CLINICAL PRACTICE

Otitis Media in Young Children

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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.*

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CME

An otherwise-healthy 9-month-old girl in whom symptoms of an upper respiratory tract infection had developed 4 days earlier presents with a 1-day history of increased fussiness and difficulty sleeping reported by a parent. On examination, she is afebrile and slightly fussy. Her right tympanic membrane, which can be visualized only partially owing to the presence of cerumen, appears opacified. How would you treat this child?

THE CLINICAL PROBLEM

Acute otitis media remains one of the most frequently diagnosed infectious diseases in children younger than 2 years of age. By 2 years of age, 41% of children will have had at least one episode of acute otitis media and 13% will have had at least three episodes.[1] Although the incidence of acute otitis media, and particularly of recurrent and refractory cases,[2] has been decreasing,[3,4] approximately 15 million cases are diagnosed each year in the United States.[3] The decrease in the incidence of acute otitis media, especially among children younger than 2 years of age,[4] is likely to be attributable to universal vaccination with pneumococcal conjugate vaccines[5] and to increased stringency in the diagnostic criteria.[6] Exposure to large numbers of other children (e.g., in day care), male sex, shorter duration of breast-feeding, exposure to tobacco smoke, Down's syndrome, and immunologic deficiencies (e.g., hypogammaglobulinemia) are associated with an increased risk of acute otitis media.[7-9]

The antecedent event in almost all cases of acute otitis media is a symptomatic viral upper respiratory tract infection. Approximately one third of viral upper respiratory tract infections are complicated by acute otitis media.[10,11] The median time between the onset of an upper respiratory infection and the development of acute otitis media is approximately 4 days.[10] Viral infection inflames the mucosa of the upper respiratory tract, including the nasopharynx and eustachian tube. Eustachian-tube dysfunction impairs the drainage of fluid from the middle ear and leads to nasopharyngeal aspiration of pathogens. Bacteria (most often *Streptococcus pneumoniae*, nontypable *Haemophilus influenzae*, and *Moraxella catarrhalis*) are isolated from the middle-ear fluid of approximately 80% of children with a bulging tympanic membrane.[12-15] Only rarely (in approximately 6 to 7% of cases) does viral infection alone (in the absence of a bacterial superinfection) result in clinical features consistent with acute otitis media.[16,17]

Considerable shifts in the balance of the three predominant bacterial pathogens have occurred over the past 20 years. In a comparison of data from the period before universal pneumococcal vaccination began in infants (i.e., before 2000, when a 7-valent version was introduced) with more-recent data (i.e., after a 13-valent version was

KEY CLINICAL POINTS

OTITIS MEDIA IN YOUNG CHILDREN

- Acute otitis media is a bacterial infection that occurs almost exclusively after a viral upper respiratory tract infection.
- Common pathogens include *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*.
- Bulging of the tympanic membrane is a defining feature.
- Children with mild or moderate symptoms can be either treated with antibiotic agents or closely observed.
- High-dose amoxicillin (80 to 90 mg per kilogram of body weight per day, divided into two doses) remains the first-line treatment. Amoxicillin–clavulanate therapy warrants consideration in children in whom *H. influenzae* is likely to predominate (i.e., those who have received antibiotics in the previous 30 days, have conjunctivitis–otitis syndrome, or have spontaneous rupture of the tympanic membrane).
- Treatment with antibiotics for 10 days resulted in less treatment failure and less use of rescue antibiotics than treatment for 5 days.
- Tympanocentesis is indicated in children with acute otitis media who have had treatment failure with multiple rounds of antibiotic therapy.
- Among children with recurrent acute otitis media, the incidence of acute otitis media during a 2-year period was similar among those who had placement of a tympanostomy tube and those who received episodic antibiotic treatment.

introduced in 2010), the proportion of middle-ear samples with *S. pneumoniae* decreased by 15 to 20% and the proportion of samples with *H. influenzae* or *M. catarrhalis* (or both) increased by 20 to 30%.[1,13,18-21] These trends are also apparent in larger studies that examined the distribution of these pathogens in the nasopharynx.[22-24] Of note, the observed increasing proportions of cases with *H. influenzae* and *M. catarrhalis* may be due in part to the vaccine-related decrease in the proportion with *S. pneumoniae*.[2] As of 2019, *S. pneumoniae* (alone or in combination with the other two pathogens) has been isolated from the middle-ear fluid in approximately 24% of children with acute otitis media, *H. influenzae* in 34%, and *M. catarrhalis* in 15%.[1,18] The introduction of the 20-valent version of the pneumococcal vaccine in 2023 will probably change the distribution of these pathogens again.

