A white paper on emerging issues in the treatment of acute otitis media

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Acute Otitis Media

Influence of the PCV-7 vaccine on changes in the disease and its management

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Studies have shown that most cases of acute otitis media (AOM) are of viral or "no bacteria isolated" origin. In these cases, watchful waiting may be appropriate. This publication addresses presumed bacterial causes of AOM for which antibiotic use may be efficacious.

Since the approval of the 7-valent pneumococcal conjugate vaccine (PCV-7) for use in children younger than 24 months in February 2000, occurrences of acute otitis media (AOM) and the frequency of recurrent AOM have declined. Based on results from early clinical trials, PCV-7 may reduce total AOM by 6% to 8%, recurrent AOM by 10% to 26%, and tympanostomy tube placements by 24%.[1,2]

Acute otitis media occurs most frequently in children between the ages of 6 months and 18 months. By the end of their first year, approximately 86% of children will experience at least 1 episode of AOM.[3]

Key Points and Recommendations

❚ Widespread use of the 7-valent pneumococcal conjugate vaccine has resulted in a shift in frequency of causative bacterial pathogens responsible for recurrent and persistent acute otitis media (AOM); disease management practice should encompass this change **(SOR: B)**.

❚ High-dose amoxicillin is the first choice for antibiotic therapy in uncomplicated bacterial AOM, although β-lactamase–producing pathogens are increasingly common primary causative agents, and amoxicillin is susceptible to β-lactamase **(SOR: B)**.

❚ Adding clavulanate to amoxicillin increases resistance to and improves effectiveness against β-lactamase–producing pathogens. Specific third-generation cephalosporins also should be included as antibiotic choices because of excellent activity against β-lactamase–producing pathogens and because of compliance advantages, such as better taste, less frequent dosing, and even shorter duration of therapy **(SOR: B)**.

PRIMARY CARE EDUCATION CONSORTIUM

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The condition remains a leading reason for visits to pediatricians and family physicians in the United States.[4] It accounted for 16 million visits in 2000.[4] This is a decrease from almost 25 million visits in 1995, prior to use of PCV-7. Additionally, AOM is associated with significant costs: In 1995, the direct and indirect costs of AOM were estimated to be about $3 billion.[5]

CHANGES IN PATHOGEN FREQUENCY FOR AOM IN THE ERA OF PCV-7

The true impact of PCV-7 on management practice is not characterized by the modest reduction in incidence of uncomplicated AOM but in the PCV-7–associated shift in

Amoxicillin is ineffective against β-lactamase–positive strains of *Haemophilus influenzae*

causative pathogens. Pre-PCV-7, 40% to 50% of cases of AOM in young children were caused by *Streptococcus pneumoniae*, 20% to 30% by *Haemophilus influenzae*, and 10% to 15% by *Moraxella catarrhalis*.[6] In studies conducted prior to 2000, diagnostic tympanocentesis isolated *S pneumoniae* from 25% to 55% of all middle ear aspirates from children with AOM.[6-8]

Conversely, 1 study published in 2001 and 2 studies published in 2004 appear to document a reverse trend with the advent of the conjugate pneumococcal vaccine.[9,10] Compared with children studied in an earlier era, those vaccinated with PCV-7 may be more likely to have *H influenzae* isolates. These studies will be described in detail below.

BACTERIAL AOM: INITIAL ANTIBIOTIC THERAPY AND SPECIFIC PATHOGENS

Current guidelines recommend amoxicillin (45 mg/kg/day) or high-dose amoxicillin (80-90 mg/kg/day) as initial therapy in presumed or documented bacterial AOM.[5] Although amoxicillin is effective against pneumococcus and β-lactamase–negative strains of *H influenzae*, it is ineffective against β-lactamase–positive strains of *H influenzae*.[9] Significant initial fail-

ures may point to a changing pathogen per population frequency. A 2004 review assessed children with continued (persistence of infection detected within 30 days after treatment completion) or refractory (clinical failure while receiving antimicrobial therapy) AOM who have received high-dose amoxicillin as initial empiric therapy. The authors noted that the rate of infection due to *H influenzae* has increased from 43% among those treated prior to the licensure of PCV-7 to 57% among those who received 2 or more doses of PCV-7.[10]

