

## Challenges in the Management of Otitis Media

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### *Presentation Summary*

Acute otitis media (AOM) and otitis media with effusion are among the most common illnesses in children, and AOM is the most frequent diagnosis for which oral antimicrobial agents are prescribed. Almost two thirds of children experience at least 1 episode of AOM by 1 year of age. Unfortunately, current management of otitis media is associated with frequent relapses and persistent middle ear effusion. An important element in improving response rates is a better understanding of the disease pathophysiology. Age at first episode is a critical determinant of recurrences, with those whose

first episode occurs in the first 6 months of life being most likely to have subsequent episodes. A number of other risk factors are associated with recurrent AOM, including family history, male gender, exposure to cigarette smoke, and day care attendance. One of the keys to successful management of the disease is to identify infants at high risk for persistent disease and to treat them aggressively to prevent recurrent episodes. Amoxicillin remains an important first-line treatment for AOM, and in communities with high incidences of penicillin-resistant strains of pneumococci, high-dose amoxicillin is recommended.

**O**titis media is primarily a disease of early childhood and should be viewed as a spectrum of illnesses that includes acute otitis media (AOM), otitis media with effusion (OME), external otitis, and chronic suppurative otitis media. This spectrum of conditions begins with acute episodes in the first year of life often with recurrence throughout early childhood and association with the persistence of middle ear effusion (fluid). The long-term sequelae of persistent effusion include conductive hearing loss, decreased language per-

ception, impaired speech and language development, and lower scores on tests of cognitive abilities.<sup>1</sup> One of the primary goals of therapy should be to reduce the overall burden of otitis media throughout childhood rather than to focus simply on treating symptomatic, acute episodes.

This decade has seen an increasing number of otitis media diagnoses (Figure),<sup>2</sup> an emergence of bacteria resistant to common antimicrobial agents, and recognition of the need for reevaluation of the role of antibiotic therapy in otitis media. Thus, the

issues that require our immediate attention are the changing epidemiology of otitis media, the appropriate use of antimicrobial therapy, and the development of prophylactic therapy.

**The Clinical Picture**

Ear disease may be divided into 4 different diagnoses. AOM is defined as the presence of fluid in the middle ear accompanied by inflammation and signs of local or systemic illness. All 3 of these conditions should be present for a diagnosis of AOM. In comparison, OME is defined as fluid in the middle ear with no signs of inflammation or illness. In this case, the role of antimicrobial therapy, if any, is limited. However, antimicrobial therapy may be considered prior to surgery for refractory cases of OME. The third diagnosis, external otitis, involves an infection of the external ear canal and is otherwise known as "swimmer's ear." This condition usually does not require a systemic antibiotic, although exacerbations may necessitate therapy. Lastly, chronic suppurative otitis media is characterized by chronic otorrhea through a perforation or tympanostomy tube and most commonly occurs in patients who have very poor eustachian tube function combined with immune incompetence. This condition usually is associated with infection caused by *Staphylococcus aureus* or *Pseudomonas aeruginosa*.

**Signs and Symptoms of AOM**

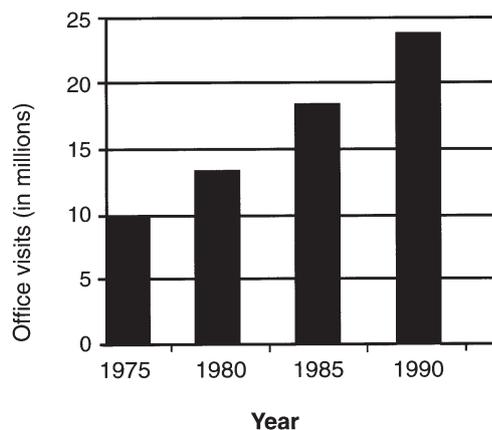
The diagnosis of AOM requires both the presence of local inflammatory signs and fluid in the middle ear as well as acute onset of symptoms. Bacterial otitis media in children may be reliably identified through the physical findings of a bulging tympanic membrane, opacification, and hypomobility of the tympanic membrane.<sup>3</sup> Inflammation of the tympanic membrane (redness) without these characteristics, including air fluid level, has not been associated with

recovery of bacterial pathogens at tympanocentesis; however, in some children it may herald the onset of AOM. Kontiokari and associates<sup>4</sup> found that earache was the symptom most clearly associated with AOM in children compared to symptoms of upper respiratory infections (URI) only. Night restlessness, fever, and sore throat (children older than 2 years of age) also were associated with AOM, but to a lesser degree. Children with AOM were more likely than children with URI to be febrile only on days 3 through 9 following onset of illness; however, fever was not discriminatory during the first 48 hours. The severity of pain and degree of fever have been associated with pneumococcal otitis,<sup>5</sup> although, the specificity is not great enough to be clinically useful.