The percentage of *S. pneumoniae* isolates that are penicillin-nonsusceptible (i.e., minimum inhibitory concentration of >1 μg per milliliter, which includes intermediate and resistant strains) has remained at approximately 40%[18] despite substantial changes in the circulating strains of pneumococcus.[1,24] The primary mechanism of resistance among penicillin-nonsusceptible strains of *S. pneumoniae* involves alterations in penicillin-binding proteins. This mechanism of resistance can usually be overcome with the use of higher concentrations of antibiotic agent at the site of infection. A higher prevalence of penicillin-nonsusceptible *S. pneumoniae* can be expected among children who have recently received treatment with beta-lactam drugs and among those who are exposed to large numbers of other children (as are present in day care or in large families).[23,25] Approximately 50% of nontypable *H. influenzae* strains produce beta-lactamase and are not susceptible to amoxicillin.[1] *M. catarrhalis* is often present together with *H. influenzae* or *S. pneumoniae*[26]; virtually all strains produce beta-lactamases and are resistant to amoxicillin.

STRATEGIES AND EVIDENCE

DIAGNOSIS

Because the standard for diagnosing acute otitis media (i.e., isolation of bacteria from middle-ear fluid) is invasive, studies evaluating the accuracy of the contribution of individual signs or symptoms to the diagnosis are lacking. In children with clinically diagnosed acute otitis media, the most frequently reported symptoms are fussiness and difficulty sleeping.[27] However, these symptoms are often also present in children with an uncomplicated upper respiratory tract infection.[27] Fever and ear tugging are also present in some children with uncomplicated upper respiratory infection.[27,28] Accordingly, the diagnosis of acute otitis media has come to rely on otoscopic findings.[29]

Videos showing otoscopic findings are available at NEJM.org

The normal tympanic membrane is translucent and pearly gray and has a ground-glass appearance that enables a clear view of the short process and the manubrium of the malleus (Fig. 1 and Video 1). Otitis media with effusion is diagnosed

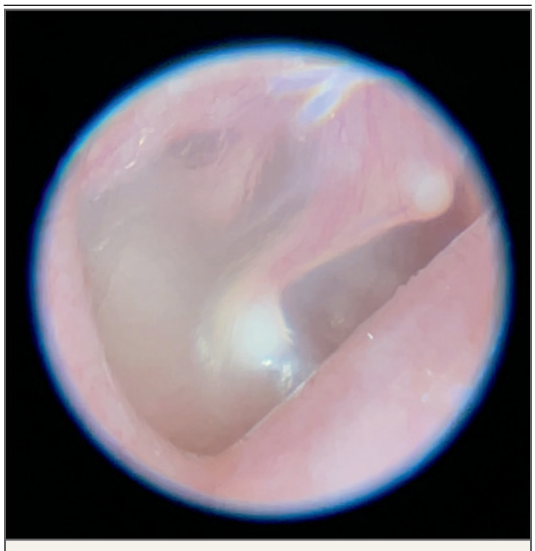

Figure 1. Normal Tympanic Membrane.
The normal tympanic membrane is translucent and pearly gray and has a ground-glass appearance that enables a clear view of the short process and the manubrium of the malleus.

when there is evidence of middle-ear effusion (opacification, decreased tympanic membrane mobility, or obscured short process) but no signs of tympanic-membrane bulging (Fig. 2 and Videos 2 and 3).[30] Otitis media with effusion may occur as the aftermath of an episode of acute otitis media or as a consequence of eustachian-tube dysfunction due to another cause, such as an upper respiratory tract infection. However, otitis media with effusion also may precede acute otitis media. In most children, otitis media with effusion resolves without intervention within a few months.

A diagnosis of acute otitis media is justified when, in addition to evidence of middle-ear effusion, any bulging of the tympanic membrane is observed (Fig. 3 and Video 4).[29] The use of bulging to define acute otitis media is based on the following indirect data: bacteria can be isolated from approximately 80% of middle-ear samples obtained from children with a bulging tympanic membrane[12-15]; children without a bulging tympanic membrane are unlikely to have middle-ear effusion[30] and therefore unlikely to have acute otitis media; expert otoscopists rely almost exclusively on the presence or absence of bulging to diagnose acute otitis media[31]; and larger treatment effects were observed in a trial that required bulging for inclusion[32] than in trials that did not.[33] Other manifestations of acute otitis media include bullous myringitis (bulging tympanic membrane with bullae) and cobblestoning of the tympanic membrane (bulging tympanic membrane with microperforations) (Fig. 3 and Videos 5 and 6).

The algorithm in Figure 4 may be used as a guide to classify otitis media as either acute otitis media or otitis media with effusion on the basis of the clinical history and otoscopic findings.[29] Isolated redness of the tympanic membrane (not to be equated with an injected or diffusely pink appearance) in the absence of bulging is uncommon; expert otoscopists diagnose acute otitis media in approximately 25% of such cases.[31] Factors complicating the diagnosis include obstructing cerumen and difficulty with patient cooperation. The technique for otoscopic examination can be reviewed in a Video in Clinical Medicine.[34]

MANAGEMENT

Many issues influence strategies for the treatment of acute otitis media. These issues include the age of the child, the severity of symptoms, and the relative risk of observation as compared with treatment.

To date, 13 randomized trials have examined the efficacy of antibiotics as compared with placebo for eradicating symptoms of acute otitis media in children. The outcomes that were investigated varied among these trials: 5 trials reported data on ear pain, and 8 reported data on composite outcomes that may or may not have included ear pain.

