathogens of the different antibiotics used in the treatment of this condition and their ability to eradicate these pathogens from MEF.<sup>(34-36,50)</sup> Studies performed since 1955 have shown that the increased resistance observed among the *S. pneumoniae* isolates is associated with a decreased ability of many drugs to eradicate this pathogen from the MEF of patients with AOM.<sup>(34-36,50,75-88)</sup> In addition, results of recent double-tympanocentesis studies performed in southern Israel have shown that cefaclor and azithromycin are in the range of placebo in their ability to eradicate *H. influenzae* following 3-4 days of treatment.<sup>(50,78,79,82,83)</sup> The double-tympanocentesis studies made also possible an evaluation of the correlation between bacteriologic efficacy and clinical outcome in AOM. Carlin et al. were the first who tried to answer this question by reviewing the clinical outcome of bacterial AOM in patients enrolled in studies of antibacterial therapy during 1979-1988. They found an 86% correlation between clinical and bacteriologic

response: 93% of subjects whose infection was eliminated had clinical resolution whereas 37% of those with bacteriologic failure had persistent symptoms or signs of clinical failure.<sup>(89)</sup> Our group investigated the relationship between the bacteriologic and clinical outcome in 123 children treated with various antibiotics and found that clinical failure at day 4-5 of therapy occurred in 37% patients in whom bacteriologic eradication did not occur vs only 3% in patients with bacterial eradication.<sup>(90)</sup> In other words, while 63% of the patients recovered clinically despite lack of MEF eradication, 91% of all cases of clinical failure occurred in those with bacterial persistence at the time of the second tympanocentesis.

#### ***Amoxicillin and amoxicillin/clavulanate***

Because of its efficacy against *S. pneumoniae* and a favorable pharmacodynamic profile, amoxicillin remains the antibiotic of first choice in the treatment of uncomplicated AOM.<sup>(16,18)</sup> The drug displays the longest time above MIC<sub>90</sub> against drug-resistant *S. pneumoniae* of any of the antibiotics approved for the treatment of AOM, is relatively inexpensive and has a long history of safety and efficacy in the treatment of AOM. Standard doses of amoxicillin-40 to 45 mg/kg/day-produce peak MEF concentrations of 1 to 6 µg/mL, a concentration that may fail to eradicate some cases of drug-resistant *S. pneumoniae*. In children with AOM, amoxicillin as 75 mg/kg/day in divided doses produces MEF concentrations of > 1 µg/mL for at least 50% of the dosing interval.<sup>(91)</sup> Recently, our group treated 50 culture-positive AOM patients with high-dose (70-90 mg/kg/day tid for 10 days) amoxicillin and demonstrated eradication rates of 92%, 88% and 62% for *S. pneumoniae*, β-lactamase-negative *H. influenzae* and β-lactamase-positive *H. influenzae*.<sup>(87)</sup> Overall, 14/50 (28%) patients failed bacteriologically on day 4-6, of whom 9 (64%) had β-lactamase-positive *H. influenzae*, suggesting that the amoxicillin high-dose regimen selected for β-lactamase-positive *H. influenzae* as the main organism to be targeted in cases of treatment failure.<sup>(87,92)</sup>

Amoxicillin/clavulanate (Augmentin) is a combination antibiotic containing amoxicillin and clavulanate potassium, a β-lactamase inhibitor which extends the spectrum of amoxicillin against β-lactamase producing bacteria.<sup>(93,94)</sup> Amoxicillin-clavulanate in a dose of 45 mg/kg/day for 10 days was sig-

nificantly more effective than azithromycin against *H. influenzae*, with bacteriological treatment success rates on day 4 to 6 of therapy of 87% versus 39%.<sup>(82)</sup> In addition, there was a trend toward greater efficacy for amoxicillin-clavulanate over azithromycin against *S. pneumoniae* (bacteriological success rates of 90% for amoxicillin-clavulanate versus 68% for azithromycin). Furthermore, AOM signs and symptoms were more likely to resolve completely or improve at end of therapy in all culture-positive patients (86% vs 70%) and in those with *H. influenzae* infections (91% vs 65%) who received amoxicillin-clavulanate compared with those who received azithromycin. In a recent multinational study evaluating the bacteriological and clinical efficacy of high-dose oral amoxicillin/clavulanate (90 mg/kg/day of amoxicillin) in 521 infants and children with AOM, 98% and 94% of all *S. pneumoniae* and *H. influenzae*, respectively, were eradicated while the clinical signs of acute inflammation were completely resolved or improved at end of therapy in 89% of the patients with bacteriologically documented AOM.<sup>(85)</sup>

