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APPLYING NEW GUIDELINES ON ACUTE OTITIS MEDIA: FROM PRINCIPLES TO PRACTICE

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Applying New Guidelines on Acute Otitis Media: From Principles to Practice

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Persistent overdiagnosis and overtreatment of acute otitis media and the resulting effects on antimicrobial resistance recently led the American Academy of Pediatrics and the American Academy of Family Physicians to issue clinical practice guidelines on the diagnosis and management of acute otitis media.

To explore the implications of these new guidelines for practicing pediatricians and family practitioners, the *Cleveland Clinic Journal of Medicine* recently convened a case-based roundtable discussion on the guidelines among a panel of pediatricians and infectious disease specialists. The roundtable began with an overview of the new guidelines by Dr. S. Michael Marcy, who served as a consultant to the American Academy of Pediatrics during the guidelines' development; his overview is reflected here in a short review article that sets the stage for the roundtable discussion that follows. The tables within the roundtable transcript were developed by consensus of the panel.

Contents

Disclosures

The following authors reported that they may have a relationship that, in the context of their contributions to this supplement, could be perceived as a potential conflict of interest:

Jennifer K. Long, PharmD, reported that she is on the speakers' bureaus of the Bayer and Pfizer corporations.

S. Michael Marcy, MD, reported that he serves as a consultant to the Abbott and GlaxoSmithKline corporations. He also reported that he discusses off-label uses of therapies.

Scott Francy, MD, Johanna Goldfarb, MD, and Camille Sabella, MD, reported no relationships that could be perceived as a conflict of interest.

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REVIEW

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New guidelines on acute otitis media: An overview of their key principles for practice

The proper management of acute otitis media (AOM) has received much attention in recent years.[1] Studies have shown this condition to be overdiagnosed and, hence, overtreated as much 50% of the time by clinicians caring for children.[2] The resulting unnecessary use of antimicrobials and the consequent increased prevalence of antibiotic resistance was felt by the American Academy of Pediatrics (AAP) and the American Academy of Family Physicians (AAFP) to warrant development of clear guidelines defining the current status of expert opinion on the appropriate diagnosis and optimal management of AOM. This article summarizes these new AAP/AAFP guidelines,[3] focusing on five key principles they set forth, with the aim of laying the groundwork for the roundtable discussion that follows.

HOW THE GUIDELINES TOOK SHAPE, AND THE QUESTIONS THEY TOOK ON

The AAP and AAFP developed the guidelines primarily by using data generated under a grant from the federal Agency for Healthcare Research and Quality (AHRQ) through the Southern California Evidence-Based Practice Center and the RAND Corporation.

At the request of these groups, experts in AOM were asked to identify the principal contemporary questions in the diagnosis and treatment of AOM. More than 40 such questions were identified and prioritized. The following seven were considered the most important:

- What is the natural history of AOM?
- What is the outcome of AOM treated with antimicrobials vs no antimicrobial therapy?
- What is the efficacy of amoxicillin compared with that of other antimicrobials?
- What is the efficacy of high-dose (80 to 90 mg/kg/day) vs standard-dose (40 mg/kg/day) amoxicillin therapy?
- What is the efficacy of twice-daily vs thrice-daily therapy?
- What is the efficacy of short-term (3-, 5-, or 7-day) vs long-term (10-day) therapy?
- What are the complications of AOM in untreated children?

To answer these questions, MEDLINE and six other databases were searched for relevant studies published between 1966 and March 1999. Approximately 3,500 citations were reviewed, of which 760 considered the identified research questions; 74 of these were randomized controlled trials that were felt to be adequate to provide a database for resolution of the key questions.

The results of this search were published as an AHRQ monograph,[4] which provided a basis for development of the AAP/AAFP guidelines. Because the AAP/AAFP guidelines were developed after completion of the literature review and publication of the monograph, they also include the results of studies published through September 2003.

AOM cannot be diagnosed without middle ear effusion—a red tympanic membrane is not enough

DEFINITION AND DIAGNOSIS OF AOM

The first portion of the guidelines deals with the definition of AOM. AOM is defined as the recent, abrupt onset (≤ 48 hours) of middle ear effusion accompanied by signs or symptoms of inflammation of the middle ear. Each of the three criteria of this definition—(1) recent, abrupt onset; (2) presence of middle ear effusion; and (3) presence of middle ear inflammation—is necessary to establish the diagnosis. It is often disregarded that middle ear effusion is a sine qua non: without it there can be no diagnosis of AOM. A red tympanic membrane is not enough.

The guidelines are limited to consideration of uncomplicated AOM—that is, AOM limited to the middle ear cleft—in otherwise healthy children from 2 months to 12 years of age. While it is recognized that the guidelines may also apply to older children and adolescents, the published studies reviewed for development of the guidelines are almost all limited to this age group.

Principle 1:

To reliably diagnose AOM, the clinician should confirm a history of abrupt onset (≤ 48 hours) of middle ear effusion and inflammation

This principle is based on the perceived need to improve the diagnosis of AOM. The diagnosis can be suspected clinically when the signs and symptoms of an upper respiratory tract infection, which frequently precedes AOM by 3 to 5 days, are accompanied by ear pain, irritability, or pulling at the ear. It is important to note, however, that pulling at the ear is an unreliable sign, as no more than 10% of children who pull at the ear actually have AOM. Fever is generally less than 40°C, and one third of children with AOM who present in the physician's office have no fever at all. Purulent drainage is, of course, diagnostic.

Up to 50% of cases of otitis media with effusion are misdiagnosed as AOM

Technical diagnostic aids

In addition to clinical signs and symptoms, certain technical aids can assist in the diagnosis of AOM: tympanocentesis, tympanography, reflectometry, and pneumatic otoscopy.

Tympanocentesis is indicated when rapid bacteriologic diagnosis and antimicrobial susceptibility are necessary. This includes the treatment of children with underlying immune deficits, such as those receiving chemotherapy; children with mastoiditis, meningitis, or other intracranial complications; and children in whom two or three sequential courses of appropriate antimicrobial therapy have failed.

