Acute otitis media: Making sense of recent guidelines on antimicrobial treatment

Several new recommendations could influence treatment choices

Michael E. Pichichero, MD, and Janet R. Casey, MD
University of Rochester Medical Center, Rochester, NY

Practice recommendations

- High-dose amoxicillin (80 to 90 mg/kg/d divided twice daily) remains the drug of choice for treatment of acute otitis media despite increasing antimicrobial resistance. (**B**)
- For persistent or recurrent acute otitis media, guidelines recommend high-dose amoxicillin/clavulanate (90/6.4 mg/kg/d), cefdinir, cefprozil, cefpodoxime, cefuroxime or ceftriaxone. (**B**)
- Increasing the dose of amoxicillin does not cover infection with β-lactamase-producing pathogens; add the β-lactamase inhibitor clavulanate to amoxicillin, or choose a cephalosporin with good activity against *S pneumoniae* and good β-lactamase stability. (**A**)
- Key factors for enhancing compliance are taste of suspension, dosing frequency, and duration of therapy. (**B**)

Empiric treatment of acute otitis media (AOM) should target *Streptococcus pneumoniae*, nontypeable *Haemophilus influenzae*, and *Moraxella catarrhalis*—these bacteria are most often isolated in AOM.[1] Group A streptococci and *Staphylococcus aureus* are involved less often.[1] Viruses are the sole AOM pathogen in fewer than 10% of cases; *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* rarely cause AOM.

Amoxicillin, 80 to 90 mg/kg/d divided twice daily, remains the drug of choice for AOM despite increasing antimicrobial resistance. Over-diagnosis of AOM and frequent spontaneous resolution of true AOM make amoxicillin the most cost-effective agent. For persistent or recurrent AOM, guidelines recommend high-dose amoxicillin/clavulanate, 90/6.4 mg/kg/d, cefdinir, cefprozil, cefpodoxime, cefuroxime, or ceftriaxone. When the diagnosis is uncertain or the child is older than 2 years, observation may be an option.

The American Academy of Pediatrics and the American Academy of Family Physicians (AAP/AAFP) guideline for management of AOM has several new recommendations that could influence antimicrobial choices for AOM. Among them are use of cephalosporins for non-anaphylaxis penicillin-allergic patients, and regard for such compliance factors as product taste, dosing frequency, and length of therapy.

Pertinent guidelines

The Drug-Resistant *Streptococcus pneumoniae* (DRSP) Therapeutic Working Group sponsored by the Centers for Disease Control and Prevention (CDC)

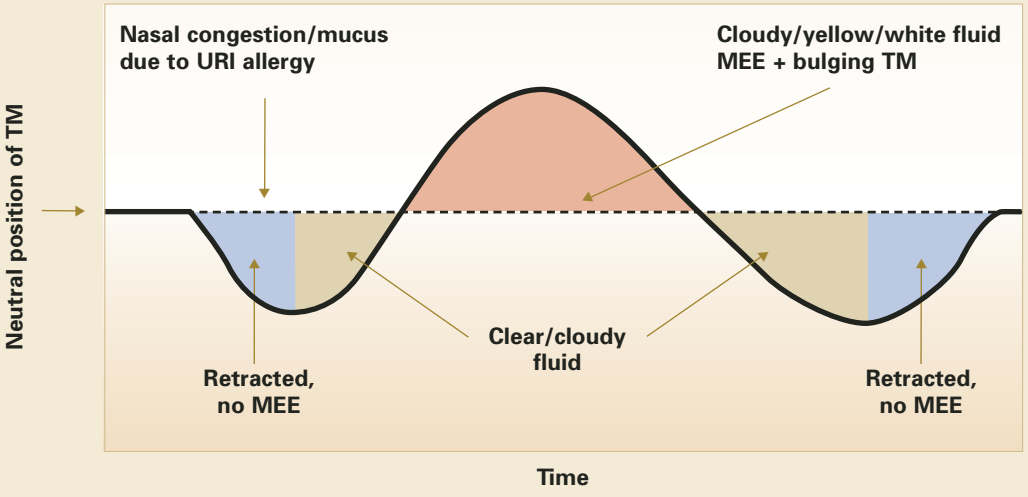
CORRESPONDING AUTHOR
Michael E. Pichichero, MD, University of Rochester Medical Center, Elmwood Pediatric Group, 601 Elmwood Avenue, Box 672, Rochester, NY 14642.
E-mail: michael_pichichero@urmc.rochester.edu.

