



Acute otitis media (AOM) is a common infection, especially in children between the ages of 6 months and 18 months. By the end of the first year of life, more than 80% of children experience at least one episode of AOM.¹ AOM was associated with significant direct and indirect costs totaling approximately \$3 billion in the United States in 1995.² A common cause of outpatient visits, AOM accounted for 16 million visits in 2000 in the United States, a significant decline from almost 25 million visits in 1995.³

An important factor contributing to this decline was the introduction of 7-valent pneumococcal conjugate vaccine (PCV-7) in February 2000.^{4,5} PCV-7 was developed to contain approximately 80% of the serotypes known to be responsible for about 80% of invasive pneumococcal disease in children younger than 6 years.^{6,7} The vaccine also accounted for 74% of penicillin-susceptible *Streptococcus pneumoniae* and 100% of pneumococci with high-level penicillin resistance in children younger than 6 years with invasive disease.⁷

Since the introduction of PCV-7, the microbiology of AOM has shifted. This article describes how it has shifted and the implications this has on management.

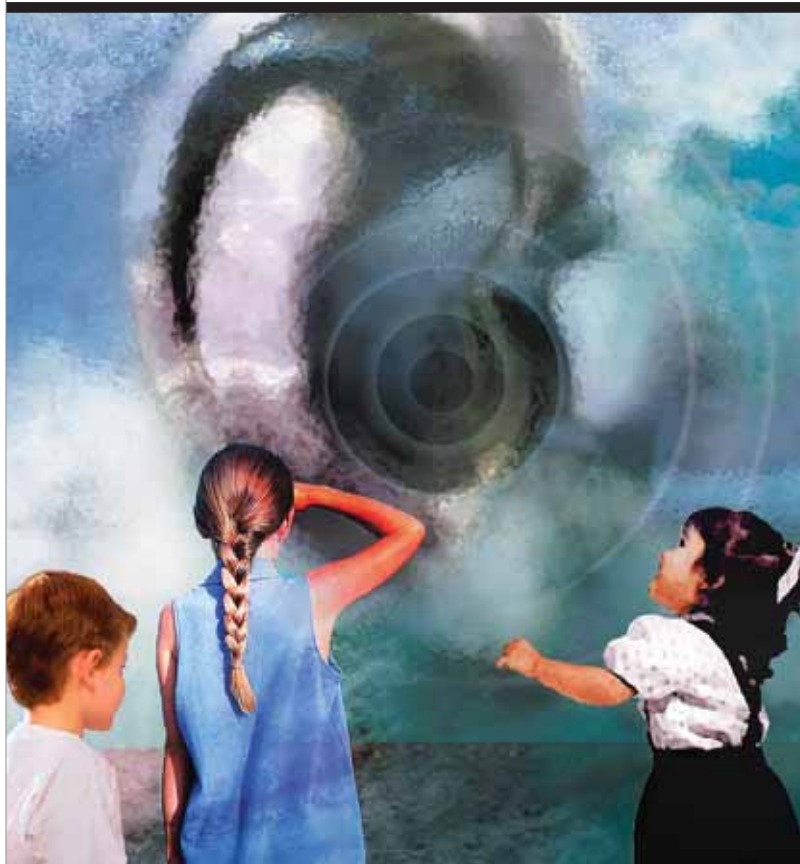
Causative Pathogens in AOM

Before 2000, 40% to 50% of AOM cases in young children were caused by *S. pneumoniae*, 20% to 30% by *Haemophilus influenzae* and 10% to 15% by *Moraxella catarrhalis*.⁸ Since 2000, several trials have observed a higher incidence of *H. influenzae* isolates (Figure 1).

In the Finnish Otitis Media Vaccine Trial, 1,662 infants received PCV-7 or a control vaccine at 2, 4, 6 and 12 months of age.⁵ At 24 months of age, a 6.9% reduction in the number of episodes of clinical AOM was observed in children vaccinated with PCV-7 compared with those who received the control vaccine. This suggested that *S. pneumoniae* serotypes were the cause in fewer AOM cases. A 34% reduction in culture-confirmed episodes of AOM also was seen in the PCV-7-vaccinated group. Other observations included a more than 50% decrease in pneumococcal AOM episodes caused

ACUTE otitis media

An Infection in Evolution/By Stephen Brunton, MD



The incidence of bacterial acute otitis media has declined in recent years. Since the introduction of 7-valent pneumococcal conjugate vaccine in 2000, *H. influenzae* has become the predominant AOM pathogen. Medication adherence is an important consideration in selecting initial empiric therapy in acute otitis media.



by vaccine or vaccine cross-reactive serotypes, a 33% increase in infections caused by other pneumococcal serotypes and an 11% increase in the proportion of AOM cases due to *H. influenzae*.

