EXPERT REVIEWS

Current management of pediatric acute otitis media

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Acute otitis media (AOM) is the most common childhood bacterial infection for which antibiotics are prescribed worldwide. The most common pathogens causing AOM in children are *Streptococcus pneumoniae*, nontypeable *Haemophilus influenzae*, *Moraxella catarrhalis* and Group A streptococcus. Antibiotic resistance is increasing among the bacterial pathogens causing AOM, with percentages of penicillin- and macrolide-resistant *S. pneumoniae* strains estimated to be between 30 and 70%, and of β-lactamase-producing *H. influenzae* ranging between 20 and 40%. The introduction of the seven-valent pneumococcal conjugated vaccine had a major role in decreasing the number of vaccine-related *S. pneumoniae* AOM episodes, recurrent AOM cases and cases requiring the insertion of ventilation tubes. In parallel, it caused a rapid shift in the microbiology of AOM, characterized by an increase in the number of nonvaccine *S. pneumoniae* serotypes and *H. influenzae* isolates. The management of AOM in childhood has evolved considerably during recent years as a result of the new insights provided by the publication of the American Academy of Pediatrics and American Academy of Family Physicians guidelines for the treatment of AOM. The new treatment guidelines establish a clear hierarchy among various antibacterials used in the treatment of AOM and also the use of an age-stratified approach to AOM by recommending an observation strategy ('watchful waiting') without the use of antibacterials for some groups of AOM patients. Adherence to such a policy in patients with uncertain/questionable AOM diagnosis and/or mild-to-moderate symptoms, in addition to its implementation in patients over 2 years of age, could substantially reduce the use of antibacterials for the treatment of AOM and play a major role in the strategy of decreasing antibacterial resistance.

KEYWORDS: acute otitis media • antibiotics • guidelines • observation • *Streptococcus pneumoniae* • vaccines

Acute otitis media (AOM) is the most common childhood bacterial infection for which antibiotics are prescribed in the USA [1,2]. AOM most commonly presents between the ages of 3 months and 3 years, with a peak incidence between 6 and 9 months of age [3]. By 1 year of age, at least 60% of children have had one episode of AOM and 17% have suffered from at least three episodes [2–5]. Increasing use of daycare centers is directly related to the rise in the incidence of AOM in children during the past 20 years [6]. Children attending daycare facilities frequently carry antibiotic-resistant organisms in their respiratory tract, leading to AOM that may be refractory to antibiotic treatment. Intensive antimicrobial usage provides the selection pressure that favors the development of resistant organisms, while the daycare centers provide the means by which these organisms can be transmitted [7].

Streptococcus pneumoniae and nontypeable *Haemophilus influenzae* are by far the most common bacterial pathogens in AOM, being recovered in up to 80–90% of cases [8–11]. During the last two decades, antibiotic-nonsusceptible *S. pneumoniae* strains have spread all over the world and their prevalence has increased dramatically in various countries [12,13]. The microbiology of AOM has changed considerably during the last few years following the introduction in the routine pediatric immunization schedules of the seven-valent pneumococcal conjugate vaccine (PCV7) [14–16]. This vaccine was shown to reduce the number of AOM episodes secondary to vaccine serotypes by 55% and the number of pneumococcal AOM cases by 34% [14–16]. However, the emergence of pneumococcal serotypes not included in the vaccine, some of them with increased rates of antibiotic resistance, as well as an absolute increase in the proportion

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of nontypeable *H. influenzae* and *Moraxella catarrhalis* isolated from AOM patients, have been observed in vaccine studies and in vaccinated children in the USA [17–24].

The management of AOM in childhood has evolved considerably during recent years as a result of publication of the American Academy of Pediatrics and the American Academy of Family Physicians guidelines for the treatment of AOM [25]. The new treatment guidelines establish a clear hierarchy among the various antibacterials used in the treatment of this disease and also the use of an age-stratified approach to AOM by recommending an observation strategy ('watchful waiting') without the use of antibacterials for some groups of patients with AOM.

The main purpose of this article is to review the evolving microbiology of AOM, particularly in the pneumococcal conjugate vaccines era, and to discuss the treatment options available for AOM patients – that is, antibiotic treatment and the 'watchful waiting' approach. The available evidence will be presented in the light of issues surrounding bacterial resistance, prevention of diseases by vaccines, bacterial eradication by appropriate antibiotics and adherence to published guidelines.

Bacteriology of AOM

Otopathogens

The most common pathogens causing AOM in children are *S. pneumoniae*, nontypeable *H. influenzae*, *M. catarrhalis* and group A streptococcus (GAS) [8–11]. Early-life nasopharyngeal colonization with these pathogens is associated with early onset of AOM, and there is a direct relationship between the frequency of colonization and the frequency of AOM [26–28].