Tympanography is quite valuable in defining the presence of middle ear effusion, which is an absolute prerequisite for the diagnosis of AOM. However, tympanography can be difficult to perform, particularly in a young febrile or otherwise uncooperative child. Obtaining a seal is often quite difficult, if not impossible, especially in children younger than 6 months of age.

Acoustic reflectometry has been advocated as a simpler way of establishing the presence of middle ear fluid. In contrast to tympanography, it does not require a seal and can also be performed through even a small opening in the cerumen in the external auditory canal. Acoustic reflectometry is a very useful diagnostic method and should become increasingly available over the next few years as it is improved and distributed more widely.

Pneumatic otoscopy is the most practical diagnostic modality for AOM. The pneumatic otoscope should be checked to assure that the bulb is current and the light is bright and white in color. If a yellow or orange bulb is used, the tympanic membrane will appear inflamed. The otoscope should be checked regularly to assure that there is appropriate pressure to move the tympanic membrane when it is pumped, that a tight seal can be applied, and that appropriate speculi are used to obtain a good seal in the external auditory canal.

An emphasis on diagnostic accuracy

One of the guidelines' main goals is to improve the accuracy with which clinicians evaluate the presence or absence of AOM. Pichichero and Poole[2] have shown clearly that a large proportion of children diagnosed with AOM instead have otitis media with effusion. As many as 50% of such cases are misdiagnosed or overdiagnosed as AOM.

Studies done in 1993 by Karma (reviewed in 1998 by Pelton[5]) examined tympanic membranes and used tympanocentesis to establish the presence or absence of infection. These studies identified certain findings that were highly correlated with AOM:

- A bulging tympanic membrane had a positive predictive value of 83% to 99%
- Distinctly impaired mobility in the presence of tympanic membrane fullness or bulging had a positive predictive value of 85% to 99%
- Redness of the tympanic membrane alone, without other findings, had a predictive value as low as 7%.

This demonstrates that the old paradigm,

"*Chief complaint: earache; physical examination: red tympanic membrane; Rx: amoxicillin,*" is simply no longer adequate or acceptable. These guidelines now make it imperative that the position of the tympanic membrane and its mobility both be described when clinicians attempt to make a diagnosis of AOM.

HOW TO ADDRESS PAIN

Principle 2:

The management of AOM should include assessment of pain. If pain is present, the clinician should provide treatment to reduce it.

A number of options for pain management are available in addition to acetaminophen, ibuprofen, and naproxen, including codeine, benzocaine drops, and myringotomy. Codeine may be used in certain cases, such as in older children, children who are not lethargic, children who are free of productive cough or wheeze, and children with reliable parents. The codeine may be given together with acetaminophen to provide further analgesic effect. Benzocaine drops have very marginal efficacy.[6] Myringotomy can be used for the child who is in extreme pain, as it provides almost immediate relief.

The utility of homeopathic medicines, osteopathic or chiropractic manipulation, and topical naturopathic agents requires confirmation. Use of home remedies such as putting warm oil in the ear canal (if otorrhea is absent), applying heat over the ear, and distraction have stood the test of time and offer little or no risk.

TO OBSERVE OR NOT TO OBSERVE?

Principle 3a:

Observation without antibiotics is an appropriate option for selected children with uncomplicated AOM based on diagnostic certainty, age, severity of illness, and certainty of follow-up

Observation without antibiotic therapy is an option clinicians may consider under certain circumstances, as outlined in Table 1. This principle is based on data generated over the last decades documenting the clinical resolution of otitis media among children given placebo or no therapy and on studies comparing response between children receiving placebo or no therapy and children receiving antimicrobials.[7,8] Questions have been raised about the validity of these data, since it was recognized that many of the children diagnosed with AOM may well have had otitis media with effusion, as previously noted. Also, many of the children studied belonged to relatively older age groups—older than 2 years in some cases, and older than 1 year in many cases—calling into question the validity of using observation alone in younger children. The median age of children with AOM is approximately 12 months, and since there is a large number of children with AOM around that age, the studies that involved those children should be considered the most appropriate for reference.

TABLE 1

Observation vs antibiotic therapy: When to use each in children with acute otitis media (AOM)

AGE OF CHILD	IF DIAGNOSIS OF AOM IS CERTAIN	IF DIAGNOSIS IS UNCERTAIN
< 6 mo	Antibiotic	Antibiotic
6 mo–2 yr	Antibiotic	Antibiotic if severe illness; observe if nonsevere illness
≥ 2 yr	Antibiotic if severe illness; observe if nonsevere illness	Observe

Observation without antibiotics may be considered under certain circumstances

Most patients will respond to symptomatic therapy

Looking at overall response rates, approximately two thirds of children with AOM will respond to symptomatic treatment alone at 24 hours, approximately 85% will respond at 2 to 3 days, and approximately 90% will respond at 4 to 7 days.[7] Treatment, when compared with symptomatic therapy, is more favorable in only 4% of children overall at 2 to 3 days; however, children under 2 years of age appear to be at a selective disadvantage, since observation alone fails in almost 25% of children in this age group with severe illness (see below).[9] As expected, there is no statistically significant difference between antimi-

TABLE 2

Microbiology of acute otitis media

ORGANISM	CASES IN WHICH THE ORGANISM IS CAUSATIVE
Haemophilus influenzae	35%–50%
Streptococcus pneumoniae	25%–40%
Moraxella catarrhalis	5%–10%
Viruses	5%–15%
No growth of bacterial agents	1%–15%

TABLE 3

Suggested antimicrobial therapy for acute otitis media

- **Amoxicillin** 80 to 90 mg/kg/day in two divided doses for 5 to 10 days, depending on patient age
- For patients with non–type I or uncertain allergy to beta-lactams: **cefdinir, cefuroxime, or cefpodoxime**
- For patients with anaphylaxis or severe allergy to beta-lactams: **azithromycin,clarithromycin, trimethoprim ± sulfamethoxazole, erythromycin-sulfisoxazole**
- For patients with vomiting or uncertain compliance, **ceftriaxone** 50 mg/kg IM

crobial treatment and symptomatic therapy at 24 hours, given that 24 hours is required for antimicrobials to have an effect on the bacteria and for there to be a diminution in the inflammatory response, which is responsible for both the middle ear effusion and the discomfort that accompany AOM.

