Treatment of otitis media

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Franco Paradisi and Giampaolo Corti

Otitis media is a very common reason for the prescription of antibiotics in children. Antimicrobial therapy is mostly empirical, based on the knowledge of the frequency and susceptibility patterns of causative pathogens and of the penetration and other pharmacokinetic properties of several oral antibiotics. Pharmacoeconomic considerations must also be taken into account. Curr Opin Infect Dis 11:659–665.

Infectious Disease Unit, University of Florence School of Medicine, Florence, Italy

Correspondence to: Franco Paradisi, Infectious Disease Unit, University of Florence School of Medicine, Nuovo Ospedale San Giovanni di Dio, Via di Torre Galli 3, I-50143 Firenze, Italy
Tel: +39 055-7192537; fax: +39 055-7192505; e-mail: infdis@cesit1.unifi.it

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Abbreviations

AOM	acute otitis media
BLP	β-lactamase-producing
ERY/S	erythromycin/sulfisoxazole
MEF	middle ear fluid
MIC	minimal inhibitory concentration
OME	otitis media with effusion
PRSP	penicillin-resistant *Streptococcus pneumoniae*
RTI	respiratory tract infection
TMP/SMX	trimethoprim/sulphamethoxazole

Introduction

Otitis media is a common clinical condition in children, in whom it is the main indication for outpatient antimicrobial use; such prescriptions doubled between 1980 and 1992 in the USA [1]. By 3 years of age, a number of children – approximately 40% in Sweden and more than 80% in the USA – will have developed at least one episode of acute otitis media (AOM) and 10–20% of children will have had recurrent infections [2•]. Acute otitis media is generally a mild disease, but it can become chronic or lead to hearing loss, mastoiditis and severe intracranial complications (meningitis, brain or extradural abscess, subdural empyema and lateral sinus thrombosis), thus antibiotics are almost invariably prescribed. In the USA alone, an annual cost of more than $3 billion is reported for medical and surgical treatment of otitis media: antibiotic prescription for this disease accounts for more than 90% of all antimicrobial use in younger children [3], whereas the placement of ventilating tubes is the second most common surgical procedure after circumcision [4]. This paper reviews current concepts and new information on the antibiotic therapy of otitis media, including some pharmacoeconomic considerations that are becoming increasingly important in the present economic climate.

Diagnosis of acute otitis media

The diagnosis of AOM is generally based on the clinical picture, that is, the presence of middle ear fluid (MEF), as demonstrated by pneumatic otoscopy or newer diagnostic tools (tympanometry, acoustic reflectometry), in association with signs or symptoms of acute local (ear pain, otorrhoea, hearing loss) or systemic (fever, irritability, etc.) illness.

Middle ear fluid sampling by tympanocentesis, performed before and during antibiotic treatment, would be the most appropriate method of guiding antimicrobial therapy and monitoring its outcome [5•], based on the so-called in-vivo sensitivity test introduced by Howie and Ploussard three decades ago. However, logistical problems or cultural resistance to the use of an invasive procedure in a common and uncomplicated clinical condition such as AOM have meant that tympanocentesis is frequently not performed. One alternative is to take a nasal or nasopharyngeal swab; this non-invasive method can provide helpful microbiological information [6], although it shows a poor (30%) predictive value in the aetiological diagnosis of AOM and it cannot replace the bacteriological assessment of the efficacy of antibiotic therapy by means of tympanocentesis sampling [7•].

Consequently, the choice of antimicrobial treatment for AOM is often empirical, based on the knowledge of microbiological and pharmacokinetic properties of a drug that must meet two conditions: it should be bactericidal against the causative pathogens, and it should reach the MEF in concentrations above the minimal inhibitory concentration (MIC) fast enough to inhibit and possibly kill bacteria.

