

A Review of Recommended Antibiotic Therapies With Impact on Outcomes in Acute Otitis Media and Acute Bacterial Sinusitis

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Acute otitis media (AOM) and acute bacterial sinusitis (ABS) management is becoming increasingly complex, with continual changes in the pathogens responsible for these conditions. Treatment involves the selection of an efficacious agent displaying a favorable adherence profile. Although antibiotic efficacy is critical to treatment successes, therapy adherence is arguably of equal importance, because failure to adhere to even the most effective therapy can ultimately lead to clinical failure and undermine treatment efforts. The dual importance of efficacy and adherence requires additional consideration when treating pediatric infections. Managed care organizations (MCOs) are increasingly aware that a balance is needed when weighing efficacy and adherence issues with antibiotics. In one study, a health maintenance organization initiated a guideline compliance education and provider-reporting pathway program among 900 physicians, nurse practitioners, and physician assistants in Rochester, NY, resulting in increased quality of care and a reduction in pharmacy costs.¹

More health plans should use provider and patient education strategies to improve provider compliance to national guidelines. Formulary redevelopment can improve care if efforts are made to evaluate emerging disease management issues, including the shifting microbiology of the organisms implicated in AOM and ABS, medication costs, and the evaluation of products with the best reported adherence. The purpose of this paper is to present the main costs of AOM and ABS, review the impact of treatment failures, and discuss the dual role of

efficacy and adherence in the treatment of AOM and ABS.

Direct and Indirect Costs of AOM and ABS

The total costs of both AOM and ABS can be high. Direct AOM and ABS costs are typically based on medication use and physician visits. Annual estimates of direct AOM costs range from \$1.96 billion to \$4.1 billion,^{2,3} whereas direct sinusitis costs (as a primary diagnosis) are estimated at \$1.8 billion.⁴ However, direct costs represent only a portion of the total economic burden of illness. Indirect costs can include the expense of care for sick children, transportation costs, the value of work time lost, baby-sitting fees, ancillary medication costs, and expenditures for treatment of adverse effects.⁵ Indirect costs are estimated at \$1.02 billion for AOM² and \$1.6 billion for ABS.⁴ These significant indirect costs emphasize that AOM and ABS impose a considerable economic burden for the patient, family, or employer who is purchasing health insurance coverage in part or in full.

Impact of Treatment Failures

Treatment failure can lead to persistent or recurrent infection, which in turn leads to an increase in overall cost of care.⁶ Poor efficacy is in part responsible for persistent and recurrent infections, with prior antibiotic use increasing the likelihood of treatment

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failure by enhancing the risk of infection from resistant organisms.^{7,8} An incorrect diagnosis and poor adherence to therapy also contribute to poor treatment outcomes. Primary care physicians refer and ear, nose, and throat (ENT) surgeons operate on patients with persistent and recurrent infection.⁹ Consequently, improved adherence to diagnostic criteria and appropriate antibiotic selection according to national treatment guidelines may improve the management of AOM and ABS.⁶

As discussed in the previous article, treatment success and the cost of therapy can be attributed greatly to therapy adherence.¹⁰ Adherence is influenced by factors such as tolerability, patient and caregiver preference, dosing regimen/duration of therapy, palatability, and satisfaction with therapy.^{5,11-16} For example, tolerability and ease of administration may increase adherence to prescribed therapy,¹⁴ and a shorter duration of therapy (ie, 5 days vs 10 days) is shown to improve therapy adherence.¹⁵ To predict the likelihood of treatment success in AOM and ABS, it is important to look at components of adherence for agents used to treat these conditions.

Benefits of Judicious Treatment Selection: Current Therapies

When selecting an agent for the treatment of AOM and ABS, the main contributors to favorable outcomes—efficacy and adherence—should be examined closely. Judicious antibiotic selection should positively affect the entire healthcare system. This merits review of the guideline-endorsed antibiotics (Table 1), the antibiotics not endorsed, and the rationale for the distinction between the 2 groups of drugs.

Guideline-endorsed Antibiotics

Amoxicillin. Amoxicillin is the mainstay of treatment for AOM and ABS and is currently recommended as first-line therapy in both of these conditions.^{17,18} Amoxicillin is effective against *Streptococcus pneumoniae*, including penicillin nonsusceptible *S pneumoniae* (PNSP) when administered in off-label high dosages (eg, 80-100 mg/kg per day in children and 1.5 g twice daily in adults). However, amoxicillin is inef-

Table 1. Guideline-endorsed Antibiotics in AOM and ABS^{7,17}

Agents
First-line Therapy
Amoxicillin
Amoxicillin/clavulanate
Second-line Therapy
Amoxicillin/clavulanate
Cefdinir
Cefpodoxime
Ceftriaxone
Cefuroxime

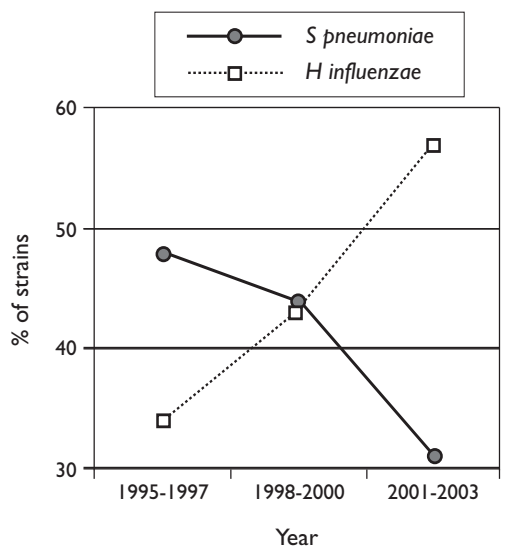
AOM indicates acute otitis media; ABS, acute bacterial sinusitis.

fective against β -lactamase-producing pathogens.^{19,20} The clinical efficacy of amoxicillin is well established, based on trials conducted from as long as 30 years ago.^{17,20}

Although amoxicillin is an acceptable drug for eradicating β -lactamase-negative *Haemophilus influenzae*, it is no better than a placebo against β -lactamase-positive *H influenzae*.²⁰ The release of the heptavalent pneumococcal conjugate vaccine (PCV7) in 2000 and its widespread use by 2004 gradually led to a documented shift in the microbiology of persistent/recurrent AOM in the pediatric population (Figure).^{21,22} This shift likely occurred in ABS because both diseases involve the same pathogens. Even adult AOM and ABS likely have experienced a pathogen shift because of a herd immunity effect of PCV7. A decrease in PNSP strains from PCV7 vaccine use alluded to *H influenzae* as the pathogen most likely responsible for AOM and ABS infection. *H influenzae* has also become more resistant to antibiotics over the years by acquiring the ability to produce β -lactamase. This shift in microbiology allegedly occurring in both AOM and ABS should be considered when evaluating the antimicrobial efficacy of amoxicillin.