EVIDENCE FROM THE MEDICAL LITERATURE

Three studies provide the major evidence concerning the pathogen shift associated with the adoption of the PCV-7 conjugate vaccine:

▌ The Finnish Otitis Media Vaccine Trial[2]
▌ A published collection of clinical trial results from a rural practice in Kentucky in which 94% of children were immunized with PCV-7[9]
▌ A prospective study conducted in a suburban community-based private practice in Rochester, NY that evaluated children with persistent or nonresponsive AOM.[10]

The Finnish Otitis Media Vaccine Trial

In this trial, 1662 infants received either the PCV-7 vaccine or a control vaccine at ages 2, 4, 6, and 12 months and were monitored from ages 6.5 months to 24 months.[2] An overall 6.9% reduction in episodes of clinical AOM were diagnosed (n = 1251) in PCV-7–vaccinated children compared with the control group (n = 1345). This suggested that fewer AOM cases were caused by the *S pneumoniae* vaccine serotypes than nonvaccine serotypes. The bacteriologic findings in the samples of middle ear fluid taken during 93% of the visits for AOM **(TABLE 1)** show a 34% reduction in culture-confirmed episodes in the PCV-7–vaccinated group, a decrease of more than 50% in pneumococcal AOM episodes caused 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*.[2]

TABLE 1

Finnish Otitis Media Vaccine Trial: Causes of AOM Episodes and Impact of PCV-7 Immunization on Incidence

CAUSE	PCV-7 EPISODES	CONTROL EPISODES	DIFFERENCE (%)
Culture-confirmed pneumococcus	271	414	34
Pneumococcal serotype in vaccine	107	250	57
Vaccine cross-reactive serotypes*	41	84	51
Other pneumococcal serotypes	125	95	33
Haemophilus influenzae	315	287	11
Moraxella catarrhalis	379	381	1

*6A, 9N, 18B, 19A, 23A.
AOM, acute otitis media; PCV-7, 7-valent pneumococcal conjugate vaccine.
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TABLE 2

Results From a Rural Kentucky Practice: Change in AOM Microbiology From Pre-PCV-7 (1992–1998) to Post-PCV-7 (2000–2003)

PATHOGEN	PRE-PCV-7 1992-1998 (N=336)		POST-PCV-7 2000-2003 (N=83)		CHANGE (%)	*P* VALUE
	n	%	n	%		
Culture-confirmed pneumococcus	160	48	26	31	17	.007
Pneumococcal serotype in vaccine	236	70	30	36	34	.003
Vaccine cross-reactive serotypes*	27	8	27	32	24	.003
Other pneumococcal serotypes†	74	22	27	32	10	NS
Haemophilus influenzae	137	41	46	32	15	.01
β-lactamase-positive	108	23	39	36	15	.007
Moraxella catarrhalis, β-lactamase-positive	31	9	9	11	2	NS

AOM, acute otitis media; n, total isolates; NS, nonsignificant; PCV-7, 7-valent pneumococcal conjugate vaccine.
*Includes 6A and 19A.
†Nonvaccine serotypes in post-PCV-7 group: 1, 11A, 15A, 29, and 33F.
Adapted with permission from Block SL, et al. *Pediatr Infect Dis J*. 2004;23:829-833.

Study Results From a Rural Kentucky Practice

In this practice, data on isolates from middle ear fluid were collected in children with severe or refractory AOM aged 7 to 24 months.[9] Data were obtained from 1992 to 1998, before the introduction of PCV-7, and from 2000 to 2003, following immunization with 3 or 4 doses of PCV-7 during the first 18 months of life.