#### ***Sulfonamide combinations***

Trimethoprim-sulfamethoxazole, a broad-spectrum antimicrobial, may be indicated today only for the treatment of childhood AOM secondary to susceptible strains of *H. influenzae*, including ampicillin-resistant strains, or *S. pneumoniae*.<sup>(95)</sup> The bacteriologic and clinical efficacy of a 10-day regimen of trimethoprim-sulfamethoxazole was recently examined in 54 children with culture-verified AOM.<sup>(86)</sup> The MEF of the 54 children contained a total of 67 organisms: *S. pneumoniae*,<sup>(24)</sup> *H. influenzae*,<sup>(40)</sup> and *S. pyogenes*.<sup>(3)</sup> Pathogens nonsusceptible to trimethoprim-sulfamethoxazole were detected among 63% of the *S. pneumoniae*, 30% of the *H. influenzae*, and 100% of the *S. pyogenes* organisms. Clinical failure was noted in 15% of the patients, with all but one occurring among the bacteriologic failures. These findings question the value of trimethoprim-sulfamethoxazole therapy in regions where bacterial strains resistant to this drug are reported.

#### ***New macrolides***

Compared with erythromycin, these newer agents may provide, at least theoretically, enhanced

MEF concentrations, tissue and leukocyte penetration, and improved gastrointestinal tolerability.<sup>(96,97)</sup> However, as with the other classes of antibiotics, *S. pneumoniae* and *H. influenzae* display increasing resistance to macrolide antibiotics.<sup>(6,13-18,29,31,32,41)</sup> Azithromycin is less active in vitro than erythromycin and clarithromycin against gram-positive organisms involved in AOM, such as *S. pneumoniae*; however, it displays greater in vitro activity against gram-negative pathogens, including *H. influenzae* and *M. catarrhalis*.<sup>(97)</sup> Having as end point the clinical improvement of the middle ear findings, short, 5-day courses of azithromycin appeared initially as effective as other antibiotic regimens in the treatment of upper respiratory infections, including uncomplicated AOM.<sup>(98,99)</sup>

The double-tympanocentesis studies showed that when *S. pneumoniae* was susceptible to azithromycin, the eradication rate approached 100%, but when the organism was macrolide resistant, the drug did not perform better than placebo.<sup>(82,83)</sup> In addition, the eradication rates of *H. influenzae* were poor and close to placebo (~50% efficacy). The poor results in these studies are probably related to the specific pharmacokinetic and pharmacodynamic properties of azithromycin, which may allow the achievement of high drug concentrations in polymorphonuclear cells, but much lower concentrations in the extracellular compartment of the MEF, where the pathogens of AOM concentrate.<sup>(100)</sup> The resistance mechanisms responsible for the resistance against *S. pneumoniae* are related to ribosomal methylase (*ermB* gene), macrolide efflux pump (*mefE* gene) or both.<sup>(101)</sup>

In studies of children with AOM that use clinical outcome as the main end point, clarithromycin has been shown to be as effective as amoxicillin and cefaclor.<sup>(102)</sup>

Prospective, controlled studies on the bacteriologic and clinical efficacy of clindamycin in the treatment of AOM are missing. When deciding to use this drug, the physician should be aware (following a MEF culture) that the AOM episode was caused by *S. pneumoniae*, and timely microbiologic information is not practical in common practice. In addition, if *H. influenzae* or *M. catarrhalis* are suspected, additional coverage for these pathogens would need to be added. Recently, *S. pneumoniae* resistant to macrolides but sensitive to clindamycin

have been described.<sup>(103)</sup> This pattern, named M resistance, was proved to be consistent with a macrolide efflux system.<sup>(103)</sup>

### **Cephalosporins**

Four second-generation cephalosporins - cefaclor, cefprozil, cefuroxime, and loracarbef - are available for the treatment of AOM. The impaired bacteriologic and clinical efficacy of cefaclor against penicillin intermediately-resistant *S. pneumoniae* and particularly against *H. influenzae* has already been proved in double-tympanocentesis studies.<sup>(75-77,79,83)</sup> In addition, cefaclor has been linked, in up to 1.5% of children, to the development of a serum sickness-like reaction characterized by erythema multiforme, arthralgia, and fever.<sup>(104)</sup>