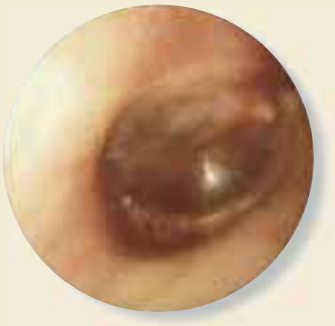
FIGURE 1

How acute otitis media develops

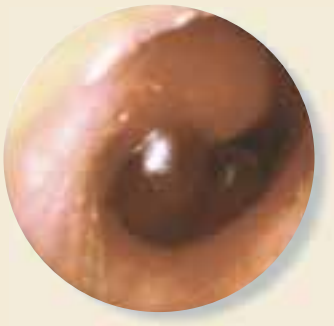
Shortly after nasal congestion develops, eustachian tube dysfunction occurs with the development of negative pressure within the middle-ear space. Air then diffuses out the middle-ear space causing a retracted TM, fluid accumulation may follow.

The middle-ear effusion (MEE) may persist and become infected with bacteria producing signs and symptoms of acute inflammation manifest as a bulging TM with purulent MEE.





Typical retracted tympanic membrane in otitis media with effusion



Typical bulging tympanic membrane in acute otitis media

The infection may resolve spontaneously as nasal congestion resolves and eustachian tube function returns or if antimicrobial agents are prescribed resolution may occur faster and more frequently. As AOM resolves, pressure within the middle ear space returns to normal and the MEE clears.