Observation alone fails in nearly 25% of children under 2 years of age with severe AOM

The observation option has certain limitations and certain provisions (Table 1). Patient age, certainty of the diagnosis, and severity of illness should determine the course of therapy. "Severe" illness is defined as illness in which the child's temperature is 39°C or higher *or* there is moderate or severe otalgia. Children with mild ear pain *and* a temperature less than 39°C are considered to have "nonsevere" illness.

The microbiology of AOM translates to broad therapy choices

The antimicrobial therapy of AOM depends, of course, on the microbiology of the infection (Table 2). In recent years, there has been an appreciation of the rising incidence of nontypable *Haemophilus influenzae* as an etiology of AOM. At present, 35% to 50% of cases of AOM are caused by nontypable *H influenzae*, 25% to 40% by *Streptococcus pneumoniae*, and 5% to 10% by *Moraxella catarrhalis*.[3] A negligible number of cases are due to other bacteria. Viruses have been identified as the sole cause of infection in 5% to 15% of cases.[10] No growth of bacterial agents has been found in 1% to 15% of cases;[3] this finding may be attributable to AOM caused by viral infection in early reports. Given this microbiology, a wide variety of antimicrobials are available for the treatment of AOM.

NAVIGATING ANTIBIOTIC CHOICES

Principle 3b:
If the decision is made to treat with an antibiotic, amoxicillin remains the initial antibiotic of choice for most children

This recommendation is based on the recognition that amoxicillin is not only effective but also has a low incidence of side effects, is cost-effective, and, by virtue of its taste, helps to assure good compliance.

The suggested antimicrobial therapy for AOM is outlined in Table 3. High-dose amoxicillin (80 to 90 mg/kg/day) is to be given in two divided doses for 5 to 10 days, depending on patient age. Children who have uncertain allergy to beta-lactams or nonanaphylactic allergy are advised to take an oral cephalosporin, such as cefdinir, cefuroxime, or cefpodoxime. Although these three oral cephalosporins have equal microbiologic efficacy, there are no clinical studies comparing their efficacy. However, there is every reason to believe that they are equally effective clinically. Cefdinir is more palatable, as demonstrated in a palatability study in adults,[11] and thus is more likely to result in good compliance.

Children with a history of anaphylaxis or severe allergy to beta-lactams warrant treatment with one of the following: azithromycin, clarithromycin, trimethoprim-sulfamethoxazole, or erythromycin-sulfisoxazole.

Concerns about resistance guide amoxicillin dosing

The rationale for use of high-dose amoxicillin (80 to 90 mg/kg/day) is to provide drug levels in the middle ear fluid adequate to eradicate strains of *S pneumoniae* that are fully susceptible to penicillin as well as strains that are nonsusceptible, which represent approximately 25% of all pneumococci isolated from middle ear fluid nationally. The susceptibility pattern is geographically dependent, with some centers reporting nonsusceptibility in 60% of strains while others report it in as few as 15%. Moreover, one third to one half of nonsusceptible strains are highly resistant to penicillin.

Higher drug levels in the middle ear fluid will eradicate not only the susceptible organisms but also those of intermediate resistance, which are defined as pneumococci for which the minimum inhibitory concentration (MIC) of penicillin is between 0.12 and 1 µg/mL. Resistant organisms, for which the MIC is greater than 2 µg/mL, would also largely be eradicated by the higher doses, and there are few resistant organisms for which the MIC of penicillin is greater than 8 µg/mL.

Giving amoxicillin in two, rather than three, divided doses will assure yet higher middle ear fluid levels of the drug. The duration of therapy depends on patient age, and the guidelines reflect the fact that few data exist on short-course therapy in younger children. Thus, it is recommended that short-course amoxicillin therapy be limited to children 6 years of age or older, for whom 5 to 7 days may suffice.

Another option for selected children

For children who are vomiting or for whom compliance cannot be assured, ceftriaxone 50 mg/kg given as a single intramuscular dose can be considered appropriate therapy. In such cases, no additional oral therapy is required and, if conjunctivitis is present, no additional ocular therapy is required.

TABLE 4

Antimicrobial therapy for children who do not respond to initial management at 48 to 72 hours

- Amoxicillin-clavulanate 90 mg/kg/day in two divided doses (to 4 g),* or
- Cefdinir, cefuroxime, or cefpodoxime, or
- Ceftriaxone 50 mg/kg intramuscularly or intravenously, three daily doses

*Can be primary therapy for children with moderate to severe otalgia or fever ≥ 39 °C.

WHAT TO DO WHEN INITIAL MANAGEMENT FAILS

Principle 4:
Lack of response within 48 to 72 hours requires reassessment to confirm AOM. If confirmed in a child initially managed with observation, an antibiotic should be prescribed. If initial management was with an antibiotic, an alternative antibiotic should be prescribed.

Reassessment may be accomplished either by reevaluation in the office or, when the reliability of the observer is known to the physician and felt to be adequate, by telephone discussion. These telephone discussions should be well documented in the patient's chart.

Table 4 provides recommendations for appropriate therapy after failure of first-line therapy. Amoxicillin-clavulanate 90 mg/kg/day should be given in two divided doses up to 4 g. Because the clavulanate moiety causes the gastrointestinal adverse effects associated with this agent, if this higher dose of amoxicillin-clavulanate is used, it is recommended that the new 14-to-1 formulation, rather than the 7-to-1 formulation, be prescribed. This can also be accomplished by diluting amoxicillin-clavulanate with equal parts of amoxicillin. Alternative therapy includes the oral cephalosporins cefdinir, cefuroxime, or cefpodoxime, or ceftriaxone 50 mg/kg/day given intramuscularly or intravenously for three daily doses.

