ABSTRACT

Introduction of the 7-valent pneumococcal conjugate vaccine (PCV-7) has been associated with a modest reduction in the incidence of acute otitis media (AOM) and a shift in the etiology of AOM pathogens. In both rural and suburban settings in which use of PCV-7 has been widespread, there has been a decrease in AOM episodes caused by Streptococcus pneumonia, the predominant AOM pathogen in the pre–PCV-7 era, and an increase in those caused by Haemophilus influenzae. Even in the decade prior to the introduction of PCV-7, tympanocentesis-based multicenter trials documented an increase in the incidence of AOM due to H influenzae, and PCV-7 appears to have accelerated this increase. The changing microbiology of AOM affects treatment choices. The American Academy of Pediatrics/American Association of Family Physicians-recommended first-line agent for most children with AOM, high-dose amoxicillin (80-90 mg/kg/day), may not be the agent of first choice in the real-world setting in which local resistance patterns and other important variables such as cost, adverse events profiles, and adherence issues determine antibiotic selection. For children who fail initial amoxicillin therapy, the increasing predominance of H influenzae warrants consideration of a wider array of treatment options than just high-dose amoxicillin/clavulanate. The excellent coverage of H influenzae as well as most penicillin-susceptible and penicillin-intermediate S pneumoniae provided by the cephalosporins cefdinir, cefuroxime, and cefpodoxime makes these agents reasonable treatment options for initial empiric therapy as well as amoxicillin treatment failures.

A acute otitis media (AOM) is among the leading reasons for visits to US pediatricians and primary care providers, accounting for 16 million visits in 2000. The incidence of AOM peaks between 6 and 18 months of age, and 86% of children will experience at least one episode of AOM by age 1 year. In 1995, the estimated direct cost of AOM was $1.96 billion, while indirect costs were estimated to be $1.02 billion.

In February 2000, the 7-valent pneumococcal conjugate vaccine (PCV-7) was approved for use in children younger than 24 months to prevent invasive disease caused by the 7 pneumococcal serotypes 14, 6B, 19F, 18C, 23F, 4, and 9V. These serotypes cause 80% of invasive infections in children younger than 6 years of age. PCV-7 induces protective antibody responses (>0.15 μg/mL) in more than 90% of infants after administration of 3 doses at 2, 4, and 6 months of age. An additional dose given at 12 to 15 months of age elicits a booster response and may enhance long-term immune memory.

In a clinical study at Kaiser Permanente in Northern California, 37,868 young children were randomized to receive PCV-7 (n = 18,927) or a control
vaccine (n = 18,941). The children received the primary series of 3 doses at 2, 4, and 6 months of age, as well as a booster dose at 12 to 15 months of age. Results of the study showed that PCV-7 was safe and effective for prevention of invasive disease, otitis media, and pneumonia in children younger than 5 years of age. Among fully vaccinated children (ie, 3 primary doses and the booster dose), the efficacy of PCV-7 was 97% against invasive pneumococcal disease for vaccine serotypes (P < .001). The risk of radiograph-positive pneumonia was reduced by 32% in the first year of life and by 23% in the first 2 years, but it was reduced by only 9% in children older than 2 years.

In children who received PCV-7 and completed the primary series per protocol, AOM episodes were reduced by 6.6% (95% confidence interval, 4.3-8.8). This modest reduction in the incidence of AOM as well as the shifting etiology of AOM pathogens will have important socioeconomic benefits.

**Acute Otitis Media: Implications of Vaccine Use**

The introduction of a vaccine commonly alters the bacterial etiology of infections. Approximately 20,000 cases of invasive *Haemophilus influenzae* disease occurred in the United States in the early 1980s. In 1985, the first *H influenzae* type B (Hib) vaccine was introduced followed by a conjugate Hib vaccine in 1987. The widespread use of these vaccines has resulted in a greater than 99% decline in the invasive disease compared with the early 1980s.

This dramatic decline in invasive *H influenzae* was an impressive public health benefit but it also altered the bacterial etiology of AOM. As *H influenzae* decreased, *Streptococcus pneumoniae* became the more prevalent cause of bacterial AOM. Now that a conjugate pneumococcal vaccine has been mandated for children it makes sense to investigate how this PCV-7 vaccine may be altering the etiology of AOM.

