Management

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**AN OVERVIEW OF STRATEGIES FOR MANAGEMENT**

In this introductory section, a summary of strategies for treatment and prevention of acute otitis media (AOM) is presented. In subsequent sections, we review the data available about antimicrobial agents and their efficacy for treatment of acute infections, the role of nonbacterial drugs, surgical options for the child with severe and recurrent disease, and chemoprophylaxis and immunoprophylaxis. Figure 1 is an algorithm for treating AOM and the middle-ear effusion that persists after the acute infection.

**AOM**

Infants and children who have signs and symptoms of AOM should receive an antimicrobial agent with efficacy against the three major bacterial pathogens, *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*. The option of observation may be considered for the child who has mild to moderate signs and symptoms and/or uncertain diagnosis and is older than 2 years of age.
Selection of drugs is based on clinical and microbiologic efficacy, acceptability (e.g., taste, texture) of the oral preparation, absence of side effects and toxicity, convenience of dosing schedule, and cost. As of this writing, 19 drugs are approved by the United States Food and Drug Administration (FDA) for therapy of AOM (Table 1). Ofloxacin otic and ciprofloxacin (with dexamethasone) are approved for acute otorrhea in children who have tympanostomy tubes in place. Amoxicillin remains the current drug of choice because it continues to be effective, safe, and relatively inexpensive. Doubling the dosage schedule from 40 mg/kg/d to 80 mg/kg/d in 2 doses is now recommended, and increases the concentration of the drug in the middle ear. The increased concentrations provide activity against most intermediate non-susceptible strains of *Streptococcus pneumoniae* and many of the resistant strains. Although most experts agree on the continued use of amoxicillin as the drug of choice for initial treatment of AOM, there is less agreement on the appropriate drug to use when the child has severe disease at onset or when amoxicillin fails; amoxicillin clavulanate (in a dosage schedule of 80 to 90 mg/kg/d in 2 doses), cefuroxime axetil, and intramuscular ceftriaxone have been recommended. If an oral cephalosporin is chosen, cefdinir may be preferable to cefuroxime axetil because of better taste. A macrolide (erythromycin plus sulfisoxazole; azithromycin, or clarithromycin) is the preferred drug for AOM for children who are allergic to β-lactam antimicrobial agents; trimethoprim-sulfamethoxazole has become less useful because of the large proportion of strains of pneumococci that are resistant.

Duration of therapy is based on clinical trials and tradition. Most clinical trials and standard pediatric practice include a 10-day course of an oral antimicrobial agent. Other dosage schedules, longer or shorter than the traditional 10-day course, have been investigated. Azithromycin, cefpodoxime, and cefdinir are now approved for 5-day courses. Azithromycin is also approved for 1- and 3-day schedules. A single dose of intramuscular ceftriaxone was found to be as effective as 10-day courses of amoxicillin and trimethoprim-sulfamethoxazole but may require second or third doses if the episode of AOM is due to a resistant pneumococcus. For other oral drugs, including amoxicillin-clavulanate, a 10-day course is preferable to a shorter course for infants (younger than 2 years), children with severe acute disease (including otorrhea), children with histories of severe and recurrent AOM, and children with some defect in immune response.

The clinical course of a child who receives appropriate antimicrobial therapy includes significant resolution of acute signs within 48 to 72 hours. Initial instructions to the parent should indicate the need to contact the physician if the signs or symptoms are worse at any time or are unimproved at 72 hours. Persistent ear pain or systemic signs, including fever, signal the need for reevaluation to examine for other foci of infection, to determine the need for another antimicrobial agent, or to perform tympanocentesis and myringotomy to
incise and drain the middle-ear abscess and culture the fluid to determine the pathogen.

Incision and drainage are of value initially for patients with unusually severe earache or systemic toxicity. Myringotomy provides immediate relief by draining the abscess. Tympanocentesis or needle aspiration of the middle-ear fluid before therapy is of value in identifying the microbial pathogen. Tympanocentesis for microbial diagnosis should be considered in children who are toxic, who have severe suppurative or nonsuppurative complications (ie, mastoiditis or facial nerve palsy), who fail to improve on antibiotic therapy, or who have underlying conditions that compromise immune functions.

Follow-up visits should be made to determine that the child has recovered from the acute infection and to diagnose persistent middle-ear effusion if it is present. A visit at 10 to 14 days is useful only if the parent reports that the illness has not resolved. Most children will still have asymptomatic fluid in the middle ear at the 10- to 14-day visit, which does not require further antibiotic therapy; however, persistent signs of illness, such as an inflamed tympanic membrane, may warrant extending therapy to 21 days. A subsequent visit at 2 to 3 months is valuable in determining the duration of middle-ear effusion after the acute episode and for identifying

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**Table 1. ANTIMICROBIAL AGENTS APPROVED FOR TREATMENT OF OTITIS MEDIA AND DOSAGE SCHEDULES: UNITED STATES 2006**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Trade Name</th>
<th>No. of Doses ×Day</th>
<th>Number of Days</th>
<th>Dosage (kg/d)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Penicillins</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>Amoxil (GlaxoSmithKline) various</td>
<td>2–3</td>
<td>10</td>
<td>40–80 mg</td>
</tr>
<tr>
<td>Amoxicillin-clavulanate</td>
<td>Augmentin, Augmentin ES 600 (GlaxoSmithKline)</td>
<td>2</td>
<td>10</td>
<td>40–80 mg (90 mg for Augmentin ES 600)</td>
</tr>
<tr>
<td><strong>Cephalosporins</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cefaclor</td>
<td>Ceclor (Lilly); various</td>
<td>3</td>
<td>10</td>
<td>40 mg</td>
</tr>
<tr>
<td>Cefdinir</td>
<td>Omnicef (Abbott)</td>
<td>1–2</td>
<td>5 or 10</td>
<td>14 mg</td>
</tr>
<tr>
<td>Cefixime</td>
<td>Suprax, various</td>
<td>1</td>
<td>10</td>
<td>8 mg</td>
</tr>
<tr>
<td>Cefpodoxime proxetil</td>
<td>Vantin (Pfizer); various</td>
<td>2</td>
<td>5</td>
<td>10 mg</td>
</tr>
<tr>
<td>Cefprozil</td>
<td>Cefzil (Bristol-Myers Squibb)</td>
<td>2</td>
<td>10</td>
<td>30 mg</td>
</tr>
<tr>
<td>Cefditolene</td>
<td>Cefxin (Schering-Plough)</td>
<td>1</td>
<td>10</td>
<td>9 mg</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>Rocephin (Roche)</td>
<td>1 IM</td>
<td></td>
<td>50 mg</td>
</tr>
<tr>
<td>Cefuroxime axetil</td>
<td>Cefxin (GlaxoSmithKline/LifeCycle Ventures); various</td>
<td>2</td>
<td>10</td>
<td>30 mg</td>
</tr>
<tr>
<td><strong>Macrolides</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Azithromycin</td>
<td>Zithromax (Pfizer)</td>
<td>1</td>
<td>1</td>
<td>30 mg</td>
</tr>
<tr>
<td>Loracarbef</td>
<td>Lorabid (Monarch)</td>
<td>2</td>
<td>10</td>
<td>30 mg</td>
</tr>
<tr>
<td><strong>Macrolides</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>Biaxin (Abbott)</td>
<td>2</td>
<td>10</td>
<td>15 mg</td>
</tr>
<tr>
<td>Erythromycin + sulfonamides</td>
<td>Pediazole (Ross Products Division, Abbott)</td>
<td>4</td>
<td>10</td>
<td>50 mg (E) + 150 mg (S)</td>
</tr>
<tr>
<td><strong>Sulfonamides</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trimethoprim HCl oral solution</td>
<td>Primsol (Ascent Pediatrics)</td>
<td>2</td>
<td>10</td>
<td>10 mg</td>
</tr>
<tr>
<td>Trimethoprim-sulfamethoxazole</td>
<td>Bactrim (Roche); Septra (Monarch); various</td>
<td>2</td>
<td>10</td>
<td>8 mg (T) – 40 mg (S)</td>
</tr>
<tr>
<td><strong>Ototopicals</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ofloxacin otic (with tympanostomy tubes)</td>
<td>Floxin Otic (Daiichi)</td>
<td>2</td>
<td>10</td>
<td>5 drops</td>
</tr>
<tr>
<td>Ciprofloxacin- dexamethasone otic (with tympanostomy tubes)</td>
<td>Ciprodex (Alcon)</td>
<td>2</td>
<td>7</td>
<td>4 drops</td>
</tr>
</tbody>
</table>

IM = intramuscular.
children who may be candidates for tympanostomy tube placement.

Symptomatic therapy, including analgesics, antipyretics, and local heat, usually is helpful. An oral decongestant, such as pseudoephedrine hydrochloride, may relieve nasal congestion, and antihistamines may help patients with known or suspected nasal allergy. However, the efficacy of antihistamines and decongestants in treating AOM has not been proven. Antihistamines may be considered contraindicated for the child with AOM. Chonmaitree and colleagues found that antihistamines administered at the time of initial antibiotic therapy of AOM resulted in prolonged time of middle-ear effusion contrasted with corticosteroid, which was equivalent to placebo.11

**Persistent Middle-Ear Effusion Following AOM**

After antibiotic therapy for an episode of AOM, 30 to 70% of infants and children will have a persistent middle-ear effusion that can last for weeks to months. The mean duration of persistent middle-ear effusion after an episode of AOM is approximately 23 days. Without further treatment, only 6 to 26% will have an effusion remaining in the middle ear 3 months after the onset of the acute episode.12-17 Because most effusions resolve spontaneously without further treatment, and most patients are relatively asymptomatic, nonsurgical or surgical treatment for this stage of AOM, such as another course of an antimicrobial agent, usually is not recommended. Indeed, the Centers for Disease Control and Prevention (CDC) and the American Academy of Pediatrics specifically advise against retreatment of asymptomatic infants and children with an antimicrobial agent when middle-ear effusion persists after an initial course of antibiotic for AOM.2 This practice is thought to be contributing to the ever-increasing rate of antibiotic-resistant otitic bacteria.18 Thus, watchful waiting is advised for children with persistent middle-ear effusion. For a further description of management of effusion that persists for 3 months or longer (ie, chronic otitis media with effusion) see the section “Otitis Media with Effusion” in this overview and the subsequent section “Management of Otitis Media with Effusion”).

**Prevention of AOM**

The physician should design a management strategy for the child with severe and recurrent AOM. The strategy should include education of the parents, chemoprophylaxis, immunoprophylaxis, and a consideration of surgery. Selected children may require diagnostic tests for host problems, including immune and anatomic defects.

Parents should be informed about the risk factors for AOM. Although host features are not subject to change, parents may be empowered to change environmental risk features, such as eliminating cigarette smoking from the household, reducing use of a pacifier, and encouraging home or family day care or small-group out-of-home care.2

Chemoprophylaxis has proven to be successful in preventing new symptomatic episodes of middle-ear infections. However, use of a modified and prolonged course of an antimicrobial agent may result in selection of resistant bacteria in the nasopharynx. Breakthrough episodes are likely to occur and may be due to multidrug-resistant pneumococci or β-lactamase-resistant *H. influenzae*. Because of the concern for development of resistant strains, chemoprophylaxis should be reserved for patients who have three or more documented episodes of AOM in 6 months, or four or more episodes in 12 months.

The heptavalent conjugate pneumococcal vaccine (Prevnar, Wyeth-Lederle Vaccines, Philadelphia, PA) has been documented to prevent AOM in immunized children and benefits children with AOM, including a 57% decrease in vaccine-type pneumococcal disease.19,20 Parenteral and intranasal administration of influenza virus vaccines resulted in a decreased number of cases of AOM compared with the control group.21-23 The live attenuated, temperature-sensitive influenza virus vaccine is
administered by means of a nasal spray (FluMist, MedImmune, Gaithersburg, MD) but currently is FDA-approved only for patients 5 to 49 years of age. The parenteral influenza virus vaccine is now recommended for all infants 6 to 24 months of age and also should be given in the fall to older children who had recurrent episodes of AOM the preceding winter.

If the child continues to suffer from recurrent episodes of AOM after these steps have been taken, myringotomy with tympanostomy tube insertion is valuable in preventing recurrent episodes of AOM. Tympanostomy tubes provide ventilation to the middle ear, preventing middle-ear negative pressure from developing during an upper respiratory tract infection, and providing drainage of middle-ear effusion from the middle ear down the eustachian tube into the nasopharynx. Although inflammation of the middle-ear mucosa due to viruses or bacteria may still develop in the children, the number of symptomatic episodes of AOM decreases. Adenoidectomy, irrespective of the size of the adenoids, has been shown to reduce the rate of recurrent episodes of AOM in children who have had one or more tympanostomy tube insertions. However, adenoidectomy was not shown to be effective in the long term for children who had not received tympanostomy tubes previously.

Nevertheless, adenoidectomy may be indicated as an adjunct to initial tympanostomy tube insertion if the adenoids are the cause of chronic upper airway obstruction due to hypertrophy. Tonsillectomy is withheld at any stage unless there are other compelling indications, such as for children who have had recurrent pharyngotonsillitis or moderate to severe chronic airway obstruction caused by hypertrophy of the tonsils. We do not recommend adenoidectomy in infants when prevention of recurrent AOM is the only indication. Indeed, a recent clinical trial from Canada failed to show a significant advantage of a concurrent adenoidectomy during myringotomy and tympanostomy tube placement in children younger than 2 years of age.

Figure 2 shows three examples of children with recurrent AOM, chronic otitis media with effusion, or both.

For identification of underlying host features that predispose to infection, the following diagnostic tests should be considered for selected children who suffer recurrent episodes of AOM:

- Examination for anatomic defects, such as submucosal cleft palate or obstruction of the upper airway by tumor.
- A search for respiratory allergy.
- Radiographic studies to define presence of paranasal sinusitis.

Figure 2. Three examples of children with recurrent acute otitis media or chronic otitis media with effusion, or both, related to available management options. (1) Patients with recurrent acute otitis media without chronic otitis media with effusion between attacks can be treated with a prophylactic antimicrobial agent, tympanostomy tubes, or continuation of antibiotic treatment of each episode. (2) Children with 3 months or more of bilateral chronic otitis media with effusion, or 6 months or more of unilateral effusion, should be considered candidates for tympanostomy tubes. (3) When recurrent acute otitis media is superimposed on chronic otitis media with effusion, tympanostomy tubes should be advised.
Immunologic studies to identify defects in cellular or humoral immunity (see “Prevention of AOM” and “Surgical and Mechanical Management”).

**Otitis Media with Effusion**

Management of patients with otitis media with effusion is currently the subject of considerable debate. However, we now have enough evidence-based information to make some of the important decisions regarding treatment (vs. no treatment) and to know which therapeutic options are effective.²⁹

Otitis media with effusion in most children will resolve without active treatment in 2 or 3 months,³⁰ but treatment may be indicated in some children because of the possible complications and sequelae associated with this condition. Because hearing impairment of some degree usually accompanies a middle-ear effusion,³¹ treatment may be warranted when long-standing hearing loss is present. Although the significance of this hearing loss is still uncertain, such a loss may impair cognitive and language function and result in disturbances in psychosocial adjustment.³² Important factors to consider in deciding to treat (and which treatment) or not to treat include

1. Significant associated conductive hearing loss
2. Occurrence in young infants—because they are unable to communicate their symptoms and may have suppurative disease
3. Associated acute suppurative upper respiratory tract infection
4. Concurrent permanent conductive and sensorineural hearing loss
5. Presence of speech-language delay associated with effusion and hearing loss
6. Alterations of the tympanic membrane, such as a retraction pocket
7. Middle-ear changes, such as adhesive otitis media or ossicular involvement
8. Previous surgery for otitis media (eg, tympanostomy tube placement or adenoidectomy)
9. Frequently recurring episodes
10. Persistence of the effusion for 3 months or longer in both ears or for 6 months or longer in only one ear (ie, chronic otitis media with effusion) before considering tympanostomy tube placement

The most compelling indication to consider for active treatment is progression of the disease into the chronic stage.²,¹⁸,³³ If active treatment is elected, options are limited. Even though a combination of an oral decongestant and antihistamine was previously thought to be effective and was widely used, two Pittsburgh studies involving more than 1,000 infants and children failed to demonstrate these drugs’ efficacy in eliminating middle-ear effusion.³⁴,³⁵ Despite the apparent efficacy of systemic corticosteroid therapy in clinical trials,³⁶ an official government guideline found that the risks of this option in children outweigh its possible benefits.³³ Clinical trials have not been reported that have tested the efficacy of topical nasal corticosteroid treatment, immunotherapy, and control of allergy in children who have nasal allergy and middle-ear disease. Nevertheless, this method of management seems reasonable in children who have frequently recurrent or chronic otitis media with effusion and evidence of upper respiratory allergy. Inflation of the eustachian tube–middle ear by the Politzer’s method or Valsalva’s maneuver has been advocated for more than a century for this condition. However, a randomized controlled trial by Chan and Bluestone found a lack of efficacy of middle-ear inflation for chronic effusion,³⁷ and therefore it is not recommended in children; efficacy in adults remains uncertain. Inflation may be effective for all age groups for management of middle-ear effusion that follows barotrauma (eg, after air travel or scuba diving).

Of all the medical treatments that have been advocated for otitis media with effusion, a trial of an antimicrobial agent appears to be most appropriate. A meta-analysis by Rosenfeld and Post on the effect of antimicrobial agents in treatment of otitis media with effusion affirmed their efficacy.³⁸ Two other meta-analyses also
verified their short-term effect, but there was no long-term efficacy.\textsuperscript{33,39} A 2004 guideline from the American Academy of Pediatrics about otitis media with effusion stated that treatment with antimicrobial agents had not been demonstrated to be effective long-term therapy for otitis media with effusion but was an option for parents who refused surgery.\textsuperscript{2}

As in AOM, amoxicillin is a reasonable choice for treating otitis media with effusion; a clinical trial conducted in Pittsburgh demonstrated its efficacy, albeit limited, in 518 infants and children.\textsuperscript{35} Other antimicrobial agents have also been recommended, but none have been reported more effective than amoxicillin at this time; cefaclor, erythromycin-sulfisoxazole, and ceftibuten have been shown to be equal or inferior to amoxicillin.\textsuperscript{40,41} A 10-day course of amoxicillin is recommended, but a longer duration of therapy with this or any other antimicrobial agent is not recommended at this time. A clinical trial compared the efficacy of a 10-day course of amoxicillin with a 20-day regimen and found that the longer therapy provided no advantage over the shorter therapy.\textsuperscript{14}

When the effusion is chronic, surgical intervention should be considered, especially when antimicrobial therapy fails. Even though one government guideline recommends either antimicrobial therapy or tympanostomy tube insertion for bilateral chronic effusions (ie, of 3 to 4 months duration) associated with hearing loss,\textsuperscript{33} and the recent one does not recommend antibiotic therapy,\textsuperscript{2} we recommend a trial of amoxicillin therapy, regardless of the level of hearing, before considering surgical intervention.\textsuperscript{42} In fact, a trial of antibiotic therapy for children who had chronic otitis media with effusion conducted in The Netherlands by primary care physicians—who normally reserve these drugs for severe AOM only—was found to be so effective that they recommended a course before referring the patient to an otolaryngologist for possible surgery.\textsuperscript{43}

Myringotomy with tympanostomy tube placement or adenoidectomy and myringotomy, with and without tube insertion, have been demonstrated to be effective in children with chronic effusions that are unresponsive to a trial of antibiotics. Two Pittsburgh clinical trials showed that tympanostomy tube insertion was more effective than myringotomy without tube insertion or no surgery (ie, control) for chronic effusions.\textsuperscript{44,45} Adenoidectomy, in conjunction with myringotomy with and without tympanostomy tube placement, has been shown to be effective for chronic effusions in two large, well-controlled clinical trials in children.\textsuperscript{25,46} Our preference is to recommend only tympanostomy tube insertion if the child has not had tubes inserted in the past and does not have nasal obstruction caused by adenoid hypertrophy because the two Pittsburgh studies showed that approximately one half of the subjects did not require another operation.\textsuperscript{44,45} If obstructive adenoids are present, we recommend their removal at the initial procedure. For children who have recurrence of chronic effusion after extrusion of the tubes and who need a second surgical procedure, we advise an adenoidectomy, regardless of adenoid size, with myringotomy; the decision to place tympanostomy tubes at this operation is made on an individualized basis. Even though the Guideline Panels do not recommend adenoidectomy—in the absence of adenoid disease—for this indication in children younger than 4 years,\textsuperscript{33} a Pittsburgh trial showed that the procedure was effective for subjects in this age group.\textsuperscript{25} We have discussed this difference of opinion in detail elsewhere.\textsuperscript{47} However, we do not recommend adenoidectomy, with or without tonsillectomy, for prevention of otitis media below the age of 2 years, unless there are other compelling indications for adenoidectomy, such as obstructive sleep apnea due to hypertrophy of the adenoids.

Tonsillectomy in conjunction with adenoidectomy for chronic effusions has been shown in a clinical trial in Great Britain to provide no significant benefit over adenoidectomy alone.\textsuperscript{48} Tonsillectomy is not recommended unless there are other compelling indications, such as frequently recurrent throat infections\textsuperscript{27} or severe air-way obstruction secondary to grossly enlarged tonsils.\textsuperscript{2}
STRATEGIES FOR MANAGING EUSTACHIAN TUBE DYSFUNCTION

Eustachian tube dysfunction can occur in the absence of middle-ear effusion. Abnormal function of the eustachian tube can cause otologic symptoms despite the lack of otitis media. The symptoms can be intermittent or persistent, and the severity of the complaints can be mild, moderate, or severe. At the time of examination, the tympanic membrane may appear normal, and its mobility may or may not be impaired when tested with a pneumatic otoscope or by tympanometry. The tympanic membrane may or may not be retracted. The condition can be either of short duration (acute) or long-standing (chronic). The child will commonly have a past history of episodes of acute otitis media, otitis media with effusion, or both. Two types of eustachian tube dysfunction can be present: obstruction or abnormal patency (see Chapter 3). Rapid alterations in barometric pressure, such as when flying in an airplane or scuba diving, can also cause obstruction of the eustachian tube (ie, otitic barotrauma) that can result in otologic symptoms, especially in children who have an underlying eustachian tube dysfunction.

Eustachian Tube Obstruction

When the eustachian tube is obstructed but no middle-ear effusion is present, the tube periodically opens to regulate (ventilate) the gas pressure within the middle-ear cavity but at less frequent intervals than normal. In this case, high negative intratympanic pressure may be present for transient or prolonged periods (i.e., acute or chronic). The obstruction of the tube can be anatomic (mechanical), functional (failure of the opening of the tube), or both. Anatomic obstruction may be due to infection or allergy, or possibly adenoids, whereas functional obstruction is idiopathic. This type of intermittent middle-ear ventilation can cause periods of otalgia, a feeling of fullness or pressure, hearing loss, popping and snapping-noises, tinnitus, disequilibrium, or even vertigo. These symptoms are more commonly encountered in older children and teenagers than in young children. Most likely, infants and young children have these symptoms but rarely complain. Patients frequently have otologic symptoms on awakening and then periodically during the rest of the day. When symptomatic, the child commonly has a retracted tympanic membrane, which will have limited or no mobility to applied negative pressure and no mobility when positive pressure is applied during pneumatic otoscopy, indicating the presence of negative pressure in the middle-ear cavity. Tympanometry can be helpful in confirming and documenting the high middle-ear negative pressure (see Chapter 7). However, a child may have no evidence of middle-ear negative pressure at the time of the examination because the pressure can fluctuate during the course of the day. Audiometric testing frequently reveals normal hearing, but if high negative middle-ear pressure is present, a mild conductive hearing loss may be due to the impaired middle-ear compliance. This disorder is relatively common in children during puberty, especially in girls, and it can be present even with no past history of middle-ear infection.

Management for a child with eustachian tube obstruction is related to the frequency, severity, and duration of the symptoms and the underlying cause. If the condition is present only during episodes of an acute upper respiratory tract infection, medical treatment is directed toward relief of the nasal congestion, and the patient and parent should be counseled that the disorder will resolve spontaneously. A systemic decongestant may be helpful. Inflating the middle ear can be tried (see later section, “Inflation of the Eustachian Tube–Middle Ear”). If the symptoms are extremely troublesome and interfere with concentration, a myringotomy may be required, but it is rarely necessary.

If the symptoms are chronic, a search should be made for an underlying cause (e.g., paranasal sinusitis, nasal allergy, or hypertrophy of the adenoids), and if one is found, appropriate management should be instituted. There is frequently a strong family history of middle-ear disease, which implies a hereditary factor in children who have not only otitis media but also
eustachian tube obstruction (see Chapter 4). If no underlying cause is uncovered, a trial with a systemic decongestant may be helpful or inflating the eustachian tube–middle ear may be tried, but there is no evidence that these treatment options are effective for the long term. If the nonsurgical methods are not successful and the symptoms are troublesome to the child, myringotomy and tympanostomy tube insertion may be necessary; the symptoms will be alleviated while the tubes are functioning. The condition, even though chronic, usually resolves with advancing age, but some children, especially adolescents, may need to have the tympanostomy tubes replaced several times, and some may even need a “permanent” tympanostomy tube (see later, “Myringotomy and Tympanostomy Tube Placement”).

When eustachian tube obstruction is chronic, sequelae such as atelectasis of the middle ear (and tympanic membrane) can progress into a retraction pocket and then a cholesteatoma. Ossicular damage can also occur, which can result in permanent conductive hearing loss (see Chapter 9).

Abnormally Patent (Patulous) Eustachian Tube

At the other end of the spectrum of eustachian tube dysfunction is abnormal patency. In its extreme form, the hyperpatent eustachian tube is open even at rest (i.e., patulous). Lesser degrees of abnormal patency result in a semipatulous eustachian tube that is closed at rest but has low tubal resistance to airflow compared with the normal tube. A patulous eustachian tube may be caused by abnormal tube geometry or a decrease in extramural pressure, such as occurs as a result of weight loss, or possibly mural or intraluminal changes. These last conditions may be seen when the extracellular fluid is altered by medical treatment of another unrelated condition. Interruption of the innervation of the tensor veli palatini muscle has also been shown to be a cause of a hyperpatent eustachian tube.

A patulous eustachian tube is a relatively uncommon clinical finding in adolescents and adults, but it is even less common in young children. When present, this disorder can be misdiagnosed as eustachian tube obstruction and inappropriately treated. The patient frequently complains of hearing his or her own breathing or voice (autophony) in the ear. Otoscopic examination reveals a tympanic membrane that moves medially on inspiration and laterally on expiration; the movement can be exaggerated with forced respiration. The condition is relieved when the patient is recumbent because extramural pressure in the eustachian tube is increased by paratubal venous engorgement in this position. The patient should therefore be examined in the sitting position. The diagnosis can also be made by measuring the impedance of the middle ear. A tympanogram is obtained while the patient is breathing normally, and a second one is obtained while the patient holds his or her breath. Fluctuation in the tympanometric line should coincide with breathing. The fluctuation can be exaggerated by asking the patient to occlude 1 nostril and close the mouth during forced inspiration and expiration or by having the patient perform the Toynbee or Valsalva maneuver (see Chapters 3 and 7).

Management of a patulous eustachian tube depends on first determining the cause of the problem. If the symptoms are of relatively short duration, the condition may subside without any active treatment. In children and teenagers, this condition is usually self-limited and probably related to changes in the structure and function of the eustachian tube and adjacent areas secondary to rapid growth and development. Interruption of the neuromuscular component of the eustachian tube may be the cause, such as from trauma or surgery, but more commonly, rapid weight loss is the underlying pathogenesis. In adults, a neurologic disorder may be present; but in children, the condition is most commonly idiopathic. When the symptoms are disturbing and the condition is chronic, active treatment is indicated. Myringotomy with tympanostomy tube insertion may be helpful in some patients, probably owing to the coexistence of obstruction and abnormal patency. However, tympanostomy
tube placement may exaggerate the symptoms if the tube is consistently hyperpatent.

Insufflation of powders into the eustachian tube and instillation of 2% iodine or 5% trichloroacetic acid solution have been advocated. Infusion of an absorbable gelatin sponge solution has also been suggested, as has injection of polytetrafluoroethylene (Teflon) into the paratubal area. All of these methods have major disadvantages. They are, for the most part, irreversible and may not improve the condition or may provide only temporary relief. Total obstruction of the eustachian tube can also be a complication. Stroud and colleagues have suggested the transposition of the tensor veli palatini through a palatal incision, but the procedure has not been shown to be safe and effective in a large number of patients by other investigators. DiBartolomeo and Henry reported initial success in treating 8 of 10 patients who had patulous tubes with a new intranasal medication composed of diluted hydrochloric acid, chlorobutanol, and benzyl alcohol. The safety and long-term efficacy of this experimental treatment have not been confirmed.

At present, the most logical choice for relief when the discomfort becomes severe is a procedure that alleviates the symptoms simply, reversibly, and without untoward reactions. A technique described by Bluestone and Cantekin has been used successfully in adults but is rarely indicated or necessary in children because the patulous tube condition is usually self-limited in this population. The procedure involves placement of a plastic catheter into the middle-ear end of the eustachian tube.

**Otitic Barotrauma**

Many parents and children, and their attending physicians, are concerned about flying in airplanes when a child has otitis media. Barotitis usually occurs in individuals who have eustachian tube obstruction, either functional or mechanical. On ascent, the normal eustachian tube opens spontaneously (i.e., there is forced opening), and the relative positive middle-ear gas pressure is equilibrated with the cabin pressure. Most commercial aircraft are pressurized to an equivalent altitude of 7000 feet. On descent, however, the eustachian tube does not open spontaneously; the tube opens by active swallowing (i.e., contraction of the tensor veli palatini muscle) to equilibrate the relative negative middle-ear pressure. If the eustachian tube is totally mechanically obstructed, which is extremely rare in children and adults, the patient will have otalgia and barotitis on both ascent and descent. Because functional eustachian tube obstruction is the most common type of dysfunction of the tube, the child will have difficulty only on descent because the tube can easily open spontaneously during ascent, but not on descent. Infants and children, even those without a history of middle-ear disease, frequently have trouble on descent because their ability to actively open the tube by swallowing is inefficient compared with that of most adults (see Chapter 3). The child may have few or no symptoms during flying in an airplane until he or she develops an upper respiratory tract infection or during a period in which allergic rhinitis is present (i.e., inflammation of the tube is superimposed on a preexisting functional obstruction). Evidence that infants have relatively inefficient active tubal opening is crying during descent. Crying probably inflates their middle ears—a physiologic compensatory mechanism.

Symptomatic and persistent barotitis is the result of the eustachian tube’s being persistently closed, or even locked, after descent (see Chapter 3). Tympanic membrane movement is retracted, and high negative middle-ear pressure is present. The middle-ear mucous membrane can actually tear, resulting in bleeding in the middle ear (hemotympanum) secondary to the alterations in middle-ear gas pressure and the pressure in the airplane cabin. A middle-ear effusion can be present and is secondary to the negative middle-ear pressure. If the child has a preexisting middle-ear effusion, there is little or no movement of the tympanic membrane and thus no otalgia on descent. If the child has had recurrent otitis media and has eustachian tube dysfunction,
However, but no effusion, otalgia and barotitis are possible; symptoms are similar to those described before when eustachian tube obstruction is present. Indeed, Weiss and Frost evaluated 14 children, ranging from 3 to 11 years of age, who had middle-ear effusion in 1 or both ears before an air flight. None of the children experienced difficulty in the ears with effusion, but 2 of the children had symptoms attributable to barotitis in a contralateral effusion-free ear.

We recommend that children who have middle-ear effusion present in both ears fly in commercial aircraft without any preventive medication. If the child has had recurrent otitis media, however, or signs and symptoms of eustachian tube dysfunction, and there is no middle-ear effusion in either ear, prevention is advisable. We recommend an oral decongestant, such as pseudoephedrine hydrochloride, before the flight and a topical nasal decongestant, such as oxymetazoline, immediately before descent; administer 2 sprays in each nostril and then repeat with 2 more sprays in about 5 minutes. Most patients have little or no difficulty with this method of prevention.

Scuba diving is an uncommon recreational activity in young children but a common one in older children and adolescents. The pathophysiologic process during descent and ascent is similar to that described before during airplane flying, and the methods of prevention and treatment are also similar. However, we do not recommend scuba diving for children who have recurrent or chronic otitis media or eustachian tube obstruction because an adverse outcome may occur, and it may even be life-threatening if severe vertigo develops.

Scuba diving is not a physiologic activity that evolved in humans, and when this activity is associated with possible severe ear complications, it should be avoided. However, airplane flying is part of our current culture and therefore should not be withheld from children who have middle-ear problems. Fortunately, infants and children who have tympanostomy tubes in place have no difficulty during flying because their middle-ear pressure is always equilibrated with the ambient pressure.

**BACTERIAL PATHOGENS AND ANTIMICROBIAL SUSCEPTIBILITY**

Decisions about optimal chemotherapy for otitis media are based on information about (1) the pathogens isolated from middle-ear fluids; (2) the in vitro activity of antimicrobial agents against these pathogens; (3) the clinical pharmacologic action of antimicrobial agents of value, including concentrations of drug achieved in middle-ear fluid; and (4) the results of clinical and microbiologic studies. The effective antimicrobial agent sterilizes the middle-ear infection, produces resolution of acute signs and symptoms within 72 hours, and prevents supplicative complications.

Development of resistance to antimicrobial agents has been a constant feature of antimicrobial drug therapy since the sulfonamides were introduced in the mid-1930s. Identification of β-lactamase–producing strains of *H. influenzae* and *M. catarrhalis* in the 1970s and the increased incidence of multidrug-resistant pneumococci in the 1980s are important factors in deciding whether to treat AOM and, if the decision is made to treat, which antimicrobial agent should be chosen. Clinicians should be aware of the data for drug resistance in their community, the risk features associated with increased resistance, and the clinical implications for use and selection of antimicrobial agents.

The preferred antimicrobial agent for the patient with otitis media must be active against *Streptococcus pneumoniae*, *H. influenzae*, and *M. catarrhalis*, the three most important bacterial pathogens in all age groups. Group A streptococcus and *Staphylococcus aureus* are less frequent causes of AOM. Gram-negative enteric bacilli must be considered when otitis media occurs in the newborn infant and other hosts with immune defects. Anaerobic bacteria appear to have a limited role in chronic otitis media and a minimal role in AOM. The characteristics of
the pathogens responsible for otitis media are reviewed in Chapter 5 “Microbiology”.

**Streptococcus pneumoniae**

Pneumococci historically have been susceptible in vitro to penicillins, cephalosporins, macrolides, and clindamycin. Resistance rates are high to trimethoprim-sulfamethoxazole. Chloramphe- nicol and sulfonamides have moderate activity. Aminoglycosides are relatively ineffective. Clinical and microbiologic resistance of pneumococci to penicillin and other antimicrobial agents was identified in South Africa in the 1970s, and in the early 1990s, pneumococcal strains resistant to penicillin and other antimicrobial agents emerged throughout the world, including the United States.

Antimicrobial susceptibility testing of *Streptococcus pneumoniae* requires adherence to established standards of inoculum size and appropriate growth media. Isolates are tested by broth dilution assays and the E test (AB Biodisk NA, Solna, Sweden) which uses paper strips impregnated with the test antibiotic and placed on the surface of agar plates covered with a lawn of the test organism. Interpretative definitions for breakpoints of susceptible or resistant are recommended by the National Committee for Clinical Laboratory Standards (NCCLS).

Pneumococci are resistant to β-lactam antibiotics due to altered penicillin-binding proteins resulting in reduced affinity for the antibiotics. Penicillin resistance correlates directly with resistance to broad-spectrum cephalosporins. Macrolide resistance is expressed as two phenotypes: the more common T phenotype is an efflux pump associated with the MEFE gene and does not affect clindamycin susceptibility; the MLS phenotype is a result of the ERMAM gene encoding erythromycin-ribosomal methylase, which blocks the binding of macrolide and clindamycin antibiotics.

Pneumococcal strains are designated penicillin-susceptible and -non-susceptible. The non-susceptible strains are termed intermediate or resistant according to the minimal inhibitory concentration (MIC). Increments of drug needed to inhibit the organism are exhibited by non-susceptible strains:

- Penicillin-susceptible strains are inhibited by MICs of less than 0.12 μg/mL.
- Penicillin-non-susceptible strains include
  - Intermediate strains inhibited by 0.12 to 1 μg/mL.
  - Resistant strains require 2 μg/mL or more for inhibition.

The clinical relevance of these numbers lies in comparing the MIC of the strain of bacteria with levels of antibiotic achievable at the site of infection. Most infections caused by intermediate strains may be treated adequately with usual doses of penicillins, and even some resistant strains may be inhibited. For example, the usual dosage schedule of amoxicillin achieves peak concentrations of approximately 2 μg/mL in middle-ear fluid (Table 2); most of the intermediate strains and some resistant strains are likely to be inhibited by concentrations of amoxicillin in middle-ear fluids. Doubling the dose of amoxicillin achieves approximately twice these concentrations at the site of infection with resultant inhibition of an increased number of resistant strains of pneumococci.

Emergence of penicillin resistance in a community usually begins with identification of intermediate strains, which increase and are followed by fully resistant strains. Surveys of susceptibilities of *Streptococcus pneumoniae* in the United States throughout the 1990s were uniform in indicating increasing rates of resistance each year. US survey data for 1997 were reported by Jacobs and colleagues; non-susceptible strains varied by region between 35.8% and 62.4%, whereas 17.9% of all strains showed intermediate resistance, and 32.5% were highly resistant. Doern and colleagues reported similar findings based on clinical isolates collected from 33 medical centers nationwide during the winter of 1999-2000: 34% of the isolates were penicillin-non-susceptible (MIC = 0.12 μg/mL) and 21.5%
were high-level resistant (MIC = 2 μg/mL). Data from a population-based surveillance developed by the CDC in conjunction with several state health departments indicate that the incidence of drug-resistant pneumococci has stabilized or decreased in recent years, including 2003 and 2004. Current and past data for drug resistance for various bacterial pathogens, including pneumococcus, are available at the CDC web site (www.cdc.gov/ncidod/dbmd/abcs). The reduction in single and multi-drug resistance is likely due to one or both of the following factors: the reduction in pneumococcal diseases resulting from the universal usage in infants in the United States of the conjugate pneumococcal vaccine; and the education of physicians and parents to restrict use of antimicrobial agents for appropriate uses.

