REVIEW ARTICLE

Pediatr Drugs 2003; 5 Suppl. 1: 1-12
1174-5878/03/0001-0001/$30.00/0

Acute Otitis Media in Pediatric Medicine

Current Issues in Epidemiology, Diagnosis, and Management

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Contents

Abstract

Acute otitis media (AOM) is not only the most common bacterial infection in children in the United States, it is also the most common indication for the prescription of antibiotics. Unfortunately, antibiotic resistance to pathogens (*Streptococcus pneumoniae, Haemophilus influenzae,* and *Moraxella catarrhalis)* typically causative of AOM, continues to increase. More than 30% of the beta-lactamase producing *H. influenzae* are resistant to amoxicillin and virtually all strains of *M. catarrhalis* are beta-lactamase–positive. The emergence of multidrug-resistant strains, particularly *S. pneumoniae*, complicates the management of AOM and increases the risk for treatment failure. Because of growing resistance, the Centers for Disease Control and the American Academy of Pediatrics promote the judicious use of antibiotics in the treatment of AOM. Their recommendations emphasize the importance of distinguishing AOM from otitis media with effusion, minimizing the use of antibiotics, and discerning between first- and second-line antibiotics in the treatment of simple uncomplicated AOM versus non-responsive/recurrent AOM. Because spontaneous cure rates are lower in complicated AOM and AOM secondary to *S. pneumoniae* infection, antibiotic therapy remains an appropriate treatment option for most children with AOM. When amoxicillin, the treatment of choice in AOM, is not effective or not tolerated in children, the prescriber should consider an alternative that displays not only excellent antimicrobial activity against the suspected pathogens, but also characteristics, such as convenient dosing, tolerability, and palatability, that promote compliance and adherence in children. The cephalosporins offer an alternative to penicillins. Cephalosporins such as cefuroxime axetil (second-generation) and cefdinir and cefpodoxime proxetil (third-generation), offer a broad spectrum of activity and are approved for use in a convenient once- or twice-daily dosing schedule, thus increasing the likelihood of compliance with the full course of therapy. Cefdinir is a possible second-line alternative to amoxicillin for children with AOM, particularly among children who are likely to be noncompliant with a two- to three-times-daily dosing schedule, and those instances where there is a high likelihood for, or a known infection with an amoxicillin-resistant pathogen.

1. Introduction

A common disease in the pediatric setting, acute otitis media (AOM) secondary to bacterial infection can pose a therapeutic challenge. Current treatment guidelines advocate the judicious use of antibiotics, with amoxicillin advocated as first-line therapy. However, if amoxicillin is not effective or well tolerated, choosing an effective antibiotic can be a daunting decision, made more difficult by the increasing antibiotic resistance of many pathogens that cause AOM. This article will elucidate some of the important issues surrounding the treatment of AOM by reviewing current data on the epidemiology and pathophysiology of bacterial AOM, including the emergence of treatment-resistant bacterial strains, and by examining and clarifying the oral antibiotic options available for the management of AOM in children.

2. Epidemiology

Although AOM can occur at any age, it is principally a disease of the young; approximately 80% of infections occur in children.[1,2] Indeed, AOM most commonly presents between the ages of 3 months and 3 years, with a peak incidence between 6–9 months.[3] As the most commonly diagnosed bacterial infection in young children in the US, AOM is associated with a substantial economic burden that approaches $3.8 billion annually, predominantly attributable to the cost of antibiotic therapy.[4,5] By one year of age, at least 60% of children have experienced one AOM episode and 17% have suffered at least three episodes. The risk for recurrence appears related to the age of initial onset; 60% of the children who have had their first episode before the age of 6 months experience at least two recurrences within the subsequent two years.[3] During the last 2 decades, the incidence of AOM has increased in the US, possibly as a result of the increased use of day care.[6] Children who attend day care centers are more likely to experience upper respiratory infections, including AOM, when compared with children who receive day care in a family home.[7] For all children, however, a family history of upper respiratory disease is a major predisposing factor. Exposure to environmental tobacco smoke has also been implicated as a risk factor for AOM,[8] as has male gender, a sibling history of recurrent AOM, early disease occurrence, and not being breast-fed.[9] In the Greater Boston Otitis Media Study, breast-feeding for only three months decreases the risk for AOM during the first year of life.[10,11] 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.[12]