A meta-analysis of these trials showed that children assigned to receive antibiotics had a 29% lower risk of persistent symptoms at 2 to 3 days, a 24% lower risk of persistent symptoms at 4 to 7 days, and a 67% lower risk of persistent symptoms at or before 10 to 12 days than those who had been assigned to receive placebo. The corresponding number needed to treat with antibiotics to achieve symptom eradication at these time points were 20 at 2 to 3 days, 17 at 4 to 7 days, and 7 at or before 10 to 12 days.[33] No significant difference in symptom eradication was noted during the first 24 hours, but a difference would not be expected given the pharmacokinetics of the agents being used. The use of antibiotics halved the risk of contralateral acute otitis media episodes (from 19% to 10%; number needed to treat, 11)

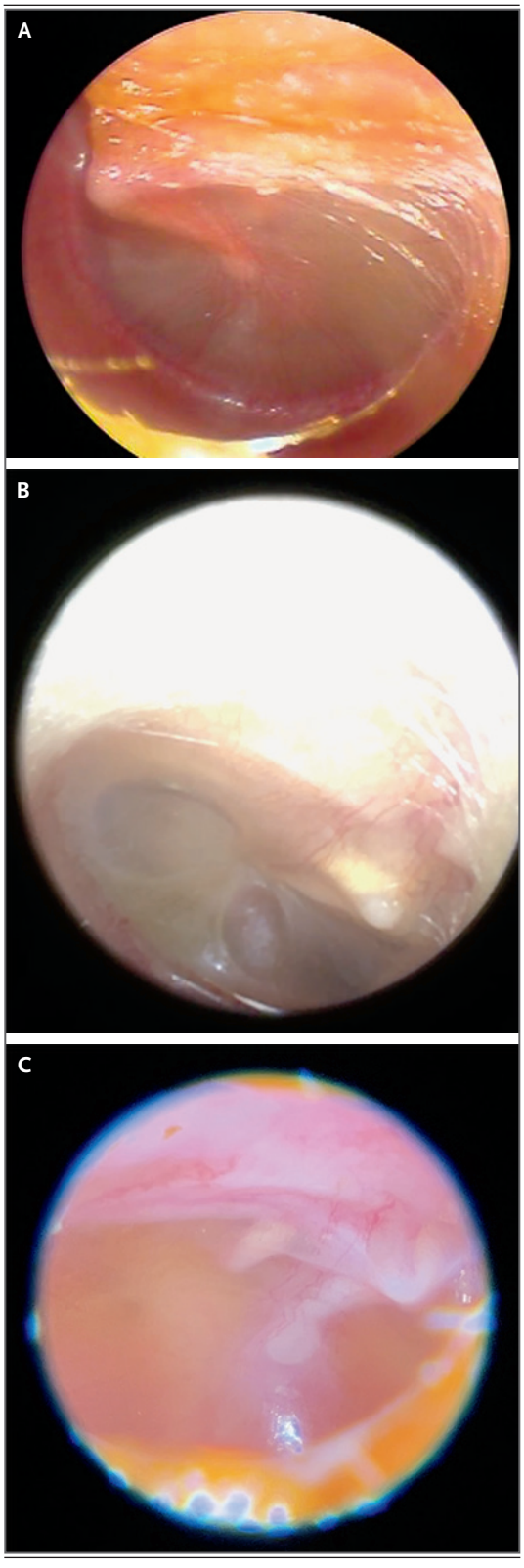

Figure 2. Manifestations of Otitis Media with Effusion.
Panel A shows an opaque neutral tympanic membrane, Panel B an opaque tympanic membrane with visible air-fluid levels, and Panel C an amber tympanic membrane.

and reduced the risk of tympanic-membrane perforations by two thirds (from 5% to 2%; number needed to treat, 33). Of note, in 11 of the 13 trials, a large proportion of the enrolled children had nonbulging tympanic membranes, which could have biased the pooled results toward the null. In the 1 trial that measured symptoms with the use of a validated scale, the risk of persistent symptoms was 67% lower among children randomly assigned to receive amoxicillin–clavulanate than among those who had been assigned to receive placebo (number needed to treat, 7).[32]

Because symptoms of acute otitis media also rapidly abate without the use of antibiotics[32,35] and because the incidence of suppurative complications is very low,[36] a reasonable strategy in nonsevere cases is expectant observation without immediate antibiotic treatment. How severity should be defined has not been well studied, and thus a wide variety of definitions are used.[37,38] Severity of symptoms could be established informally or measured with the use of validated scales.[39] The severity of otoscopic signs or of fever at presentation can also be used. However, to date, trials have not unequivocally established a link between these severity measures and efficacy.[40,41]

Adverse events that have been associated with antibiotic treatment of acute otitis media were examined in a meta-analysis that included 82 studies.[42] Diarrhea was the most frequent side effect, occurring in approximately 1 in every 5 children treated with high-dose amoxicillin–clavulanate and in 1 in every 8 children treated with amoxicillin (number needed to harm of 9 and 15, respectively).[42] The use of antibiotics early in life has also been associated with the later development of allergies, asthma, and obesity.[43]