In a large pediatric group practice in rural Kentucky, isolates from middle ear fluid were collected in children between the ages of 7 months and 24 months who had severe or refractory AOM.⁹ A comparison was made between isolates obtained from 1992 to 1998 ($n=336$) and from 2000

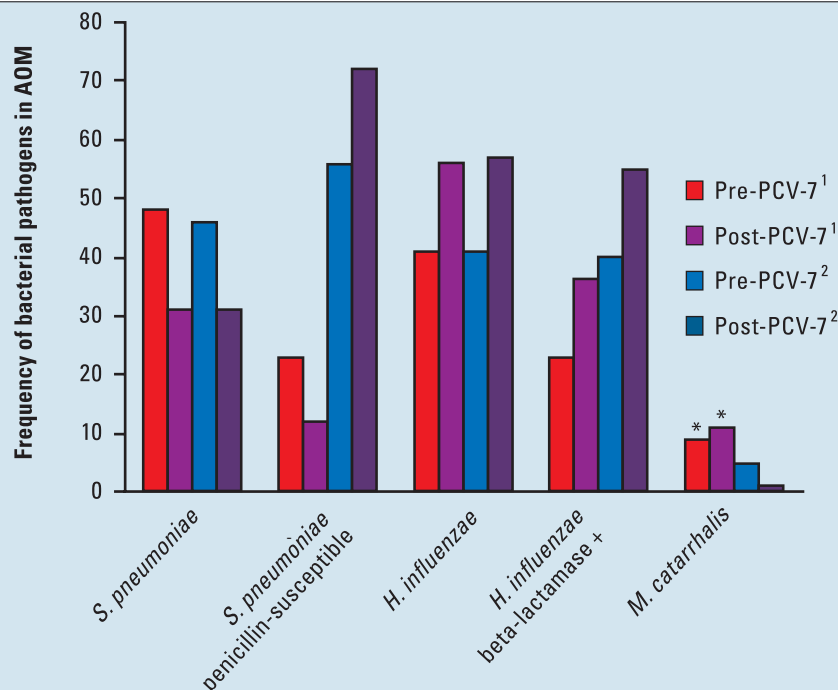
to 2003 ($n=83$). The proportion of culture-confirmed pneumococcus was reduced between these two time periods from 48% to 31%, a 35% reduction. The decrease in proportion of AOM episodes resulting from PCV-7 serotypes was 34%. The proportion of Gram-negative pathogens increased from 50% to 66%, which was mostly accounted for by a 37% increase in non-typable *H. influenzae* organisms. The percentage of beta-lactamase-producing Gram-negative organisms also increased

Table 1 Implications of PCV-7

- 6% to 8% reduction in total episodes of AOM
- 10% to 26% reduction in recurrent AOM
- 24% reduction in tympanostomy tube placement
- Shift in bacterial etiology
 - Decreased incidence of *S. pneumoniae*
 - Decreased incidence of penicillin-resistant isolates
 - Increased incidence of *H. influenzae*
 - Increased incidence of beta-lactamase-positive isolates

Adapted from: Fireman B, Black SB, Shinefield HR, Lee J, Lewis E, Ray P. Impact of the pneumococcal conjugate vaccine on otitis media. *Pediatr Infect Dis J*. 2003;22:10-16; and Eskola J, Kilpi T, Palmu A, et al. Efficacy of a pneumococcal conjugate vaccine against acute otitis media. *N Engl J Med*. 2001;344:403-409.

Figure 1 Frequency of Bacterial Pathogens in AOM



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1. 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;23:829-833.
2. Casey JR, Pichichero ME. Changes in frequency and pathogens causing acute otitis media in 1995-2003. *Pediatr Infect Dis J*. 2004;23:824-828.

from 32% to 47% of the total pathogens.

The Prospective Rochester, N.Y., Trial, enrolled 551 children with persistent or nonresponsive AOM who underwent tympanocentesis to identify bacterial isolates from 1995 to 2003.¹⁰ Children received initial empiric treatment with either amoxicillin 40 to 50 mg/kg/day given as three doses (from 1995 to 1997) or amoxicillin 80 to 100 mg/kg/day as two doses (from 1998 to 2003).