3. Clinical Presentation

Otitis media, a non-specific inflammation of the middle ear, occurs in two major forms: AOM and otitis media with effusion (OME). The distinction may be clinically challenging because these pathologies commonly represent a continuum, with OME sometimes following AOM. Nonetheless, an accurate differential diagnosis is essential for ensuring appropriate treatment, since overdiagnosis of AOM is common,[13] and antibiotics are not indicated for OME.[6] AOM accounts for 65–75% of all instances of otitis media.[14] 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.[15] These generalized symptoms may mimic a viral syndrome, such as an upper respiratory infection. In OME, by contrast, children present with asymptomatic middle ear effusion, although a "plugged ear" sensation may be present. Because the symptoms of AOM are not sufficiently specific, an otoscopic examination of the tympanic membrane is essential for an accurate differential diagnosis.[16] Normally, the tympanic membrane has a neutral, slightly concave profile, not bulging or retracted. Further, it displays a translucent, pearly gray color and is elastic, quickly responding to positive and negative air pressure. In AOM and OME, tympanic membrane mobility is either reduced or absent. Children with AOM have otoscopy findings of inflammation in the middle ear, a bulging tympanic membrane that is opaque with pronounced erythema, and prominent vessels. It should be noted that an erythremic tympanic membrane with normal mobility is not diagnostic of otitis media, but a normal physiologic feature in crying children, particularly during an upper respiratory infection. Children with OME, by contrast, typically have a translucent tympanic membrane, without bulging or other evidence of infection or inflammation.[16] Eustachian tube congestion often accompanies nasal congestion in children with an upper respiratory tract infection.[13] Blockage of the eustachian tube can cause gas from the middle ear space to migrate across the tympanic membrane, producing a membrane retraction that, without the use of otoscopy or tympanometry, can be confused with the bulging tympanic membrane characteristic of AOM. Further, retraction of the tympanic membrane may be associated with mild otalgia. In the context of a viral upper respiratory infection, this combination of symptoms can lead to a misdiagnosis of AOM and, in turn, inappropriate antibiotic treatment.

4. Pathophysiology

Although multifactorial, the pathogenesis of AOM is typically linked to inflammation and blockage of the eustachian tube.[17] The eustachian tube, which is shorter and flatter in young children and thus more prone to infection, provides a conduit for the clearance of secretions from the middle ear into the nasopharynx. Any upper respiratory tract infection that causes blockage of the eustachian tube can lead to AOM. For most children who develop AOM, the

antecedent pathologic event is a viral upper respiratory infection in which pathogens migrate along the mucosa of the nasopharynx into 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.[6] Indeed, a link between viral upper respiratory infections and AOM appears clear. Samples of middle ear secretions from children with AOM in which viruses were isolated revealed viral and bacterial coinfections in up to 65% of cases.[18] Among the viruses recovered from the middle ear of children with upper respiratory infections, the respiratory syncytial virus (RSV) is isolated most commonly, followed by parainfluenza virus, human rhinovirus, influenza virus, enteroviruses, and adenoviruses.[19] Respiratory viruses may degrade eustachian tube function by triggering the release of inflammatory mediators from epithelial cells. Moreover, some respiratory viruses can suppress the function of polymorphonuclear cells and increase the adherence of bacteria to epithelial cells, providing a favorable environment for the development of AOM.[20] Yet, bacteria are by far the leading pathogens in AOM; only about 20% of the AOM cases are caused by viral infections alone.[19] In AOM, the principle bacterial isolates are the same as those that typically infect the upper respiratory tract in children. Moreover, in newborns, the causative pathogens are also those encountered in older age groups, except that Gram-negative enteric bacilli sometimes causes suppurative otitis media in infants.[21] After the neonatal period, *S. pneumoniae* are not only the most frequent bacterial isolates in AOM, occurring in 40% or more of the infections, but also the least likely to resolve spontaneously.[22,23] *H. influenzae* and *M. catarrhalis* are the second and third most common bacterial isolates in AOM, with frequencies of 30–40% and 3–20%, respectively.[5]

5. Bacterial Resistance

Disconcertingly, antibiotic resistance is increasing among the bacterial pathogens implicated in the development of AOM. The percentage of *S. pneumoniae* strains demonstrating resistance to penicillin and amoxicillin ranges between 30–70%,[24-28] and 11% are resistant to third-generation cephalosporins.[24] The percentage of nonsusceptible *S. pneumoniae* isolated from the middle ear fluid of children with AOM non-responsive to initial antibiotic therapy was reported to be even higher and may reach more than 80% of all isolates.[29] Additionally, the percentage of beta-lactamase–producing *H. influenzae* and *M. catarrhalis* strains has increased markedly in the last decade, thus increasing resistance to beta-lactam antibiotics. In 1997, approximately 30% of the *H. influenzae* isolates displayed resistance to amoxicillin; more than 90% of these by beta-lactamase production. Moreover, virtually all strains of *M. catarrhalis* were beta-lactamase–positive.[30] 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 has continued to increase, at least partially the result of inappropriate use of antibiotic therapy.[31]