Nonresponders to second-line therapy should be considered for tympanocentesis

Further failure calls for tympanocentesis or cautious use of clindamycin

Children who do not respond to second-line therapy should be considered for tympan-

TABLE 5

Strategies for preventing acute otitis media through risk-factor reduction

- Breast-feed rather than bottle-feed
- Eliminate supine bottle-feeding
- Eliminate exposure of the child to tobacco smoke
- Eliminate pacifier use
- Modify group day care activities
- Provide the child with influenza and pneumococcal conjugate vaccinations
- Have the child investigated for atopy and immunodeficiency

ocentesis, particularly if they have persistent symptoms that are concerning to the clinician, persistently high fever, or persistent severe pain. Therapy can then be adjusted on the basis of Gram stain results and subsequently fine-tuned on the basis of culture and susceptibility studies, which will, however, not become available for 48 to 72 hours.

Overuse of clindamycin clearly will reduce its future utility

If tympanocentesis is not available (or while the results of susceptibility studies are awaited), use of clindamycin should be considered. High-dose amoxicillin-clavulanate, as second-line therapy, will have eradicated not only the beta-lactamase–positive *H influenzae* and *M catarrhalis* but also *S pneumoniae* that may have escaped treatment during the first regimen using high-dose amoxicillin alone. Of the remaining organisms, the most likely would be highly resistant *S pneumoniae*, of which approximately 93% to 95% of organisms remain susceptible to clindamycin. Overuse of clindamycin clearly will reduce its utility in the future, so clinicians are cautioned to restrict its use only to children who do not respond to second-line therapy.

ADVICE FOR REDUCING THE RISK OF AOM

Principle 5:
Clinicians should encourage AOM prevention through reduction of risk factors

This includes encouraging breast-feeding over bottle-feeding, particularly among mothers who have had other children with recurrent AOM or who themselves had a history of recurrent AOM (this also applies if the child's father had a history of recurrent AOM).

Elimination of supine bottle-feeding, elimination of exposure to tobacco smoke in the household, and elimination of pacifier use may also reduce the incidence of AOM.

For children who attend day care centers, particularly large centers, it may be ideal for the parents to seek smaller groups or eliminate day care entirely if their work schedules or economic conditions permit.

Influenza vaccination, either with the parenteral formulation[12] or with the new cold-adapted intranasal vaccine,[13] has been shown to reduce the overall incidence of AOM in children by approximately 30% during the influenza season. A more recent study, however, could find no efficacy of killed vaccine in preventing AOM during influenza season in children 6 to 23 months of age.[14] The recent recommendation by the Advisory Committee on Immunization Practice to immunize all children over 6 months of age with influenza vaccine eliminates the specific intent of using the vaccine for prevention of AOM.

Immunization with pneumococcal conjugate vaccine has been shown to reduce the incidence of AOM by varying degrees. Although the incidence of AOM caused by those serotypes present in the vaccine is significantly decreased, the overall effect of the vaccine on the incidence of AOM is quite limited. A large HMO study found a 6% reduction in the incidence of AOM,[15] a 7.8% reduction in the frequency of office visits due to AOM, and a 6% reduction in antibiotic prescriptions.[16] A subsequent Finnish study, while also noting a mean 6% reduction in AOM incidence, reported confidence intervals around the mean of less than 1.0, indicating the possibility of no efficacy at all.[17] Although the reduction in the overall incidence of single episodes of AOM is marginal, it is clear that the use of pneumococcal conjugate vaccine will reduce both the incidence of recurrent AOM (ie, five cases or more) and the incidence of the need for tympanostomy tubes by 20% to 25% annually.[15,16]

Children who have recurrent AOM should be investigated for allergy and immunodeficiency. However, children with immunodeficiency will rarely present with

recurrent AOM alone; they usually have an increased frequency and severity of other upper or lower respiratory tract infections and other infections.

Strategies for reducing risk factors for AOM are summarized in Table 5.

A ROLE FOR ALTERNATIVE MEDICINE?

No recommendations can be made at this time regarding complementary or alternative medicine for AOM, given the limited and controversial data currently available.

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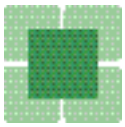
Pneumococcal conjugate vaccine reduces rates of recurrent AOM and the need for typanostomy tubes



From principles to practice: Case-based applications of the acute otitis media guidelines

CASE 1

A 4-year-old boy presents with a 24-hour history of fever and right-sided ear pain following 2 to 3 days of rhinorrhea and congestion. The boy is not toxic-appearing, and physical examination is normal except for bulging and impaired mobility of his right tympanic membrane.

Diagnosis starts with careful distinctions

Dr. Camille Sabella—Dr. Francy, one of the goals of the new guidelines for the management of acute otitis media (AOM)[1] is to help the clinician achieve better diagnostic accuracy. What are the diagnostic findings that help distinguish AOM from otitis media with effusion?

Dr. Scott Francy—Definitive diagnosis requires careful examination of the tympanic membrane and the use of a pneumatic otoscope. Pneumatic otoscopy allows us to examine the mobility of the tympanic membrane, which improves diagnostic sensitivity. The otoscope should have sufficient bulb brightness as well as the correct speculum size so that an airtight seal can be achieved. Cerumen that obstructs visualization of the tympanic membrane must be removed.

It is important to differentiate clinically between AOM and otitis media with effusion because the management of these two entities is different. However, one study has shown that general pediatricians in the United States can accurately differentiate between these two entities only 50% of the time.[2]

The diagnosis of otitis media with effusion is made accurately when bubbles or an air–fluid interface are seen and there is decreased or absent mobility of the tympanic membrane. Also, the tympanic membrane often takes on an abnormal color, such as white, yellow, or amber.

The diagnosis of AOM is made clinically by detection of the presence of middle ear effusion together with the acute onset of middle ear inflammation. This typically is done by use of pneumatic otoscopy, although tympanography, acoustic reflectometry, or tympanocentesis may also be used. The diagnosis of AOM cannot be made without the presence of middle ear effusion. Signs of middle ear inflammation include purulent drainage or a bulging or full tympanic membrane with hemorrhagic, white, or yellow discoloration of the membrane. It is important to remember that redness of the tympanic membrane is a nonspecific finding and may be caused by crying alone, without infection. Thus, the child who has erythema without fullness or bulging of the tympanic membrane should not be diagnosed with AOM.