Respiratory syncytial virus is the most common virus recovered in AOM, followed by parainfluenza virus, rhinovirus, influenza virus, enterovirus and adenovirus [29]. Nevertheless, bacteria are still the leading pathogen in AOM, and only approximately 20% of AOM cases are caused by viruses alone [30].

Resistance to antibiotics

Among the bacterial pathogens, *S. pneumoniae* and nontypeable *H. influenzae* each occur in 40% or more of infections [8–11]. Antibiotic resistance is increasing among the bacterial pathogens causing AOM, with the percentage of penicillin- and amoxicillin-resistant *S. pneumoniae* strains between 30 and 70% [12,13,31–33]. The proportion of nonsusceptible *S. pneumoniae* isolated from the middle ear fluid (MEF) of children with AOM nonresponsive to initial antibiotic therapy is even higher and may reach 80% or more of all isolates [34]. In a multinational study, 30% of *S. pneumoniae* isolates were intermediately or fully resistant to penicillin during 1994–1995; of these, 31% were in Central and Eastern Europe, 52% in Israel and 21% in the USA [11]. In southern Israel, while 15% of *S. pneumoniae* strains isolated from the MEF of children with AOM were nonsusceptible to penicillin in 1992; this number rose to 58% in 1998 and 71% in 1999 [35]. Resistance to macrolides rose from 3 to more than 30% and resistance to trimethoprim–sulfamethoxazole (TMP–SMX) increased from 13 to over 50%. Resistance to three antibiotic classes (defined as multidrug-resistant *S. pneumoniae*) rose from 1 to 17% [35]. In another study analyzing 876 pneumococcal AOM isolates recovered in southern Israel, 68% were resistant to more than one antibiotic drug, 61% were resistant to penicillin and 13% were resistant to more than three antibiotic classes [36].

The danger of the increasing resistance to traditional antibiotic drugs is an increase in antibiotic recurrent and/or nonresponsive (complicated) AOM [37]. If signs and symptoms of AOM persist for 48–72 h after the initiation of antibiotics, it is likely that antimicrobial therapy failed to treat the original infection and did not eradicate the initial pathogens, leading to a persistent (nonresponsive to therapy) AOM episode [37]. Furthermore, when *S. pneumoniae*-AOM was treated inappropriately, the disease outcome was worse than for AOM caused by any other organism [38].

Recurrent AOM

Clinical recurrent AOM (R-AOM) is defined as the reappearance of AOM after completion of treatment of an initial episode of AOM accompanied by clinical cure. True bacteriological R-AOM requires the presence of an organism identical to that isolated during the original AOM episode. R-AOM is common in otitis-prone children (defined as those children with three or more AOM episodes occurring in the previous 6 months, or four or more episodes in 1 year preceding the current AOM episode). By the age of 1 year, more than 60% of children will have experienced one episode of AOM and 17% will have suffered from at least three episodes [4]. In a study on the relationship between AOM pathogens isolated in 108 cases of early clinical R-AOM diagnosed 3–4 weeks after completion of a successful antibiotic course and pathogens causing the initial AOM episode, Leibovitz *et al.* found that the majority (72%) of R-AOM episodes were new infections [39]. The authors showed that most true bacteriological R-AOM cases developed within the first 2 weeks after completion of antibiotic therapy, but even during this time most recurrences were caused by a new pathogen.

S. pneumoniae *serotypes*

In a multinational study of pneumococcal serotypes causing AOM in children, the major pneumococcal serotypes identified in MEF cultures were, in descending order, 19F, 23F 14, 6B, 6A, 19A and 9V [40]. The highest antibiotic resistance is found in serotypes 6B, 9V, 14, 19F and 23F. These serotypes were most associated with resistance to one or more antibiotics, and were associated with recurrent and nonresponsive AOM [11,36,40]. In a study determining the ability of the PCV7 to cover AOM isolates (especially drug-resistant ones) among 500 pneumococcal isolates from AOM patients in the USA during 1996–1999, Joloba *et al.* reported that 418 (84%) belonged to vaccine-related serogroups [41]. Most isolates (98–100%) that were resistant to the antimicrobial agents tested were covered by PCV7.