Pneumococcal resistance is universal and found in varying incidence in all countries. Rates of penicillin resistance of pneumococci have been increasing during the 20-year period beginning in 1980; Spain, France, Hungary, and Israel have reported rates in excess of 40%; Korea and the Far East have the highest reported resistance to date—exceeding 80%; The Netherlands, in contrast, has a rate of less than 1%. In Spain, the incidence of penicillin-resistant pneumococci rose from 6% in 1979 to 44% in 1989; approximately one half of the non-susceptible strains had MICs greater than 2 μg/mL.

The increase in resistance to penicillin has been accompanied by increased resistance to other antimicrobial agents. The proportion of resistant strains is usually lower for oral cephalosporins compared with penicillin, and resistance to macrolides (erythromycin, clarithromycin, and azithromycin) and to clindamycin is lower than to the β-lactam drugs. Few strains of Streptococcus pneumoniae are resistant to the newer fluoroquinolones; Doern and colleagues

| Table 2. CONCENTRATION OF ANTIMICROBIAL AGENTS IN SERUM AND MIDDLE-EAR FLUIDS |
|-----------------|----------|--------|--------|--------|
| Agent           | Dosage (mg/kg) | S      | MEF    | MEF/S  | Investigator |
| Penicillin V    | 13 PO      | 8.1    | 1.8    | 0.22   | Kamme et al |
|                 | 26 PO      | 15.5   | 6.3    | 0.41   |             |
| Ampicillin      | 10 PO      | 4.3    | 1.2    | 0.28   | Lahikainen et al |
| Amoxicillin     | 10 PO      | 4.8    | 2.2    | 0.46   | Howard et al |
|                 | 13.3 PO    | 11.2   | 2.8    | 0.25   | Krause et al |
|                 | 15 PO      | 13.6   | 5.6    | 0.41   | Klimmek et al |
| Bacampicillin   | 800 total IM* | 7.7  | 2.4    | 0.31   | Vistanen and Lahikainen |
| Cefaclor        | 10 PO      | 7.0    | 1.3    | 0.19   | Ginsburg et al |
|                 | 13 PO      | 3.6    | 0.96   | 0.30   | Barr et al |
| Cefuroxime      | 250 total PO | 5.4  | 1.2    | 0.22   | Haddad et al |
| Cefixime        | 8 PO       | 2.5    | 1.5    | 0.52   | Hamson et al |
| Cefpodoxime     | 5 PO       | NA     | 0.2    | NA     | Nelson et al |
| Cefprozil       | 15 PO      | 5.5    | 2.0    | 0.36   | Kafetzis et al |
| Cefditobuten    | 9 PO       | 5.9    | 4.03   | 0.80   | Barr et al |
| Loracarbef      | 7.5 PO     | 4.2    | 2.0    | 0.48   | Kusmiesz et al |
| 15 PO           | 9.3       | 3.9    | 0.42   |        |             |
| Cefotaxime      | 25 IM/IV   | 5.8    | 2.1    | 0.36   | Danon |
| Ceftriaxone     | 50 IM      | NA     | 35     | NA     | Gudnasson et al |
| Erythromycin    | Estolate   | 15 PO  | 3.6    | 1.7    | 0.49   | Ginsburg et al |
|                 | Ethylsuccinate | 15 PO | 1.2   | 0.5    | 0.42   |             |
| Clarithromycin  | 7.5 PO     | 1.7    | 2.5    | 1.47   | Guay and Craft |
| 14-Hydroxymetabolite | 0.8 | 1.3 | 1.62 |
| Azithromycin    | 10 PO      | 0.07   | 2.32   | 3.14   | Dagan et al |
| Sulfonamide (trisulfapyrimidine) | 30 PO | 13.4 | 8.3 | 0.62 | Howard et al |

*Single dose administered to adults. IM = intramuscular; IV = intravenous; MEF = middle ear fluids; NA = not available; PO = orally; S = serum.
reported an incidence of 1% or less among isolates of *Streptococcus pneumoniae* collected in the winter of 1999–2000. High rates of resistant pneumococci to trimethoprim-sulfamethoxazole have been reported throughout the world. This antimicrobial agent is inexpensive and is the most frequently used drug for respiratory infections in developing countries. A study of pneumococci obtained from the lower respiratory tract of Pakistani children during the winters of 1986 to 1989 identified 31% resistant to trimethoprim-sulfamethoxazole. In two surveys of US medical centers, 11.9% and 30.3% of pneumococcal strains were resistant to trimethoprim-sulfamethoxazole. No vancomycin-resistant pneumococci have been identified.

Risk features for multidrug-resistant pneumococci include use of an antimicrobial agent in the preceding 28 days, hospitalization, and out-of-home day care. Isolates from mucosal surfaces such as the throat and nasopharynx yield higher rates of resistance than do isolates from body fluids such as blood and cerebrospinal fluid. Isolates from children have higher rates of resistance than do isolates from adults, probably because prior antibiotic use is more likely in children. In the United States, resistance rates vary by region and were highest from patients in the southeastern states.

No clinical features distinguish infection with resistant organisms from infection by susceptible organisms, and there does not appear to be increased virulence of the disease caused by resistant strains. The proportion of cases of pneumococcal otitis media that fail because of resistance to penicillin or amoxicillin is uncertain, but well-documented cases of clinical and microbiologic failure have occurred in meningitis due to moderately resistant strains. Pneumococcal meningitis due to strains resistant to ceftriaxone or cefotaxime has also been reported. At present, susceptibility testing should be considered for strains of *Streptococcus pneumoniae* causing otitis media that do not respond to an appropriate course of a usually effective antimicrobial agent. No change in use of amoxicillin as the drug of choice for AOM is currently necessary, but physicians need to be alert for unexpected clinical or microbiologic failures that may herald an increasing problem with pneumococcal resistance.

**Haemophilus influenzae**

Strains of *H. influenzae* responsible for otitis media may be subdivided on the basis of production of β-lactamase and susceptibility to amoxicillin. Almost all amoxicillin-resistant strains of *H. influenzae* produce the enzyme β-lactamase, which breaks open the β-lactam ring, rendering the drug ineffective. Amoxicillin- or ampicillin-sensitive strains of *H. influenzae* are only slightly less susceptible to penicillin G than they are to ampicillin, but they are much less susceptible to penicillin V and the penicillinase-resistant penicillins. Addition of a β-lactamase inhibitor, clavulanic acid, to oral amoxicillin provides activity against *H. influenzae* without regard to production of the enzyme. Oral and parenteral second- and third-generation cephalosporins are active against *H. influenzae* and are effective against ampicillin-sensitive and ampicillin-resistant strains. Erythromycin and the new macrolides (azithromycin and clarithromycin) have decreased activity against *H. influenzae*.

Amoxicillin-resistant strains of both nontypeable and type B *H. influenzae* have been reported throughout the United States. The resistance appears to be an abrupt change with few resistant strains detected before 1972. Because the resistance to ampicillin is based on production of a β-lactamase that hydrolyzes the penicillin nucleus, all penicillins that are susceptible to β-lactamase, including penicillin G, penicillin V, ampicillin, amoxicillin, carbenicillin, ticarcillin, and piperacillin, are likely to be ineffective against these strains. The incidence of β-lactamase–producing strains varied between 20% and 45% in Pittsburgh between 1981 and 1989, and was 41.6% and 33.5% in two 1997 US surveys. Strains of *H. influenzae* that were β-lactamase–negative but resistant to amoxicillin and
amoxicillin-clavulanate have also been identified. A multicenter survey of antibiotic resistance among clinical isolates of *H. influenzae* in the United States in 1994 and 1995 identified 38.9% resistant to amoxicillin, including 4.5% of strains resistant to amoxicillin-clavulanate (presumably resistant on the basis of a mechanism other than production of β-lactamase).65 Thornsberry and colleagues found only 1 of 672 strains of *H. influenzae* that was β-lactamase-negative but resistant to amoxicillin-clavulanate.57

Drug-resistant strains of *H. Influenzae* unassociated with β-lactamase production have also been documented for other antimicrobial agents commonly used to treat otitis media. Some cephalosporins (cefaclor, loracarbef, and cefprozil) have rates of resistant *H. influenzae* of 5 to 12% overall and 13 to 32% for β-lactamase-producing strains; resistance has been less than 1% for others (cefixime, cefituben, and cefuroxime). Trimethoprim-sulfamethoxazole–resistant strains were identified in Boston (12.3%) from 1987 to 198966 and in the US multihospital survey (10.2%) from 1996 to 1997.57 Although few strains of *H. influenzae* are resistant in vitro to the new macrolides (azithromycin and clarithromycin),57 clinical studies indicate frequent microbiologic failures on the basis of middle-ear aspirates of patients with AOM.67 No fluoroquinolone-resistant strains were identified among 1,029 strains tested in the multihospital survey.57

**Moraxella catarrhalis**

Most current strains of *M. catarrhalis* produce β-lactamase and are resistant to ampicillin, amoxicillin, and other β-lactamase–susceptible penicillins but are susceptible to the combination of amoxicillin-clavulanate, cephalosporins, macrolides, chloramphenicol, and trimethoprim-sulfamethoxazole.68 A survey of 444 strains of *M. catarrhalis* obtained from 51 medical centers in the United States found that 93% were β-lactamase producers.57 As is the case with *H. influenzae*, the isolation of β-lactamase–producing strains of *M. catarrhalis* was noted first in 1980, Kamme reported in 1970 that all 108 strains of *M. catarrhalis* isolated in the Department of Clinical Bacteriology in Lund, Sweden, were highly susceptible to penicillin G and ampicillin. In 1980, 15% of strains of *M. catarrhalis* isolated in the same laboratory produced β-lactamase.69 A similar experience was described in nearby Finland; the proportion of strains of *M. catarrhalis*–producing β-lactamase increased to 60% in 1983 from 0% in 1978 and to 80% in 1990.70

Shurin and coworkers and Kovatch and associates, from Cleveland and Pittsburgh, respectively, reported that more than 20% of isolates from acute middle-ear effusions had *M. catarrhalis* and that three fourths of those isolates produced β-lactamase.71,72 The temporal change in the incidence of β-lactamase–producing strains of *M. catarrhalis* in Pittsburgh was documented by Bluestone and coworkers.64

*M. catarrhalis* resistance to selected cephalosporins is increased for β-lactamase–producing strains. Almost all *M. catarrhalis* are susceptible in vitro to the macrolides, quinolones, and trimethoprim-sulfamethoxazole.57

**Groups A and B Streptococci**

No known strains of groups A and B streptococci are resistant to the penicillins. These streptococci are markedly sensitive to the penicillins, cephalosporins, chloramphenicol, and clindamycin. Resistance to erythromycin and the newer macrolides has increased in past years but remains low in the United States at 2 to 4%.73 They are relatively resistant to aminoglycosides and to sulfonamides. Trimethoprim-sulfamethoxazole in combination is more active than either component alone, but clinical efficacy is uncertain against group A streptococci. The current increase in invasive and toxin-producing strains of group A streptococcus causing toxic shock syndrome and tissue necrosis is not associated with a change in the antimicrobial susceptibility pattern of the streptococci. Recent evidence suggests that clindamycin should be added to penicillin for patients with toxin-producing group A streptococcal infections.
because clindamycin (as well as macrolides) is more effective than β-lactam antibiotics in inhibiting toxin production. 74

**Staphylococcus aureus and Staphylococcus epidermidis**

Most strains of hospital-acquired *Staphylococcus aureus* produce β-lactamase and are resistant to penicillin G and amoxicillin; the number of strains of resistant staphylococci in patients who have community-acquired disease is lower but significant. The penicillinase-resistant penicillins are the drugs of choice for initial management of the patient with suspected or documented staphylococcal otitis media. Most cephalosporins, macrolides, and clindamycin are also effective against penicillinase-producing strains.

Disease due to methicillin-resistant *Staphylococcus aureus* (MRSA) was reported shortly after the drug was introduced. The strains are usually resistant to penicillinase-resistant penicillins and to most cephalosporins but, with rare exception, vancomycin is effective. Concern has been raised for MRSA otitis media.75 In recent years, there has been increased recognition of community-acquired MRSA (CA-MRSA) strains in children without risk factors such as recent hospitalization or antibiotic use. The mechanism of action of CA-MRSA is based on the MECA gene which confers resistance by encoding a penicillin-binding protein with decreased affinity for β-lactam antibiotics. Whereas the β-lactam antibiotics act by inhibiting bacterial cell wall synthesis, the penicillin-binding protein of CA-MRSA permits cell wall synthesis despite the presence of β-lactam antibiotics. Hospital-acquired MRSA is usually multi-drug resistant but usually susceptible to vancomycin or linezolid. CA-MRSA strains are resistant to β-lactam drugs and macrolides but usually susceptible to clindamycin, trimethoprim-sulfamethoxazole and some tetracyclines (minocycline or doxycycline). Patients with serious CA-MRSA infections should be treated with intravenous vancomycin or linezolid.

For less serious CA-MRSA infections, including AOM or otitis media in children with tympanostomy tubes, clindamycin, trimethoprim-sulfamethoxazole, linezolid, or tetracycline (for children 8 years of age and older) are the preferred drugs.

Most strains of *Staphylococcus epidermidis* produce β-lactamase and are also more resistant than *Staphylococcus aureus* to the penicillinase-resistant penicillins, cephalosporins, macrolides, and clindamycin. Vancomycin is usually effective against methicillin-resistant *Staphylococcus epidermidis*.

**Gram-Negative Enteric Bacilli**

The choice of antibiotics for infections due to gram-negative bacteria depends on the particular pattern of susceptibility in the hospital or community. These patterns vary in different hospitals or communities and, from time to time, within the same institution. In most areas, the most effective agents for Proteus species (indole positive and negative), Klebsiella and Enterobacter species, and *Pseudomonas aeruginosa* are the aminoglycosides tobramycin, gentamicin and amikacin. Some oral cephalosporins (ie, cefixime and ceftibuten) and some parenteral cephalosporins (cefotixin, moxalactam, cefoperazone, cefotaxime, cefixime, ceftriaxone, and ceftriaxone) have activity against most gram-negative bacilli; ceftazidime has significant activity against *P. aeruginosa*. Because the susceptibility of gram-negative enteric bacilli is variable and unpredictable, isolates should be tested to determine the optimal choice of antimicrobial agents.

**Anaerobic Bacteria**

Most anaerobic bacteria responsible for infection and disease in the upper respiratory tract, including anaerobic cocci, gram-positive non-sporulating anaerobic bacilli, and anaerobic gram-negative bacilli, are susceptible to penicillin G.76 Some strains of anaerobic gram-negative bacilli, such as *Bacteroides melaninogenicus*, are resistant to penicillin G. *Bacteroides fragilis* is an
uncommon pathogen in the respiratory tract; most strains are resistant to penicillin G but susceptible to clindamycin, chloramphenicol, and metronidazole. The role of anaerobic bacteria in otitis media and infections of the head and neck was reviewed at a symposium held in Pittsburgh in 1989.77

**Chlamydia trachomatis and C. pneumoniae**

*C. trachomatis* and *C. pneumoniae* are susceptible to macrolides, sulfonamides, tetracyclines, and chloramphenicol. *C. trachomatis* may be associated with infection of the respiratory tract, including otitis media, in young infants; a macrolide or sulfonamide has been recommended for documented or suspected infection. Although controlled trials of efficacy of these drugs in young infants with respiratory infection have not been performed, results of uncontrolled studies suggest that either drug shortens the course of the illness. No data are available about the efficacy of any antimicrobial drugs for otitis media due to Chlamydia species.

**Mycoplasma pneumoniae**

Otitis media may accompany respiratory infection due to *M. pneumoniae*. The organisms are susceptible to macrolides and tetracyclines. Controlled trials indicate that the duration of signs of lower respiratory tract infection, such as cough, rales, and fever, is shorter in patients receiving one of these drugs, but there are no data about the efficacy of antibiotics for otitis media due to *M. pneumoniae*.

**CLINICAL PHARMACOLOGY OF ANTIMICROBIAL DRUGS OF VALUE IN OTITIS MEDIA**

The clinical pharmacologic effects of orally administered antimicrobial agents of value in otitis media are discussed in this section. Parenterally administered drugs of value for suppurative complications of otitis media are also discussed in this review. Although 19 antimicrobial agents (including two ototopical drugs) are approved for therapy of AOM, no new systemic antimicrobial drugs have been introduced for AOM since 1996.

**Penicillins**

**Penicillin G and Penicillin V**

Oral preparations of buffered penicillin G and phenoxymethyl penicillin (penicillin V) are absorbed well from the gastrointestinal tract; the peak level of serum activity of penicillin V is approximately 40% (4 to 8 µg/mL) and that of buffered penicillin G is approximately 20% (1 to 4 µg/mL) of the level achieved by the same dose of aqueous penicillin G administered intramuscularly (Table 3). Oral penicillins are satisfactory for treating mild to moderately severe infections due to susceptible organisms. Group A streptococci remain uniformly susceptible to all penicillins and cephalosporins. Penicillin V and penicillin G are of approximately equivalent efficacy in vitro against gram-positive cocci. Penicillin G and V are inactivated by the β-lactamase of *H. influenzae*; penicillin V is less effective than penicillin G against non-β-lactamase–producing *H. influenzae*. The efficacy of penicillin G against *H. influenzae* in vitro is two times less than that of amoxicillin.

**Parenteral Preparations of Penicillin G**

Parenteral penicillin G preparations include the potassium or sodium salts of aqueous penicillin and procaine and benzathine penicillin G, which modify absorption and thereby produce different patterns of peak and duration of antibacterial activity in serum and tissues. Aqueous penicillin G produces high peak levels of antibacterial activity in serum within 30 minutes of intramuscular administration but is rapidly excreted; thus, the concentration in serum is low within 2 to 4 hours after administration. Procaine penicillin G given intramuscularly produces lower levels of serum antibacterial activity (approximately 10% to 30% of the peak level) than the same dose of the aqueous form, but activity persists in serum for as long as 12 hours. Benzathine penicillin G
given intramuscularly is a repository preparation providing low levels of serum activity (approximately 1% to 2% of the peak level achieved by the same dose of the aqueous form). After administration of this drug, low concentrations of penicillin activity are measurable in serum for 14 days or more, and measurable in urine for several months. Significant pain at the site of injection is the major deterrent to widespread use of this unique antibiotic. Although little used today, benzathine penicillin G was effective for treating children with otitis media due to sensitive *Streptococcus pneumoniae*, but it would probably fail if pneumococcal strains are non-susceptible or if disease is caused by *H. influenzae*. Today, there is little use of any of the parenteral penicillins in management of AOM unless the circumstances are unique (eg, a susceptible organism in a patient who requires parenteral administration).

### Table 3. THE PENICILLINS 2006

<table>
<thead>
<tr>
<th>Generic Name</th>
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<th>Route</th>
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</thead>
<tbody>
<tr>
<td>Penicillin G</td>
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<td>PO</td>
</tr>
<tr>
<td>Aqueous</td>
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</tr>
<tr>
<td>Procaine</td>
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<td>IM</td>
</tr>
<tr>
<td>Benzathine</td>
<td>Bicillin, Permapen</td>
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</tr>
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<td>Penicillin V</td>
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**Penicillinase-resistant**

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</tr>
<tr>
<td>Oxacillin</td>
<td>Prostaphlin, Bactocil</td>
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<tr>
<td>Nafcillin</td>
<td>Unipen, Nafcil</td>
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<td>Cloxacillin</td>
<td>Tegopen, Cloxapen</td>
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<tr>
<td>Dicloxacillin</td>
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**Broad Spectrum**

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</thead>
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<td>Unasyn</td>
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</tr>
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<td>Amoxil, Wymox</td>
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<td>Augmentin</td>
<td>PO</td>
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<tr>
<td>Bacampicillin</td>
<td>Spectrobid</td>
<td>PO</td>
</tr>
<tr>
<td>Cycloxacillin</td>
<td>Cyclapen</td>
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**Extended Spectrum**

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</thead>
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<tr>
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<td>Ticarcillin</td>
<td>Ticar</td>
<td>IM, IV</td>
</tr>
<tr>
<td>Ticarcillin-clavulanate</td>
<td>Timentin</td>
<td>IM, IV</td>
</tr>
<tr>
<td>Piperacillin*</td>
<td>Pipracil</td>
<td>IM, IV</td>
</tr>
<tr>
<td>Piperacillin-tazobactam*</td>
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<td>Carbapenem</td>
<td>Primaxin</td>
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</tr>
<tr>
<td>Meropenem</td>
<td>Merrem</td>
<td>IM, IV</td>
</tr>
</tbody>
</table>

*Not available for infants and children younger than 12 years.

IM = intramuscular; IV = intravenous; PO = orally.

**Penicillinase-Resistant Penicillins**

Methicillin was the first penicillinase-resistant penicillin to be introduced and is available in parenteral form only. Oxacillin and nafcillin are available in both parenteral and oral preparations and have greater in vitro activity against gram-positive cocci. Cloxacillin and dicloxacillin are available in oral forms only and are absorbed more efficiently from the gastrointestinal tract than are the other oral drugs. Differences among these five penicillins include degree of binding to proteins, degree of degradation by β-lactamases, and in vitro level of susceptibility; however, all are effective in treating staphylococcal disease, and clinical studies have shown them to be comparable when they are used according to appropriate dosage schedules. In addition, all but methicillin have proven to be effective against infections caused by *Streptococcus pneumoniae* and group A streptococci. The penicillinase-
resistant penicillins are of value when otitis media or a complication is thought to be due to Staphylococcus aureus. The increasing incidence of methicillin-resistant Staphylococcus aureus requires a new strategy for treatment of AOM due to these organisms (see “Staphylococcus aureus and Staphylococcus epidermidis”).

**Broad-Spectrum Penicillins**

**Ampicillin and Amoxicillin.** Ampicillin and amoxicillin are effective in vitro against a wide spectrum of bacteria, including gram-positive cocci (Streptococcus pneumoniae, group A streptococci, non-β-lactamase–producing strains of Staphylococcus aureus, and oropharyngeal strains of anaerobic bacteria), gram-negative cocci (M. catarrhalis), gram-negative coccobacilli (non-penicillinase–producing strains of H. influenzae), and some gram-negative enteric bacilli (Escherichia coli and Proteus mirabilis). Both drugs are susceptible to β-lactamase–producing organisms. The β-lactam ring is cleaved, rendering the drugs inactive. Both drugs are available for oral administration; ampicillin alone is available in a parenteral form. Amoxicillin provides levels of activity in serum that are higher and more prolonged than those achieved with equivalent doses of ampicillin. An additional advantage of amoxicillin is that absorption is not altered when the antibiotic is administered with food, whereas absorption of ampicillin is decreased significantly when it is given with food. Because of its long record of safety and efficacy, amoxicillin is now the preferred oral drug for treatment of AOM, but because of concern for non-susceptible strains of Streptococcus pneumoniae, an increased dosage has been suggested (ie, 70 to 90 mg/kg/d in 2 or 3 doses).¹

**Amoxicillin-Clavulanate.** Amoxicillin combined with clavulanate potassium was introduced in 1984 for oral administration. Clavulanate potassium is the salt of clavulanic acid, a β-lactam antibiotic, with poor in vitro activity against pathogenic bacteria but potent activity as an inhibitor of β-lactamase enzymes. The addition of clavulanic acid restores the original spectrum of amoxicillin, preventing its destruction by the β-lactamases of Staphylococcus aureus (but not methicillin-resistant strains), H. influenzae, M. catarrhalis, Neisseria gonorrhoeae, E. coli, Proteus species, and anaerobic bacteria (including B. fragilis). The pharmacokinetics of amoxicillin and clavulanic acid are similar; both are rapidly absorbed and are not affected when taken with meals. The drug is now available for twice-a-day dosing. Diarrhea, abdominal pain, and nausea are more frequent with the combination than with amoxicillin alone. Loose stools and diarrhea may be explained in part by clavulanate-related increased small bowel peristalsis. Because bowel peristalsis is inhibited after ingestion of food, administration of amoxicillin-clavulanate at mealtimes reduces the rate of diarrhea.⁸⁰

Amoxicillin-clavulanate is of value for children who have severe signs of disease at onset or who have failed initial therapy with amoxicillin. The higher dosage of the amoxicillin component should be used (80 to 90 mg/kg/d in 2 doses) to include activity against non-susceptible Streptococcus pneumoniae as well as β-lactamase–producing M. catarrhalis and H. influenzae. A new high-dose preparation of amoxicillin-clavulanate was introduced in 2002 to provide the convenience of the higher dose without an increased dose of clavulanate. The new preparation contains 600 mg of amoxicillin and 42.9 mg of clavulanate per 5 mL (a 14:1 ratio).

**Ampicillin-Sulbactam.** Sulbactam is a semisynthetic β-lactam antibiotic that is an irreversible inhibitor of various P-lactamases. When combined with ampicillin, sulbactam efficiently protects ampicillin from degradation by β-lactamases. The inherent activity of ampicillin against β-lactamase–producing strains of H. influenzae, Staphylococcus aureus, and N. gonorrhoeae is expressed without inactivation of the antibiotic by the enzyme. Ampicillin-sulbactam at a 2:1 ratio is approved by the FDA for parenteral use; there is no oral preparation. The antimicrobial activity, pharmacokinetics, and clinical efficacy and safety were discussed in the...
Carbenicillin, Ticarcillin and Piperacillin. Carbenicillin and ticarcillin have a broader spectrum of activity, including *P. aeruginosa*, anaerobic bacteria, and gram-negative enteric bacilli including *Enterobacter* and *Proteus* species. High concentrations are required to inhibit the gram-negative organisms, but this disadvantage is overcome in part by the low toxicity of the drugs, even when they are given in large intravenous doses. Combination of carbenicillin or ticarcillin with an aminoglycoside such as gentamicin or tobramycin produces synergistic activity against many gram-negative enteric bacilli, and such a combination has been used effectively in initial therapy for sepsis of unknown origin or suspected of being due to gram-negative enteric bacilli in patients with malignant disease or immunosuppressive disease. An oral form of carbenicillin produces low concentrations of drug in serum and should be restricted to therapy for urinary tract infections.

Ticarcillin is similar to carbenicillin, but it is more active against some strains of *P. aeruginosa* and less active against gram-positive cocci. Because of the increased activity, smaller doses of ticarcillin than of carbenicillin may be used to treat disease due to gram-negative organisms. Ticarcillin combined with potassium clavulanate extends the antibacterial activity of ticarcillin to include *β*-lactamase–producing strains of *Staphylococcus aureus*, *Klebsiella pneumoniae*, and *B. fragilis*.

Although ticarcillin and carbenicillin have no dose-related toxicity, both drugs are disodium salts. The large amounts in which they are given include significant quantities of sodium: 1 g of carbenicillin contains 4.7 mEq, or 108 mg, of sodium per gram of drug; 1 g of ticarcillin contains 5.2 mEq, or 120 mg, of sodium per gram of drug. The amount of sodium administered may be of concern in treatment of certain patients with renal or cardiac disease.

Piperacillin has greater activity in vitro against some gram-negative bacilli, including *P. aeruginosa*, and anaerobic bacteria than carbenicillin and ticarcillin. Since piperacillin is inactivated by *β*-lactamases, it has been combined with a *β*-lactamase inhibitor, tazobactam, to provide activity against *β*-lactamase–producing staphylococci, *Enterobacteriaceae*, anaerobes, *H. influenzae*, *M. catarrhalis* and *P. aeruginosa*.

For otitis media, the primary uses of carbenicillin, ticarcillin, ticarcillin-clavulanate, piperacillin and piperacillin-tazobactam are in cases of chronic suppurative otitis media with perforation and discharge due to *P. aeruginosa* or Proteus species that are unresponsive to other forms of medical treatment, such as ototopical drops, and for which a parenteral preparation is desired.

Imipenem and Meropenem. Imipenem was introduced in 1985 as the first carbapenem antibiotic. Carbapenems have the same ring structure as the penicillins with substitution of carbon for sulfur in the five-member ring. Imipenem has the broadest antimicrobial spectrum available among *β*-lactam antibiotics, including gram-positive cocci, gram-negative cocci, gram-negative bacilli, and anaerobic bacteria and including *β*-lactamase–producing organisms. It is used as single-drug therapy for the immunocompromised patient with suspected sepsis, as an alternative to combination therapy for serious intra-abdominal infections, and as therapy for serious hospital-acquired infections but is not approved for use in children younger than 12 years of age.

Meropenem is a carbapenem antibiotic that was approved in 1996 for intravenous therapy that has a spectrum of activity similar to that of imipenem but, in contrast with imipenem, meropenem is approved for children as young as 3 months of age. Meropenem is effective for bacterial meningitis, but the data are insufficient to compare its efficacy with that of ceftriaxone or cefotaxime for infections caused by penicillin-resistant pneumococci. The broad...
spectrum of activity suggests a possible role in treatment of complicated infections of the head and neck.

**Toxicity and Sensitization**
The penicillins have minimal dose-related toxicity but may produce allergic reactions. Because most allergic reactions are believed to be due to a metabolic breakdown product of the penicillin nucleus, allergy to any one penicillin implies allergy to all.

Seizures may occur under circumstances that result in extraordinarily high concentrations of penicillin in nervous tissues: rapid intravenous infusion of single large doses, large dosage schedules for prolonged periods in patients with impaired renal function, high concentrations given by the intrathecal route, or direct application of penicillin to brain tissue (as might occur inadvertently during a neurosurgical procedure).

Nephritis has followed administration of some penicillins, most frequently after use of methicillin. The mechanism of the nephrotoxicity is uncertain, but data suggest that the renal injury is probably an immunologic reaction and not a direct toxic effect.

Thrombocytopenia with purpura due to drug-induced platelet aggregation has been noted as a rare event after use of carbenicillin and penicillin G. Penicillin-induced hemolytic anemia is associated with high and sustained levels of penicillin in the blood. Circulating red blood cells are coated with a penicillin hapten, the patient makes antibody to the penicillin antigen, the antibody binds to the altered red cell surface, and the cell undergoes lysis or sequestration.

Other uncommon adverse events include neutropenia, which may occur after use of any penicillin (white blood cell counts return to normal after the drug is discontinued); platelet dysfunction after use of carbenicillin and ticarcillin; and hepatic dysfunction reflected in elevated serum aspartate transaminase, which has been identified after use of oxacillin, nafcillin, and carbenicillin.

If toxicity is not a significant concern with the penicillins, sensitization is a most important factor.

Four types of reactions may occur after administration of a penicillin (or any drug or antigen):

1. Immediate or anaphylactic reactions occur within 30 minutes after administration and are life-threatening events. The immediate reactions are immunoglobulin E (IgE)-mediated, and the presence of IgE antibodies to penicillins and cephalosporins predicts potential subsequent immediate reactions. Clinical signs include hypotension or shock, urticaria, laryngeal edema, and bronchospasm. Acute anaphylaxis is rare after administration of penicillin (approximately 1 case per 20,000 courses of treatment in adults), but a significant number of fatalities occur each year because of the extensive use of these drugs. Children are believed to have fewer systemic reactions than adults, presumably because of less previous exposure to penicillin antigens. Oral preparations are less likely than parenteral forms to result in an immediate reaction, perhaps because antigens are altered in the gastrointestinal tract or because of slower absorption.

2. Accelerated reactions occur 1 to 72 hours after administration and are also IgE-mediated. The signs are similar to those of the immediate reaction but occur in a less severe form.

3. Late allergic reactions usually occur after 3 days and are mediated by IgG and complement. The major sign is rash. This is the most perplexing reaction to penicillin because it is nonspecific, and the rash may be caused by other drugs given at the same time or may be a sign of the infectious, usually viral, disease. Rash is associated with approximately 4% of courses of penicillins (up to 7% in the case of ampicillin).

4. Immune complex reactions include serum sickness, hemolytic anemia, and drug fever and are mediated by IgG and IgM immune
complexes. Identifying the patient who will have a significant reaction if penicillin is administered is still difficult. Serologic assays to detect antibodies to penicillin have been considered; however, such assays lack specificity.

Because the immediate reaction is largely mediated by immunoglobulin E reagin or skin-sensitizing antibody, the patient who may subsequently respond with a life-threatening reaction could be identified by use of intradermal tests with appropriate antigens. Selection of the antigens to be used for skin testing, however, is an uncertain procedure because many different antigens play roles in the allergic reaction: at least 10 metabolic breakdown products of the penicillin nucleus have been identified; macromolecular impurities are present in solutions of the drug, and high-molecular-weight penicillin polymers can be found in poorly buffered penicillin solutions standing for prolonged periods; side chains of the various penicillins may be responsible for reactions; and finally, bacterial enzymes (amidases) used to prepare semisynthetic penicillins may cause an allergic reaction. Thus, investigators have had difficulty in choosing sensitive and specific antigens to use for skin testing.

The most promising studies of skin test antigens have come from the laboratories of Levine at New York University and of Parker in St. Louis. Levine identified two materials for use in skin testing, benzylpenicilloyl polylysine and “a minor determinant mixture,” a preparation of a dilute solution of aqueous crystalline penicillin G that includes metabolic breakdown products. In contrast, Parker used four skin test antigens associated with penicillin and its products. A positive result is indicated by a wheal and flare reaction in 10 to 15 minutes and suggests a significant chance of reaction on subsequent administration of a penicillin; a negative result suggests that a significant allergic reaction will not take place. Although much effort has gone into clinical tests of these antigens, their prognostic value in children is still uncertain.

At present, the physician must rely on the patient’s history of an adverse reaction after administration of a penicillin to identify the patient who is likely to be allergic. If the reaction appears to be related to the administration of penicillin, the drug should be avoided for minor infections. If a life-threatening infection should occur and penicillin is clearly the drug of choice, as in the case of overwhelming disease due to *Streptococcus pneumoniae*, the physician may choose to administer the drug under carefully controlled conditions. A small dose may be injected initially in an extremity and followed by increasingly larger doses given every 30 minutes. Epinephrine, a tourniquet, and a tracheotomy set should be available in the event of a severe reaction during the testing period.

**Cephalosporins**

At present, there are 29 parenteral and oral cephalosporins (Table 4); nine oral cephalosporins (cephalexin, cefaclor, cefixime, cefuroxime axetil, cefprozil, cefpodoxime, ceftibuten, cefdinir, and loracarbef) and one parenteral cephalosporin (ceftriaxone) have been evaluated in clinical trials for treatment of AOM. Parenteral ceftazidime with activity against *Staphylococcus aureus* and *P. aeruginosa* is of value for treatment of chronic suppurative otitis media. The cephalosporins have been arbitrarily categorized as first, second, and third generations on the bases of time of introduction and similar in vitro activity. For the purpose of this section, oral and parenteral cephalosporins that maintain gram-positive activity and have increased gram-negative activity are categorized as third generation.

**First-Generation Cephalosporins**

The first-generation cephalosporins are effective against gram-positive cocci, including β-lactamase–producing *Staphylococcus aureus*, and have variable activity against gram-negative enteric bacilli. Six first-generation cephalosporins are currently available for use in infants and children: the parenteral drugs cephalothin, cefa-
zolin, and cephapirin; the oral products cephalexin and cefadroxil; and cephradine, which is available in both oral and parenteral forms. Cefazolin produces higher concentrations in blood than the other parenteral first-generation drugs. The three oral preparations have comparable in vitro activity. Only cephalexin has been approved by the FDA for treatment of AOM, but the drug is little used because of limited activity against *H. influenzae*.

The first-generation cephalosporins are alternatives to penicillin for disease caused by *Staphylococcus aureus*, *Streptococcus pneumoniae*, group A streptococcus, and susceptible gram-negative enteric bacilli that are resistant to other drugs. Activity against *H. influenzae* is limited. First-generation cephalosporins are not the drugs of choice for any pediatric infection but are of value for children with disease caused by susceptible organisms who have an ambiguous history of allergic reaction to a penicillin. Cefadroxil is of value for treatment of streptococcal pharyngitis because it can be administered once a day. Cephalexin may be used for mild to moderately severe staphylococcal infections of the skin and soft tissues. Cefazolin is extensively used for perioperative prophylaxis.

### Second-Generation Cephalosporins

The second-generation cephalosporins consist of six parenteral drugs (cefamandole, cefoxitin, ceforanide, cefonicid, cefotetan, and cefmetazole) and five oral preparations (cefaclor, cefprozil, ceftibuten, cefixime, and loracarbef). Each of the oral preparations has been approved for treatment of AOM with activity against pneumococci, *H. influenzae*, and *M. catarrhalis*, including β-lactamase–producing strains. None of the oral second-generation cephalosporins are considered optimal therapy for AOM. Among the parenteral preparations, cefotetan, ceforanide, cefonicid, and cefmetazole are not approved for use in infants and children.

Cefoxitin has excellent activity against anaerobic organisms, particularly *B. fragilis*, and selective activity against gram-negative enteric bacilli; it has been effective for treatment of intra-abdominal, gynecologic, and respiratory infections caused by mixed bacterial pathogens, including anaerobic bacteria. Cefotetan was introduced in 1986 with an in vitro spectrum of activity and clinical use similar to those of cefoxitin, but it is not approved for use in children.

Cefamandole is active against gram-positive cocci, including *Streptococcus aureus*, and was the first cephalosporin to be effective for infections caused by *H. influenzae* (including β-lactamase–producing strains). Reports of clinical and microbiologic failure in a small number of cases of meningitis caused by *H. influenzae* (presumably due to inadequate concentrations of drug in cerebrospinal fluid) indicate limited use of cefamandole for disease in which sepsis is not a concern.

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**Table 4. THE CEPHALOSPORINS 2006**

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Trade Name</th>
<th>Route</th>
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<tr>
<td>Cephalothin</td>
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<tr>
<td>Cefuroxime axetil</td>
<td>Ceftin</td>
<td>PO</td>
</tr>
<tr>
<td>Cefpodoxime</td>
<td>Vantin</td>
<td>PO</td>
</tr>
<tr>
<td>Cefdinir</td>
<td>Omnicil</td>
<td>PO</td>
</tr>
<tr>
<td>Moxalactam</td>
<td>Moxam</td>
<td>IM, IV</td>
</tr>
<tr>
<td>Cefoperazone*</td>
<td>Cefobid</td>
<td>IM, IV</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>Claforan</td>
<td>IM, IV</td>
</tr>
<tr>
<td>Cefixime</td>
<td>Cefixox</td>
<td>IM, IV</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>Rocephin</td>
<td>IM, IV</td>
</tr>
<tr>
<td>Cefazidime</td>
<td>Fortaz, Tazidime, Tazicef</td>
<td>IM, IV</td>
</tr>
<tr>
<td>Cefepine</td>
<td>Maxipime</td>
<td>IM, IV</td>
</tr>
<tr>
<td>Cefditoren*</td>
<td>Spectracef</td>
<td>PO, IM, IV</td>
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</tbody>
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*Not available for children.