From 2001 through 2003, children also were vaccinated with PCV-7; however, recommended vaccination schedules were compromised due to vaccine shortages. The incidence of persistent or nonresponsive AOM decreased 24% in the group that received the PCV-7 compared with those who did not. A comparison of the pathogens isolated showed a 45% decline in *S. pneumoniae* (48% vs. 31%) and a 50% increase in *H. influenzae* (38%

vs. 57%) between 1995 and 1997 and 2000 and 2003, respectively. In addition, there was a 33% increase in penicillin-susceptible *S. pneumoniae* isolates (54% vs. 72%) and a 20% increase in beta-lactamase-positive *H. influenzae* during the same time periods, respectively.

In summary, the use of PCV-7 has led to a 6% to 8% reduction in the number of AOM episodes,^{4,5} and a 10% to 26% reduction in recurrent AOM (Table 1).⁴ There also has been a shift in the incidence of causative pathogens such that *H. influenzae* has become the predominant pathogen in persons inoculated with the vaccine. In addition, a significant shift in the pneumococcal strains causing AOM has occurred such that the proportion of non-vaccine serotypes increased, accounting for 32% to 38% of pneumococcal AOM.^{5,9,10} This is clinically important, since non-vaccine pneumococcal serotypes do not carry the same level of resistance as do the serotypes contained in PCV-7. Consequently, in patients who have received PCV-7 but who have developed AOM, the infection should be less protracted and easier to treat.

Treatment of AOM

The pharmacologic treatment of bacterial infections typically is based on several factors (Table 2). In the case of AOM, the pathogen or pathogens involved and the factors that affect medication adherence are especially important.

Known or suspected pathogens. The current guidelines for AOM were developed by the American Academy of Pediatrics and the American Academy of Family Physicians in 2004. The AAP/AAFP guidelines recommend amoxicillin as first-line empiric treatment of bacterial AOM to target *S. pneumoniae*, *H. influenzae* and *M. catarrhalis*. In addition, the recommended amoxicillin dose was increased from 40 to 45 mg/kg/day to 80 to 90 mg/kg/day due to concerns about the increased prevalence of penicillin-resistant *S. pneumoniae*.

For patients who have severe illness and in those for whom additional coverage for beta-lactamase-positive *H. influenzae* and *M. catarrhalis* is desired, the guidelines recommend amoxicillin-clavulanate 90/6.4 mg/kg/day in two divided doses. In penicillin-allergic patients, the guidelines further recommend cefdinir, cefpodoxime or cefuroxime, except in cases of type 1 hypersensitivity reactions (urticaria or anaphylaxis), in which case options include azithromycin, clarithromycin and ceftriaxone.

Although the AAP/AAFP guidelines were developed in 2004, the Kentucky and New York trials, which were published subsequently, pro-

vide data suggesting that the guidelines may not be as widely applicable. Recalling that these trials demonstrated the increased importance of *H. influenzae*, including beta-lactamase-positive isolates, and the decreased importance of *S. pneumoniae*, it would seem that amoxicillin may no longer be the best first choice. In some cases, amoxicillin-clavulanate, cefdinir, cefpodoxime or cefuroxime might be preferred as initial empiric therapy for AOM.

Medication Adherence

According to a survey conducted by the AAP, several factors affect adherence to a prescription regimen for an acute illness in children (Table 3).¹¹

