Clinical Practice

This Journal *feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author's clinical recommendations.*

Otitis Media

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An otherwise healthy 17-month-old boy had a cold accompanied by two days of rhinorrhea, cough, and fever (temperature of up to 38.8°C [102°F]). On day 5 he became fussy and woke up crying multiple times during the night. The following day he was afebrile, and a physical examination was normal except for findings of slight redness of the left tympanic membrane with no middle-ear fluid and a bulging right tympanic membrane with white fluid behind it obscuring the umbo. How should this child be treated?

The Clinical Problem

Otitis media, or inflammation of the middle ear, is diagnosed more than 5 million times per year in the United States; it is the most common reason for the prescription of antibiotics in children. The diagnosis of otitis is usually followed by antibiotic treatment despite "a woeful lack of substantial evidence on the question of antibiotic therapy" for this condition.[1]

Otitis media usually follows a viral infection of the nasopharynx that disrupts the function of the eustachian tubes. Tubal dysfunction severe enough to impair ventilation and produce transient negative middle-ear pressure on tympanometry was found to occur during 66 percent of colds in schoolchildren[2] and 75 percent of colds in children in day care.[3] In patients with colds, bacteria and viruses from the nasopharynx that reach the middle ear during pressure equilibration may be cleared by the mucociliary system (Fig. 1) less effectively than usual. Bacteria may replicate in fluid in the middle ear to cause bacterial otitis media; respiratory viruses may infect the middle-ear mucosa, either alone, leading to viral otitis media, or in combination with bacteria.[4-6] Tympanocentesis has revealed *Streptococcus pneumoniae* in 20 to 35 percent of patients with acute otitis, nontypable *Haemophilus influenzae* in 20 to 30 percent, *Moraxella catarrhalis* in 20 percent, no bacteria in 20 to 30 percent, and virus with or without bacteria in 17 to 44 percent.[5-7]

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Strategies and Evidence

Diagnosis

The two requirements for a diagnosis of acute otitis media are inflammation of and fluid in the middle ear.[8,9] A retracted drum (Fig. 2A), which may be painful, is due to negative middle-ear pressure and not to bacteria. Bacterial otitis media is characterized by a bulging eardrum that has purulent fluid behind it (Fig. 2B)[10,11] or by purulent otorrhea after the tympanic membrane has been perforated. Otitis media without a bulging tympanic membrane, which is usually called acute otitis media, is much more common. Inflammation of the middle ear may be signified by local or systemic findings such as ear pain, erythema of the tympanic membrane, fever, and cold symptoms.[8,9] A red tympanic membrane without middle-ear fluid (Fig. 2C) is not acute otitis. Acute otitis must also be distinguished from otitis media with effusion, which is defined as fluid in the middle ear without local or systemic illness.

Antibiotic Therapy

Once acute otitis, which may be viral, bacterial, or both, has been diagnosed, the central issue is whether antibiotic therapy will be in the child's best interest (Table 1). A meta-analysis[12] of randomized, placebo-controlled trials found that acute otitis had resolved at one week in 81 percent of placebo recipients, as compared with 94 percent of antibiotic recipients (an absolute difference of 13 percent). More recent analyses have yielded similar findings.[9,13] In general, the rates of clinical resolution were similar in placebo and antibiotic recipients on the first day of therapy but slightly higher at three to five days and at seven days among those who received antibiotic therapy.[14,15] Amoxicillin is as effective as any other drug or drugs,[12,16] even though at least one quarter of *S. pneumoniae* strains have increased resistance to penicillin and amoxicillin, one quarter to one third of *H. influenzae* strains are resistant in vitro to amoxicillin (that is, are β-lactamase–positive), and virtually all strains of *M. catarrhalis* are resistant to amoxicillin (β-lactamase–positive). The clinical effect of a single dose of ceftriaxone or