Nontypeable H. influenzae, M. catarrhalis *& group A* β*-hemolytic streptococci*

The percentage of β-lactamase-producing nontypeable *H. influenzae* and *M. catarrhalis* has risen in the past decades, leading to increased resistance to β-lactam antibiotics. Nontypeable

H. influenzae is associated with 17–52% of cases of AOM and is more common or of the same magnitude as *S. pneumoniae* among the bacterial pathogens responsible for the disease [40–45]. In a study of the bacteriology of AOM in a cohort of Finnish children followed for the first 2 years of life, Kilpi *et al.* demonstrated an increase in the incidence of nontypeable *H. influenzae*-AOM after the age of 15 months, peaking at 19 months [46]. Furthermore, nontypeable *H. influenzae* was clearly associated with R-AOM episodes [46]. The resistance of nontypeable *H. influenzae* to antimicrobial agents has evolved significantly during the last two to three decades. Currently, the resistance rates of nontypeable *H. influenzae* isolates to amoxicillin vary from 17% to more than 50–60% in various areas of the world, particularly in France, Japan and other Southern Asia regions [44]. This resistance is essentially to β-lactam antibiotics, mainly as a result of the production of a plasmid-mediated β-lactamase, TEM-1 [47]. In addition, resistance to β-lactam antibiotics may also be due to the production of altered penicillin-binding proteins; these β-lactamase-negative ampicillin-resistant strains are relatively common in Japan and yet are still rare in North America and Europe and have not yet been associated with clinical failures in outpatients [48–50]. Nontypeable *H. influenzae*, as well as *S. pneumoniae*, was found to exist in chronic ear infections as a biofilm (a polymeric matrix attached to an inert or living surface), where bacterial growth is slow, cultures are generally negative, antibiotic penetration is difficult and therapeutic successes are not common [51–53].

In some reports, an increased proportion of *M. catarrhalis* isolation from the MEF in AOM has been shown. Kilpi *et al.* reported a 10–23% increase within a 15-year follow-up [46] and a similar pattern has also been reported in the USA and Costa Rica [54,55]. AOM caused by *M. catarrhalis* is characterized by higher proportions of mixed infections and younger age at diagnosis, lower proportions of spontaneous perforation of the tympanic membrane and no mastoiditis [56].

In the first half of the 20th Century, GAS was the pathogen most frequently isolated from patients with AOM, especially in cases where it was complicating scarlet fever and measles [57]. Since the 1950s, it has been rapidly replaced by *S. pneumoniae*, nontypeable *H. influenzae* and *M. catarrhalis*, and it is now ranked only fourth among AOM pathogens (<10% of all cases) [54]. In a large study analyzing the clinical and microbiologic characteristics of 350 infants and children aged younger than 5 years with GAS-AOM, Segal *et al.* reported that the GAS episodes were characterized by older age and higher local aggressiveness (manifested by higher rates of tympanic perforation and of mastoiditis) compared with disease caused by other AOM pathogens [58].

Impact of vaccination with pneumococcal conjugate vaccines on otopathogens

Studies conducted in the USA, Finland and the Czech Republic have evaluated the efficacy of two PCV formulations on clinical or culture-proved pneumococcal AOM [14–16,59]. In northern California (USA), among children receiving PCV7, there was a reduction of 7.0% in AOM episodes, 9.3% in frequent AOM and 20.1% in ventilatory tube placement compared with unvaccinated children [14]. The vaccine efficacy against clinically diagnosed AOM caused by pneumococcal vaccine serotypes was 66.7%. An analysis of the impact of PCV7 on AOM on the northern California initial trial group of 37,868 children followed-up to 3.5 years after immunization revealed that PCV7 reduced otitis visits by 7.8%, antibiotic prescriptions by 5.7% and tube placements by 24% [16]. In Finland, children receiving PCV7 had a 6% reduction of clinical AOM and 57% reduction of AOM caused by pneumococci of vaccine serotypes [42]. A recent study evaluated the efficacy against AOM of a PCV11 vaccine (conjugated to protein D of *H. influenzae*) and reported a 57.6% reduction in the number of cases caused by vaccine serotypes and 33.6% in AOM caused by all pathogens [59]. In addition, this vaccine conferred a 35.3% protection rate against AOM caused by nontypeable *H. influenzae*. In a population-based study in Tennessee (USA) and Rochester (NY, USA), Poehling *et al.* reported a significant reduction in otitis media visits, with declines of 118 and 430 visits per 1000 children, respectively [60,61]. Frequent otitis media episodes declined by 17 and 28%, respectively (comparing the 2000–2001 with the 1998–1999 birth cohort), while pressure-equalizing tube insertions declined by 16 and 23%, respectively. In a recent study comparing AOM-related healthcare utilization and associated antibiotic prescriptions for children younger than 2 years of age between 2004 and 1997–1999 (baseline period) in the USA, rates of ambulatory visits, antibiotic prescriptions for AOM and direct medical expenditures for AOM-related ambulatory visits and antibiotic prescriptions decreased by more than expected on the basis of previous estimates, by 42.7, 41.9 and 32.3%, respectively [62].