Selection of First- and Second-Line Antimicrobial Therapy

Data from randomized trials directly comparing the efficacy of amoxicillin with that of amoxicillin–clavulanate — the two most frequently used agents

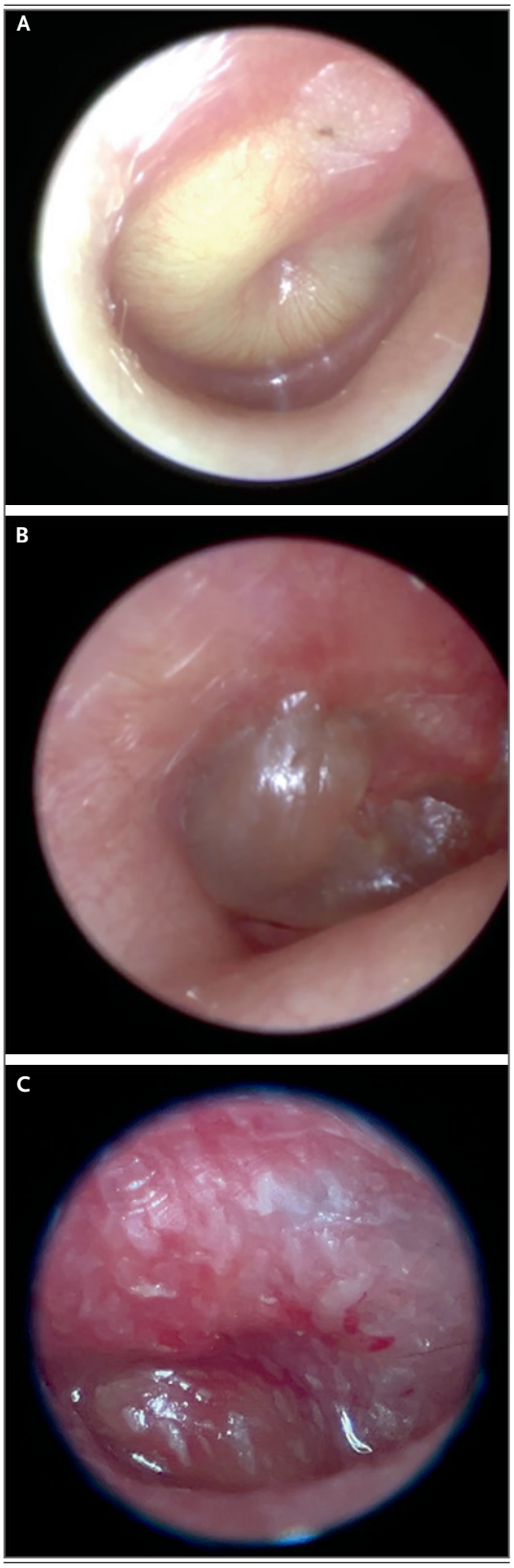

Figure 3. Manifestations of Acute Otitis Media.
Panel A shows a bulging tympanic membrane, Panel B bullous myringitis (bulging tympanic membrane with bullae), and Panel C cobblestoning of the tympanic membrane (bulging tympanic membrane with microperforations).

in the treatment of acute otitis media — are lacking. Consequently, some researchers have used observational and cost-effectiveness studies to suggest that amoxicillin may be preferred for first-line treatment.[44-46] Others, extrapolating from local trends in the in vitro susceptibility of organisms being isolated from the middle ear or the nasopharynx of children with acute otitis media, have suggested that amoxicillin–clavulanate may now be preferred as a first-line agent. Extrapolation from local microbiologic data requires one to not only assume that the children from whom samples have been obtained are representative but also to assume that in vitro susceptibility perfectly predicts clinical efficacy.

These limitations notwithstanding, available data suggest that the use of high-dose amoxicillin (80 to 90 mg per kilogram of body weight per day, administered in two divided doses) as first-line therapy for children with acute otitis media remains a reasonable approach.[6] In children in whom *H. influenzae* is likely to predominate (i.e., those who have received antibiotics in the previous 30 days, have conjunctivitis–otitis syndrome, or have spontaneous rupture of the tympanic membrane), the use of high-dose amoxicillin–clavulanate as a first-line therapy may be justified.[1,47-49] In general, the use of oral cephalosporins, which are substantially less effective than amoxicillin at eradicating penicillin-nonsusceptible *S. pneumoniae*, should be avoided.[50]

Additional Treatment Issues

Initial therapy for the child with a type I (hypersensitivity) allergic reaction to penicillin remains challenging. Although 10% of the population is considered to have an allergy to penicillin, anaphylaxis to penicillin occurs in fewer than 1% of patients[51]; as such, the referral of children with equivocal presentations to an allergist may be warranted to confirm the presence of a penicillin allergy. Topical therapy is preferred for otorrhea in children with tympanostomy tubes.[52]

The provision of oral analgesia to children with

acute otitis media is an important aspect of disease management.[53] Antihistamines and decongestants are not effective in the treatment of acute otitis media,[54] and their use is associated with drowsiness, diarrhea, rash, dizziness, and persistence of middle-ear effusion.[55]