IM = intramuscular; IV = intravenous; PO = orally.
Cefprozil is an oral cephalosporin with in vitro activity against gram-positive cocci, certain Enterobacteriaceae, and gram-negative respiratory pathogens. The drug is well absorbed from the gastrointestinal tract, has a twice-a-day dosing schedule, and has a paucity of side effects or dose-related toxicity. The clinical experience with cefprozil was reviewed at a symposium.91

Cefaclor is an oral preparation that has been effective in clinical trials of otitis media, sinusitis, and mild to moderate pneumonia. Persistence of bacterial pathogens in middle ear fluids after therapy with cefaclor for AOM has raised concern about its continued use.67 An unusual serum sickness reaction has been associated with administration of cefaclor in some patients (see “Toxicity and Sensitization”).

Cefixime is an oral preparation that has been identified as a third-generation drug because of increased activity for gram-negative organisms, but is included here for comparison with the other oral cephalosporins of value for AOM. Decreased activity against some gram-positive strains, including non-susceptible *Streptococcus pneumoniae*, has led to clinical failures in children with pneumococcal otitis media. *Staphylococcus aureus* and coagulase-negative staphylococci are relatively resistant. Administrative advantages have made the drug popular with patients: the strawberry taste is well accepted by young patients; the half-life is sufficiently long to justify use in a once-a-day dosage schedule; and the suspension does not need refrigeration, which is of value when families travel,92–94 but the decreased activity against pneumococci makes cefixime a poor choice for treatment of AOM.

Ceftibuten is an oral preparation with a spectrum of activity similar to that of cefixime and a stability to common plasmid- or chromosomemediated ß-lactamases, including some enzymes that hydrolyze parenteral third-generation cephalosporins. The half-life of 2 to 3 hours permits once-a-day dosing. Although clinical trials indicate clinical efficacy comparable to amoxicillin-clavulanate95 and cefaclor,96 the decreased activity against pneumococci makes ceftibuten a poor choice for treatment of AOM.

Loracarbef is an oral preparation that is chemically similar to cefaclor, except that the sulfur atom in the dihydrothiazine ring is replaced by a methylene group. The new drug is termed a carbacephem rather than a cephalosporin. Loracarbef is similar to cefaclor in antibacterial activity, with in vitro activity against most gram-positive cocci, *H. influenzae* and *M. catarrhalis*. The serum sickness-like reaction with rash, arthritis, and fever that has been reported with cefaclor has not been identified with loracarbef. Clinical studies identify efficacy in a twice-daily regimen.97

**Third-Generation Cephalosporins**

Cefoperazone, cefotaxime, moxalactam, ceftriaxone, ceftizoxime, cefuroxime, cefepime and ceftazidime are parenteral products with efficacy in vitro against gram-positive cocci, gram-negative enteric bacilli, and *H. influenzae*. Four oral drugs may also be categorized as third-generation cephalosporins: cefdinir, cefuroxime axetil, ceftizotoren and cefpodoxime. Third-generation cephalosporins have increased activity against gram-negative bacilli compared with the activity of first- and second-generation cephalosporins but retain activity against gram-positive cocci. However, activity against *Staphylococcus aureus* is limited, requiring caution in use for serious staphylococcal infections. Cefoperazone and ceftizotoren have not been approved for use in children younger than 12 years.

Moxalactam was equivalent to ampicillin or chloramphenicol for treatment in children of meningitis caused by *H. influenzae*98 and was equivalent to amikacin (when each was used in combination with ampicillin) for treatment of meningitis in neonates that was caused by gram-negative enteric bacilli.99 Moxalactam alone was successful in curing cases of chronic suppurative otitis media and malignant external otitis due to *P. aeruginosa*.100

Ceftriaxone is effective against gram-positive cocci, including *Staphylococcus aureus*, group A streptococci, *Streptococcus pneumoniae*, *H. influenzae*, and selected gram-negative enteric bacilli. The unique quality of ceftriaxone is the long
duration of effective concentrations of drug in blood and tissues; the serum half-life is approximately 6.5 hours. Serum concentrations are significantly higher for more than 24 hours compared to MICs of bacteria causing AOM and infections of the head and neck. High concentrations are achieved in the middle ear, which persist for more than 48 hours after a single intramuscular dose of 50 mg/kg.\textsuperscript{101} For diseases requiring prolonged therapy, ceftriaxone may be of value for use outside the hospital in single daily intramuscular doses or for intravenous administration in children with venous access. A single dose of intramuscular ceftriaxone was equivalent in clinical efficacy to 10 days of amoxicillin,\textsuperscript{8} trimethoprim-sulfamethoxazole,\textsuperscript{7} and amoxicillin-clavulanate.\textsuperscript{102} The single intramuscular dose was favored by parents compared with the traditional 10 days of oral drug.\textsuperscript{103} For children whose therapy with amoxicillin and other oral agents for AOM has failed, ceftriaxone was clinically and microbiologically effective when administered in three consecutive daily intramuscular doses.\textsuperscript{9,104,105} An alternative regimen for children whose initial therapy with amoxicillin has failed is a single dose of ceftriaxone (50 mg/kg) and observation during 48 hours; if clinical signs resolve, no further therapy is necessary. If clinical signs persist, a second dose is administered and, if necessary, a third dose.\textsuperscript{4}

Cefitoxime has a spectrum of activity similar to that of cefotaxime and moxalactam. Clinical experience with the drug in children is limited. Although cefitoxime has been approved for treatment of meningitis caused by \textit{H. influenzae} and \textit{Streptococcus pneumoniae}, its role in pediatric infectious diseases is uncertain.

Ceftazidime was introduced for clinical use in the United States in 1985. The drug is highly resistant to inactivation by a broad spectrum of \(\beta\)-lactamases and has excellent activity in vitro against \textit{P. aeruginosa}, including strains resistant to antipseudomonal penicillins. Its use in middle-ear infections in children is for treatment of chronic suppurative otitis media or other infections in which \textit{P. aeruginosa} plays an important role.

Cefepime is a parenteral cephalosporin with excellent activity against gram-positive organisms and enhanced gram-negative activity, including \textit{P. aeruginosa}, and thus would be of value in therapy of chronic suppurative otitis in which gram-negative pathogens are a concern.

Cefuroxime is available in oral and parenteral forms and is of value in treating otitis media, sinusitis, orbital cellulitis, and severe pneumonias. The oral preparation, cefuroxime axetil, is considered an alternative for patients whose initial therapy with amoxicillin fails, but the suspension has a bitter taste, limiting its acceptability in infants and young children.

Cefpodoxime proxetil is an oral preparation with in vitro activity against both gram-negative and gram-positive organisms of importance in otitis media. The drug has a half-life of 2.1 to 2.8 hours, which permits maintenance of therapeutic levels in a twice-daily oral dosage schedule. The in vitro activity, pharmacokinetics, and clinical experience are provided in the proceedings of a symposium.\textsuperscript{106} The drug is approved for treatment of AOM with a dosage schedule of once a day for 5 days.

Cefdinir is active against penicillin-susceptible strains of \textit{Streptococcus pneumoniae} and \(\beta\)-lactamase positive and negative strains of \textit{H. influenzae}. Peak concentrations achieved in serum after single doses of 14 mg/kg were 3.86 \(\mu\)g/mL. Mean middle-ear concentrations were approximately 15\% of corresponding plasma concentrations. In two studies, cefdinir administered once or twice a day in a 14 mg/kg/d dosage schedule had comparable efficacy to amoxicillin-clavulanate administered 3 times a day in a 40 mg/kg/d dosage schedule (both drugs for 10 days) in treatment of AOM.\textsuperscript{107,108} Cefdinir is approved for treatment of AOM in a 5-day or 10-day course of 14 mg/kg/d in 1 or 2 doses. Cefpodoxime, cefuroxime, and cefdinir are the oral cephalosporins of choice for AOM, although cefdinir has a superior taste and is likely to achieve superior compliance. The role of cefdinir for pediatric infectious diseases was reviewed in a 2000 symposium.\textsuperscript{109}
**Toxicity and Sensitization**

The cephalosporins, like the penicillins, are safe for children and have almost no dose-related toxicity. Physicians should be alert for the uncommon reactions, including kidney problems, alcohol intolerance, serum–sickness-like reactions, and bleeding. Nephrotoxicity has been reported in adults who received cephalexin combined with gentamicin.\(^8^4\) Bleeding problems as a result of hypoprothrombinemia, thrombocytopenia, or platelet dysfunction have been associated with several cephalosporins (in particular, moxalactam). Bleeding due to hypoprothrombinemia was reversed by administration of vitamin K.

The cephalosporins may produce allergic reactions similar to those caused by the penicillins. There is cross-sensitization among the cephalosporins, and allergy to one implies allergy to all (as is the case with the penicillins). Various degrees of immunologic cross-reaction of penicillins and cephalosporins have been demonstrated in vitro and in animal models.\(^1^1^0\) Patients with a history of penicillin allergy have shown increased reactivity to cephalosporins. Some patients who are allergic to penicillin, however, have increased incidence of hypersensitivity to unrelated drugs, and it is still uncertain whether the penicillin-allergic patient reacts to a cephalosporin because of cross-allergenicity. Pichichero reviewed the evidence for prescribing cephalosporin antibiotics for penicillin-allergic patients, including information on cross-reactivity of penicillins and cephalosporins, the importance of the side chain in the immune response to cephalosporins and the relationships of chemical structures of side chains of the cephalosporins.\(^8^6\) He concludes that it is safe to readminister a penicillin or a cephalosporin provided that the initial reaction was not IgE-mediated. If the history of a penicillin or cephalosporin reaction is consistent with an immediate or accelerated IgE-mediated reaction, then neither \(\beta\)-lactam drug should be readministered to the patient. Thus, most patients who have an ambiguous history of rash associated with administration of a penicillin may be given cephalosporins without occurrence of an adverse reaction.

An unusual serum–sickness-like reaction has been reported in children who received cefaclor.\(^1^1^1\) The children developed a generalized pruritic rash, similar to erythema multiforme; in some cases, it was accompanied by purpura and arthritis, with pain and swelling in the knees and ankles. The signs appeared 5 to 19 days after the start of therapy with cefaclor and generally disappeared within 4 to 5 days after the drug was discontinued. The children had no history of allergy to a penicillin or a cephalosporin. Levine compared rates of serum sickness reactions to cefaclor and amoxicillin in 2,026 children who received 4,871 courses of the antibiotics.\(^1^1^2\) Serum sickness (defined as arthritis/arthralgia plus a rash or urticaria) or erythema multiforme occurred in 11 children who received cefaclor (1.1%) and in no children given amoxicillin.

**Macrolides**

The macrolides possess a many-membered lactone ring attached to one or more deoxy sugars. The first macrolide, erythromycin, was introduced in the 1950s as the drug of choice for penicillin-allergic patients. Two oral macrolide antibiotics, clarithromycin and azithromycin, were introduced for use in infants and children in 1994 to 1996. Azithromycin differs from erythromycin in having a methyl-substituted nitrogen in its 15-member lactone ring. Clarithromycin has a 14-member ring structure with a methoxy group in position C6 of the lactone ring of erythromycin. The two new macrolides, compared with erythromycin, have prolonged half-lives, high and prolonged concentrations in cells and tissues, increased in vitro activity against selected organisms, and possibly less gastrointestinal distress. Pharmacologic and clinical data about the new macrolides are reviewed in the proceedings of a symposium on the macrolides and similar compounds,\(^1^1^3,1^1^4\) the proceedings of a symposium about the use of clarithromycin in pediatric infections,\(^1^1^5\) and the
proceedings of two symposia about use of azithromycin in childhood infections.116,117

**In Vitro Activity**
All the macrolides are effective against gram-positive cocci, group A streptococci, pneumococci, susceptible *Staphylococcus aureus*, and *M. catarrhalis*. Clarithromycin and azithromycin have greater activity than erythromycin against *H. influenzae*. Other organisms of importance in respiratory infections that are susceptible to the macrolides include *M. pneumoniae*, Legionella species, Chlamydia species, *Bordetella pertussis*, and *Corynebacterium diphtheriae*. The new drugs are also active against *Chlamydia pneumoniae* and *Mycobacterium avium*-intracellulare.

Two mechanisms of pneumococcal resistance to macrolides have been identified: ribosomal methylase genes (erm class of genes) and macrolide efflux genes (mef genes). The erm genes encode methylation of a specific base of 23S ribosomal ribonucleic acid (rRNA). Methylation blocks the binding of macrolides resulting in high-level resistance (erythromycin MIC > 128 \( \mu \text{g/mL} \)); these strains are usually resistant to clindamycin. The mef genes encode an efflux pump that bacteria use to expel macrolides. High concentrations of macrolide may overcome the pump (erythromycin MIC < 16 \( \mu \text{g/mL} \)) forcing enough macrolide into the bacterium to produce an antibacterial effect; these strains are usually sensitive to clindamycin. About one-third of invasive strains of macrolide-resistant *Streptococcus pneumoniae* carry the erm gene and the other two-thirds carry the mef genes. The level of resistance among mef strains has increased in the past few years\(^ {118,119} \), thus, even strains that in the past had lower-level resistance have become increasingly resistant to achievable concentrations of macrolides. A CDC study of invasive strains of *Streptococcus pneumoniae* in Atlanta indicated an increase in frequency of macrolide resistance from 16% in 1994 to 32% in 1999; the increase was a result of dissemination of mef genes in the disease-causing strains of *Streptococcus pneumoniae*.\(^ {119} \)

**Clinical Pharmacology**
Erythromycin, azithromycin, and clarithromycin are well absorbed from the gastrointestinal tract.\(^ {120} \) Because food decreases absorption of azithromycin, the drug should be administered 1 hour before or 2 hours after meals. Food does not affect the bioavailability of erythromycin or clarithromycin; hence, the drugs may be given without regard to meals.

Biliary excretion is the major route of elimination of the macrolides. The prolonged half-lives permit a once-a-day dosage schedule for azithromycin and a twice-a-day schedule for clarithromycin, in contrast to erythromycin, which is administered 4 times a day.

Concentration in cells and tissues occurs with each macrolide but most prominently with azithromycin, and, to a lesser degree, with clarithromycin. High concentrations of drug have been identified in polymorphonuclear leukocytes, fibroblasts, alveolar macrophages, tonsils, sinus and middle-ear fluids, and middle-ear mucosa.\(^ {121} \)

**Clinical Efficacy**
Erythromycin may be considered for treatment of otitis media that is known to be caused by *Streptococcus pneumoniae*, group A streptococcus, and *Staphylococcus aureus* (mild to moderate disease), although the drug has variable activity against *H. influenzae* and thus should not be relied on as the single antibiotic for treating AOM. *C. trachomatis* is a cause of otitis media in young infants (2 weeks to 6 months of age); this disease appears to respond to therapy with either sulfonamides or erythromycin.

A fixed combination of erythromycin ethylsuccinate and sulfisoxazole is available and effective for treatment of AOM. Each 5 ml contains 200 mg of erythromycin activity and the equivalent of 600 mg of the sulfonamide. The combination provides activity against the pneumococcus and ampicillin-sensitive and ampicillin-resistant strains of *H. influenzae*. The combination drug is of value for children who are allergic to penicillin or whose initial therapy...
with amoxicillin fails and who may have infection due to an ampicillin-resistant strain of *H. influenzae*.

Azithromycin was approved for treatment of AOM initially in a once-a-day/5-day regimen. A study by Block and colleagues demonstrated efficacy of a single dose of azithromycin (30 mg/kg) for children with AOM. In 2002, azithromycin was approved by the FDA in dosage schedules of 30 mg/kg in a single dose. At present, three schedules of azithromycin are available: a single daily dose; 10 mg/kg once daily for 3 days; or, as previously available, a 5-day schedule, 10 mg/kg as a single dose on the first day followed by 5 mg/kg/d on days 2 to 5.

Higher concentrations of azithromycin are achieved in cells and tissues than in serum. High concentrations are achieved in white blood cells and lung tissue concurrently with low serum concentrations. As an example, the concentrations of macrolides in polymorphonuclear leukocytes are a multiple of that in serum: the ratio for erythromycin is four- to eightfold, for azithromycin 25- to 50-fold and more than 15-fold for clarithromycin. Dagan and colleagues compared serum and middle-ear concentrations in 14 patients; serum concentrations varied between 0.01 and 3.2 mg/mL, whereas middle-ear fluid concentrations varied between 0.24 and 13 μg/mL. However, if cells are removed from the middle-ear specimen before the assay and only cell-free middle-ear fluid is tested, the concentrations are comparable to those in serum.

Clinical trials comparing the efficacy of a once-a-day/5-day course of azithromycin with a 3-times-a-day/10-day course of amoxicillin-clavulanate indicate comparability of the two regimens. However, a concern about the efficacy of azithromycin for AOM caused by *H. influenzae* has been raised by microbiologic studies of fluids before and after therapy. Dagan and colleagues compared the bacteriologic efficacy of azithromycin and cefaclor for treatment of AOM and found a high incidence of bacteriologic failure in both arms of the study. Tympanocenteses were performed on entry into the study and 3 to 4 days after onset of treatment. Microbiologic failure was correlated with the susceptibility of the organism. Treatment failure was frequent in children with AOM due to *H. influenzae* in the cefaclor group (53%) and the azithromycin group (52%). The failure to eradicate the organism in the azithromycin patients was puzzling because most had high concentrations of drug in the middle ear (varying between 0.5 and 13 μg/mL). Animal studies suggest that the failure to clear *H. influenzae* at day 3 to day 4 in the azithromycin arm may be a result of a slower rate of eradication and that sterilization does occur, but later in the course of therapy.

Clarithromycin has a spectrum of activity similar to that of erythromycin but has increased activity against *H. influenzae* as a result of its active metabolite, 14-hydroxy clarithromycin. Concentrations of clarithromycin and the active metabolite in middle-ear fluid exceed concentrations in serum; serum concentrations of clarithromycin and metabolite were 1.73 μg/mL and 0.82 μg/mL, respectively, and middle-ear fluid concentrations were 2.53 μg/mL and 1.27 μg/mL. Clinical trials of children with AOM document comparability of clarithromycin with cefaclor, amoxicillin, and amoxicillin-clavulanate.

Macrolides have been demonstrated to have anti-inflammatory effects. The intracellular accumulation of the macrolides into neutrophils and other tissues combined with penetration into biofilms and the anti-inflammatory activity have led to randomized placebo-controlled trials in patients with cystic fibrosis. In studies in children and adults, patients who received azithromycin demonstrated improved lung function and fewer respiratory exacerbations. Whether or not the effects on inflammation or penetration into biofilms play a role in acute or chronic otitis media is unknown.

**Toxicity and Side Effects**

In general, the macrolides are safe, with few reports of toxicity or sensitization. The estolate of erythromycin may give rise to a cholestatic jaundice that is believed to be a result of a hypersensitivity reaction. The jaundice has been
reported to occur almost exclusively in adults who receive the estolate for more than 14 days and usually resolves when administration of the drug is stopped. Few cases of jaundice in children have been reported, but physicians should consider a limit of therapy to 10 days and be alert for signs of liver toxicity.133

Concurrent use of erythromycin and theophylline in patients with asthma has been a concern because of the effect of the antibiotic on the pharmacokinetics of theophylline. Increases in serum theophylline concentrations have been demonstrated with erythromycin and clarithromycin but not with azithromycin.

Clindamycin

Clindamycin is effective in vitro against gram-positive cocci, including Streptococcus pneumoniae. Many penicillin-resistant strains of Streptococcus pneumoniae are susceptible to clindamycin; a multihospital study of 1,275 isolates of Streptococcus pneumoniae identified only 6.3% that were resistant to clindamycin.57 Clindamycin is also active against a wide range of anaerobic bacteria, including penicillin-resistant Bacteroides species. Clindamycin provides higher levels of activity in serum and oral absorption is not decreased when the drug is taken with food. Because of its limited activity against H. influenzae, clindamycin can be used as initial therapy for otitis media only when the pathogen is identified as a susceptible gram-positive coccus; or clindamycin can be used in combination with a drug, such as a sulfonamide, that is active against Haemophilus species when the organism is not known. Clindamycin should be added to the β-lactam regimen for the patient who has signs of toxin-producing group A streptococci. Because β-lactam drugs inhibit cell wall synthesis, toxin production may persist while the patient is on therapy unless a drug that inhibits protein synthesis, such as clindamycin or a macrolide, is added.74

The oral suspension of clindamycin has a bitter taste and may not be tolerated by some children. Diarrhea is a common side effect, but enterocolitis, of concern in adults, is rare in children. Antibiotic-associated colitis has been reported in as many as 10% of adult patients after treatment with clindamycin. The epithelium of the colon undergoes necrosis, the mucous glands dilate, and an inflammatory plaque forms and adheres loosely to the underlying epithelium. This disease has been associated with other antibiotics that alter intestinal flora, including ampicillin,134 tetracycline, chloramphenicol, and lincomycin. Overgrowth of toxin-producing strains of Clostridium difficile is responsible for most cases of antibiotic-associated colitis. The antibiotic suppresses the normal flora in the colon, and the Clostridium difficile organisms proliferate and produce an enterotoxin that is responsible for the disease. Most of these reactions have occurred in elderly patients, those with severe illness, and those receiving multiple antimicrobial agents.135 Thus, a concern for enterocolitis should not limit the use of clindamycin for children.

Sulfonamides and Trimethoprim-Sulfamethoxazole

The first sulfonamide (and the first drug of the modern antimicrobial era), Prontosil (Bayer, Cologne, Germany), was reported in 1935 by Domagk to be effective against infections due to β-hemolytic streptococci.136 Sulfapyridine was introduced in 1938 and was the first antimicrobial agent effective for pneumococcal pneumonia. Soon after the introduction of these drugs, however, both streptococci and pneumococci developed resistance to the sulfonamides. Today, sulfonamides are used to treat many infections in children, including otitis media caused by nontypeable strains of H. influenzae, usually in combination with a penicillin or erythromycin to provide coverage for Streptococcus pneumoniae. Sulfoxazole was used successfully by Perrin and colleagues for prophylaxis in children with recurrent episodes of AOM.137

Trimethoprim-sulfamethoxazole is an antimicrobial combination with significant activity
against a broad spectrum of gram-positive cocci and gram-negative enteric pathogens. Trimethoprim is more active than the sulfonamide, but the mixture is significantly more effective than either drug alone. The drugs act in synergy by blocking the sequence of steps by which folic acid is metabolized: the sulfonamide competes with and displaces $p$-aminobenzoic acid in the synthesis of dihydrofolate; trimethoprim binds dihydrofolate reductase, inhibiting conversion of dihydrofolate to tetrahydrofolate. The effect of sulfonamide in bacteria is circumvented in the mammal, which obtains folates from food sources. The reaction inhibited by trimethoprim is similar in bacteria and mammals but differs quantitatively in the extent of binding of the drug to the enzyme. Mammalian dihydrofolate reductase is 60,000 times less sensitive to trimethoprim than is the enzyme from *E. coli*.

Sulfamethoxazole was chosen as the sulfonamide to use in combination with trimethoprim because the drugs have similar patterns of absorption and excretion. Both are well absorbed from the gastrointestinal tract, and food does not affect absorption. A parenteral preparation is available. Rapid absorption and peak serum activity occur between 1 and 4 hours after oral administration; serum activity persists for more than 12 hours, but there is no significant accumulation after repeated doses given at 12-hour intervals.

Monotherapy with trimethoprim alone was approved for treatment of AOM by the FDA in early 2000. Published data about safety and efficacy for AOM for trimethoprim are limited. The proposed advantage of trimethoprim alone compared with trimethoprim-sulfisoxazole is equivalent efficacy with fewer side effects.

Adverse reactions to the combination include rashes similar to those previously associated with sulfonamides (maculopapular or urticarial rashes, purpura, photosensitivity reactions, and erythema multiforme bullosum) and gastrointestinal symptoms, primarily nausea and vomiting. Hematologic indices have been carefully evaluated because of the antifolate activity of trimethoprim. Leukopenia, thrombocytopenia, agranulocytosis, and aplastic anemia have been associated with administration of trimethoprim-sulfamethoxazole, but the incidence of these adverse reactions is low. Hemolysis may occur in patients with erythrocyte deficiency of glucose-6-phosphate dehydrogenase. Despite the low incidence of blood dyscrasias and generalized skin disorders, the Committee on Safety of Medicine of the United Kingdom limited the indications for trimethoprim-sulfamethoxazole, including use for AOM in children to only when there is good reason to prefer the combination.  

The combination of trimethoprim-sulfamethoxazole in children has been effective in treatment of AOM caused by *Streptococcus pneumoniae* or *H. influenzae* (including $\beta$-lactamase–producing strains). An increasing proportion of strains of *Streptococcus pneumoniae* are resistant to trimethoprim-sulfamethoxazole; 21% of nasopharyngeal isolates obtained from Boston children with AOM were resistant. In most studies of antimicrobial resistance among clinical isolates of *Streptococcus pneumoniae*, trimethoprim-sulfamethoxazole has the highest rate of resistance. Doern and colleagues noted 30.3% of clinical isolates obtained nationwide in the United States during the winter of 1999–2000 were resistant to the combination. The drug is not effective when group A streptococcus or *Staphylococcus aureus* is the causative organism of AOM. It is also not recommended for pharyngitis caused by group A streptococcus. The combination had been used with success for children who were allergic to penicillins or whose initial course of ampicillin failed because of $\beta$-lactamase–producing strains of *H. influenzae*, but the high rates of pneumococcal resistance limit value of the combination drug.

**Vancomycin**

Vancomycin is a parenterally administered antimicrobial agent with a spectrum of activity limited to gram-positive organisms. It is usually administered by the intravenous route because intramuscular injection causes pain and tissue
necrosis. Ototoxicity and nephrotoxicity were effects of high concentrations in serum of early preparations, but improvements in the manufacturing process have resulted in a product that is believed to have lower toxicity. The principal uses of vancomycin in children are initial treatment of life-threatening pneumococcal infections pending results of susceptibility tests on the isolate, serious disease caused by Staphylococcus aureus or Staphylococcus epidermidis resistant to the penicillinase-resistant penicillins (methicillin-resistant staphylococci) and of sepsis caused by enterococci in the patient who has a significant history of allergy to penicillin.

Vancomycin is one of the few drugs (rifampin, fusidic acid, and bacitracin are others) effective in vitro against penicillin-resistant strains of Streptococcus pneumoniae. To date, there are no vancomycin-resistant strains of Streptococcus pneumoniae. In areas with high rates of pneumococcal resistance to penicillins and cephalosporins, the CDC suggests empirical therapy with vancomycin in addition to an extended-spectrum cephalosporin for cases of meningitis potentially caused by Streptococcus pneumoniae until results of culture and susceptibility testing are available. The value of vancomycin for otitis media is restricted to cases due to penicillin- or cephalosporin-resistant gram-positive cocci.

**Tetracyclines**

Tetracyclines are effective against a broad range of microorganisms, including gram-positive cocci and some gram-negative enteric bacilli. Tetracycline should not be considered a substitute for penicillin for patients with otitis media caused by, or suspected of being caused by, gram-positive cocci because a significant proportion of group A streptococci and some strains of Streptococcus pneumoniae are resistant. A possible use of the tetracyclines for otitis media is treatment of uncommon infections in children older than 8 years as a result of Chlamydia pneumoniae or M. pneumoniae.

Seven tetracycline compounds are available for oral administration in the United States: tetracycline, chlortetracycline, oxytetracycline, Declomycin (demethylchlortetracycline), methacycline, doxycycline, and minocycline. Tetracycline, chlortetracycline, doxycycline, and minocycline are also available for intravenous administration. With few exceptions, there are only minor differences in the in vitro activity of the different preparations. Minocycline, however, may be effective against some strains of community-acquired methicillin-resistant Staphylococcus aureus.

Tetracyclines are deposited in teeth during the early stages of calcification and cause dental staining. A relationship between the total dosage and the degree of visible staining has been established. Tetracyclines cross the placenta, and discoloration of teeth has been seen in babies of mothers who received tetracycline or its analogs after the sixth month of pregnancy. The permanent teeth are stained if the drug is administered after the age of 6 months and before the age of 6 years. Other adverse effects include phototoxicity (particularly with Declomycin), nephrotoxicity (with tetracycline hydrochloride, oxytetracycline, and Declomycin), and vestibular toxicity (with minocycline).

There are few indications for administering a tetracycline to a young child with infections of the respiratory tract, including otitis media; other effective drugs are available for almost all
infections for which tetracycline might be considered. For children 8 years of age and older, a tetracycline may be considered as an alternative to erythromycin for disease due to *M. pneumoniae* or chlamydial infections (psittacosis, trachoma, and inclusion conjunctivitis) and rickettsial diseases, including Rocky Mountain spotted fever.

**Aminoglycosides**

Aminoglycosides provide broad coverage against gram-negative enteric bacilli and some gram-positive organisms (such as *Staphylococcus aureus*), are rapidly bactericidal, and are readily absorbed after administration. The major concerns in their use are nephrotoxicity, ototoxicity, and poor diffusion across biologic membranes, including passage into cerebrospinal fluid. The aminoglycosides of current importance are streptomycin, kanamycin, gentamicin, tobramycin, and amikacin. A major use in otitis media is for chronic suppurative otitis media, which is frequently caused by *P. aeruginosa* and other gram-negative bacilli. Although it is not covered in this monograph, the aminoglycosides are of value for suppurative and malignant otitis externa.

The in vitro activity of these antibiotics against gram-negative enteric bacilli varies and must be defined for each institution on the basis of current sensitivity tests. Streptomycin is not included in routine disk sensitivity tests currently because results for many years indicated that it is ineffective against a significant proportion of gram-negative enteric bacilli. The other aminoglycosides are active against most isolates of *E. coli* and Enterobacter, Klebsiella, and Proteus species. At present, gentamicin, tobramycin and amikacin are the most active of the aminoglycosides against these organisms and against *P. aeruginosa*. The spectra of activity of gentamicin and tobramycin are similar, and strains resistant to one are usually resistant to the other. The major advantage of tobramycin is its activity against some strains of *P. aeruginosa* that are resistant to gentamicin. Amikacin is similar to gentamicin and tobramycin in its spectrum of activity, but there is little cross-resistance, and some gram-negative organisms resistant to these aminoglycosides are sensitive to amikacin.

The aminoglycosides have significant in vitro activity against *Staphylococcus aureus* but are less effective for group A and B streptococci and *Streptococcus pneumoniae*. A combination of a penicillin and an aminoglycoside results in more rapid killing and lower concentration of drug required to inhibit selected strains of gram-negative enteric bacilli and enterococci.

After parenteral administration, the aminoglycosides distribute rapidly in extracellular body water, with slow accumulation in tissues. Peak levels occur in serum between 1 and 2 hours after administration, and significant activity persists for 6 to 8 hours. Penetration across biologic membranes is variable, and diffusion into cerebrospinal fluid is limited (the concentration in cerebrospinal fluid is approximately 10% of the peak serum concentration).

All aminoglycosides may produce renal injury and ototoxicity. In general, gentamicin and tobramycin are more likely to affect vestibular function, and amikacin and kanamycin are more likely to damage the cochlear apparatus, but both functions may be affected by each drug. The cochlear effect may present as a high-frequency hearing loss or tinnitus; vestibular disturbances include vertigo, nystagmus, and ataxia. Some of the effects may be reversible, but permanent damage is frequent. Nephrotoxicity may present as albuminuria, the presence of white and red blood cells and casts in the urine sediment, or elevation of blood urea nitrogen or serum creatinine. Toxicity appears to be dose-related, although eighth nerve damage has followed the use of relatively small doses in patients with renal failure. Toxicity has not been a significant problem in children with normal kidney function who were treated with aminoglycosides according to currently recommended dosage schedules. Toxicity has usually been associated with administration of large doses for a long time, previous therapy with other aminoglycosides, administration of the drugs to patients with impaired kidney function, and
concurrent administration of other agents that are potentially nephrotoxic (eg, the diuretics furosemide and ethacrynic acid).

Concentrations of aminoglycosides in serum are variable and unpredictable. Patients who receive a prolonged course of aminoglycosides or who have impaired renal function require careful monitoring to determine safety as well as efficacy of the aminoglycoside. Blood should be obtained to determine drug concentration at the expected peak (1 to 2 hours after parenteral administration) or trough (before the next dose, that is, 8 or 12 hours after the last administration). Specimens of blood should be obtained early in the course of therapy (within the first 3 days) to be certain that effective levels in serum are achieved and at subsequent intervals (every 3 to 4 days) to determine that the concentration of aminoglycoside in serum is below the level of toxicity. The desired peaks for the aminoglycosides are 5 to 10 mg/mL for gentamicin and tobramycin, and 15 to 25 mg/mL for kanamycin and amikacin. The trough should not exceed 2 mg/mL for gentamicin and tobramycin or 10 mg/mL for kanamycin and amikacin. The toxic ranges are considered to be 14 mg/mL for gentamicin and tobramycin and 40 mg/mL for kanamycin and amikacin. Dosage schedules should be modified if concentrations in serum are either too low, and therefore inadequate for optimal therapy, or too high and potentially toxic.

The major use of aminoglycosides for otitis media in children is for serious disease that is caused by or suspected of being caused by gram-negative enteric bacilli; this includes infections of the neonate and suppurative complications of AOM in the child with a malignant neoplasm or immunologic defect. Aminoglycosides may be of value alone or in combination with a broad-spectrum penicillin for chronic suppurative otitis media caused by *P. aeruginosa*. The aminoglycosides may be administered by the intramuscular or intravenous (by slow drip during 1 to 2 hours) route. Oral preparations are not absorbed.

Published proceedings of symposia should be consulted for more specific information about the pharmacologic actions and clinical uses of gentamicin, tobramycin, and amikacin.

## Chloramphenicol

Chloramphenicol is active against many gram-positive and gram-negative bacteria and chlamydiae. Oral preparations are well absorbed. The intravenous route is preferred for parenteral administration because lower levels of serum activity follow intramuscular use. The drug diffuses well across biologic membranes, even in the absence of inflammatory reaction. Approximately 70% of the concentration of chloramphenicol in serum is present in cerebrospinal fluid of patients with meningitis, and similar high concentrations would be expected in the middle ear. Chloramphenicol may be of value for selected cases of otitis media caused by organisms (particularly gram-negative enteric bacilli) resistant to other drugs and uniquely susceptible to chloramphenicol.

The major limiting factor in the use of chloramphenicol is its toxic effect on bone marrow. A dose-related anemia occurs in most patients receiving high dosages for more than a few days. The anemia is concurrent with therapy and ceases when the drug is discontinued; it is characterized by decreased reticulocyte count, increased concentration of serum iron, and cytoplasmic vacuolization of early erythroid and myeloid precursors in bone marrow.

Aplastic anemia is a rare (approximately 1 case per 20,000 to 40,000 courses of treatment) and idiosyncratic reaction that is usually fatal. Most cases of aplastic anemia follow use of the oral preparation of chloramphenicol; few reports have been published of aplastic anemia that followed parenteral administration alone. In some of these cases, other drugs or the patient’s disease could have been responsible for the aplastic anemia. Because few patients receive chloramphenicol by the parenteral route only, compared with the extensive worldwide oral use of chloramphenicol (particularly in the many countries of Central and South America and Africa, where the oral drug is available
without a prescription), and because the incidence of aplastic anemia is so low, we cannot be certain that aplastic anemia occurring almost exclusively after oral use is a true event or one of statistical chance. Because cases of aplastic anemia after parenteral administration are extraordinarily rare, clinicians should not avoid the intravenous use of chloramphenicol when it is indicated.

Because of the wide variability in concentrations of chloramphenicol in serum of infants and children, monitoring of serum concentrations is required 2 or 3 times a week during therapy. Peak serum concentrations should be 15 to 25 mg/mL to be safe and effective.\textsuperscript{152}

Metronidazole

Although introduced in 1959 for treatment of \textit{Trichomonas vaginalis} infections, metronidazole is now more widely used for infections caused by anaerobic bacteria. The drug diffuses well into all tissues in both oral and parenteral forms. Anaerobic bacteria may play a role in chronic otitis media and complications that follow, including severe acute sinusitis, chronic sinusitis and brain abscesses. Metronidazole should be added to the regimen for treatment of abscesses that may include anaerobic bacteria.

Polymyxins

Polymyxin and colistin are highly effective in vitro against a broad spectrum of gram-negative enteric bacilli, including \textit{P. aeruginosa}. These drugs do not diffuse well across biologic membranes, however, and are usually effective only when they are applied topically, as would be the case for external otitis media.

Fluoroquinolones

The fluoroquinolones have a broad spectrum of activity, good oral absorption, and good tolerability, but they are proscribed for use in pediatrics because of arthropathies in juvenile animals. Nevertheless, because the quinolones are the only oral drugs with activity against \textit{P. aeruginosa}, they have been used in pediatric patients with pseudomonal infections, particularly children with cystic fibrosis, as well as in children with chronic suppurative otitis media, malignant external otitis, pseudomonal osteomyelitis, and febrile neutropenia.\textsuperscript{153} Topical ofloxacin and ciprofloxacin with dexamethasone are approved for use in children with AOM who have tympanostomy tubes in place and for chronic suppurative otitis media. Goldblatt and colleagues demonstrated clinical and microbiologic equivalence for topical ofloxacin and oral amoxicillin-clavulanate for purulent otorrhea in children with tympanostomy tubes.\textsuperscript{154}

The history of use of quinolones in pediatrics begins with the introduction of nalidixic acid in 1962, mostly for infections of the urinary tract. The arthropathy and osteochondrosis were first described in weight-bearing joints in juvenile animals in 1972. Although there is no evidence that quinolones cause joint manifestations in children, the family of drugs has caused arthropathies in every juvenile animal species tested, which led to a restriction of use of quinolones in children and adolescents younger than 18 years.

Many products with a broad spectrum of activity have become popular oral agents in adults, including ciprofloxacin, norfloxacin, enoxacin, ofloxacin, gatifloxacin and levofloxacin, among others. Although the use of quinolones in pediatrics has been a subject of frequent discussion, the FDA has approved only ciprofloxacin for the indication of chronic urinary tract infection for which it is uniquely effective. There are no other approved indications for this class of drugs for children younger than 18 years. New 8-methoxyfluoroquinolones have activity against resistant pneumococci and \(\beta\)-lactamase–producing \textit{H. influenzae} and administrative advantages, such as once-a-day therapy. Systemic ciprofloxacin may be considered for chronic suppurative otitis media due to \textit{P. aeruginosa} that failed therapy with aural toilet and ototopical agents. In a study of the bacteriologic and clinical efficacy of gatifloxacin in children with severe and recurrent disease
including tympanocenteses before and during therapy, the drug was demonstrated to be highly effective but there is no liquid suspension available and the manufacturer chose not to seek FDA approval. The results of clinical trials and the potential role of fluoroquinolones for severe and recurrent AOM were discussed by Dagan and colleagues.