As shown in **TABLE 2,** the pre-PCV-7 group of children (N = 336; 1992-1998) had a proportion of 48% culture-confirmed pneumococcus vs a proportion of 31%

TABLE 3

The Prospective Rochester, New York Study: Pathogens Isolated in Persistent AOM and AOM Treatment Failure Pre- and Post-PCV-7

PATHOGEN	PRE-PCV-7 1998-2000 (N=204)		POST-PCV-7 2000-2003 (N=152)		CHANGE (%)	P VALUE
	n	%	n	%		
*Streptococcus pneumoniae**	50	44	28	31	13	.017
Penicillin nonsusceptible	12	24	4	14	10	NS
Haemophilus influenzae	49	43	51	57	14	.012
β-lactamase-positive	16	33	28	55	22	.044
Moraxella catarrhalis	6	5	1	1	4	NS

AOM, acute otitis media; N, total isolates; NS, nonsignificant; PCV-7, 7-valent pneumococcal conjugate vaccine.
*Pneumococcal serotyping was not done.
Adapted with permission from Casey JR, Pichichero ME. *Pediatr Infect Dis J*. 2004;23:824-828.

β-lactamase-positive organisms increased 56% following PCV-7 vaccine introduction compared with pre-PCV-7 rates

in the PCV-7-vaccinated group (N = 83; 2000-2003), a 17% decrease. The decrease in proportion of AOM episodes resulting from vaccine serotypes was 34%.

In this investigation, 28% of the pre-PCV-7 group and 34% of the post-PCV-7 group had received antibiotic therapy within the previous 3 days. Additionally, 59% and 76%, respectively, had received antibiotic therapy within the preceding 30 days. There were increases of 30% in vaccine cross-reactive serotypes and 45% in nonvaccine serotypes. Vaccine cross-reactive serotypes 6A and 19A accounted for most of the penicillin-nonsusceptible *S pneumoniae* strains in the vaccinated population.

Most impressive, however, in the post-PCV-7 group, was that gram-negative bacteria, mainly *H influenzae,* accounted for two thirds of AOM isolates, an increase from 41% in the pre-PCV-7

group to 56% in the vaccinated group. A 56% increase was noted in β-lactamase–positive organisms from the pre-PCV-7 group to the post-PCV-7 group. The combined *H influenzae* and *M catarrhalis* β-lactamase–producing organisms accounted for nearly half of all isolates.[9]

The Prospective Rochester, New York Study

Changes in pre- and post-PVC-7 patterns also were seen in a prospective study of 551 children with persistent or nonresponsive AOM (defined as nonresponders after 1 or 2 empiric antibiotic courses or failures after 48 hours of treatment). These children underwent tympanocentesis to identify bacterial isolates during the 9-year period from 1995 to 2003.[10]

From 1995 to 1997, enrollees received a standard dose of amoxicillin (40-50 mg/kg, divided into 3 doses daily) as initial empiric treatment. From 1998 to 2000 and 2001 to 2003, all children received high-dose amoxicillin (80-100 mg/kg, divided into twice-daily doses).

During the latter period, the children also were vaccinated with PCV-7, with 63% receiving the primary series of 3 doses and 10% receiving the booster dose. In this investigation, shortages in vaccine supply,

discussed below, caused vaccination schedules to be compromised.