In children younger than 24 months of age, a 5-day course of antibiotic treatment does not appear to be effective. The percentage of children with treatment failure was approximately twice as high among those who had been randomly assigned to receive 5 days of antibiotics as among those who had been assigned to receive 10 days of treatment (34% vs. 16%).[56] The incidence of adverse events was not significantly lower in the 5-day group than in the 10-day group.[56]

Children with refractory acute otitis media who have had treatment failure with multiple courses of oral antibiotics can be treated with intramuscular ceftriaxone (50 mg per day for 3 days).[57] In addition, tympanocentesis, which involves puncturing the tympanic membrane and aspirating middle-ear fluid, may be performed to relieve pressure and permit the identification and evacuation of infecting organisms. The technique and complications of tympanocentesis can be reviewed in a Video in Clinical Medicine.[58]

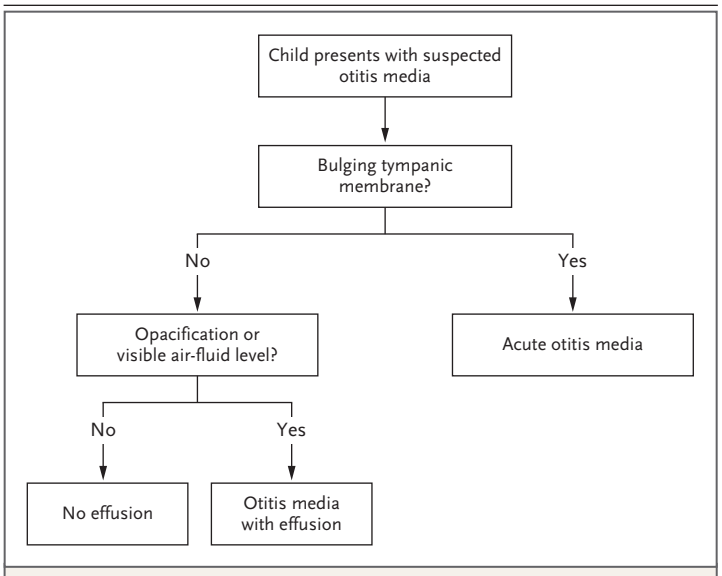

Figure 4. Algorithm for Distinguishing Acute Otitis Media from Otitis Media with Effusion.

Adapted from Shaikh et al.[29]

Recurrent Acute Otitis Media

Recurrent acute otitis media is conventionally defined as three or more episodes occurring within 6 months or as four or more episodes occurring within 12 months. Children with recurrent acute otitis media often undergo placement of a tympanostomy tube, which makes it the most frequently performed surgical procedure in this age group. The efficacy of tympanostomy-tube placement in the prevention of recurrences of acute otitis media has been evaluated in six trials. The first five trials had considerable methodologic limitations, were performed before routine pneumococcal vaccination was introduced, and included relatively small numbers of children (≤200). Those trials suggested that participants who underwent placement of a tympanostomy tube had one fewer episode of acute otitis media in the first 6 months after tube insertion than participants who received medical treatment (antibiotics for episodes of acute otitis media).[59] However, in a more recent, larger trial that involved children with recurrent acute otitis media, the incidence of acute otitis media during a 2-year follow-up period was similar among children who underwent tympanostomy-tube placement and those who received episodic antibiotic treatment.[60]

COMPLICATIONS AND SEQUELAE

Acute mastoiditis, the most common suppurative complication of acute otitis media, occurs when bacterial infection extends from the middle-ear cavity to the adjacent mastoid air cells. When antibiotics are used, mastoiditis has been reported in approximately 2 children per 10,000; when antibiotics are not used, mastoiditis has been reported in approximately 4 children per 10,000.[36] Other complications, all of which are considerably less common than acute mastoiditis,[61-63] include facial-nerve palsy and labyrinthitis. Chronic suppurative otitis media is characterized by painless chronic otorrhea with tympanic-membrane rupture. In low-resource settings, chronic suppurative otitis media may follow an episode of acute otitis media and is one of the most frequent causes of acquired hearing loss worldwide.

AREAS OF UNCERTAINTY

To my knowledge, no trials have directly compared amoxicillin with amoxicillin–clavulanate

for the treatment of acute otitis media, and no trials have compared amoxicillin with placebo for this disease since the introduction of universal pneumococcal vaccination. Most placebo-controlled trials to date have not comprehensively examined all relevant outcomes of acute otitis media; even fewer have used validated measures to assess outcomes. Trials to evaluate heterogeneity of treatment effect are lacking. Accordingly, the subgroups of children who receive no benefit from antibiotic treatment and who should therefore be observed are unclear. Although the available evidence suggests that systemic, not topical, treatment is appropriate in children who have acute otitis media with a spontaneously ruptured tympanic membrane,[64,65] more studies are needed.

GUIDELINES

The recommendations given in this article differ from current guidelines in several respects.[6,37] First, on the basis of data published after the 2013 publication of guidelines from the American Academy of Pediatrics,[40] I do not recommend different treatment options according to whether the disease is in one or both ears. Second, I have not seen compelling data to support the continued use of the definition of severe disease that is used in the guidelines (body temperature of >39°C or the presence of severe otalgia as defined by the presence of holding, tugging, or rubbing of the ear). No interaction between severity defined in this way and efficacy has been shown in placebo-controlled clinical trials to date.[32,41] Moreover, otalgia, which in preverbal children can manifest in a wide range of behaviors (e.g., irritability and disturbed sleep),[27,28] was too narrowly defined in this definition of severity.