Older children, such as the boy in this case, often will complain of pain and, less often, of hearing loss. In this setting, with a history of rapid onset of fever and especially after an upper respiratory tract infection, AOM should be suspected. Ear-pulling, irritability, fever, and, in older children, hearing loss are nonspecific symptoms and do not correlate well with infection.

In cases in which pneumatic otoscopy is difficult, tympanography or acoustic reflectometry may be available in the physi-

cian's office and can be helpful in identifying middle ear effusion.

Dr. Sabella—How would the new guidelines help you in managing this patient with AOM?

Dr. Francy— First of all, the child should be assessed for the degree of pain that he is having and treated with analgesics accordingly. I have not found analgesic drops helpful, given their short duration of action. Over-the-counter analgesics such as acetaminophen and ibuprofen are effective. I have not had to resort to the use of codeine for pain control.

In terms of antimicrobial therapy for this child, the new guidelines offer the option of observation without antibiotics for a child 2 years of age or older who has nonsevere illness. However, since this child has a fever and has significant otalgia, I would treat with antibiotics if I were certain of the diagnosis.

Observation alone: How realistic is it?

Dr. Johanna Goldfarb— Would you ever not treat this child?

Dr. Francy— If the child had these findings on physical examination but was afebrile (< 38 °C), was in minimal or no discomfort, and had no previous history of otitis media, I think 2 to 3 days of observation would be an option, after educating the parents about why I was choosing to not treat.

Dr. Goldfarb— The practical question is whether a practicing pediatrician in the United States in 2004 can follow this guideline and not treat this patient. In Europe, physicians have a long tradition of not treating older children with otitis media. However, it seems to me that if the diagnosis of AOM were clear-cut, it would be difficult to not treat the child with antibiotics. Also, there are many practical problems with the observation option, from the child being able to return to school to the parents being able to go back to work, as well as the follow-up needed in 2 to 3 days.

Dr. Michael Marcy— The observation option for selected children with AOM is based on data showing spontaneous resolution 70% to 90% of the time.[3] Because much of the data is from studies limited to children 2 years of age or older, in some cases based upon uncertain diagnostic methods, and because children younger than 2 years of age, particularly those with severe disease, do not appear to do well without antibiotic therapy, the observation option is applicable only for those children 2 years of age or older who have nonsevere illness, or in whom the diagnosis is not clear-cut.

In terms of follow-up, the guidelines state that the observation option is valid only for those children in whom follow-up is assured. It must also be emphasized that the decision whether to observe a child with AOM should take into consideration the fact that antimicrobial therapy results in adverse events in 5% to 15% of children.[4] This results in discomfort, increased phone calls, and another office visit. All of these factors, as well as findings that there does not appear to be an increased incidence of mastoiditis in children with AOM who undergo observation alone, have led to the guidelines' inclusion of the observation option.

Dr. Sabella—What would you say to the parents of a child for whom you had made the diagnosis of AOM but chosen not to treat?

Dr. Francy— I think you talk to the parents and you educate them about the reasons not to treat: the fact that most cases of AOM resolve spontaneously and that anytime we treat with any medicine, antibiotics included, there can be adverse effects. Certainly otitis media with effusion does not require antibiotic therapy, and I mention that even when I have a case of AOM. I then talk about the fact that overuse of antibiotics can lead to antibiotic resistance, and I explain what that means in lay terms and how it eventually can lead to decreased drug effectiveness and a larger problem for all of us. This is probably the most important point of all, and most parents will understand it.

Dr. Marcy— To explain otitis media with effusion, I tell parents that the ear hurts

The practical question is whether a US pediatrician in 2004 can follow this guideline and not treat this patient.
—Dr. Johanna Goldfarb

because the eustachian tube is blocked, like what happens in the mountains or up in an airplane. But I explain that what I see does not give me evidence of infection in the middle ear, and I add that although in some cases these effusions will become infected, the overwhelming majority resolve by themselves, and that using antibiotics will neither prevent nor alter the course of a subsequent infection.

Dr. Goldfarb—And it may select more resistant bacteria in that child and in the community.

Factors to weigh in initial antibiotic choice

Dr. Sabella—What would be your choice of antimicrobial agent for the child in this case once you had made a decision to treat?

Dr. Francy—My first-line choice would be amoxicillin.

The observation option is valid only for those children in whom follow-up is assured.

—Dr. Michael Marcy

Dr. Marcy—Yes, according to the guidelines, amoxicillin continues to be first-line therapy. However, if the child is severely ill, another option is to start with amoxicillin-clavulanate. In other words, if the child has a high fever and severe pain on presentation, you want to assure coverage of *Haemophilus influenzae* and *Moraxella catarrhalis*, which have 30% to 50% resistance and virtually 100% resistance, respectively, to amoxicillin.[3]

Dr. Goldfarb—So amoxicillin-clavulanate is an option in such circumstances regardless of patient age?

Dr. Marcy—Yes.

Dr. Francy—I think this is a clinical decision. A child with a fever to 39.2 °C who is running around the room and relatively playful is different from a child with a high fever who is ill.

Dr. Goldfarb—When would you use amoxicillin-clavulanate in the older child with AOM?

Dr. Francy—I would use it very rarely as my initial agent. The factors to consider include recent antibiotic use, whether there is a history of recurrent otitis media, and overall previous medical history. If this child doesn't have recurrent otitis media and doesn't have a toxic appearance, and if I can assure phone follow-up or a return trip to my office, then I would choose amoxicillin.

Dr. Sabella—It is important to point out that, given the natural history of AOM, an infection with *H influenzae* or *M catarrhalis* is more likely to resolve spontaneously than an infection caused by *Streptococcus pneumoniae*. Because of this, I believe that the use of amoxicillin-clavulanate as first-line therapy for AOM should be discouraged.

Duration of illness: Important but often elusive

Dr. Sabella—One more question about this case: Would your management of this child be different if he presented with a 48-hour history of fever rather than a 24-hour history?