**Ototopical Agents**

Currently available antimicrobial suspensions that are used extensively as ototopical drugs include colistin, neomycin, and hydrocortisone (Cortisporin TC Otic Suspension, King Pharmaceuticals, Bristol, TN); polymyxin, neomycin, and hydrocortisone (Coly-Mycin S Otic, King Pharmaceuticals); tobramycin and dexamethasone (TobraDex, Alcon Laboratories, Fort Worth, TX); ciprofloxacin and hydrocortisone (Cipro HC Otic, Alcon Laboratories); ciprofloxacin and dexamethasone (Ciprodex, Alcon Laboratories); and ofloxacin (Floxin Otic, Daiichi Pharmaceutical Corp, Montvale, NJ). Antiseptic ototopical drops such as acetic acid are commonly used in developing countries and are believed to be effective. All of the above have been used for otitis externa. The use of ototopical agents to treat chronic supplicative otitis media was reviewed by Bluestone and Klein.

Only ofloxacin otic solution and ciprofloxacin-dexamethasone otic were effective for treatment of AOM in children with tympanostomy tubes who presented with acute otorrhea. The ofloxacin study evaluated the efficacy of 10 days of administration of otic solution twice a day and amoxicillin-clavulanate orally 3 times a day; the clinical cure rate measured as the cessation of otorrhea was 76% for ofloxacin versus 69% for amoxicillin-clavulanate. The eradication rates were similar for *Streptococcus pneumoniae*, *H. influenzae*, and *M. catarrhalis*, but ofloxacin had superior cure rates for *Staphylococcus aureus* and *P. aeruginosa*. Roland and colleagues suggested that ciprofloxacin-dexamethasone otic is more effective than ofloxacin otic. The efficacy of the otic suspensions for AOM in children with tympanostomy tubes indicates that the high concentrations of drug that reach the middle ear mucosa through the perforation or tympanostomy tube result in high clinical and microbiologic cure rates. Additional advantages of otic versus systemic antimicrobial administration include lesser systemic adverse events (eg, diarrhea) and absence of effect on the upper respiratory flora, and, therefore, absence of selection of resistant bacteria.

**Antiviral Drugs**

A broad array of antiviral agents are now available for treatment of herpes simplex virus and varicella-zoster virus infections (acyclovir,
famciclovir, valacyclovir), human immunodeficiency virus infection (multiple), cytomegalovirus infection (ganciclovir, foscarnet, cidofovir, fomiviren), hepatitis B and C (lamivudine and interferon-α, alone or in combination with ribavirin for the C virus), enterovirus infection (plecanaril), respiratory syncytial virus (RSV) infection (ribavirin), and influenza virus infection (amantadine, rimantadine, zanamivir, and oseltamivir). Of these agents, only drugs active against influenza virus and RSV infections are of interest for management of otitis media. New agents directed against viruses responsible for respiratory tract infection will, undoubtedly, be introduced during the next few years and alter the management of otitis media. The availability of agents with activity against specific viruses will hasten the introduction of new diagnostic techniques for isolating and identifying viral infections.

Amantadine, 1-adamantanamine hydrochloride, is active against influenza virus A. A syrup is available for use in infants and young children, and the drug is well absorbed. When started before exposure to influenza A, amantadine is 70 to 90% effective in preventing illness. Treatment begun within 48 hours after onset of illness decreases duration of fever and symptoms by 1 to 2 days. The drug has little or no activity against influenza B, and higher concentrations than can be safely achieved in humans are required to inhibit rubella, parainfluenza virus, and RSV. Although the precise mode of action is unknown, antiviral activity appears to be due to interference with virus uncoating rather than direct inactivation of infectious virus. Rimantadine is four- to tenfold more active than amantadine and has a similar mechanism of activity but is, in general, better tolerated than amantadine. Neither drug is approved for children younger than 1 year. There are no data specific to prevention of AOM, but it is likely that prevention of influenza virus A infection also decreases otitis media caused by this infection. The circulating influenza viruses in the United States in the winter of 2005–2006 were resistant to amantadine and rimantadine, and the CDC recommended that they not be used for treatment or prophylaxis. The interested physician should consult the CDC Web site (www.cdc.gov) for the latest information about influenza activity and choices of therapeutic agents. The CDC search engine has information for both health care personnel and lay individuals and is maintained on a daily basis.

Zanamivir and oseltamivir are inhibitors of influenza A and B virus neuraminidases and are effective for infection caused by both influenza viruses (whereas amantadine and rimantadine are active against only influenza A). Administration of zanamivir by nasal spray or inhalation within 30 hours of onset of symptoms was effective in shortening the duration and severity of symptoms of influenza A and B virus infections in adults. Prophylactic use was 84% effective in preventing febrile influenza. Oseltamivir was effective in adults for both prevention and treatment of influenza A and B virus infections. If the drug is started within 36 hours of onset of symptoms, it can decrease the severity and duration of symptoms and the incidence of upper respiratory complications. Prophylactic administration was 87% effective in preventing culture-proven influenza virus infection. Both zanamivir and oseltamivir are approved by the FDA for prevention as well as treatment of influenza virus infections.

Ribavirin is a synthetic nucleoside that inhibits a wide variety of deoxyribonucleic acid (DNA) and RNA viruses. Infants with bronchiolitis or pneumonia caused by RSV showed improvement with aerosolized ribavirin, and the drug is now approved for treatment of hospitalized infants. Ribavirin is teratogenic in animals and is contraindicated in pregnancy. Because the aerosol is dispersed in the patient’s environment, it is recommended that a hood or other entrapment device be used and that pregnant health care workers not be involved in the care of patients receiving the drug. Ribavirin is rapidly transported into cells, where it is converted by cellular enzymes to monophosphate, diphosphate, and triphosphate derivatives that then
inhibit viral or virally induced enzymes involved in viral nucleic acid synthesis.

Interferons are proteins released by cells in response to infection or other stimuli and induce a temporary antiviral state in uninfected cells. The interferon genes have been cloned into bacterial and yeast plasmids, and large quantities of interferon are available. Interferon α-2 has been administered as an intranasal spray against infection caused by rhinoviruses and coronaviruses—causes of the common cold. Interferon-α was administered as a nasal spray for short-term prophylaxis against the common cold in the household. Almost all the effect was against rhinovirus infections, with no preventive benefit for colds caused by other agents. At present, the only approved uses of interferon-α are for chronic hepatitis as a result of hepatitis B and C viruses and papillomavirus infections; uses for respiratory tract infections have not been exploited.

ALTERNATIVE AND COMPLEMENTARY THERAPIES

Various alternative and complementary therapies, including osteopathic and chiropractic manipulation, herbal remedies, and homeopathic medicine, are used in management of otitis media. The scientific basis for evaluating these therapies is almost nonexistent, but some investigators are framing questions for appropriate study to identify safety as well as efficacy.

Garlic extract has activity against multidrug-resistant pneumococci, β-lactamase–producing *H. influenzae*, and methicillin-resistant *Staphylococcus aureus* and has a synergistic effect with vancomycin against vancomycin-resistant enterococci. Unfortunately, the antibacterial activity of garlic disappears when the extract is heated and does not survive the acid pH of gastric juice. Herbal and homeopathic remedies are used extensively to treat acute and chronic otitis media. Claims for various herbs include the decongestant effect of Ephedra leaves and stalks, the anti-inflammatory effect of chamomile, and the immune-stimulating effect of Echinacea leaves, stalks, and roots. Barnett and coworkers evaluated homeopathic treatment of AOM in a pilot study of 24 children. Although only two children required antibiotic therapy, this result may be no more than expected to resolve AOM without use of antimicrobial agents. The authors indicate the challenges of evaluating homeopathic therapy for acute and chronic otitis media, including demographic differences in families who seek homeopathic versus allopathic care, the large number of homeopathic remedies used (10 different medications were used for the initial therapy in the 24 patients), and different outcome measures (failure of one homeopathic medicine to cure the disease is not viewed as a failure of therapy if a subsequent homeopathic medicine cures the patient).

FEATURES OF ADMINISTRATION OF ANTIMICROBIAL AGENTS

Dosage Schedules

Dosage schedules of antimicrobial agents useful in AOM are listed for infants (beyond the newborn period) and children in Table 1. Parenteral administration should be considered for severe infections caused by less susceptible organisms and when sepsis or suppurative complications are present or imminent (Table 5).

The clinical pharmacologic action of antimicrobial agents administered to the newborn is unique and cannot be extrapolated from the results of studies done in older children or adults. Physiologic and metabolic processes that affect the distribution, metabolism, and excretion of drugs undergo rapid changes during the first few weeks of life. The increased efficiency of kidney function after the first 7 days of life requires a decrease in the interval between doses of penicillins and aminoglycosides to maintain high concentrations of drug in blood and tissues. Thus, different dosage schedules are provided for the first week of life and for subsequent weeks of
the neonatal period. Otitis media in the neonate (up to 20 days of age) may occur alone or be accompanied by signs of sepsis, and usually warrants parenteral therapy.

Food Interference with Absorption

The absorption of some oral antimicrobial agents is significantly decreased when the drug is taken with food or near mealtime. These drugs include unbuffered penicillin G, penicillinase-resistant penicillins (nafcillin, oxacillin, cloxacillin, and dicloxacillin), ampicillin, azithromycin, and lincomycin. Milk, milk products, and other foods or medications containing calcium or magnesium salts interfere with absorption of the tetracyclines. Absorption of penicillin V, buffered penicillin G, amoxicillin, oral cephalosporins currently available, chloramphenicol, erythromycin, clarithromycin, and clindamycin is only slightly affected by food. Antibiotics whose absorption is affected by concurrent administration of food should be taken 1 or more hours before or 2 or more hours after meals.

Intravenous and Intramuscular Administration

After intravenous administration of most antimicrobial agents, there is a period when the concentration of drug in serum is higher than that after intramuscular administration. No therapeutic advantage of intravenous administration of antibiotics, however, as opposed to intramuscular administration, has been demonstrated. Intravenous administration should be used if the patient is in shock or suffers from a bleeding diathesis. If prolonged parenteral therapy is anticipated, the pain on injection and the small muscle mass of the young child preclude the intramuscular route and make intravenous therapy preferable. Although intramuscular benzathine penicillin has been used in combination with a sulfonamide for treatment of AOM,
single-dose intramuscular ceftriaxone is the only parenteral agent to be evaluated in clinical trials. One-dose ceftriaxone was equivalent to 10 days of oral amoxicillin or trimethoprim-sulfamethoxazole. Antibacterial concentrations in blood are similar after oral and intravenous administration of trimethoprim-sulfamethoxazole. Parenteral administration may be preferred for the patient unable to take oral trimethoprim-sulfamethoxazole. Because intramuscular administration of tetracyclines and erythromycin causes local irritation and pain, these drugs should be administered parenterally by the intravenous rather than the intramuscular route.

The physician must be alert for thrombophlebitis that may result from prolonged intravenous administration and sterile abscesses that may follow intramuscular administration. The technique and complications of intramuscular injections were reviewed by Bergeson and colleagues. In general, the site of injection in young infants is the upper lateral thigh; in children older than 2 years, it is the gluteal area; for older children, it is the deltoid muscle. After selection of the proper site and insertion of the needle into the muscle, negative pressure is applied by pulling back on the plunger to be certain that the needle is not in a blood vessel.

**Use of Drugs for Children in School or Day Care**

Infants and children may return to school or a day care center during a course of antimicrobial therapy. Because of the problems with administration of drugs outside the home, physicians should use medications that are given infrequently and need only simple directions. Drugs that are administered once or twice a day are preferred. Use of chewable tablets may be of value in reducing the need for the school or day care provider to measure specific amounts of liquid suspension. Single-dosage regimens, such as intramuscular benzathine penicillin G for group A streptococcal infections, may be advantageous. Guidelines for administration of medications in school prepared by the Committee on School Health of the American Academy of Pediatrics may also serve as a model for the physician who is prescribing drugs to be administered in day care. Administration of medications in day care is addressed by Smith and Aronson.

**Compliance**

The most frequent drug-related factor in failure of antibiotic therapy is inadequate compliance. Frequency of dosing is important. If possible, administration of a dose in day care is to be avoided because of the uncertainty of compliance by caretakers. Once or twice a day is now the rule for new antimicrobial agents for infants and young children. Schedules that are shorter have administrative advantage; for example, azithromycin is now available in a one-dose regimen and a once-a-day for 3- and 5-day schedules. Cefpodoxime and cefdinir may be administered in a twice-a-day schedule for 5 days. A single dose of intramuscular ceftriaxone ensures compliance but may not be acceptable to all parents (or children). Current clinical trials include shorter courses of oral antimicrobial agents for management of AOM, but there is concern about shorter-than-recommended courses of oral drugs in infants younger than 2 years.

**Palatability**

Unacceptable taste or odor of drugs may result in poor compliance. Demers and colleagues performed a blinded comparison of taste for 14 commonly prescribed pediatric suspensions. The study participants (pediatric staff, house staff, and other health care workers) compared the drugs in a manner similar to wine tasting, including texture, smell, taste, and aftertaste. Cefixime, cephalexin, and cefaclor had the highest overall scores. Dicloxacillin and erythromycin-sulfisoxazole were the least acceptable. Other investigators have noted similar results in a study by Steele and colleagues, suspensions of cefuroxime, cefpodoxime, and erythromycin plus
sulfisoxazole were “judged to be so unpalatable as to potentially jeopardize compliance.”

Dagan and colleagues also noted a “refusal” rate of 56% for cefuroxime contrasted with a “refusal” rate of 11% for amoxicillin. Schwartz noted that a chocolate syrup chaser helped children tolerate the taste of cefuroxime; chocolate syrup masked the taste of antibiotics better than applesauce and apple juice. Powers and colleagues conducted crossover taste trials in children 4 to 8 years of age using a “smile-face” scoring system; children preferred the taste of the oral suspension of cefdinir to that of amoxicillin-clavulanate, cefprozil and azithromycin (the last three were approximately equivalent). Steele and colleagues updated studies of taste ratings of antibiotic suspensions based on appearance, smell, texture, taste, and aftertaste: loracarbef, cefdinir, and cefixime scored highest; amoxicillin-clavulanate, cefpodoxime proxetil, and cefuroxime ranked lowest; and azithromycin, ciprofloxacin, trimethoprim-sulfamethoxazole, and clarithromycin were in the intermediate group (Table 6). The authors added ratings based on other compliance variables, including cost, duration of therapy (5 vs. 10 days) and dosing intervals. Duration of therapy (ie, 5 days vs. 10 days) was considered more important than dosing intervals for antibiotics dosed at once- or twice-daily intervals.

Administration of the initial dose of a new antimicrobial agent in the office or clinic has the advantage of determining whether the product is acceptable to the patient. (In addition, this practice provides immediate therapy rather than the patient waiting for a prescription to be filled.) Although the practice of providing samples has been eliminated in some facilities, availability of samples or starter doses is of value in determining acceptability of the product and avoiding problems with compliance.

### Failure to Comply

Mattar and coworkers evaluated treatment given at home for children with otitis media. Full compliance with prescribed medications occurred in only 5 of 100 patients. Factors limiting compliance included incorrect dosage schedules (36%); early termination (37%); inadequate dispensing of medication at drugstores (15%); spilled medicine (7%); and a series of other errors by physician, pharmacist, and parent (Table 7). Compliance improved to more than one-half when hospital pharmacy personnel gave patients and parents verbal and written instructions for administration of medications that were dispensed with a calibrated measuring device and a calendar to record doses taken. Single-dose intramuscular ceftriaxone would be of value for families that have difficulty maintaining a multi-dose 10-day oral schedule in infants and young children. A survey of parents indicated a preference for single-dose intramuscular therapy for AOM over standard 10-day oral therapy. Other drug-related factors that play roles in failure of compliance include inappropriate dosage schedule and inadequate duration of therapy. Some antimicrobial agents deteriorate on prolonged storage. Adherence to expiration dates recommended by the manufacturer safeguards against inadequate potency of the drug.

### Pharmacologic Interactions

Concurrent administration of an antimicrobial agent and a second drug may result in altered

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**Table 6. TASTE SCORES FOR SELECTED ANTIMICROBIAL SUSPENSIONS OF VALUE FOR ACUTE OTITIS MEDIA**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Overall Taste Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loracarbef</td>
<td>1</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</td>
</tr>
</tbody>
</table>

*Based on appearance, smell, texture, taste, and aftertaste.
pharmacokinetics of either drug. The tubular secretion of penicillins and most cephalosporins is blocked by probenecid. This effect can be exploited by coadministration of probenecid (in a dosage of 10 mg/kg 4 times a day in children to a maximal dosage of 500 mg/kg 4 times a day) to produce a higher peak and more sustained level of antimicrobial activity.

Administration of chloramphenicol with the anticonvulsant drugs phenobarbital and phenytoin leads to significant changes in concentrations of the antibiotic in serum; lower serum concentrations of chloramphenicol resulted when phenobarbital was coadministered, whereas higher serum concentrations of chloramphenicol were detected when phenytoin was coadministered. Phenobarbital may have induced the activity of hepatic endoplasmic reticulum, thereby increasing the metabolism of chloramphenicol, resulting in decreased concentrations of active antibiotic in serum and tissues. Phenytoin may cause induction of hepatic microsomal enzymes and compete with chloramphenicol for binding sites, resulting in elevated serum concentration of one or both drugs, possibly to toxic levels. Patients who receive chloramphenicol and anticonvulsant therapy require monitoring of serum concentrations to be certain of the safety and efficacy of the antibiotic.184

Erythromycin and clarithromycin interfere with the hepatic metabolism of theophylline, resulting in increased serum concentrations of theophylline that may produce nausea, vomiting, and other signs of toxicity. Coadministration of the drugs may be prescribed for children with asthma. An alternative antibiotic should be considered, and if a suitable alternative is not optimal therapy, the dosage schedule of theophylline should be reduced and serum levels monitored.186

DIFFUSION OF ANTIMICROBIAL AGENTS INTO MIDDLE-EAR FLUIDS

Although studies of concentrations of various drugs in serum and middle-ear fluid differ in dosage schedules, time of collection, and methods of assay, the results indicate that most antimicrobial agents of value for treatment of AOM achieve significant concentrations in middle-ear fluid. Because the middle ear is embryologically, morphologically, and physiologically part of the respiratory tract, penetration of systemically administered antibiotics into middle-ear mucosa and middle-ear fluid provides a model for dynamics of diffusion of antibiotics in other areas of the respiratory tract.

The interested reader will find data about diffusion of the listed antimicrobial agent into middle-ear fluid of patients with acute or chronic middle-ear infection in two review articles186,187 and the references in Table 8.

These studies of penetration of systemically administered antibiotics have limitations in design that need to be considered in interpreting the results.
1. Most include specimens obtained after a single dose, whereas Sundberg and coworkers showed that concentrations of erythromycin increased in middle-ear fluids when specimens were obtained after multiple doses. The increment with successive doses may be applicable to some or all antimicrobial agents.

2. Standard curves of antibiotics are prepared in buffered solutions, which may not represent an adequate control for middle-ear fluid.

3. Results of assays of materials obtained at various intervals after administration of drug give different concentrations in middle-ear fluids and different ratios of middle-ear fluid with simultaneously obtained serum. Peak values occur at different times for different drugs. Therefore, results of fluids obtained at one sample time may not provide adequate indication of penetration into middle-ear fluid.

4. Homogenization of mucoid or purulent middle-ear fluid is difficult.

5. Specimens containing blood should be excluded. Specimens of middle ear fluid for a study of cefixime penetration into middle-ear fluid included blood. Blood-contaminated specimens should be identified and deleted from analyses.

6. The condition of the mucosa should be identified. Differences in penetration may vary, depending on the degree of inflammation of the mucosa, and this may not be identified or known by the investigator.

7. Binding of antimicrobial agents to protein may provide a prolonged duration of activity in the middle ear but low concentrations at any point in time.

8. Some drugs, such as the macrolides, have high intracellular concentrations which may not be apparent if the cellular content is removed from the middle ear fluid specimen.

Despite these limitations, data from assays of concentrations of drug in middle-ear fluid provide useful information which, along with in vitro susceptibility data, guide the choice of antimicrobial agents for otitis media. Harrison correlated the susceptibility of the bacterial pathogens and the antibiotic concentrations in middle-ear fluid to predict potential clinical efficacy.
Significant concentrations of most of the drugs tested appeared promptly in middle-ear fluid. The concentrations of drug in the middle-ear fluid were, in general, parallel, although lower than concentrations of drug in serum. The peak activity in middle-ear fluid was delayed compared with peak activity achieved in serum, but duration of activity was similar in both serum and middle-ear fluid. Concentrations of penicillin V and ampicillin in middle-ear fluid of patients with chronic otitis media were lower than concentrations in the fluid of patients with acute disease, but concentrations of amoxicillin, erythromycin, and cefaclor were similar in acute and chronic effusions.

Purulent fluids had higher concentrations of drug than did mucoid or serous fluids, and concentrations were similar to those found in purulent fluids of children with AOM. The penicillins and cephalosporins achieved concentrations in middle-ear fluids that were approximately one-fifth to one-third of the levels present in serum. Sulfonamides and erythromycin achieved middle-ear concentrations that were approximately 50% of serum concentrations. Concentrations of the macrolides azithromycin and clarithromycin in middle-ear effusions were far higher than in serum, reflecting the intracellular concentration of the drugs.

**STERILIZATION OF MIDDLE-EAR FLUIDS BY ANTIMICROBIAL AGENTS**

To determine the ability of antimicrobial agents to eradicate bacterial pathogens from middle-ear fluids of children with AOM, investigators have used serial aspirates of the infected fluids to determine the drug’s microbiologic efficacy. The initial aspirate identifies the bacterial pathogen of the acute middle-ear infection; the second aspirate, days after initiation of therapy, defines the ability of the drug to eradicate the infection. Virgil Howie and John Ploussard, pediatricians in practice in Huntsville, AL, in 1969 published results of their dual aspirates, termed by the authors the in vivo sensitivity test. Since then, Dr. Howie, at the University of Texas School of Medicine in Galveston, and other investigators have used similar techniques to document the microbiologic efficacy of new antibacterial drugs and to correlate clinical and microbiologic results (Table 9). The microbiologic efficacy of antibacterial drugs for AOM defined by the in vivo efficacy test is summarized in a review. However, most of these studies were performed prior to the increase in multidrug-resistant pneumococci. The most current data using the double technique has been presented by Dagan and colleagues and are summarized in Table 10.

The placebo effect is instructive in identifying resolution of acute middle-ear infection without antimicrobial agents. Whereas pneumococci resolved without antimicrobial agents in 20% of cases, approximately one-half of the infections caused by nontypeable *H. influenzae* were sterile.

<table>
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<tr>
<th>Table 9. EVALUATION OF NEW ANTIMICROBIAL AGENTS FOR OTITIS MEDIA: INFECTIOUS DISEASES SOCIETY OF AMERICA—1992</th>
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<tr>
<td><strong>In vitro activity of test drug</strong></td>
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<td>Effective for major pathogens</td>
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<td>In vivo efficacy in animal model</td>
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<td>Selection of comparison drug</td>
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<td>Current standard therapy or known effective agent</td>
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<td>Enrollment criteria for patients</td>
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<td>Definition of disease: middle-ear effusion plus a sign of acute illness</td>
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<td>Exclusions: antimicrobial agents 7 days</td>
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<td>Use of tympanocentesis to define microbiology (approx. 100 patients)</td>
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<tr>
<td>Sufficient sample size to identify differences in study and comparison drugs</td>
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<td>Times for evaluation after onset of therapy (for a 10-day course of oral drug)</td>
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<td>3–5 days to define initial cure/failure</td>
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<td>6–14 days to identify relapse</td>
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<td>15–28 days to identify recurrence</td>
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<th>Table 10. COMPARATIVE EFFICACY* OF ANTIBACTERIAL AGENTS FOR ACUTE OTITIS MEDIA: THE “POLYANNA PHENOMENON”</th>
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<td><strong>Microbiologic Efficacy</strong></td>
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<tr>
<td>Success in eradicating bacteria</td>
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<td>Failure to eradicate bacteria</td>
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<td>Nonbacterial otitis media</td>
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Adapted from Marchant CD et al. *Tympanocentesis and clinical evaluation 3 to 6 days after onset of therapy.*
at the time of the second aspirate. Although no placebo studies are available with *M. catarrhalis* as the pathogen, a spontaneous clearance rate may be assumed for the β-lactamase–producing organisms when a β-lactamase–susceptible penicillin is used; most infections cleared in the absence of an effective antimicrobial agent. The differential clearing of the bacteria with relative persistence of pneumococci but substantial resolution of infection caused by nontypeable *H. influenzae*, and possibly *M. catarrhalis*, is likely to be associated with some immune or bacteriostatic factor in the middle-ear fluid that acts to sterilize the middle-ear fluid of these organisms.

The results of the in vivo susceptibility test are generally consistent with data available from in vitro assays of the drugs against the major bacterial pathogens and the concentrations of drug achieved in the middle-ear fluids. Susceptible pneumococcal infections were efficiently sterilized by most penicillins, cephalosporins, and macrolides. Sulfonamides alone were ineffective but trimethoprim-sulfamethoxazole effectively sterilized the middle ear fluid of susceptible pneumococci. Three doses of ceftriaxone administered intramuscularly, oral amoxicillin, and cefuroxime axetil had the best rates of eradication of non-susceptible pneumococci.

When infection caused by *H. influenzae* was present, penicillin V (phenoxymethyl penicillin) usually failed, and failure rates in excess of 20% were evident for the cephalosporins (cefadroxil and cefprozil) and the macrolides (erythromycin, azithromycin, and clarithromycin). Amoxicillin was highly effective in eradicating non–β-lactamase–producing strains but was no better than placebo for eradicating β-lactamase–producing strains; amoxicillin-clavulanate restored the efficacy of amoxicillin for all strains of *H. influenzae*. Single-dose intramuscular ceftriaxone uniformly sterilized middle-ear fluids infected with *H. influenzae*.

The correlation of bacteriologic efficacy and clinical results was discussed by Marchant and colleagues (see Table 10). Clinical success by days 3 to 6 was usually achieved (93%) when the bacterial pathogen was eradicated from the middle ear. When the drug was ineffective and failed to sterilize the middle-ear infection, clinical success was still evident in a majority of patients (62%), probably a result of the placebo effect for *Haemophilus* and *Moraxella* infections or other reasons noted before. When a bacterial pathogen was not isolated from the middle-ear fluids, clinical success occurred in 80% of the patients.

**CRITERIA FOR CHOICE OF ANTIMICROBIAL AGENTS FOR AOM**

**History of Antimicrobial Therapy**

Poultices, purgatives, and eardrops were the treatments of choice for AOM in the 19th century. Physicians who cared for children with severe AOM had available only the surgical techniques of incision and drainage of the middle-ear abscess. Most physicians were accomplished in performing myringotomy, and the myringotomy knife was standard equipment. If otorrhea was noted, “some warm milk and water ought to be carefully injected by a syringe 3 or 4 times a day, in order to wash out the matter.” Removal of secretions from the nasopharynx with a warm spray of salt and water was advocated by Wurdemann in 1892.

In the pre-antibiotic era, β-hemolytic streptococci and *Staphylococcus aureus* accounted for 25% and 11% of middle-ear isolates (pneumococci accounted for 27% and “influenza” for 2% of isolates). The introduction of the sulfonamides, then the penicillins and broad-spectrum antibiotics, led to a variety of effective regimens for AOM and chronic suppurative otitis media. The microbiology of AOM changed during the early years of the antibiotic era, with pneumococci and *H. influenzae* emerging as the major pathogens and β-hemolytic streptococci and *Staphylococcus aureus* relegated to minor roles. At first, penicillin G or V alone was used extensively, but Mortimer and Watterson in 1956 pointed out that penicillin was inadequate for infection caused by *H. influenzae* and suggested that the addition of a sulfonamide be
considered for mild to moderate infections and chloramphenicol for severe disease. With the introduction of ampicillin in 1962, amoxicillin in 1974, and amoxicillin-clavulanate in 1985, a variety of oral cephalosporins and new macrolides have provided a broad array of effective antimicrobial agents for management of AOM.

**Antibacterial Drug Resistance**

The increasing incidence of multidrug-resistant *Streptococcus pneumoniae* and *H. influenzae* has raised concerns about the continued efficacy of antimicrobial agents. Antibiotic resistance has been, is now, and will be a problem in managing infectious diseases.

Development of resistance was evident from the first experiences with chemotherapy. Sulfonamides were initially effective against group A streptococci and pneumococci, but within 10 years after introduction, these streptococcal species had developed modes of resistance. Each subsequent decade brought new challenges in the form of development of resistance of important bacterial pathogens to available antimicrobial agents. In the past, the response of industry and research laboratories has been to introduce new drugs effective against the resistant strains, but it is possible that resistant strains will emerge that will be unaffected by available or investigational drugs.

Selection of resistant bacteria is promoted in the patient by current or prior antimicrobial agents and in the community by the amount of drug used (see “*Streptococcus pneumoniae*”). Carriage of susceptible strains in the nasopharynx is eliminated by an effective antimicrobial agent but non-susceptible strains are likely to persist. Thus, antibiotic therapy does not directly increase the number of resistant strains in the upper respiratory tract, but, by eliminating susceptible strains, permits resistant strains to multiply and spread to contiguous areas such as the middle ear.

Because of the need to restrict the use of antimicrobial drugs to thwart the further development of resistant bacteria, national organizations have developed protocols for judicious use of antimicrobial agents. The CDC and the American Academy of Pediatrics have developed guidelines for appropriate use of antimicrobial agents for pediatric upper respiratory tract infections, including AOM (see below “Current Recommendations for Antimicrobial Agents for AOM”).

**Assessing Clinical and Microbiologic Efficacy**

The efficacy of antimicrobial agents for otitis media may be assessed in terms of clinical and microbiologic results. Clinically, we expect effective drugs to produce a significant decrease in signs and symptoms of disease in 48 to 72 hours, to limit the duration of time of middle-ear effusion, and to prevent complications of disease that occur by extension to adjacent tissues.

The major microbiologic criterion for efficacy of antimicrobial drugs is sterilization of the middle-ear infection as documented by double-tap studies. Studies indicate that bacterial antigens persist in middle-ear fluid, although the antibiotic may have rid the ear of viable organisms. Pneumococcal polysaccharide has been identified in most fluids in which the organism is isolated and in many specimens that have no bacterial growth. The role of these bacterial products in diseases and the effect of antibacterial drugs in processing and eliminating the antigens are unknown but may be important in dealing with the problem of effusion that persists after acute infection.

The immunologic process of otitis media is incompletely understood, and little information is available about the effect of antimicrobial agents on the development of local and systemic immunity after acute or chronic otitis media. Do antibiotics limit the immune response to infection in the middle ear? Do antibiotics differ in their effect on local or systemic immunity of the middle ear? How will these features of the immune response affect the duration of fluid in the middle ear? How will these features affect type-specific protection against the same bac-
Design of Clinical Trials

Techniques for evaluating the efficacy of antimicrobial agents in children with AOM have undergone significant changes in the past 30 years. Before 1960, most US studies were performed without tympanocentesis and, thus, without a specific microbiologic diagnosis. Children were enrolled for the evaluation of two or more drugs, the definition of otitis media was broadly stated and included signs such as inflammation of the tympanic membrane (which most experts now do not accept as a suitable sole criterion for otitis media with effusion), the drugs were assigned randomly, and results of therapy were presented in general terms such as good response and therapeutic failure. The results were usually ambiguous and demonstrated only minimal differences between the drugs studied. Although it is possible to design a study without microbiologic diagnosis, the early studies lacked sufficient sample size of enrolled patients to identify differences of the new drug compared with those of the standard preparation.

Tympanocentesis to define the etiologic agent in the middle-ear fluid of children with otitis media with effusion had been common in clinical trials by Scandinavian investigators, but it became customary in US studies only in the 1960s. About this time, more investigators, both in the private practice of pediatrics and in academic centers, became interested in various aspects of middle-ear infection, including evaluation of antimicrobial agents. The study designs were more precise, many studies were double-blind, sterilization was defined in some studies by re-aspiration of persisting middle-ear fluid, compliance was evaluated by assessment of use of the drug (weighing returned bottles of medication or assay of urine for antimicrobial activity), the clinical course was followed with precise end points, and side effects and toxicity of the antimicrobial agents were carefully assessed by clinical evaluation and laboratory tests. Dual aspirate studies to define microbiologic efficacy have provided important data about the biology of the disease. In recent years, many investigators have limited dual aspirate studies to children in whom initial therapy fails to provide a basis for appropriate choice of drug and give insight into the reasons for drug failure.

Guidelines for evaluating anti-infective drugs for infectious diseases, including otitis media, were developed by the Infectious Diseases Society of America (IDSA) for the FDA in 1992. These guidelines (see Table 9) remain appropriate 15 years later as the basis for considering the validity of clinical trials of antimicrobial agents for therapy of AOM. An FDA Anti-Advisory Committee in 2002 underlined the importance of initial tympanocentesis to provide microbiologic data that could be correlated with clinical results. Although there is general consensus about the elements of appropriate study design for evaluation of new antimicrobial agents, controversy continues about various aspects of published studies.

Clinical Criteria

The diagnosis of AOM requires three elements: (1) a history of acute onset of signs and symptoms; (2) the presence of middle ear fluid; and (3) signs and symptoms of middle ear inflammation. The specific signs or symptoms include ear pain, ear drainage, and hearing loss; nonspecific findings include fever, lethargy, irritability, anorexia, vomiting, and diarrhea. The presence of middle-ear effusion is defined by any of the following: bulging of the tympanic membrane; limited or absent mobility of the tympanic membrane; air-fluid level behind the tympanic membrane or otorrhea. Middle ear inflammation is defined by distinct erythema of the tympanic membrane or distinct otalgia.

Microbiologic Criteria

Microbiologic criteria are determined by aspiration of middle-ear fluids. Both ears should be aspirated when the patient has bilateral disease.
**Activity of the Test Drug**

The drug under consideration should have proven in vitro activity against *Streptococcus pneumoniae*, *H. influenzae*, and *M. catarrhalis*. In vivo evidence of sterilization of bacterial pathogens may be obtained with use of an appropriate dosage schedule in an animal model of AOM (such as the chinchilla).

**Demographic Characteristics of Study Population**

Clinical studies should be conducted with patients of different age groups and racial backgrounds and with similar risk factors for severe and recurrent infections (eg, attendance in large group day care, family history of AOM). Because most severe and recurrent disease occurs in children 2 years of age and younger, infants should make up at least half of the enrollees. Children should be excluded if they have focal anatomic, physiologic, or systemic immune defects; have received a systemic antimicrobial agent within the past 7 days; and are 12 weeks of age or younger.

**Selection of the Comparison Drug**

The control agent should be selected on the basis of expected patterns of in vitro susceptibility of the common bacterial pathogens or should be considered the current standard in the community for treating otitis media. In the United States, the comparator drug and its dosage schedule must be FDA-approved. The optimal design is double-blinded and, where appropriate, a double-dummy design adds to the validity of blindedness.

**Initial Study with Documentation of Microbiology**

A small trial (approximately 100 patients with a minimum of 20 cases due to each of the three major bacterial pathogens) should be conducted in which middle-ear aspiration and culture are performed for all patients to document the unique microbiology of the population to be studied. Repeated aspiration of middle-ear fluid is required only if there is evidence of clinical failure. Because the number of centers that perform tympanocenteses is presently limited and a second aspiration of middle-ear effusion cannot be recommended for children who are clinically cured or improved, the microbiologic response is correctly termed presumptive eradication.

**Clinical Evaluation without Documentation of Microbiology**

If the presumed microbiologic response rate is favorable—80% or larger—a comparative trial with an active control should be conducted. A double-blind study design is desirable whenever feasible, or at a minimum, the evaluator should be blinded.

**Statistical Significance and Power**

The sample size should be determined to provide significance with sufficient power (0.80 is appropriate for most studies) to determine an expected difference between the test drug and the standard. For example, a sample size of 440 evaluable patients would be required to identify a significant difference with a power of 0.80 with an expected cure rate of 80 to 90%.

**Evaluating the Drug Regimen**

After enrolment, observations should be made 3 to 5 days after initiation of therapy and at least 2 and then 4 to 6 weeks later. The precise period of post-treatment evaluation will vary according to knowledge of the anticipated duration of anti-infective activity of the test drugs. At each visit, an interval medical history, otoscopic examination, and an objective measurement, such as tympanometry or acoustic reflectometry, should be performed. Children should be assessed at each visit for other foci of infection and for adverse effects of the test drug.

**RESULTS OF CLINICAL TRIALS OF ANTIMICROBIAL AGENTS FOR AOM**

A summary of results of selected clinical trials of various antimicrobial agents in children with...
AOM between 1969 and 2000 is given in Table 11. The list includes only studies that identified the bacterial cause by aspiration of middle-ear fluid. The clinical results were consistent with the results that would be expected on the bases of in vitro studies of the activity of antimicrobial agents and data about concentrations of drug achieved in middle-ear fluid.

“Clinical cure” is defined as resolution of signs and symptoms (exclusive of middle-ear effusion) within 72 hours of onset of therapy in a child who remains well through the period of observation. “Failure” is defined as persistent signs or symptoms or clinical deterioration or new foci within 72 hours of onset of therapy. Failure may be the result of an ineffective drug or an organism that is not susceptible to appropriate antibacterial therapy (virus infection) or serious disease with multiple foci. “Relapse” is defined as reappearance of signs and symptoms

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<th>Investigator (year of publication)</th>
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of AOM after initial response during or within 4 days of conclusion of therapy and should be considered a failure of therapy or a new infection. "Recurrence" is defined as reappearance of signs and symptoms of AOM 5 to 14 days after the conclusion of therapy and may not be a result of a fault in the therapeutic regimen but may be associated with a new infection. Recurrence is likely in children who are exposed to viral or bacterial pathogens in day care or school.

Factors influencing outcome of treatment of AOM include age (children younger than 18 months had higher rates of failure than did children who were older), history of ear infections (children with recurrent otitis media were more likely to have treatment failure), concurrent virus infection and occurrence in the winter respiratory season, and failure of the parents to comply with the prescribed regimen. Knowledge of the risk factors for possible failure of the antimicrobial agents to achieve a clinical cure should promote closer observation of children at risk.