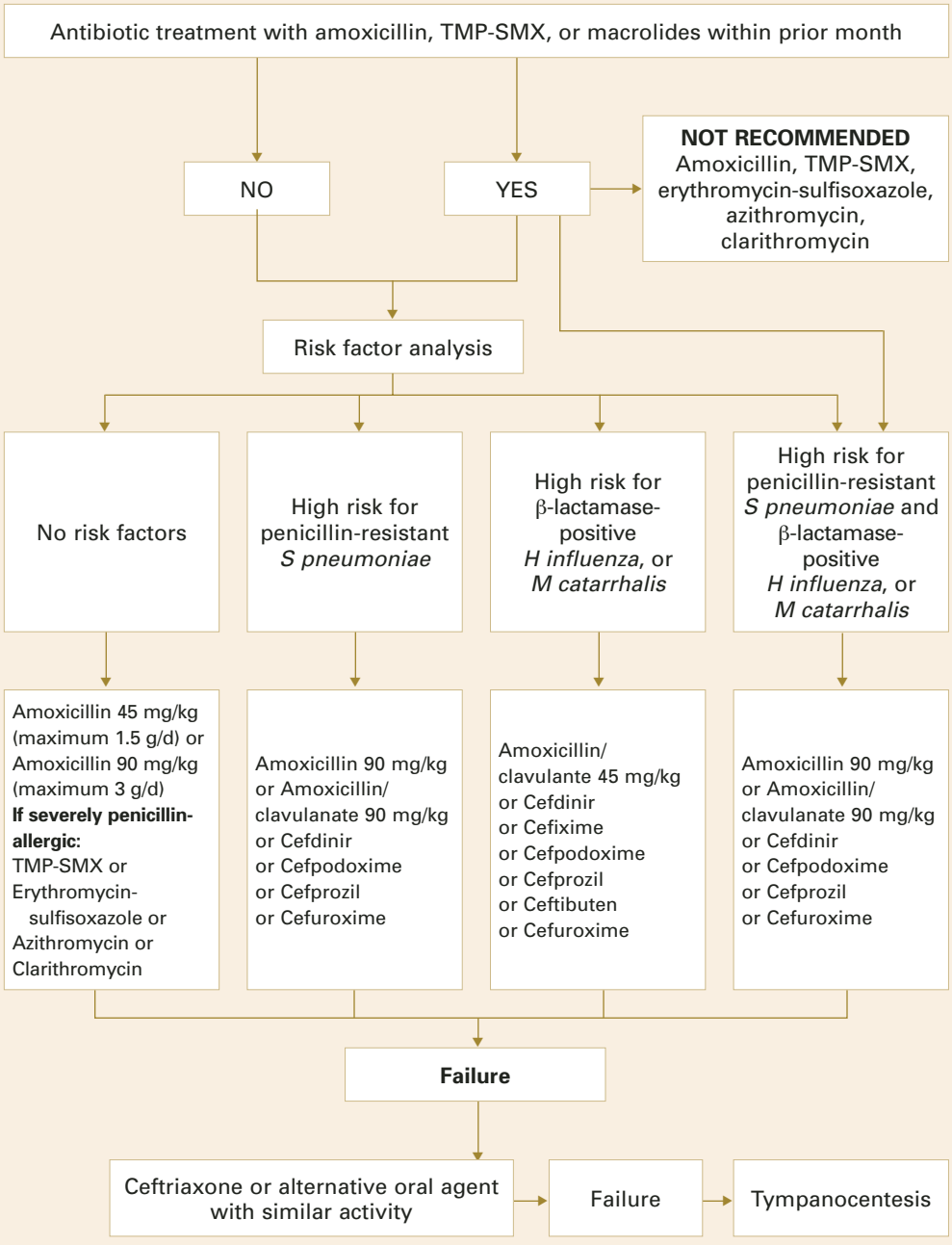
published recommendations for the management of AOM in 1999.[2] A guideline on the treatment of persistent and recurrent AOM based on the recommendations made by the CDC were published by a Clinical Advisory Committee in 2000.[3] The AAFP and AAP published a new guideline in 2004.[4]

What the guidelines agree on

AOM may be difficult to diagnose. The history and symptoms are neither sensitive nor specific enough to make an accurate diagnosis of AOM.[5,6] Although various definitions of AOM have been proposed, all agree that AOM is a diagnosis based on visualization of the tympanic membrane

FIGURE 2

Clinical algorithm by the Clinical Advisory Committee on Treatment of Recurrent and Persistent AOM



Algorithm for treatment of persistent and recurrent acute otitis media

and assessment of middle-ear fluid status. Certain physical signs, including bulging of the tympanic membrane, distortion of the light reflex, redness, and disappearance of the translucency of the tympanic membrane are typical of AOM (**FIGURE 1**).[7]

AOM must be differentiated from OME. It is crucial to distinguish between AOM

FAST TRACK

It is crucial to distinguish between AOM and otitis media with effusion, which is not treated with antimicrobials

Acute otitis media's etiologic profile today

Both penicillin-intermediate *S pneumoniae* (minimum inhibitory concentration [MIC] 0.12–1.0 μg/mL) and resistant *S pneumoniae* (penicillin MIC ≥2.0 μg/mL) are common causes of AOM in the United States.[10] Further complicating treatment, most resistant strains of S pneumoniae are also resistant to other classes of antimicrobials, such as macrolides, trimethoprim/sulfamethoxazole, and clindamycin.

A steadily increasing number of *H influenzae* and nearly all *M catarrhalis* strains are β-lactamase producers.[11] These resistant pathogens are most commonly isolated from children in day care, from children younger than 2 years of age, during the winter months, from children recently treated with antimicrobials, and from those who have not responded to treatment.[3,12]

Extensive and often inappropriate use of antimicrobials has contributed to increased resistance, which complicates treatment of AOM, increases treatment failure, has motivated a search for newer drugs effective against resistant strains.