In the pre–PCV-7 era, 40% to 50% of cases of AOM in young children were caused by *S pneumoniae*, 20% to 30% by *H influenzae*, and 10% to 15% by *Moraxella catarrhalis*. Studies using diagnostic tympanocentesis isolated *S pneumoniae* from 25% to 55% of all middle ear aspirates from children with AOM. However, recent data suggest that this pattern is changing among infants immunized with PCV-7. In the Finnish Otitis Media Vaccine Trial, 1662 infants received either the PCV-7 vaccine or a control vaccine at 2, 4, 6, and 12 months of age and were then followed from age 6.5 months to 24 months. Results of the study showed an overall reduction of 6.9% in episodes of clinical AOM diagnosed in children vaccinated with PCV-7 compared with the control group (1251 vs 1345, respectively), suggesting a shift in causative pathogens.

The bacteriologic findings in samples of middle ear fluid obtained during 93% of visits for AOM in the Finnish trial indicate a 34% reduction in culture-confirmed episodes in the group receiving pneumococcal vaccine, a decrease of more than 50% in pneumococcal AOM episodes caused by vaccine or vaccine cross-reactive serotypes, and an increase of 33% in infections caused by other pneumococcal serotypes. Of particular interest was the 11% increase in the proportion of AOM cases due to *H influenzae* (Table 1).

This change in the proportion of pathogens in AOM also has been observed recently in studies conducted in rural and suburban practices in the United States. One practice in rural Kentucky has participated in a number of clinical trials of PCV-7 and other vaccines and therefore has been able to immunize 94% of children in the practice with 3 or 4 doses of PCV-7.

### Table 1. Causes of AOM Episodes and Impact of PCV-7 Immunization

<table>
<thead>
<tr>
<th>Cause</th>
<th>No. of Episodes</th>
<th>Percentage Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Culture-confirmed pneumococcus</td>
<td>271</td>
<td>34% ↓</td>
</tr>
<tr>
<td>Pneumococcal serotype in vaccine</td>
<td>107</td>
<td>57% ↓</td>
</tr>
<tr>
<td>Vaccine cross-reactive serotypes</td>
<td>41</td>
<td>51% ↓</td>
</tr>
<tr>
<td>Other pneumococcal serotypes</td>
<td>125</td>
<td>33% ↑</td>
</tr>
<tr>
<td><em>Haemophilus influenzae</em></td>
<td>315</td>
<td>11% ↑</td>
</tr>
<tr>
<td><em>Moraxella catarrhalis</em></td>
<td>379</td>
<td>1% ↑</td>
</tr>
</tbody>
</table>

* 6A, 9N, 18B, 19A, 23A.

AOM = acute otitis media; PCV-7 = 7-valent pneumococcal conjugate vaccine.

Adapted with permission from Eskola et al. Efficacy of a pneumococcal conjugate vaccine against acute otitis media. *N Engl J Med*. 2001;344(6):403-409. Copyright © 2001 Massachusetts Medical Society. All rights reserved.
during the first 18 months of life. Among children 7 to 24 months of age with severe or refractory AOM, a comparison of isolates from middle ear fluid obtained in 1992 to 1998, before introduction of PCV-7, with isolates obtained from 2000 to 2003, following PCV-7 immunization, found a 35% decrease (48% vs 31%) in the proportion of AOM episodes due to \textit{S. pneumoniae}, including a 49% decrease (70% vs 36%) in those due to vaccine serotypes (Table 2).\textsuperscript{13} Twenty-eight percent of the pre–PCV-7 and 34% of the post–PCV-7 cohort had received antibiotic therapy within the prior 3 days, and 59% and 76% had received antibiotic therapy within the prior 30 days.\textsuperscript{13} In contrast to the Finnish data, which showed replacement of pneumococcal vaccine serotypes with nonvaccine serotypes,\textsuperscript{12} there was an increase in vaccine cross-reactive serotypes (32% vs 8%) and nonvaccine pneumococcal serotypes (32% vs 22%) in the Kentucky cohort.\textsuperscript{13} Vaccine cross-reactive serotypes 6A and 19A accounted for most of the penicillin-nonsusceptible \textit{S. pneumoniae} strains in the vaccinated population.\textsuperscript{13} The most notable finding post–PCV-7 was that gram-negative bacteria, mainly \textit{H. influenzae}, accounted for two thirds of AOM isolates.\textsuperscript{13} Beta-lactamase–producing organisms also accounted for nearly half of all isolates.\textsuperscript{13}