Aetiology of acute otitis media

Streptococcus pneumoniae, *Haemophilus influenzae* and, to a lesser extent, *Moraxella catarrhalis* are the most frequent causative pathogens in AOM, responsible for up to 80% of all cases. Other less common agents include *S. pyogenes*, *Staphylococcus. aureus*, enteric Gram-negative bacilli, anaerobes and viruses [8]. *Streptococcus pneumoniae* is isolated in 30–55% of patients with AOM, H. influenzae in 20–30%, M. catarrhalis in 10–20%, *S. pyogenes* in 3–4% and *S. aureus* in 1–3%. Viruses can be present in up to 20% of patients. *Mycoplasma pneumoniae* is not considered a significant agent, and Chlamydiae (both *C. pneumoniae* and *C. trachomatis*) are generally associated with AOM in infants alone [9]. Serotypes 19, 23, 6 and 14 are prevalent among *S. pneumoniae* isolates, whereas the vast majority (>90%) of *H. influenzae* strains are untypeable, particularly since the introduction of the conjugate polysaccharide type-b vaccine [10•].

A recent multinational study [11••] has compared the aetiology of AOM in three different regions of the world: Eastern Europe, Israel and the USA. The prominent role of *S. pneumoniae* and *H. influenzae* has been confirmed with an isolation rate of 30% and 17% respectively, albeit there were differences in their geographic distribution: *S. pneumoniae* was isolated in 35% of patients in Eastern Europe, 21% in Israel and 26% in the USA, and *H. influenzae* in 11, 27 and 26%, respectively. *Moraxella catarrhalis* (4%) was on the whole less prevalent than *S. pyogenes* (7%), whereas the pathogenic role of *S. aureus*, isolated from 5% of culture samples, was uncertain.

As noted above, the aetiology of AOM is uniformly homogeneous worldwide, with only a few geographic changes. Indeed, the most important trend in the microbiology of AOM during recent years has been an increase in antibiotic resistance among the three major pathogens, namely *S. pneumoniae*, *H. influenzae* and *M. catarrhalis*.

Acute otitis media pathogens and bacterial resistance

Of the two main types of antibiotic resistance, altered penicillin binding protein targets are the cause of penicillin resistance among pneumococcal isolates, whereas the production of β-lactamases is the key factor in the genesis of ampicillin resistance in *H. influenzae* and *M. catarrhalis* strains [12•]. These resistant pathogens have appeared almost simultaneously: β-lactamase-producing (BLP) *H. influenzae* and *M. catarrhalis* in the mid1970s, penicillin-resistant *S. pneumoniae* (PRSP) in the early 1980s. Since then they have spread worldwide, reaching disturbingly high rates of prevalence in some areas [13].

According to both microdilution techniques, intermediately penicillin-resistant pneumococci are identified by an MIC of 0.1–1 μ/ml and highly penicillin-resistant strains by an MIC of >2 μg/ml [14]. It has been suggested that in the evolution of PRSP several phases can be distinguished, from a fully susceptible phase, with very low MICs of 0.008–0.03 μg/ml, to high and very high-level resistance phases, in which MICs of between 2 and 16 μg/ml are found [15•].

An international multicentre study [16] showed worrying results on antimicrobial susceptibility patterns of pathogens responsible for community-acquired respiratory tract infections (RTIs). In the USA, 11.3% of pneumococcal isolates were found to be intermediately resistant to penicillin and 7% fully resistant, whereas in Europe levels of 12.6 and 16.2%, respectively, were observed, with large intercountry variations: highly resistant strains amounted to less than 2% in Germany, the UK and Italy, and to 20–30% in France and Spain. Even more recently, similar rates of intermediate or full resistance of pneumococci to penicillin have emerged in Eastern Europe (31%) and the USA (21%), whereas a rate of 52% has been reported in Israel [11••]; the prevalence of PRSP was higher in younger infants (under 12 months of age) probably as a result of Eustachian tube dysfunction, age-dependent immunological impairment, or increasingly early exposure in daycare centres. Furthermore, an increased resistance to oral (12–25%) and parenteral (3–12%) cephalosporins, trimethoprim/sulphamethoxazole (TMP/SMX) (18%) and macrolides (10%) has been observed in PRSP isolates [17]. In particular, macrolide resistance has been found in 3–5% of penicillin-susceptible strains, 20% of penicillin-intermediate isolates and 30% of penicillin-resistant strains in Europe, with higher percentages in countries which have the highest macrolide consumption (France and Spain) [15•].