Dr. Marcy—Yes, the guidelines indicate that the observation option is valid for 48 to 72 hours. If a child presents after already having 48 hours of discomfort and pain, and if we find by examination that this is truly AOM, then in fact that child already has undergone an observation period, and I would treat the child immediately. It is interesting to speculate that as clinicians utilize observation of AOM with increasing frequency, parents may also begin to incorporate a 48-hour delay in seeking care for their child with mild to moderate illness.

Dr. Francy—From a practical standpoint, it is not always possible to know the exact duration of the illness because of differing parental reports. Also, a frequent scenario is the child who is seen late in the afternoon after a 36-hour history of illness. The point to stress here is that these are guidelines and not every clinical situation will be clear-cut.

CASE 2

A 9-month-old girl presents with a 24-hour history of fever and irritability. On physical examination, she is febrile to 38.9 °C as measured rec-

tally. She is irritable but consolable and is not toxic-appearing in her mother's arms. Physical examination is normal except for mild upper respiratory symptoms and a bulging, erythematous left tympanic membrane.

Dr. Goldfarb— How would you manage this infant, Dr. Francy?

Dr. Francy— Observation would not really be an option, given the child's age and the fact that there is a documented fever of 38.9 °C and irritability, although she is not toxic-appearing. Again, after having made an appropriate and correct diagnosis of AOM, which I think is very important to state again, I would treat with amoxicillin 80 to 90 mg/kg/day, in two divided doses.

The microbiology behind dosing decisions

Dr. Sabella—What is the rationale behind using high-dose amoxicillin, specifically in regard to *S pneumoniae* resistance?

Dr. Jennifer Long— There are two key factors to keep in mind with regard to high-dose amoxicillin: the mechanism of resistance of *S pneumoniae*, and the pharmacodynamics of the beta-lactams.

In regard to the mechanism of resistance, it actually is mediated not by beta-lactamase but by a change in the penicillin-binding protein, which is a graded resistance. This type of resistance can be overcome by increasing the dose of amoxicillin (Table 1).

The pharmacodynamics of beta-lactams are such that the duration for which the serum level of the antibiotic is above the minimum inhibitory concentration (MIC) is probably the critical factor in bacterial killing. There are many in vitro and animal studies, as well as studies looking at levels in children,[5–8] showing that as the amoxicillin dose is increased to the range of 80 to 90 mg/kg/day, the time above the MIC in both the plasma and the middle ear fluid is indeed increased as well.

Dr. Goldfarb— Does twice-daily (BID) dosing, as compared with three-times-daily (TID) dosing, significantly affect the duration of time that the drug level is above the MIC, given the short half-life of the beta-lactams?

TABLE 1

Mechanisms of antimicrobial resistance among organisms that cause acute otitis media

MECHANISM OF RESISTANCE	ORGANISMS	CAN RESISTANCE BE OVERCOME BY RAISING DOSE OF ANTIMICROBIAL?
Beta-lactamase production	Haemophilus influenzae Moraxella catarrhalis	No
Alteration of penicillin-binding proteins	Streptococcus pneumoniae	Yes

Dr. Long— Because amoxicillin has linear pharmacokinetics, doubling its dose results in a doubling of the peak level achieved. The half-life will stay the same, which for amoxicillin is roughly 1 hour. This results in serum levels above 1 µg/mL for anywhere from 40% to 50% of the dosing interval, depending on whether 80 or 90 mg/kg/day is given. The optimal time above the MIC that is needed for efficacy is debated, but it is generally thought to range from 30% to 40%, although some experts advocate that 60% to 70% is ideal.[7]

Dr. Sabella— And this can be achieved with BID dosing as well as TID dosing?

Dr. Long— Yes. The area under the curve, which translates to the duration above the MIC for the whole 24-hour period, is roughly the same with 8-hour dose intervals as with 12-hour dose intervals.

Dr. Marcy— The other thing to remember about BID dosing is that it improves compliance. TID dosing simply doesn't work for a child in a day care center.

Dr. Francy— Right—there's no question that compliance is better with BID dosing.

Dr. Sabella— Will high-dose amoxicillin be

If it's explained in lay terms, most parents understand how resistance leads to decreased drug effectiveness and a larger problem for us all.
—Dr. Scott Francy

TABLE 2

Risk factors for acquisition and carriage of resistant S pneumoniae

Age younger than 2 years
Previous treatment with a beta-lactam antibiotic
Group day care attendance
Underlying medical illness
Recent hospitalization

effective if you are dealing with a fully resistant strain of *S pneumoniae*—for instance, one for which the MIC is 2 µg/mL?

Dr. Long—Because of the high peak serum levels that are achievable with high-dose amoxicillin—15 to 22 µg/mL[6–9]—it should be effective.

Three-times-daily dosing simply doesn't work for a child in a day care center.
—Dr. Michael Marcy

Dr. Marcy—Yes, it has been shown that with dosing of 90 mg/kg/day, peak levels in middle ear fluid will be significantly higher than 2 µg/mL.[6] Fortunately, even most highly resistant strains of *S pneumoniae* are not resistant to concentrations above 8 µg/mL. Those that are may present a problem.

Dr. Sabella—This point is especially important for children who are at increased risk of infection with resistant *S pneumoniae* (Table 2).

Dr. Long—It should be noted that dosages also increase the time above the MIC. For example, studies have shown that the time above the MIC, assuming an MIC of 4 µg/mL, is 38% for high-dose amoxicillin-clavulanate (90/6.4 mg/kg/day given in two divided doses) compared with 23% for the standard dose (45/6.4 mg/kg/day given in two divided doses). In addition, high-dose amoxicillin achieves middle ear fluid concentrations between 3 and 8 µg/mL for at least 3 hours after the dose.[10–12]

Duration of therapy: Age matters, but err on the long side

Dr. Sabella—What about duration of therapy, Dr. Marcy? In the child with AOM who is 6 years of age or older, would you think about a shorter duration of therapy?