Amoxicillin is well tolerated and has favorable taste scores in suspension for-

Figure. Percentage of Total Pathogens Causing Persistent AOM and AOM Treatment Failure That Were *Streptococcus pneumoniae* or *Haemophilus influenzae* in Rochester, NY, 1995-2003



The change in frequency of *S pneumoniae* isolation was significantly lower ($P = .049$), and the frequency of *H influenzae* isolations was significantly higher over time ($P = .021$).

AOM indicates acute otitis media.

mulation for pediatric patients.¹⁵ Interestingly, a recent willingness-to-pay study in AOM patients evaluating compliance (defined as having no missed doses) and adherence (defined as taking medication on time) reported that amoxicillin therapy had the poorest ratings (75% and 59%, compliance and adherence, respectively), significantly lower than amoxicillin/clavulanate (85% and 66%), azithromycin (91% and 79%), cefprozil (71% and 64%), and clarithromycin (78% and 65%).²³ Amoxicillin had the lowest tolerability rate,²⁴ and its taste did not appear to impact compliance. Poor compliance could be the result of the dosage frequency in the study (3 times daily) or the prescribing regimen of 7 to 10 days.

Amoxicillin/clavulanate. The addition of clavulanate to amoxicillin provides the combination product with additional activity against β -lactamase-producing pathogens. As with amoxicillin, extra-strength amoxi-

cillin/clavulanate (90/6.4 mg/kg/day) has shown high bacterial eradication rates for PNSP of 90% and 94% in 2 studies.^{25,26} Based on its efficacy, extra-strength amoxicillin/clavulanate is recommended for the second-line treatment of uncomplicated AOM, first-line therapy for persistent/recurrent AOM, and first-line treatment for mild, moderate, or severe ABS.^{7,17,18}

Tolerability of amoxicillin/clavulanate is problematic. In many head-to-head trials against other AOM and ABS treatments (including cefdinir, cefprozil, and cefuroxime), the adverse event rate for amoxicillin/clavulanate exceeds that of the comparator agent.²⁷⁻³⁴ In most of these studies, gastrointestinal effects (such as diarrhea) are the most frequently reported adverse event of amoxicillin/clavulanate therapy.

The data related to amoxicillin/clavulanate's palatability is also not favorable. A series of 6 randomized, single-blind, crossover trials compared the taste and smell of oral antibiotic suspensions in children. Amoxicillin/clavulanate was consistently significantly inferior in taste and smell acceptance compared with cefdinir, another guideline-endorsed drug in both the single- and multi-center studies.³⁵

Cefpodoxime. The third-generation cephalosporin cefpodoxime is one of the recommended agents for AOM and ABS. Its efficacy in AOM is demonstrated in non-inferiority trials versus standard-strength amoxicillin/clavulanate, cefaclor, cefixime, and amoxicillin.³⁶⁻⁴⁰ In these trials, clinical response or clinical cure rates were similar in 2 trials of cefpodoxime and cefaclor (success rates of 93.6% and 95% vs 91.6% and 90%, respectively; $P = NS$)^{37,38} and a single trial with cefixime (clinical cure rate 56% vs 54%; $P = NS$).³⁹ Trial results comparing cefpodoxime and standard-strength amoxicillin/clavulanate have conflicted; and in one trial, the clinical cure rate of twice-daily cefpodoxime (68%) did not differ from that of 3-times-daily standard-strength amoxicillin/clavulanate (65%; $P = .57$),³⁶ whereas a similar trial demonstrated a difference in clinical cure rates between treatments favoring cefpodoxime (60% vs 40%; $P = .003$).⁴⁰ Cefpodoxime was also compared with amox-

icillin in the treatment of ABS and was equivalent with clinical response rates of 96% and 91%, respectively.⁴¹

In the trials, cefpodoxime had a similar adverse event profile to amoxicillin, cefaclor, cefixime, and regular-strength amoxicillin/clavulanate,^{36,37,39-41} with gastrointestinal and dermatological adverse events most frequently reported.³⁶

Adherence to once-daily cefpodoxime can be improved over amoxicillin or amoxicillin/clavulanate from differences in dosing regimen (once- or twice-daily cefpodoxime vs 2- to 3-times-daily amoxicillin or amoxicillin/clavulanate), although no difference in adherence was noted in 1 head-to-head trial.⁴⁰ Palatability may play a key role in determining adherence with cefpodoxime for children. One blinded taste study measuring 12 antibiotic suspensions by smell, texture, taste, aftertaste, and overall acceptance found cefpodoxime significantly inferior in aftertaste to comparators.¹²

