

Recurrent and persistent otitis media

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Synopsis. Recurrent acute otitis media occurs during the first several years of life in approximately 20 to 30% of the pediatric population. A clinical challenge closely related to recurrent otitis media is persistent otitis media, manifested by persistence during antimicrobial therapy of symptoms and signs of middle ear infection (treatment failure) and/or relapse of acute otitis media within 1 month of completion of antibiotic therapy. Recurrent and persistent otitis media infections are early childhood problems with identifiable risk factors. Differentiation of these infections from otitis media with effusion is important in avoiding misdiagnosis and overtreatment with antibiotics.

The predominant pathogens of recurrent and persistent acute otitis media are antibiotic-resistant *Streptococcus pneumoniae* and beta-lactamase-producing *Haemophilus influenzae*. A working group convened by the Centers for Disease Control recommended three antibiotics for the treatment of recurrent and persistent acute otitis media: (1) amoxicillin/clavulanate in combination with amoxicillin (high dose amoxicillin regimen, 80 to 90 mg/kg/day); (2) cefuroxime axetil (standard dose, 30 mg/kg/day); and (3) ceftriaxone (possibly requiring up to three injections to optimize clinical success). Other antibiotics were considered suboptimal or had accumulated insufficient data upon which to base a judgment.

Conclusions. Optimal management of recurrent and persistent acute otitis media is a clinical challenge. Accurate diagnosis of acute otitis media is the first step in optimal management. Selection of appropriate antibiotic therapy should take into account the major pathogens (*S. pneumoniae*, *H. influenzae* and *Moraxella catarrhalis*) and the occurrence of antibiotic resistance.

RECURRENT ACUTE OTITIS MEDIA

Eight of 10 children experience at least 1 episode of

acute otitis media, the most common disease of childhood, by the time they have reached 1 year of age.^{1, 2} If at least 3 episodes occur in 6 months or 4 episodes in 12 months, then the patient is said to experience recurrent acute otitis media. In a 7-year prospective study of 500 Boston children, Teele et al.³ found that 20% of children experienced 3 to 5 episodes of acute otitis media in their first year of life. These children often proved to be prone to repeated episodes of acute otitis media over the next several years (Fig. 1). In another prospective Minneapolis study⁴ reported in 1999, 20% of children suffered recurrent acute otitis media. There is some evidence that the prevalence of recurrent otitis media is increasing. In a national health interview survey⁵ the prevalence of recurrent acute otitis media was found to increase from 18.7% in 1981 to 26.9% in 1988. The greatest increase occurred in infants younger than 12 months of age. These studies indicate that recurrent acute otitis media occurs during the first several years of life in approximately 20 to 30% of the pediatric population.

RISK FACTORS FOR RECURRENT ACUTE OTITIS MEDIA

Risk factors for recurrent acute otitis media include an episode of acute otitis media in the first 6 months of life,^{3, 6} age less than 3 years,^{3, 5-7} parental smoking³ and day-care attendance.^{4, 5, 8} The propensity to develop recurrent acute otitis media shows a strong genetic component⁹; Daly et al.⁴ found that recurrent otitis media by 6 months of age was strongly related to maternal otitis media history. The prevalence of recurrent acute otitis media is higher among affluent white children as opposed to African-American, Hispanic or

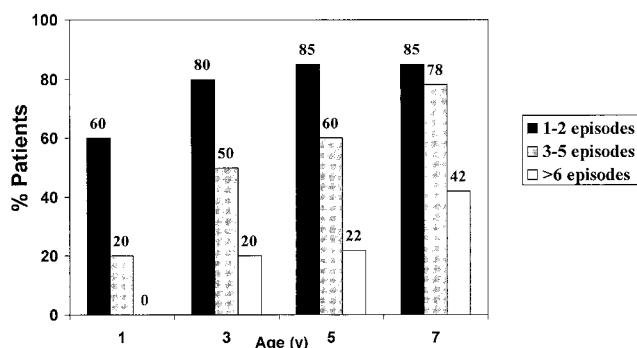


FIG. 1. Percentages of patients with 1 to 2, 3 to 5 or more than 6 cumulative episodes of acute otitis media as a function of age.