In accordance with the above data on the antimicrobial susceptibility patterns of *S. pneumoniae*, what would be the best therapeutic approach to AOM thought to be caused by *S. pneumoniae*? Although severe pneumococcal infections such as meningitis require treatment with parenteral β-lactams (cefotaxime, ceftriaxone, meropenem) or vancomycin, the need for parenteral agents in patients with less serious infections such as AOM is doubtful. An in-vitro pharmacokinetic model comparing the pharmacodynamics of amoxicillin against penicillin-susceptible and -nonsusceptible pneumococcal strains when middle-ear pharmacokinetics were simulated [18••] demonstrated the following: for penicillin-susceptible strains, it may be possible to extend the interval between doses of amoxicillin from 8 to 12 hours without compromising efficacy; for penicillin-

nonsusceptible strains, especially those exhibiting an intermediate resistance, increasing the daily dosage of amoxicillin to 70–90 mg/kg in two divided doses may be sufficient for an effective therapy. Moreover, amoxicillin and amoxicillin/clavulanate (amoxiclav) demonstrated the best activity against penicillin-susceptible (100% for both) and intermediate (95 and 97%, respectively) isolates, whereas fully PRSP was fairly susceptible to clindamycin (83%), erythromycin and chloramphenicol (70%) [11••].

The issue of BLP Gram-negatives is also important. Less than 10% of *H. influenzae* strains are β-lactamase positive in Germany, Italy and the UK, compared with 20–30% in France and Spain and approximately 30% in the USA [16], whereas rates of 13 and 26% have been observed in Eastern Europe and Israel, respectively [11••]. A reduced susceptibility of *H. influenzae* to amoxicillin (69%), macrolides (clarithromycin, 84%), and second-generation cephalosporins (cefaclor, 82%) has been found, whereas susceptibility rates close to 100% are typical with amoxiclav and third-generation oral cephalosporins (cefixime and cefpodoxime) [19]. Results of the Alexander Project show that 81.2% of *M. catarrhalis* isolates from Europe (from 77.3% in Italy to 91.4% in Germany) and 86.1% from the USA are BLP [15•], but others have reported figures of more than 90% [11••,20]. Amoxicillin possesses a poor activity against these strains, whereas a 99–100% efficacy has been reported with other antimicrobial agents such as amoxiclav, oral cephalosporins, macrolides and TMP/SMX [21].

It is well known that much of the bacterial resistance reported worldwide results from increased selective pressure linked to an extensive and often incorrect use of antibiotics. Spanish researchers have recently published worrying data on the frequency of PRSP as an agent of AOM in their country [22•]; during the study period they noted a highly significant difference between the isolation rate of PRSP from children with AOM not recently treated (50%) and recently treated (90.5%) with antibiotics, and even the percentages of BLP *H. influenzae* (43 and 23%, respectively) were significantly different. If one considers that in the USA several million antimicrobial prescriptions for nonspecific upper RTIs, bronchitis and even the common cold are issued every year [23•], it is obvious that campaigns to improve awareness in patients, physicians and public health officials and to limit unnecessary antibiotic use in general, and in AOM in particular, have been started [24,25•,26•].

Pharmacokinetics of antimicrobials for acute otitis media therapy

Achieving appropriate concentrations in the MEF is the second condition an antimicrobial drug must meet for effective treatment of AOM. It has been calculated that an 80–85% successful outcome of AOM therapy is achieved when the MEF concentration of the drug exceeds the MIC_{90} for at least 40–50% of the dosing interval [27]. Despite some potential problems that can affect antibiotic penetration into the MEF – the positive pressure created by purulent inflammatory MEF, a concurrent viral infection, or the same MEF acting as a sequestered compartment – most antimicrobial agents seem to reach adequate middle ear concentrations [28].