Cefdinir. Guidelines recommend cefdinir as a primary treatment choice for penicillin-allergic patients^{7,17,18} and in mild or moderate ABS and AOM.^{7,18} The efficacy of cefdinir for the treatment of AOM and ABS is demonstrated in numerous comparative clinical trials. A multicenter, prospective study evaluated 357 AOM patients from 6 months to 6 years old randomized to either cefdinir oral suspension 7 mg/kg q12h for 5 days or azithromycin oral suspension 10 mg/kg once daily on day 1 and 5 mg/kg once daily on days 2 through 5.⁴² Clinical cure rates were comparable between cefdinir and azithromycin (87% and 85%, respectively). Short courses of therapy with cefdinir or azithromycin were comparable in AOM pediatric cases.⁴² Another prospective multicenter study in 425 patients found that although there was no significant difference in overall clinical cure rates between cefdinir (14 mg/kg divided twice daily) and regular-strength amoxicillin/clavulanate (45/6.4 mg/kg divided twice daily), cefdinir was more effective than regular-strength amoxicillin/clavulanate (92% vs 77%; $P = .019$) in the subset of patients documented with prior PCV7 vaccination.³⁴ A randomized study in the United Kingdom

compared cefdinir 14 mg/kg once daily, cefdinir 7 mg/kg twice daily, or regular-strength amoxicillin/clavulanate 13.3 mg/kg 3 times daily, finding efficacy clinically equal among groups.⁴³ A similar trial of 384 AOM patients found that a 10-day course of therapy resulted in similar eradication rates with once-daily cefdinir (83%), twice-daily cefdinir,⁴⁴ and 3-times-daily regular-strength amoxicillin/clavulanate (86%).⁴⁵ Clinical cure rates were 83% with a 10-day regimen of cefprozil and 80% with a 5-day regimen of cefdinir in an open-label tympanocentesis trial of 177 children up to 12 years of age.⁴⁶ For the treatment of ABS, 2 multicenter trials with nearly 1800 patients found that 10 days of therapy with cefdinir 600 mg/day dosed once or twice daily was as effective as 10 days of amoxicillin/clavulanate 500 mg 3 times a day.⁴⁷

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The tolerability profile of cefdinir in comparison with other AOM and ABS agents is favorable. In a study of 425 patients aged 6 months to 6 years old with nonrefractory AOM who were randomized to cefdinir (14 mg/kg, divided twice daily for 5 days) or regular-strength amoxicillin/clavulanate (45/6.4 mg/kg, divided twice daily for 10 days) found that 24% of the cefdinir subjects reported a drug-related adverse event, significantly less than the 38% of subjects receiving amoxicillin/clavulanate ($P < .002$).³⁴ Furthermore, fewer subjects receiving cefdinir discontinued therapy because of drug-related adverse events (0.5%) than subjects receiving amoxicillin/clavulanate (1.9%). Another study

examining the same agents, doses, and duration of therapies found a higher percentage of amoxicillin/clavulanate patients with vomiting compared with cefdinir ($P = .016$), with more parents of children in the cefdinir group reporting that their child took 100% of their medication ($P = .005$).¹¹ In another trial, a comparison of 5 days of therapy with azithromycin (10 mg/kg on day 1, 5 mg/kg on days 2-5) or cefdinir (7 mg/kg twice daily) in 357 children between the ages of 6 months and 6 years showed no difference between agents in the incidence of adverse events.⁴⁸ Parent-reported compliance with therapy (defined as >80% of the prescribed regimen) was 99% for both the azithromycin and cefdinir groups.

A previously described analysis of 6 randomized, single-blind, crossover trials also demonstrated that at 4 geographically diverse US study sites, children rated the taste of cefdinir suspension significantly higher than that of either amoxicillin/clavulanate potassium or cefprozil.

A pooled evaluation of 7 randomized, single-blind, crossover trials found cefdinir oral suspension was preferred by children between the ages of 4 and 8 years old over other antibiotic suspensions.⁴⁹ A previously described analysis of 6 randomized, single-blind, crossover trials also demonstrated that at 4 geographically diverse US study sites, children rated the taste of cefdinir suspension significantly higher than that of either amoxicillin/clavulanate potassium or cefprozil. The analysis also found that the smell of cefdinir suspension was rated significantly better than that of amoxicillin/clavulanate potassium, cefprozil, or azithromycin.³⁵ A taste test trial evaluated a physician's likelihood to prescribe antibi-

otics (amoxicillin used as baseline comparator) and found that cefdinir was preferred over all other antibiotics except loracarbef in taste, even after such ratings were adjusted based on cost. The study also reported that cefdinir led in all ratings after adjusting the ratings for duration of therapy and dosing interval except azithromycin.¹⁵ Results from a parent-reported survey demonstrated that a 5-day course of cefdinir was preferred over a 10-day regimen of amoxicillin/clavulanate, with significant differences in satisfaction, tolerability, and compliance favoring cefdinir.¹¹

Cefuroxime. Cefuroxime, a second-generation cephalosporin, is active against some PNSP strains and has notable activity against β -lactamase-producing organisms.^{50,51} Numerous trials demonstrated the utility of cefuroxime in AOM. Three trials compared 10 days of therapy with cefuroxime and regular-strength amoxicillin/clavulanate.³¹⁻³³ Two trials with a total of 740 children^{31,32} found no difference in efficacy between the agents, with satisfactory outcomes reported in 84% and 77% of cefuroxime patients and 95% and 74% of amoxicillin/clavulanate patients, respectively. The third trial of 377 children found a higher percentage of patients receiving cefuroxime with complete resolution of symptoms (62%) than regular-strength amoxicillin/clavulanate (52%) and cefaclor (46%).³³ Also of note, an open-label, randomized, multicenter trial compared a 5-day course of twice-daily cefuroxime with 3-times-daily amoxicillin/clavulanate suspension for 8 or 10 days in children from 6 to 36 months with AOM; there was no difference between treatments in clinical cure rates (86%, 88%, and 88%, respectively).³⁰ Two trials have documented the efficacy of cefuroxime in childhood ABS,^{52,53} but both were small placebo-controlled trials without an active comparator group. The 5-day course of cefuroxime may improve treatment adherence due to the relatively short course of treatment. Furthermore, there were fewer side effects observed with cefuroxime than regular-strength amoxicillin/clavulanate in comparative trials.³¹⁻³³