Strikingly similar changes following the introduction of PCV-7 were seen in a prospective study conducted in a suburban, community-based private practice in Rochester, NY, in which 551 children with persistent or nonresponsive AOM (defined as nonresponders after 1 or 2 empiric antibiotic courses or failures after 48 hours on treatment) underwent tympanocentesis to identify bacterial isolates during a 9-year period from 1995 to 2003.\textsuperscript{14} From 1995 to 1997, all enrollees received a standard dose of amoxicillin (40-50 mg/kg divided 3 times daily) as initial empiric treatment. From 1998 to 2000 and 2001 to 2003, all children received high-dose amoxicillin (80-100 mg/kg divided twice daily) as initial empiric treatment; during the latter period children also received PCV-7. During the period of 2001 to 2003, the majority of children (63%) received the primary series of 3 doses of PCV-7, but only 10% received the booster dose.\textsuperscript{14}

As shown in Table 3, post–PCV-7 there was a 30% decrease in the proportion of \textit{S. pneumoniae} isolates (44% vs 31%, \(P = .017\)) and a commensurate increase (33%) in the proportion of \textit{H. influenzae} isolates (43% vs 57%, \(P = .012\)) compared with the pre–PCV-7 peri-

### Table 2. Change in AOM Microbiology from Pre–PCV-7 (1992-1998) to Post–PCV-7 (2000-2003)

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Culture-confirmed pneumococcus</td>
<td>48% (n = 336)</td>
<td>31% (n = 83)</td>
<td>35% ↓</td>
</tr>
<tr>
<td>Pneumococcal serotype in vaccine</td>
<td>70%</td>
<td>36%</td>
<td>49% ↓</td>
</tr>
<tr>
<td>Vaccine cross-reactive serotypes*</td>
<td>8%</td>
<td>32%</td>
<td>30% ↑</td>
</tr>
<tr>
<td>Other pneumococcal serotypes†</td>
<td>22%</td>
<td>32%</td>
<td>45% ↑</td>
</tr>
<tr>
<td>\textit{Haemophilus influenzae}</td>
<td>41%</td>
<td>56%</td>
<td>36% ↑</td>
</tr>
<tr>
<td>Beta-lactamase–positive</td>
<td>23%</td>
<td>36%</td>
<td>56% ↑</td>
</tr>
<tr>
<td>\textit{Moraxella catarrhalis}, Beta-lactamase–positive</td>
<td>9%</td>
<td>11%</td>
<td>22% ↑</td>
</tr>
</tbody>
</table>

\(P = .017\)

* Includes 6A and 19F.
† Nonvaccine serotypes in post PCV-7 group: 1, 11A, 15A, 29, and 33F.
Adapted with permission from Block et al. Community-wide vaccination with heptavalent pneumococcal conjugate significantly alters the microbiology of acute otitis media. \textit{Pediatr Infect Dis J.} 2004;23(9):829-833.\textsuperscript{13}


<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Pre–PCV-7 (n = 204)</th>
<th>Post–PCV-7 (n = 152)</th>
<th>Percentage Change P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>\textit{Streptococcus pneumoniae}*</td>
<td>44%</td>
<td>31%</td>
<td>30% ↓ .017</td>
</tr>
<tr>
<td>Penicillin nonsusceptible</td>
<td>24%</td>
<td>14%</td>
<td>10% ↓ .012</td>
</tr>
<tr>
<td>\textit{Haemophilus influenzae}</td>
<td>43%</td>
<td>57%</td>
<td>33% ↑ .012</td>
</tr>
<tr>
<td>Beta-lactamase–positive</td>
<td>33%</td>
<td>55%</td>
<td>22% ↑ .044</td>
</tr>
<tr>
<td>\textit{Moraxella catarrhalis}</td>
<td>5%</td>
<td>1%</td>
<td>4% ↓ .044</td>
</tr>
</tbody>
</table>

\(P = .017\)

* Pneumococcal serotyping was not done.
od (1998-2000).\textsuperscript{14} There was also a significant increase in the proportion of beta-lactamase–producing \textit{H influenzae} (33\% vs 55\%, \textit{P} = .044) and a trend toward an increased proportion of penicillin-susceptible \textit{S pneumoniae} isolates (58\% vs 72\%, \textit{P} = .017) post–PCV-7.\textsuperscript{14} In addition, there was a 24\% reduction (\textit{P} = .009) in the frequency of the diagnosis of persistent AOM or AOM treatment failure.\textsuperscript{14} These changes were considered to be the result of the introduction of PCV-7 rather than the switch from standard-dose to high-dose amoxicillin.