Distinguishing relapse (renewal of clinical signs after initial resolution due to the initial microorganism) or recurrence (renewal of clinical signs after initial resolution because of a new organism) may not be possible without aspiration of the middle-ear fluid. Leibovitz and colleagues provided microbiologic data by performing double tap studies within 3 to 4 weeks after onset of therapy in 108 consecutive patients with recurrent signs of acute otitis media. Bacteriologic relapse was defined as the presence of the identical pathogen as that isolated before therapy. The authors concluded that most recurrent episodes of AOM occurring within 1 month from completion of antibiotic therapy were new infections. Most bacteriologic relapses occurred within 14 days after completion of therapy but during this time recurrences caused by new pathogens were likely.

Rather than performing double tap studies on all children in a clinical trial, the design may include an initial aspirate of middle-ear fluid and a reaspiration only for children who have clinical failure. Schwartz and colleagues evaluated children in whom clinical disease did not respond after a 10-day course of ampicillin, amoxicillin, or erythromycin-sulfonamide mixture. Middle-ear fluid was aspirated and cultured for bacteria: ampicillin-resistant H. influenzae was found in approximately one-third (31%), ampicillin-susceptible strains of Streptococcus pneumoniae or H. influenzae were identified in approximately one-half (51%), and no bacterial growth was found in the other fluids. Boston children who failed to respond to therapy were studied in a similar fashion with the following results: 19% had organisms resistant to initial therapy, and 57% had no bacteria isolated from the middle-ear fluids. Pichichero and Pichichero evaluated the microbiology of patients in whom initial therapy failed. Typanocenteses provided middle-ear fluids of 83 patients who had been initially treated with amoxicillin: 44 patients had no growth; Streptococcus pneumoniae was isolated from 18 (although only 2 were found to be non-susceptible of 11 tested); H. influenzae was isolated from 7 (5 were β-lactamase–positive); and M. catarrhalis was isolated from 7 (all β-lactamase–positive).

Thus, these data indicate that some children who fail to respond clinically do so because of a bacterial pathogen resistant to initial therapy, but many children have bacteria that are susceptible to the drug, and some have negative bacterial cultures and presumably have a non-bacterial microorganism as the cause of otitis media or some other reason for the persistent fever. The child who fails to respond to therapy in 48 to 72 hours, or later relapses, should receive a new antimicrobial regimen that provides effective activity against organisms that might be resistant to the initial therapy (ie, β-lactamase–producing organisms that would inactivate ampicillin).

The bacteriologic features of middle-ear infection in children who have recurrent episodes of AOM are, in general, similar to those found in first episodes: the predominant pathogens are Streptococcus pneumoniae (although of different
serotypes) and nontypeable strains of *H. influenzae*. Because antibiotics administered in the preceding 30 days may result in selection of resistant strains, consideration should be given to the choice of an antimicrobial agent effective against pathogens resistant to the previously administered antibiotic.

**CURRENT RECOMMENDATIONS FOR ANTIMICROBIAL AGENTS FOR AOM**

In May 2004, the American Academy of Pediatrics (AAP) and the American Association of Family Physicians (AAFP) published a clinical practice guideline on the diagnosis and management of AOM. The intent of the guideline was to evaluate the published evidence on the management of uncomplicated AOM in children from 2 months to 12 years of age without signs or symptoms of systemic illness unrelated to the middle ear. The most controversial part of the guideline was a recommendation that selected children could be managed without antimicrobial agents and the recommendation is discussed above. For children who warranted therapy, the antimicrobial drug recommendations are presented in Table 12 and the following sections discuss the basis for the choices made by the two academies. The recommendations were subdivided: (1) antimicrobial agents for initial therapy; (2) antimicrobial agents for patients who failed initial therapy. Both sets of recommendations were subdivided into patients with mild or severe disease based on temperature of 39°C or greater and/or severe otalgia.

**Antibacterial Agents for Children with Non-severe AOM**

Amoxicillin has been the drug of choice for initial treatment of AOM since its introduction in the early 1970s because of its spectrum of activity against the major bacterial pathogens, its low cost, and the infrequency of side effects. The conclusion of the AAP guideline was that amoxicillin remains the antimicrobial drug of first choice for treating non-severe AOM. The bases for the recommendation were the pharmacodynamic profile (amoxicillin displays the longest time above MIC 90) against drug-resistant pneumococci of any of the commonly available oral agents, long record of safety and clinical efficacy in treating otitis media, narrower spectrum of activity than many of the alternative agents, and low cost. The recommendation recognized that amoxicillin might fail for resistant pneumococci and that β-lactamase production that would inactivate amoxicillin was identified in approximately 35% of strains of *H. influenzae* and 90% of strains of *M. catarrhalis*, but that otitis media caused by these two pathogens was more likely to resolve spontaneously.

The guideline suggested that the amoxicillin dosage be increased to 80 to 90mg/kg/d.

| Table 12. RECOMMENDED ANTIBACTERIAL AGENTS FOR PATIENTS WHO ARE BEING TREATED INITIALLY WITH ANTIBACTERIAL AGENTS OR WHO HAVE FAILED INITIAL MANAGEMENT WITH ANTIBACTERIAL AGENTS |
|---|---|---|---|---|
| Temperature ≥39°C and/or Severe Otolgia | At Diagnosis for Patients Being Treated Initially with Antibacterial Agents* | Clinically Defined Treatment Failure at 48 to 72 Hours after Initial Management with Antibacterial Agents |
| No | Amoxicillin 80 to 90 mg/kg/d | Non-Type I: cefdinir, cefuroxime, cefpodoxime; Type I: azithromycin, clarithromycin | Amoxicillin-clavulanate (90 mg/kg/d of amoxicillin component, with 6.4 mg/kg/d of clavulanate) |
| Yes | Amoxicillin-clavulanate (80 mg/kg/d of amoxicillin with 6.4 mg/kg/d of clavulanate) | Ceftriaxone—1 or 3 days | Ceftriaxone—3 days |

*From American Academy of Pediatrics.2*  
*Choices are the same for patients who were initially managed with observation but require therapy at 48 to 72 hours.*
Administration of amoxicillin in lower doses (40 to 45 mg/kg/d) achieves peak middle-ear fluid concentrations of 1 to 6 g/mL, which would be expected to inhibit susceptible and most intermediate strains of pneumococci. Higher doses of amoxicillin (70 to 90 mg/kg/d) in two doses achieve concentrations in the middle ear of 3 to 8 g/mL for 3 hours or longer after the dose. These concentrations would be likely to inhibit most of the non-susceptible strains of pneumococci. Thus, the higher dosage is now preferable because it is inclusive of susceptible and the vast majority of non-susceptible strains.

**Antimicrobial Choices for Children with Severe AOM**

The guideline recommended that children with temperatures 39°C and/or severe otalgia should receive high-dose amoxicillin-clavulanate (90 mg/kg/d of amoxicillin with 6.4 mg/kg/d of clavulanate) or as an alternative (including children with suspected penicillin allergy) intramuscular ceftriaxone.

**Antimicrobial Choices for Children Who Fail Initial Therapy**

Although experts agree about initial therapy of AOM, regimens for children who fail initial amoxicillin are more controversial. High-dose amoxicillin-clavulanate or multiple doses (3) of intramuscular ceftriaxone were recommended in the 2004 guidelines (see Table 12). For patients with initial failure who were allergic to penicillin ceftriaxone (non-type I), clindamycin or tympanocentesis was recommended. Each of the recommended alternatives to amoxicillin for treatment of otitis media is reasonable, but each has some limiting feature:

1. High-dose amoxicillin-clavulanate responds to concern about failure of amoxicillin due to β-lactamase–producing organisms but would not provide an advantage if failure is due to high-level, resistant pneumococci.

2. Intramuscular ceftriaxone in a schedule of three daily doses was recommended on the basis of limited information about efficacy of three doses. Parents would be discouraged by the regimen of three intramuscular doses. An alternative regimen would be a single intramuscular dose of ceftriaxone and subsequent doses at 48-hour intervals dependent on the resolution of clinical signs.

3. Clindamycin has a low rate of pneumococcal resistance but has minimal activity against *H. influenzae* and *M. catarrhalis*. The physician would need to know that the episode was due to *Streptococcus pneumoniae* (presumably on the basis of a positive culture of middle-ear fluid). Because this circumstance is likely to be uncommon, the recommendation of clindamycin has limited utility.

**Management of the Child Who Is Allergic to Amoxicillin**

If the patient is thought to be allergic to amoxicillin and the reaction was not a type I hypersensitivity (urticaria or anaphylaxis), the guidelines suggest an oral cephalosporin (cefdinir, cefuroxime, or cefpodoxime proxetil) can be used. Pichichero reviewed the evidence supporting use of cephalosporin antibiotics for penicillin-allergic patients and concurred with the guideline recommendation. Trimethoprim-sulfamethoxazole and a macrolide are the only currently available products for the child with AOM who has a history of type 1 reaction to amoxicillin or other β-lactam antibiotics. Because resistance of pneumococci to trimethoprim-sulfamethoxazole is high in many regions of the United States, and, in some areas, more frequent than penicillin resistance, the combination drug must be used only in communities where it is known to still be effective. Among the macrolides, erythromycin plus sulfisoxazole is effective, but some children will refuse the agent because of taste or gastrointestinal upset. A one-, three- or five-day regimen of azithromycin, or a 10-day course of clarithromycin, may be preferred.
Dosage Schedules and Duration of Therapy

Dosage schedules have been determined on the bases of studies of clinical pharmacology and results of clinical trials. For many years, the standard duration of oral therapy was 10 to 14 days, although it is uncertain how that course was decided. Results of studies that addressed the issue of duration of therapy suggest that many children improve with shorter courses of therapy, but some may require longer treatment.\(^{217-225}\) Five days of a single dose per day of azithromycin was found to provide clinical results equivalent to 10 days of amoxicillin-clavulanate.\(^{122}\) A 5-day course of oral cefpodoxime proxetil and cefdinir is also approved by the FDA. A single dose of intramuscular ceftriaxone that provides concentrations of active drug in the middle ear for 48 hours or longer was clinically equivalent to 10 days of amoxicillin\(^{8}\) or trimethoprim-sulfamethoxazole.\(^{7}\)

Some patients may require therapy of longer duration. Infants younger than 2 years have higher rates of success with 10 days than with 5 days of amoxicillin-clavulanate.\(^{219}\) The success rate in children younger than 2 years who received amoxicillin-clavulanate in a twice-a-day dosage schedule for 10 days was twice that of children who received the drug for 5 days.\(^{222}\) Children aged 6 to 12 years had equivalent clinical success with the 5-day and 10-day regimens; children aged 2 to 5 years benefited by 10-day rather than 5-day regimens. The study by Hendrickse and colleagues suggested that patients with AOM with intact tympanic membranes were satisfactorily treated with a 5-day course, but children with spontaneous purulent drainage required longer therapy.\(^{221}\) Paradise reviewed current studies of short-course antimicrobial therapy for AOM and concluded that a short course was inadequate for infants and young children.\(^{5}\)

The AAP guideline acknowledges that the optimal duration of therapy for patients with AOM is uncertain because studies comparing standard duration of treatment (10 days) to short-duration treatment were often limited by inadequate sample size, few or no children under two years of age, exclusion of children with severe and recurrent otitis and absence of appropriate criteria for diagnosis of AOM.\(^{201}\) The guideline committee concluded that the standard 10-day duration of therapy was optimal for children younger than 2 years of age and children with severe disease. For children 6 years of age and older with mild to moderate disease, a 5- to 7-day regimen was recommended. The 10-day regimen could be used selectively in children 2 to 5 years of age. The guidelines did not specifically address antimicrobial agents approved by the FDA for shorter courses, but these agents would not be bound by the 10-day recommendation including the 1-, 3- and 5-day course of azithromycin, the 5-day courses of cefpodoxime and cefdinir and single-dose intramuscular ceftriaxone.

Observation Versus Antimicrobial Therapy for Children with AOM

Historical Context

Before the introduction of sulfonamides in 1936, management of AOM included watchful waiting, or, when the suppurative process produced severe clinical signs or complications, use of myringotomy to drain the middle-ear abscess. Spread of infection to the mastoid, meninges, or other intracranial foci was a feared complication of otitis media.

Early therapeutic trials identified the value of the new antimicrobial drugs for resolution of clinical signs and decreased incidence of mastoiditis and other complications. In 1938, the frequency of mastoidectomy associated with AOM was 20%; by 1948, it was 2.5%\(^{226}\); and in some studies, it dropped to zero.\(^{227}\) Today, suppurative complications of AOM are prevalent only in regions with limited access to medical care, and the severity of complications is similar to that identified in the pre-antibiotic era. The effective antimicrobial agent sterilizes the middle-ear abscess and results in resolution of acute signs and symptoms in more than 90% of
children by day 3. The duration of middle-ear effusion is shorter in treated than in untreated children.13

The majority of children with AOM respond clinically without use of antimicrobial agents. Those who improve without such drugs include up to one-third of children with AOM who have a sterile effusion and are presumed to have a viral infection. The microbiologic data (see “Sterilization of Middle-Ear Fluids by Antimicrobial Agents”) indicate that approximately 20% of children with pneumococcal otitis media, 50% of children with initial aspirates that grow H. influenzae, and approximately 75% of children with otitis media caused by M. catarrhalis clear the organism from the middle ear and have resolution of acute signs of illness without using an appropriate antibacterial drug.193 Some children will have a sterile effusion from a prior episode of AOM with persistent effusion and have an intercurrent illness, not AOM. In addition, physicians may fail to distinguish otitis media with effusion as AOM.

Results of Therapeutic Trials Including Children Who Received Placebo

The use of a placebo group in a comparative trial with one or more antimicrobial agents has been studied by many investigators in the past 30 years. These studies have given important insights into the pathogenesis of middle-ear infections and provide a context for assessing the efficacy of antimicrobial agents and consideration of the option of observation rather than antimicrobial therapy for children diagnosed with AOM. The results do not describe the natural course of otitis media, because most include a drainage procedure—either tympanocentesis (aspiration) or myringotomy (incision and drainage). Some studies used only clinical criteria, raising questions about the accuracy of diagnosis, whereas other studies used aspiration of middle-ear fluid to define the microbiologic agents and confirm the presence of middle-ear fluid.

Rudberg evaluated 1,365 patients with acute, uncomplicated otitis media treated on an inpatient or outpatient basis at the Ear, Nose, and Throat Department of Sahlgrenska Sjukhuset, Gothenberg, between January 1951 and May 1952.228 All patients were confined to bed and had their ears drained daily by syringe, as long as discharge was present. If spontaneous perforation did not occur, myringotomy was performed. Four regimens of antimicrobial agents were used: penicillin G tablets or a triple sulfonamide preparation (alone or in combination), or an intramuscular injection of a combination of benzathine and procaine penicillin G. A fifth group received none of the drug regimens. The criteria for efficacy included the duration of discharge and incidence of complications. Between 236 and 333 cases were included in each group. Duration of ear discharge was significantly shortened in infections caused by pneumococcus and H. influenzae in patients who received penicillin or sulfonamide preparations, compared with those who received placebo. Infections due to Staphylococcus aureus and β-hemolytic streptococcus were favorably altered by use of penicillin. Complications, including exacerbation of clinical signs, mastoiditis, and failure of the infection to subside, occurred significantly more often in the placebo group than in the groups receiving penicillin, but the complications in patients receiving a sulfonamide were not significantly different from those of the placebo group. Mastoiditis occurred in 44 of 254 patients receiving placebo (17%), in 4 of 267 patients treated with sulfonamides, and in none of 844 patients treated with one of the penicillin regimens. The highest incidence of complications occurred in patients with disease caused by β-hemolytic streptococcus and H. influenzae.

In 1953, Lahikainen reported a study of children who were treated by use of myringotomy alone or combined with penicillin G.229 The duration of discharge was significantly decreased in the group who received the antibiotic. No complications occurred in the penicillin-treated group, although 9 of 153 patients who had myringotomy alone developed complications,
including 7 cases of mastoiditis, 1 case of meningitis, and 1 case of sinus thrombosis and brain abscess that resulted in death.

van Dishoeck and coworkers reported that 50% of 400 children treated with eardrops alone recovered in 7 to 17 days, but 13 children developed mastoiditis.\(^{230}\)

Halstead and colleagues in 1968 identified clinical improvement in a majority of untreated patients with suppurative otitis media (almost all had cultures that were positive for \textit{Streptococcus pneumoniae} or \textit{H. influenzae}), but two-thirds of the children (13 of 19) continued to be ill.\(^{231}\)

Lorentzen and Haugsten evaluated 505 children, and from these, three treatment groups were defined: myringotomy, penicillin V, and penicillin V combined with myringotomy.\(^{232}\) Significantly more failures occurred in the myringotomy group (15%) than in the penicillin group (4%) or the penicillin plus myringotomy group (5%). Thus, penicillin V was more efficacious than myringotomy alone, but myringotomy did not add to the effectiveness of the drug.

van Buchem and colleagues reported that antimicrobial therapy had no effect on the outcome of children with AOM.\(^{233}\) The investigators enrolled 171 children in a double-blind study of four regimens: amoxicillin alone, amoxicillin plus myringotomy, and neither drug nor surgery. Children aged 2 to 12 years were enrolled by 12 general practitioners in or near Tilburg, The Netherlands. The results suggested that the clinical course (pain, temperature, otoscopic appearances, and recurrence rate) was not different in any of the groups, although ears had discharge for a longer time and eardrums took longer to heal (neither difference significant) in the children treated without antibiotics. The authors concluded that “symptomatic therapy with nose drops and analgesics seems a reasonable initial approach to AOM in children.”\(^{234}\) Critics of the 1981 study identify flaws in the study design and analysis of results and question the validity of the conclusions.\(^{235}\)

The criticisms focus on the age of the patients (excluding infants, who have the highest age-specific incidence of disease), the small number of patients in each treatment group, the methods of statistical analysis, the absence of microbiologic data, the absence of definition of disease, the failure to assess observer reliability for the many participating physicians, and the failure to consider important variables of disease in randomization for therapy.

van Buchem and colleagues performed a second trial in which 4,860 children aged 2 years or older with AOM were treated with nose drops and analgesics alone for the first 3 or 4 days.\(^{233}\) Children whose condition took “an unsatisfactory course” (high temperature, otalgia, or persistent discharge) were treated with antimicrobial drug alone or combined with myringotomy. More than 90% of the children recovered within a few days with use of this regimen, but two developed mastoiditis. Group A streptococci were cultured from ear fluids of 39% of the children with the unsatisfactory course who underwent myringotomy; \textit{Streptococcus pneumoniae} was cultured from 17%, but \textit{H. influenzae} was cultured from only 1 child (1.4%). Again, the most important criticism of this study is the absence of children younger than 2 years. Because AOM is more severe in children younger than 2 years, the failure of the two studies by van Buchem and colleagues to include children younger than 2 years compromises the importance of the results. The Dutch protocols include management of infants younger than 2 years, but the data supporting such recommendations are unclear because data are not available from the studies of van Buchem and coworkers.

Engelhard and coworkers randomly assigned 105 Israeli infants, aged 3 to 12 months, with AOM to either an antimicrobial agent or myringotomy, or both.\(^{236}\) At the end of treatment, 60% of both the antibiotic-treated groups (with and without myringotomy) recovered, compared with only 23% of those in the myringotomy (without antibiotic) group. The investigators concluded that myringotomy alone is inadequate therapy for treating AOM in infants and that the addition of myringotomy
to antibiotic treatment will not shorten the recovery period.

Kaleida and colleagues from the Otitis Media Research Center in Pittsburgh evaluated amoxicillin or placebo for management of non-severe otitis media.\textsuperscript{13} Enrollment criteria were based on an otalgia scoring system that took into account estimated parental anxiety and reliability and assigned points for each hour of earache or apparent discomfort and also included temperatures less than 39.5°C rectally. Initial treatment failure occurred in 7.7% of 527 episodes managed with placebo and 3.9% of 522 episodes managed with amoxicillin (Table 13). Children with severe disease were randomized to receive amoxicillin, amoxicillin and myringotomy, or placebo and myringotomy. Initial treatment failure occurred in 9.6% of 167 episodes treated with amoxicillin alone, 11.5% of 104 episodes managed with amoxicillin and myringotomy, and 23.5% of 35 episodes managed with placebo and myringotomy. The authors concluded that amoxicillin is warranted for both non-severe and severe AOM, but routine use of myringotomy, either alone or combined with an antimicrobial agent, did not benefit the patient.

Howie reviewed studies of microbiologic efficacy with various therapeutic regimens, including a placebo group.\textsuperscript{194} Pneumococci persisted in most untreated patients (81%), whereas one-half of patients with initial aspirates of nontypeable \textit{H. influenzae} had sterile aspirates on second culture.

These studies suggest that many cases of middle-ear infection resolve spontaneously or with the assistance of surgical drainage. The data indicate that pneumococcal otitis media is unlikely to resolve clinically or microbiologically, whereas infection as a result of \textit{H. influenzae} and possibly \textit{M. catarrhalis} clears without antibiotics in approximately 50% of cases.

Damoiseaux and colleagues conducted a double-blind trial of amoxicillin versus placebo for AOM that was of importance because only infants under 2 years of age were enrolled.\textsuperscript{237} The study was conducted in 53 general practices in the Netherlands, and criteria for AOM included acute onset, inflammation of the tympanic membrane, and acute otorrhea. The status of the middle ear (aerated or fluid-filled) was not included in the criteria. Children who received amoxicillin had a shorter duration of fever and less analgesic use than children who received placebo (Table 14). The results are surprising in prolonged duration of pain and large proportion of clinical failures at day 11 in both amoxicillin- and placebo-treated children. One child in the placebo group was admitted to hospital with meningitis; the culture was sterile, but the Gram stain “suggested streptococcal meningitis.” The authors concluded that the “seven to eight children aged 6 to 24 months with AOM needed

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\textbf{Outcome} & \textbf{Amoxicillin (522 Episodes)} & \textbf{Placebo (527 Episodes)} & \textbf{P Value} \\
\hline
Initial treatment failure & 3.9\% & 7.7\% & <.009 \\
Effusion at 2 weeks & 46.9\% & 62.5\% & <.001 \\
Effusion at 6 weeks & 45.9\% & 51.5\% & NS \\
Recurrence at 2–6 weeks & 27.9\% & 27.6\% & NS \\
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\caption{AMOXICILLIN OR MYRINGOTOMY OR BOTH FOR ACUTE OTITIS MEDIA}
\end{table}

\begin{table}[h]
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\begin{tabular}{|l|c|c|c|}
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\textbf{Outcome} & \textbf{Amoxicillin (167 Episodes)} & \textbf{Amoxicillin + Myringotomy (104 Episodes)} & \textbf{Placebo + Myringotomy (35 Episodes)} \\
\hline
Initial treatment failure & 9.6\% & 11.5\% & 23.5\% \\
Effusion at 2 weeks & 60.6\% & 56.4\% & 52.2\% \\
Effusion at 6 weeks & 55.7\% & 51.6\% & 35.0\% \\
Recurrence at 2–6 weeks & 40.9\% & 35.2\% & 17.2\% \\
\hline
\end{tabular}
\caption{AMOXICILLIN VS. AMOXICILLIN + MYRINGOTOMY VS. PLACEBO + MYRINGOTOMY FOR SEVERE ACUTE OTITIS MEDIA}
\end{table}

From Kaleida PH et al.\textsuperscript{13}

\textit{NS} = not significant; none of the differences were statistically significant except for placebo + myringotomy versus drug groups in children older than 2 years.
to be treated with antibiotics to improve symptomatic outcome at day 4 in one child. This modest effect does not justify prescription of antibiotics at the first visit provided close surveillance can be guaranteed.”

Little and colleagues compared immediate with delayed prescribing of antibiotics for AOM. The children were 6 months to 10 years of age; 62% of the children in the immediate treatment group, and 57% of the children in the delayed treatment group, were older than 3 years. The authors presented cumulative data and did not distinguish results for infants versus older children. On average, children prescribed antibiotics immediately had shorter illness, fewer nights disturbed, and less analgesic use, although none of the differences were significant.

Ruohola and colleagues evaluated antibiotic treatment of acute otorrhea through tympanotomy tubes in a randomized double-blind placebo-controlled study. Children received amoxicillin-clavulanate or matching placebo for 7 days with daily suction of middle-ear fluid through the tympanotomy tube. The median duration of tube otorrhea was significantly shorter in the children who received the antimicrobial agent rather than the placebo (3 vs. 8 days). At the conclusion of the 7-day period of treatment, tube otorrhea was resolved in 28 of 34 children (82%) who received amoxicillin-clavulanate contrasted with resolution of otorrhea in 13 of 32 children (41%) who received placebo.

McCormick and colleagues performed a clinical trial of observation versus immediate antibiotic treatment in children with AOM who were 6 months to 12 years of age. Of the 223 children who were recruited, 57% were less than 2 years of age. Compared with watchful waiting, the antibiotic group had the following results: symptom scores on days 1 to 10 resolved faster; fewer doses of pain medication were required; 16% fewer failures were identified. On day 12, 69% of the tympanic membranes and 25% of the tympanograms were normal in antibiotic-treated children, compared to 51% normal tympanic membranes and 10% normal tympanograms in the watchful waiting group. Of the children in the watchful waiting group, 66% completed the study without need of antibiotics.

The results of these trials of management of AOM including placebo are interpreted differently by the various investigators and commentators. A core issue remains the accuracy of diagnosis, which is questioned by experts for many of the studies in which the diagnosis was based solely on clinical criteria and in which a large number of physicians participated. In addition, many of the studies did not enroll children under 2 years of age or did not analyze results for children younger and older than 2 years of age. The disease is different in the two age groups because of factors likely associated with the anatomy, physiology, and immunology of the child during the various periods of life. Nevertheless, the data indicate that many children do not need antibacterial agents, including:

- those whose acute disease is due to viral agents, and the course is unaffected by antibacterial agents;

<table>
<thead>
<tr>
<th>Measure</th>
<th>Amoxicillin (112–117)</th>
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<tr>
<td>% Persistent symptoms* at day 4</td>
<td>59</td>
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<td>% No improvement in eardrum at day 4</td>
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<td>.30</td>
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<td>% Clinical failure* at day 11</td>
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<td>Mean consumption of analgesia (dose)</td>
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<td>.004</td>
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</table>

*Earache or fever, crying, irritability.

1Persistent symptoms or absence of improvement in tympanic membrane.
• those children with bacterial infection who improve without antimicrobial agents, including 20% of episodes of AOM caused by *Streptococcus pneumoniae* and 50% caused by *H. influenzae*. As the practice of initial observation is stimulated by the guidelines of the US academies, we will learn more about the optimal criteria for choice of observation vs. initial antimicrobial therapy.

**Dutch Perspective**

On the basis of studies by van Buchem and colleagues and others, many physicians in Western Europe manage AOM by symptomatic treatment and observation and use antimicrobial agents only if the illness persists for 3 or more days. The Dutch guidelines for managing AOM are listed in Table 15. There is increased interest in this management plan because of concern for resistance of the bacterial pathogens of AOM. Surveillance of pneumococcal resistance suggests that a key factor in the incidence of resistant strains is the volume of antimicrobial drugs used in the community. Studies from the Netherlands indicate a rate of resistance that is among the lowest among reporting countries.

**American Perspective**

Because the low incidence of single and multidrug resistance is probably associated with the decreased volume of antimicrobial agent used in the community, and because otitis media is the most frequent reason for using antimicrobial drugs in children, the practice of observation alone for initial management of selected children was proposed by authoritative groups in the United States, including the American Academy of Pediatrics, the American Association of Family Physicians, and the American Academy of Otorhinolaryngology. A joint publication of guidelines for management of AOM was published in 2004 and provided the first recognition by US academies of initial observation rather than antimicrobial therapy for management of children diagnosed with AOM. The recommendation in the guidelines was that “observation without use of antibacterial agents in a child with uncomplicated AOM is an option for

<table>
<thead>
<tr>
<th>Table 15. GUIDELINES FOR MANAGEMENT OF ACUTE OTITIS MEDIA: DUTCH COLLEGE OF GENERAL PRACTITIONERS</th>
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</thead>
<tbody>
<tr>
<td><strong>Patients 2 Years and Older</strong></td>
</tr>
<tr>
<td>Analgesia; decongestive nose drops</td>
</tr>
<tr>
<td>Parent instructions:</td>
</tr>
<tr>
<td>Recovery within 3 days—no follow-up</td>
</tr>
<tr>
<td>Return if symptoms persist or worsen (pain ± fever ± sickness)</td>
</tr>
<tr>
<td>If drum perforates, follow-up 2 weeks after onset of running ear</td>
</tr>
<tr>
<td>If earache ± fever persist, amoxicillin (if contraindicated, erythromycin) for 7 days</td>
</tr>
<tr>
<td>Parent instructions:</td>
</tr>
<tr>
<td>Re-evaluate if no improvement after 48 hours of drug</td>
</tr>
<tr>
<td>If no improvement in ear signs—referral</td>
</tr>
<tr>
<td><strong>Patients 6 Months to 2 Years</strong></td>
</tr>
<tr>
<td>Act as for older children, but more active attitude related to higher probability of deterioration</td>
</tr>
<tr>
<td>Visit or phone contact 24 hours after initial examination</td>
</tr>
<tr>
<td>If no improvement—another 24 hours of observation or amoxicillin (if contraindicated, erythromycin) for 7 days</td>
</tr>
<tr>
<td>Contact 24 hours later; examination if necessary</td>
</tr>
<tr>
<td>If no improvement—referral</td>
</tr>
<tr>
<td><strong>Special Patients</strong></td>
</tr>
<tr>
<td>(Younger than 6 months, recurrent episodes [3 or more within a year], immunocompromised hosts)</td>
</tr>
<tr>
<td>Start amoxicillin (or erythromycin) for 7 days</td>
</tr>
<tr>
<td>Reevaluate at 24 hours</td>
</tr>
<tr>
<td>Refer if patient deteriorates</td>
</tr>
<tr>
<td>Follow-up 2 weeks after evaluation</td>
</tr>
</tbody>
</table>

selected children based on diagnostic certainty, age, illness severity, and assurance of follow-up. Observation is an appropriate option only when follow-up can be ensured and antibacterial agents started if symptoms persist or worsen.” The observation guidelines apply only to children with uncomplicated AOM and do not apply to recurrent or persistent AOM or to patients with underlying conditions that predispose to AOM. The recommendations for the various age groups with certain or uncertain diagnosis are listed in Table 16.

The management plan has the following elements:

- distinguishing “certain diagnosis” from “uncertain diagnosis”; certain diagnosis defined as rapid onset, signs of middle-ear effusion, and signs and symptoms of middle-ear inflammation;
- distinguishing “severe illness” from “non-severe illness”; severe illness defined as moderate to severe otalgia or fever of 39°C or greater;
- all infants under 6 months of age would receive antibacterial therapy;
- all infants 6 months to 2 years would receive antibacterial therapy, but observation could be considered for children with “uncertain diagnosis” and “non-severe illness”;
- toddlers 2 years of age or older would receive antibacterial therapy if the diagnosis is certain and the illness is severe; if the illness is not severe or the diagnosis is uncertain, the child may be observed when follow-up can be assured and antibacterial agents started if symptoms persist or worsen.

These guidelines have been the subject of extensive discussion. Wald discussed errors in design in many of the studies that were cited as evidence that antimicrobial agents had only a modest effect on the course of AOM. She noted that the evidence was insufficient to conclude that the role of antibiotics is minimal in most cases of AOM. Rather the inappropriate use of antibiotics for management of AOM was the result of misdiagnosis.

Some physicians in practice in the United States have responded to the suggestion of withholding antibiotics from children with AOM with skepticism. Dr. Frank Stefanec of Boardman, Ohio, noted that in the private practice of pediatrics in the United States, withholding antibiotics for the child with AOM would not be accepted by most parents: “they need to get the kid back to day care or school; they can’t afford another sleep-less night; the siblings are complaining that they can’t sleep with the baby crying all night; and they don’t want to pay another $20 co-pay.” His parents’ response is “Treat the kid and get him better. Don’t fool with him.” Dr. Stan L. Block of Bardstown, Kentucky, presented another perspective: “We should be kind to little children... the pain of AOM in younger children treated with antibiotics improves dramatically within a few days.” In contrast, Siegel and colleagues offered parents of children with uncomplicated AOM and temperature less than 101.5°F who had not had AOM in the previous 3 months an option of initial observation with pain medication and a prescription for an antibiotic. The acronym for the program was SNAP (safety-net antibiotic prescription). The parents were instructed not to fill the prescription unless symptoms either increased or did not resolve after 48 hours. The parents of 78% of 194

| Table 16. GUIDELINES FOR MANAGEMENT OF ACUTE OTITIS MEDIA – AMERICAN ACADEMY OF PEDIATRICS AND AMERICAN ACADEMY OF FAMILY PHYSICIANS |
|------------------|----------------|----------------|
| Age (mo)         | Certain Diagnosis* | Uncertain Diagnosis |
| < 6              | Antibiotics       | Antibiotics      |
| 6-24             | Antibiotics       | Antibiotics if severe |
| > 24             | Antibiotics if severe; Observe if not severe | Observe |

*Certain diagnosis = middle-ear effusion, rapid onset, sx middle-ear inflammation
†Non-severe = Mild otalgia; T < 39°C orally or < 39.5°C rectally in past 24 hours.
children who were enrolled reported that the pain medication alone was effective. The children in the study were one to 12 years of age and the average age was 5.0 years, indicating that the majority of patients were toddlers or school age. The observation alternative would appear to be readily acceptable for older children and their parents; the real test of acceptability would be a study of SNAP in the infant age group.

In summary, it is likely that appropriately diagnosed AOM will remain a disease that is treatable with an antimicrobial agent. Children under 2 years of age with a diagnosis of AOM should be treated with an antimicrobial agent. Observation may be considered for children 2 years of age and older with mild to moderate signs or uncertain diagnosis.

**MANAGEMENT OF OTITIS MEDIA WITH EFFUSION**

**Duration of Middle-Ear Effusion after AOM**

Persistence of middle-ear effusions after acute infection suggest a need to consider duration of fluid in the middle ear among the criteria for efficacy of an antimicrobial agent. The clinical trial by Kaleida and coworkers in which amoxicillin was compared with placebo in infants and children who had “non-severe” AOM showed that amoxicillin was associated with a statistically shorter duration of middle-ear effusion, compared with placebo, at the completion of treatment of each episode during the 1 year the subjects were in the study.13 Because middle-ear effusion is associated with hearing loss, this finding lends further support to our recommendation of treating with an antimicrobial agent all children who have AOM.31

Most therapeutic trials show similar durations of middle-ear effusions for the drugs evaluated, including drugs of different families such as penicillins, cephalosporins, sulfonamides, and macrolides. One of the few studies to demonstrate a difference in duration of effusion examined the efficacy of cefaclor and amoxicillin in children with AOM.243 Fourteen days after the onset of therapy, more children who received cefaclor had aeration of the middle ear (59 of 106, 55.7%) than did children who received amoxicillin (40 of 97, 41.2%; p = .05). On day 42, the proportion of children with normal aerated ears was the same: 68.9% for cefaclor and 67.5% for amoxicillin. It is possible that the differences on day 14 were related to differing effects of the antimicrobial drugs on the inflammatory response in the middle ear, whereas by day 42, host factors were dominant and little difference would be expected, irrespective of the antibiotic used.

The pathogenesis of prolonged duration of middle-ear effusion after middle-ear infection remains obscure. The failure of different types of antimicrobial agents to effectively alter duration despite the use of drugs that achieve high concentrations in tissue (macrolides) or high concentrations in serum and presumably middle-ear fluids (ceftriaxone) means that the drugs are inadequate as probes to provide insights into the pathogenesis of middle-ear effusion.

**Results of Clinical Trials of Antimicrobial Agents for Otitis Media with Effusion**

Bacterial pathogens are identified in approximately one-third of children with chronic otitis media with effusion on the basis of culture of middle-ear fluids at the time of tympanostomy tube placement.244-246 The role of the bacteria in persistence of middle-ear fluid is uncertain. One hypothesis is that the bacteria or their antigens or products are a factor in the continued secretion of fluids by the mucosa. Would a course of an appropriate antimicrobial agent assist in ridding the ear of fluid?

Many investigators have considered courses of 10 days to 6 months of different antimicrobial agents for children with persistent middle-ear effusion.

In greater Boston, trimethoprim-sulfamethoxazole (8 mg trimethoprim and 40 mg sulfamethoxazole/kg/d in 2 doses) was administered for 4 weeks to 200 children aged 2 to 5
years with middle-ear effusion present for longer than 12 weeks. The proportion of children who were free of effusion at the 4-week observation was significantly higher for the antibiotic group (58%) than for the observation group (6%).

Cefaclor was given to children for treatment of otitis media with effusion by Ernstson and coworkers. Children were randomized to receive cefaclor (20 mg/kg twice daily) or no antimicrobial therapy during the 10 days preceding the day appointed for surgery. On the day scheduled for surgery, 24 of 46 treated children had resolved the middle-ear effusion compared with 5 of 45 untreated children ($p < .001$). Eighteen of the 24 primarily healed children remained unoperated on at a follow-up period with a median of 20 months.

Amoxicillin-clavulanate administered for 1 month was compared with placebo in a randomized, double-blind study of Danish children with otitis media with effusion. The incidence of effusion was significantly reduced at the end of the treatment period (61% resolution in children who received amoxicillin-clavulanate contrasted with 30% in children in the placebo group), and the difference remained significant at 3 and 5 months but not at 10 months. van Balen and colleagues evaluated the efficacy of amoxicillin-clavulanate for children who had been observed to have bilateral middle-ear effusions for 3 months. 433 children, aged 6 months to 6 years, were randomized to receive amoxicillin-clavulanate (20 mg/kg amoxicillin) or placebo 3 times a day for 14 days. At the 2-week follow-up, the antibiotic-treated group had significantly lower rates of effusion in one or both ears (77% vs. 93%).

Amoxicillin was evaluated in 488 children in the greater Pittsburgh area who had persistent middle-ear effusion. Mandel and coworkers reported that those treated with amoxicillin for 2 weeks had higher rates of resolution of the effusion at 2 and 4 weeks after initiation of treatment than did placebo-treated control subjects.