Palatability and satisfaction concerns with cefuroxime were noted. Cefuroxime

was consistently ranked 10th or 11th out of 11 antibiotic suspensions in terms of appearance, smell, texture, taste, and aftertaste by a group of 86 physicians.¹⁵ An open-label study of more than 12 000 outpatient children younger than 12 years of age in which antibiotic taste was graded on a 5-category scale (very unpleasant to very pleasant) found that cefuroxime was 1 of 3 antibiotics (along with clarithromycin and cefpodoxime) rated as unpleasant or very unpleasant by 50% or more of patients.¹⁶ Furthermore, parents and caregivers were asked to rate their satisfaction with the study antibiotics on a 5-category scale (extremely satisfied to extremely dissatisfied). Of the 10 antibiotics examined, 9 achieved scores of extremely satisfied or satisfied at least 80% of the time, with only cefuroxime receiving less than 80% (65.2%). Poor parent satisfaction scores with cefuroxime were attributed to the agent's poor taste and a higher overall failure rate.¹⁶

Nonguideline Recommended

Azithromycin. The efficacy of azithromycin was compared with amoxicillin⁵⁴ and both regular- and extra-strength amoxicillin/clavulanate^{26,55-63} for the treatment of AOM in many clinical trials, with variable results. A study of single-dose azithromycin versus high-dose amoxicillin (90 mg/kg/day)⁵⁴ in addition to many of the non-inferiority studies comparing 3- and 5-day regimens of azithromycin to a 10-day regular-strength amoxicillin/clavulanate (40-45 mg/kg/day)⁵⁷⁻⁶³ found both agents equally efficacious in AOM. These results were also seen in a comparison of a 3-day regimen of azithromycin to a 10-day regular-strength regimen of amoxicillin/clavulanate.⁶⁴ A single tympanocentesis study using high-dose azithromycin (20 mg/kg/day for 3 days) found the 2 antibiotics comparable when using clinical end points.⁵⁵ However, 2 double tympanocentesis studies of AOM each found extra-strength amoxicillin/clavulanate showing superior mid-therapy bacteriologic and end-of-therapy clinical efficacy compared with azithromycin.^{26,56} The 2 studies also noted that azithromycin was no more effective than placebo for the eradication of *H influenzae*.

The efficacy of azithromycin is further compromised by the rising rate of macrolide resistance. A meta-analysis evaluated 29 studies from 1998 to 2003 from diverse geographic regions, a majority of which were conducted in the United States and Europe. The analysis evaluated macrolide resistance in azithromycin, clarithromycin, or erythromycin linked to 7 different respiratory illnesses, including otitis media and acute sinusitis. Of note, mean resistance of *S pneumoniae* isolates to azithromycin was 27.2%.⁶⁵

An open-label study of more than 12 000 outpatient children younger than 12 years of age in which antibiotic taste was graded on a 5-category scale (very unpleasant to very pleasant) found that cefuroxime was 1 of 3 antibiotics (along with clarithromycin and cefpodoxime) rated as unpleasant or very unpleasant by 50% or more of patients.

Because double tympanocentesis studies^{26,56} found that azithromycin was no more effective than placebo in eradicating *H influenzae*, the current pediatric guidelines endorse azithromycin (and clarithromycin) for the treatment of AOM and ABS only when the patient has an anaphylactic allergy to penicillin.^{7,17,18,66} The in vitro resistance of both *H influenzae* and PNSP also suggest that macrolides may not be optimal for treatment of AOM or ABS in children.^{18,67,68} Even with data pointing to azithromycin's lack of efficacy in this population, it is still one of the most commonly prescribed macrolides, especially for upper respiratory illness.⁶⁹ Azithromycin's popularity with physicians and patients is likely

from the agent's short dosing frequency, duration, and decreased pill burden.

Azithromycin has an appealing once-daily regimen for either 1, 3, or 5 days, which is attractive not only to physicians but also to parents who would benefit from the decreased burden of administering multiple doses. In a taste test, children preferred the taste of azithromycin over amoxicillin/clavulanate, erythromycin, ethylsuccinate/sulfisoxazole, and clarithromycin.⁷⁰ In a study with cephalosporins, taste and smell acceptance ratings were significantly different between azithromycin and cefdinir, with the children favoring cefdinir.³⁵ One survey found no significant differences in taste between azithromycin and cefprozil or amoxicillin/clavulanate, all of which were inferior to cefixime.⁷¹ A double-blind, double-dummy, multicenter clinical trial compared a 3-day course of high-dose azithromycin with a 10-day course of extra-strength amoxicillin/clavulanate in children with recurrent or persistent AOM. Compliance, defined as 80% of the prescribed regimen, was 99% in the azithromycin group versus 93% for amoxicillin/clavulanate ($P = .018$).⁵⁵ Compliance with therapy was 100% in 2 tympanocentesis studies; a feat easily achieved as both studies examined single-dose azithromycin.^{72,73} Near-universal adherence to therapy can be expected

following the administration of a single-dosed drug at the point of diagnosis, and administering an agent in the clinic or emergency department may avoid any social or cost barriers encountered by sending patients to a pharmacy. However, these benefits are wasted if the agent is not efficacious.

Cefprozil. Efficacy results from non-inferiority trials involving cefprozil (many conducted in the early 1990s) show comparability to other cephalosporins and regular-strength amoxicillin/clavulanate.^{27,29,46,74,75} However, cefprozil's diminishing in vitro activity against contemporary β -lactamase-producing *H influenzae* (now accounting for up to 64% of *H influenzae* isolates²¹) reduces this agent's appeal as a choice in the treatment of AOM and ABS. Consequently, cefprozil is not guideline recommended as a preferred cephalosporin for use in AOM or ABS.^{7,17,18}

Drug-related adverse event rates for cefprozil range from 5.8% to 19% in comparative trials.^{27,29,74,75} Diarrhea and other gastrointestinal complaints are the most frequently reported side effects among cefprozil users. The incidence of diarrhea among cefprozil users appears similar to that of cefitibuten⁷⁴ and less than that reported by amoxicillin/clavulanate users.²⁷⁻²⁹