Although the design of these 2 studies makes it difficult to determine how much of the change seen in AOM pathogens was secondary to the choice of prior antibiotic therapy or to the use of PCV-7, it is clear that a microbiologic shift is occurring. Even in the decade prior to the introduction of PCV-7, tympanocentesis-based multicenter trials documented an increase in the incidence of \textit{H influenzae}, and this increase appears to have accelerated following the introduction of PCV-7.

**Utilization of PCV-7**

In August 2001, a serious shortage of PCV-7 developed in 34 state immunization programs.\textsuperscript{15} As a result, in September 2001, the Centers for Disease Control and Prevention (CDC) advised physicians to administer PCV-7 only to children younger than 12 months and to those aged 1 to 5 years who were at increased risk of pneumococcal disease. Vaccinations for healthy children aged 1 to 2 years and boosters for healthy children who had completed the primary series were to be deferred.\textsuperscript{16} However, fewer than 30\% of practices changed their policies for administration of PCV-7.\textsuperscript{15} Continued shortages prompted the CDC first to recommend the temporary suspension of the fourth dose of PCV-7 for healthy children\textsuperscript{17} and, subsequently, both the third and fourth doses in order to conserve vaccine supplies.\textsuperscript{18} In July 2004, the CDC reported that PCV-7 production problems appeared to have been resolved and that projected deliveries should provide sufficient supplies for every child to receive 3 doses of vaccine. In September, the CDC announced that the supply of vaccine is now sufficient to meet national demand for the routine 4-dose schedule of the vaccine.\textsuperscript{19} For children who are incompletely vaccinated, the CDC has provided a catch-up schedule, with highest priority being given to children younger than 5 years who are at high risk for invasive pneumococcal disease, followed by healthy children younger than 24 months who have not yet received any doses of PCV-7, and healthy children younger than 12 months who have not yet received 3 doses of vaccine.\textsuperscript{19}

**Herd Immunity**

Despite the fact that the shortage of PCV-7 prevented universal immunization of US children with 4 doses of vaccine, evidence of herd immunity and a decrease in antibiotic resistance in pneumococcal pathogens has been reported throughout the United States.\textsuperscript{20,21} The Northern California Kaiser Permanente medical program has an annual birth cohort of 38 000 infants. As of March 2003, 157 471 children in this program had received one or more doses of vaccine; however, because of the vaccine shortage, only 24\% of those aged 2 years or less had received all 4 doses.\textsuperscript{21} Nonetheless, there was a 91\% reduction in invasive pneumococcal disease of all serotypes among children younger than 2 years, and an 84\% reduction in those younger than 5 years.\textsuperscript{21} The risk of invasive pneumococcal disease was significantly reduced among all individuals older than 5 years (25\%, \textit{P} < .0001), as well as those aged 20 to 39 years (52\%, \textit{P} = .0009) and those 60 years of age and older (27\%, \textit{P} = .0006).\textsuperscript{21} This herd effect was seen despite vaccine shortages and with only a minority of children having received the fourth dose of PCV-7.\textsuperscript{21} In addition, the proportion of pneumococcal isolates resistant to penicillin decreased significantly from 28.9\% in 1998 through 1999 to 19.5\% in 2001 through 2002 (\textit{P} < .001).\textsuperscript{21}

A similar decrease (29\%) in the rate of pneumococcal disease in both young children and adults has been seen throughout the United States,\textsuperscript{20,21} along with a 35\% reduction in the rate of disease caused by non–penicillin-susceptible pneumococcal strains.\textsuperscript{20} The reduction in the carriage of vaccine-related pneumococcal serotypes among vaccinated children may be the reason for the reduction in risk for adults with whom they are in contact, including parents (age 20-40 years) and grandparents (age 60 years and older).\textsuperscript{20,21}