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less affluent children.⁵ This finding may be an artifact of the more frequent access to medical care and consequent greater opportunity to detect recurrent acute otitis media among affluent white children. Children with recurrent acute otitis media compared with those not suffering from it experience nasopharyngeal colonization with acute otitis media pathogens more frequently,¹⁰ and the density of the bacteria is higher.¹¹

PERSISTENT ACUTE OTITIS MEDIA

A clinical challenge closely related to recurrent otitis media is persistent otitis media, traditionally defined on the basis of response to antibiotic therapy. Persistent otitis media is manifested by persistence during antimicrobial therapy of symptoms and signs of middle ear infection (treatment failure) and/or relapse of acute otitis media within 1 month of completion of antibiotic therapy. When two episodes of otitis media occur within 1 month, it may be difficult to distinguish recurrence of acute otitis media (i.e. a new episode) from persistent otitis media (i.e. relapse).

Most often an episode of acute otitis media occurring shortly after completion of antibiotic therapy reflects treatment failure. In this case the selected antibiotic eradicates the susceptible strains of the infecting pathogen but fails to eradicate the small inocula of resistant strains (perhaps a single organism). Because the inflammatory response subsides with initial antibiotic treatment, symptoms are relieved; the tympanic membrane may appear near normal; and the middle ear effusion may change from yellow (reflecting the presence of pus) to gray/white. Nevertheless, once the antibiotic therapy has been discontinued, the resistant organisms begin to multiply, and shortly thereafter a clinical presentation of acute otitis media redevelops.

Persistent episodes of acute otitis media should be distinguished from middle ear effusion continuing after an episode of acute otitis media has been effectively treated. The continuation of middle ear effusion for weeks to months after effective treatment of an episode of acute otitis media is a manifestation of the natural history of the disease. Continuing middle ear effusion after antibiotic treatment of acute otitis media probably does not constitute a new episode of acute otitis media if the patient does not manifest signs of local or systemic infection. A second course of antibiotics should not be administered in the absence of renewed signs of infection. If, on the other hand, continuing middle ear effusion is accompanied by second onset of local or systemic infectious signs such as fever or ear pain, treatment with a second course of antibiotics may be indicated.

STRATEGIES FOR PREVENTION OF RECURRENT AND PERSISTENT ACUTE OTITIS MEDIA

As the considerations above suggest, accurately diagnosing acute otitis media and differentiating it from

otitis media with effusion is difficult.¹² The two diagnoses are often confused and even used interchangeably.¹³ Misdiagnosis of acute otitis media may occur for a number of additional reasons. Many physicians rely on history and symptoms as major diagnostic clues, although symptom reports are neither sensitive nor specific.¹⁴⁻¹⁶ Failing to remove wax, using an otoscope that provides inadequate light, or employing small speculum, all of which impair visualization of the tympanic membrane, can lead to inadequate physical examination and consequent failed diagnosis.^{12, 17, 18} Physicians often use the observation of tympanic membrane redness as a prime diagnostic clue despite the fact that crying, in causing the tympanic membrane to become red, reduces the specificity of tympanic membrane redness as a diagnostic criterion.

Pneumatic otoscopy should be used to facilitate the diagnosis of acute otitis media and to distinguish acute otitis media from otitis media with effusion. Most family physicians and many pediatricians, however, do not routinely perform pneumatic otoscopy.¹⁹ Tympanometry or acoustic reflectometry can be helpful as aids in diagnosis and follow-up.²⁰⁻²³

Tympanocentesis is now recommended as a diagnostic and therapeutic tool for physicians to use for patients with persistent and recurrent acute otitis media.²⁴ This procedure is returning to the purview of the primary care provider.²⁵ The CDC therapeutic working group on acute otitis media management recommended that clinicians learn to perform tympanocentesis or establish a referral source to someone who can.²⁴ Drainage of a middle ear infection via tympanocentesis may have therapeutic benefits in breaking the cycle of persistent and recurrent acute otitis media (Reference²⁶ and author's unpublished observations). In addition the information provided by culture and susceptibility testing may be valuable in helping to select antibiotics to reduce the likelihood of additional treatment failure.²⁵

MOST COMMON PATHOGENS IN RECURRENT AND PERSISTENT OTITIS MEDIA

During the 1980s *Haemophilus influenzae* was the most common pathogen isolated, usually after failed amoxicillin therapy, in persistent acute otitis media.^{27, 28} In the 1990s the proportion of acute otitis media patients harboring antibiotic-resistant *Streptococcus pneumoniae* increased²⁹; these organisms concurrently came to predominate in persistent and recurrent acute otitis media.^{27, 29-41} *S. pneumoniae* is now the predominant pathogen associated with persistent acute otitis media^{27, 29, 30, 38, 42} (Table 1). Other pathogens to consider include *H. influenzae*, *Moraxella catarrhalis*, *Streptococcus pyogenes*, *Staphylococcus aureus* and mixed infections of the foregoing bacterial species.^{27, 29, 30, 38, 42} Higher prevalences of antibiotic-

TABLE 1. Pathogens isolated in persistent and previously untreated acute otitis media
Results expressed as percentages of patients.