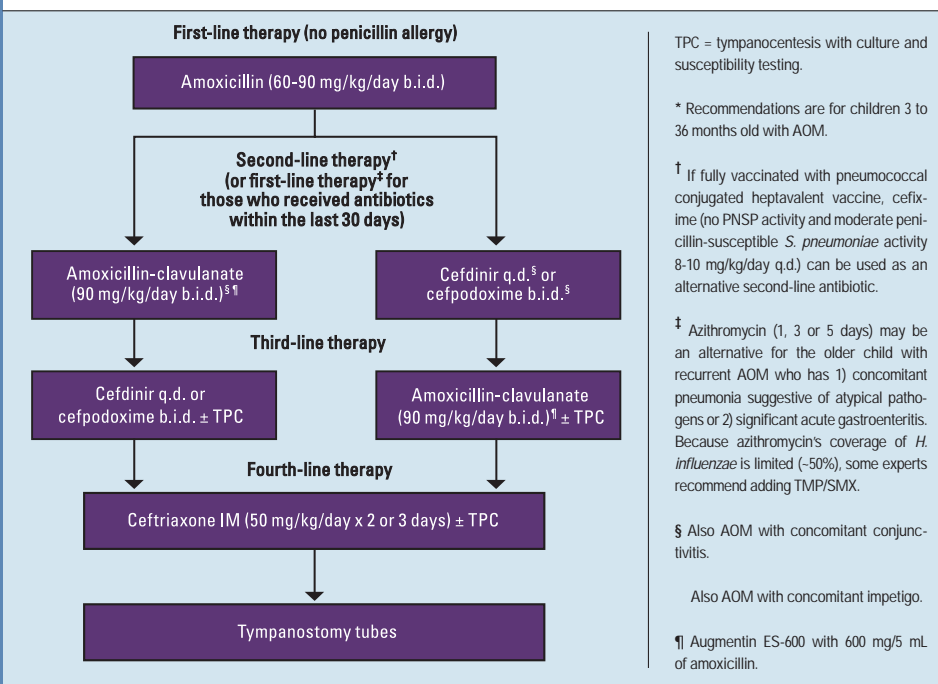
Dosing frequency. Along with duration, dosing frequency is an important determinant of medication adherence. Medication adherence is 10% to 20% better with five days than with 10 days of antibiotic therapy,^{12,13} and is significantly better with one or two daily doses compared with three or more daily doses.¹⁴⁻¹⁶ Antibiotics for AOM that can be given once daily for five days or less include azithromycin, cefdinir and cefpodoxime. These three antibiotics are the only antibiotics included in the AAP/AAFP guideline recommendations that are approved by the Food and Drug Administration for short-term (that is, five days or less) treatment of bacterial AOM.

Taste/palatability. Several studies have compared the taste of various antibiotic suspensions commonly used in children. One recent investigation involving 86 physicians and health care personnel compared 11 antibiotics with amoxicillin with respect to appearance, smell, texture, taste and aftertaste.¹⁷ Significant differences were observed (Table 4). The three most palatable antibiotic suspensions were loracarbef, cefdinir and cefixime.

Side effects. The majority of drugs commonly used for AOM have a longstanding history of being safe. Gastrointestinal complications, such as diarrhea, nausea/vomiting and gastritis, are the most common adverse events. Dose-dependent diarrhea is more common with amoxicillin-clavulanate.

Patient education. Medication adherence can be improved by educating patients and their caregivers. An important part of the educational process is to determine and take into account constraints and issues of the patient and the caregiver. For example, few patients and caregivers have a suitable device to measure the appropriate volume of antibiotic suspension. Providing a measuring device to the patient or caregiver, and marking on the device the appropriate volume of antibiotic, can greatly improve adherence.

Figure 2
Antibiotic Choices for AOM*



TPC = tympanocentesis with culture and susceptibility testing.

* Recommendations are for children 3 to 36 months old with AOM.

† If fully vaccinated with pneumococcal conjugated heptavalent vaccine, cefixime (no PNSP activity and moderate penicillin-susceptible *S. pneumoniae* activity 8-10 mg/kg/day q.d.) can be used as an alternative second-line antibiotic.

‡ Azithromycin (1, 3 or 5 days) may be an alternative for the older child with recurrent AOM who has 1) concomitant pneumonia suggestive of atypical pathogens or 2) significant acute gastroenteritis. Because azithromycin's coverage of *H. influenzae* is limited (~50%), some experts recommend adding TMP/SMX.

§ Also AOM with concomitant conjunctivitis.

Also AOM with concomitant impetigo.

¶ Augmentin ES-600 with 600 mg/5 mL of amoxicillin.

Adapted with permission from: Block SL, Harrison CJ. Basis for antibiotic selection. In: Block SL, Harrison CJ, eds. *Diagnosis and Management of Acute Otitis Media*. 3rd ed. Caddo, Okla: Professional Communications Inc.; 2005:85-139.

Similarly, rounding the dose up to the next appropriate convenient volume can be helpful. As an example, 2.5 mL is much easier to measure than 2.37 mL.

Other issues to discuss include potential interactions with other drugs and food, as well as the need for refrigeration.