FAST TRACK

All guidelines recommend oral amoxicillin as first-line therapy for acute otitis media

and otitis media with effusion (OME) because OME is usually not treated with antimicrobials.[7] This is a clinical conundrum because OME often precedes and follows AOM (**FIGURE 1**).

Although OME is considered asymptomatic except for hearing loss, it is now known to cause mild to moderate otalgia associated with tympanic membrane stretching.[1,3,7] Ear tugging and poor sleep follow.

The optimal physical finding to differentiate OME from AOM is tympanic membrane position. Patients with AOM have a bulging tympanic membrane; those with OME have a neutral or retracted tympanic membrane (**FIGURE 1**). Tympanic membrane position is best assessed with pneumatic otoscopy.[1,3,7]

Tympanocentesis usually necessary. All guidelines advocate that physicians either learn the skills needed to perform tympanocentesis, or refer patients to a clinician who can perform the procedure when 2 sequential treatment failures occur and for other indications.[2–4] In cases of persistent or recurrent AOM, tympanocentesis with a culture of the middle-ear fluid may be especially useful in guiding treatment. In addition, evacuation of the middle-ear effusion can be helpful in breaking the cycle of persistent and recurrent AOM.

Criteria for choosing an antimicrobial. The most important consideration in selecting an antimicrobial is efficacy against *S pneumoniae*. Although this pathogen as a cause of AOM is decreasing in the wake of widespread use of the 7-valent pneumococcal conjugate vaccine,[8] it is also the least likely of the 3 main pathogens to resolve spontaneously without treatment.[2,9]

All guidelines also recommend that the selected antibiotic have efficacy against β-lactamase-producing strains of *H influenzae* and *M catarrhalis*.

S pneumoniae with reduced susceptibility to penicillin, and *H influenzae* that produce β–lactamase, are significantly more prevalent among children than adults, especially among children who attend day care, who have received antimicrobials within the preceding month, or who have not responded to recent treatment.[2,3] An antimicrobial chosen empirically must not only have activity against the major pathogens, but it must also achieve a peak concentration in the middle-ear fluid sufficient to eradicate *S pneumoniae* with reduced susceptibility to penicillin and retain activity if β-lactamase is produced by a gram-negative organism.

All guidelines recommend oral amoxicillin as first-line therapy in AOM. The AAP/AAFP guideline recommends increasing the dosage used for empiric treatment from 40–45 mg/kg/d to 80–90 mg/kg/d for all children, because the prevalence of penicillin-resistant *S pneumoniae* has continued to rise and has reached a level in 2004 where standard-dose amoxicillin is no longer considered adequate (see **Acute otitis media's etiologic profile today**).

Differences among the guidelines

After the CDC[2] and Clinical Advisory Committee[3] guidelines were published, the Agency for Healthcare Research and Quality (AHRQ) report[13] was released; it suggested most episodes of AOM resolve without the use of antimicrobials.

TABLE 1

Consistency of guidelines for acute otitis media

All recommend as first-line	Amoxicillin, mostly at 80–90 mg/kg/d
All recommend as second-line	Amoxicillin/clavulanate, mostly "ES" 80–90 mg/kg/d
Some recommend as second-line	Cefdinir 14 mg/kg/d Cefprozil 30 mg/kg/d Cefuroxime axetil 30 mg/kg/d Cefpodoxime 10 mg/kg/d Ceftriaxone 50 mg/kg/d
Not recommended by any guideline Unless pathogen known to be sensitive; patient had severe allergic reaction to penicillin or amoxicillin; or combined with another antibiotic that is effective against additional organisms	Azithromycin Clarithromycin Trimethoprim/sulfamethoxazole Erythromycin/sulfisoxazole Cefaclor Loracarbef Cefixime Ceftibuten Clindamycin

Therefore, the AAP/AAFP guideline[4] included a watchful waiting option in its clinical algorithm.