Dr. Marcy—The formal recommendation remains 10 days for children younger than 6 years of age. A shorter duration of therapy—5 to 7 days—may be appropriate for children 6 years of age or older. This applies not only to amoxicillin and amoxicillin-clavulanate but also to the cephalosporins and to the third-line drugs that are not FDA-approved for short-course therapy.

Personally, I treat children up to 2 years of age with amoxicillin or amoxicillin-clavulanate for 10 days, those between 2 years and 4 years of age for 7 days, and those 4 years of age or older for 5 days. In truth, I would guess that a large proportion of parents stop therapy within a day or two of their child's improvement and that it makes little difference what we recommend.

CASE 3

The 9-month-old infant from Case 2 is treated with high-dose amoxicillin and returns in 48 hours with continued fever and irritability. The examination remains normal except for continued erythema and bulging of the left tympanic membrane.

Reassessment by phone vs face-to-face

Dr. Marcy—Any child who does not respond to primary therapy warrants reassessment, either by direct physical examination or by telephone assessment, depending on the reliability of the parent or caregiver who is observing the child. The clinician has to decide whether or not to accept telephone assessment. Many parents and caregivers simply will be unable to come in for an office visit, so then it must be decided whether the child is well enough to warrant treatment over the phone alone. Whatever decision is made, a telephone conversation should be thoroughly documented in the chart.

The question of giving a prescription "on call," or a contingency prescription, to parents also has been raised. That decision also rests with the physician, but there are risks. Parents and caregivers cannot always be relied upon to accurately judge how ill their child is. They may well fill the "on call" prescription to treat

what they think is simply unresolved AOM when, in fact, their child is sicker with an underlying condition, such as pneumonia, empyema, or meningitis, that would require parenteral antibiotic treatment. The responsibility for the decision to proceed with a course of inadequate oral therapy in those situations rests not only with the parent or caregiver but also with the physician if there was no medical reassessment before starting antibiotics.

Dr. Sabella—What are the microbiologic considerations for the child in whom high-dose amoxicillin therapy has failed?

Dr. Marcy—Well, a child who does not respond to high-dose amoxicillin has a residual microbiology that may involve one of several organisms. A significant percentage of these children have been shown to actually suffer from a viral illness,[3] and the persistent fever is caused by the underlying viral illness—not necessarily a viral AOM but simply an underlying viral upper respiratory tract infection. Assuming that this is bacteriologic failure, the high-dose amoxicillin will have killed 50% to 70% of the *H influenzae* organisms, 75% to 90% of the pneumococci, and none of the *M catarrhalis* organisms.[3]

Alternative therapies: Recommendations and rationale

Dr. Sabella—Given the possibility of bacteriologic failure, what are the second-line agents to be considered at this point?

Dr. Marcy—These would include the use of amoxicillin-clavulanate, which will eliminate the remaining 30% of *H influenzae* organisms and all of the *M catarrhalis*. High-dose amoxicillin-clavulanate may also eliminate some pneumococci that were not fully eradicated in the first 48 hours, but that is a lesser consideration at this time.

Other alternative therapies after amoxicillin failure include the oral cephalosporins cefuroxime, cefpodoxime, and cefdinir for children with non–type I allergies to beta-lactams.

Additionally, the use of ceftriaxone, given intramuscularly once daily for 3 days, can be considered.

TABLE 3

Eradication of S pneumoniae in children with acute otitis media treated with high-dose amoxicillin-clavulan

SUSCEPTIBILITY OF S PNEUMONIAE TO PENICILLIN AT BASELINE	ERADICATION RATE, DAGAN ET AL[18]	ERADICATION RATE, PACKAGE INSERT[9]
MIC ≤ 0.25 mg/L (penicillin-susceptible or -intermediate)	83/83 (100%)	—
MIC 0.5–1.0 mg/L (penicillin-intermediate)	5/5 (100%)	—
MIC 2 mg/L (penicillin-resistant)	19/20 (95%)	19/19 (100%)
MIC 4 mg/L (penicillin-resistant)	12/14 (86%)	12/14 (86%)
All S pneumoniae	122/125 (98%)	121/123 (98%)

MIC = minimum inhibitory concentration

Dr. Sabella—Dr. Long, what is relevant for physicians to know about the pharmacology of high-dose amoxicillin-clavulanate?

Dr. Long—Clavulanate is a suicide beta-lactamase inhibitor, so it covalently binds to and inactivates beta-lactamases. Across the various amoxicillin-clavulanate preparations, the amount of amoxicillin increases while the amount of clavulanate remains the same. Thus, these formulations are designed to deliver higher doses of amoxicillin without increasing the concentration of clavulanate. My concern with these formulations is that with BID dosing, there is a theoretical chance that not enough clavulanate will be present for the entire dosing interval, whereas this is less of a risk with TID dosing.

Dr. Marcy—Clinically, this does not appear to be a problem (Table 3).

Dr. Long—Yes. In fact, a report published a

few years ago compared clavulanate levels with BID vs TID dosing and showed that higher levels of clavulanate actually were achieved with BID dosing.[8] I cannot find a suitable pharmacologic or pharmacodynamic explanation for this phenomenon.

Dr. Marcy— We should point out that it's the clavulanate, and not the high-dose amoxicillin, that is responsible for these preparations' gastrointestinal side effects—the vomiting, the diarrhea, and the abdominal pain.

Dr. Goldfarb— Let's turn to the cephalosporin second-line agents. Dr. Long, what should physicians know about these agents' antimicrobial spectrum and pharmacodynamics?

Dr. Long— The oral cephalosporins that are included in the guidelines—cefuroxime, cefpodoxime, and cefdinir—have good activity against penicillin-susceptible strains of *S pneumoniae*. However, it is important to note that they are inferior to amoxicillin in activity against pneumococcal strains that are intermediately or fully resistant to penicillin. Because these agents are stable against beta-lactamases, they have excellent activity against *H influenzae* and *M catarrhalis*.