In general, oral cephalosporins reach MEF concentrations that are 25–60% of serum concentrations [29•]. Amoxicillin demonstrates a similar pattern, whether or not it associated with clavulanic acid, whereas the new macrolides clarithromycin and, especially, azithromycin achieve MEF concentrations higher than serum concentrations [28].

On the basis of their microbiological and pharmacokinetic properties, a number of antimicrobial agents are suitable to treat AOM: for example, high-dose amoxicillin whether or not in combination with clavulanic acid, oral cephalosporins of second (cefaclor, cefprozil, cefuroxime axetil, loracarbef) and third (cefixime, cefpodoxime proxetil) generation, the combination erythromycin/sulfisoxazole (ERY/S), the new macrolides azithromycin and clarithromycin, and TMP/SMX [30••].

Antibiotic therapy of acute otitis media

There is a lot of confusion about the optimal management of AOM. Many physicians still prescribe amoxicillin for the initial therapy of all episodes, but some prefer a β-lactamase-stable drug for fear of BLP organisms. A meta-analysis of over 5000 children treated for uncomplicated AOM in 33 randomized trials [31] was conducted in order to evaluate the efficacy of antibiotic therapy over a placebo or no medication; and the comparative efficacy of several antimicrobial agents versus amoxicillin, which is considered the drug of choice. The first research hypothesis was justified by the finding that 20% of AOM episodes caused by *S. pneumoniae*, 50% by *H. influenzae* and 75% by *M. catarrhalis* have a spontaneous rate, so that it can be difficult to prove the contribution of an antibiotic to successful therapy [32]. The results of the meta-analysis were that antibiotic treatment has a slight significant advantage over placebos or no therapy, with a 13% increase in the rate of primary control of AOM (from 81% of placebo or no drug to 91% of standard- or extended-spectrum antimicrobial treatment); worryingly, six out of every seven patients either would not need antibiotics or would not respond to them [31]. Another more recent meta-analysis has demonstrated an even more modest benefit from antimicrobial treatment of AOM: to prevent prolonged ear pain in one child 17 children would need early treatment [33]. The second objective of Rosenfeld and co-workers' meta-analysis [31] addressed the comparative efficacy of several molecules. They found that amoxicillin and TMP/SMX were as effective and safe as more expensive antibiotics such as amoxiclav, cephalosporins and macrolides; therefore they concluded that the choice of drug should be guided by safety and affordability and not by antibacterial spectrum.

However, other authors argue that, on the basis of the local prevalence of BLP *H. influenzae* and *M. catarrhalis*, amoxiclav can be considered as the first-line agent for treatment of AOM as opposed to amoxicillin alone [34•]. Indeed, amoxiclav is becoming the reference drug in many comparative trials because of its activity against both BLP strains and – if given at high doses – intermediately PRSP [35]. Amoxiclav has proved as effective as cefixime and cefdinir, although it is less well tolerated because of its gastrointestinal effects, in the 10-day treatment of AOM [36,37] and more effective than cefpodoxime proxetil in reducing nasopharyngeal carriage of *S. pneunomiae* in children with AOM [38•]. To overcome the issue of gastrointestinal toxicity, a new twice-daily formulation of amoxiclav is now available, which is associated with at least equivalent efficacy and significantly less diarrhoea and more compliance than the original thrice-daily formulation [38,40].

Typically, antimicrobial treatment of AOM consists of the administration of an oral agent. The only parenteral drug tested in clinical trials, cited in the medical literature and authorised even by the US Food and Drug Administration is ceftriaxone, which at the single intramuscular dose of 50 mg/kg has shown an efficacy and tolerability similar to those of amoxiclav and TMP/SMX. The use of this expensive and broad-spectrum cephalosporin can be justified in children with poor absorption of oral drugs or with a decreased compliance as a result of family circumstances [41•,42]. It is well known that poor compliance is the most common cause of therapeutic failure [43•]. An interesting study on the preferences of parents for antibiotic treatment of AOM has verified that a single intramuscular dose is by far more appreciated than 10-day oral amoxiclav, with compliance rates for ceftriaxone of 85% before and 83% after therapy [44]. However, although parents should be involved in medical decision making and, indeed, often want to be included in the choice of an antimicrobial agent for their child [45], in our opinion this is not a valid reason for selection of single-dose ceftriaxone in AOM; disadvantages such as higher cost and risk of emerging resistance should be more important considerations.