6. Treatment of Acute Otitis Media

6.1 Current Treatment Approaches in AOM

During the last decade, the prescribing pattern for upper respiratory infections, including AOM, has undergone an important shift. Although population-based prescription rates remain higher for AOM than for any other bacterial infection in children, antimicrobial prescribing rates have decreased overall during the last decade.[32] These decreases have been spurred by findings that show a high rate of spontaneous remission in children with uncomplicated AOM, and concerns about the increasing rate of antibiotic resistance. In one meta-analysis that covered a 25-year period, AOM resolved spontaneously at 7–14 days in 80% of children; there was a 95% resolution rate for antibiotic-treated children.[33]

Antibiotics are the standard of care for the treatment of AOM in the US and many other countries all over the world.[33] Although antibiotic therapy is required for only 20–30% of all patients with AOM, most are treated with antibiotics because this small population cannot be quickly and easily identified. The main goal of antibiotic therapy is to eradicate the causative pathogens from the middle ear fluid (MEF). However, classical AOM antibiotic studies, comparing various drugs and which efficacy was measured by symptomatic relief only, were generally performed on small numbers of patients and failed to discern major differences among drugs in the treatment of AOM. These studies were undoubtedly affected by the so-called "Pollyanna phenomenon" as described by Marchant et al.[34] who showed that, because of the high rate of spontaneous recovery in AOM, drugs with poor antibacterial activity may appear as effective as highly efficacious drugs. As a result of this phenomenon, a difference in bacteriologic efficacy of 20%, for example, will be associated with a much smaller difference (6%) in clinical outcome; such a clinical difference may be reached in antibiotic studies looking for clinical outcome by increasing the number of recruited patients to hundreds or even thousands in each comparative study arm. "Classical" clinical efficacy studies generally enroll much smaller numbers of patients and therefore are not able to discern any significant difference among the drugs under investigation. In addition, these studies suffer from other methodologic problems, such as lack of tight enrollment criteria (unable to exclude children with otitis media with effusion associated with a non-specific intercurrent illness) and inclusion of children >2 years who generally have milder, self-limited forms of

the disease. An appropriate demonstration of bacteriologic eradication of AOM pathogens can only be obtained 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[35] and named by them "*in vivo* sensitivity test," has the great advantage of being able, following the enrollment of relatively few patients, to discriminate between the efficacy of different drugs used in the treatment of AOM. The double-tympanocentesis studies are difficult to conduct and require close collaboration between pediatricians, ENT specialists, and microbiologists, and therefore, are performed in only a small number of medical centers. On the other hand, the results provided by such studies are straightforward, consistent, and unbiased. A "historical" double-tympanocentesis study performed by Howie et al. showed a major difference in the persistence of different AOM pathogens in the MEF of patients receiving placebo therapy; when a second tympanocentesis was performed on days 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.[36]

When is antibiotic therapy for AOM appropriate? Some investigators advocate withholding antibiotic treatment for AOM completely or delaying treatment for two days after symptom onset.[37] In the actual clinical setting, cumbersome diagnostic procedures, such as tympanocentesis, are unlikely to be performed routinely. Therefore, because the causative organism is generally not identified, empiric treatment is warranted. Children least likely to experience spontaneous remission in AOM are those that may derive the greatest benefit from appropriate antibiotic therapy.[13] The natural history of non-responsive AOM is not as favorable as that of uncomplicated AOM. Recent studies demonstrated a high correlation between antibiotic-resistant *S. pneumoniae* strains and treatment failure; only 14–21% of *S. pneumoniae* isolated from patients with non-responsive AOM were susceptible to the antibiotic drug previously prescribed.[29] However, this trend was not evident for *H. influenzae* isolates; more than 77% of *H. influenzae* isolated from non-responsive AOM patients were susceptible, according to the National Committee for Clinical Laboratory Standards breakpoints (but not to pharmacokinetic/pharmacodynamic ones) to the previously administered antibiotic.[29,38]

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.[39] These recommendations underscore the importance of distinguishing AOM from OME and prescribing antibiotics only for the former, minimizing the use of the antibiotics for AOM, and discerning between first- and second-line antibiotics in the treatment of simple uncomplicated AOM versus non-responsive/recurrent AOM. The guidelines continue to recommend amoxicillin therapy as initial treatment for AOM.[23] Antimicrobial therapy in children with AOM is generally most beneficial when pathogenic bacteria are isolated from the middle ear to guide antibiotic selection; 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 7–14 days.[39] In addition, young children under the age of 2 years tend to benefit more from antibiotic treatment than older children.[13] It should also be noted that middle ear effusion in AOM may persist for weeks, or even months, after antibiotic therapy has been completed. In fact, after antibiotic treatment, MEF is present in 70% of children at 2 weeks, in 50% at 1 month, in 20% at 2 months, and in 10% at 3 months. Thus, in otherwise asymptomatic children with AOM, further antimicrobial therapy is unnecessary.[11,40,41]