**Epidemiology**

AOM and OME are among the most common illnesses in children, and AOM is the most frequent diagnosis for which oral antimicrobial agents are prescribed. Otitis media occurrence peaks in children between the

**Figure.** Office Visits in the United States With a Principal Diagnosis of Otitis Media, 1975-1990



Source: Reference 2.

ages of 6 and 18 months; almost two thirds of children experience at least 1 episode of AOM, and 17% experience 3 or more episodes by 1 year of age. A few children, 5% to 6%, have as many as 6 episodes of AOM in their first year of life.<sup>6</sup> However, in general, frequent episodes in infancy do not indicate an immune deficiency. The frequency of AOM recurrences by age at initial episode as reported by the Greater Boston Otitis Media Study Group is presented in Table 1.

The age at first episode is a critical determinant of recurrences. In the Boston study, of the 140 children whose first episode occurred after 12 months of age, 50% did not have a repeat episode of AOM, while 62% of the 237 children whose first episode occurred before age 6 months had at least 2 subsequent episodes of AOM. The decline in recurrent otitis media observed in older children may be the result of a more mature immune system or better eustachian tube function. This remains an unresolved debate between otolaryngologists and immunologists, but both factors are likely to be important. By age 6, 60% of children no longer have episodes of AOM, and only 3% have recurrent episodes.<sup>6</sup> A child who continues to have recurrent otitis media after 6 years of age should be evaluated for predisposing or underlying conditions, such as immunoglobulin G (IgG) subclass deficiency.

An ethnic component also constitutes part of the overall picture, with indigenous populations affected disproportionately by this disease. American Indians,<sup>7,8</sup> Inuits,<sup>9,10</sup> and Australian Aborigines<sup>11</sup> are more prone to AOM than nonnative populations. Indigenous groups may have more problems with eustachian tube dysfunction, immune incompetence, and crowded living conditions. A higher frequency of severe disease characterized by chronically draining ears is frequently observed in this cohort.<sup>12</sup>

A variety of other risk factors have been associated with otitis media in children (Table 2). Patient factors include eustachian tube dysfunction, a compromised or immature immune system (eg, human immunodeficiency virus), a family history of otitis media (especially in siblings), and male gender.<sup>13</sup> Environmental risk factors include exposure to cigarette smoke,<sup>14,15</sup> use of a pacifier,<sup>12</sup> not being breast-fed,<sup>6,16</sup> sleep position, the presence of siblings in the household, and attendance at group day care.

**Table 1.** Age at First Episode of AOM and Number of Subsequent Episodes in 24 Months of Observation

Age at First Episode	No. of Patients	Percentage of Patients Experiencing Additional Episodes of AOM		
		0	1	≥2
1-6 mo	237	14	24	62
7-12 mo	163	25	32	43
≥12 mo	140	50	24	26

AOM = Acute otitis media.

Source: Teele DW, Klein JO, Rosner BA, and the Greater Boston Otitis Media Study Group. Epidemiology of otitis media during the first seven years of life in children in greater Boston: A prospective, cohort study. *J Infect Dis* 1989;160:83-94. Reproduced with permission from The University of Chicago Press.

**Table 2.** Risk Factors for Otitis Media in Children

Environmental Risk Factors	Patient Risk Factors
Exposure to cigarette smoke	Eustachian tube dysfunction
Not breast-fed	Immunocompromised
Sleep position on stomach or side	Family history
Use of pacifier	Male gender
Day care attendance	

Day care attendance is a major risk. Children attending these institutions are exposed both to viruses that predispose them to bacterial infections and to the pneumococci, *Haemophilus influenzae*, and *Moraxella catarrhalis* that cause the subsequent bacterial infections. The risk of recurrent disease is also much higher in children attending day care.<sup>13</sup> In a well-regarded study,<sup>17</sup> the incidence of surgical intervention with tubes was sixfold greater for children in day care than for children in home care. Considering these risk categories, managing this disease aggressively is clearly needed for those attending day care and in infants whose initial episode occurred before 6 months of age.