Palatability may play a key role in determining adherence with cefprozil. One blinded taste study that measured 12 antibiotic suspensions by smell, texture, taste, after-taste, and overall acceptance found the taste of cefprozil scored lower than the taste of cephalexin, cefixime, and cefaclor.¹² In addition, another small study found the taste of cefprozil inferior to cefixime and similar to amoxicillin/clavulanate,⁷¹ a product with known palatability issues. A series of 6 randomized, single-blind, crossover trials in 715 children 4 to 8 years of age found the taste and smell acceptance of cefprozil to be significantly inferior to cefdinir.³⁵

Outcomes

The agents available for the treatment of AOM and ABS appear to have differing efficacy and adherence-enhancing profiles (Table 2). Amoxicillin has long been consid-

Cefdinir, cefpodoxime, and cefuroxime have all been recommended in leading guidelines as efficacious choices in the treatment of children with AOM and ABS, but cefpodoxime and cefuroxime have poor taste ratings; only cefdinir and cefpodoxime are available in once-daily dosing, and only cefdinir is approved for short-course therapy in AOM.

ered the first-line agent for the treatment of AOM and ABS because of its efficacy against *S pneumoniae* as well as its low cost and favorable taste, yet it lacks efficacy against β -lactamase-producing *H influenzae*. Amoxicillin/clavulanate provides coverage of β -lactamase-producing *H influenzae* offers, but amoxicillin/clavulanate's palatability was reportedly disappointing compared with other antibiotics, especially compared with a number of cephalosporins. Although azithromycin's short-course therapy along with reports of taste preference indicate excellent adherence, numerous experts question its efficacy against *H influenzae* and only recommend its use in cases of penicillin allergy.^{7,17,18} Cefdinir, cefpodoxime, and cefuroxime have all been recommended in leading guidelines as efficacious choices in the treatment of children with AOM and ABS, but cefpodoxime and cefuroxime have poor taste ratings; only cefdinir and cefpodoxime are available in once-daily dosing, and only cefdinir is approved for short-course therapy in AOM.

Prescription cost can influence patient adherence with therapy. An agent with an unfavorable placement on a managed care formulary (nonformulary or a tier with a high copayment) requires the patient to bear a higher cost burden, which may delay or lower prescription redemption rates. Excessive antibiotic cost may lead the patient or pharmacist (acting on the patient's behalf) to call and petition the prescriber to select a less costly agent. Non-adherence to therapy places the patient at risk for treatment failure and the subsequent cost consequences of managing recurrent and persistent AOM and ABS. Judicious prescribing of agents that have the greatest likelihood of both efficacy and adherence is a crucial strategy in maximizing health outcomes.

Although few comparative data are available on the cost of care and outcomes with the antibiotics discussed in this article, it is not unreasonable to conclude that those agents with favorable efficacy and adherence profiles are most likely associated with the best outcomes and the lowest cost of care. When the cost of treatment failure (includ-

Table 2. Relative Efficacy and Tolerability

Relative Rank	Efficacy*	Tolerability†
Best	Ceftriaxone (3 injections)	Amoxicillin
	Amoxicillin/clavulanate ES	Azithromycin
	Gatifloxacin‡	Cefdinir
	Levofloxacin‡	
Better	Cefdinir	Cefprozil
	Cefuroxime	Gatifloxacin‡
	Cefpodoxime	Levofloxacin‡
	Cefprozil	
Good	Amoxicillin	Amoxicillin/clavulanate ES
	Azithromycin	Trimethoprim/sulfamethoxazole (TMP/SMX)
Marginal	TMP/SMX	Cefpodoxime
		Ceftriaxone (3 injections) Cefuroxime

*Efficacy as measured by double-tap results and pharmacokinetic-pharmacodynamic parameters.

†Tolerability as measured by taste, dosing frequency, duration of treatment, and number of visits.

‡Fluoroquinolones are not FDA-approved for treatment of acute otitis media or acute bacterial sinusitis in children because of concerns of arthrotoxicity.⁷⁶ ES indicates extra strength.

ing the cost of second-line therapy and possibly specialist care and surgical intervention) is factored into the total cost of care, it becomes clear that adherence-enhancing antibiotics with superior coverage of likely pathogens will result in successful, cost-effective therapy.

Conclusion

AOM and ABS are common diseases in children and adults with far-reaching societal consequences. With a variety of antibiotics available for these conditions, selecting the most appropriate agent can be challenging for prescribers. However, clinical practice guidelines and current research provide efficacy and adherence data that help prescribers determine the optimal antibiotic therapy that maximizes positive health outcomes. Treatment failures can have a wide

array of consequences, leading to an increase in bacterial resistance to antibiotic agents and further increasing the overall economic impact of illness. There is concern that antibiotic resistance will subsequently render commonly used agents less efficacious, further adding to the public health burden. In light of this, it is crucial for the provider to properly select agents that are not only efficacious but also adherence-enhancing.

MCOs have an opportunity to improve the health of their members and also reap potential savings by: (1) critically evaluating products that promise both efficacy and adherence to maximize the likelihood of positive health outcomes while preventing treatment failure in light of the emerging shift in microbiology in AOM and ABS; (2) educating prescribers with guidelines, research, and materials to aid in clinical diagnosis and appropriate agent selection and to inform and encourage patient compliance; and (3) educating patients and caregivers about community resistance and strategies to maximize therapy adherence to prevent recurrence.

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REFERENCES

1. Greene RA, Beckman H, Chamberlain J, et al. Increasing adherence to a community-based guideline for acute sinusitis through education, physician profiling, and financial incentives. *Am J Manag Care.* 2004;10(10):670-678.

2. Marcy M, Takata G, Shekelle P, et al. *Management of Acute Otitis Media. Evidence Report/Technology Assessment No. 15 (Prepared by the Southern California Evidence-based Practice Center under Contract No. 290-97-0001). AHRQ Publication No. 01-E010.* Rockville, Md: Agency for Healthcare Research and Quality; 2001.