Against the backdrop of growing antimicrobial resistance, the appropriate choice of an antibiotic for the treatment of AOM has become even more important. The selection should be based on efficacy against the common pathogens involved in AOM, ability to achieve meaningful concentrations in the middle ear, favorable adverse event profile, convenience of administration, and palatability, an especially important feature in children.[24] Adherence to antibiotic therapy can generally be promoted using a regimen of antibiotics that requires less frequent dosing (once or twice daily) and shorter courses of therapy (5 days or less), although short courses have been proven to be inferior particularly in the treatment of AOM in children <2 years of age and in those with non-responsive or recurrent episodes of AOM.[42]

6.2 Antibiotics Indicated for the Treatment of AOM

Despite a body of evidence suggesting they are overused, antibiotics, when prescribed judiciously and taken according to the prescribed regimen, remain the cornerstone of treatment of AOM. Although antibiotics from several different classes are approved for the treatment of AOM (table I) and individual agents differ in their actions against major bacterial pathogens involved in AOM (table II), it should be noted that differences in the effectiveness of an antibiotic in the treatment of this condition may be obscured by the previously mentioned "Pollyanna phenomenon," or the fact that as many as 80% of the children with AOM may improve with placebo treatment.[34]

6.2.1 Penicillins

Currently, no single oral antibiotic eradicates all of the pathogens involved in the development of AOM, especially drug-resistant *S. pneumoniae*.[43] Nonetheless, because of its efficacy

Table I. Oral antibiotics used to treat acute otitis media

Drug class	Drug product (brand)	Daily dosage	Duration of therapy
Penicillins	Amoxicillin	40 mg/kg q 8 h or q 12 h*	10 days
	Amoxicillin-clavulanate (Augmentin)	40 mg/kg as amoxicillin q 8 h*	10 days
Sulfonamide combinations	Trimethoprim-sulfamethoxazole (Bactrim, Septra)	8 mg/kg of trimethoprim and 40 mg/kg sulfamethoxazole q 12 h	10 days
Macrolides and combinations	Azithromycin (Zithromax)	30 mg/kg given as a single dose, or 10 mg/kg once daily for 3 days, or 10 mg/kg as a single dose on the first day followed by 5 mg/kg/day on days 2 through 5.	1–5 days
	Erythromycin-sulfisoxazole (Eryzole, Pediazole)	40–50 mg/kg of erythromycin q 6 h not to exceed 2 g erythromycin or 6 g sulfisoxazole/day	10 days
	Clarithromycin (Biaxin)	7.5 mg/kg q 12 h	10 days
Cephalosporins	Cefaclor (Ceclor)	20–40 mg/kg q 8–12 h	10 days
	Cefdinir (Omnicef)	7 mg/kg q 12 h	5–10 days
		14 mg/kg q 24 h	10 days
	Cefixime (Suprax)	8 mg/kg q 12 h or q 24 h	10 days
	Cefpodoxime proxetil (Vantin)	10 mg/kg q 12 h	5 days
	Cefprozil (Cefzil)	15 mg/kg q 12 h	10 days
	Cefuroxime axetil (Ceftin, Kefurox, Zinacef)	30 mg/kg q 12 h	10 days
	Loracarbef (Lorabid)	30 mg/kg q 12 h	10 days
	Ceftibuten (Cedax)	9 mg/kg q 24 h	10 days

*Use 80 to 90 mg/kg/day of amoxicillin.

Adapted from Sagraves[24] with data from Taketomo[107]

against *S. pneumoniae* and a favorable pharmacodynamic profile, amoxicillin remains the antibiotic of choice in the treatment of uncomplicated AOM.[23] Indeed, amoxicillin displays the longest time above minimum inhibitory concentration $(MIC)_{90}$, the concentration that will inhibit 90% of a collection of bacterial isolates, against drug-resistant *S. pneumoniae* of any of the antibiotics approved for treatment of AOM. Additionally, amoxicillin is relatively inexpensive and has a long history of safety and efficacy in

Table II. Oral antibiotic activity against specific strains

Drug class	Drug product (brand)	*Streptococcus pneumoniae*/PRSP	*Haemophilus influenzae*	*Moraxella catarrhalis*
Penicillins	Amoxicillin	+++/+*	++	+
	Amoxicillin-clavulanate (Augmentin)	+++/++	+++	+++
Sulfonamide combinations	Trimethoprim-sulfamethoxazole (Bactrim, Septra)	+++/–	++	+++
Macrolides and combinations	Azithromycin (Zithromax)	+++/–	–	++
	Erythromycin-sulfisoxazole (Eryzole, Pediazole, Sulfimycin)	+++/–	–	–
	Clarithromycin (Biaxin)	+++/+	+	++
Second-generation cephalosporins	Cefprozil (Cefzil)	+++/+	++	+++
	Cefuroxime axetil (Ceftin, Kefurox, Zinacef)	+++/++	+++	+++
	Loracarbef (Lorabid)	+++/+	+++	++
	Cefaclor (Ceclor)	+++/–	–	+++
Third-generation cephalosporins	Cefdinir (Omnicef)	+++/–	+++	+++
	Cefixime (Suprax)	+/–	+++	+++
	Cefpodoxime proxetil (Vantin)	+++/+++	+++	+++
	Ceftibuten (Cedax)	+++/–	++	+

*Use 80 to 90 mg/kg/day of amoxicillin.