While viruses are rarely isolated from middle ear fluid, they have a distinct role in setting the stage for colonization by bacteria. Up to 50% of children who present with otitis media at a physician's office have had a viral upper respiratory tract infection within the preceding 2 weeks. In particular, respiratory syncytial virus (RSV) appears to put children at risk.<sup>18</sup> RSV most likely impairs eustachian tube function, enhances bacterial colonization, and possibly impairs host immune function. Thus, prevention of viral infections may be one way to reduce the occurrence of otitis media.

### Management of AOM

Unfortunately, the current management of otitis media is associated with frequent relapses and persistent middle ear effusion. In a 1996 study of treatment for AOM, the successful clinical response rate at days 12 to 14 was 78.3% in children up to 2 years old, but this rate had fallen to 40.3% at days 32 to 38.<sup>19</sup>

An important element in improving response rates is a better understanding of the pathophysiology of the disease. Otitis media is a 4-part process that involves inadequate host defen-

ses that allow viral upper respiratory infections to develop, which in turn result in eustachian tube dysfunction, which sets the stage for a bacterial infection to develop. An important aspect of otitis media is that middle

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ear effusion usually resolves gradually over time. Assuming 100% of the affected children have middle ear fluid at the time of diagnosis, 40% will still have effusion 1 month later, and 20% will have persistent fluid 2 months after diagnosis (personal data, 1998). Six months later, a small percentage of children will still have fluid in the middle ear.

Evidence indicates 10% to 20% of children spend more than half of their first 2 years of life with middle ear effusion.<sup>6</sup> The major concern is that the presence of fluid can cause a conductive hearing loss precisely at the time when language acquisition is at its apex. Hearing loss may lead to a decreased perception of language during the critical first 2 years of life, possibly resulting in impaired speech development,<sup>20</sup> poor performance on standardized speech and language tests, and lower scores on tests of cognitive ability.<sup>6</sup>

### Pathogens and Antibiotics

The microbial etiology of AOM is similar worldwide: *Streptococcus pneumoniae*, *H. influenzae*, *M. catarrhalis*, and group A streptococcus are the causative pathogens (Table 3). The most common cause is *S. pneumoniae*, which accounts for

35% to 45% of infections.<sup>21</sup> Resistant *S. pneumoniae* is increasing worldwide, and increases in penicillin-resistant pneumococci have been reported in all areas of the United States. In a recent study of children in Kentucky with AOM, 31% of pneumococci isolates demonstrated decreased susceptibility to penicillin, with nearly half of the strains being highly resistant (minimum inhibitory concentration [MIC]  $\geq 2\mu\text{g/mL}$ ). More alarming, these highly resistant strains were resistant to most antimicrobials commonly used to treat AOM.<sup>21</sup>

Although bacterial infections of the middle ear sometimes resolve on their own, antibiotic therapy has proven to be very successful in eradicating infections. A study conducted in Cleveland demonstrated that bacteriologic success, documented by tympanocentesis and culture, has a correlation with clinical success; 93% of patients in whom the pathogen was eliminated also experienced a resolution of signs and symptoms.<sup>22</sup> In contrast, only 60% of children in whom

middle ear pathogens persisted showed clinical improvement.<sup>22</sup> Although not possible to perform in everyday clinical practice, a dual tap system of pathogen identification via sequential tympanocentesis and culture has provided valuable data that validate *in vitro* and experimental animal work as well as the pharmacokinetic characteristics of various drugs. In addition, the efficacy of many antibiotics in current use has been confirmed by studies such as these.<sup>23</sup> Amoxicillin is still the appropriate first-line treatment for AOM, having shown favorable outcomes in children with AOM caused by penicillin-intermediate (ie, moderately resistant) pneumococci.<sup>21</sup> Additionally, its MICs against resistant strains of *S. pneumoniae* are lower than those of other  $\beta$ -lactams.<sup>24</sup>