Disagreement over watchful waiting. The CDC guideline did not comment on spontaneous resolution and watchful waiting as an option, and the Clinical Advisory Committee[3] did not agree with the often quoted 70% to 80% spontaneous resolution. The Clinical Advisory Committee and Wald[14] expressed concerns that the included studies used poor enrollment criteria and likely misclassified some benign upper respiratory infections and OME as AOM. Wald resigned from the AAP/AAFP writing group in a dispute on this issue. She and the Clinical Advisory Committee favored effective antibiotic therapy because it more rapidly resolves the clinical signs and symptoms of AOM,[13] and because children who receive only symptomatic treatment have consistently higher failure rates than those treated with antimicrobials.[13]

How compliance factors influence treatment outcomes. The CDC guidelines[2] did not give weight to the taste of the medication, frequency of dosing, duration of therapy, or adverse side effects (rash, spitting, vomiting, and diarrhea). The Clinical Advisory Committee guideline[3] and the AAP/AAFP guideline[4] viewed these compliance factors as important in selecting an appropriate antimicrobial for children.[3,12,15]

Two new antibiotics were licensed following publication of the CDC and Clinical Advisory Committee Guidelines—amoxicillin/clavulanate extra-strength, and the third-generation cephalosporin, cefdinir. Cefdinir was endorsed by the Clinical Advisory Committee and the AAP/AAFP guideline, given the drug's efficacy and compliance-enhancing features—ie, pleasant taste, once- or twice-per-day dosing, and a 5-day course for AOM treatment.

Which drugs get priority. In the event initial amoxicillin treatment fails, all guidelines recommend high-dose amoxicillin/clavulanate as a preferred second-line agent.

In addition, the CDC and Clinical Advisory Committee guidelines cite one or several of the cephalosporins as preferred second-line agents, including ceftriaxone, cefdinir, cefpodoxime, cefprozil, or cefuroxime.

The AAP/AAFP guideline endorsed cefdinir, cefpodoxime, cefuroxime, and ceftriaxone as alternatives to amoxicillin and amoxicillin/clavulanate for patients with

FAST TRACK

The AAP/AAFP guidelines viewed compliance as important in selecting an antimicrobial for children

TABLE 2

AOM treatment recommendations by the CDC DRSP Working Group

ANTIBIOTICS IN PRIOR MONTH?	DAY 0	CLINICALLY DEFINED TREATMENT FAILURE ON DAY 3	CLINICALLY DEFINED TREATMENT FAILURE ON DAY 10–28
No	High-dose amoxicillin; or usual-dose amoxicillin	High-dose amoxicillin/clavulanate; or cefuroxime axetil; or IM ceftriaxone	Same as day 3
Yes	High-dose amoxicillin; or high-dose amoxicillin/clavulanate; or cefuroxime axetil	IM ceftriaxone; or clindamycin; tympanocentesis	High-dose amoxicillin/clavulanate; or cefuroxime axetil; or IM ceftriaxone; tympanocentesis

High-dose amoxicillin = 80–100 mg/kg/d. High-dose amoxicillin clavulanate = 80–100 mg/kg/d for the amoxicillin component (requires newer formulation, or combination with amoxicillin). Ceftriaxone injections recommended for 3 days. Clindamycin is not effective against *H influenzae* or *M catarrhalis*.

FAST TRACK

No guidelines recommend TMP/SMX or azithromycin as a second-line choice unless a severe reaction is a confounding factor

"non-type I allergy." The addition of cefdinir was based on satisfactory efficacy and high-compliance potential. Designation of the preferred cephalosporins as "alternatives" was not explained.

No guideline recommends trimethoprim/sulfamethoxazole (TMP/SMX) or azithromycin as a preferred second-line choice unless a severe reaction like anaphylaxis due to penicillin allergy is a confounding factor. Other antibiotics are recommended alone or in combination in some but not all guidelines (**TABLE 1**).