PRSP = Penicillin-resistant *S. pneumoniae*; +++ = good coverage; ++ = average coverage; + = minimal coverage; – = no coverage.

Adapted from Sagraves[24] with data from Justice et al.[108]

the treatment of AOM.[23] Standard doses of amoxicillin, 40–50 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*. No oral antimicrobial agent consistently eradicates penicillin–nonsusceptible *S. pneumoniae*.

In children with AOM, higher doses of amoxicillin, 75 mg/kg/day in divided doses, produces MEF concentrations of >1 μg/mL for at least 50% of the dosing interval.[44] Higher doses, up to 90 mg/kg/day, given as amoxicillin-clavulanate, achieve MEF concentrations of 3–8 μg/mL, concentrations perhaps sufficient to eliminate penicillin-nonsusceptible species. Recently, our group reported results from 50 culture-positive AOM patients treated 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*, beta-lactamase–negative *H. influenzae,* and beta-lactamase–positive *H. influenzae,* respectively. Overall, 14 (28%) of 50 patients failed bacteriologically on days 4–6, of whom 9 (64%) had beta-lactamase–positive *H. influenzae*, suggesting that the amoxicillin high-dose regimen selected for beta-lactamase–positive *H. influenzae* as the main organism to be targeted in cases of treatment failure.[45] However, it is important to note that doses above 45 mg/kg/day have not been approved by the FDA.[23] In children with AOM, amoxicillin-clavulanate, 45 mg/kg/day for 10 days, when compared with azithromycin, 10 mg once daily for the first day followed by 5 mg for the next 4 days, has been found to be significantly more effective against *H. influenzae*. On day 4–6 of therapy bacteriologic treatment success rates vary from 87% for amoxicillin-clavulanate to 39% for azithromycin.[46] In addition, there is a trend toward greater efficacy for amoxicillin-clavulanate over azithromycin against *S. pneumoniae*. Bacteriological success rates are 90% for amoxicillin-clavulanate versus 68% for azithromycin on days 4–6 of therapy. Regarding the clinical efficacy of the two drugs, on days 12–14, signs and symptoms were more likely to resolve completely or improve in all culture-positive patients (86% vs 70%) and in those with *H. influenzae* infections (91% vs 65%) who received amoxicillin-clavulanate versus azithromycin. If amoxicillin therapy for AOM is ineffective, a tympanocentesis or a culture of MEF may be used to identify the etiologic pathogen and to act as a guide for selecting alternative antibiotic therapy. Bacterial resistance to amoxicillin is typically mediated by either the production of beta-lactamase enzymes (*H. influenzae* and *M. catarrhalis*) or the modification of the penicillin-binding sites (*S. pneumoniae*).[47] During the 1990s, penicillin-resistant *S. pneumoniae* strains were more frequently isolated in the US, with isolation rates of 40% in children attending day care centers and 17% overall in children with AOM. In children, the prominent risk factors for the development of penicillin-resistant *S. pneumoniae* include attendance to a child care center, the presence of refractory AOM, <2 years of age, and the presence of AOM predisposing conditions, such as upper respiratory infections.

If an alternative to amoxicillin is selected empirically, the ideal antibiotic should display a broad spectrum of activity, with efficacy against beta-lactamase–producing pathogens, such as *H. influenzae* and *M. catarrhalis*, as well as drug-resistant *S. pneumoniae*.[23]

6.2.2 Sulfonamide Combinations

Trimethoprim-sulfamethoxazole (TMP-SMX), a broad-spectrum antimicrobial, may be indicated only for the treatment of childhood AOM secondary to susceptible strains of *H. influenzae*, including ampicillin-resistant strains, or *S. pneumoniae*.[48] TMP-SMX has often been used as first- and second-line therapy for AOM, with efficacy and tolerability reported as at least comparable to amoxicillin-clavulanate.[49] Yet, the frequency of isolation of TMP-SMX–resistant strains of *S. pneumoniae* and *H. influenzae* continues to increase, accompanied by an increase in treatment failures.[50] The bacteriologic and clinical efficacy of a 10-day regimen of TMP-SMX was recently examined in 54 children (aged 3 to 32 months) with culture-verified AOM.[50] The MEF of the 54 children contained a total of 67 organisms: *S. pneumoniae* (24), *H. influenzae* (40), and *S. pyogenes* (3). Pathogens non-susceptible to TMP-SMX (MIC >0.5 μg/mL) were detected among 63% of the *S. pneumoniae*, 30% of the *H. influenzae*, and 100% of the *S. pyogenes* organisms. Further, nine new pathogens emerged during treatment, most were (77%) TMP-SMX–resistant. Clinical failure was noted in 8 (15%) of the 54 patients, with all but one occurring among the bacteriologic failures. Additionally, ten of the children relapsed after treatment. These findings indicate that TMP-SMX is not indicated in regions where resistant TMP-SMX strains are reported. In addition, the use of TMP-SMX has been associated with the development of Stevens-Johnson syndrome.[51]