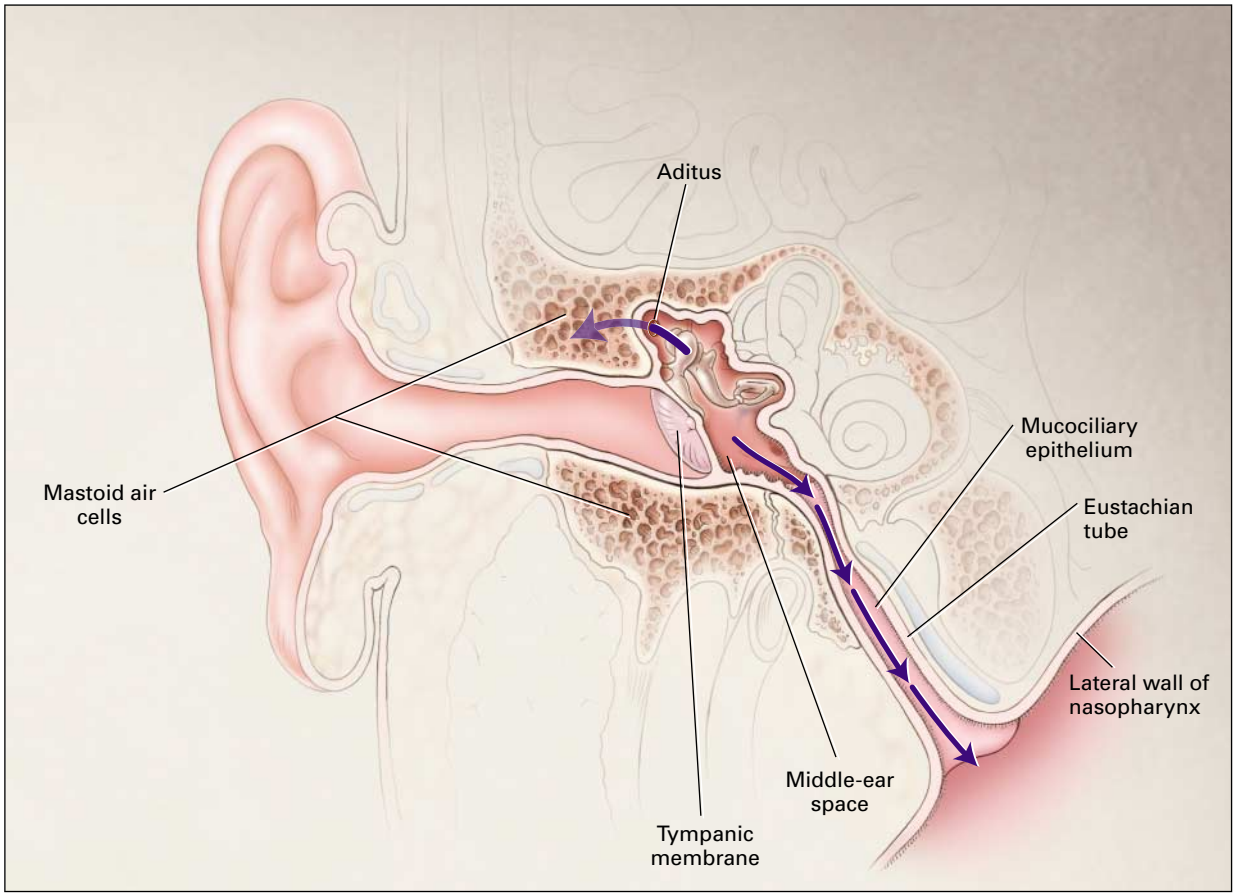

Figure 1. The Middle Ear.

The tympanic membrane forms the lateral wall of the box-shaped middle ear. The function of the eustachian tube is to equilibrate middle-ear pressure with that in the nasopharynx. Bacteria and viruses resident in the nasopharynx may reach the middle ear during pressure equilibration. One third of the middle-ear mucosa and the entire eustachian tube are lined with mucociliary epithelium to transport bacteria from the middle ear back to the nasopharynx. Air from the middle ear enters the mastoid air cells by way of the aditus.