Particulars of the CDC recommendations

In choosing preferred agents, the CDC gave primary consideration to pharmacokinetic/pharmacodynamic data and to clinical efficacy trials that used tympanocentesis results (especially double tympanocentesis) as evidence of diagnosis and bacteriologic outcome. Of the 16 FDA-approved drugs for the treatment of AOM, many lacked data on efficacy against multidrug-resistant *S pneumoniae* or β-lactamase-producing *H influenzae*.

Following its review of the evidence base in 1997–1998, the CDC selected amoxicillin as the treatment of choice. The amoxicillin dose varied. If a child had been treated with an antibiotic in the preceding month, was aged <2 years, or had attended day care, the dose was increased from 40–45 mg/kg/d to 80–90 mg/kg/d.

High-dose amoxicillin/clavulanate, cefuroxime axetil, and intramuscular ceftriaxone (3 injections) were endorsed as the most appropriate alternative antimicrobials.

If resistant *S pneumoniae* was the isolate identified with tympanocentesis, clindamycin became another choice (**TABLE 2**).

Recommendations from a clinical advisory committee

A clinical advisory committee made recommendations focused on the medical management of persistent and recurrent AOM.[5] Persistent AOM was defined as the persistence of the signs and symptoms of middle-ear infection following 1 or 2 courses of antimicrobials, whereas recurrent AOM was defined as 3 or more episodes of AOM in a 6-month time span or 4 or more episodes in a 12-month time span.

These guidelines coincide with the CDC guidelines in that amoxicillin/clavulanate (amoxicillin, 45–90 mg/kg/d; clavulanate, 6.4 mg/kg/d), cefuroxime axetil, and intramuscular ceftriaxone were endorsed as appropriate agents for persistent and recurrent AOM. Based on an

TABLE 3

AAP/AAFP criteria for treatment decisions in children with acute otitis media

AGE	CERTAIN DIAGNOSIS	UNCERTAIN DIAGNOSIS
Under 6 months	Antibacterial therapy	Antibacterial therapy
6 months to 2 years	Antibacterial therapy	Antibacterial therapy if severe illness. Observation option* if non-severe illness.
2 years or older	Antibacterial therapy if severe illness. Observation option* if non-severe illness	Observation option*

Modified from the New York State Department of Health and the New York Region Otitis Project Committee[20,21]
*Observation is an appropriate option only when follow-up can be assured and antibacterial agents started if symptoms persist or worsen.
Non-severe illness is mild otalgia and fever <39°C in the past 24 hours. Severe illness is moderate to severe otalgia or fever ≤39°C. A certain diagnosis of AOM meets all 3 criteria: 1) rapid onset, 2) signs of middle-ear effusion, and 3) signs and symptoms of middle-ear inflammation.

analysis of clinical outcomes, cefpodoxime, cefprozil, and cefdinir were also recommended in this treatment algorithm (**FIGURE 2**).[16–19]

AAP/AAFP guideline details

The AAP/AAFP guideline recommended antimicrobials or observation for children with AOM, taking into consideration patient age and certainty of the diagnosis (**TABLE 3**).

In recommending the observation option, the committee cited rising bacterial resistance, injudicious antibiotic use, viruses as a common cause of AOM, a high spontaneous cure rate for AOM (80%–90%), and the lack of a substantial increase in complications when such a strategy is applied (as in the Netherlands).

Amoxicillin, 80–90 mg/kg/d, was selected by the AAP/AAFP as the empiric antibiotic preferred for AOM. High-dose amoxicillin/clavulanate or ceftriaxone were recommended if amoxicillin treatment fails, or as alternatives to amoxicillin in the presence of any 1 of 3 CDC guideline risk factors: (1) antibiotic treatment in the past month, (2) patient younger than 2 years of age, or (3) day care attendance (**TABLE 4**).

Cefdinir, cefpodoxime, or cefuroxime were recommended for patients allergic to penicillin, unless the allergic reaction was severe, such as anaphylaxis (**TABLE 4**). Azithromycin or clarithromycin were preferred for patients with severe penicillin allergy.