Further evidence of this herd immunity is indicated by the changes in racial differences in the epidemiology of invasive pneumococcal disease seen in 5 Tennessee counties after the introduction of PCV-7.\textsuperscript{22} These changes occurred even though fewer black children than white children had PCV-7 coverage (31.2\% vs 47.6\%).\textsuperscript{22} Before approval of the vaccine, rates of invasive pneumococcal disease were higher in children
younger than 2 years and in blacks. With introduction of PCV-7, racial differences in incidence rates of invasive pneumococcal disease were largely eliminated, particularly in young children. In fact, the rate of invasive pneumococcal disease in black children younger than 2 years decreased 83% and was similar to that in white children.22 In addition, the proportion of antibiotic-nonsusceptible pneumococcal isolates, previously higher among white children, was similar in whites and blacks of all ages.22

**SEROTYPE REPLACEMENT**

With licensure of PCV-7 in the United States, there has been a significant shift in the pneumococcal strains causing AOM. Studies of children treated at urban medical centers and in a rural Kentucky pediatric practice have documented an increase in the proportion of nonvaccine serotypes, which now account for 32% to 38% of pneumococcal AOM.13,23,24 A similar increase (33%) in nonvaccine serotypes was seen among vaccinated children in the Finnish trial.12 Data from a 9-year longitudinal surveillance study of invasive pneumococcal disease at 8 US children’s hospitals found a decrease in penicillin resistance of 20% among vaccine serotypes for the first time in 2002. Continued surveillance will be important to monitor switching and/or replacement of pneumococcal serotypes and clinical trials are currently under way to determine if additional pneumococcal serotypes will optimize coverage.

**CURRENT RECOMMENDATIONS FOR INITIAL TREATMENT AND TREATMENT FAILURES**

The recent American Academy of Pediatrics/American Academy of Family Physicians (AAP/AAFP) guidelines recommend high-dose amoxicillin (80-90 mg/kg/day) as initial therapy for a child with AOM who has not received a recent course of antimicrobial therapy, does not have severe infection or a history of type 1 penicillin hypersensitivity (ie, urticaria or anaphylaxis), and does not have risk factors that increase the risk of recurrence (eg, large-group day care attendance or age <2 years).2 For children failing to respond to amoxicillin after 48 to 72 hours, the guidelines recommend high-dose amoxicillin/clavulanate (90 mg/kg/day of amoxicillin with 6.4 mg/kg/day of clavulanate in 2 divided doses). If the patient has a non-type 1 allergy to amoxicillin, the oral cephalosporins cefdinir, cefpodoxime, and cefuroxime are appropriate alternatives. Azithromycin or clarithromycin are options for patients with type 1 penicillin allergy. A standard 10-day course of therapy is recommended for children younger than 6 years and for children with severe disease; however, a 5- to 7-day course may be appropriate for children 6 years of age and older with mild to moderate disease.2

For children who are vomiting or cannot otherwise tolerate oral medication, a single dose of parenteral ceftriaxone (50 mg/kg) is recommended. A 3-injection sequence of ceftriaxone (one 50-mg/kg injection for 3 consecutive days) is recommended as an alternative for children who fail to respond to treatment with amoxicillin/clavulanate.2

**IMPACT OF CHANGING MICROBIOLOGY POST-PCV-7 ON TREATMENT CHOICES**

Amoxicillin is effective against pneumococcus and beta-lactamase–negative strains of *H influenzae*.25 It is also safe, fairly inexpensive, and palatable. However, antibiotic selection for the child who has failed initial high-dose amoxicillin therapy, in whom the predominant pathogen is likely to be beta-lactamase–producing *H influenzae* rather than penicillin-nonsusceptible *S pneumoniae*, is an issue of great interest.25,26 Among children with persistent or refractory AOM who have received high-dose amoxicillin (80-100 mg/kg divided twice daily) as initial empiric therapy, the rate of infections due to *H influenzae* has increased from 43% among those treated prior to licensure of PCV-7 to 57% among those who received 2 or more doses of PCV-7.14

While high-dose amoxicillin/clavulanate provides adequate coverage of penicillin-resistant *S pneumoniae*, there is new clinical evidence to suggest distinctly greater efficacy when using an alternative antimicrobial regimen that provides adequate coverage of beta-lactamase–producing *H influenzae*, such as one of the second- or third-generation cephalosporins.