5 days of azithromycin was not different from the effect of 7 to 10 days of amoxicillin.[9]

Whether antibiotic therapy reduces the risk of prolonged illness in children six months to two years of age was examined in a trial comparing amoxicillin and placebo in 240 children in the Netherlands, where the background rates of resistance to amoxicillin are 1 percent for *S. pneumoniae* and 6 percent for *H. influenzae*.[17] About a third of the patients had bulging or perforated tympanic membranes. Otitis was more prolonged in children two years of age or younger than in older children in other studies, but antibiotic therapy had a limited effect, reducing the incidence of persistent symptoms by 13 percent on day 4 and shortening the duration of fever by one day.

Fifty percent of children have middle-ear fluid for a month after the resolution of acute otitis, regardless of whether they received antibiotic or placebo.[12,14,18] Fluid clears by three months in 90 percent of children whether or not they received antibiotics.[12,18] A meta-analysis of randomized trials found that two to four weeks of antibiotic therapy for otitis media with effusion had a small, but consistent, transient effect on residual fluid.[19] At one month there was an absolute difference in the rates of resolution of 16 percent in favor of antibiotic therapy, but there was no difference in the proportions of children who had residual fluid at three months.

Resistant Otitis Media

Resistant bacterial otitis media is recognized by the persistence of fever, otalgia, and red, bulging tympanic membranes or by persistent otorrhea after three or more days of antibiotic therapy.[20,21] Culture of purulent fluid yielded bacteria that were resistant to the prescribed antibiotic in only one third of cases.[20,22]

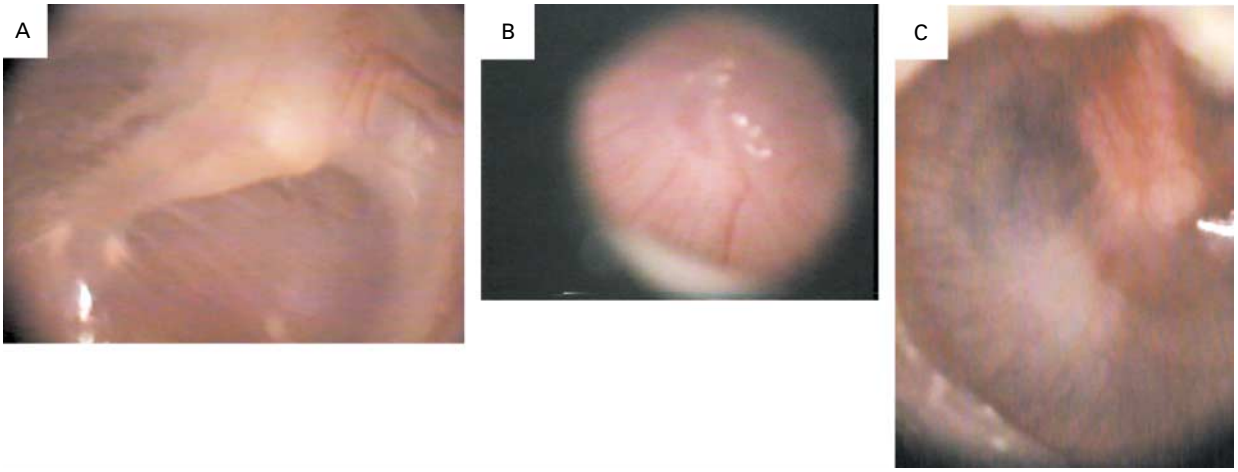

Figure 2. Appearance of the Tympanic Membrane in Children.

Panel A shows a retracted tympanic membrane, which increases the prominence of the handle of the malleus. The umbo is visible. Panel B shows bacterial otitis media, characterized by a bulging tympanic membrane and purulent fluid behind the tympanic membrane. The umbo and the handle of the malleus are obscured. Panel C shows a red tympanic membrane without fluid in the middle ear. The malleus and umbo are visible. (Photographs courtesy of Dr. Carlos Armengol, Pediatric Associates of Charlottesville, Va.)