Possible Approach to Initial Therapy

Given the evolving microbiology of AOM in children who have received PCV-7 and the myriad issues to consider, Block and Harrison have developed an algorithm to guide the selection of initial empiric therapy for AOM (Figure 2).¹⁸ A similar algorithm has been developed for the non-severely penicillin-allergic child (Figure 3).¹⁹

Summary

The treatment of bacterial AOM has evolved significantly in recent years, due in part to the use of PCV-7. This vaccine has altered the microbiology of AOM such that *H. influenzae* is the predominant pathogen in patients vaccinated with PCV-7. In addition, the frequency of beta-lactamase-positive *H. influenzae*, as well as penicillin-susceptible *S. pneumoniae*, has increased. For these reasons, amoxicillin, even in high doses, may no longer be the preferred agent for initial

Table 2
Antibiotic Selection For Acute Otitis Media

- Known or suspected pathogen(s)
- Local pathogen susceptibility patterns
- Likelihood of developing or promoting resistance
- Need to avoid initial treatment failure
- Safety
- Palatability
- Frequency and duration of use
- Cost

therapy. Alternatively, high-dose amoxicillin-clavulanate or cefdinir, cefpodoxime or cefuroxime are oral agents that may be used because of their activity against the evolving microbiology in bacterial AOM.

In considering these and other antibiotic options for bacterial AOM, issues related to medication adherence must be weighed in consultation with patients and their caregivers. These issues include dosing frequency and duration, palatability, side effects, drug and food interactions, cost, refrigeration and the ability to measure and deliver the dose. □

Table 3 Medication Adherence in Children

Here are the factors affecting adherence to a prescription medication for an acute illness in children. Figures represent the percentage of pediatricians reporting the factor.

- Frequency of dosing schedule (96%)
- Unpleasant taste (91%)
- Side effects (88%)
- Duration of dosing schedule (87%)
- Unpleasant palatability (87%)
- Parental perception of medication effectiveness (86%)

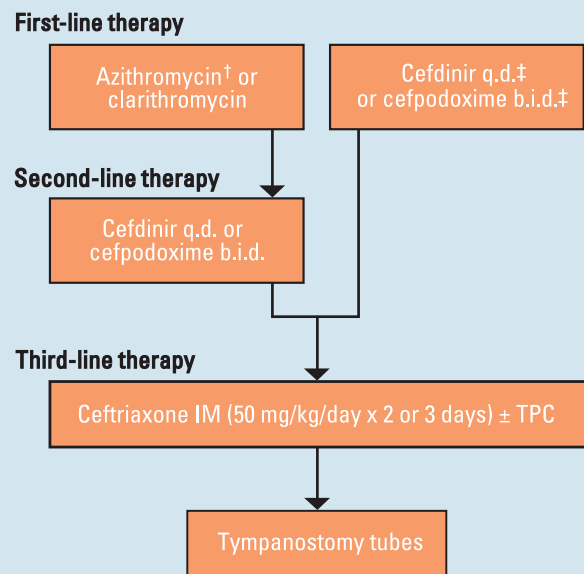
Adapted from: American Academy of Pediatrics Division of Health Policy Research. Periodic survey #44: patient compliance with prescription medications. Available at: <http://www.aap.org/research/periodicsurvey/ps44bexs.htm>. Accessed August 30, 2006.

Table 4 Taste of Antibiotic Suspensions

Most to least palatable:	
• Loracarbef	• Trimethoprim-sulfamethoxazole
• Cefdinir	• Clarithromycin
• Cefixime	• Trimethoprim
• Azithromycin	• Amoxicillin-clavulanate
• Ciprofloxacin	• Cefpodoxime
	• Cefuroxime

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

Figure 3 Antibiotic Choices for AOM For the Non-Severely Penicillin-Allergic Child



TPC = tympanocentesis with culture and susceptibility testing.

* Recommendations are for children 3 to 36 months old with AOM.

† Because azithromycin's coverage of *H. influenzae* is limited (~50%); also AOM with concomitant pneumonia suggestive of atypical pathogens. Use of one of the newly approved regimens (10 mg/kg/day x 3 days or 30 mg/kg as one dose) is preferred. Lower success rates might be expected for macrolide/azalide therapy of AOM in an era of increasing prevalence of *H. influenzae* as the cause of AOM (post-PCV-7 use).

‡ Also AOM with concomitant conjunctivitis.

Adapted with permission from: Block SL, Harrison CJ. First-line antibiotic therapy. In: Block SL, Harrison CJ, eds. *Diagnosis and Management of Acute Otitis Media*. 3rd ed. Caddo, Okla: Professional Communications Inc.; 2005:141-156.

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