A recent investigator-blinded study compared 5 days of cefdinir (14 mg/kg given twice daily) versus 10 days of amoxicillin/clavulanate (45 mg/kg amoxicillin base given twice daily) in children with nonrefractory AOM.27 Overall clinical cure rates were found to be comparable for cefdinir 88% versus amoxicillin/clavulanate 85%, (95% confidence interval, -4.9–9.3).27
Looking at the subpopulation of children aged 6 to 24 months who had received PCV-7, an even higher response rate was seen in those children treated with cefdinir (92% vs 77%, P = .019, 95% confidence interval, 3.5 to 26.2). Although tympanocentesis was not done in this study, the investigators speculate that this difference in efficacy probably reflected the increase in gram-negative organisms seen with use of PCV-7, particularly H influenzae.

Given the increasing importance of H influenzae in populations immunized with PCV-7, it will be essential that future trials establish the PCV-7 status of the participants and report the results accordingly. Emerging data indicate that the proportion of S pneumoniae has been reduced and that H influenzae has become the predominant AOM pathogen in the post–PCV-7 era. Because S pneumoniae is the pathogen most often associated with the symptomatic AOM that commonly precipitates tympanocentesis, it may be more difficult to recruit patients for tympanocentesis trials in the United States.

**FIRST-LINE versus FIRST-CHOICE ANTIMICROBIAL AGENTS**

While AAP/AAFP guideline recommendations of antimicrobial agents are based, for the most part, on data derived from clinical trials, the data may not reflect comparable patient populations. For example, the difference in response rates among children who had received PCV-7 and those who had not highlights the difficulty in assessing data from clinical trials in which the PCV-7 status of those enrolled is not known. Recent multinational trials of AOM often combine results from centers in countries such as Costa Rica and Chile, where PCV-7 has not been widely used, with those from US centers where the majority of children have received PCV-7.29

Consequently, the AAP/AAFP-recommended first-line agent for the initial treatment of most children with uncomplicated AOM may, under certain clinical circumstances, not be the agent of first choice. In the real-world setting, the choice of antibiotic therapy for the child with AOM is based on knowledge of local resistance patterns, which determines the pathogens that need to be covered, and other important variables such as cost, adverse event profiles, and adherence issues (ie, taste/palatability, convenience of regimen).

In terms of pathogen coverage, when a child has failed initial therapy with high-dose amoxicillin, a switch to one of the cephalosporins, cefdinir, cefuroxime, and cefpodoxime or amoxicillin/clavulanate provide excellent coverage for H influenzae.30,31

Another important issue for successful patient outcomes is patient adherence. If a patient is nonadherent because of taste, dosing, or adverse effects, the antibiotic prescribed will be less effective than expected. On the other hand, if another antibiotic has a more palatable taste, a more convenient dosing schedule, and is better tolerated, patient adherence and subsequent treatment effectiveness will be greater.

Although clinical trial data suggest that a 10-day course of therapy is more effective than a 5-day course in children younger than 2 years,32,33 administration of a full 10-day course of treatment may be problematic. The ability to administer the full course of therapy in pediatric patients depends mainly on the frequency of dosing and the taste of the antibiotic suspension prescribed. In a comparison of oral antibiotic suspensions, compliance was shown to vary widely: cefaclor (85%), amoxicillin (77%), trimethoprim/sulfamethoxazole (73%), and cefuroxime axetil (67%). More than one half of the children had AOM, but up to 33% of the children with AOM did not complete their prescribed 10-day course of therapy.35 More recently, a comparison of parent-reported outcomes among children aged 6 months to 6 years who received either cefdinir (14 mg/kg divided twice daily for 5 days) or amoxicillin/clavulanate (45/6.4 mg/kg divided twice daily for 10 days) found that significantly more parents in the cefdinir group reported that their child received 100% of the medication (68% vs 53%, P<.01). Overall, parents rated cefdinir statistically significantly better than amoxicillin/clavulanate in taste (P >.0001) and ease of use (P = .009).36 In an evaluation of the palatability of oral suspensions commonly prescribed for the treatment of AOM, each of 6 trials compared cefdinir oral suspension with one of the following oral suspensions: amoxicillin/clavulanate, azithromycin, or cefprozil. Children aged 4 to 8 years preferred the taste and smell of cefdinir. The taste and smell of cefdinir were rated good or really good by 85% and 71% of subjects, respectively; average ratings for the comparators were 63% and 64% for taste and smell, respectively.37
In another comparison of 11 oral antimicrobial agents, cefdinir and loracarbef received the highest ratings compared with other commonly prescribed agents (Table 4).38 When scores that were adjusted for overall taste and cost were further adjusted for duration of therapy (5 days vs 10 days), 5-day cefdinir received the highest rating.38