As vaccine pneumococcal serotypes are those that are most likely to be resistant to antibiotics, widespread implementation of the vaccination program with PCV7 in the USA was expected to result in a major decrease in disease caused by antibiotic-resistant pneumococci in children and (by herd immunity) in adults. However, data on AOM and pneumonia are limited, and the main information available relates to invasive pneumococcal diseases and nasopharyngeal colonization. In an analysis of 1647 *S. pneumoniae* isolates obtained from patients with invasive and noninvasive disease in 41 US medical centers in two periods (1999–2000 and 2004–2005), Richter *et al.* reported that the prevalence of isolates with intermediate penicillin resistance increased from 12.7 to 17%, the prevalence of penicillin-resistant isolates decreased from 21.5 to 14%, the prevalence of isolates resistant to erythromycin increased from 25.7 to 29.1%, and the prevalence of multidrug-resistant isolates did not change (22.4 vs 20%) [63]. In 2007, Farrell *et al.* reported on serotype distribution, PCV7 coverage and antimicrobial susceptibility among *S. pneumoniae* (invasive and respiratory isolates) collected from children 0–14 years of age in 2000–2001 (2033 isolates), 2002–2003 (1740) and 2003–2004 (1591) [64]. The most common serotypes in 2004 were the nonvaccine types 19A, 6A, 3, 15 and 35B, as well as vaccine serotype 19F. Antimicrobial resistance rates among the nonvaccine serotypes from respiratory tract sites increased for penicillin-resistant *S. pneumoniae* from 12.7 to 16.1% when comparing 2000–2001 with 2003–2004, for penicillin-intermediate resistant *S. pneumoniae* from 20.1 to

31.5%, for erythromycin from 21.2 to 31.6%, and for multidrug resistance from 24.6 to 31.6% [64]. Results from the analysis of antibiotic-resistant *S. pneumoniae* carriage show that vaccinated daycare center attendees had a marked reduction in nasopharyngeal colonization of antibiotic-resistant *S. pneumoniae* [65–67].

In parallel, the introduction of PCV7 had a major role in causing a rapid shift in the microbiology of AOM, characterized by an increase in the number of nonvaccine *S. pneumoniae* serotypes and nontypeable *H. influenzae* isolates. This effect on the microbiology of AOM in the postvaccine era was evaluated in two prospective studies in Kentucky (USA) and Rochester (NY, USA) [17,18], which found that widespread use of the vaccine resulted in a decrease of approximately 50% in the proportion of *S. pneumoniae* AOM, a similar increase in AOM cases caused by nontypeable *H. influenzae* (with a significant increase in cases caused by β-lactamase-producing isolates) and a decrease by 24% in the number of complicated AOM cases.

An unexpected consequence of immunization with the conjugated vaccines is the simultaneous and impressive increase in the carriage rates of nonvaccine-serotype pneumococci among vaccinated children. This finding is termed replacement colonization and was observed in most, but not all, of the nasopharyngeal carriage and some AOM studies [17,18,65–67]. To date, only the Finnish study using PCV7 has shown evidence of replacement AOM disease with nonvaccine-type pneumococcal strains following vaccination [16]. In this study, children in the vaccine group had 33% more episodes of AOM caused by serotypes not included in the vaccine or related vaccine types and also by nontypeable *H. influenzae* and *M. catarrhalis*. Recently, Brook and Grober reported on the recovery of significantly higher numbers of *Staphylococcus aureus* (including methicillin-resistant *S. aureus*) from spontaneously draining MEFs of AOM patients after the introduction of the routine pneumococcal vaccination [68].

In this context, the recent reports of the increasing rates of invasive pneumococcal diseases and AOM cases with *S. pneumoniae* serotype 19A in the USA, particularly in light of being antibiotic-resistant and also multidrug-resistant (MDR), raise considerable concern that this occurrence might be a consequence of post-PCV7 changes in the pneumococcal flora [22–24,69–71]. In southern Israel, approximately 20% of all pneumococcal AOM episodes recorded during 1998–2001 were caused by serotypes not included in, and not immunologically related to, PCV7 [70]. In addition, the Israeli researchers have characterized MDR strains of nonvaccine types that represented capsular switch variants of clones of PCV7 serotypes [71]. Such variants could potentially become highly successful pathogens in the pediatric population; however, these changes occurred before the introduction of PCV7 and therefore cannot be attributed to a selective pressure exerted by the vaccine. Dagan *et al.* analyzed the distribution of *S. pneumoniae* serotypes causing AOM (before the introduction of PCV7) in Jewish and Moslem Bedouin children living in southern Israel, both populations characterized by high antibiotic prescription rates [72]. In total, 413 out of the 4150 pneumococcal AOM episodes were caused by serotype 19A, which increased in the Bedouins from 8.7% of all pneumococcal AOM during 1999–2000 to 14.6% in the season 2004–2005. In addition, penicillin resistance among the 19A serotypes increased in Bedouin children from 6.9 to 62.5% during the same period, erythromycin resistance increased from 7 to 43.8% and MDR increased from 4.3 to 43.8%. The authors demonstrated, by molecular analysis, that two multidrug-resistant 19A serotype *S. pneumoniae* clones were introduced and quickly spread in the Bedouin population during 2001–2002 and suggested that the increase in the 19A serotype recovery rates and its antibiotic resistance, occurring in the absence of antipneumococcal immunization with PCV7, was mainly related to antibiotic overuse [72].