The duration of antimicrobial treatment of AOM has different and fundamental implications. A 10-day course of an oral antibiotic has always been the standard regimen and continues to be recommended in the USA, whereas a number of randomized trials conducted in Europe have addressed the use of shorter therapeutic courses. This is normally feasible with azithromycin, a recently developed azalide drug that is effective in the 5-day and even 3-day formulation for treatment of several RTIs because of its very prolonged elimination half-life [46]. Three to seven days of antimicrobial treatment are generally as effective as the traditional 10 days, with the potential advantages of a shorter course such as fewer adverse effects, enhanced compliance, reduced risk of emerging bacterial resistance and lower therapeutic and overall costs [47••]. However, it must be emphasised that short-term treatment has been associated with a significantly higher rate of clinical failure in children younger than 2 years of age [39], possibly because of their less effective immune system or long-lasting ear and nose congestion caused by repeated viral upper RTIs, thus the traditional 10-day treatment is still recommended in this age group [48•] as well as in patients more likely to be infected with resistant organisms or with severe or complicated AOM [9].

Holland is the country with the lowest consumption of antibiotics for AOM: only 31% of patients are treated [49]. Indeed, a conservative approach to children with AOM has been the rule in Holland for a decade: symptomatic treatment alone is provided for the first 2–3 days, possibly followed by amoxicillin for several days if symptoms of AOM persist. This therapeutic strategy is justified by Dutch experts with the conclusions drawn in seven randomized, blinded, placebo-controlled trials over the past 30 years, in which neither short- nor long-term significant differences were demonstrated. The Dutch approach to children with AOM would have the advantage of reduced bacterial resistance and diminished economic costs. In the latter case, increased expenses resulting from telephone calls and additional visits would be offset by reduced use or duration of antimicrobials and diminished surgery visits linked to adverse effects. Suppurative complications of this therapeutic strategy would be minimal, as mastoiditis has been observed in 0.04% of untreated patients and meningitis in none [50•,51•]. The same approach has been adopted in Iceland [52].

In the economic climate of today, pharmacoeconomic considerations are becoming very important. Although the average antibiotic cost accounts for only 13% of the average total (direct and indirect) costs of treating a single episode of AOM, more than one-half of general practitioners and paediatricians continue to prescribe the least expensive antimicrobial agent, namely amoxicillin [53]. However, this aminopenicillin drug seems to be the most economical not only for the wholesale price but also for the total cost, including significant expenses such as physician fees, value of work time lost and transportation costs [54]. Interestingly, a recent study comparing the antibiotic prescribing patterns of US physicians [55••] has concluded that the clinical outcomes associated with more expensive antibiotics (amoxiclav, cephalosporins) were no better than those of less expensive agents (amoxiclav, TMP/SMX, ERY/S); significantly, the former accounted for 30% of prescriptions and for 77% of expenditures, the latter for 67 and 21%, respectively. Although some cost-effective antimicrobial agents (TMP/SMX, ERY/S) are less palatable than other more recent and expensive drugs [56], we believe that patients and their parents must make every effort to ensure that palatability does not affect compliance significantly.

Our closing opinion is fully in agreement with the very recent recommendations for judicious use of antimicrobial agents in otitis media provided by the US Centers for Disease Control and Prevention [57••]: every episode of AOM in children aged over 2 years should be treated with a 5- to 7-day course of an oral antibiotic; as most antimicrobial failures are reported in children younger than 2 years of age, a traditional 10-day course is still advisable in these patients as well as in children with severe or complicated AOM. As first-line treatment, we prefer a safe and economic agent such as high-dose amoxicillin or, in patients allergic to β-lactams, TMP/SMX. More expensive and extended-spectrum drugs (amoxiclav, oral cephalosporins, macrolides) should be used only if local epidemiology predicts the risk of therapeutic failure because of a very high prevalence of BLP organisms. Single-dose intramuscular ceftriaxone should be limited to a few select patients, namely children who might have either a poor absorption of oral drugs or a decreased compliance through family circumstances (i.e. nomads or immigrants).