	Persistent Acute Otitis Media (n = 200)	Previously Untreated Acute Otitis Media (n = 150)
No growth or nonpathogen	51	36
<i>Streptococcus pneumoniae</i>	25	38
<i>Haemophilus influenzae</i>	6	9
<i>Moraxella catarrhalis</i>	5	8
<i>Streptococcus pyogenes</i>	5	6
<i>Staphylococcus aureus</i>	5	2
Mixed	3	2
Total	100	100

resistant *S. pneumoniae* and beta-lactamase-producing strains of *H. influenzae* should be anticipated among patients recently treated with antibiotics for recurrent otitis media compared with patients not recently treated (Table 2).³²⁻⁴⁰

Many middle ear fluid cultures from patients with persistent acute otitis media produce no bacterial growth (Table 3).^{30, 32-34, 36, 38-40} This finding suggests that the infecting bacteria are often eradicated by the preceding antibiotic therapy or host defenses. Symptoms and signs of inflammation that may persist after bacterial eradication may cause confusion regarding persistence of infection. When a patient experiences persistent or recurrent acute otitis media despite antibiotic therapy, the therapeutic failure is often attributed to bacterial resistance. Although bacterial resistance may account for approximately 50% of these cases of treatment failure, the bacteria isolated from patients with recurrent or persistent acute otitis media are equally often susceptible to current or recent therapy (Table 4).^{32-35, 37-40} These failures not resulting from bacterial resistance may be attributed to inadequate dose, a dosing error, poor compliance, poor absorption or atypical pharmacokinetics or pharmacodynamics of the antibiotic that was selected.⁴¹

SHORTENED DURATION OF THERAPY

Ten days of antibiotic therapy for acute otitis media has been recommended as a standard in the United

States for many decades. The efficacy of shorter courses of antibiotic has recently (1997) been comprehensively reviewed.⁴³ In a 1998 metaanalysis, shortened courses of antibiotics (4 to 5 days) were as likely as 10-day courses to be successful for most patients older than 2 years of age with uncomplicated acute otitis media.⁴⁴

There is currently insufficient evidence from randomized trials to recommend shorter treatment courses for patients younger than 2 years of age,⁴⁵ an unfortunate situation in light of the fact that this age group has the highest incidence of persistent and recurrent acute otitis media.^{3, 5-7} Resistant pathogens are more likely to be found in patients younger than 2 years compared with older patients.⁴² Also the favorable natural history of acute otitis media is not as pronounced in children younger than 2 years compared with those older than 2 years of age.^{31, 46}

A 1999 study from the Elmwood Pediatric Group in Rochester, NY (ME Pichichero et al., 2000, submitted for publication) suggests that age less than 2 years is not a significant determinant of antibiotic failure with 5-day compared with 10-day therapy. Efficacy rates of the therapeutic courses did not differ as a function of age but were reduced among children who had received a course of antibiotic therapy (signaling the occurrence of a recurrent or persistent infection) in the previous month. This finding suggests that persistent and recurrent acute otitis media patients, and not necessarily patients less than 2 years of age, are the high risk group to fail shortened therapy. For children of all ages with uncomplicated acute otitis media, the benefits of shorter courses of antibiotic treatment are considerable. Patients and parents prefer shorter courses of treatment; better compliance is achieved; and a reduced length of antibiotic exposure might slow the development and spread of resistant pathogens.

SELECTING APPROPRIATE ANTIBIOTICS TO TREAT RECURRENT AND PERSISTENT ACUTE OTITIS MEDIA

When selecting an antibiotic for persistent and recurrent acute otitis media, most clinicians rely on

TABLE 2. Bacteriology of unresponsive/persistent acute otitis media when organisms are isolated
Results expressed as percentage of isolates.

Reference	<i>Streptococcus pneumoniae</i>	Penicillin-resistant <i>Streptococcus pneumoniae</i>	<i>Haemophilus influenzae</i> or <i>Moraxella catarrhalis</i>	Beta-lactamase-positive Strains	<i>Streptococcus pyogenes</i> or <i>Staphylococcus aureus</i>
32	17	20	58	33	12
33	24	0	76	50	0
34	20	18	61	33	18
35	27	0	73	70	Not reported
36	55	87	45	32	Not reported
37	51	11	31	86	21
38	81	44	19	58	Not reported
39	54	79	56	23	3
40	39	78	41	54	3

TABLE 3. Frequency of negative bacterial cultures in persistent acute otitis media