TABLE 1. RECOMMENDATIONS FOR THE TREATMENT OF OTITIS MEDIA.

CONDITION	TREATMENT
Otitis media with bulging tympanic membrane	Immediate treatment with high-dose amoxicillin (80–100 mg/kg of body weight per day orally) for 7 days*
Otitis media without bulging tympanic membrane	Delayed antibiotic-prescribing strategy†
Recurrent acute otitis media	Delayed antibiotic-prescribing strategy† Immunization with influenza vaccine
Resistant bacterial otitis	High-dose amoxicillin–clavulanate (80–100 mg of amoxicillin/kg per day orally) for 7 days, cefuroxime axetil (30 mg/kg twice a day orally) for 7 days, or ceftriaxone (50 mg/kg per day intramuscularly) for 3 days

*For children who are allergic to penicillin, preferred alternatives include cefuroxime axetil or another second-generation cephalosporin (other than cefaclor, which may cause a serum-sickness–like reaction), azithromycin, or ceftriaxone (50 mg per kilogram once).

†The delayed antibiotic-prescribing strategy is as follows: initiate treatment with full-dose acetaminophen; provide a prescription for amoxicillin to be used only if otalgia or fever persists or if there is no clinical improvement after 48 to 72 hours; advise the patient's parents that antibiotics do not work very well against otitis and have virtually no effect during the first 24 hours; explain the disadvantages of antibiotics to patient's parents — they may have side effects (e.g., diarrhea and rash); and select for resistant bacteria.[15]

In the absence of data on the efficacy of antibiotics for resistant bacterial otitis, one expert panel recommended high-dose amoxicillin–clavulanate, cefuroxime axetil, or intramuscular ceftriaxone for three days.[21] Tympanocentesis may help guide therapy.

Delayed Antibiotic Therapy

The small percentage of children who will benefit from an antibiotic are not easily identified at the time of diagnosis. One strategy to minimize unnecessary prescribing of antibiotics is to delay treatment for 48 to 72 hours after the diagnosis to determine whether there is spontaneous clinical improvement.[15,23] This approach is used in the Netherlands: children, particularly those younger than two years of age, are closely monitored, and a seven-day course of antimicrobial therapy is begun only when there is no improvement in symptoms within one to two days in children

younger than two and within three days in children who are two years of age or older. This policy is associated with a 31 percent rate of antibiotic use for acute otitis media (far lower than that in the United States) and with decreased resistance among causative organisms.[23]

The effectiveness in general practice of this delayed prescribing strategy was assessed in a randomized trial[15] involving 315 children 6 months to 10 years of age with acute red ear (41 percent were 3 years of age or younger). Seven to 9 percent of the children had perforated eardrums, and 46 percent had bulging eardrums. Children were randomly assigned to receive amoxicillin either immediately or after a delay of three days (the prescription was available to be picked up). Parents were advised to provide full doses of acetaminophen for pain and fever. Immediate antibiotic use reduced the duration of symptoms, including crying during the day and sleep disturbances at night, by about one day and decreased acetaminophen use. However, the benefit occurred mainly after the first 24 hours, when the symptoms were diminishing anyway. The parents of only 36 of the 150 children in the delayed-antibiotics group (24 percent) picked up the antibiotic prescription, reflecting the fact that the parents recognized that the symptoms were resolving on their own within three days in the majority of children. Three quarters of the parents in the delayed-antibiotics group were satisfied with their child's treatment.