Current management of pediatric AOM

Observation ('watchful waiting') approach

Since antibiotic therapy plays a major role in the selection of increasingly resistant bacteria, the observation option ('watchful waiting') in the treatment of AOM was reconsidered during the last few years as an appropriate management option for certain children. This management choice is based on diagnostic certainty, age, severity of illness and assurance of follow-up. The American Academy of Pediatrics recommends this option in children over 6 months of age who do not present with severe illness, or in whom the diagnosis is uncertain (Table 1). By contrast, immediate antibiotic therapy is recommended for children younger than 6 months of age and for all those with a severe form of the disease, due to the association with increased risk of failure when using the 'watchful waiting' policy [25]. Nevertheless, for children in the desired age ranges, previous reports have consistently shown that most children do well, without serious adverse sequelae, even without antibiotic therapy. It is stated that between seven and 20 children must be treated with antibiotics in order for one to derive benefit from the treatment [73–75]. van Buchem *et al.* reported already in the early 1980s that only 2.7% of 4860 Dutch children less than 2 years of age given only symptomatic treatment developed severe illness defined by persistent fever, pain or discharge after 3–4 days [76]. Similarly, in another trial in the UK comparing children treated immediately with children receiving delayed antibacterial therapy after 72 h, 76% of children in the delayed treatment group never required antibacterial therapy [77]. The group that received antibacterial agents at diagnosis experienced on average 1 day less of illness and needed one teaspoon less of acetaminophen. On the other hand, a greater proportion of children in the immediate antibacterial therapy group achieved symptomatic improvement during the first 3 days following diagnosis [77].

The broad implementation of the 'watchful waiting' policy is not supported by some opinion leaders in the field, who are not convinced that the evidence supporting its effectiveness is available at the present time in the literature [78–81]. The major criticism of the published studies supporting this approach relates to a lack of stringent diagnostic criteria in the choice of the patients, diagnostic inaccuracy, lack of enrollment of patients with more severe symptoms, exclusion of infants, the small number of patients enrolled, a lack of microbiologic data and a lack of consistency in approach and follow-up among the many participating physicians.

Table 1. Criteria for initial antibacterial agent treatment or observation ('watchful waiting') in children with acute otitis media.

Age	Certain* diagnosis: severe disease‡	Certain diagnosis: mild disease	Uncertain diagnosis
<6 months	Antibiotic therapy	Antibiotic therapy	Antibiotic therapy
6 months–2 years	Antibiotic therapy	Observation	Observation
>2 years	Antibiotic therapy	Observation	Observation

*A certain diagnosis of acute otitis media meets all three criteria: rapid onset, signs of middle ear effusion, and signs and symptoms of middle ear inflammation.
‡Severe illness: moderate-to-severe otalgia and/or fever >39°C
Adapted from [25].

In fact, current data show that the more severely affected patients are expected to benefit from early antibiotic treatment [82]. In a meta-analysis study reporting on the effectiveness of antibiotics in 1643 children 6 months–12 years of age with AOM, Rovers *et al.* showed that children under 2 years of age with bilateral disease (which may represent approximately two-thirds of all AOM patients [83]) and children presenting with otorrhea derived the most beneficial effect from immediate initiation of antibiotic treatment [82]. Kaleida *et al.* compared nonsevere and severe AOM episodes and showed that the treatment failure rate was higher by 3.8% only in children with nonsevere AOM who received placebo compared with those who received amoxicillin, while the failure rate in patients with severe AOM was 23.5% in the placebo plus myringotomy group compared with 9.6% in patients treated with amoxicillin alone [84].

Bacterial eradication

The best method for selecting the most appropriate and effective drugs against any of the specific pathogens causing AOM is the '*in vivo* sensitivity test' [85,86]. In this method, two aspirates and bacterial cultures of MEF are performed on enrolled patients with AOM: the first before antibacterial administration and the second during the course of treatment (3–5 days). The major advantage of this method resides in its ability to discriminate between the efficacies of various antibacterial compounds and predict clinical outcome, while enrolling relatively few patients.