In communities with documented high incidences of penicillin-resistant strains of pneumococci, first-line therapy with high-dose amoxicillin (80 to 90 mg/kg/day) is recommended for young outpatients with AOM. Amoxicillin remains safe at these doses, and a recent study demonstrates higher middle ear fluid concentrations with this regimen.<sup>25</sup> One option for patients who do not respond to initial therapy is treatment with a combination of amoxicillin (40 to 45 mg/kg/day) plus amoxicillin/clavulanate (45 mg/kg/day). Other therapeutic options in patients allergic to penicillin include trimethoprim/sulfamethoxazole or a macrolide. Recalcitrant cases may require tympanocentesis or tympanostomy tube placement.<sup>20</sup> If amoxicillin-resistant pneumococci are documented (MIC  $\geq 2.0\mu\text{g/mL}$ ), oral clindamycin (30 mg/kg/day for 10 to 21 days) or parenteral ceftriaxone (50 mg/kg/day for 3 to 5 days) may be appropriate.<sup>21</sup>

Some researchers suggest that antibiotics should not be used at all when initially treating AOM because the condition rarely involves serious complications, and symptoms usually

**Table 3.** Bacterial Pathogens Isolated From Middle Ear Aspirates in Infants and Children With Acute Otitis Media

Bacterial Pathogen	Percentage of Children With Pathogen*			
	1952-1981		1985-1992	
	Mean	Range	Mean	Range
<i>Streptococcus pneumoniae</i>	33	26-53	38	27-52
<i>Haemophilus influenzae</i>	21	14-31	27	16-52
<i>Moraxella catarrhalis</i>	3	0-4	10	2-15
Streptococcus, group A	8	0.3-24	3	0-11
<i>Staphylococcus aureus</i>	2	0-3	2	0-16
Miscellaneous bacteria	1	0-2	8	0-24
None or nonpathogenic	31	2-47	28	12-35

\*Percentage greater than 100 because of nontypeable pathogens per middle ear effusion. Source: Bluestone CD, Klein JO. *Otitis Media in Infants and Children* 2nd ed; Philadelphia, PA. Used with permission from WB Saunders, 1995.

resolve within 7 to 10 days. Recent studies confirm an improved outcome for children with severe AOM (including substantial fever and pain) treated with antibiotics compared to placebo or myringotomy alone.<sup>26</sup> Even with AOM that is not severe, a small advantage in the group treated with antibiotics can be demonstrated. In the first 3 to 5 days, antibiotic therapy makes a significant difference in the resolution of symptoms such as fever, pain, and otorrhea. However, after 6 weeks or more, there is not a significant difference between patients treated with antibiotics and those left untreated.

Valid reasons for antibiotic therapy of AOM exist. Most cases of otitis media caused by *S. pneumoniae* and half of those caused by *H. influenzae* will not resolve without medical treatment.<sup>12</sup> Withholding antibiotics for otitis media in young children is most risky because of the potential for suppurative complications and the high incidence of recurrences. Language development delays and the possible negative impact on cognitive development are also serious concerns. In addition, consideration must be given to the course of AOM in the preantibiotic era, when chronic perforations, chronically draining ears, and suppurative complications of otitis media were seen in many children, and spread of infection to the mastoid or meninges was a potential complication of the disease.<sup>12</sup> After the introduction of sulfonamides and penicillin in the late 1930s, the rate of these complications fell from about 20% to 5%, and by 1948 the frequency of mastoidectomy was only 2.5%.<sup>27</sup> The dramatic reduction in intracranial complications and the subsequent decrease in mortality that followed the introduction of antibiotics cannot be ignored, and antimicrobial treatment of otitis media in infants remains the standard of care in the United States.<sup>28</sup>

The duration of therapy for AOM has recently been evaluated by inves-

tigators.<sup>29,30</sup> Children younger than 2 years of age, especially those in day care, substantially benefited from 10 days of therapy compared with 5 days.<sup>29</sup> Of those children who received 10 days of therapy, fewer children had signs and symptoms of AOM on days 10 to 14, which likely reflected a lower relapse/recurrence rate in that cohort. For children older than 2

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years of age, the difference in outcome between 10 days of therapy and 5 days is less substantial, and many experts recommend 5 days of therapy in regions that do not have a high proportion of multidrug-resistant *S. pneumoniae*. Because of my clinical experience in this area, I support the use of short-course antimicrobial therapy in children older than 2 years of age who have a prompt response to therapy, showing resolution of signs and symptoms within 48 to 72 hours of initiating treatment.

The goal of therapy in AOM should be eradication of bacterial pathogens in the middle ear, resolution of middle ear fluid, and prevention of hearing loss and recurrent acute infection. Antibiotics should not be administered simply to resolve persistent fluid in the absence of other symptoms, such as inflammation and systemic illness. Finally, one of the keys to successful management of the disease is to identify infants at high risk for persistent disease and to treat them aggressively to prevent recurrent episodes, persistent effusion, hearing loss, and speech delay.