Cefuroxime displays the greatest in vitro activity against penicillin-resistant *S. pneumoniae*, and it is also active against beta-lactamase-producing *H. influenzae* and *M. catarrhalis*. Among oral cephalosporins, cefuroxime-axetil is the only one reaching MEF levels over the MIC values for both *S. pneumoniae* and *H. influenzae* for ~40% of the dosing interval. Cefuroxime-axetil bacteriologic and clinical efficacy has been recently proven in a double-tympanocentesis study.<sup>(75,77)</sup>

Although cefprozil displays acceptable activity against penicillin-resistant *S. pneumoniae*, it is less active against *H. influenzae* and it is hydrolyzed by beta-lactamases.<sup>(105)</sup> Its bacteriologic efficacy has not yet been evaluated in prospective, comparative, double-tympanocentesis studies. Loracarbef is somewhat more active than cefaclor against *H. influenzae* and *M. catarrhalis*, but is less active in vitro against *S. pneumoniae* and particularly against penicillin-intermediate and resistant strains.

Oral third-generation cephalosporins-ceftibuten, cefixime, cefpodoxime, and cefdinir-generally display improved antimicrobial activity and greater stability against many beta-lactamases, when compared with second-generation agents.<sup>(106-109)</sup> In addition, they display longer half-lives and lower peak-serum concentrations, permitting use as once-daily (ceftibuten, cefixime, and cefdinir) or twice-daily (cefpodoxime and cefdinir) regimens. All oral third-generation cephalosporins are quite active against beta-lactamase-producing strains of *H. influenzae* and *M. catarrhalis*,<sup>(75-77)</sup> with ceftibuten displaying the highest activity against *H. influenzae*.<sup>(78)</sup> Their bacterio-

logical efficacy of ceftibuten has yet to be proved in comparative double-tympanocentesis studies.

While a single 50 mg/kg/day ceftriaxone regimen was approved by FDA for the treatment of AOM, we consider that there is no place today for ceftriaxone therapy in the management of simple, uncomplicated AOM, with the exception of the cases of persistent vomiting and lack of compliance with oral drugs. The use of ceftriaxone has to be limited as a second and even third line of therapy for non-responsive AOM.<sup>(6,16,18,34,35)</sup> Recently, a 3-day 50 mg/kg/day ceftriaxone regimen was shown to be significantly superior to a 1-day regimen in the treatment of non-responsive AOM, and this difference was found to be mainly due to the superior eradication rate of resistant *S. pneumoniae* by the 3-day regimen.<sup>(81,84)</sup>

### Quinolones

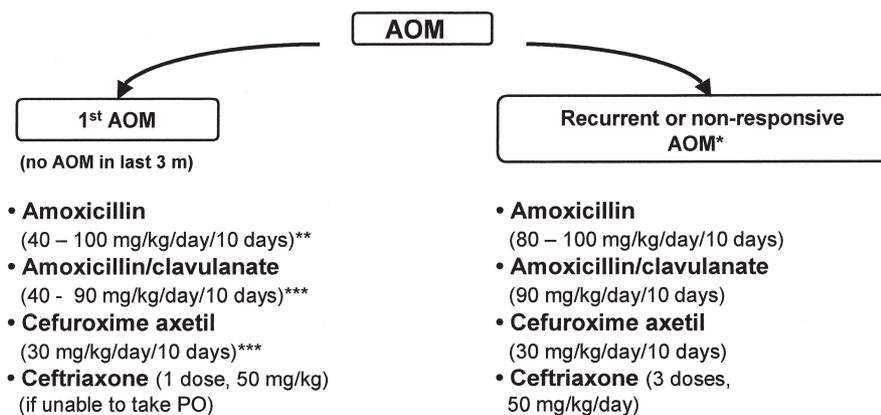
As a result of the growing evidence on their safe use in pediatric patients, the quinolone antibiotics have already been evaluated in various clinical trials in children. The new respiratory fluoroquinolone gatifloxacin is at present time the only representative of this antibiotic class for which data from double-tympanocentesis studies in the treatment of children with recurrent/nonresponsive AOM are available. The drug achieved 100% and 94% eradication rates,

respectively, for *H. influenzae* and *S. pneumoniae* after 4-6 days of therapy and clinical cure/improvement at end of treatment was seen in 90% of the patients.<sup>(88)</sup>