Study results **(TABLE 3)** show that in the post-PCV-7 group, there was a 13% decrease in the proportion of *S pneumoniae* isolates and a 14% increase in the proportion of *H influenzae* isolates compared with the pre-PCV-7 group (1998-2000 enrollees). An increase of 22% for β-lactamase–positive bacteria was also observed, along with a trend toward an increased proportion of penicillin-susceptible *S pneumoniae* isolates (58% vs 72%; *P* = .017) post-PCV-7.[10] A 24% reduction (*P* = .009) in the frequency of the diagnosis of persistent or AOM treatment failure occurred in the period after PCV-7 vaccination. These changes were considered to be the result of the use of the conjugate pneumococcal vaccine rather than of the change in amoxicillin dosing.[10]

PNEUMOCOCCAL SEROTYPE SHIFTS
In addition to the change in causative pathogens, use of the conjugate pneumococcal vaccine appears to have led to a significant shift in the pneumococcal strains causing AOM. Studies at urban medical centers and in the Kentucky practice documented an increase in the proportion of nonvaccine serotypes, accounting for 32% to 38% of pneumococcal AOM.[10-12] A 33% increase was seen in the Finnish Trial.[2] These nonvaccine pneumococcal serotypes do not carry the same level of resistance seen with those serotypes included in PCV-7.

PCV-7 CONJUGATE VACCINE
The PCV-7 conjugate vaccine was approved for use in February 2000. It is a 7-valent pneumococcal conjugate of the capsular antigens of the *S pneumoniae* serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F, individually conjugated to diphtheria CRM197 protein.[13] These serotypes have been responsible for approximately 80% of invasive pneumococcal disease in children younger than 6 years in the United States.[13,14] They also accounted for 74% of penicillin-susceptible *S pneumoniae* and 100% of pneumococci with high-level penicillin resistance isolated from children younger than age 6 years with invasive disease during a 1993-1994 surveillance by the Centers for Disease Control and Prevention (CDC).[13]

Mechanism of Action and Recommended Immunization Schedule
The conjugate vaccine is converted to a T-cell–dependent antigen, antibody formation is enhanced, and memory B cells are primed.[14]

The recommended immunization schedule was established as 3 primary doses at ages 2, 4, and 6 months and a booster dose at 12 to 15 months.[1] It is the first multivalent pneumococcal vaccine approved for use in children younger than 24 months.

An 89% reduction in invasive pneumococcal disease was observed in children receiving 1 or more doses, and the vaccine appears to reduce nasopharyngeal carriage of vaccine serotypes.[15,16]

Despite vaccine shortages, a 29% decrease in the rate of pneumococal disease in both children and adults was observed

The older 23-valent polysaccharide vaccine does not stimulate good response in children younger than 2 years of age[14] and does not reduce mucosal carriage or limit the spread of resistant strains.[15]

PCV-7 Supply Since 2000
In August 2001, a serious shortage of the vaccine developed in 34 state immunization programs.[17] The following month, the CDC advised physicians to administer it only to children younger than 12 months and to those aged 1 to 5 years at increased risk of pneumococcal disease.[18] As demand continued despite the change in recommendations, the CDC further changed recommendations to conserve vaccine supply, first suspending the fourth dose temporarily in healthy children[19] and then discontinuing both the third and fourth doses.[11] In July 2004, production problems seemed to have resolved; the CDC recommended that every child receive 3 doses. In September, supplies were adequate for return to the 4-dose schedule.[12] As of June 2004, 67.7% of children aged 24 months had received 3 or

TABLE 4

Compliance-Enhancing Ranking of Antibiotic Suspensions

STRONGLY COMPLIANCE-ENHANCING
- Amoxicillin
- Cefdinir (Omnicef)
- Loracarbef (Lorabid)
- Cefaclor (Ceclor)
- Cefixime (Suprax)

MODERATELY COMPLIANCE-ENHANCING
- Cefprozil (Cefzil)
- Ceftibuten (Cedax)

EQUIVOCAL COMPLIANCE-ENHANCING
- Azithromycin (Zithromax)

NOT COMPLIANCE-ENHANCING
- Amoxicillin-clavulanate (Augmentin)
- Erythromycin-sulfasoxazole (Pediazole)
- TMP-SMX (Bactrim or Septra)

DISCOURAGES COMPLIANCE
- Cefpodoxime (Vantin)
- Clarithromycin (Biaxin)
- Cefuroxime (Ceftin)

TMP-SMX, trimethoprim sulfamethoxazole

Sources: Adapted from Steele RW, et al. *Pediatr Infect Dis J.* 2001;20:1-5.
Demers DM, et al. *Pediatr Infect Dis J.* 1994;13:87-89.
Ruff ME, et al. *Pediatr Infect Dis J.* 1991;10:30-33.

more doses of PCV-7.[20] Thus, the effects of PCV-7 on the changing microbiology of AOM may only now, at the end of 2005, be fully realized.