3. Bondy J, Berman S, Glazner J, Lezotte D. Direct expenditures related to otitis media diagnoses: extrapolations from a pediatric Medicaid cohort. *Pediatrics.* 2000;105(6):E72.

4. Ray NF, Baraniuk JN, Thamer M, et al. Healthcare expenditures for sinusitis in 1996: contributions of asthma, rhinitis, and other airway disorders. *J Allergy Clin Immunol.* 1999;103(3 pt 1):408-414.

5. Wandstrat TL, Kaplan B. Pharmacoeconomic impact of factors affecting compliance with antibiotic regimens in the treatment of acute otitis media. *Pediatr Infect Dis J.* 1999;16(2 suppl):S27-S29.

6. Brixner DI. Improving acute otitis media outcomes through proper antibiotic use and adherence. *Am J Manag Care.* 2005;11(6 suppl):S202-S210.

7. Anon JB, Jacobs MR, Poole MD, et al. Antimicrobial treatment guidelines for acute bacterial rhinosinusitis. *Otolaryngol Head Neck Surg.* 2004;130(1 suppl):1-45.

8. Block SL, Hedrick JA, Tyler RD, Smith RA, Harrison CJ. Microbiology of acute otitis media recently treated with aminopenicillins. *Pediatr Infect Dis J.* 2001;20(11):1017-1021.

9. Poole MD. Acute bacterial rhinosinusitis: clinical impact of resistance and susceptibility. *Am J Med.* 2004;117(suppl 3A):29S-38S.

10. Poole MD, Portugal LG. Treatment of rhinosinusitis in the outpatient setting. *Am J Med.* 2005;118(suppl 7A):45S-50S.

11. Cifaldi MA, Paris MM, Devcich KJ, Bukofzer S. Parent-reported outcomes for treatment of acute otitis media with cefdinir or amoxicillin/clavulanate oral suspensions. *Paediatr Drugs.* 2004;6(6):387-393.

12. Demers DM, Chan DS, Bass JW. Antimicrobial drug suspensions: a blinded comparison of taste of twelve common pediatric drugs including cefixime, cefpodoxime, cefprozil and loracarbef. *Pediatr Infect Dis J.* 1994;13(2):87-89.

13. El Chaar GM, Mardy G, Wehlou K, Rubin LG. Randomized, double blind comparison of brand and generic antibiotic suspensions: II. A study of taste and compliance in children. *Pediatr Infect Dis J.* 1996;15(1):18-22.

14. McCracken GH Jr. Treatment of acute otitis media in an era of increasing microbial resistance. *Pediatr Infect Dis J.* 1998;17(6):576-579.

15. Steele RW, Thomas MP, Begue RE. Compliance issues related to the selection of antibiotic suspensions for children. *Pediatr Infect Dis J.* 2001;20(1):1-5.

16. Steele RW, Blumer JL, Kalish GH. Patient, physician, and nurse satisfaction with antibiotics. *Clin Pediatr (Phila).* 2002;41(5):285-299.

17. American Academy of Pediatrics Subcommittee on Management of Acute Otitis Media. Diagnosis and management of acute otitis media. *Pediatrics.* 2004;113(5):1451-1465.

18. Clinical practice guideline: management of sinusitis. *Pediatrics.* 2001;108(3):798-808.

19. Lister PD, Pong A, Chartrand SA, Sanders CC. Rationale behind high-dose amoxicillin therapy for acute otitis media due to penicillin-nonsusceptible pneumococci: support from in vitro pharmacodynamic studies. *Antimicrob Agents Chemother.* 1997;41(9):1926-1932.

20. Piglansky L, Leibovitz E, Raiz S, et al. Bacteriologic and clinical efficacy of high dose amoxicillin for therapy of acute otitis media in children. *Pediatr Infect Dis J.* 2003;22(5):405-413.

21. Block SL, Hedrick J, Harrison CJ, et al. Community-wide vaccination with the heptavalent pneumococcal conjugate significantly alters the microbiology of acute otitis media. *Pediatr Infect Dis J.* 2004;23(9):829-833.

22. Casey JR, Pichichero ME. Changes in frequency and pathogens causing acute otitis media in 1995-2003. *Pediatr Infect Dis J.* 2004;23(9):824-828.