One impediment to the use of the delayed-antibiotic strategy is the fear of an increased risk of acute mastoiditis. In the Netherlands, Norway, and Denmark, which have rates of prescription of antibiotics for otitis of 31 percent, 67 percent, and 76 percent, respectively, the incidence of mastoiditis was approximately 4 cases per 100,000 children per year over a five-year period.[24] In Canada and the United States, where the rates of prescription of antibiotics for otitis exceed 96 percent, the incidence was approximately 2 cases of mastoiditis per 100,000 children per year.[24] Restricted use of antibiotics for acute otitis was associated with twice the rate of acute mastoiditis, but this difference amounted to only 2 additional cases of mastoiditis per 100,000 children per year.[24]

Prevention

Proof of the concept that viral respiratory tract infections either predispose children to bacterial otitis media or cause viral otitis media is provided by studies of the effect on acute otitis of immunization with influenza vaccine[25,26] and of the treatment of influenza with a neuraminidase inhibitor.[27] In Finland[25] and the United States,[26] children in day-care centers who were randomly assigned to receive influenza vaccine had a 33 to 36 percent reduction in the number of diagnosed cases of acute otitis media, as compared with placebo recipients, during the six weeks when influenzavirus was in the community. The ability of the antiviral agent oseltamivir to prevent acute otitis media was examined in a randomized, controlled trial of children 1 to 12 years old who had influenza but who did not have acute otitis media at the time of randomization.[27] Acute otitis developed in 27 percent of 200 placebo recipients and 16 percent of 183 recipients of oseltamivir during the four-week follow-up, a difference of 40 percent. Clearly, prevention (or treatment) of the single respiratory viral infection for which we have a vaccine reduces the occurrence of acute otitis in young children while the virus is circulating in the community, but it does not have an effect during the remainder of the year.[26]

Evidence of the ability of a bacterial vaccine to prevent acute otitis media, on the other hand, is not so promising. In two trials, immunization of infants with a seven-valent conjugate pneumococcal vaccine was not very effective in preventing acute otitis during an 18-month follow-up, up to the age of two years.[7,28] The difficulty with this approach is apparent in an analysis of the bacteriologic data from the Finnish trial.[7] Tympanocentesis in 1345 episodes of otitis in the 831 control children showed that 334 episodes (25 percent) were caused by pneumococcal serotypes that either were included in the vaccine or cross-reacted with the serotypes in the vaccine. These are the episodes that the vaccine could be expected to prevent. Among vaccinated children, 148 such episodes of otitis occurred, for an efficacy rate of 56 percent in preventing otitis due to vaccine-related serotypes. Since 186 episodes of pneumococcal otitis were prevented, the overall efficacy rate should have been 14 percent (186 of 1345 episodes); however, the overall efficacy rate was only 6 percent, owing to a 33 percent increase in the rate of acute otitis due to pneumococcal serotypes that were not included in the vaccine, an 11 percent increase in otitis due to *H. influenzae*, and a small increase in the number of culture-negative cases on tympanocentesis. Thus, the effect of vaccination in preventing otitis due to vaccine-related serotypes of pneumococci was counteracted by an increase in otitis caused by other bacterial pathogens of the upper airway.

Recurrent Acute Otitis Media

Recurrent otitis media is usually defined as three or more episodes of acute otitis within 6 months or four episodes within 12 months. A meta-analysis of antibiotic prophylaxis — one strategy for the prevention of recurrent acute otitis media — demonstrated that prophylaxis with sulfisoxazole, trimethoprim–sulfamethoxazole, or amoxicillin resulted in an average decrease of 0.11 episode per child-month, or about 1 episode

of acute otitis per year, in qualifying children.[19] This small benefit is generally outweighed by the disadvantage of promoting antibiotic resistance.