In the event alternative antibiotic therapy failed, it was recommended that the patient receive 3 injections of ceftriaxone or undergo tympanocentesis to make a bacteriologic diagnosis.

Clindamycin was proposed as an option for presumed penicillin-resistant pneumococcal infection not responding to the previous regimens.

Implementing guideline recommendations in clinical practice

Amoxicillin usually first choice. Of the available oral agents, amoxicillin has the greatest in vitro activity against pneumococci.[2,20] In addition to an excellent pharmacokinetic profile, amoxicillin has a long history of safety and clinical efficacy when used to treat AOM. Because resistant *S pneumoniae* are highly prevalent in the US, a higher dose of amoxicillin (80–90 mg/kg/d in divided doses) has become the first-line therapy.[2–4]

FAST TRACK

AAP/AAFP guidelines recommend high-dose amoxicillin/clavulanate or ceftriaxone if amoxicillin treatment fails

TABLE 4

AAP/AAFP therapy options for AOM in varying clinical circumstances

At diagnosis when observation is not an option
Recommended: Amoxicillin 80-90 mg/kg/d
Alternative for penicillin allergy: Non-type I: cefdinir, cefuroxime, cefpodoxime; Type I: azithromycin, clarithromycin

Clinically defined failure of observation option after 48 to 72 hours
Recommended: Amoxicillin 80-90 mg/kg/day
Alternative for penicillin allergy: Non-type I: cefdinir, cefuroxime, cefpodoxime; Type I: azithromycin, clarithromycin

Clinically defined failure of initial antibiotic treatment after 48 to 72 hours
Recommended: Amoxicillin/clavulanate (90 mg/kg/d of amoxicillin component, with 6.4 mg/kg/d of clavulanate)
Alternative for penicillin allergy: Non-Type I: ceftriaxone—3 days; Type I: clindamycin

At diagnosis when observation is not an option
Recommended: Amoxicillin/clavulanate (90 mg/kg/d of amoxicillin with 6.4 mg/kg/d of clavulanate
Alternative for penicillin allergy: Ceftriaxone—1 or 3 days

Clinically defined failure of observation option after 48 to 72 hours
Recommended: Amoxicillin/clavulanate (90 mg/kg/d of amoxicillin with 6.4 mg/kg/d of clavulanate)
Alternative for penicillin allergy: Ceftriaxone 1 or 3 days

Clinically defined failure of initial antibiotic treatment after 48 to 72 hours
Recommended: Ceftriaxone 3 days
Alternative for penicillin allergy: Tympanocentesis, clindamycin

Covering for β-lactamase-producing pathogens. However, increasing the amoxicillin dose does not cover the patient at risk for infection with β-lactamase-producing pathogens. In this case, add the β-lactamase inhibitor, clavulanate, to amoxicillin (Augmentin ES), or choose a cephalosporin with good activity against *S pneumoniae* and good β-lactamase stability.

What to do when initial treatment fails. Treatment failure can occur for a variety of reasons besides poor drug efficacy: incorrect diagnosis, poor compliance, inadequate drug dose or frequency, atypical pharmacokinetics or pharmacodynamics, concurrent viral infection, or highly resistant bacteria.[12] In most cases in which amoxicillin therapy fails, there is no single perfect alternative. That is why several antimicrobials are recommended as second-line agents by the various guidelines. Without firm identification of a causative agent by tympanocentesis, select an agent effective against β-lactamase-producing pathogens and multi-drug-resistant *S pneumoniae*.[2,3,12]

Abandoned treatments. Trimethoprim/sulfamethoxazole and erythromycin-sulfisoxazole are no longer recommended as first- or second-line treatments for AOM, except as alternatives for patients with severe penicillin-allergy. Recent studies have shown substantial pneumococcal resistance to these agents.[2,10,21]