### Current Therapeutic Recommendations

The Drug-resistant *S. pneumoniae* Therapeutic Working Group of the CDC has recently published new guidelines for the treatment of AOM in the present era of pneumococcal resistance Fig. 3.<sup>(18)</sup> These guidelines represent a major step forward in the rational approach to the management of AOM. According to these guidelines, amoxicillin (40-50 mg/kg/day or the high dosage of 70-90 mg/kg/day) represents the first-line treatment of choice for AOM. In cases of clinical failure after three full days of therapy, we recommend the performance of a diagnostic (and in many situations therapeutic) tympanocentesis, particularly in areas with a high prevalence of antibiotic-resistant *S. pneumoniae*.

The three second-line antibiotic drugs recommended at present time for clinical failures are: 1) amoxicillin/clavulanate (the 45 mg/kg/day amoxicillin dose or in the future the 90 mg/kg/day dose) for 10 days; 2) cefuroxime-axetil for 10 days; 3) intramuscular ceftriaxone (50 mg/kg/day) for 3 days.



\* diagnostic and therapeutic tympanocentesis and MEF culture recommended before initiation of second-line therapy  
 \*\* 40-50 mg amoxicillin/kg/day recommended for empiric treatment of 1st AOM episode or in children > 2 years of age or in geographic areas with low prevalence of pneumococcal penicillin resistance  
 \*\*\* for the empiric treatment of 1st AOM episode in neonates / immunocompromised patients / AOM patients who received antibiotics for AOM during last month

**Fig. 3** The antibiotic management of acute otitis media in the era of antibiotic-resistant *S. pneumoniae*.

## Vaccines

The heptavalent pneumococcal conjugate vaccine (PREVENAR), approved in the United States in 2000, produces only a slight reduction in the risk for AOM of 6 to 7%, yet it decreases the proportion of AOM resulting from *S. pneumoniae*.<sup>(110-112)</sup> Indeed, in the Finnish otitis media study, pneumococcal AOM cases caused by vaccine serotypes were reduced by 57% and the overall number of pneumococcal AOM episode was reduced by 34%.<sup>(111)</sup> In addition, use of this vaccine in locations where penicillin-resistant *S. pneumoniae* are prevalent may reduce carriage of this pathogen and dampen antibiotic resistance. However, a replacement phenomenon, with emergence of pneumococcal serotypes not included in the vaccine as well as an absolute increase in the *H. influenzae* and *M. catarrhalis* AOM cases, has been already observed in the vaccinated children in efficacy studies and after the introduction of routine immunization in the United States.<sup>(111,113)</sup> Further studies will be needed to determine the effect of this serotype replacement for both invasive and mucosal disease and whether the proportion of multi-resistant pneumococcal isolates in the community will decrease as hypothesized.

## Conclusions

An accurate differential diagnosis of AOM is essential for ensuring appropriate treatment, since overdiagnosis of disease is common and antibiotics are not indicated for otitis media with effusion, which commonly follows AOM. The last decade has seen major changes in the epidemiology of AOM with an earlier onset of disease and a greater proportion of children with recurrent/complicated AOM. The major problems encountered in the antibiotic therapy of AOM are the tremendous increase in the resistance to antibiotics of its main pathogens and the lack of tight criteria in the selection of the appropriate antibiotic drugs for the treatment of this disease. In the treatment of children with AOM, clinical studies suggest an essential equivalence in efficacy among the different classes of antibiotics indicated for this condition. However, only double-tympanocentesis studies with a bacteriologic end point truly allow discernment between effective and less appropriate drugs in the treatment of AOM. The

recently published guidelines for the treatment of AOM in the present era of pneumococcal resistance represent a major step forward in the rational approach to the management of this disease by establishing a clear hierarchy among the various therapeutic agents used in the treatment of simple and complicated AOM. A seven valent pneumococcal conjugate vaccine was recently licensed in the United States for universal immunization of infants younger than 2 years and has demonstrated efficacy for prevention of serotype-specific pneumococcal AOM.

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