Unresponsive acute otitis media

Approximately 10% of children with AOM treated with a 10-day course of antibiotics continue to have clinical symptoms and otoscopic findings of inflammation after 48 hours of therapy, primarily when a viral upper RTI is present simultaneously. The same causative agents as in untreated patients are isolated, although a higher frequency of PRSP and BLP *H. influenzae* is observed [58•]. Unresponsive AOM in a child treated with amoxicillin can be treated with TMP/SMX and vice versa. More expensive drugs such as amoxiclav, third-generation cephalosporins and newer macrolides offer minimal advantage in covering highly resistant organisms such as PRSP. If unresponsive AOM persists after a second course of antibiotics, tympanocentesis in order to drain the effusion, isolate the pathogen and find its antimicrobial susceptibility patterns is indicated [4]. Otherwise, β-lactamase-stable drugs such as amoxiclav or an oral cephalosporin can be used as a second-line treatment for unresponsive AOM [28].

Recurrent acute otitis media

Recurrent middle-ear infections are defined as three or more episodes of AOM within 6 months. This situation indicates the so-called 'otitis-prone' child, in whom recurrent AOM is facilitated by host and environmental risk factors [2•]. Antibiotic prophylaxis can facilitate the emergence of bacterial resistance [59], nevertheless it is employed for preventing recurrences of AOM although a meta-analysis [60] demonstrated that treatment of nine children is required to show an improved outcome in one. Daily low-dose antibiotics (i.e. amoxicillin 20 mg/kg, sulfisoxazole 75 mg/kg) are administered for no more than 6 months [4]. Insertion of ventilation tubes for at least 6 months must be reserved for children unresponsive to prophylactic antibiotics and those with severe conductive hearing impairment [61•]. Other possible interventions include eliminating dummies and smoking in the home, reducing daycare centre attendance and giving influenza and pneumococcal vaccines [57••].

Otitis media with effusion

Otitis media with effusion (OME) is associated with mixed bacterial flora in approximately 50% of cases [10•]. Recently, the role of *C. pneumoniae* as causative pathogen of upper RTI has been re-examined as it has been isolated from 9.4% of children with OME by the polymerase chain reaction technique [62•].

There is still debate on the usefulness of antimicrobial agents in OME. Two former meta-analyses [60,63] concluded that there is a small but statistically significant impact of antibiotics on the resolution of OME, although it is a short-term effect. On the other hand, some experts recommend that, in the absence of AOM, children with MEF should not be treated with antimicrobial agents at all [64]. We believe that the guidelines recently published by the US Agency for Health Care Policy and Research provide a valid approach to this issue: clinical and otoscopic observation alone should be considered the preferred option, whereas antibiotic therapy or insertion of tympanostomy tubes is the proper choice for children in whom bilateral effusion persists for at least 3 months and is accompanied by significant bilateral hearing loss [57••]. As for therapy of AOM, amoxicillin and TMP/SMX can be regarded as the drugs of choice, although the increasing prevalence of *C. pneumoniae* could require the use of ERY/S. If the local prevalence of BLP organisms such as *H. influenzae* is high, β-lactamase-stable drugs such as amoxiclav [65•] or an oral cephalosporin are valid alternatives.

Conclusion

Each episode of AOM should be treated with a 5- to 7-day course (10-day in children aged under 2 years) of amoxicillin or, in patients allergic to β-lactams, TMP/SMX. In areas with high prevalence of BLP organisms such as *H. influenzae*, therapy with β-lactamase-stable antibiotics such as amoxiclav, oral cephalosporins or newer macrolides can be considered. Tympanocentesis is advisable in children with AOM that has not responded to more than two antimicrobial courses. Antibiotic prophylaxis or, alternatively, insertion of ventilation tubes are indicated to prevent recurrences. Either medical or surgical treatment is required in OME only if significant bilateral hearing loss occurs.

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