6.2.3 Macrolides

In children, the macrolides, especially the newer agents such as azithromycin and clarithromycin, were considered effective and safe antibiotics in the treatment of AOM and possible second-line alternatives to penicillins.[52] Compared with erythromycin, these newer agents may provide, at least theoretically, enhanced MEF concentrations, tissue and leukocyte penetration, and improved gastrointestinal tolerability.[53] However, as with the other classes of antibiotics, some of the common pathogens involved in AOM, *S. pneumoniae* and *H. influenzae,* display increasing resistance to macrolide antibiotics. For instance, in the US, resistance to macrolides among these pathogens has reached 25–30%; in Japan, resistance rates now exceed 50%.[54] 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*.[55] For instance, the MIC_{90} of azithromycin against *H. influenzae* is four- to eightfold lower than erythromycin and eightfold lower than clarithromycin,

while against *M. catarrhalis* it is about fourfold more active. Using the clinical improvement of the middle ear findings as an end-point, short, 5-day courses of azithromycin appeared initially as effective as other antibiotic regimens in the treatment of upper respiratory infections, including uncomplicated AOM.[56,57] In one such study that evaluated 154 children with uncomplicated AOM, a 3-day azithromycin regimen (single, daily 10 mg/kg dose) resulted in a cure rate of 79%, significantly higher than the 58% cure rate seen with a 10-day amoxicillin regimen (30 mg/kg/day in three divided doses).[58] However, in investigational otitis media, tympanocentesis performed 4–6 days after the initiation of therapy in children with non-typeable *H. influenzae* revealed the presence of persistent infection in 50% of the cultures.[59] The bacteriologic efficacy of azithromycin, was studied by our group in two consecutive studies. These 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 the placebo.[46,60] In addition, the eradication rates of *H. influenzae* were poor and close to the rates of the 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.[61] In children 6 months to 16 years of age, the efficacy of clarithromycin in the treatment of AOM is comparable, at least theoretically, to that seen with other macrolides, beta-lactam antibiotics, and the cephalosporins. In studies that use clinical outcome as the main end-point, clarithromycin has been shown to be as effective as amoxicillin and cefaclor in children with AOM.[62,63] In addition, erythromycin-sulfisoxazole, 50 mg/kg/day, given in three divided doses for 10 days, was as effective as amoxicillin-clavulanate in children with AOM.[64]

6.2.4 Clindamycin

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,* a caveat 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.

6.2.5 Cephalosporins

6.2.5.1 Second-generation cephalosporins

Four second-generation cephalosporins, cefaclor, cefprozil, cefuroxime, and loracarbef, are indicated for the treatment of AOM. In <1.5% of children, cefaclor has been linked to the development of a serum sickness-like reaction characterized by erythema multiforme, arthralgia, and fever.[51] Consequently, cefuroxime, cefprozil, and loracarbef are more commonly used for the treatment of AOM.[65] 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 agent 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.[66,67] Because of poor palatability, its use as a liquid formulation suitable for administration to children has been limited; however, a new, more palatable, 250 mg suspension is now available.[47] Although cefprozil displays acceptable activity against penicillin-resistant *S. pneumoniae*, it is less active against *H. influenzae* and is hydrolyzed by beta-lactamases.[68] Its bacteriologic efficacy has not yet been evaluated in prospective, comparative, double-tympanocentesis studies. Loracarbef is somewhat more active than cefaclor against *H. influenzae,* but is less active *in vitro* against *M. catarrhalis* and *S. pneumoniae,* particularly against penicillin-intermediate and resistant-strains.[69,70] The use of loracarbef has not been associated with the development of a serum sickness-like reaction. Generally, the third-generation cephalosporins are more active against the pathogens responsible for AOM.