Herd Immunity and Reduction in Carriage

Despite the shortages of vaccine during the first years of use, evidence of herd immunity and a decrease in antibiotic resistance in pneumococcal pathogens has been reported throughout the United States.[21,22] A 29% decrease in the rate of pneumococcal disease in both young children and adults has also been observed, along with a 35% reduction in the rate of disease caused by nonpenicillin-susceptible pneumococcal strains.[21] The reduction in carriage among vaccinated children may be the reason.[21,22] Because of the impact of PCV-7, it will be important to record immunization history when collecting AOM data.

AOM TREATMENT CHOICES

The basis of recommendations for treating AOM depends on the presumed responsible pathogens, their susceptibility to antibiotics, and concerns for developing resistance, all influenced by clinical trial data. In practice, however, empiric choices are often made based on knowledge of local resistance patterns and of other patient characteristics; that is cost concerns, adverse event profiles, need to avoid initial treatment failure, adherence issues (eg, taste or palatability), convenience, and duration of dosing regimen.

All current guidelines recommend oral amoxicillin as first-line therapy in documented or presumed bacterial AOM. The 2004 American Academy of Pediatrics/ American Academy of Family Physicians' (AAP/AAFP) guidelines[4] recommended increasing the dosage used for empiric treatment from 40 to 45 mg/kg/day to 80 to 90 mg/kg/day for all children. This was a result of concerns about the prevalence of penicillin-resistant *S pneumoniae* for which standard-dose amoxicillin is inadequate.[23]
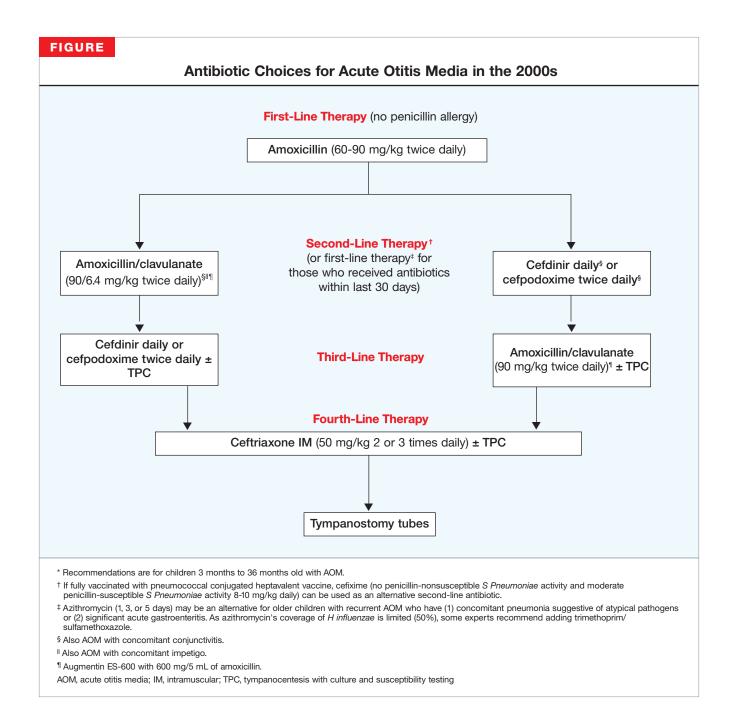
The guidelines were written and published before the data from the Kentucky and New York studies were available; therefore, although the guidelines recommended that empiric treatment of bacterial AOM should target *S pneumoniae*, *H influenzae*, and *M catarrhalis*, the pathogen shift discussed previously might today produce a modified antibiotic selection paradigm. The pathogen mix in persistent or recurrent AOM has already led to a guideline recommendation for high-dose amoxicillin/ clavulanate, 90/6.4 mg/kg/day, cefdinir, cefprozil, cefpodoxime, cefuroxime, or ceftriaxone in these patients.[23]