- 23. Chenevier DJ, LeLorier J.** A willingness-to-pay assessment of parents' preference for shorter duration treatment of acute otitis media in children. *Pharmacoeconomics*. 2005;23(12):1243-1255.
- 24. Straetmans M, Palmu A, Auranen K, Zielhuis GA, Kilpi T.** The effect of a pneumococcal conjugate vaccine on the risk of otitis media with effusion at 7 and 24 months of age. *Int J Pediatr Otorhinolaryngol*. 2003; 67(11):1235-1242.
- 25. Dagan R, Hoberman A, Johnson C, et al.** Bacteriologic and clinical efficacy of high dose amoxicillin/clavulanate in children with acute otitis media. *Pediatr Infect Dis J*. 2001;20(9):829-837.
- 26. Hoberman A, Dagan R, Leibovitz E, et al.** Large dosage amoxicillin/clavulanate, compared with azithromycin, for the treatment of bacterial acute otitis media in children. *Pediatr Infect Dis J*. 2005;24(6):525-532.
- 27. Kafetzis DA.** Multi-investigator evaluation of the efficacy and safety of cefprozil, amoxicillin-clavulanate, cefixime and cefaclor in the treatment of acute otitis media. *Eur J Clin Microbiol Infect Dis*. 1994;13(10): 857-865.
- 28. Arguedas AG, Zaleska M, Stutman HR, Blumer JL, Hains CS.** Comparative trial of cefprozil vs amoxicillin clavulanate potassium in the treatment of children with acute otitis media with effusion. *Pediatr Infect Dis J*. 1991;10(5):375-380.
- 29. Hedrick JA, Sher LD, Schwartz RH, Pierce P.** Cefprozil versus high-dose amoxicillin/clavulanate in children with acute otitis media. *Clin Ther*. 2001;23(2): 193-204.
- 30. Pessey JJ, Gehanno P, Thoroddsen E, et al.** Short course therapy with cefuroxime axetil for acute otitis media: results of a randomized multicenter comparison with amoxicillin/clavulanate. *Pediatr Infect Dis J*. 1999;18(10):854-859.
- 31. Gooch WM III, Blair E, Puopolo A, et al.** Clinical comparison of cefuroxime axetil suspension and amoxicillin/clavulanate suspension in the treatment of pediatric patients with acute otitis media with effusion. *Clin Ther*. 1995;17(5):838-851.
- 32. Mclinn SE, Moskal M, Goldfarb J, et al.** Comparison of cefuroxime axetil and amoxicillin-clavulanate suspensions in treatment of acute otitis media with effusion in children. *Antimicrob Agents Chemother*. 1994;38(2): 315-318.
- 33. Pichichero M, Aronovitz GH, Gooch WM, et al.** Comparison of cefuroxime axetil, cefaclor, and amoxicillin-clavulanate potassium suspensions in acute otitis media in infants and children. *South Med J*. 1990;83(10): 1174-1177.
- 34. Block SL, Busman TA, Paris MM, Bukofzer S.** Comparison of five-day cefdinir treatment with ten-day low dose amoxicillin/clavulanate treatment for acute otitis media. *Pediatr Infect Dis J*. 2004;23(9):834-838.
- 35. Powers JL, Gooch WM III, Oddo LP.** Comparison of the palatability of the oral suspension of cefdinir vs amoxicillin/clavulanate potassium, cefprozil and azithromycin in pediatric patients. *Pediatr Infect Dis J*. 2000;19(12 suppl):S174-S180.
- 36. Mendelman PM, Del Beccaro MA, Mclinn SE, Todd WM.** Cefpodoxime proxetil compared with amoxicillin-clavulanate for the treatment of otitis media. *J Pediatr*. 1992;121(3):459-465.
- 37. Tsai HY, Huang LM, Chiu HH, et al.** Comparison of once daily cefpodoxime proxetil suspension and thrice daily cefaclor suspension in the treatment of acute otitis media in children. *J Microbiol Immunol Infect*. 1998; 31(3):165-170.
- 38. MacLoughlin GJ, Barreto DG, de la Torre C, et al.** Cefpodoxime proxetil suspension compared with cefaclor suspension for treatment of acute otitis media in paediatric patients. *J Antimicrob Chemother*. 1996; 37(3):565-573.
- 39. Asmar BI, Dajani AS, Del Beccaro MA, Mendelman PM.** Comparison of cefpodoxime proxetil and cefixime in the treatment of acute otitis media in infants and children. Otitis Study Group. *Pediatrics*. 1994;94(6 pt 1):847-852.
- 40. Gehanno P, Barry B, Bobin S, Safran C.** Twice daily cefpodoxime proxetil compared with thrice daily amoxicillin/clavulanic acid for treatment of acute otitis media in children. *Scand J Infect Dis*. 1994;26(5):577-584.
- 41. von Sydow C, Savolainen S, Soderqvist A.** Treatment of acute maxillary sinusitis—comparing cefpodoxime proxetil with amoxicillin. *Scand J Infect Dis*. 1995;27(3): 229-234.
- 42. Block SL, Cifaldi M, Gu Y, Paris MM.** A comparison of 5 days of therapy with cefdinir or azithromycin in children with acute otitis media: a multicenter, prospective, single-blind study. *Clin Ther*. 2005;27(6):786-794.
- 43. Adler M, McDonald PJ, Trostmann U, Keyserling C, Tack K.** Cefdinir vs amoxicillin/clavulanic acid in the treatment of suppurative acute otitis media in children. *Pediatr Infect Dis J*. 2000;19(12 suppl):S166-S170.
- 44. Howie VM, Ploussard JH.** Efficacy of fixed combination antibiotics versus separate components in otitis media. Effectiveness of erythromycin estolate, triple sulfonamide, ampicillin, erythromycin estolate-triple sulfonamide, and placebo in 280 patients with acute otitis media under two and one-half years of age. *Clin Pediatr*. 1972;11(4):205-214.
- 45. Block SL, McCarty JM, Hedrick JA, et al.** Comparative safety and efficacy of cefdinir vs amoxicillin/clavulanate for treatment of suppurative acute otitis media in children. *Pediatr Infect Dis J*. 2000;19(12 suppl):S159-S165.
- 46. Block SL, Hedrick JA, Kratzer J, Nemeth MA, Tack KJ.** Five-day twice daily cefdinir therapy for acute otitis media: microbiologic and clinical efficacy. *Pediatr Infect Dis J*. 2000;19(12 suppl):S153-S158.
- 47. Gwaltney JM Jr, Savolainen S, Rivas P, et al.** Comparative effectiveness and safety of cefdinir and amoxicillin-clavulanate in treatment of acute community-acquired bacterial sinusitis. Cefdinir Sinusitis Study Group. *Antimicrob Agents Chemother*. 1997;41(7):1517-1520.
- 48. Block SL, Busman TA, Kapral D, Cifaldi MA, Paris MM.** Cefdinir twice-daily demonstrated similar efficacy, satisfaction, ease of use and compliance when com-

pared with azithromycin once-daily in the treatment of acute otitis media. Presented at 6th Early Childhood Caries, Paris, France, December 1-3, 2004.

49. Holas C, Chiu YL, Notario G, Kapral D. A pooled analysis of seven randomized crossover studies of the palatability of cefdinir oral suspension versus amoxicillin/clavulanate potassium, cefprozil, azithromycin, and amoxicillin in children aged 4 to 8 years. *Clin Ther.* 2005;27(12):1950-1960.

50. Barry B, Gehanno P, Blumen M, Boucot I. Clinical outcome of acute otitis media caused by pneumococci with decreased susceptibility to penicillin. *Scand J Infect Dis.* 1994;26(4):446-452.

51. Schatz BS, Karavokiros KT, Taubel MA, Itokazu GS. Comparison of cefprozil, cefpodoxime proxetil, loracarbef, cefixime, and cefitibuten. *Ann Pharmacother.* 1996;30(3):258-268.