6.2.5.2 Third-generation cephalosporins

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.[71-76] 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*,[77-79] with ceftibuten displaying the highest activity against *H. influenzae*.[80] Ceftibuten is less active against *M. catarrhalis* (MIC_{90} 4.0 μg/mL) and penicillin-susceptible *S. pneumoniae* (MIC_{90} 4.0–8.9 μg/mL) than other third-generation antibiotics. However, within the MEF, it may achieve concentrations that surpass the MIC for many of the organisms involved in AOM.[81] Like other beta-lactam antibiotics, ceftibuten is not active against penicillin-resistant *S. pneumoniae*. In patients with otitis media, ceftibuten has been reported to be less effective than cefaclor against infection secondary to *S. pneumoniae*.[82] The manufacturer thus recommends that ceftibuten be administered empirically only when adequate antimicrobial coverage against *S. pneumoniae* has been previously given. In the treatment of children with AOM, ceftibuten once daily was found to be as effective

and well tolerated as cefprozil twice daily over the 10-day treatment period, with clinical improvement seen in over 80% of the children in each group.[83] In children with recurrent AOM, a 10-day course of ceftibuten was associated with a significantly lower rate of recurrence (4.5%) than a 5-day treatment course (21.4%) at 2 weeks after the end of treatment.[84] Again, the bacteriological efficacy of ceftibuten has not yet been proven in a comparative double-tympanocentesis study. Cefixime has demonstrated well tolerated efficacy in the treatment of otitis media in children, as well. In a large clinical study that included over 25,000 children with AOM, 86% were considered either cured or improved after once-daily cefixime treatment for 10 days.[85] Other investigators have shown that cefixime is as effective as amoxicillin-clavulanate in AOM, and may display greater patient acceptability and significantly fewer side effects, especially diarrhea and vomiting.[86] However, *in vitro* susceptibility testing of amoxicillin-clavulanate, penicillin G, and 6 cephalosporin antibiotics (cefpodoxime, cefuroxime, cefprozil, cefaclor, loracarbef, and cefixime) against 65 strains of *S. pneumoniae* demonstrated that cefixime was the least potent of all tested agents.[26] Among 30 children with otitis media due to *S. pneumoniae,* cure rates were 93% after treatment with amoxicillin compared with 75% with cefixime.[87] Although not a statistically significant difference, these findings may have clinical significance, but the bacteriological efficacy of the drug has never been evaluated in a double-tympanocentesis study. Cefpodoxime and cefdinir appear to have the broadest spectrum of activity among the oral cephalosporins, with relatively greater activity against penicillin-susceptible *S. pneumoniae* and intermediate penicillin-resistant *S. pneumoniae*.[47,78,88] Cefpodoxime, given twice daily for 5–10 days, has also been shown to be effective in the treatment of AOM in children, with cure or improvement rates ranging from 60–95%, and overall efficacy comparable to that seen with amoxicillin-clavulanate, cefaclor, cefuroxime, and cefixime.[88-93] In young children with AOM, the clinical response rates with cefpodoxime were significantly higher after a 10-day than after a 5-day treatment period.[94] Convincing data regarding its bacteriologic efficacy in eradicating the main AOM pathogens is still missing. Cefdinir exhibits a set of properties: a broad spectrum of activity, convenient dosing schedule, favorable adverse event profile, and a pleasant taste. These qualities make it a possible alternative to amoxicillin in the treatment of children with AOM. Cefdinir exhibits a broad range of antimicrobial activity against Gram-positive and Gram-negative species. Its activity against Gram-positive organisms, including *S. pneumoniae*, is generally greater than that of other orally administered third-generation cephalosporins.[95] An open-label study examined the activity of cefdinir 7 mg/kg twice daily for 5 days against pathogens obtained from the MEF of children aged 6 months to 12 years of age with tympanometry-confirmed AOM.[96] Of the 134 pathogens isolated, *S. pneumoniae* (51.5%) was the most common, followed by *H. influenzae* (32.8%), beta-lactam–positive *M. catarrhalis* (11.2%), and *S. pyogenes* (4.5%). Clinical cure rates in evaluated patients were 77% after 1 week. Presumptive eradication rates at the end of therapy were 73% and 50% for patients with penicillin-intermediate and penicillin-resistant *S. pneumoniae*, respectively. A 5-day course of cefdinir at a dose of 7 mg/kg twice daily has been shown to be as effective as a 10-day course of cefprozil at a dose of 15 mg/kg twice daily in the treatment of non-refractory AOM, with cure rates for either treatment exceeding 80% at the end of therapy.[97] In the treatment of suppurative otitis media in children 6 months to 12 years of age, cefdinir 14 mg once daily or 7 mg/kg twice daily provided efficacy comparable to amoxicillin-clavulanate 13.3 mg/kg three times daily for 10 days.[98] In this study, the incidence of side effects was statistically lower in the cefdinir once-daily group. In a separate study, either cefdinir 14 mg/kg once daily or 7 mg/kg twice daily was as effective as amoxicillin-(40 mg/kg) clavulanate (10 mg/kg) three times daily over a 10-day treatment period in children with unrefractorynon-refractory AOM. Presumptive eradication rates for *S. pneumoniae* were significantly lower with the cefdinir twice-daily regimen (55.2%) and marginally lower for the cefdinir once-daily regimen (80%), when compared with the amoxicillin-clavulanate eradication rate (89.5%). Gastrointestinal side effects were significantly less common with either cefdinir dosing regimen when compared with amoxicillin-clavulanate. Prospective, double-tympanocentesis studies are presently being performed using a 25 mg/kg once-daily dosage.