Testing the activity of cephalosporins against beta-lactamase-producing strains of H influenzae can be unreliable.
—Dr. Camille Sabella

All three of these oral cephalosporins are given twice daily, although cefdinir can also be given as a once-daily, 14-mg/kg dose. Cefdinir is the most palatable of the three agents, as shown in the only comparative palatability study of antimicrobial suspensions, which was conducted in adults because of its impracticality in infants and young children.[13]

Ceftriaxone, which is given intramuscularly, has excellent antimicrobial activity against all of the potential pathogens discussed and is clinically effective against even resistant strains of *S pneumoniae*. Its long half-life allows once-daily administration.

Dr. Goldfarb— Dr. Marcy, given your role as a consultant to the American Academy of Pediatrics for the development of these guidelines, what was the rationale behind the selection of these particular cephalosporins for recommendation in the guidelines?

Dr. Marcy— Cefuroxime was chosen because it was recommended by the Centers for Disease Control and Prevention's Drug-resistant *Streptococcus pneumoniae* Therapeutic Working Group in consensus recommendations published in 1999.[12] Cefpodoxime was added because of its activity against *H influenzae* and *M catarrhalis* as well as against some drug-resistant strains of *S pneumoniae*, as noted in those same consensus recommendations. Cefdinir was chosen because of its increased palatability over cefuroxime and cefpodoxime.[13]

Dr. Goldfarb— Was consideration given to recommending macrolides as second-line agents?

Dr. Marcy— It was felt that the macrolides have limited efficacy against all the etiologies of AOM. Thus, the macrolides, along with trimethoprim-sulfamethoxazole and erythromycin-sulfisoxazole, are listed in the guidelines only as alternatives for patients who have a history of anaphylaxis or severe allergy to beta-lactam agents.

Dr. Goldfarb— What about consideration for other cephalosporins, such as cefprozil, as second-line agents?

Dr. Marcy— In regard to cefprozil, there was a concern that it was inferior to the recommended agents in its in vitro activity against *H influenzae*.

Dr. Goldfarb— It is important to note, however, that clinical trials have not demonstrated that cefprozil has inferior activity against beta-lactamase–producing *H influenzae*.

Dr. Sabella—I understand that, from a microbiologic standpoint, testing the activity of these agents against beta-lactamase–producing strains of *H influenzae* is problematic and often unreliable. This may explain the discrepancy between in vitro susceptibility and the fact that this agent seems to work well clinically.

Dr. Goldfarb— Yes, I believe that cefprozil should be added to the list of oral cephalosporins that can be used as second-line agents.

Dr. Sabella—Dr. Francy, what is your choice of second-line agent for the child in whom high-dose amoxicillin has failed?

Dr. Francy—I typically use amoxicillin as a first-line agent and then use amoxicillin-clavulanate as the second-line agent.

Fallbacks after further failure: Tympanocentesis, ceftriaxone, clindamycin

Dr. Goldfarb—Is the ceftriaxone alternative something you find useful in your practice, and when would you use it?

Dr. Francy—If amoxicillin-clavulanate fails, I first think about having the otolaryngologists at our institution perform a tympanocentesis. In cases when this has not happened, I have used ceftriaxone.

Dr. Goldfarb—What dosage schedule do you use?

Dr. Francy—I typically use 50 mg/kg for three daily doses.

Dr. Marcy—With this regimen, it appears that about 75% of patients are cured after the first dose and 98% are cured with three doses.[14]

Dr. Sabella—Dr. Marcy, are there times when you may consider a single dose of ceftriaxone for the treatment of AOM?

Dr. Marcy—There is evidence from two outpatient clinical trials that a single dose of ceftriaxone is adequate primary therapy for AOM.[15,16] One of these studies compared a single dose of ceftriaxone with trimethoprim-sulfamethoxazole, to which at least 90% of pneumococcal strains were susceptible at the time, and showed that a single dose is sufficient.[15] In the guidelines, the option for use of single-dose ceftriaxone is restricted to primary therapy for a child who is vomiting or refusing oral antibiotics, or a child for whom compliance with an oral regimen is in question. It is important to stress that when ceftriaxone is given as a second- or third-line agent following treatment failure, the recommendation is for three daily doses.

Dr. Sabella—The guidelines mention clindamycin as an alternative for the child who has not responded to a second-line agent. When would you use clindamycin?

Dr. Marcy—The guidelines offer this option in situations where tympanocentesis is not available and second-line therapy has failed. The usual progression would be amoxicillin to amoxicillin-clavulanate to ceftriaxone. Clindamycin would be an alternative to ceftriaxone because nationwide about 95% of strains of pneumococci that are highly resistant to penicillin remain susceptible to clindamycin.[17]

Dr. Long—There is concern that with the increasing use of both clindamycin and the macrolides for AOM, the percentage of pneumococcal strains that are susceptible to clindamycin will decrease. We have already seen this here in Cleveland, where only 89% of strains of pneumococci are susceptible to clindamycin.

Dr. Marcy—Resistance to clindamycin and resistance to erythromycin very frequently go hand in hand.

Dr. Sabella—I think it is inevitable that with the increasing incidence of macrolide-resistant pneumococci, we are going to be seeing clindamycin resistance as well. In fact, I believe that clindamycin should be used for AOM only if there is a documented positive culture indicating that the organism is penicillin-resistant but clindamycin-susceptible.

Dr. Marcy—From a practical standpoint, if you have a child who has not responded to a second-line therapy, such as amoxicillin-clavulanate or an oral cephalosporin or ceftriaxone, then that child has been ill for 96 hours, and at that point you are doing a tympanocentesis. But you won't have your culture and susceptibility results for another 48 hours. In that case, you may contemplate using clindamycin pending the results of the tympanocentesis.

Dr. Goldfarb—I think that we would treat the child with ceftriaxone, not clindamycin. But if there were confirmation from tympa-

Here in Cleveland, already only 89% of pneumococcal strains are susceptible to clindamycin.
—Dr. Jennifer Long

nocentesis that the organism was a penicillin-resistant pneumococcus that was susceptible to clindamycin, then oral clindamycin would be a good alternative.

Dr. Long—We would stress that clindamycin should be used only when there is documentation or a likelihood that you are dealing with a resistant strain of *S pneumoniae*, given that clindamycin has no activity against the other common causes of AOM—namely, *H influenzae* and *M catarrhalis*.

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