52. Kristo A, Uhari M, Luotonen J, et al. Cefuroxime axetil versus placebo for children with acute respiratory infection and imaging evidence of sinusitis: a randomized, controlled trial. *Acta Paediatr.* 2005;94(9):1208-1213.

53. Gurses N, Kalayci AG, Islek I, Uysal S. Cefuroxime axetil in the treatment of acute sinusitis in childhood. *J Antimicrob Chemother.* 1996;38(3):547-550.

54. Arguedas A, Empanaza P, Schwartz RH, et al. A randomized, multicenter, double blind, double dummy trial of single dose azithromycin versus high dose amoxicillin for treatment of uncomplicated acute otitis media. *Pediatr Infect Dis J.* 2005;24(2):153-161.

55. Arrieta A, Arguedas A, Fernandez P, et al. High-dose azithromycin versus high-dose amoxicillin-clavulanate for treatment of children with recurrent or persistent acute otitis media. *Antimicrob Agents Chemother.* 2003;47(10):3179-3186.

56. Dagan R, Johnson CE, McLinn S, et al. Bacteriologic and clinical efficacy of amoxicillin/clavulanate vs. azithromycin in acute otitis media. *Pediatr Infect Dis J.* 2000;19(2):95-104.

57. Dunne MW, Latiolais T, Lewis B, et al. Randomized, double-blind study of the clinical efficacy of 3 days of azithromycin compared with co-amoxiclav for the treatment of acute otitis media. *J Antimicrob Chemother.* 2003;52(3):469-472.

58. Khurana CM. A multicenter, randomized, open label comparison of azithromycin and amoxicillin/clavulanate in acute otitis media among children attending day care or school. *Pediatr Infect Dis J.* 1996;15(9 suppl):S24-S29.

59. McLinn S. A multicenter, double blind comparison of azithromycin and amoxicillin/clavulanate for the treatment of acute otitis media in children. *Pediatr Infect Dis J.* 1996;15(9 suppl):S20-S23.

60. Aronovitz G. A multicenter, open label trial of azithromycin vs. amoxicillin/clavulanate for the management of acute otitis media in children. *Pediatr Infect Dis J.* 1996;15(9 suppl):S15-S19.

61. Schaad UB. Multicentre evaluation of azithromycin in comparison with co-amoxiclav for the treatment of acute otitis media in children. *J Antimicrob Chemother.* 1993;31(suppl E):81-88.

62. Mohs E, Rodriguez-Solares A, Rivas E, el Hoshy Z.

A comparative study of azithromycin and amoxicillin in paediatric patients with acute otitis media. *J Antimicrob Chemother.* 1993;31(suppl E):73-79.

63. Daniel RR. Comparison of azithromycin and co-amoxiclav in the treatment of otitis media in children. *J Antimicrob Chemother.* 1993;31(suppl E):65-71.

64. Ng DK, Chow PY, Leung L, et al. A randomized controlled trial of azithromycin and amoxicillin/clavulanate in the management of subacute childhood rhinosinusitis. *J Paediatr Child Health.* 2000;36(4):378-381.

65. Halpern MT, Schmier JK, Snyder LM, et al. Meta-analysis of bacterial resistance to macrolides. *J Antimicrob Chemother.* 2005;55(5):748-757.

66. Dowell SF, Butler JC, Giebink GS, et al. Acute otitis media: management and surveillance in an era of pneumococcal resistance—a report from the Drug-resistant *Streptococcus pneumoniae* Therapeutic Working Group. *Pediatr Infect Dis J.* 1999;18(1):1-9.

67. Ednie LM, Visalli MA, Jacobs MR, Appelbaum PC. Comparative activities of clarithromycin, erythromycin, and azithromycin against penicillin-susceptible and penicillin-resistant pneumococci. *Antimicrob Agents Chemother.* 1996;40(8):1950-1952.

68. National Committee for Clinical Laboratory Standards. *Performance standards for antimicrobial susceptibility tests (M100-S8).* Villanova, Pa: National Committee for Clinical Laboratory Standards, 1998.

69. Hyde TB, Gay K, Stephens DS, et al. Macrolide resistance among invasive *Streptococcus pneumoniae* isolates. *JAMA.* 2001;286(15):1857-1862.

70. Matsui D, Lim R, Tschen T, Rieder MJ. Assessment of the palatability of beta-lactamase-resistant antibiotics in children. *Arch Pediatr Adolesc Med.* 1997;151(6):599-602.

71. Angelilli ML, Toscani M, Matsui DM, Rieder MJ. Palatability of oral antibiotics among children in an urban primary care center. *Arch Pediatr Adolesc Med.* 2000;154(3):267-270.

72. Arguedas A, Loaiza C, Perez A, et al. A pilot study of single-dose azithromycin versus 3-day azithromycin or single-dose ceftriaxone for uncomplicated acute otitis media in children. *Curr Ther Res.* 2003;64(suppl A):A16-A29.

73. Dunne MW, Khurana C, Mohs AA, et al. Efficacy of single-dose azithromycin in treatment of acute otitis media in children after a baseline tympanocentesis. *Antimicrob Agents Chemother.* 2003;47(8):2663-2665.

74. Blumer JL, Forti WP, Summerhouse TL. Comparison of the efficacy and tolerability of once-daily cefitibuten and twice-daily cefprozil in the treatment of children with acute otitis media. *Clin Ther.* 1996;18(5):811-820.

75. Gehanno P, Berche P, Boucot I, et al. Comparative efficacy and safety of cefprozil and amoxicillin/clavulanate in the treatment of acute otitis media in children. *J Antimicrob Chemother.* 1994;33(6):1209-1218.

76. Pichichero ME, Arguedas A, Dagan R, et al. Safety and efficacy of gatifloxacin therapy for children with recurrent acute otitis media (AOM) and/or AOM treatment failure. *Clin Infect Dis.* 2005;41(4):470-478.