CONCLUSIONS AND RECOMMENDATIONS

With regard to the child in the vignette, I would first determine the severity and trajectory of symptoms of acute otitis media by having a detailed discussion with the parent. The child was fussy approximately half the time when awake and slept only a few hours at night. Next, with the help of assistants who could securely hold the child's head, hands, and body, I would remove cerumen from the child's external auditory canal. If the right tympanic membrane was intact and moderately bulging, I would discuss the pros and cons of amoxicillin treatment with the parent. I would also recommend acetaminophen for the management of symptoms.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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AUTHOR INFORMATION

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REFERENCES

1. Kaur R, Morris M, Pichichero ME. Epidemiology of acute otitis media in the postpneumococcal conjugate vaccine era. Pediatrics 2017;140(3):e20170181.
2. Dagan R, Pelton S, Bakaletz L, Cohen R. Prevention of early episodes of otitis media by pneumococcal vaccines might reduce progression to complex disease. Lancet Infect Dis 2016;16:480-92.
3. Hu T, Done N, Petigara T, et al. Incidence of acute otitis media in children in the United States before and after the introduction of 7- and 13-valent pneumococcal conjugate vaccines during 1998-2018. BMC Infect Dis 2022;22:294.
4. Kawai K, Adil EA, Barrett D, Mangan-ella J, Kenna MA. Ambulatory visits for otitis media before and after the introduction of pneumococcal conjugate vaccination. J Pediatr 2018;201:122-127.e1.
5. de Sévaux JL, Venekamp RP, Lutje V, et al. Pneumococcal conjugate vaccines for preventing acute otitis media in children. Cochrane Database Syst Rev 2020;11:CD001480.
6. Lieberthal AS, Carroll AE, Chonmaitree T, et al. The diagnosis and management of acute otitis media. Pediatrics 2013;131(3):e964-99.
7. Bowatte G, Tham R, Allen KJ, et al. Breastfeeding and childhood acute otitis media: a systematic review and meta-analysis. Acta Paediatr 2015;104:85-95.
8. Kørvel-Hanquist A, Koch A, Niclasen J, et al. Risk factors of early otitis media in the Danish national birth cohort. PLoS One 2016;11(11):e0166465.
9. Paradise JL, Rockette HE, Colborn DK, et al. Otitis media in 2253 Pittsburgh-area infants: prevalence and risk factors during the first two years of life. Pediatrics 1997;99:318-33.
10. Chonmaitree T, Alvarez-Fernandez P, Jennings K, et al. Symptomatic and asymptomatic respiratory viral infections in the first year of life: association with acute otitis media development. Clin Infect Dis 2015;60:1-9.
11. Revai K, Mamidi D, Chonmaitree T. Association of nasopharyngeal bacterial colonization during upper respiratory tract infection and the development of acute otitis media. Clin Infect Dis 2008;46(4):e34-e37.
12. Mather MW, Drinnan M, Perry JD, Powell S, Wilson JA, Powell J. A systematic review and meta-analysis of antimicrobial resistance in paediatric acute otitis media. Int J Pediatr Otorhinolaryngol 2019;123:102-9.
13. Ngo CC, Massa HM, Thornton RB, Cripps AW. Predominant bacteria detected from the middle ear fluid of children experiencing otitis media: a systematic review. PLoS One 2016;11(3):e0150949.
14. Kaur R, Adlowitz DG, Casey JR, Zeng M, Pichichero ME. Simultaneous assay for four bacterial species including Alloiococcus otitidis using multiplex-PCR in children with culture negative acute otitis media. Pediatr Infect Dis J 2010;29:741-5.
15. Sillanpää S, Oikarinen S, Sipilä M, et al. Moraxella catarrhalis might be more common than expected in acute otitis media in young Finnish children. J Clin Microbiol 2016;54:2373-9.
16. Sawada S, Okutani F, Kobayashi T. Comprehensive detection of respiratory bac-