### Prevention of Otitis Media: New Horizons

Prevention of otitis media by preventing bacterial colonization of the respiratory tract must be emphasized. Currently available interventions include prophylactic antibiotics, influenzae and pneumococcal polysaccharide vaccines, and tympanostomy tube insertion. Chemoprophylaxis has been successful in preventing recurrent episodes of AOM or in reducing the number of such episodes. Concern for emerging resistance has resulted in a reevaluation of indications for chemoprophylaxis. In general, it is currently limited to children with 3 or 4 episodes within a 6-month time period. Amoxicillin 20 mg/kg/day or sulfisoxazole 50 mg/kg/day given throughout the respiratory infection season to those children allergic to penicillin is effective in preventing new episodes of AOM. However, after antibiotics are discontinued, many children experience recurrences of the condition.<sup>12,31</sup>

Vaccines need to be developed against respiratory viral and bacterial pathogens such as RSV and nontypeable *H. influenzae*. A pneumococcal vaccine is now available for children older than 24 months who have recurrent episodes of otitis media, and a new conjugate vaccine has shown good antibody response in trials with children as young as 6 months of age.<sup>32</sup> A recent study investigated the efficacy of a pneumococcal conjugate vaccine in children 2, 4, 6, and 12 to 15 months of age.<sup>33</sup> Although results for otitis media and pneumonia are pending, the pneumococcal conjugate vaccine appears to be highly effective in preventing invasive disease in young children. Universal childhood immunization with this vaccine is likely to be recommended for children younger than 3 years of age to prevent invasive disease caused by *S. pneumoniae*. Use in children older than 3 should include those at high risk for AOM (Table 2). Reduction in

the colonization of the respiratory tract by pneumococci and *H. influenzae* through the use of topical or nasal spray therapy is another potential strategy. Improving eustachian tube function using surfactants, which may reduce the risk of otitis media in children with functional impairment, is currently being studied.

### ... REFERENCES ...

1. Teele DW, Klein JO, Rosner BA, and the Greater Boston Otitis Media Study Group. Otitis media with effusion during the first three years of life and development of speech and language. *Pediatrics* 1984; 74:282-287.
2. Schappert SM. *Office visits for otitis media: United States, 1975-90*. Hyattsville, MD: Vital and Health Statistics. National Center for Health Statistics. Centers for Disease Control. US Department of Health and Human Services. 1992; Advance Data No. 214:1-18.
3. Karma PH, Sipilä MM, Kataja MJ, Penttilä MA. Pneumatic otoscopy and otitis media. II. Value of different tympanic membrane findings and their combinations. In: Lim DJ, Bluestone CD, Klein JO, Nelson JD, Ogra PL, eds. *Recent Advances in Otitis Media*. Proceedings of the Fifth International Symposium. Burlington, Ontario, Canada: Decker;1993:41-45.
4. Kontiokari T, Koivunen P, Niemelä M, Pokka T, Uhari M. Symptoms of acute otitis media. *Pediatr Infect Dis J* 1998;17:676-679.
5. Howie VM, Ploussard JH, Lester RL Jr. Otitis media: A clinical and bacteriological correlation. *Pediatrics* 1970;45:29-35.
6. Teele DW, Klein JO, Rosner BA, and the Greater Boston Otitis Media Study Group. Epidemiology of otitis media during the first seven years of life in children in greater Boston: A prospective, cohort study. *J Infect Dis* 1989;160:83-94.
7. Thomson M. Otitis media: How are First Nations children affected? *Can Fam Physician* 1994;40:1943-1950.
8. Harris SB, Glazier R, Eng K, McMurray L. Disease patterns among Canadian aboriginal children. *Can Fam Physician* 1998; 44:1869-1877.
9. Tower EA. Chronic otitis media in Alaskan natives: 1954-1979: An historical perspective. *Alaska Med* 1979;21:48-52.