Erythromycin-sulfisoxazole, cefaclor, amoxicillin, or placebo was administered in a sequel by the same investigators. The study reaffirmed that amoxicillin was effective in some children in resolving the middle-ear effusion; significantly more children in the amoxicillin group than in the placebo group had resolution of the effusion after 2 weeks of therapy (31.6% vs. 14.1%). The sample size was insufficient to identify the benefit of erythromycin-sulfisoxazole or cefaclor compared with that of placebo.

Sulfisoxazole in a therapeutic dosage schedule of 75 mg/kg/d in 2 daily doses for 6 months was administered to Ottawa children who were candidates for tympanostomy tube placement. The children were randomly assigned to the medical or surgical groups. Failures were defined as persistent middle-ear effusion with hearing loss of more than 25 dB, allergic reaction to the drug, or three or more episodes of AOM. At the conclusion of the 6-month period of medical therapy and 6 months after the operative procedure, 34% of the medically treated patients failed to clear the effusion, contrasted with 20% of the surgically treated children. Although the results were better in the children who received tympanostomy tubes, the success in two-thirds of children treated medically indicated the value of the course of an antimicrobial agent.

In addition to these studies, other investigators have used many study designs to evaluate medical therapies for persistent middle-ear effusion: erythromycin-sulfisoxazole in combination with a decongestant; erythromycin ethylsuccinate or sulfisoxazole; trimethoprim-sulfamethoxazole combined with prednisone; and cefaclor. In general, the regimens demonstrated short-term benefits. Where observations were of sufficient duration, long-term benefits were usually absent. Once antimicrobial treatment ended in the two trials evaluating the efficacy of amoxicillin and amoxicillin-clavulanate, the likelihood of recurrence of the middle-ear effusion was high, indicating that the benefit of the medical therapy was temporary. These data suggest that antibiotic therapy may not alter the underlying pathologic process, and observation is necessary for the child who clears the middle-ear effusion.
initially with medical therapy but may subsequently have a recurrence. In addition, there were three meta-analyses published in the span of a few years that addressed the efficacy of antimicrobial treatment of otitis media with effusion, and all three of the analyses showed efficacy.33,38,39

**Medical Therapy of the Child with Otitis Media with Effusion**

Although the data remain incomplete about medical therapy for the child with persistent middle-ear effusion, the available information is sufficiently consistent and compelling to warrant considering a plan for use of a prior antimicrobial agent for children who are candidates for ventilating tube placement. The interested reader should review the articles discussed in the preceding published reports. There are a number of variables among the investigations, including different enrolment criteria (age, duration of effusion, laterality of effusion), varying antimicrobial agents alone or combined with adjunctive therapy, duration of therapy, length of follow-up, and criteria for diagnosis, that the results of the studies have to be considered individually rather than cumulatively. A 2004 clinical practice guideline about otitis media with effusion reviewed management of otitis media with effusion, including the use of antimicrobial therapy.2

The Clinical Practice Guideline for Otitis Media with Effusion in Young Children, by Stool and colleagues, was an attempt by the Agency for Health Care Policy and Research, which is part of the Public Health Service, U.S. Department of Health and Human Services, to provide health care providers, policymakers, and the public with a guideline for management.33 The focus of the report was on children aged 1 to 3 years. The guideline panel of experts reached the following conclusions about management of otitis media with effusion in this age group:

1. Environmental risk factor control was recommended, such as avoidance of exposure to tobacco smoke, child day care, and bottle-feeding (as opposed to breast-feeding).

2. Antimicrobial treatment is effective and was recommended as an option to “observation” when the duration of the effusion is less than 3 months, and as an option to myringotomy and tympanostomy tube placement if the effusion persists for longer than 3 months, is bilateral, and is associated with a hearing deficit (defined as 20 dB hearing threshold level or worse in the better hearing ear). Tympanostomy tube placement is recommended when the effusion meets these criteria and persists for longer than 4 months.

3. Systemic decongestants and antihistamines are ineffective and were not recommended for any age group.

4. Steroid therapy was not recommended for any age group.

5. Adenoidectomy was not recommended for this age group.

6. Tonsillectomy was not recommended for any age group.

7. With regard to allergy management and other therapies, such as chiropractic, holistic, naturopathic, traditional or indigenous, and homeopathic, no recommendations were made.

We published our opinion about the strengths and weaknesses of this guideline.47 The guideline recommends either observation or active treatment with an oral antimicrobial agent when the duration of effusion is less than 3 months. We agree with this recommendation not only for children in the 1- to 3-year age group but also for children who are older than 3 years.

There are many factors that should enter into management decisions. One important factor is the status of the child’s hearing. The recommendation in the guideline is to test a child’s hearing when the effusion persists for 3 months or longer; if there is bilateral effusion and hearing loss of 20 dB or worse, treatment should be instituted.
We are concerned about this recommendation for the following reasons: (1) hearing loss is not the only factor that should enter into the clinician's decision-making process; (2) availability and feasibility of testing infants and children in the usual primary care setting are uncertain; and (3) the level of hearing loss selected is arbitrary and not based on data that established that a chosen level is more or less deleterious than another. More important, two clinical trials, in which hearing was tested monthly for up to 3 years in children who had persistent otitis media with effusion, revealed that hearing fluctuated during the period.\textsuperscript{44,45} In the first trial, subjects who had normal or only mild hearing loss were randomly assigned to be observed (i.e., control group), and one half of these children subsequently developed "significant" hearing loss during the first year of the trial and had tympanostomy tubes inserted because they were designated "treatment failures."\textsuperscript{44}

We also recommend assessing hearing when the effusion is chronic, but only if it is practical. Ideally, determination of the level of hearing would be helpful before tympanostomy tube insertion is considered.\textsuperscript{256} However, if the child is found to have relatively normal hearing at one time and is to be observed and not actively treated, we advise serial evaluations to determine whether the hearing has deteriorated. Formal audiometric testing is not necessarily needed at these intervals because gross evaluation of the hearing is often sufficient. Development of hearing loss or delay or alteration in the child's speech and language would prompt the clinician to actively treat, rather than continue to observe, the child.

In addition to the problem of hearing fluctuation associated with middle-ear effusion, structural changes (e.g., cholesteatoma, ossicular dislocation, adhesive otitis media) within the middle ear can develop (although the incidence is probably low) secondary to persistent inflammation, irrespective of the level of hearing in that ear. Numerous reports describe long-term sequelae in children who had cleft palate and chronic otitis media with effusion and who were evaluated before tympanostomy tubes were used as often as they are today; these included relatively high rates of permanent conductive and sensorineural hearing loss as well as development of cholesteatoma in an unacceptable number of patients.\textsuperscript{257}

Factors other than hearing loss that we consider important in making the decision to initiate medical treatment include the following:

1. the presence of bilateral effusion in contrast to disease in only one ear;
2. pneumatic otoscopic examination that reveals complete opacification and limited or no mobility of the tympanic membrane, as opposed to a tympanic membrane that has good mobility and is translucent in which only bubbles of air or an air-fluid level is present;
3. occurrence in young infants, because it is difficult to assess hearing in this age group in the usual clinical setting, and they are unable to communicate their symptoms and may have suppurative disease;
4. children who have had one or more insertions of tympanostomy tubes or an adenoidectomy in the past, who are probably at higher risk for persistent and recurrent disease than are those children who have had no prior surgery for otitis media;
5. presence of cleft palate or other craniofacial abnormalities, upper respiratory allergy, or a deficiency or impairment of immunologic status;
6. an associated acute purulent upper respiratory tract infection;
7. concurrent permanent conductive-sensorineural hearing loss, especially in children who rely on a hearing aid;
8. presence of dysequilibrium, vertigo, or tinnitus;
9. alterations of the tympanic membrane, such as severe atelectasis, especially a deep retraction pocket in the posterosuperior quadrant or the pars flaccida, or both;
10. middle-ear changes, such as adhesive otitis media or ossicular involvement;
11. effusion that persists for 3 months or longer (ie, chronic otitis media with effusion); and
12. when the episodes recur frequently, such as in 6 or more of the preceding 12 months.

We recommend amoxicillin for first-line therapy when antibiotic treatment is elected because the clinical trials by Mandel and coworkers demonstrated efficacy, and no other microbial agent has been more effective than amoxicillin. Mandel and colleagues showed that cefaclor and erythromycin-sulfisoxazole are not as effective. However, other antimicrobial agents that are β-lactamase stable drugs, such as amoxicillin-clavulanate, or an oral cephalosporin (other than cefaclor) in therapeutic doses may be effective because they provide more complete coverage. The dosage schedule is a therapeutic dosage for 2 weeks; to date, no published clinical trials have shown that therapy for longer than 2 weeks is effective. If children clear the effusion, they should be reevaluated at monthly intervals because of the high rate of recurrence of effusion. If children fail to clear the effusion and were candidates for tympanostomy tube placement, then the procedure is performed. The Clinical Practice Guideline about otitis media with effusion recommended that antimicrobial drugs should not be used for routine management of otitis media with effusion but should be considered as an option when surgery is avoided.

The efficacy of medical treatment such as decongestants, antihistamines, and steroids for decreasing the duration of middle-ear effusions, as well as the role of tympanostomy tube insertion and adenoidectomy, is discussed later in this review.

**ADJUNCTIVE THERAPIES FOR MANAGEMENT OF OTITIS MEDIA**

**Pain Management**

AOM may be associated with substantial pain as the middle-ear abscess expands and presses against the tympanic membrane. As the pressure against the membrane increases, there is pressure on the central vessels with resultant ischemia, necrosis, and perforation followed by elimination of the pain of the abscess. Myringotomy provides similar relief as occurs with spontaneous perforation.

Samuel Johnson in 1750 remarked, “Those that do not feel pain seldom think that it is felt.” Johnson’s observation may be pertinent to the limited discussion of alleviating or decreasing the duration of the pain of AOM, not only in infants but in all patients. Various products have been used for otalgia but none have been adequately studied. Mild to moderate pain may be managed with acetaminophen or ibuprofen or external application of heat or cold. Topical agents such as benzocaine may provide brief benefit in patients over 5 years of age. Narcotic analgesics with codeine or analogs should be reserved for patients with severe pain.

The 2004 Clinical Practice Guideline recommended that assessment of pain should be included in management of AOM and recommended various treatments: for mild to moderate pain – acetaminophen or ibuprofen; for severe pain – analgesia with codeine or analogs or myringotomy; additional remedies that might be of value in selected patients include distraction, external application of heat or cold, topical applications of benzocaine or naturopathic agents.

**Antihistamines**

Chonmaitree and colleagues performed a randomized, placebo-controlled trial of an antihistamine and a corticosteroid as adjuncts to antimicrobial therapy for children with AOM. Children 3 months to 6 years of age received one dose of intramuscular ceftriaxone and either chlorpheniramine maleate (0.35 mg/kg/d) and/or prednisolone (2 mg/kg/d) or placebo for 5 days: 44 children were enrolled in each of four groups – placebo, corticosteroid, antihistamine, and both drugs. Clinical outcome rates and recurrences did not differ with the treatment group, but children who received antihistamine alone had significantly longer duration of middle-ear effusion (median, 73 days) than did children in any of the groups (placebo = 25 days, corticosteroid = 23
days, both drugs = 36 days). These results suggest that antihistamines should not be used for treatment of AOM since the drug may prolong the duration of middle-ear effusion.

**Decongestants**

Nasal and oral decongestants, administered either alone or in combination with an antihistamine are currently among the most popular medications for treatment of otitis media with effusion. The common concept is that these drugs reduce congestion of the mucosa of the eustachian tube. Several investigators have evaluated decongestants with or without antihistamines, but the quality of design of the programs has varied, making the results difficult to interpret.260–266

In a double-blind study, Roth and coworkers showed that pseudoephedrine hydrochloride decreased nasal resistance in adults who had an upper respiratory infection.267 Past studies, using a modified inflation-deflation manometric technique to assess eustachian tube function in children who had had recurrent or chronic otitis media with effusion, showed that the eustachian tube obstruction was functional rather than mechanical.268,269 Further studies during periods of upper respiratory infection, however, showed that eustachian tube function was decreased from the baseline measurements at these times.270 This decrease was attributed to intrinsic mechanical obstruction superimposed on the functional obstruction. To determine the effect of an oral decongestant with or without an antihistamine on the ventilatory function of the eustachian tube, two separate studies were conducted in 50 children who had had chronic or recurrent otitis media with effusion and in whom tympanostomy tubes had been inserted previously.271 The first was a double-blind study that compared the effect of an oral decongestant, pseudoephedrine hydrochloride, with that of a placebo in 22 children who developed an upper respiratory infection during an observation period. Certain measures of eustachian tube function were significantly elevated above baseline values during the upper respiratory infection, which was attributed to intrinsic mechanical obstruction of the eustachian tube. The study found that oral decongestants tended to alter these parameters of eustachian tube function in the direction of the baseline (before upper respiratory infection) values. Even though the effect was statistically significant, the favorable changes in measurements of tubal function were only partial and were more prominent on the second day of the trial, after the subjects had received four doses of the decongestant. The administration of a nasal spray of 1% ephedrine, however, had no effect on eustachian tube function in these children.

The second study was a double-blind crossover design. In this study of 28 children who did not have an upper respiratory infection, the effect of a decongestant-antihistamine combination (pseudoephedrine hydrochloride and chlorpheniramine maleate) was compared with that of a placebo. When the subjects were given the decongestant-antihistamine medication, there were favorable changes in certain eustachian tube function measures that were not observed when the children received the placebo. Again, the response differences between the two groups were statistically significant.

Lildholdt and coworkers evaluated the effect of a topical nasal decongestant spray on eustachian tube function in 40 children with tympanostomy tubes.272 They assessed five parameters of tubal function, using a modified inflation test and forced-response test before and after spraying the nose with either oxymetazoline hydrochloride or placebo, according to a double-blind study design. The results showed no significant differences between the two treatment groups of the study in children who had severe tubal dysfunction, as documented by the constrictions of the eustachian tube lumen during swallowing.

Cantekin and coworkers, in a double-blind, placebo-controlled, randomized clinical trial of an oral decongestant and antihistamine combination in 553 infants and children with otitis media with effusion, showed no efficacy of these drugs.34 In addition, side effects such as irritability and sleepiness were more common in
children in the drug group than in subjects who received placebo. Mandel and associates reported that amoxicillin was effective compared with placebo in treatment of otitis media with effusion. \textsuperscript{35} However, adding a combined oral decongestant and antihistamine to amoxicillin provided no additional benefit over amoxicillin alone; more side effects were noted in children who received the decongestant and antihistamine combination.

Stillwagon and colleagues recruited 10 adult volunteers who had ragweed allergic rhinitis and underwent progressive intranasal challenge with ragweed pollen out of the ragweed season. \textsuperscript{273} Before the challenge, the subjects received either chlorpheniramine maleate and phenylpropanolamine or placebo in a double-blind, randomized crossover design. All the subjects had had objective measurements of nasal and eustachian tube function before and after the challenge. The investigators found a beneficial effect of the drug therapy on nasal and eustachian tube function compared with placebo, and concluded that there is a role for antihistamine-decongestant treatment of allergic rhinitis as well as of potential allergen-induced eustachian tube dysfunction. Turner and Darden evaluated the effect of intranasal instillation of a topical adrenergic decongestant, phenylephrine nose drops, on decreasing abnormal middle-ear pressures that developed in infants with a common cold. \textsuperscript{274} They found no significant difference in abnormal negative middle-ear pressures between subjects randomized to receive the topical decongestants and those randomized to receive placebo nose drops 1 hour after instillation.

The conclusion from these studies is that topical or systemic decongestants and antihistamines for otitis media with effusion are not warranted but may be effective for less severe conditions such as eustachian tube obstruction. \textsuperscript{271} These agents may also be effective for those patients who have allergic rhinitis causing their tubal dysfunction. \textsuperscript{273} In children receiving systemic decongestants and antihistamines, however, side effects are common, and some, such as visual hallucinations, are disturbing. Extended use of the topical nasal decongestant oxymetazoline hydrochloride may cause rebound nasal swelling in adults, and the effect of long-term use in children has not been reported. In a randomized, double-blind, placebo-controlled study by Clemens and colleagues, the combination of an antihistamine-decongestant did not even relieve the symptoms of the common cold in 59 preschool children, but it did have a significantly greater sedative effect than placebo. \textsuperscript{275}

The Clinical Practice Guidelines for Otitis Media with Effusion published in 1994 and reiterated in 2004 concluded that antihistamine-decongestant therapy is ineffective and did not recommend treatment of this disease with these agents for infants and children of any age. \textsuperscript{2,33}

### Corticosteroids

New insights into the pathogenesis of inflammation and the key roles that inflammatory mediators play have directed investigators to use anti-inflammatory drugs for prevention of central nervous system disease and resultant sequelae. \textsuperscript{276} The results of animal studies indicated efficacy of dexamethasone to reduce brain water content, cerebrospinal fluid pressure, cerebrospinal fluid pleocytosis, lactate concentration, tumor necrosis factor activity, and other indices of meningeal inflammation. These studies were the basis for a series of investigations in children with meningitis. The results indicated efficacy of dexamethasone in prevention of hearing loss and other neurologic sequelae when the drug was administered at the time of or before use of antimicrobial agents for infants with meningitis caused by \textit{H. influenzae} or \textit{Streptococcus pneumoniae}.

Rosenfeld and colleagues reported the results of their meta-analysis of the effect of systemic steroids on otitis media with effusion. \textsuperscript{36} They included 8 of the 10 published studies in their analysis and found that systemic steroids were beneficial, especially in combination with antimicrobial therapy, but concluded that the question of safety and efficacy still had not been adequately answered. However, Berman recom-
mended a regimen of corticosteroid and antibiotic for management of otitis media with effusion persisting for 6 to 9 weeks or longer: prednisone, 1 mg/kg/d in 2 divided doses for 7 days, combined with a broad-spectrum antibiotic, such as trimethoprim-sulfamethoxazole, for 21 days. He estimated the probability of cure of the effusion was 15% for observation only, 39% for antibiotic alone, and 64% for antibiotic plus steroid.277

Hemlin and colleagues, in a randomized, double-blind, placebo-controlled study, evaluated the effect of a combination of cefixime and betamethasone for treatment of chronic otitis media with effusion in 142 children aged 2 to 12 years.278 They found a 24% rate difference between cefixime with betamethasone and cefixime with placebo, but no long-term effect because of the high relapse rate in both groups; both groups were significantly better than no treatment (placebo), but again, no long-term efficacy was reported.

More recently, Mandel and coworkers reported the outcome of a randomized, double-blind, placebo-controlled clinical trial of the effect of the combination of amoxicillin (40 mg/kg/d in 3 doses a day for 14 days) and prednisolone (0.5 mg/kg 2 times a day for 10 days, then 4 times a day for 4 days) in 144 children aged 12 months to 9 years who had chronic otitis media with effusion.279 The rate difference in the proportion who were effusion-free at 2 weeks between the amoxicillin with steroid-placebo group and the amoxicillin with active-steroid group was approximately 17%, but this effect was less at 4 weeks and was no longer statistically significant. The investigators concluded that the lack of a dramatic and long-lasting effect precluded a recommendation for use in all children with chronic otitis media with effusion.

From these few studies, it appears that a short course of systemic corticosteroid therapy is of uncertain safety and efficacy in alleviating the problems of otitis media with effusion in children. At this time, the potential adverse side effects associated with administration of a systemic corticosteroid for otitis media do not appear to justify its routine use in infants and children. Indeed, the Clinical Practice Guidelines published in 1994 and reiterated in 2004 concluded that corticosteroid therapy is not recommended for infants and children of any age because of its unproven efficacy and potential adverse side effects.2,33

**Surfactant**

Because there is some evidence that surfactant may play a role in eustachian tube function,280–282 there may be a role for treatment of eustachian tube dysfunction and otitis media with nebulized surfactant. Indeed, studies in animal models have demonstrated some beneficial effect of this therapy,283,284 but clinical studies with nebulized surfactant have not been reported.

**Montelukast Sodium**

Montelukast sodium (Singulair, Merck, West Point, PA), is a selective leukotriene receptor antagonist that is extensively used for relief of symptoms of allergic rhinitis and for prophylaxis and chronic treatment of asthma. Because leukotrienes are associated with development of inflammation as well as airway edema and smooth muscle contraction, Coombs suggested a potential value in decreasing the duration of effusion following AOM. A pilot study of treatment of AOM with amoxicillin with or without montelukast suggested efficacy of montelukast in reducing the time of effusion following an episode of AOM.285

**Chiropractic Manipulation**

Chiropractic manipulation is used for children with acute and chronic otitis media. Sawyer and colleagues conducted a pilot study in 20 patients aged 6 months to 6 years with otitis media with effusion and concluded that a randomized, controlled trial would be feasible.286
**Osteopathic Manipulation**

Mills and colleagues studied the effects of osteopathic manipulative treatment as an adjunctive therapy in children with recurrent AOM. Children who had the intervention contrasted with control patients had fewer episodes of AOM and fewer surgical procedures during the 6 months following enrolment.

**Allergy Control**

Because the precise role of allergy in the development of otitis media with effusion has not been documented, and because it can be difficult to establish or confirm the diagnosis of allergy with certainty, it is currently not possible to quantify the relative efficacy of allergic management of otitis media with effusion in children. Despite this dilemma, owing to a lack of information, some clinicians advocate allergy management for infants and children who have recurrent or chronic otitis media with effusion. Other physicians doubt that allergy plays any part in the origin of otitis media with effusion and rarely, if ever, consider directing their treatment of a patient with this problem to a possible underlying allergy. For example, Bluestone and Shurin and Paradise, in extensive reviews of otitis media in infants and children, did not include control of allergy as a management option. On the other hand, some include allergy in the differential diagnosis if there are one or more of the following: (1) past or present atopy in the child; (2) family history of allergy; or (3) signs of upper respiratory allergy present at the time of the clinical examination. These investigators have employed various regimens in their management of allergies, but all have reported obtaining good results from such treatment. However, in a double-blind, crossover study by Friedman and coworkers that involved adult volunteers without otitis media, eustachian tubes became obstructed when the subjects were challenged intranasally with the antigen to which they were sensitive, but not when they were challenged with a placebo (ie, an antigen to which they were not sensitive). In a subsequent study, Skoner and coworkers showed that nasal function and eustachian tube function were altered during natural pollen exposure. They also found that the eustachian tube is anatomically and functionally altered in type I allergic reactions of the nose, but tubal dysfunction is transient and does not result in a middle-ear effusion. They concluded, however, that this dysfunction does interfere with middle-ear and tubal clearance.

Hurst, as a sole author and with Venge, demonstrated an elevated level of eosinophil cationic protein in the middle-ear effusion and mucosa of patients with allergies and otitis media, which suggests that type I allergy has a role in the pathogenesis of otitis media. In a more recent study, Hurst and Venge found marked elevations of myeloperoxidase in the middle ears of atopic patients with chronic otitis media with effusion, as compared with non-atopic individuals with middle-ear effusions, which suggests that atopy may contribute to the pathogenesis of the disease.

Bernstein and coworkers suggest that there is some supporting evidence that food immune complexes, mainly dairy products, may be an important etiologic factor in otitis-prone infants. However, there is no study reported that has shown elimination of dairy products in otitis-prone infants to be effective. Unfortunately, none of these studies were based on randomized, controlled trials in children with otitis media. Nevertheless, there is some evidence that chronic and recurrent otitis media with effusion may be associated with upper respiratory tract allergy. Therefore, until our knowledge of the origin, method of diagnosis, and management of allergy as related to otitis media with effusion increases, managing the allergy should be considered a treatment option when a child has recurrent or chronic middle-ear disease and evidence of upper respira-
tory tract allergy. The clinician should be prompted to further evaluate the possibility that the child has an upper respiratory tract allergy by a history of itching of the eyes, nose, or throat; paroxysms of sneezing; and chronic or frequently recurrent watery rhinorrhea with or without the classic signs of nasal allergy. However, because no convincing clinical trials of the treatment options have been reported, no single method of treatment can be recommended. Currently, we recommend allergy control and, in selected children, immunotherapy. Even though clinical trials that evaluated the safety and efficacy of the newer topical nasal steroids (eg, beclomethasone aqueous) have not been reported, we do recommend their use in the hope that improved nasal function will improve eustachian tube function and subsequently prevent and even treat middle-ear effusion. Intranasal cromolyn sodium may also be beneficial, but again, no data support its use, and most children have difficulty with compliance because it must be used frequently during the day. Even though there are no data to support use of the antihistamine-decongestant combinations in allergic children who have otitis media, there is some evidence from the study by Stillwagon and colleagues that these agents may benefit adults. A study in an animal model of otitis media and nasal allergy by Suzuki and colleagues showed a beneficial effect of the anti-allergic drug azelastine hydrochloride to promote clearance of middle-ear effusion.

**PREVENTION OF RECURRENT EPISODES OF AOM**

Preventing new episodes of AOM in children who are otitis-prone may be achieved by several surgical and medical procedures and altering the environment. Chemoprophylaxis with use of modified courses of antimicrobial agents for prolonged periods has been studied extensively and found to be successful. New products with anti-infective qualities are in early stages of investigation for prevention of recurrent AOM. Xylitol was demonstrated in two studies to reduce the incidence of AOM in Finnish children; oligosaccharides prevent microbial pathogens from adhering to carbohydrate receptors on mucosal cell surfaces and are currently under study in Finland for prevention of otitis media. Immunization with the new pneumococcal heptavalent conjugate vaccine (PCV-7) and various virus vaccines suggests promise in limiting the impact of infectious agents in causing acute infections. Tympanostomy tube placement and adenoidectomy have been effective in reducing the incidence of acute middle-ear infections. Finally, parents of children with problems of middle-ear infections can be empowered to limit the risks for acute infection in their child.

**Chemoprophylaxis**

The rationale for chemoprophylaxis to prevent AOM is that a modified dose of antimicrobial agents administered during a prolonged period will decrease the rate or intensity of upper respiratory tract colonization by bacterial pathogens. Once the bacterial load is reduced, even though the child is still vulnerable to viral respiratory infections or allergic reactions that can obstruct the eustachian tube, the proliferation of bacteria that produces AOM is less likely to occur. The increased incidence of multidrug bacterial resistance and the associated prior use of antimicrobial agents as a risk factor has dampened enthusiasm for chemoprophylaxis to assist the child with recurrent episodes of AOM. The use of a modified dose of an effective antimicrobial agent may be expected to eliminate sensitive organisms but may result in selection and proliferation of resistant strains. Nevertheless, chemoprophylaxis may be of value for selected children who suffer from recurrent AOM.

To consider chemoprophylaxis, the physician must be assured that the benefits of decreased risk of infection outweigh the risks of prolonged use of the drug. For any form of chemoprophylaxis, the following criteria should be considered:

1. The patient is at risk if infection occurs.
2. The microorganisms are known and are consistent causes of disease.
3. The microorganisms are unlikely to develop resistance to the drug used for a prolonged course.

4. The drug is well tolerated and can be administered in a convenient dosage and form.

5. The drug has limited side effects or toxicity.

The bacteriology of otitis media is well documented and consistent; Streptococcus pneumoniae, M. catarrhalis, and nontypeable strains of H. influenzae are the major bacterial pathogens. The sulfonamides and penicillins are available in a variety of convenient forms that are well tolerated in infants and older children. Drug toxicity is minimal with these two families of drugs, but allergic reactions are to be expected. The most important concern, at present, is the risk of selective pressure of the drug for emergence of resistant organisms. The concern for development of resistance warrants careful selection of children who would, on balance, benefit from a chemoprophylactic regimen.

Children are at risk for recurrent episodes of AOM during a relatively short period of life: most episodes occur between the ages of 6 and 24 months. If the child who is susceptible to recurrent otitis media could be protected from infection during this period, the morbidity of middle-ear disease in infancy might be limited.

There are a paucity of data about the bacteriology and antimicrobial susceptibility of bacteria responsible for breakthrough episodes during chemoprophylaxis. The few studies of middle-ear aspirates of episodes of AOM during chemoprophylaxis suggest that the same species of bacteria are responsible—pneumococcus, H. influenzae, and M. catarrhalis—but there may be selection of resistant strains. In their study of amoxicillin prophylaxis versus placebo, Casselbrant and colleagues found the same proportion of bacterial species responsible for breakthrough episodes, including pneumococci and β-lactamase–producing H. influenzae and M. catarrhalis, no unusual pathogens emerged to colonize the infants or cause AOM; no susceptibility assays were done. An increase was identified in the number of penicillin-resistant bacteria in the oropharynx of 20 children receiving amoxicillin for prophylaxis of otitis media studied by Brook and Gober.

None of the investigators of published reports of use of chemoprophylaxis noted an increase in side effects or toxicity in the children who received prolonged modified courses of chemoprophylaxis. The incidence of side effects was no greater than would be expected from use of the same drugs for treatment of acute infections.

**Published Reports**

Chemoprophylaxis is extensively used to manage recurrent episodes of AOM. A survey of children who had at least one episode of AOM during the year and were cared for in a large health insurance plan in New England in 1994 to 1995 identified use of chemoprophylaxis in 9% of the children for a mean duration of approximately 60 days. The drugs used for prophylaxis were amoxicillin, trimethoprim-sulfamethoxazole, and sulfisoxazole; approximately one-third of patients receiving chemoprophylaxis took each drug. Breakthrough episodes were most frequent in the children receiving sulfisoxazole (20.4%) and least frequent in children receiving amoxicillin (13.2%) and trimethoprim-sulfamethoxazole (15.5%). There are data from subsequent years of analysis that the percentage of children who received chemoprophylaxis declined from 1994 to 1995 (9%) and 1997 to 1998 (5.6%).

Among the first investigations of chemoprophylaxis for children with recurrent AOM, and the most influential, was the study of Perrin and coworkers. Sulfisoxazole or a placebo was administered to 54 children aged 11 months to 8 years who had three or more episodes in the previous 18 months or a total of five episodes. In the double-blind trial, children received a placebo or 500 mg of sulfisoxazole twice a day for 3 months. They were then switched to the alternative regimen for another 3-month period. A significant decrease in new episodes of AOM occurred in the group of children receiving the antimicrobial agent. The older children, aged 6 to 8 years, showed minimal or insignificant decrease...
in incidence of otitis media when receiving the prophylactic regimen.

Many controlled clinical trial reports of modified courses of antimicrobial agents compared with placebo, surgery, or historical controls have been published. The majority of studies used a sulfonamide or ampicillin or amoxicillin; a few evaluated penicillin V or a macrolide (erythromycin or azithromycin), and some studies included a group with ventilating tube placement. Most of the reports indicated benefit to the enrollees: efficacy of amoxicillin varied from 44 to 67%; efficacy of sulfonamides (including trimethoprim-sulfamethoxazole) was 40 to 88%, with one reporting a low value of 8%. Teele and colleagues evaluated antimicrobial prophylaxis in infants who had experienced either a first episode of AOM before 6 months of age or two episodes before the first birthday, failure was defined as two discrete episodes of AOM during prophylaxis or 90 continuous days of middle-ear effusion. One hundred and seventeen children were randomized to receive amoxicillin, sulfisoxazole or placebo. Six months after entry into the study, 70% of children who received amoxicillin were AOM-free, contrasted with 47% who received sulfisoxazole and 32% who received a placebo. An exception to the experience of benefit to those who received chemoprophylaxis is a study by Roark and Berman; no benefit was identified for children who received amoxicillin in a dosage of 20 mg/kg/d administered in one or two doses per day.

The efficacy of intermittent use of the prophylactic agent with first signs of upper respiratory tract infection was variable. Because the signs of upper respiratory tract infection and AOM may be concurrent, intermittent use appears less likely to succeed than continuous use of chemoprophylaxis. A meta-analysis summarizing results of studies of chemoprophylaxis concluded that the benefit to treated children was an average decrease in the number of episodes of AOM of 0.11 episodes per patient-month, or approximately one episode per year. Children who were most likely to benefit by chemoprophylaxis were younger than 2 years and in out-of-home child care.

Few of the studies evaluated middle-ear effusion or asymptomatic middle-ear effusion. Mandel and colleagues identified efficacy of amoxicillin in preventing recurrent episodes of otitis media with effusion and decreased percentage of time with middle-ear effusion as well as decreased incidence of AOM. The rates per person-year of new episodes of disease in the amoxicillin and placebo groups were as follows: AOM, 0.28 versus 1.04; and otitis media with effusion, 1.53 versus 2.15.

The results of the various studies of chemoprophylaxis should be evaluated separately rather than cumulatively because of the variations in criteria for enrollees, differences in number of patients evaluated, different durations of drug use, and varying periods of observation. Nevertheless, the pattern of decreased number of episodes in children who receive prolonged courses of appropriate antimicrobial agents is consistent.

Plan for Prophylaxis

We proposed a plan for chemoprophylaxis in the first issue of The Pediatric Infectious Disease Journal in January 1982 that has continued to be of value over the years. The principles have been reaffirmed by the American Academy of Pediatrics Report of the Committee on Infectious Diseases and a consensus statement by members of the American Academy of Pediatrics and the CDC in 1998. The 2004 guidelines of the AAP and AAFP did not address chemoprophylaxis.

Who?

Children who have had three distinct and well-documented episodes of AOM in 6 months or four episodes in 12 months should be considered for the program. Because of the epidemiologic data indicating that children who have episodes of acute infection early in life, or who have siblings with severe and recurrent ear infections, are otitis-prone, children who have one episode in the first 6 months and have a family history of ear infections, or have two
episodes in the first year of life, should be considered for chemoprophylaxis.

Which Drugs?
A sulfonamide and amoxicillin were the agents used most frequently in published studies and provide the advantages of demonstrated efficacy, safety, and low cost. Trimethoprim-sulfamethoxazole is effective and extensively used, but the manufacturer states in the package insert that the drug is not indicated for prophylaxis or prolonged administration for otitis media. A survey of children in a large group health insurance program indicated that fewer children receiving prophylactic regimens had breakthrough episodes with use of amoxicillin (13.2%) and trimethoprim-sulfamethoxazole (15.5%) than with sulfisoxazole (20.4%).

What Dosage?
Half the therapeutic dose is administered once a day (usually bedtime offers maximal compliance, but any consistent time during the day is satisfactory): amoxicillin, 20 mg/kg; sulfisoxazole, 50 mg/kg. The recent recommendation to double the therapeutic dosage of amoxicillin for acute infection suggests that an increase in the prophylactic dosage to 40 mg/kg once a day may be warranted.

How Long?
During the winter and spring, when respiratory tract infections are most frequent, treatment is advised for a period up to 6 months.

What Type of Follow-up?
Children should be examined at approximately 2-month intervals when they are free of acute signs to determine whether middle-ear effusion is present. Management of prolonged middle-ear effusion should be considered separately from prevention of recurrences of acute infection.

How Should Acute Infections Be Treated?
Acute infections are expected to occur, although at a lesser rate, during the course of prophylaxis.

The infection should be treated with the alternative regimen since the modified dosage schedule may have resulted in selection of bacteria resistant to the prophylactic regimen. An effective oral or parenteral cephalosporin (ceftriaxone) or amoxicillin-clavulanate is a suitable alternative for children on a prophylactic regimen of amoxicillin or a sulfonamide.

Xylitol
Finnish investigators demonstrated that xylitol sugar was effective in preventing new episodes of AOM. Xylitol is a five-carbon sugar alcohol that can be produced from birch trees and is found in various fruits, such as raspberries and plums. Xylitol is used extensively as a sweetener in toothpaste, chewing gum, and other foods. Because xylitol inhibits growth of Streptococcus mutans, it is used throughout Scandinavia and Great Britain to prevent dental caries. Kontiokari and colleagues demonstrated inhibition of growth of Streptococcus pneumoniae in vitro, stimulating the investigators to develop protocols to prevent AOM.

Two published studies have demonstrated efficacy of xylitol in preventing AOM. In the first, xylitol or sucrose (control) chewing gum was administered five times a day to 306 children in out-of-home group day care (mean age, 4.9 years). During the 2-month period of observation, one or more episodes of AOM were experienced by 20% of children receiving control (sucrose) gum compared with 12.1% of the children receiving xylitol gum. There was no difference in carriage of pneumococci in the treated and control children. In the second study, 857 healthy children were recruited from day care centers to receive control or xylitol syrup, control or xylitol chewing gum, or xylitol lozenges five times a day during a 3-month period of observation. The incidence rates of AOM per patient-year were 3.03 in control and 2.01 in xylitol syrups ($p = .006$), 1.69 in control, and 1.04 in xylitol chewing gum ($p = .012$), and 1.33 in the lozenge group. The higher rates in the syrup group were due to the younger age of patients.
who received syrup rather than gum or lozenge. Xylitol administered only during respiratory infections failed to prevent AOM.319 These results are promising; however, corroborative studies need to define optimal use in children who are otitis-prone, to develop data on the pharmacokinetics and mechanism of action of xylitol, and to consider different dosage schedules that would increase compliance (contrasted with the five times per day schedule used in the original studies).

Oligosaccharides

Many viral and bacterial respiratory pathogens bind to carbohydrate receptors on the respiratory mucosa. Natural oligosaccharides act as decoys in the mucosa (and in saliva, tears, urine, sweat, and breast milk) to bind to the carbohydrate-binding proteins of the microbial pathogens and prevent attachment. One of the major defenses for the neonate is the ability of oligosaccharides in breast milk to prevent bacterial attachment and protect against respiratory and enteric infections. Anderson and colleagues showed that a human milk oligosaccharide could inhibit binding of Streptococcus pneumoniae to desquamated cells of the human nasopharynx and oropharynx.320 Zopf and Roth described the potential of large-scale manufacture of human oligosaccharides for use in studies of prevention of various infectious diseases, including AOM.321 Oligosaccharides interfere with establishment and progression of experimental pneumococcal pneumonia. Intratracheal administration of the oligosaccharides together with bacteria decreased pneumococcal load in the lungs of rabbits and protected against bacteremia. Intranasally administered oligosaccharides prevented colonization of the nasopharynx of infant rats.322 The first and only clinical trial of an oligosaccharide for prevention of AOM was performed by Ukkonen and colleagues.323 In a study in Finland, 507 children were enrolled in a randomized, double-blind, placebo-controlled trial over a 3-month period. The oligosaccharide failed to prevent new episodes of AOM, and the nasopharyngeal carriage of Streptococcus pneumoniae, H. influenzae, and M. catarrhalis was not affected by treatment.