terial and viral pathogens in the middle ear fluid and nasopharynx of pediatric patients with acute otitis media. Pediatr Infect Dis J 2019;38:1199-203.
17. Patel JA, Nguyen DT, Revai K, Chonmaitree T. Role of respiratory syncytial virus in acute otitis media: implications for vaccine development. Vaccine 2007;25:1683-9.
18. Kaur R, Fuji N, Pichichero ME. Dynamic changes in otopathogens colonizing the nasopharynx and causing acute otitis media in children after 13-valent (PCV13) pneumococcal conjugate vaccination during 2015-2019. Eur J Clin Microbiol Infect Dis 2022;41:37-44.
19. Ricci Conesa H, Skröder H, Norton N, Bencina G, Tsoumani E. Clinical and economic burden of acute otitis media caused by Streptococcus pneumoniae in European children, after widespread use of PCVs — a systematic literature review of published evidence. PLoS One 2024;19(4):e0297098.
20. Eskola J, Kilpi T, Palmu A, et al. Efficacy of a pneumococcal conjugate vaccine against acute otitis media. N Engl J Med 2001;344:403-9.
21. Kilpi T, Ahman H, Jokinen J, et al. Protective efficacy of a second pneumococcal conjugate vaccine against pneumococcal acute otitis media in infants and children: randomized, controlled trial of a 7-valent pneumococcal polysaccharide-meningococcal outer membrane protein complex conjugate vaccine in 1666 children. Clin Infect Dis 2003;37:1155-64.
22. Cohen R, Biscardi S, Levy C. The multifaceted impact of pneumococcal conjugate vaccine implementation in children in France between 2001 to 2014. Hum Vaccin Immunother 2016;12:277-84.
23. Rybak A, Levy C, Bonacorsi S, et al. Antibiotic resistance of potential otopathogens isolated from nasopharyngeal flora of children with acute otitis media before, during and after pneumococcal conjugate vaccines implementation. Pediatr Infect Dis J 2018;37(3):e72-e78.
24. Martin JM, Hoberman A, Paradise JL, et al. Emergence of Streptococcus pneumoniae serogroups 15 and 35 in nasopharyngeal cultures from young children with acute otitis media. Pediatr Infect Dis J 2014; 33(11):e286-e290.
25. Angoulvant F, Cohen R, Doit C, et al. Trends in antibiotic resistance of Streptococcus pneumoniae and Haemophilus influenzae isolated from nasopharyngeal flora in children with acute otitis media in France before and after 13 valent pneumococcal conjugate vaccine introduction. BMC Infect Dis 2015;15:236.
26. Conway IO, Kurs-Lasky M, Shaikh N. Moraxella catarrhalis infrequently cultured from middle ear fluid of children with acute otitis media. Pediatr Infect Dis J 2023;42(11): e416-e417.
27. Shaikh N, Hoberman A, Paradise JL, et al. Development and preliminary evaluation of a parent-reported outcome instrument for clinical trials in acute otitis media. Pediatr Infect Dis J 2009;28:5-8.
28. Shaikh N, Kearney DH, Colborn DK, et al. How do parents of preverbal children with acute otitis media determine how much ear pain their child is having? J Pain 2010;11:1291-4.
29. Shaikh N, Hoberman A, Rockette HE, Kurs-Lasky M. Development of an algorithm for the diagnosis of otitis media. Acad Pediatr 2012;12:214-8.
30. Karma PH, Penttilä MA, Sipilä MM, Kataja MJ. Otoscopic diagnosis of middle ear effusion in acute and non-acute otitis media. I. The value of different otoscopic findings. Int J Pediatr Otorhinolaryngol 1989;17:37-49.
31. Shaikh N, Stone MK, Kurs-Lasky M, Hoberman A. Interpretation of tympanic membrane findings varies according to level of experience. Paediatr Child Health 2016;21:196-8.
32. Hoberman A, Paradise JL, Rockette HE, et al. Treatment of acute otitis media in children under 2 years of age. N Engl J Med 2011;364:105-15.
33. Venekamp RP, Sanders SL, Glasziou PP, Rovers MM. Antibiotics for acute otitis media in children. Cochrane Database Syst Rev 2023;11:CD000219.
34. Shaikh N, Hoberman A, Kaleida PH, Ploof DL, Paradise JL. Diagnosing otitis media — otoscopy and cerumen removal. N Engl J Med 2010;362(20):e62.
35. Tähtinen PA, Laine MK, Huovinen P, Jalava J, Ruuskanen O, Ruohola A. A placebo-controlled trial of antimicrobial treatment for acute otitis media. N Engl J Med 2011; 364:116-26.
36. Thompson PL, Gilbert RE, Long PF, Saxena S, Sharland M, Wong IC. Effect of antibiotics for otitis media on mastoiditis in children: a retrospective cohort study using the United Kingdom general practice research database. Pediatrics 2009;123:424-30.
37. Suzuki HG, Dewez JE, Nijman RG, Yeung S. Clinical practice guidelines for acute otitis media in children: a systematic review and appraisal of European national guidelines. BMJ Open 2020;10(5):e035343.
38. Ovnat Tamir S, Shemesh S, Oron Y, Marom T. Acute otitis media guidelines in selected developed and developing countries: uniformity and diversity. Arch Dis Child 2017;102:450-7.
39. Shaikh N, Lee MC, Kurs-Lasky M. Modification of an outcome measure to follow symptoms of children with acute otitis media. Pediatr Res 2024 July 3 (Epub ahead of print).
40. Hoberman A, Ruohola A, Shaikh N, Tähtinen PA, Paradise JL. Acute otitis media in children younger than 2 years. JAMA Pediatr 2013;167:1171-2.
41. Kaleida PH, Casselbrant ML, Rockette HE, et al. Amoxicillin or myringotomy or both for acute otitis media: results of a randomized clinical trial. Pediatrics 1991;87: 466-74.
42. Hum SW, Shaikh KJ, Musa SS, Shaikh N. Adverse events of antibiotics used to treat acute otitis media in children: a systematic meta-analysis. J Pediatr 2019;215: 139-143.e7.
43. Duong QA, Pittet LF, Curtis N, Zimmermann P. Antibiotic exposure and adverse long-term health outcomes in children: a systematic review and meta-analysis. J Infect 2022;85:213-300.
44. Gerber JS, Ross RK, Bryan M, et al. Association of broad- vs narrow-spectrum antibiotics with treatment failure, adverse events, and quality of life in children with acute respiratory tract infections. JAMA 2017;318:2325-36.
45. Shaikh N, Dando EE, Dunleavy ML, et al. A cost-utility analysis of 5 strategies for the management of acute otitis media in children. J Pediatr 2017;189:54-60.e3.
46. Frost HM, Bizune D, Gerber JS, Hersh AL, Hicks LA, Tsay SV. Amoxicillin versus other antibiotic agents for the treatment of acute otitis media in children. J Pediatr 2022; 251:98-104.e5.
47. Kaur R, Casey JR, Pichichero ME. Relationship with original pathogen in recurrence of acute otitis media after completion of amoxicillin/clavulanate: bacterial relapse or new pathogen. Pediatr Infect Dis J 2013; 32:1159-62.
48. Levy C, Varon E, Ouldali N, et al. Bacterial causes of otitis media with spontaneous perforation of the tympanic membrane in the era of 13 valent pneumococcal conjugate vaccine. PLoS One 2019;14(2): e0211712.
49. Marchisio P, Esposito S, Picca M, et al. Prospective evaluation of the aetiology of acute otitis media with spontaneous tympanic membrane perforation. Clin Microbiol Infect 2017;23(7):486.e1-486.e6.
50. Arguedas A, Dagan R, Leibovitz E, Hoberman A, Pichichero M, Paris M. A multicenter, open label, double tympanocentesis study of high dose cefdinir in children with acute otitis media at high risk of persistent or recurrent infection. Pediatr Infect Dis J 2006;25:211-8.
51. Shaker M, McWilliams S, Greenhawt M. Update on penicillin allergy delabeling. Curr Opin Pediatr 2020;32:321-7.
52. Chee J, Pang KW, Yong JM, Ho RC-M, Ngo R. Topical versus oral antibiotics, with or without corticosteroids, in the treatment of tympanostomy tube otorrhea. Int J Pediatr Otorhinolaryngol 2016;86:183-8.
53. Bertin L, Pons G, d'Athis P, et al. A randomized, double-blind, multicentre controlled trial of ibuprofen versus acetaminophen and placebo for symptoms of acute otitis media in children. Fundam Clin Pharmacol 1996;10:387-92.
54. Coleman C, Moore M. Decongestants and antihistamines for acute otitis media in children. Cochrane Database Syst Rev 2008; 3:CD001727.
55. Chonmaitree T, Saeed K, Uchida T, et al. A randomized, placebo-controlled trial of the effect of antihistamine or corticosteroid treatment in acute otitis media. J Pediatr 2003;143:377-85.
56. Hoberman A, Paradise JL, Rockette HE,