Reference	No. of Patients	% of Cultures with No Growth
32	43	57
33	45	18
34	148	28
36	293	50
38	137	49
39	63	32
40	186	32

TABLE 4. Bacterial susceptibility in acute otitis media from 1040 patients unresponsive to preceding antibiotic therapy

Reference	No. of Patients	% Sensitive*	% Resistant*
32	43	56	44
33	45	62	38
34	148	62	38
35	62	41	59
36	293	38	62
37	63	67	33
38	137	55	45
39	63	48	52
40	186	65	35

* Percent of bacterial isolates sensitive or resistant to the preceding antibiotic therapy given to the patient within 30 days of tympanocentesis.

clinical efficacy data. Consideration should also be given to antibiotic concentrations achievable in middle ear fluid relative to the concentration necessary to kill the relevant pathogens. The CDC working group recommended two selection criteria: (1) the antibiotic should be effective against most drug-resistant *S. pneumoniae*; and (2) the antibiotic should be effective against beta-lactamase-producing *H. influenzae* and *M. catarrhalis*.²⁴ On the basis of these criteria, the CDC working group recommended three antibiotics: (1) amoxicillin/clavulanate in combination with amoxicillin (high dose amoxicillin regimen, 80 to 90 mg/kg/day); (2) cefuroxime axetil (standard dose, 30 mg/kg/day); and (3) ceftriaxone (possibly requiring up to three injections to optimize clinical success) (Table 5). Cefprozil and cefpodoxime also were mentioned as candidate agents but were not included in the selected drugs because of insufficient clinical efficacy data. Another possible agent, cefdinir, was not yet licensed.

In forming their recommendations the CDC working group relied primarily on trials in which tympanocentesis was performed to avoid the problem of basing recommendations on patients who had been inaccurately diagnosed. The results of selected trials are shown in Figure 2.^{39, 47-50} These data support the selection of amoxicillin/clavulanate, cefuroxime axetil and ceftriaxone as preferred agents for recurrent and persistent acute otitis media.

Practical considerations may sometimes preclude the use of these preferred agents. For example, to follow the amoxicillin/clavulanate dosing recommendations, it would be necessary to dispense two prescriptions, one prescription for amoxicillin/clavulanate and a second prescription for amoxicillin. Dispensing two prescriptions creates the opportunity for confusion between the antibiotic dosing instructions. A high dose amoxicillin formulation of amoxicillin/clavulanate has been studied^{51, 52} and will soon become available in the United States.

Cefuroxime axetil has a bitter taste and aftertaste that some children find offensive. As a consequence they might refuse to take the antibiotic or spit/vomit the medication. Administering cefuroxime axetil with white grape juice or a chocolate-containing food such as chocolate syrup, chocolate ice cream or chocolate pudding can diminish this compliance challenge. Schwartz has found that administration of cefuroxime axetil suspension with a chocolate syrup chaser to children with acute otitis media renders the aftertaste of cefuroxime axetil as palatable as that of amoxicillin and more palatable than that of cefpodoxime proxetil or clarithromycin.⁵³

Families sometimes prefer a single injection of ceftriaxone to avoid issues of child refusal to take oral medications.⁵⁴ Use of a single injection ceftriaxone in uncomplicated acute otitis media; in children who are toxic, highly febrile or vomiting or who have diarrhea is recommendable. One injection may be adequate for some cases of recurrent acute otitis media.⁵⁵ However, treatment of resistant *S. pneumoniae* infections may require two or three separate injections on two or three separate days.^{39, 48} a compliance challenge for working

TABLE 5. Acute otitis media treatment recommendations*

Adapted with permission from Dowell et al.²⁴

Antibiotics in Prior Month	Day 0	Clinically Defined Treatment Failure on Day 3	Clinically Defined Treatment Failure on Days 10 to 28
No	High dose amoxicillin†; usual dose amoxicillin	High dose amoxicillin/clavulanate†; cefuroxime axetil; im ceftriaxone	
Yes	High dose amoxicillin; high dose amoxicillin/clavulanate; cefuroxime axetil	im ceftriaxone‡; clindamycin§ or tympanocentesis	High dose amoxicillin/clavulanate; cefuroxime axetil; im ceftriaxone or tympanocentesis

* Recommended drugs are those for which strong evidence for efficacy exists.

† High dose amoxicillin, 80 to 90 mg/kg/day. High dose amoxicillin/clavulanate, 80 to 80 mg/kg/day of the amoxicillin component with 6.4 mg/kg/day of clavulanate.

‡ Documented efficacy in acute otitis media treatment failures if three daily doses are used.