By using the double-tympanocentesis method, spontaneous cure of AOM was shown to be significantly more common in AOM due to *M. catarrhalis* and nontypeable *H. influenzae* than in AOM due to *S. pneumoniae* [38,85]. The double-tympanocentesis studies revealed a good correlation between certain pharmacokinetic/pharmacodynamic parameters, such as the time above the MIC and bacterial eradication [86], and proved that high-dose amoxicillin is the best oral drug option for the eradication of penicillin-resistant *S. pneumoniae* [87]. Macrolides (in particular azithromycin) were not found to be effective against *H. influenzae* and macrolide-resistant *S. pneumoniae* [88–90]. The poor results in the double-tympanocentesis studies using azithromycin 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 [91].

The resistance mechanisms responsible for resistance against *S. pneumoniae* are related to ribosomal methylase (*ermB* gene), the macrolide efflux pump (*mefE* gene) or both [92]. One dose of intramuscular ceftriaxone was found to be efficacious against *H. influenzae* and penicillin-susceptible *S. pneumoniae* but three doses are needed for the treatment of AOM caused by penicillin-nonsusceptible *S. pneumoniae* [93]. As a result of a lack of efficacy against *H. influenzae* and *S. pneumoniae*, TMP–SMX is no longer a valuable choice in the empiric treatment of AOM [94]. Mostly important, the double-tympanocentesis studies clearly demonstrated the importance of bacteriological eradication in improving the clinical outcome during antibiotic treatment and also in the prevention of further episodes of R-AOM [95,96].

Antibiotic treatment

Appropriate antibacterial therapy has to take into consideration the fact that *S. pneumoniae* is the most virulent pathogen causing AOM [97–99]. However, this fact should not imply that other organisms, particularly *H. influenzae*, should not be targeted in the empiric therapy of AOM [100,101].

When antibiotic treatment of AOM is considered necessary, the current guidelines recommend amoxicillin as the first-line drug choice (Figure 1) [25]. The reason for this recommendation is its general effectiveness when used in appropriate doses against susceptible and intermediately resistant *S. pneumoniae* [87]. In children with AOM, amoxicillin 75 mg/kg/day in divided doses produces MEF concentrations of over 1 µg/ml for at least 50% of the dosing interval [102]. The drug is also safe, affordable, has an acceptable taste and a relatively narrow microbiologic spectrum. However, the amoxicillin high-dose regimen was shown to select for β-lactamase-positive nontypeable *H. influenzae* and highly-resistant *S. pneumoniae* as the main organisms to be targeted in cases of treatment failure [87]. In a metanalysis attempting to define the biologic variations in amoxicillin pharmacokinetic/pharmacodynamic parameters for the treatment of AOM in children and their possible relationship with treatment failures, Pichichero *et al.* identified studies that evaluated ampicillin or amoxicillin intestinal absorption, serum concentrations and/or MEF concentrations [103]. The authors showed that the intestinal bioavailability of amoxicillin depends on passive diffusion and a saturable 'pump' mechanism producing variable serum concentrations of the drug, and therefore substantial differences from patient to patient in serum (five- to 30-fold) and MEF (up to 20-fold) concentrations of amoxicillin occur following oral administration, while 15–35% of children may have no detectable amoxicillin in MEF.

In patients with severe illness (defined by persistent fever, pain or ear discharge after 3–4 days), those requiring additional coverage for β-lactamase-positive nontypeable *H. influenzae* and *M. catarrhalis* or immunocompromised patients, therapy should be initiated with high-dose amoxicillin–clavulanate