et al. Shortened antimicrobial treatment for acute otitis media in young children. N Engl J Med 2016;375:2446-56.
57. Leibovitz E, Piglansky L, Raiz S, et al. Bacteriologic efficacy of a three-day intramuscular ceftriaxone regimen in nonresponsive acute otitis media. Pediatr Infect Dis J 1998;17:1126-31.
58. Shaikh N, Hoberman A, Kearney DH, Yellon R. Tympanocentesis in children with acute otitis media. N Engl J Med 2011;364(2):e4.
59. Venekamp RP, Mick P, Schilder AG, Nunez DA. Grommets (ventilation tubes) for recurrent acute otitis media in children. Cochrane Database Syst Rev 2018;5:CD012017.
60. Hoberman A, Preciado D, Paradise JL, et al. Tympanostomy tubes or medical management for recurrent acute otitis media. N Engl J Med 2021;384:1789-99.
61. Mattos JL, Colman KL, Casselbrant ML, Chi DH. Intratemporal and intracranial complications of acute otitis media in a pediatric population. Int J Pediatr Otorhinolaryngol 2014;78:2161-4.
62. Pellegrini S, Gonzalez Macchi ME, Sommerfleck PA, Bernáldez PC. Intratemporal complications from acute otitis media in children: 17 cases in two years. Acta Otorrinolaringol Esp 2012;63:21-5.
63. Ren Y, Sethi RKV, Stankovic KM. Acute otitis media and associated complications in United States emergency departments. Otol Neurotol 2019;40:847.
64. Rovers MM, Glasziou P, Appelman CL, et al. Predictors of pain and/or fever at 3 to 7 days for children with acute otitis media not treated initially with antibiotics: a meta-analysis of individual patient data. Pediatrics 2007;119:579-85.
65. Hullegie S, Damoiseaux RAMJ, Hay AD, et al. Topical or oral antibiotics in childhood acute otitis media and ear discharge: a randomized controlled non-inferiority trial. Fam Pract 2024;41:857-61.

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