§ Clindamycin is not effective against *Haemophilus influenzae* or *Moraxella catarrhalis*.

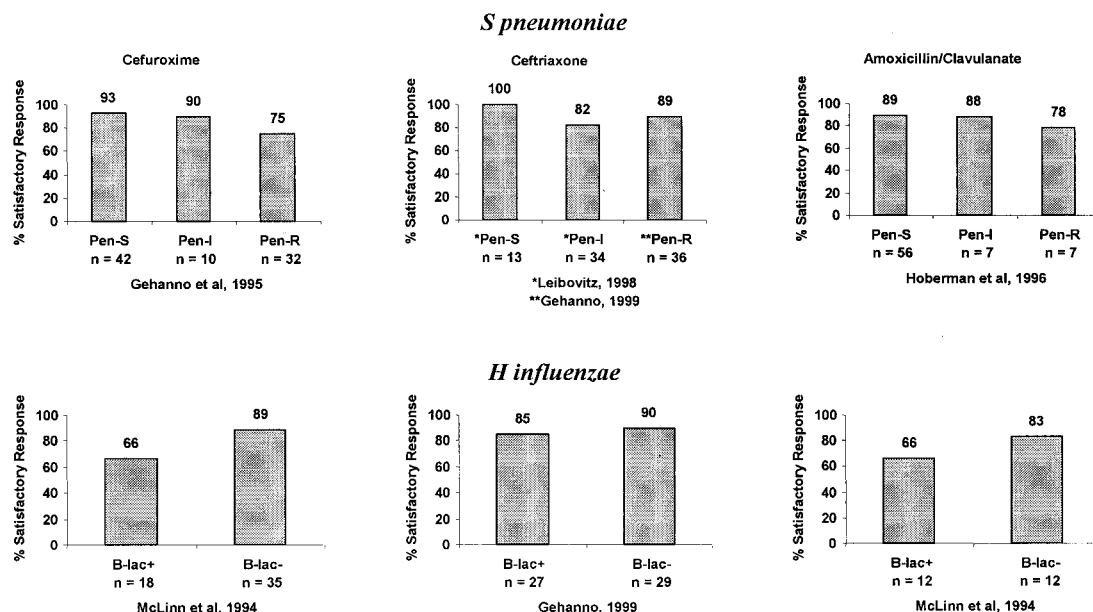


FIG. 2. Percentage of patients reporting a satisfactory response after treatment with CDC working group-recommended antibiotics for recurrent and persistent acute otitis media. Pen-S, Pen-I and Pen-R, penicillin-resistant, intermediate penicillin resistance, and penicillin-susceptible, respectively. B-lac+ and B-lac-, beta-lactamase-positive and beta-lactamase-negative, respectively.

parents and a regimen associated with a high cost. Because of these practical considerations, cefprozil, cefpodoxime and cefdinir perhaps should be included as candidates for therapy in persistent and recurrent acute otitis media.

Beyond the identification of preferred agents as treatments for persistent and recurrent acute otitis media, the CDC working group made several other important recommendations. First they recommended routinely starting with standard dose or high dose amoxicillin therapy for simple acute otitis media. This recommendation is consonant with the high frequency of overdiagnosis and the high spontaneous cure rate of simple acute otitis media. Second they recommended that a decision to continue with initial therapy or to switch therapy be timed to occur 48 h after the initiation of therapy. The need to switch therapy should be based on failure of the patient to respond clinically. Third amoxicillin/clavulanate, cefuroxime or high dose amoxicillin were recommended as appropriate first line choices among patients who have received an antibiotic within the previous month. Finally the CDC working group recommended follow-up examination on completion of therapy, usually 3 to 4 weeks after diagnosis unless symptoms recur sooner.²⁴

CONCLUSIONS

Optimal management of persistent and recurrent acute otitis media is a clinical challenge.⁵⁶ Accurate diagnosis of acute otitis media is the first step in optimal management. Selection of appropriate antibiotic therapy should take into account the major pathogens (*S. pneumoniae*, *H. influenzae* and *M. catarrhalis*)

and the occurrence of antibiotic resistance. Clinicians should be aware of pharmacokinetic and pharmacodynamic features of antibiotics, including the percent of antibiotic absorbed, tissue penetration, antibiotic half-life and achievable levels of antibiotic in middle ear fluid. Furthermore, clinicians selecting an antibiotic should consider compliance-influencing factors such as side effect profile, the dosing frequency, the duration of therapy and the taste/aftertaste. No single agent is ideal for all patients. Treatment strategy should be tailored to the patient's needs while appropriate attention to microbial resistance patterns is maintained.⁵⁶

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