Zinc

Weekly zinc supplements were found to be protective against pneumonia and suppurative otitis media in a study of poor, urban children in southeastern Bangladesh.324 Zinc deficiency is common in these populations, and daily regimens of zinc had been found to prevent pneumonia mostly in children older than 2 years of age. Children two to 12 months of age were enrolled and received weekly supplements for one year. Suppurative otitis media was defined as purulent ear discharge. Zinc had a protective effect against suppurative otitis media: there were 394 episodes in 427 child years in the zinc group contrasted with 572 episodes in 511 child years in the placebo group (p = .002). These studies were performed in children who were likely to be zinc deficient; no similar studies of the effect of zinc on the incidence of suppurative otitis media have been performed in developed countries where zinc deficiency is likely to be less frequent.

Vaccines and Immunoprophylaxis

Pneumococcal Vaccines

Although a pneumococcal polysaccharide vaccine was introduced in the United States more than 25 years ago, it had limited efficacy in infants two years of age and younger and only a modest effect in prevention of AOM. In contrast, the PCV-7 is immunogenic in infants beginning at the age of 2 months and has demonstrated efficacy for prevention of bacteremia, meningitis, pneumonia, and otitis media.19,20,325 The vaccine was approved by the FDA in February 2000, and more than 80 million doses had been distributed in the United States by the end of 2005 (Peter Paradiso, personal communication, December 2005). An 11-valent pneumococcal polysaccharide vaccine conjugated with an outer membrane protein of nontypeable H. influenzae was found to be effective against AOM due to Streptococcus
pneumoniae and H. influenzae but was not commercially available as of spring 2006. The serotypes present in the available pneumococcal vaccines are listed in Table 17.

**History of the Development of Pneumococcal Vaccines.** The first pneumococcal vaccine was a whole-cell, heat-killed product that was found to be effective in reducing mortality from pneumonia in South African mine workers. The success of the vaccine apparently went unappreciated, and little attention was paid to the development of a vaccine during the next 20 years. In the 1930s, the type specificity and immunogenicity of the pneumococcal capsular polysaccharide was described. Type-specific serum therapy produced from immunization of horses with capsular polysaccharides was effective in reducing the mortality of bacteremic pneumococcal pneumonia. The first capsular polysaccharide vaccine prepared from four types was evaluated in Air Force recruits during World War II; the vaccine was 87% effective in reducing disease caused by the four vaccine types, but it had no effect on disease due to other types that were responsible for most disease among the recruits. Again, there was little follow-up to the initial success of the polysaccharide vaccine, probably because of the dramatic results of treatment with penicillin and the broad-spectrum antimicrobial agents. Not until the 1970s was a 14- and then a 23-type pneumococcal polysaccharide vaccine introduced and the efficacy of a pneumococcal vaccine for preventing AOM first evaluated. The results were disappointing for the group in greatest need: children younger than 2 years. Few of the types in the vaccine were sufficiently immunogenic to provide protection against invasive disease or otitis media in infants. The problem of decreased immunogenicity of polysaccharide vaccines for infants was resolved with development of the conjugate technology used successfully to produce the H. influenzae type b vaccine and the introduction of PCV-7.

### Pneumococcal Polysaccharide Vaccines.

Although the pneumococcal polysaccharide vaccines are of limited importance in preventing otitis media in infants, the experience in otitis media trials with the polysaccharide vaccines is worthy of presentation because of the positive and negative results obtained.

More than 90% of isolates of Streptococcus pneumoniae from middle-ear fluids are among the 23 types present in the pneumococcal polysaccharide vaccines. The 23 types are listed in Table 17. Each polysaccharide is extracted, separated, and combined into the final vaccine. A 0.5-mL dose contains 25 mg of each polysaccharide type dissolved in isotonic saline solution containing 0.25% phenol as a preservative; it is administered subcutaneously or intramuscularly. The vaccine is well tolerated. Children who receive the vaccine have some pain, erythema, and induration at the site of injection, and a small number have a minimal elevation in temperature.

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Each antigen produces an independent antibody response. In children older than 2 years and adults, antibody develops in approximately 2 weeks. Studies in children indicate that, as with polysaccharide vaccines prepared from capsular materials of *H. influenzae* type b and *Neisseria meningitidis* group C, children younger than 2 years exhibit unsatisfactory serologic responses to a single-dose regimen. *N. meningitidis* group A and *Streptococcus pneumoniae* type 3, however, evoke significant antibody responses in infants as young as age 6 months, suggesting that some polysaccharides are adequate immunogens in young infants.332,333

Investigations of 8- and 14-type pneumococcal vaccines to prevent recurrent episodes of AOM were initiated in 1975 in Boston, MA, and Huntsville, AL, and in 1977 in Oulu and Tampere, Finland.142,333–335 Types of *Streptococcus pneumoniae* present in the vaccine were isolated less frequently from middle-ear fluids of children in the vaccine group with acute episodes of otitis media after immunization than from children in the control group in each of the three studies.

Despite a decrease in middle-ear infections due to pneumococcal types present in the vaccine, the clinical experience of children younger than 2 years in the vaccine groups was similar to that of children in the control groups. In general, the number of children who had one or more episodes of AOM and the mean number of episodes of AOM after immunization were similar in the vaccine and control groups.

**Conjugate Pneumococcal Polysaccharide Vaccines.** A heptavalent conjugate vaccine employing CRM 197 as the protein carrier (PCV-7 Prevnar, Wyeth Vaccines, Philadelphia, PA) was approved by the FDA in February 2000. The seven serotypes available in PCV-7 are listed in Table 17. The vaccine is immunogenic in children as young as 2 months325; infants responded to each conjugate polysaccharide type with concentrations of antibody believed to be protective against invasive disease. Protective titers were achieved after doses administered at ages 2, 4, and 6 months but waned during the following 6 months, requiring a booster between the ages of 12 and 15 months. Post-licensure surveillance of PCV-7 for safety indicates absence of unanticipated severe adverse events following administration of the vaccine.336

Two clinical trials, one in northern California and the second in Finland, established the efficacy of PCV-7 for prevention of pneumococcal AOM. Beginning in October 1995, the heptavalent conjugate pneumococcal vaccine was administered to almost 38,000 children in northern California in a double-blind trial.20,325 The children received either the pneumococcal conjugate vaccine or meningococcus type C CRM 197 vaccine. The vaccine was effective in preventing vaccine-type invasive disease (97.4% efficacy in fully vaccinated cases) and pneumonia (18% decrease for radiographically identifiable disease). For otitis media, data were available from clinical records of office visits, emergency department visits, and hospitalizations. The vaccine reduced the number of episodes of otitis media and number by otitis media visits by 7.0% and 7.8%, respectively; it reduced the antibiotic prescriptions by 5.8% and reduced the number of procedures for placement of ventilating tubes by 23%.

Bacteriologic efficacy of PCV-7 was evaluated in studies of Finnish children (Table 18).19 The same schedule was used as for the California studies; the sole difference was the use of hepatitis B vaccine as the control. Bacteriologic diagnosis was based on aspiration of middle-ear fluids in patients with AOM. The reduction in the number of episodes in the per-protocol analysis was 57% against culture-confirmed, serotype-specific AOM, 34% against culture-confirmed pneumococcal AOM (irrespective of the serotype), and 6% against AOM irrespective of etiology. Of concern was a 33% increment in nonvaccine serotype AOM in children who received the pneumococcal vaccine and an increase of 11% in episodes of AOM due to *H. influenzae* in pneumococcal immunized children.

In the Czech Republic and Slovakia an 11-valent vaccine with pneumococcal conjugated to
a carrier protein D of nontypeable *H. influenzae* was evaluated for protection against AOM. The vaccine prevented 52% of AOM episodes due to pneumococcal vaccine serotypes and 35.3% of episodes due to nontypeable *H. influenzae*. The vaccine reduced the incidence of AOM due to vaccine-related cross-reactive pneumococcal serotypes by 65.5% and did not significantly change the incidence of AOM due to non-vaccine serotypes.

Immunization of children with PCV-7 followed by the 23-valent pneumococcal polysaccharide vaccine in children one year of age and older failed to reduce the incidence of AOM in children who had two or more episodes of AOM in the year before entry into the vaccine trial. The same vaccine regimen had no effect on recurrent otitis media with effusion in children two years of age and older who had prior histories of persistent otitis media with effusion. These data suggest that children with risk features for recurrent AOM or persistent otitis media with effusion must receive the conjugate pneumococcal vaccine in the first year of life if the vaccine is to be effective. Alternatively, some children with risk features for severe and recurrent AOM are not likely to be protected by the conjugate vaccine.

Universal immunization of infants with PCV-7 alters the microbiologic flora of the upper respiratory tract. Nasopharyngeal carriage of pneumococcal serotypes in PCV-7 decreased in immunized children but was accompanied by an increase in carriage of non-vaccine types. In addition, immunization with PCV-7 may affect the composition of bacterial pathogens in the nasopharynx. Studies in Israel and the Netherlands demonstrated that carriage of *Streptococcus pneumoniae* vaccine serotypes was inversely related to carriage of *Staphylococcus aureus*. The Dutch authors suggested this resulted from competition with colonization of vaccine-serotype pneumococci and *Staphylococcus aureus*. Block and colleagues in Bardstown, KY, noted a change in bacteria isolated from middle ear fluids in children with refractory AOM for years prior to and following the introduction of PCV-7. The proportions of *Streptococcus pneumoniae* isolates decreased from 48% in 1992 to 1998 to 31% for the years following the introduction of PCV-7 (2000 to 2003), whereas the recovery of nontypeable *H. influenzae* increased from 41% to 56% for the two time periods. Casey and Pichichero in Rochester, NY, found similar results.

On the basis of data on efficacy and safety, PCV-7 was recommended by the AAP and Advisory Committee on Immunization Practices (ACIP) in 2000 for all infants in a four-dose schedule at ages 2, 4, 6, and 12 to 15 months. Vaccination also is recommended routinely for children 24 to 59 months who are at high risk of invasive pneumococcal disease. Since patients with cochlear implants are at risk for pneumococcal meningitis, the ACIP recommended in 2003 that all patients with cochlear implants should receive the age-appropriate pneumococcal vaccination series, and those persons planning to receive a cochlear implant should be vaccinated two or more weeks prior to surgery.
With the widespread distribution of the first conjugate pneumococcal vaccine, investigators and clinicians will need to monitor the impact of the vaccine on the incidence of invasive and local disease. If the vaccine is effective in reducing disease caused by pneumococcal types present in the vaccine, will there be an increase in pneumococcal disease due to types not in the vaccine? Will the vaccine blunt the increasing incidence of multidrug-resistant pneumococci? Because the conjugate vaccine appeared to be more effective in preventing invasive disease than in preventing AOM, investigators need to focus on the reasons for the difference in efficacy. Is it possible that more serum or more local antibody is required or a qualitatively different type of antibody is needed to further reduce otitis media due to vaccine-type pneumococci? A protein-based vaccine that would be effective for protection against all pneumococci has been sought for many years, since it would not be restricted to protection against selected serotypes, as is the case with the current generation of conjugate pneumococcal vaccines. Briles and colleagues have developed candidate pneumococcal proteins, surface protein A and pneumolysin, that are protective against pneumococcal pneumonia in mice but have not been evaluated in humans.

**Nontypeable Haemophilus influenzae Vaccines**

Because non-typeable *H. influenzae* lacks capsular materials, different techniques are necessary to develop a vaccine. Current investigations focus on use of outer membrane proteins (OMP) as candidate antigens to develop a vaccine and antibodies that would alter the antigens that are critical for adherence of the organism to epithelial cells. Recent studies of OMP of Haemophilus isolates have focused on P6. To date, P6 DNA sequences from *H. influenzae* isolates have been identified making P6 a vaccine candidate antigen for inclusion in a Haemophilus vaccine.

**Influenza Virus Vaccines**

Two influenza virus vaccines are now available: an inactivated influenza vaccine produced in embryonated eggs, which is administered intramuscularly (usually containing three virus strains chosen on the basis of annual surveillance of those likely to be prevalent that respiratory season), and a cold-adapted, live, attenuated influenza vaccine administered as a nasal spray. At present, the nasal spray has an indication limited to healthy subjects 5 to 49 years of age. Both vaccines are effective in reducing the incidence of influenza-like illness by 70% to 80% and both have been demonstrated to reduce the incidence of AOM during the influenza season. The parenteral vaccine resulted in a 36% decline in otitis media in children attending a day care center. A similar reduction (30%) in episodes of febrile otitis media was also reported in children after administration of the live, attenuated, cold-adapted intranasal influenza vaccine. Use of currently available influenza virus vaccine should be part of the strategy for reducing the incidence of AOM for children with recurrent and severe disease. Both the American Academy of Pediatrics and the Advisory Committee on Immunization Practices want more extensive use of influenza vaccine in infants. Annual influenza immunization is recommended in all children 6 through 59 months of age. The more extensive use of influenza virus vaccines in infants will likely have a substantial effect in reducing the incidence of AOM during the influenza season.

**Immunoprophylaxis of Respiratory Syncytial Virus Infections**

Respiratory syncytial virus is the virus most closely associated with AOM. Isolates are frequently present in the nasopharynx or middle-ear effusion of patients with AOM alone or accompanied by a bacterial pathogen. Efforts to develop a safe and effective vaccine for RSV have been unsuccessful. Early attempts at active RSV immunization with a formalin-inactivated vaccine demonstrated enhancement of disease in...
vaccine recipients on subsequent exposure to natural RSV.\textsuperscript{353}

Immunoprophylaxis against RSV disease has progressed with use of high-titered RSV immune globulin\textsuperscript{354} and the introduction of palivizumab, an RSV monoclonal antibody immune globulin with high titers of neutralizing RSV antibody.\textsuperscript{355} The RSV immune globulin, but not the monoclonal antibody, was effective in reducing the number of episodes of AOM.

**Protective Effect of Immune Globulins**
Specific serum antibody is correlated with protection from homotypic infection, and disease prevention may be achieved (albeit for limited duration) by administration of immune globulins. Because infants who have recurrent episodes of AOM usually improve with age, it is possible that a program of passive immunization might be effective.

Diamant and colleagues suggested that patients with recurrent episodes of AOM associated with hypogammaglobulinemia or agammaglobulinemia benefit by frequent administration of gamma globulin.\textsuperscript{356} Children aged 1 to 7 years were enrolled after the first referral to the otolaryngologist. Children born on an odd date were given gamma globulin at their first visit and then once a month for 6 months. Children born on an even date received no gamma globulin. Of the 113 children treated, 10 had one or more episodes of AOM during the months of administration of the gamma globulin; of 118 untreated children, 25 had one or more episodes of the disease during the same time period. The protective effect of the gamma globulin persisted during the 8 months after cessation of administration; 25 episodes occurred in the treated group and 53 in the untreated group. In the untreated group, some patients had up to five episodes, whereas no patient in the treated group had more than two episodes of AOM.\textsuperscript{356} Protection against AOM by bacterial polysaccharide immune globulin is discussed later.

**Empowering Parents**
Parents should be informed about the risk features of otitis media. Although little can be done about host features, other than to suggest prognosis for severe and recurrent disease, some environmental factors may be altered to provide more protection for the infant. Education of the parents should focus on the following before or after the birth of the infant:

1. Breastfeeding should be encouraged.
2. The home should be made a smoke-free environment.
3. Crowded living conditions, poor sanitation, and episodic and inadequate medical care should be alleviated with cooperation of social services and guidance of the health care provider.
4. Pacifier use should be discouraged.
5. Family or small group out-of-home day care should be encouraged.
6. The day care facility should be inspected by parents for adequate room and ventilation and adherence of caretakers to hand washing and other infection control measures.

**SURGICAL AND MECHANICAL MANAGEMENT**

**Inflation of the Eustachian Tube–Middle Ear**

Procedures that force air through the eustachian tube and into the middle ear and mastoid cavities have been used for more than 100 years in an effort to normalize negative intratympanic pressure and to eliminate middle-ear effusion. Valsalva’s maneuver and Politzer’s method are the most commonly used in children.\textsuperscript{357,358} Catheterization of the eustachian tube is of limited usefulness in children because the procedure can be frightening and is technically difficult to perform in young patients.

Theoretically, inflating the eustachian tube and middle ear should be an effective treatment option for children with certain types of otitis media with effusion or atelectasis, or both. However, in reality, there are several problems with this method of management. The self-inflation method of Valsalva is somewhat difficult for children to learn because it is a technique
involving forced nasal expiration with the nose and lips closed. Cantekin and colleagues tested 66 children between the ages of 2 and 6 years who had had chronic or recurrent otitis media with effusion and who had functioning tympanostomy tubes in place. They asked each subject to try to blow his or her nose with the glottis closed (Figure 3). None of these children could passively open their eustachian tubes and force air into the middle ear with Valsalva’s maneuver. It was concluded that the Valsalva method of opening the eustachian tube in this age group was not successful owing to possible tubal compliance problems.

Unfortunately, children in this age group have a high incidence of otitis media; for infants, who have the highest incidence of otitis media, the procedure cannot be used at all.

Politzer’s method of opening the eustachian tube involves inserting the tip of a rubber air bulb into one nostril while the other nostril is compressed by finger pressure (Figure 4) and then asking the child to swallow while the rubber bulb is compressed. Some children complain of a sudden “pop” in the ear as the positive pressure is forced up the eustachian tube and they experience discomfort with the procedure. This method is also extremely difficult to perform in infants.

The major difficulty with both methods is determining whether the middle ear is actually inflated by the procedure. If a child hears a pop or has a pressure sensation in the ear, there is only presumptive evidence that air is passing into the middle ear. Auscultation of the ear (listening for the sound of air entering the middle ear during the procedure) is helpful in determining whether the procedure is successful, but a sound may be heard even when air does not enter the middle ear. Objective otoscopic evidence that the middle ear is actually inflated is the presence of bubbles or a fluid level behind the tympanic membrane when these findings were not present before inflation. Another excellent method for determining objectively whether the inflation is successful is to obtain a tympanogram before and after the procedure; the compliance peak should shift toward, or be in, the positive pressure zone after inflation. If none of the results of these presumptive or objective methods of determining the success of inflation are definitive, the clinician cannot be certain that the procedure has been therapeutic. Failing to achieve a successful result may be related to: (1) inability of the patient to learn the method; (2) insufficient nasopharyngeal overpressure to open the eustachian tube passively; (3) eustachian tube abnormality; or (4) a middle ear filled with a thick, mucoid effusion.

Unfortunately, the beneficial effect of Valsalva’s maneuver and Politzer’s method for treatment of otitis media with effusion or
atelectasis has been subjected to only a limited number of randomized, controlled trials. Most of the evidence has been anecdotal until recently. Gottschalk described remarkable success with a modification of Politzer’s method in more than 12,000 patients; the average course of treatment was a minimum of 12 inflations in the office on 3 separate days. Schwartz and coworkers have shown that it is possible to inflate the middle ears of children at home with Politzer’s method; they documented the results of the method by tympanometry but did not test its efficacy. Kaneko and coworkers inflated the ears of 149 children aged 3 to 9 years and reported success related to season, but this trial did not include a control group.

Fraser and colleagues reported one of the first controlled trials of this method, and they were not able to demonstrate its efficacy. Chan and Bluestone also conducted a randomized clinical trial of 40 Pittsburgh children, most of whom had chronic otitis media with effusion that was unresponsive to antimicrobial treatment. All the children were taught how to use the specially developed system, which consisted of a flowmeter attached to a disposable anesthesia mask, based on a modified Valsalva’s maneuver. The children were stratified according to their ability to achieve eustachian tube opening as determined by tympanometry. Subjects were randomly assigned either to autoinflation 3 times each day for 2 weeks or to no inflation (ie, control). Of the 19 children who autoinflated their ears, only 1 patient (5%) was effusion-free at the end of the trial, which was comparable to the control group; only 2 (10%) of 21 control subjects were without middle-ear effusion. The investigators concluded that autoinflation as conducted in the trial was ineffective for treatment of otitis media with effusion.

In a later clinical trial from Denmark by Stangerup and coworkers, however, autoinflation was considered to be effective with use of a new device that consists of a balloon attached to a nasal tube (Otovent, Technilab, Montreal, Canada), which the child inserts into one nostril and blows up through one side of the nose while the other side is closed with the child’s finger pressure. The technique could be taught only to children who were 3 years of age and older, and during the trial, many of the children failed to use the instrument the prescribed 3 times daily during the 2-week regimen. In those children who had type B tympanograms on entry, the investigators concluded that the tympanometric conditions were “better” in the treated group than in the untreated children at the end of the 2 weeks, but there were no statistically significant differences after 2 or 3 months between the two groups. Because the effect was “short lasting,” they advocated repeated use. This study had several shortcomings— for example, tympanometry only to identify middle-ear effusion and analysis by ear and not by subject; the safety and efficacy of this device await further study, especially when it is used repeatedly by children who have chronic and recurrent disease.

At present, it is reasonable to recommend autoinflation of middle ears for the following conditions:

- Barotrauma (after flying or swimming) should respond ideally to autoinflation if atelectasis with high negative pressure or otitis media with effusion or both are present. A recent clinical trial showed that inflation of the middle ear was helpful under these circumstances because the condition is usually not due to chronic eustachian tube dysfunction, and inflation may resolve the acute disorder rapidly.

- When a middle-ear effusion not caused by barotrauma is found in a patient who only occasionally has a problem and in whom frequently recurrent or chronic disease is not suspected, the procedure may also be successful, especially if a small amount of serous effusion is visible behind a translucent tympanic membrane. It is unlikely, however, that a mucoid or purulent effusion could be evacuated by this technique, and if it could be, it would probably recur immediately after the procedure.

Therefore, it is unlikely that inflation will be successful in alleviating frequently recurrent or chronic eustachian tube dysfunction for any
length of time. There is also a remote possibility that bacteria can be forced into the middle ear from the nasopharynx during this procedure, and repeated autoinflation could cause the tympanic membrane to lose its stiffness (become hypercompliant).

**Myringotomy and Tympanocentesis**

Myringotomy, or the incision of the tympanic membrane for AOM, was first described by Sir Ashley Cooper in 1802. This procedure became increasingly popular until the 1940s, when antimicrobial agents came into wide use. Now, myringotomy is reserved for selected cases and performed primarily by otolaryngologists and a handful of primary care physicians; the indications are usually limited to those children who have severe otalgia or suppurative complications, or both. However, with a recent increase in the prevalence and incidence of AOM and chronic otitis media with effusion, considerably more effort has been made to study the efficacy of myringotomy in management of this disease. In the past, some clinicians thought that the potential benefit from more liberal use of the procedure in cases of AOM might be not only relief of otalgia but a decrease in persistence and recurrence rates. Also, when chronic otitis media with effusion is present, myringotomy may be as effective in eliminating the middle-ear effusion as when the procedure is followed with tympanostomy tube insertion, with its attendant complications and sequelae (assuming a surgical procedure is indicated at all). More recently, some clinicians thought that myringotomy for AOM could be a substitute for antimicrobial therapy, which would decrease the need for antibiotics and the rate of antibiotic-resistant otogenous bacteria. However, as we show below, these assumptions have been tested in randomized clinical trials.

The results of studies conducted in the past to determine the efficacy of myringotomy for AOM are shown in Table 19.

There have been two excellent randomized clinical trials that have addressed this question. In one from Israel, Engelhard and colleagues randomly assigned 105 infants who had AOM to one of three treatment options: (1) amoxicillin-clavulanate, (2) myringotomy plus placebo (for amoxicillin-clavulanate), and (3) amoxicillin-clavulanate and myringotomy. The two myringotomy groups were double-blinded. With otoscopic findings as an outcome measure, 60%

<table>
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<tr>
<th>Investigator</th>
<th>Procedure</th>
<th>Number of Subjects</th>
<th>Percentage with Persistent Effusion after 10 To 14 Days</th>
<th>Percentage with Persistent Effusion after 4 Weeks</th>
<th>Percentage with Persistent Effusion after 6 Weeks</th>
<th>Statistical Significance Achieved</th>
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<td>Roddey et al</td>
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<td>56</td>
<td>-</td>
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</table>

AB = antibiotic; AB&M = antibiotic and myringotomy.

*Episodes of acute otitis media for infants and children.
of the infants receiving the antibiotic, with or without myringotomy, recovered, whereas only 23% of subjects who received myringotomy and placebo recovered. The investigators concluded that adding myringotomy to the amoxicillin-clavulanate did not appear to affect either the persistence of infection after treatment or the residual middle-ear effusion.

In Pittsburgh, Kaleida and coworkers randomly assigned children who had “severe” AOM to receive 10 days of amoxicillin, myringotomy with placebo (for amoxicillin), or both amoxicillin and myringotomy; infants in the trial received only amoxicillin with or without myringotomy. Outcome included an algorithm of findings on otoscopy (by a validated otoscopist; ie, against myringotomy findings), tympanometry, and acoustic reflex testing. There were statistically more initial treatment failures in those children who received myringotomy alone, compared with those who received amoxicillin, with or without the myringotomy. Subjects assigned to receive amoxicillin alone and amoxicillin and myringotomy had similar outcomes. The investigators concluded that amoxicillin (or an equivalent antimicrobial agent) is indicated for treatment of AOM and that the data did not support the routine use of myringotomy, either alone or combined with amoxicillin. However, the authors did recommend myringotomy for selected infants and children, such as for those with severe otalgia, for those whose antimicrobial treatment fails, and in cases with a suppurrative complication.

Indications

There is ample evidence, as shown above, that the routine use of myringotomy for all children with AOM is not necessary, but there are certain indications for which there is consensus.

Suppurative Complications

When a child has acute mastoiditis, labyrinthitis, facial paralysis, or one or more of the intracranial suppurrative complications (such as meningitis), myringotomy and aspiration should be performed as an emergency procedure. Tymanocentesis should precede myringotomy to identify the causative organism. In addition, in such cases, a tympanostomy tube should be inserted in an attempt to provide prolonged drainage.

Severe Otalgia Requiring Immediate Relief

Even though some studies have failed to show that myringotomy alleviated earache, Roddey and colleagues did show that acute pain was relieved in those children who received myringotomy. Culture of the effusion is reasonable because the middle ear is being opened, but it is not absolutely necessary if there is no reason to suspect that an unusual organism is present.

Myringotomy and Tymanocentesis

Although not as compelling as the preceding indications, whenever diagnostic tymanocentesis is indicated, myringotomy for drainage may follow the needle aspiration, especially when a copious amount of middle-ear effusion is identified by the tymanocentesis. Myringotomy may then reasonably follow tymanocentesis: (1) when AOM is present and the child is critically ill; (2) when there is persistent or recurrent otalgia or fever, or both, despite adequate and appropriate antimicrobial therapy; (3) when AOM occurs during the course of antimicrobial therapy given for another infection, and when the agent should be effective against the most common organisms causing the otitis media (eg, amoxicillin or ampicillin); (4) when otitis media occurs in the neonatal period; and (5) when otitis media occurs in the immunologically compromised host. (The specific indications and techniques for tymanocentesis are discussed in the section “Diagnosis.”)

The benefit of performing myringotomy on all infants and children with AOM is not recommended at present, but it is a reasonable procedure, especially if otalgia is present. If a middle-ear effusion persists after 10 to 14 days of antimicrobial therapy, myringotomy may also be appropriate if the child is still symptomatic. However, if the child is relatively asymptomatic,
The indications for the procedure are less valid because most effusions at this stage are expected to clear spontaneously during the next several weeks. If the middle-ear effusion persists for longer than 3 months, surgical drainage is a reasonable choice. If the procedure can be performed without the need for a general anesthetic, myringotomy alone is appropriate, with the physician reserving the insertion of a tympanostomy tube in case the effusion recurs soon after the myringotomy incision heals. If a general anesthetic is required to perform the surgical drainage of chronic otitis media with effusion, however, myringotomy with tympanostomy tube insertion is the preferred procedure. This recommendation is appropriate because Gates and colleagues and Mandel and coworkers showed that myringotomy with insertion of a tympanostomy tube was more effective than myringotomy alone in children who have chronic otitis media with effusion that is unresponsive to antimicrobial therapy (see "Myringotomy and Tympanostomy Tube Placement").

Tympanocentesis is a needle aspiration of the middle-ear contents for diagnostic purposes, but myringotomy is a procedure in which an incision of the tympanic membrane by a myringotomy knife is made to provide adequate drainage (Figure 5). To accomplish this goal, the incision should be large enough to provide not only adequate and prolonged drainage into the external auditory canal but also aeration of the middle ear to enhance drainage down the eustachian tube. When AOM is present in the infant or young child, adequate restraint employing a sheet or board specially designed for restraining children may be all that is needed; sedation is not necessary. For older children, however, sedation or even general anesthesia may be required. The use of a topical solution of phenol gently applied to the exact spot on the tympanic membrane to be opened may be all that is necessary in older children and teenagers. The myringotomy incision should be a wide circumferential incision encompassing both inferior quadrants of the tympanic membrane to provide adequate drainage, and an attempt should be made to aspirate as much of the middle-ear effusion as possible. Insertion of the suction tip through the incision of the tympanic membrane will frequently enhance removal of the effusion and provide a larger opening, which, it is hoped, will remain open longer than with just an incision alone.

The procedure can be performed through an otoscope with a surgical head attached, but for better magnification and binocular vision, the otomicroscope is desirable. For the routine case,
the otoscope is adequate and makes the procedure readily available to the clinician in settings other than an operating room or otologic outpatient area, where an otomicroscope would be available. By becoming proficient with the otoscope in performing myringotomy, the physician can perform the procedure in emergency departments, in-patient pediatric units, the child’s home, or any other setting in which a child is examined and is in need of myringotomy. In almost all conditions in which myringotomy is performed, diagnostic tympanocentesis may precede it.

There are few complications of performing a myringotomy properly. The persistent otorrhea that follows the procedure and is the most common finding after myringotomy can hardly be considered a complication because it is the desired outcome. However, the discharge may become profuse and cause an eczematoid external otitis. If this occurs, the problem will usually be eliminated by meticulous cleaning of the external auditory canal with a cotton-tipped applicator; instillation of otic drops containing hydrocortisone, neomycin, and polymyxin; and insertion of a small piece of cotton (which should be changed frequently) in the outer canal. Dislocation of the incudostapedial joint, severing of the facial nerve, and puncture of an exposed jugular bulb are dreaded complications but are so rare in experienced hands that they should not deter the trained practitioner from employing the procedure when it is indicated. The most common sequelae of the procedure are persistent perforation, atrophic scar, and tympanosclerosis at the site of the incision. Even though the incidence of these conditions has not been systematically studied in a prospective manner, the risk of any or all occurring should not outweigh the benefits of myringotomy when it is indicated. These sequelae would arise in children who require repeated myringotomy, and a tympanostomy tube should be considered in these patients, even though this is not without complications and sequelae.

It has been suggested by some that the myringotomy incision be created with a laser when middle-ear effusion is present. This would be an effort to prolong the duration of the opening in the hope of preventing tympanostomy tube placement. However, to date, randomized clinical trials that have compared the short- and long-term efficacy and complications of laser myringotomy with myringotomy and insertion of tympanostomy tube are lacking, and thus this procedure should be considered experimental and of uncertain benefit.

**Myringotomy and Tympanostomy Tube Placement**

Myringotomy with tympanostomy tube insertion is currently the most common surgical procedure performed in children that requires general anesthesia.

It has been estimated that 2 million tubes are manufactured yearly and, presumably, inserted through the tympanic membranes of probably more than 1 million patients.

Even though there remains uncertainty among many clinicians and investigators regarding the safety and efficacy of tympanostomy tube placement, we now have the results of clinical trials to arrive at reasonable criteria for tube insertion.

**Clinical Trials**

**Otitis Media with Effusion**

Several studies have addressed the question of the efficacy of myringotomy and tympanostomy tube insertion for treatment of otitis media with effusion, but all had problems in design and methodology. However, there are three trials that have given us evidenced-based indications for use of tympanostomy tube placement for chronic otitis media with effusion:

1. Gates and associates evaluated 578 Texas children in a trial that randomly assigned children aged 4 to 8 years who had chronic otitis media with effusion that was unresponsive to antimicrobial therapy, into one of four surgical treatment groups: myringotomy,
The study did not include a control group of no surgery, but all three of the other treatments did statistically better than myringotomy without tube placement (see “Tonsillectomy and Adenoidectomy”).

2. Mandel and coworkers conducted a study in 109 children who had chronic otitis media with effusion that had been unresponsive to antimicrobial therapy and randomly assigned subjects to receive myringotomy, myringotomy and tympanostomy tube, or no surgery (control). During this three-year trial, in which subjects were evaluated monthly and whenever an ear, nose, and throat illness supervened, patients who had tympanostomy tubes inserted had less middle-ear disease and better hearing than either children who had only myringotomy or those subjects in whom no surgery had been performed. In addition, one-half of the subjects in the myringotomy group had to have tympanostomy tubes inserted during the first year of the trial because of an excessive number of myringotomies to control their disease. Likewise, one-half of the subjects in the control group required tympanostomy tube insertion during the course of the year because they developed “significant” hearing loss associated with their chronic middle-ear effusion, even though none of the children had this degree of hearing loss when they entered the trial. At least one of the children, however, had at least one bout of otorrhea when the tubes were in place, but these episodes were usually easily treated and short-lasting, although two children did develop chronic otorrhea that required intravenous antimicrobial therapy to eliminate the drainage. In addition, one patient who had tubes inserted eventually needed bilateral tympanoplasties to repair chronic tympanic membrane perforations that persisted after the tubes spontaneously extruded. Myringotomy (without tube) provided no major advantage over no surgery (ie, control) regarding percentage of time with middle-ear effusion, number of bouts of AOM, and number of subsequent surgical procedures. The investigators concluded that myringotomy and tympanostomy tube placement provided more effusion-free time and better hearing than either myringotomy without tube insertion or no surgery, but some patients who received tubes did develop otorrhea, and perforation was a problem in one of the children. Because the researchers considered the interpretation of this trial to be difficult because of the complexities of the design, the protocol was revised and a second clinical trial was conducted.

3. In their second trial, Mandel and colleagues randomized 111 children into the same three groups as in the first study: myringotomy, myringotomy and tympanostomy tube insertion, and no surgery (control). As in the first trial, subjects were reexamined at least every month for 3 years. Outcomes observed in this trial were similar to those reported in the first study. Again, subjects in the myringotomy and tube group had less time with middle-ear effusion and better hearing than either those children who had only a myringotomy performed or the group that had no surgery.

Similar to the initial trial, otorrhea occurred in 41% of those who were randomized to the tympanostomy tube group, and three subjects developed chronic perforations after the tubes extruded; two of these children eventually required a tympanoplasty when the perforation failed to spontaneously heal after 2 years.

On the basis of these two randomized clinical trials that evaluated a total of 220 subjects, the investigators recommended myringotomy and tympanostomy tube insertion as the first surgical procedure to perform, as opposed to myringotomy alone, for children who have otitis media with effusion that is unresponsive to nonsurgical treatment and is persistent for 4
months or longer. Even though Gates and colleagues recommended an adenoidectomy and myringotomy (without tympanostomy tube insertion) as “the initial surgical procedure,” Mandel and coworkers recommended reserving adenoidectomy for those children who required another surgical procedure if otitis media recurred after extrusion of the initial tube. This recommendation was made because the study by Gates and colleagues in 1987 showed that adenoidectomy in their population was only a little better than myringotomy and tympanostomy tube and because, in the two studies by Mandel and coworkers, approximately 50% of the subjects required only one myringotomy and tube insertion during the three-year trial. If the child has significant nasal obstruction because of obstructive adenoids, however, adenoidectomy and myringotomy (with or without tympanostomy tube insertion) as an initial procedure is a reasonable option.

Recurrent AOM
Three randomized clinical trials that tested the efficacy of tympanostomy tube insertion to prevent recurrent AOM have been recognized as being helpful:

1. Gebhart in Columbus, Otio, evaluated otitis-prone infants, of whom 50% had tubes inserted and 50% had no surgery. Efficacy was demonstrated, but infants with middle-ear effusion were also enrolled, and follow-up was limited to 6 months.

2. Gonzalez and coworkers, in a multicenter study conducted in the United States Army, enrolled 65 otitis-prone infants into a trial that randomly assigned subjects into three groups: sulfisoxazole prophylaxis, tympanostomy tubes, and placebo. Similar to the Gebhart trial, infants were entered with and without middle-ear effusion, not stratified, and observed for only 6 months. Infants in the tympanostomy group did significantly better if they had middle-ear effusion at entry, but the attack rates of AOM were not reduced significantly in those subjects who were effusion-free at the time of random assignment.

3. Casselbrant and colleagues randomly assigned 264 Pittsburgh children aged 7 to 35 months to one of three groups: amoxicillin prophylaxis (20 mg/kg/d in 1 dose at bedtime), myringotomy and tympanostomy tube insertion, and placebo. Unlike the two previously reported trials, this one entered only patients who had no middle-ear effusion and observed the children monthly and whenever an ear, nose, and throat illness supervened for 2 years. The average rate of new bouts of AOM was significantly reduced in those subjects who were in the amoxicillin prophylaxis group compared with the tube or placebo group. There was no significant difference between the tympanostomy tube and placebo groups for this outcome measure. Postoperative otorrhea through a tympanostomy tube was considered to be an episode of AOM, which occurred at about the same rate as the number of episodes of AOM in the placebo group. However, the bouts of otorrhea were usually asymptomatic and less troublesome than when acute middle-ear infection developed in the placebo and amoxicillin prophylaxis groups. When the average portion of time with otitis media of any type (ie, AOM, otorrhea, or otitis media with effusion) was evaluated, the tube group had only 6.6% compared with 10% for the amoxicillin group and 15% for subjects who received placebo. The amoxicillin group had adverse side effects in 7%, primarily urticaria and vaginitis, and 3.9% of the tympanostomy tube group developed persistent perforation of the tympanic membrane; all of these eventually healed spontaneously. Because relatively long-term antimicrobial prophylaxis may be related to development of resistant bacteria, this question was addressed in the trial, but there were no consistent differences in percentages of β-lactamase–positive H. influenzae or M. catarrhalis found in the serial nasopharyngeal cultures between
those who received amoxicillin prophylaxis and those who were in the placebo group. During the two-year trial, 70% of the subjects who were randomly assigned to the tube group required only one procedure, whereas 26% needed a second set of tubes inserted; only one child (1%) had to have three sets of tubes.

The investigators recommended that amoxicillin prophylaxis be the first method used to prevent the recurrent episodes in infants and young children, the age group included in the trial. If this fails, tympanostomy tube placement is the next option. They also recommended that children who are prescribed prophylaxis be reevaluated periodically, even if they are symptom-free, because asymptomatic middle-ear effusion may develop.