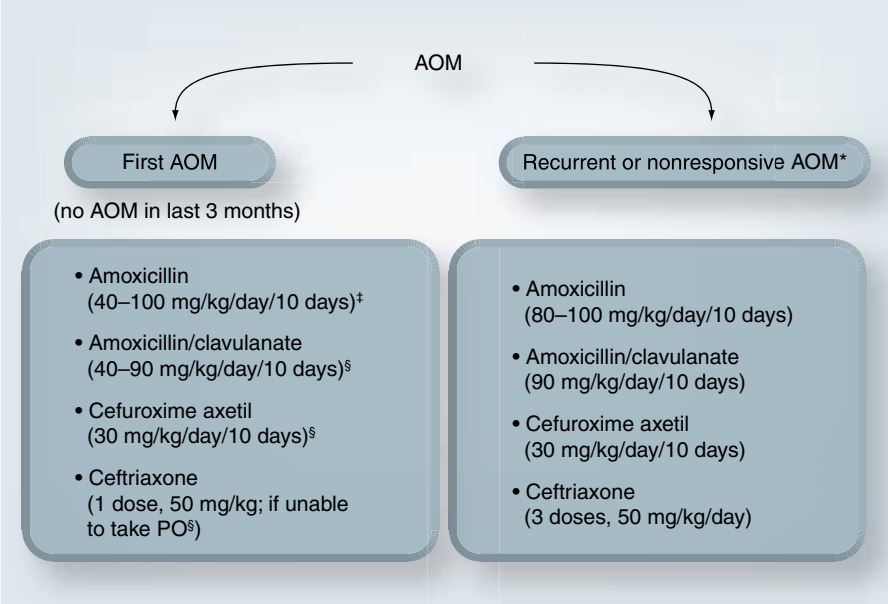

Figure 1. Present recommendations for the antibiotic management of acute otitis media in children.
*Diagnostic and therapeutic tympanocentesis and MEF culture recommended before initiation of second-line therapy.
‡40–50 mg amoxicillin/kg/day recommended for empiric treatment of first AOM episode, in children older than 2 years of age or in geographic areas with a low prevalence of pneumococcal penicillin resistance.
§For the empiric treatment of first AOM episode in neonates/immunocompromised patients/AOM patients who received antibiotics for AOM during last month.
AOM: Acute otitis media; MEF: Middle ear fluid; PO: Oral.

(90 mg/kg/day of amoxicillin and 6.4 mg/kg/day of clavulanate in two divided doses) [104]. In addition, the American Academy of Pediatric guidelines recommend high-dose amoxicillin–clavulanate (rather than amoxicillin) in the treatment of AOM in children attending daycare centers [25].

If the patient is allergic to amoxicillin and the allergic reaction was not a type I IgE-mediated hypersensitivity reaction, cefdinir (14 mg/kg/day in one or two doses), cefpodoxime (10 mg/kg/day once daily) or cefuroxime axetil (30 mg/kg/day in two divided doses) can be used (Table 1) [105]. However, the microbiologic efficacy of oral cephalosporins against *S. pneumoniae* obtained from pediatric isolates may be expected to decrease; susceptibility to oral cephalosporins was shown to shift from more than 90% in penicillin-susceptible *S. pneumoniae* isolates to approximately 38% for cefuroxime/cefpodoxime and from approximately 7% for cefaclor in penicillin-intermediate to 0% in penicillin-resistant isolates [106].

If a type I allergic reaction did occur, azithromycin (10 mg/kg/day on day 1 followed by 5mg/kg/day for 4 days as a single dose) can be used. Recently, in a baseline only-tympanocentesis study evaluating the clinical response at end of therapy and after 1 month of therapy, Arguedas *et al.* reported that a single high dose of azithromycin (30 mg/kg) was as effective as high-dose amoxicillin for the treatment of children with AOM [107]. Alternatively, clarithromycin (15 mg/kg/day in two divided doses) is an option if an antibacterial agent from a different class is considered necessary. Three doses of clindamycin 30–40 mg/kg/day may be a good alternative therapy in cases of *S. pneumoniae* susceptible to clindamycin in patients allergic to penicillin. However, prospective, controlled studies on the bacteriologic and clinical efficacy of clindamycin in the treatment of AOM are lacking and the drug is not efficacious against *H. influenzae*. In patients who cannot tolerate oral medications, a dose of parenteral ceftriaxone (50 mg/kg) has been shown to be effective for the initial treatment of simple, uncomplicated AOM [25,108].

For children under 2 years of age who present with severe disease, a 10-day treatment course is recommended. For children older than 2 years of age with mild-to-moderate disease, a 5–7-day course should be sufficient [25].

The three second-line antibiotic drugs recommended at present for clinical failures are high-dose amoxicillin–clavulanate, cefuroxime–axetil and intramuscular ceftriaxone (50 mg/kg/day) for 3 days. If AOM persists, tympanocentesis is recommended for bacteriologic diagnosis.

Prevention

Given the growing number of resistant otopathogens causing AOM, prescribing preventive chemoprophylaxis in children with AOM should be done with caution, possible only in those patients with well-defined R-AOM episodes (three or more AOM episodes during the last 6 months or four or more episodes during the last year).

During infancy and early childhood, major efforts must be carried out in order to reduce and possibly eliminate the environmental risk factors associated with development of AOM and causing treatment failures (e.g., by placing the child in daycare centers with a small number of children and possibly thus reducing the incidence of respiratory tract infections; implementation of breastfeeding for at least the first 6 months of lifel avoiding supine bottle feeding; reducing or eliminating pacifier use in the second 6 months of life; and eliminating exposure to passive tobacco smoke [25]). However, many of these risk factors have presented with some ambiguity in the literature and therefore the utility of these interventions is unclear.

During the last decade, Uhari *et al.* have examined the role of xylitol, a polytol sugar alcohol that has the ability to inhibit the growth of *S. pneumoniae in vitro*, in the prevention of AOM [109,110]. In two older studies, children who chewed xylitol gum daily had significantly fewer AOM episodes compared with children who chewed sucrose-based chewing gum [109,110]. However, in a recent study enrolling 663 healthy children attending daycare centers, the administration of xylitol as a chewing gum or liquid mixture three times a day for a 3-month period during the respiratory infections season failed to prevent AOM [111].