If an increase in the proportion of β-lactamase–producing pathogens due to PCV-7 occurs, amoxicillin may no longer be the best first choice.

Selecting Among Recommended Antibiotic Choices

As antibiotic preparations for treating bacterial AOM are oral suspensions, taste is a major factor for pediatric patients. **TABLE 4** summarizes comparative taste ratings for antibiotic suspensions based on several studies and shows the range, from those that can enhance compliance to those that discourage compliance.[23]

FIGURE

Antibiotic Choices for Acute Otitis Media in the 2000s

First-Line Therapy (no penicillin allergy)

Amoxicillin (60-90 mg/kg twice daily)

Second-Line Therapy[†]
(or first-line therapy[‡] for
those who received antibiotics
within last 30 days)

Amoxicillin/clavulanate
(90/6.4 mg/kg twice daily)[§||¶]

Cefdinir daily[§] or
cefpodoxime twice daily[§]

Cefdinir daily or
cefpodoxime twice daily ±
TPC

Third-Line Therapy

Amoxicillin/clavulanate
(90 mg/kg twice daily)[¶] ± TPC

Fourth-Line Therapy

Ceftriaxone IM (50 mg/kg 2 or 3 times daily) ± TPC

Tympanostomy tubes

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

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

‡ Azithromycin (1, 3, or 5 days) may be an alternative for older children with recurrent AOM who have (1) concomitant pneumonia suggestive of atypical pathogens or (2) significant acute gastroenteritis. As azithromycin's coverage of *H influenzae* is limited (50%), some experts recommend adding trimethoprim/sulfamethoxazole.

§ Also AOM with concomitant conjunctivitis.

|| Also AOM with concomitant impetigo.

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

AOM, acute otitis media; IM, intramuscular; TPC, tympanocentesis with culture and susceptibility testing

Adverse events, especially diarrhea, nausea/vomiting, and gastritis, are also of concern. These are shortcomings of amoxicillin/clavulanate, which has a higher incidence of diarrhea and nausea than cephalosporins.[24]

Dosing frequency is also a factor among recommended agents. Amoxicillin, amoxicillin/clavulanate, cefprozil, and cefpodoxime require twice-daily dosing. Cefdinir can be effective at once-daily dosing.[24]

Duration of approved therapy is perhaps the most critical selection factor given the reality of patient behaviors. Cefpodoxime and cefdinir are the only 2 FDA-approved agents for 5-day treatment of bacterial AOM that are also guideline-recommended.

Amoxicillin may no longer be the best first choice for AOM if there is an increase in β-lactamase-producing pathogens

Choices for Effective Initial Therapy

Considering the changing microbial population in bacterial AOM and the increasing concern of effectiveness of amoxicillin and other antibiotics against β-lactamase–producing *H influenzae*, the choice of therapy may need modification. Specifically, that may mean changing the choice of effective antibiotic, taking into consideration the compliance-enhancing advantages of available options.

Based on efficacy, the overall prevalence of antibiotic-resistant AOM pathogens for PCV-7-vaccinated children, the potential for adverse effects, and patient compliance issues, Block and Harrison developed an algorithm **(FIGURE)** for the management of AOM diagnosed by strict criteria in an otherwise healthy child between 4 months and 36 months old.[24] As the environment of AOM evolves, the choices for treatment must be not only effective but also the best and most appropriate. ■

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