Whether the placement of tympanostomy tubes is beneficial depends on the type of otitis media. Placement of tubes significantly reduced the rate of recurrence of episodes of acute otitis media with bulging eardrums in one study[29] but had no effect on the rate of recurrent acute otitis media without bulging eardrums in another study.[30] Otorrhea of the tubes is a common problem when the tubes remain in place longer.[31] Adenoidectomy had no effect[32,33] or only a limited effect[34] on recurrent acute otitis. Tonsillectomy plus adenoidectomy reduced the rate of acute otitis by 0.7 episode per child only in the first year of a three-year follow-up, but this approach was associated with a 15 percent rate of perioperative complications.[32] The frequency of recurrences can be expected to diminish with age.[35]

AREAS OF UNCERTAINTY

It remains unclear how to identify, at the time of diagnosis, the small percentage of children with acute otitis media who will benefit from antibiotic therapy. The appropriate duration of oral antibiotic therapy for bacterial otitis media is also not clear. A 7-to-10-day course has been the standard, but supportive evidence is lacking.[8] A five-day course is thought by some to be inadequate for severe cases. Some clinicians advocate the routine use of antibiotics or longer courses (or both) in children younger than two years old who have acute otitis media, but in a placebo-controlled trial, antibiotic therapy had the same limited effect in ameliorating disease in this age group as it did in older children.[17]

The optimal treatment for children with recurrent otitis media has not been identified. Although vaccination against influenzavirus is likely to be useful, the effect of immunization with a conjugate pneumococcal vaccine on recurrent otitis media would be expected to be small.[7]

GUIDELINES

Five principles for the judicious use of antibiotics in children with otitis media have been devised under the auspices of the Centers for Disease Control and Prevention and the American Academy of Pediatrics.[8] First, the diagnosis of otitis media should not be made unless fluid is present in the middle ear. Second, otitis media should be classified as acute otitis media or otitis media with effusion on the basis of the presence or absence of signs and symptoms of acute illness. Third, in contrast to acute otitis media, otitis media with effusion should not be treated with an antibiotic. Fourth, effusion is likely to persist after the treatment of acute otitis and does not require repeated treatment. Fifth, antibiotic prophylaxis for acute otitis should be used only in accordance with strict criteria. These guidelines were devised before the results of the large trial of delayed antibiotic prescribing[15] became available and, thus, do not address this strategy. The guidelines do acknowledge that at least one quarter of the diagnoses of otitis media fit the definition of otitis media with effusion and that avoiding antimicrobial treatment in this group would eliminate "6 to 8 million courses of unnecessary antibiotic therapy . . . each year."[8]

CONCLUSIONS AND RECOMMENDATIONS

In patients with acute otitis media, bacteria are only part of the problem in what is usually a self-limited disease, and antibiotic therapy can correct only the part of the problem that is due to bacteria. Acute otitis will resolve within one week without antibiotic therapy in more than four fifths of children; prescribing an antibiotic increases this rate by only 13 percentage points.[12] When antibiotic therapy is used, amoxicillin is as good as any other antibiotic despite the fact that a third of the bacteria are resistant to this drug in vitro. In the month after acute otitis, one half of children have residual middle-ear fluid, and the fluid usually disappears by three months, whether or not antibiotics have been prescribed. Thus, the practice of rechecking the patient's ears two weeks after treatment is unwarranted. In only a third of cases is persistent bacterial otitis associated with an infection with bacteria that are resistant to the prescribed antibiotic. In such cases, the usual approach is to switch to a β-lactamase–resistant antibiotic (such as amoxicillin–clavulanate).

Because the child described in the case vignette has bacterial otitis media, as evidenced by the bulging tympanic membrane with visible pus, I would recommend immediate antibiotic therapy. High-dose amoxicillin would be the first choice for therapy in view of the frequency of infection with penicillin-resistant pneumococci. Acute otitis without bulging eardrums, which is much more common, is likely to clear spontaneously, and use of the delayed antibiotic-prescribing strategy (waiting 48 to 72 hours to prescribe antibiotics while giving the patient acetaminophen)[15] is appropriate, especially for cases of recurrent otitis media, because as parents become more familiar with the pattern of their child's illness, they are able to recognize that most episodes will resolve without antibiotic therapy. Finally, antibiotic therapy for otitis media with effusion is not in the child's best interest.[8]

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