In a study evaluating the effect of recolonization with α-streptococci (bacteria with the ability to interfere with the growth of common otopathogens in the nasopharynx), Roos *et al.* treated 108 otitis media-prone children 6 months–1 year of age with antibiotics and streptococcal (or placebo) solution sprayed into the nose for 10 additional days and also for another 10 days at day 60 of the follow-up [112]. The authors reported that after 3 months of follow-up, 22 children (42%) given the streptococcal spray were healthy and had a normal tympanic membrane compared with 12 (22%) of those given placebo and suggested that selected bacteria with the ability to inhibit the growth of common otopathogens can be used in order to prevent recurrences of AOM.

Expert commentary

S. pneumoniae and nontypeable *H. influenzae* are by far the most common bacterial pathogens to be targeted in the management of AOM, particularly in the present era of increasing antibiotic resistance. The microbiology of AOM has changed considerably during the last few years following the introduction of PCV7 and additional conjugate vaccines into the routine pediatric immunization schedules. PCV7 routine immunization caused a major reduction in the number of vaccine-related *S. pneumoniae*-AOM episodes but, in parallel, was associated with a rapid shift in the microbiology of AOM, characterized by an increase in the number of nonvaccine *S. pneumoniae* serotypes (some of them MDR) and nontypeable *H. influenzae* isolates. The present treatment guidelines for AOM in children establish a clear hierarchy among the various antibacterials used in the treatment of this disease and also the use of an age-stratified approach to AOM by recommending an observation strategy ('watchful waiting') without the use of antibacterials for some groups of patients with AOM. When antibiotic treatment of AOM is considered necessary, the current guidelines recommend amoxicillin as the first-line drug of choice. The antibiotics choices for treatment failures are few and include high-dose amoxicillin/clavulanate and three shots of parenteral ceftriaxone.

Five-year view

The next 5 years will see a continuation of the present trend, associated with universal immunization with pneumococcal conjugate vaccines, with decreasing rates of AOM overall and of pneumococcal AOM in particular. The introduction of the 13-valent conjugate pneumococcal vaccine will provide coverage for two additional important vaccine-related serotypes, 6A and 19A. The PCV10 vaccine conjugated to protein D of *H. influenzae,* in addition to its effect on pneumococcal AOM, will hopefully provide significant protection against nontypeable *H. influenzae*. The main pathogens recovered from the MEF of patients with AOM will be, most probably, nontypeable *H. influenzae*, *M. catarrhalis* and nonvaccine pneumococci (whose resistance to antibiotics is expected to increase). No significant developments are expected from the drug companies with respect to the launch of new antibiotic drugs for the treatment of AOM. Amoxicillin and amoxicillin–clavulanate will remain the main oral antibiotic drugs to be used for the treatment of AOM. The observation option for the treatment of AOM without antibiotic treatment will be broadly implemented in medical practice and further research will provide important insights into its impact on the clinical outcome of children with AOM.

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Key issues

- *Streptococcus pneumoniae* and nontypeable *Haemophilus influenzae* are by far the most common bacterial pathogens to be targeted in the management of acute otitis media (AOM).
- Antibiotic resistance is increasing among the bacterial pathogens causing AOM, with the percentage of penicillin- and amoxicillin-resistant *S. pneumoniae* strains between 30 and 70%, and of β-lactamase-producing nontypeable *H. influenzae* of 17–60%.
- The introduction of the seven-valent pneumococcal conjugate vaccine (PCV7) had a major role in decreasing the number of vaccine-related *S. pneumoniae* AOM episodes, recurrent AOM cases and cases requiring insertion of ventilation tubes.
- In parallel, the introduction of PCV7 had a major role in causing a rapid shift in the microbiology of AOM, characterized by an increase in the number of nonvaccine *S. pneumoniae* serotypes (some of them multidrug resistant) and nontypeable *H. influenzae* isolates.
- The best method to select the most appropriate and effective drugs against any of the specific pathogens causing AOM is the *in vivo* sensitivity test.
- Bacteriologic eradication is essential in improving the clinical outcome during antibiotic treatment and also in the prevention of further episodes of recurrent AOM.
- The American Academy of Pediatrics and the American Academy of Family Physicians guidelines for the treatment of AOM establish a clear hierarchy among the various antibacterials used in the treatment of this disease.
- When antibiotic treatment of AOM is considered necessary, the current guidelines recommend amoxicillin as the first-line drug of choice.
- The antibiotics choices for treatment failures are limited and include high-dose amoxicillin/clavulanate and three shots of parenteral ceftriaxone.
- The observation strategy ('watchful waiting') without use of antibacterials for some groups of patients with AOM represents an important therapeutic option, which will hopefully make a major contribution to decreasing antibiotic resistance.

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