The palatability of cefdinir was explored in a series of six randomized single-blind, crossover studies that included 715 children aged 4–8 years.[99] In these studies, the oral suspension of cefdinir was compared with an oral suspension of amoxicillin-clavulanate, cefprozil, or azithromycin. The children reacted to questions about the taste or smell of the oral suspension using a visual smile-face scale that ranged from 5 (“really good”) to 1 (“really bad”). The taste of cefdinir was rated at least “good” by 85% of the children. In comparison, 63% of the children rated the taste of amoxicillin-clavulanate, cefprozil, or azithromycin as at least “good.” The smell of cefdinir was rated at least “good” by 71% of the children. In contrast, 64% of the children rated the smell of the comparator as at least “good.” The findings indicate that the strawberry milk shake flavor of cefdinir is well accepted by children and may encourage increased adherence to the prescribed regimen on AOM.

7. Vaccines

Two vaccines, the polysaccharide and the conjugate, offer some benefit in the prophylaxis of AOM caused by *S. pneumoniae*. The heptavalent pneumococcal conjugate vaccine, approved in the US in 2000, produces only a slight reduction in the risk for AOM

of 6–7%, yet it decreases the proportion of AOM resulting from *S. pneumoniae*.[100,101] Thus, use of this vaccine in locations where penicillin-resistant *S. pneumoniae* are prevalent may reduce carriage of this pathogen and lessen antibiotic resistance. The polysaccharide vaccine fails to provide reliable immunity in children <2 years of age, a high-risk group for AOM. However, children >2 years of age with recurrent and severe AOM may derive modest benefits.[102] It should be noted that an increase in disease caused by nonvaccine serotypes and *H. influenzae* has been reported.[103]

8. Adherence Issues

Several characteristics of an antibiotic influence the compliance to, and thus the ultimate success of, the prescribed regimen. These include tolerability, dosing frequency, palatability, and cost. Overall, the oral antibiotics used to treat AOM are generally well tolerated, with gastrointestinal reactions, hypersensitivity reactions, and rash (diaper dermatitis) being the most commonly reported adverse events.[47] Newer antimicrobials typically cause fewer gastrointestinal side effects, such as diarrhea, than older agents, and in most cases, these reactions are mild or moderate in severity. Frequent antibiotic dosing diminishes adherence in children.[104] Parents generally have difficulty administering an antibiotic more than twice daily. When both parents work, child-parent interactions typically occur in the morning and evening.[13] This typical routine accommodates dosing that is required once or twice daily. The recommended duration of dosing for the antibiotics approved for the treatment of AOM is presented in table I. Virtually all of the antibiotics indicated for the treatment of AOM have a recommended 10-day treatment course, except for the 5-day courses of therapy for cefpodoxime, cefdinir, and azithromycin. The use of an antimicrobial with an infrequent dosing schedule along with a short course of therapy should encourage adherence in the pediatric setting, which should reduce the risk of development and spread of resistant organisms. In children, palatability of an antibiotic suspension can become one of the most important factors influencing adherence.[105] Cephalosporin suspensions are generally more pleasant tasting and better accepted than suspensions containing penicillin.[106] The taste and smell of cefdinir appears particularly well accepted in children aged 4–8 years.[99] Whether this taste and smell preference will extend to young children aged 3 months to 3 years, the group most vulnerable to AOM, remains uncertain, but appears likely. When considering the cost of an antibiotic, up-front drug cost should not be viewed in isolation, but only as one aspect of a drug's true cost-effectiveness. The overall cost-effectiveness of an antibiotic may be determined by a variety of factors, among them efficacy, adherence, and tolerability, as well as initial cost. Antibiotics that promote adherence, especially in children, may reduce the rate of antibiotic resistance caused by inappropriate dosing, as well as reduce the rate of treatment failures and, thus, the overall cost of treatment.

9. Conclusions

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. In the pediatric setting where amoxicillin, the recommended initial treatment for AOM, has failed therapeutically or is not well tolerated, the choice of a subsequent antibiotic therapy can be a daunting process. In instances of amoxicillin treatment failure, the chances for pathogen eradication and clinical resolution with an alternative antibiotic may be substantially reduced.[47] In this context, adherence issues may become the important determinants in the choice of an antibiotic. For children with AOM, antibiotics that are effective in eradicating the main AOM pathogens from the MEF, are well tolerated, require infrequent dosing and short courses of therapy, and have an appealing taste and smell, will likely foster compliance with the dosing regimen and, thus, treatment success.

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