These findings offer additional perspectives to the AAP/AAFP recommendation of high-dose amoxicillin/clavulanate as the only agent for initial therapy for the child with AOM who has severe illness (ie, moderate to severe otalgia or fever of >39°C) and in whom additional coverage for M catarrhalis and beta-lactamase–positive H influenzae is desired. Studies in the United States have shown that these children frequently have pneumococcal infections28 for which high-dose amoxicillin is adequate, although more recent studies conducted since the introduction of PCV-7 and after publication of the AAP/AAFP treatment guidelines suggest that the percentage of cases caused by H influenzae is increasing.13,14 Therefore, an agent with greater activity against H influenzae may be preferred.

Clearly, each practitioner must select the antibiotic oral suspension that best meets the needs of the individual patient and caregiver in order to maximize compliance and optimize therapeutic efficacy in the treatment of AOM.

**SUMMARY**

Since the introduction of PCV-7 in the United States in 2000, the microbiology of AOM appears to be changing. Studies of PCV-7–vaccinated, otitis-prone children with recurrent or refractory AOM in urban, suburban, and rural populations have found a significant decrease in the proportion of middle ear infections caused by S pneumoniae and a significant increase in infections due to beta-lactamase–producing H influenzae. Despite vaccine shortages that have prevented universal immunization of US children with the recommended 4 doses of PCV-7 (the primary series of 3 doses plus the booster dose), herd immunity and a decrease in antibiotic-resistant pneumococci seem to be occurring. As vaccine supplies now permit administration of the full PCV-7 series, it is expected that H influenzae will become the predominant AOM pathogen in children younger than 2 years, probably including those who present for treatment of an initial episode.

In view of these changes, treatment options for AOM will need to consider a broader spectrum of causative agents. For children who fail initial amoxicillin therapy, the increasing predominance of H influenzae warrants consideration of a wider array of treatment options than just high-dose amoxicillin/ clavulanate. The cephalosporins cefdinir, cefuroxime, and cefpodoxime provide excellent coverage of H influenzae as well as most penicillin-susceptible and penicillin-intermediate S pneumoniae. Therefore, they represent reasonable treatment options for initial empiric therapy as well as amoxicillin treatment failures.

Treatment guidelines change as new information and new therapeutic modalities become available. Clearly, the impact of PCV-7 on the microbiology of AOM in the United States will be an important consideration as guidelines for the treatment of AOM evolve.

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Overall Rating*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loracarbef</td>
<td>1 (best)</td>
</tr>
<tr>
<td>Cefdinir</td>
<td>2</td>
</tr>
<tr>
<td>Cefixime</td>
<td>3</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>4</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>5</td>
</tr>
<tr>
<td>Trimethoprim-sulfamethoxazole</td>
<td>6</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>7</td>
</tr>
<tr>
<td>Trimethoprim</td>
<td>8</td>
</tr>
<tr>
<td>Amoxicillin/clavulanate</td>
<td>9</td>
</tr>
<tr>
<td>Cefpodoxime</td>
<td>10</td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>11 (worst)</td>
</tr>
</tbody>
</table>

*Using amoxicillin as the standard, each drug was evaluated for appearance, smell, texture, taste, and aftertaste. The overall rating was derived by taking the average rating for taste multiplied by 3, average rating for aftertaste multiplied by 2, and average ratings for appearance, smell, and texture multiplied by 1. Adapted with permission from Steele et al. Compliance issues related to the selection of antibiotic suspensions for children. Pediatr Infect Dis J. 2001;20(1):1-5.
REFERENCES