**Rationale for Placement of Tympanostomy Tubes**

There are now results of controlled clinical trials showing that tympanostomy tube insertion can be beneficial in selected infants and children because middle-ear disease is reduced and hearing is restored, although there are known complications and sequelae associated with the surgery. The rationale for the procedure may be found in certain physiologic and pathophysiologic aspects of the nasopharynx, eustachian tube, middle ear, and mastoid air cell system that are related to the pathogenesis of otitis media. The eustachian tube has three important physiologic functions in relation to the middle ear (see Figure 5): (1) middle-ear pressure regulation, (2) drainage of secretions down the eustachian tube, and (3) protection of the middle ear from the entry of unwanted nasopharyngeal secretions.384

A functioning tympanostomy tube maintains ambient pressure within the middle ear and mastoid and provides adequate drainage both down the eustachian tube and through the tympanostomy tube. Therefore, two physiologic functions of the eustachian tube are fulfilled by the tympanostomy tube. The protective function of the eustachian tube may be impaired by tympanostomy tube insertion because conventional tympanostomy tubes leave an opening in the tympanic membrane, and the physiologic middle-ear air cushion is not present if the tympanic membrane is open. Therefore, reflux of nasopharyngeal secretions into the middle ear may be enhanced when a tympanostomy tube eliminates the middle-ear air cushion, a situation that can result in reflux otitis media and otorrhea (see “Pathogenesis”).

The ideal eustachian tube prosthesis would be a transtympanic tube that fulfills all three of the important physiologic functions of the eustachian tube: pressure regulation, drainage, and protection.

**Recommended Indications for Insertion of Tympanostomy Tubes**

**Chronic Otitis Media with Effusion**

As described above we now have the results of three clinical trials that provide evidence-based efficacy of tympanostomy tube insertion for chronic otitis media with effusion.29,44–46

Patients who have had bilateral otitis media with effusion that has been unresponsive to nonsurgical treatment, which should include a course of an antimicrobial agent, and that has been present for at least 3 months are reasonable candidates for tympanostomy tube insertion. For children who have unilateral effusion, the duration can probably be extended to 6 months before tympanostomy tube placement is considered because hearing is assumed to be good in the unaffected ear. Factors to be taken into account in the decision-making process to insert tubes for chronic effusion, in addition to the duration, are the degree of hearing loss, the type and amount of effusion thought to be within the middle-ear cleft (eg, observed small amount of serous effusion with air-fluid level and bubbles versus a completely opaque, immobile tympanic membrane), and the presence of a retraction pocket. Attendance in child day care has been shown to increase the frequency of tympanostomy tube insertion. In a study by Postma and associates, 31% of 346 children who attended day care had
tympanostomy tubes in place compared with only 11% of 63 age- and sex-matched children who were in home care; also, the reintubation rate was 36% in the day care children compared with only 11% in those who were in home care.

Even though myringotomy alone did not prove to be effective compared with myringotomy and tympanostomy tube insertion in the trials conducted by Mandel and associates and Gates and colleagues, it would seem reasonable to attempt a myringotomy and aspiration of the middle-ear effusion before inserting a tympanostomy tube in both older children and adults who are cooperative and who do not require general anesthesia. If the effusion rapidly recurs, a tympanostomy tube can usually be inserted, again without the need for a general anesthetic. If general anesthesia is necessary to perform a myringotomy in infants and children who have chronic effusion (as is invariably the case in this age group), however, insertion of a tympanostomy tube at the time of the myringotomy is the preferred treatment.

Removal of a middle-ear effusion that is asymptomatic, especially when significant hearing loss is not present, is questionable. All such children have some degree of conductive hearing loss if they are observed closely, however, and the short- and long-term effects of even modest degrees of hearing loss may have an impact on certain aspects of the child's development. Indeed, in the first clinical trial conducted by Mandel and coworkers, patients with significant hearing loss were not randomized into the no surgery (control) group; however, one-half of these subjects developed significant hearing loss at the end of the first year and became treatment failures. Because hearing loss is usually present, there may or may not be developmental problems when the effusion occurs in early childhood. Even though the effect on child development is uncertain at present, there may be an adverse effect on balance. In addition, it is not known what chronic irreversible changes, such as adhesive otitis media, tympanosclerosis, ossicular discontinuity, or cholesteatoma, might occur in the middle-ear space if such an effusion is not treated. Therefore, the ultimate decision for use of tympanostomy tubes for chronic otitis media with effusion must be based on many factors, most of which remain arbitrary. At present, however, it seems to be reasonable to insert tympanostomy tubes in selected children to remove the effusion, to restore hearing, and to prevent possible complications and sequelae of recurrent and chronic otitis media with effusion.

The Clinical Practice Guideline for Otitis Media with Effusion in Young Children by Stool and colleagues concluded that myringotomy with tympanostomy tube placement is an alternative to antimicrobial treatment when the otitis media with effusion persists for longer than 3 months, is bilateral, and is associated with a hearing deficit (defined as 20 dB hearing threshold level or worse in the better ear). Tympanostomy tube placement is recommended when the effusion meets these criteria and persists for longer than 4 months. In contradistinction to the recommendation of the guideline that limits tube insertion to those children who have bilateral chronic effusion and a bilateral hearing loss (greater than 20 dB), we recommend the procedure irrespective of the child's hearing assessed at one point in time. Assessment of hearing at one point in the time course of chronic otitis media is more reliable than the parents' rating of hearing, although the clinical trial by Mandel and colleagues demonstrated the fluctuation in hearing over time associated with this disease. Although it was not addressed in the guideline, we recommend tube placement when a unilateral otitis media with effusion persists for 6 months or longer, and we reserve placement of tympanostomy tubes for those patients with chronic effusion that is unresponsive to a trial of appropriate antimicrobial agent (see “Guideline for Managing Otitis Media with Effusion”). Despite the widespread dissemination of these guidelines in 1994, there is some evidence that they are not being followed by many clinicians. Hsu and colleagues examined the medical care of 59 patients with chronic otitis media with effusion and reported that the adherence rate to
the guideline was 0%. Delayed referral occurred in 34% of children, and 25% were referred prematurely. The authors of this study recommended more timely referral to otolaryngologists. Apparently, the guideline is not perceived as being helpful to pediatricians in clinical practice. A review of physicians’ adherence to clinical practice guidelines showed poor adherence, not only to the otitis media guideline but to other published guidelines in medicine as well.

More recently, the American Academy of Pediatrics Guideline recommends myringotomy and tympanostomy tube placement when the effusion persists for 4 months or longer, with hearing loss or other signs or symptoms in children who are at risk (eg, developmental delay, cleft palate), and with structural damage to the tympanic membrane.

**Recurrent AOM**

We now have the outcomes of clinical trials that have demonstrated that tympanostomy tubes prevent recurrent AOM, to some degree; acute otorrhea may still develop after tube insertion. Presumably, the tube prevents aspiration of infected nasopharyngeal secretions into the middle ear, because ambient rather than negative middle-ear pressure would be present. Absence of negative middle-ear pressure could also prevent accumulation of a noninfected middle-ear effusion. In addition, a non-intact tympanic membrane would allow excellent drainage down the eustachian tube of any secretions entering the middle ear. In children with semipatulous eustachian tubes, however, reflux of nasopharyngeal secretions can be enhanced when the tympanic membrane is not intact, resulting in otorrhea secondary to reflux otitis media. Now that we have approved ototopical agents (without the addition of systemic antimicrobial agents), such as ofloxacin otic solution 0.3% (Floxin Otic, Daiichi Pharmaceutical Corp., Montvale, NJ) for post-tympanostomy tube acute otorrhea, tympanostomy tube insertion is an even more compelling option than long-term, low-dose antimicrobial prophylaxis.

Myringotomy with insertion of a tympanostomy tube is helpful for children who suffer frequent, recurrent attacks of AOM. Three or more episodes during the preceding 6 months, or at least four episodes during the preceding year (with the last episode occurring during the preceding 6 months), would be indications for performing this procedure; these were the entry criteria for the study by Casselbrant and coworkers. For such children, however, a trial of antimicrobial prophylaxis is an acceptable alternative management option, and myringotomy with insertion of tympanostomy tubes is reserved for those children in whom chemoprophylaxis has failed. Antimicrobial prophylaxis should be considered only in those children who have no evidence of a middle-ear effusion between the acute attacks.

**Other Indications**

Other indications for tympanostomy tube placement are: eustachian tube dysfunction that is chronic or recurrent and unresponsive to medical management; atelectasis of the middle ear that is chronic (with or without retraction pocket); suppurative complications (eg, facial paralysis, mastoiditis); and at the time of tympanoplasty when eustachian tube dysfunction is chronic (Table 20).

**When Should Tympanostomy Tubes Be Removed?**

In general, once tubes have been inserted, they should be permitted to extrude spontaneously into the external auditory canal and not be removed too early. The rationale for such management is based on experience rather than on any controlled clinical trials. In children with tympanostomy tubes in place, eustachian tube function has not been shown to change significantly, even after several years.

There are indications to remove tubes in selected children. Tympanostomy tubes can be removed as an office procedure without the aid of either local or general anesthesia, especially
when the tube is partially extruded or there is chronic infection involving the tympanic membrane. In children, however, tympanostomy tubes are frequently removed under general anesthesia in the operating room because the procedure is usually painful, and the rim of the perforation can be denuded of epithelium and the defect closed (ie, “paper patch” myringoplasty) after removal of the tube; we prefer to use Steri-Strip to close the defect. 395

Most tympanostomy tubes remain in the tympanic membrane for 6 to 12 months, although some have been known to remain in place for years. In the three Pittsburgh studies that evaluated the Armstrong-type tube for treatment of chronic otitis media with effusion44,45 and prevention of recurrent AOM,24 the tube life was approximately 1 year; 50% were extruded in 12 months, and 75% in 18 months. In children in whom tympanostomy tubes have been inserted bilaterally and in whom one tube subsequently extrudes but the other remains in place for a prolonged period, the remaining tube can usually be removed if the opposite middle ear remains free of high negative middle-ear pressure or middle-ear effusion, or both, for at least 1 year after the spontaneous extrusion of the opposite tube. This method of management is based on the observation that eustachian tube function is usually about the same in both ears in children. If high negative middle-ear pressure or otitis media with effusion or both occur during the observation period, the tube in the opposite ear should not be removed. Unfortunately, this method of management cannot be used in adults, because eustachian tube function may not be symmetric.

Removal of tympanostomy tubes depends on several factors, such as the following:

- Age of the child
- Duration of time the tube has remained in place
- Unilateral versus bilateral tubes
- Status of the contralateral ear when that tympanic membrane is intact
- Eustachian tube function
- Presence or absence of recurrent or chronic otorrhea (and frequency, severity, and duration of otorrhea)
- Patency of the tube
- Season of the year

The age of the child is one of the most important factors because most studies of the epidemiology of otitis media show that the disease has a peak in infancy and declines rapidly after approximately 6 years of age. Indeed, a recent report that described the outcome of 126 children who had their tympanostomy tubes removed revealed that those who had retained the tubes for 2 years and longer and who were 7 years of age and older had a high complication rate from the retained tubes, but when retained tubes were removed in children who were younger than 7 years of age, some required reinsertion due to recurrence of middle-ear disease.396 In addition, the structure and function of the eustachian tube and the child’s immunity are more mature usually after 6 years. Therefore, removal of tubes in children who are 6 years and older is more
desirable than in children who are younger. Removing the tube in selected children who are younger, however, may be of benefit, such as when there is unilateral recurrent otitis media through a tube—apparently due to reflux of nasopharyngeal secretions into the middle ear—that is not controlled medically, and the contralateral tympanic membrane is intact (no tube is present) and that ear has been free of middle-ear disease for 1 year or longer. The indications for removal of tubes are as follows:

1. A unilateral tympanostomy tube is retained in children who are 6 years or older when the contralateral tympanic membrane is intact and the middle ear has been free of disease for 1 year or longer.
2. Selected similar children younger than 6 years may also be candidates. For these children, the decision is based on the factors listed in the preceding.
3. Bilateral tympanostomy tubes are retained in children in whom eustachian tube function is now considered within normal limits because of growth and development, or a nonsurgical (eg, allergy control or treatment) or surgical (eg, adenoidectomy or repair of cleft palate) management may have improved eustachian tube function.
4. Frequently recurrent otitis media through a tympanostomy tube is not prevented by antimicrobial prophylaxis. Important in decision-making are frequency, severity, and duration of the episodes; age of the patient; and duration the tube has been in place.
5. After chronic otitis media, especially when the criteria described in the first two points are met.
6. The tympanostomy tube is imbedded in granulation tissue, which is unresponsive to medical treatment.

### Complications and Sequelae of Tympanostomy Tube Insertion

One of the major concerns that patients, parents, and physicians have when tympanostomy tube insertion is being considered is the safety of the general anesthetic. In a study from Buffalo, Markowitz-Spence and colleagues evaluated 510 children who had tubes placed for possible complications of the general anesthetic. No complications were identified in 83%, and there was a minor degree of airway obstruction in 12%. In the remaining patients, only 1.4% had severe airway obstruction during the procedure; there were no serious complications or deaths. The authors concluded that the procedure is relatively safe, especially when the anesthesia is delivered by a pediatric anesthesiologist. In a more recent study by Hoffman and associates of 3,198 infants and children who had tubes inserted with the aid of a general anesthetic, the procedure was shown to be safe when performed in a tertiary care children’s hospital; however, the most significant predictor of a minor anesthetic event was a preexisting medical condition or concurrent acute illness.

Intraoperative complications from the procedure are rare, but Brodish and Woolley encountered two children who had vascular injuries as a result of the myringotomy incision; one child had an abnormally high jugular bulb, and the other had an exposed carotid artery in the middle ear. Both children were successfully treated for these congenital malformations. These cases emphasize the unique role of otolaryngologists in performing this surgical procedure. They are fully aware of these rare complications and can appropriately respond when such an emergency occurs.

Less severe and more commonly known complications and sequelae related to the tympanostomy tube insertion include scarring of the tympanic membrane (tympanosclerosis) and localized or diffuse membrane atrophy, with or without retraction pockets, or atelectasis, or both. The scarring is most likely of the tympanic membrane, which is said to occur in approximately 50% more tympanic membranes after tube insertion than if the tube had not been inserted; but in most cases, this degree of scarring of the tympanic membrane is a cosmetic issue because tympano-
sclerosis is rarely identified within the middle ear in infants and children, and the hearing is uninvolved.\textsuperscript{401}

Less commonly, a perforation may remain at the insertion site after extrusion of the tube. The rate of perforation varies from 0.5\% to 25\%, depending on the type of tube and the number of tubes inserted into the same tympanic membrane over time; permanent tubes have the highest rate and the more conventional ones have a low frequency of perforation.\textsuperscript{403–406} In the Pittsburgh clinical trials that evaluated the safety and efficacy of tympanostomy tube insertion for chronic otitis media with effusion and to prevent recurrent AOM, a total of 215 infants and children were prospectively observed for at least 2 to 3 years after entry, and 32 (14.8\%) developed a perforation at the tube site after spontaneous extubation.\textsuperscript{24,44,45} However, almost all of these perforations eventually closed; 3 (1.4\%) children did have to have a tympanoplasty after the perforations failed to close after 2 years, and another child had a persistent perforation that lasted 4 years. A review from Israel of 2,604 tympanostomy tube placements revealed a rate of 3.06\% perforation; perforations occurred more frequently in children younger than 5 years, when the indication for placement was to prevent AOM, with the use of Goode T-tubes, and in patients who required reinsertion of tubes.\textsuperscript{407}

On rare occasions, a cholesteatoma may develop, usually at the tube insertion site, either by invagination of squamous epithelium or from a retraction pocket that develops, owing to persistent eustachian tube dysfunction and the subsequent middle-ear pressure. Golz and colleagues reported the rate of cholesteatoma to be 1.1\% and attributed this relatively high rate to the use of Goode T-tubes when repeated tubes were needed.\textsuperscript{408} Other complications include secondary infection accompanied by otorrhea through the tube and dislocation of the tube into the middle-ear cavity.

The most common complication of tympanostomy tube insertion is otorrhea through the lumen of the tube. Otorrhea commonly occurs immediately after tube insertion, especially when a mucoid or purulent effusion is aspirated at the time of the myringotomy; the rate is approximately 12\%,\textsuperscript{409–415} but it has been reported by some to be more than 30\%.\textsuperscript{416,417}

After insertion of tympanostomy tubes, otorrhea can occur at any time while the tubes remain in place and patent. This otorrhea that occurs after the postoperative period is usually the result of reflux of nasopharyngeal secretions into the middle ear or contamination from the external canal. Otorrhea occurs in two-thirds of infants with unrepaired cleft palates who have had tympanostomy tubes inserted for treatment of chronic otitis media with effusion and who are observed during the first 2 years of life.\textsuperscript{418} Otorrhea may also occur in children without cleft palates in whom tubes have been inserted. In the three Pittsburgh clinical trials, otorrhea occurred at least once in approximately 50\% of the subjects during the course of the 2- and 3-year studies.\textsuperscript{24,44,45} This rate is higher than that reported in the past, probably because the subjects were reevaluated every month and whenever they had an ear, nose, or throat illness and some of the episodes were not evident to the parents. Valtonen and associates observed 281 children prospectively for 5 years after tympanostomy tube placement and reported that otorrhea was more common when the indication was for otitis media with effusion than for prevention of recurrent AOM; extrusion of the tube was more common after posttube otorrhea and required reinserter.\textsuperscript{419} In a recent meta-analysis conducted by Kay and co-workers of reports published in the literature from 1966 to 1999 of sequelae of tympanostomy tubes, the following rates were found: postoperative otorrhea, 16\%; later otorrhea, 26\%; recurrent otorrhea, 7.4\%; and chronic otorrhea, 3.8\%.\textsuperscript{420}

When otorrhea occurs, a culture should be taken from the middle ear by obtaining an aspirate through the tympanostomy tube. A preliminary culture of the ear canal and meticulous cleaning of the ear canal should precede the aspiration of the middle ear.
Antimicrobial therapy should be guided by the results of the middle-ear culture and susceptibility studies; the same pathogens that cause AOM in the community are usually isolated. In a study reported by Mandel and colleagues, the common causative organisms were isolated from infants and young children, primarily during the winter months; during the summer months, especially in older children, *P. aeruginosa* was cultured.421

Postoperative tympanostomy tube otorrhea can now be treated successfully with ototopical agents, such as ofloxacin otic solution 0.3% (Floxin Otic, Daiichi Pharmaceutical Corp.), even without concurrent administration of a systemic antimicrobial agent.154,392 Ciprofloxacin-dexamethasone otic solution (Ciprodex, Alcon) has also been approved by the FDA for treatment of acute otorrhea in children with tympanostomy tubes (the data are not yet published). When the otorrhea is unresponsive to oral systemic antimicrobial agents and aural ototopical medications, a more intensive work-up and treatment are indicated, which usually includes the use of intravenous antimicrobials.422 Despite a report that mastoidectomy is needed in 1.1% of children with recurrent or chronic otorrhea,419 intravenous therapy is highly effective in eliminating the chronic otorrhea without the need to resort to mastoidectomy. Children with Down syndrome tend to have recurrent otorrhea that may be difficult to control,423 but the alternative is to leave chronic otitis media with effusion untreated with its attendant hearing loss in these already handicapped children.

When episodes of AOM frequently recur despite a functioning tympanostomy tube, antimicrobial prophylaxis should be given to prevent the recurrent middle-ear infection and otorrhea. The selection of antibiotic and dose are the same as those recommended for antimicrobial prophylaxis alone.

In general, as concluded by Kay and associates from their recent meta-analysis, sequelae of tympanostomy tube placement “are common but generally transient (otorrhea) or cosmetic (tympanosclerosis, focal atrophy).”420 They recommended ongoing surveillance of children who have tympanostomy tubes in place, because sequelae are frequent and can lead to more severe problems if not identified in a timely fashion. Follow-up should be a team approach between the otolaryngologist, who inserted them and is ultimately responsible, and the primary care physician.

**Protection of the Ear When Tubes Are in Place**

Despite a meta-analysis by Lee and associates that showed no increase in the otorrhea rate when ears of children were left unprotected on exposure to water,424 water from bathing or swimming should not be allowed to enter the middle ear through the tympanostomy tube because contamination frequently results in otitis media and discharge. Protecting the ears during swimming is a minor nuisance and may prevent otorrhea. During bathing or hair washing, a wad of either lamb’s wool or cotton covered with petroleum jelly should be inserted into the external auditory meatus. Doc’s Proplugs (International Aquatic Trades, Santa Cruz, CA) are usually effective in protecting the middle ear and may be used to permit the patient to swim; surface swimming is recommended only, because diving or swimming deeply under water may lead to contamination of the middle ear.

**Tonsillectomy and Adenoidectomy**

Adenoidectomy performed either separately or in combination with tonsillectomy is the most common major surgical procedure employed to prevent otitis media. Myringotomy with tympanostomy tube insertion is the most common minor surgical procedure for otitis media.175

Tonsillectomy and adenoidectomy are the most common major operations performed in the United States; it is estimated that one-fourth of all children have a tonsillectomy and adenoidectomy during childhood. Such operations account for approximately 50% of all major surgical operations performed on children, approximately
25% of all hospital admissions of children, and 10% of hospital bed-days used by children. In 1994 in the United States, approximately 426,000 procedures on the tonsils and adenoids (140,000 adenoidectomies and 286,000 adenotonsillectomies) were performed in children who were younger than 15 years,\textsuperscript{425} which represents a substantial reduction from the more than 1 million such operations performed a few decades earlier. More recent data have been difficult to obtain because many of these operations have been short-stay or outpatient procedures during the past few years. The question is: do the potential benefits of adenoidectomy, with or without tonsillectomy, to prevent otitis media outweigh the known risks of these operations?\textsuperscript{426}

**Clinical Trials**

In the past, there was a great deal of uncertainty and skepticism concerning the efficacy of adenoidectomy for treatment and prevention of otitis media. The trials in the past suffered from several design flaws and methodologic shortcomings.\textsuperscript{427–431} However, we now have results from randomized clinical trials that provide evidence-based indications for adenoidectomy.

In a study conducted in Bristol, England, of children with bilateral chronic otitis media with effusion, Maw randomly assigned subjects into adenoidectomy, adenoidectomy and tonsillectomy, and nonsurgical control.\textsuperscript{432} Tympanostomy tubes were inserted into only one ear of each child; the contralateral ear was not operated on and was observed for 1 year. One-third of the children in the nonsurgical control group had resolution of their middle-ear effusion during the year, and one-third of the two surgical groups had persistent or recurrent disease after adenoidectomy with or without tonsillectomy. Maw concluded that adenoidectomy conferred benefit in approximately one-third of the subjects, but those children likely to benefit from the operation could not be identified before surgery. In addition, he reported that adding tonsillectomy to the adenoidectomy had no more beneficial effect than adenoidectomy alone.

Gates and coworkers randomly assigned 578 4- to 8-year-old Texas children who had chronic otitis media with effusion that was unresponsive to antimicrobial therapy to one of four surgical procedures: myringotomy; myringotomy and tympanostomy tube insertion; adenoidectomy and myringotomy; and adenoidectomy, myringotomy, and tympanostomy tube insertion.\textsuperscript{46} The myringotomy group had a greater percentage of time with middle-ear effusion, a greater percentage of time with hearing loss, the shortest time to first recurrence, and more surgical procedures repeated during the two-year follow-up period than did the other three groups. Adenoidectomy and myringotomy, with and without tympanostomy tube insertion, was more effective than myringotomy and tube insertion; however, the mean time to first recurrence was longer in both groups that included tympanostomy tube insertion. Gates and associates concluded that adenoidectomy, irrespective of adenoid size, should be considered when surgical therapy is indicated in children (of the age group studied) who are severely affected by chronic otitis media with effusion; their recommendation is for adenoidectomy and myringotomy without tympanostomy tube insertion, because purulent otorrhea through the tube was a problem in their study. When otitis media recurred after adenoidectomy and myringotomy, however, it occurred earlier than when a tube was inserted at the time of the myringotomy.

At the Children's Hospital of Pittsburgh, Paradise and colleagues entered 213 children into their study.\textsuperscript{25} The criteria for entry into the study were documented episodes of recurrent AOM or chronic otitis media with effusion in a child who had had a myringotomy and insertion of a tympanostomy tube at least once previously. Of the 213 subjects, 99 (46%) were randomly assigned to either adenoidectomy or control; tympanostomy tubes were inserted in both groups if criteria were met for duration and frequency of middle-ear disease. The other 114 children (54%) remained in the study, but their parents declined to participate in the random assignment. The decision to permit an ade-
noidectomy or not was left to parental preference. After initial examination, each patient was examined every 6 weeks and during any respiratory illness. Pneumatic otoscopy was performed at every visit. A trained interviewer telephoned each home every 2 weeks to determine whether there had been apparent or suspected illness; to make sure that any ill child was brought in promptly for examination; and to obtain routine information on school attendance, medication use, and a number of minor symptoms.

Allergy screening was part of every child’s work-up. A nasal smear was examined for eosinophils, and a battery of skin tests using common inhalant allergens was applied. Other regularly performed studies included lateral soft tissue radiographs of the nasopharynx to assess adenoid size, sinus radiographs when sinusitis was suspected, and audiometry and tympanometry to evaluate hearing and middle-ear status and tympanic membrane compliance.

The degree of middle-ear disease developing in the adenoidectomy and non-adenoidectomy groups was measured on the basis of three main parameters: the number of episodes per year of otitis media with effusion, months of middle-ear effusion, and frequency with which myringotomy is carried out subsequent to the child’s entering the clinical trial.

Data concerning subjects assigned randomly either to receive adenoidectomy or to enter the non-adenoidectomy control group were maintained separately from data concerning subjects whose parents declined randomization and opted for or against adenoidectomy.

In both trials, the randomly assigned clinical trial and the nonrandom one, outcomes favored adenoidectomy compared with no adenoidectomy. In both trials, the control group outcomes were biased because some subjects who were in the control and non-adenoidectomy groups and had persistent middle-ear disease crossed over into the adenoidectomy group; if such severely affected children had remained in the control and non-adenoidectomy groups, the outcomes most likely would have favored the adenoidectomy groups even more than was found. The most statistically significant differences were detected in the randomized clinical trial. The adenoidectomy group had 47% less time with otitis media than did the control group during the first year of the trial and 37% less disease in the second year. The number of episodes of AOM was also less in the adenoidectomy group, 28% in subjects who received adenoidectomy and 35% in those who did not. The investigators concluded that adenoidectomy is indicated on an individualized basis for those children who have recurrence of their middle-ear disease after tympanostomy tubes are extruded.

More recently, a clinical trial that was also conducted at the Children’s Hospital of Pittsburgh evaluated the efficacy of adenoidectomy or adenotonsillectomy for prevention of recurrent AOM in children who had not received tympanostomy tube placement in the past. The design and methods were similar to those described in the previous trial conducted by the same research team, except that none of the subjects had previously been treated with tympanostomy tubes, and the children were randomly assigned not only to adenoidectomy and control (ie, no surgery) but also to an adenotonsillectomy group. A total of 461 children (410 observed), aged 3 to 15 years, were enrolled in two parallel trials: 305 subjects enrolled (266 observed) without recurrent throat infection or tonsillar hypertrophy (ie, three-way trial), and 157 subjects enrolled (144 observed) who had such conditions randomized to either adenotonsillectomy or control group (ie, two-way trial). All subjects had a history of three or more attacks of AOM in the previous 6 months, or four or more episodes within the previous 12 months, with at least one attack being of recent onset. The efficacy of surgery was modest and limited to the first year of the trial. Because there was only short-term efficacy of both adenoidectomy and adenotonsillectomy, and given the risks of these operations, neither is recommended as a first surgical procedure for children who have not received a previous tube insertion and whose only indication for either operation is recurrent AOM. Adenoidectomy, as shown in the previously
conducted clinical trial, is effective when the child has had previous tube placement and is recommended. Because the benefit of adenoidectomy at this stage is effective for the long term, but not as effective for the short term, bilateral tympanostomy tube placement at the time of adenoidectomy should provide short-term relief.

**Clinical Practice Guidelines**

The Clinical Practice Guideline Otitis Media with Effusion in Young Children by Stool and colleagues recommended that “tonsillectomy should not be performed, either alone or with adenoidectomy, for treatment of otitis media with effusion in a child of any age. [Strong recommendation based on limited scientific evidence and strong Panel consensus.]”

Regarding adenoidectomy, the panel concluded that, “adenoidectomy is not recommended for treatment of otitis media with effusion in a child age 1 through 3 years in the absence of specific adenoid pathology. [Based on limited scientific evidence and Panel majority opinion.]” We agree with the guideline panel that tonsillectomy, without any specific pathologic process, such as chronic airway obstruction due to hypertrophy or recurrent acute tonsillitis that meets the criteria of Paradise and coworkers, is inappropriate. On the other hand, we disagree with the panel regarding adenoidectomy. The guideline panel concluded that adenoidectomy is “not recommended” for children aged 1 to 3 years “when adenoid pathology is not present” because they apparently concluded that there are limited data available from randomized clinical trials to support their recommending the operation for this indication in this age group; the trial conducted by Paradise and colleagues had only about 30 children who were younger than 4 years, and the subjects in the study by Gates and coworkers included only those children between the ages of 4 and 8 years. (Curiously, the list of references in the guideline does not include either of these two trials.)

We have registered our assessment of the strengths and weaknesses of these guidelines. We believe that adenoidectomy in younger children may be effective. The phrase “not recommended” is an improper designation because at this time we do not know whether the procedure is effective in young children. We concur with the panel that the age of the patient may be important because, in the usual operative setting, adenoidectomy is a greater risk in young infants. However, we consider children who are 2 and 3 years of age to be possible candidates for adenoidectomy if they meet the relatively stringent criteria used in the two clinical trials described before.

The more recent guideline from the American Academy of Pediatrics also noted that “information about adenoidectomy in children less than 4 years old, however, remains limited.”

A clinical trial currently under way at the Children’s Hospital of Pittsburgh is addressing the efficacy of adenoidectomy in children aged 2 and 3 years who have chronic otitis media with effusion. It is hoped this will answer the question raised by these guideline panels.

**Summary and Conclusions**

At present, the clinician who is faced with a child who has recurrent AOM or chronic otitis media must decide whether the potential benefits of these operative procedures outweigh the costs and potential risks after assessment of each child individually. That assessment should include, among others (1) the type of otitis media (ie, recurrent or chronic otitis media with effusion or recurrent AOM, or both); (2) the frequency, duration, and severity of the middle-ear disease; (3) the age of the child, because children younger than 3 years are at greater risk for complications from adenoid surgery than are older children; (4) the presence of other coexisting conditions that would make adenoidectomy or tonsillectomy more compelling, such as frequently recurrent pharyngotonsillitis or upper airway obstruction caused by obstructive adenoids or tonsils, which, of course, includes sleep apnea; (5) the presence or...
absence of upper respiratory tract allergy or infection, including sinusitis$^{434}$, and (6) the thoughtful consideration of other management options, such as watchful waiting, antimicrobial prophylaxis, or myringotomy and insertion of tympanostomy tubes. Decisions for or against these options should include the child (if the child is old enough to comprehend) and the parents.

**Recurrent AOM**

Currently, we withhold adenoidectomy as an initial procedure when surgery is being considered and opt for myringotomy with insertion of tympanostomy tubes for infants and children who have had at least three or more episodes of AOM within the previous 6 months or four or more attacks during the previous 12 months, with at least one episode being of recent onset (see “Myringotomy and Tympanostomy Tube Placement”). This procedure has been demonstrated to be effective for these criteria in the clinical trial conducted by Casselbrant and colleagues.$^{24}$ Antimicrobial prophylaxis is an alternative management option at this stage, although development of antimicrobial-resistant pneumococcus is a possibility with this approach.$^{1}$

Adenoidectomy at this time is reserved for those children who have hypertrophy of the adenoids that causes a significant degree of nasal airway obstruction. On the basis of the second clinical trial reported by Paradise and associates,$^{26}$ neither adenoidectomy nor adenotonsillectomy is recommended initially for children who have not previously received tympanostomy tube placement when recurrent AOM is the only indication for their removal. Tonsillectomy may also be initially indicated if the child also meets criteria for recurrent throat infections as defined in the clinical trial by Paradise and associates,$^{27}$ such as three or more episodes of throat infection per year for 3 or more years, or five or more episodes for each of the previous 2 years, or seven or more attacks within the previous year. Documentation of one or more of these episodes is recommended to confirm the parents’ history, and one or more—but not necessarily all—of the following should also be present during the episode: (1) tonsillar exudate, (2) fever, (3) enlarged and tender cervical lymph nodes, or (4) positive culture for group Aβ-hemolytic streptococcus (not all episodes have to be positive for this organism). For children less severely affected, such as only four or five episodes of throat infection in 1 year, a clinical trial by Paradise and coworkers showed that the subjects in the tonsillectomy groups had significantly fewer throat infections than those in the control groups (ie, no surgery), but the mean incidence of moderate-to-severe episodes of throat infection was low in the control groups (ie, statistically significant but not clinically significant)$^{435}$ Thus, it was concluded that, for children with a modest number of throat infections, neither tonsillectomy nor adenotonsillectomy should be recommended for general application. Rather, we advocate applying the criteria of the first clinical trial.$^{27}$

Although no clinical trial has demonstrated efficacy, significant pharyngeal airway obstruction caused by hypertrophy of the tonsils may be another indication for their removal at the time of initial tympanostomy tube placement.

If the child continues to have recurrent attacks of AOM after the initial tubes extrude, then adenoidectomy, irrespective of size, is recommended on the basis of the outcomes of the first clinical trial reported by Paradise and colleagues in 1990. As noted before, however, this surgery is associated with more risk in infants than in older children, and, therefore, reinsertion of the tympanostomy tubes without the addition of adenoidectomy is a more reasonable option for this age group; the 1990 trial by Paradise and associates did not include infants. Insertion of tympanostomy tubes, in addition to adenoidectomy, at this stage is optional, but because children may continue to have recurrent episodes during the first postoperative period, we prefer to also place tympanostomy tubes at the time of this surgery. Thus, we do not recommend adenoidectomy in infants when prevention of recurrent AOM is the only indication.

Indeed, a recent clinical trial from Canada failed to show a significant advantage of a concurrent adenoidectomy during myringotomy
and tympanostomy tube placement in children younger than 2 years of age. But, even in infants, if there is evidence of obstructive sleep apnea due to hypertrophy of the adenoids, then adenoidectomy is a reasonable option. Also, as described before, the addition of tonsillectomy may be warranted if there are other compelling indications, such as frequently recurrent attacks of throat infection or upper airway obstruction due to enlarged tonsils.

**Chronic Otitis Media with Effusion**

Myringotomy with tympanostomy tube placement is also recommended when chronic otitis media with effusion is unresponsive to a course of antibiotic treatment, is bilateral for at least 3 to 4 months (or unilateral for 6 or more months), and is not improving. This operation has been demonstrated to be effective for initial surgical treatment of chronic otitis media with effusion in the two clinical trials conducted by Mandel and colleagues (see “Myringotomy and Tympanostomy Tube Placement”). Adenoidectomy is withheld because the clinical trial by Gates and coworkers showed only modest efficacy—compared with myringotomy and tympanostomy tube only—as the first surgical procedure, but it is considered, along with tympanostomy tube insertion, when the child has a significant degree of nasal obstruction caused by enlarged adenoids. Myringotomy alone is not recommended.

If the child has recurrence of chronic otitis media with effusion after spontaneous extrusion of the tympanostomy tubes, then adenoidectomy, irrespective of size, is advised, in addition to myringotomy, with or without reinsertion of the tubes; the criteria for duration related to laterality of the middle-ear effusion are similar to those recommended for initial tube placement. The 1990 trial by Paradise and associates supports the recommendation for adenoidectomy in addition to insertion of tympanostomy tubes at this stage of the disease. Adenoidectomy for children with this stage of the disease has greater efficacy than for the subjects studied in the trial by Gates and colleagues (1987) because patients who have had one or more previously inserted tympanostomy tube procedures are more severely affected children.

Because the trial by Maw (1983) failed to show any increased benefit by adding tonsillectomy to the adenoidectomy in children who had had chronic otitis media with effusion, this procedure is not recommended, at the time of either the initial or any subsequent surgery, when prevention of otitis media is the only indication. However, like our recommendations for this operation when adenoidectomy is elected in the attempt to prevent recurrent AOM, other compelling indications might prompt tonsillectomy, such as frequently recurrent throat infections or pharyngeal airway obstruction caused by hypertrophied tonsils.

The 2004 recommendations for surgery from the American Academy of Pediatrics are essentially the same as we have stated above.

**Guidelines for Audiologic and Otolologic Referral**

The primary care provider is responsible for management of the child with otitis media. The primary care physician treats acute episodes and determines when special services should be provided. These services include audiologic assessments and consideration of surgical therapies. We suggest the following guidelines for referral:

- Audiologic assessment
- Parental concern for decreased hearing
- Speech and language delay
- Inattentive behavior
- Behavior change at home, day care, or school
- Otolologic referral
- An attack of AOM that is unresponsive to appropriate and adequate antimicrobial therapy that may require tympanocentesis-myringotomy to relieve otalgia and fever and to identify the causative organism
- Recurrent episodes of AOM, such as three or more episodes within the previous 6 months or four or more episodes within the previous 12 months, with the last attack being of recent
onset, especially when the frequency, severity, and duration are unaffected by antimicrobial prophylaxis

- Middle-ear effusion for 3 months or longer in both ears (ie, chronic) or 6 months or longer in one ear, which has been unresponsive to a course of antibiotic (eg, 10-day course of amoxicillin)
- Recurrent otitis media with effusion in which each episode fails to meet criteria for being chronic, yet the cumulative duration is excessive, such as 6 of the preceding 12 months
- Middle-ear effusion associated with hearing loss of 25 dB or more that is unresponsive to medical treatment
- Persistent high negative middle-ear pressure, retraction pocket, or atelectasis of the middle ear
- Symptoms associated with eustachian tube dysfunction, such as fluctuating hearing loss, otalgia, or tinnitus that is chronic or recurrent and causing concern for the child or parent or both
- Speech and language delay associated with recurrent otitis media
- Persistent otorrhea through a tympanostomy tube that is unresponsive to initial appropriate and adequate medical treatment (eg, ototopical or oral antimicrobial agents)
- Acquired anatomic abnormality, such as persistent perforation of the tympanic membrane, with or without chronic supplicative otitis media, or presence (or suspicion) of cholesteatoma
- Suppurative complication of AOM present or suspected, such as mastoiditis, labyrinthitis, or facial palsy, or any associated central nervous system signs or symptoms, such as severe headache, blurred vision, and ataxia.

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