10. Christensen R. Health problems among Alaska Eskimo infants and young children. *Arct Med Res* 1990;49:63-67.
11. Thomas DP, Heller RF, Hunt JM. Clinical consultations in an Aboriginal community-controlled health service: A comparison with general practice. *Aust N Z J Public Health* 1998;22:86-91.
12. Klein JO, Bluestone CD. Management of otitis media in the era of managed care. *Adv Pediatr Infect Dis* 1996;12:351-386.
13. Paradise JL, Rockette HE, Colborn K, et al. Otitis media in 2253 Pittsburgh-area infants: Prevalence and risk factors during the first two years of life. *Pediatrics* 1997;99:318-333.
14. DiFranza JR, Lew RA. Morbidity and mortality in children associated with the use of tobacco products by other people. *Pediatrics* 1996;97:560-568.
15. Etzel RA, Balk SJ, Bearer CF, et al. Environmental tobacco smoke: A hazard to children. *Pediatrics* 1997;99:639-642.
16. Faden H, Duffy L, Wasielewski R, et al. Relationship between nasopharyngeal colonization and the development of otitis media in children. *J Infect Dis* 1997;175:1440-1445.
17. Wald ER, Dashefsky B, Byers C, Guerra N, Taylor F. Frequency and severity of infections in day care. *J Pediatrics* 1988;112:540-546.
18. Giebink GS. Vaccination against middle-ear bacterial and viral pathogens. *Ann N Y Acad Sci* 1997;830:330-352.
19. Hoberman A, Paradise JL, Block S, et al. Efficacy of amoxicillin/clavulanate for acute otitis media: Relationship to *Streptococcus pneumoniae* susceptibility. *Pediatr Infect Dis J* 1996;15:955-962.
20. Bluestone CD, Klein JO. *Otitis Media in Infants and Children*, 2nd ed. Philadelphia, PA: WB Saunders;1995:56:147-240.
21. Block SL, Harrison CJ, Hedrick JA, et al. Penicillin-resistant *Streptococcus pneumoniae* in acute otitis media risk factors, susceptibility patterns and antimicrobial management. *Pediatr Infect Dis J* 1995;14:751-759.
22. Marchant CD, Carlin SA, Johnson CE, Shurin PA. Measuring the comparative efficacy of antibacterial agents for acute otitis media: The "Pollyanna phenomenon." *J Pediatr* 1992;120:72-77.
23. Klein JO. Microbiologic efficacy of antibacterial drugs for acute otitis media. *Pediatr Infect Dis J* 1993;12:973-975.
24. Pankuch GA, Jacobs MR, Appelbaum PC. Comparative activity of ampicillin, amoxicillin, amoxicillin/clavulanate and cefotaxime against 189 penicillin-susceptible and resistant pneumococci. *J Antimicrob Chemother* 1995;35:883-888.
25. Seikel K, Shelton S, McCracken GH Jr. Middle ear fluid concentrations of amoxicillin after large dosages in children with acute otitis media. *Pediatr Infect Dis J* 1998;17:969-970.
26. Kaleida PH, Casselbrant ML, Rockette HE, et al. Amoxicillin or myringotomy or both for acute otitis media: Results of a randomized clinical trial. *Pediatrics* 1991;87:466-474.
27. Sorensen H. Antibiotics in suppurative otitis media. *Otolaryngologic Clin North Am* 1977;10:45-50.
28. Kenna MA. Incidence and prevalence of complications of otitis media. *Ann Otol Rhinol Laryngol* 1990;149(suppl):38-39.
29. Cohen R, Levy C, Boucherat M, Languet J, de La Rocque F. A multicenter, randomized, double-blind trial of 5 versus 10 days of antibiotic therapy for acute otitis media in young children. *J Pediatr* 1998;133:634-639.
30. Hoberman A, Paradise JL, Burch DJ, et al. Equivalent efficacy and reduced occurrence of diarrhea from a new formulation of amoxicillin/clavulanate potassium (Augmentin®) for treatment of acute otitis media in children. *Pediatr Infect Dis J* 1997;16:463-470.
31. Pelton SI. New concepts in the pathophysiology and management of middle ear disease in childhood. *Drugs* 1996;52(suppl 2):62-66.
32. Rennels MB, Edwards KM, Keyserling HL, et al. Safety and immunogenicity of heptavalent pneumococcal vaccine conjugated to CRM<sub>197</sub> in United States infants. *Pediatrics* 1998;101:604-611.
33. Black S, Shinefield H, Ray P, et al. Efficacy of heptavalent conjugate pneumococcal vaccine (Wyeth Lederle) in 7,000 infants and children: Results of the Northern California Kaiser Permanente Efficacy Trial. *Pediatr Res* 1999;45:157A.