Azithromycin widely used but not recommended. Azithromycin is commonly used for AOM in children, largely because of its compliance-enhancing feature as a once-per-day treatment given for 1, 3, or 5 days. However, no guideline endorses azithromycin for AOM unless the patient is allergic to penicillin. The reason no expert group recommends azithromycin is a consequence of pivotal double tympanocentesis studies conducted by Dagan et al[22] and Hoberman et al.[23] In the work by Dagan, eradication of *S pneumoniae* by azithromycin was slower than with amoxicillin/clavulanate,[22] and slower eradication impacts clinical outcomes.[24] But more important, Dagan et al showed that azithromycin was no more effective than placebo in eradicating *H influenzae*.[22]

Consider compliance-enhancing factors. Key factors are taste of suspension, dosing frequency, and duration of therapy. A drawback with several of the antibiotics recommended by guidelines is their taste (**TABLE 5**). Intramuscular ceftriaxone is an alternative for resistant bacterial strains and for those patients who experience nausea or simply refuse oral medications. However, in cases of resistant *S pneumoniae*, ceftriaxone typically must be administered in 3 separate injections, which is not only unappealing for young children, but difficult for parents to comply with because of additional office visits and costs.[3,12]

The factor most likely to enhance compliance is a shorter course of therapy.

Evidence is strong and growing stronger that a 5-day course of therapy is as effective as a 10-day course. In a 1997 review of the data[26] and a meta-analysis,[27] it was suggested that data were sufficient to recommend a 5-day antibiotic course for AOM in children unless the child was less than 2 years of age or otitis-prone. Subsequently, conflicting data have been published (**TABLE 6**, available online at www.jfponline.com).

Guidelines vary in their endorsement of 5-day vs 10-day or variable regimens for treatment of AOM; most favor the 10-day course for younger children (defined as <2 years old to <6 years old), pending further studies. Nevertheless, shorter courses of therapy are preferable whenever possible because the evidence suggests shorter courses improve compliance, decrease the selection of resistant pathogens, and preclude surreptitious use of leftover antibiotics retained from longer courses.[28]

What's on the horizon

Research continues on the effect of the heptavalent pneumococcal conjugate vaccine (PCV7) on reducing the prevalence of AOM. In the first studies, the vaccine's efficacy in preventing otitis media of any origin was 6% to 7%.[29,30] However, the PCV7 may be more beneficial for children with AOM than initially calculated; among those 24 to 59 months of age who have a history of recurrent AOM, the vaccine's effect is greater.[8] Other pneumococcal conjugate vaccines containing more serotypes are being developed and tested. Their impact on AOM remains to be determined.

Other classes of antimicrobials are being studied to determine their effectiveness in AOM. Two fluoroquinolones, gatifloxacin and levofloxacin—effective against the pathogens that cause AOM, including resistant *S pnuemoniae*—have undergone clinical trial evaluation in children as young as 6 months old. Safety concerns about arthropathy and tendonitis described in juvenile animals but not children appear to have been allayed.[31]

Also being studied is another antimicrobial class—the ketolides, specifically telithromycin. This third-generation macrolide has less propensity to select for macrolide-resistant pathogens, and more potent activity against macrolide- and penicillin-resistant *S pneumoniae* and against *H influenzae* than azithromycin or clarithromycin.[32] Telithromycin has shown promising results in studies of AOM treatment. ■

TABLE 5

Comparative taste ratings for antibiotic suspensions

Compliance-enhancing, strongly
- Amoxicillin
- Cefaclor (Ceclor)
- Cefdinir (Omnicef)
- Cefixime (Suprax)
- Loracarbef (Lorabid)

Compliance enhancing, moderately
- Cefprozil (Cefzil)
- Ceftibuten (Cedax)

Equivocal compliance enhancement
- Azithromycin (Zithromax)

Not compliance-enhancing
- Amoxicillin-clavulanate (Augmentin)
- Erythromycin-sulfisoxazole (Pediazole)
- TMP-SMZ (Bactrim or Septra)

Discourages compliance
- Cefpodoxime (Vantin)
- Cefuroxime (Ceftin)
- Clarithromycin (Biaxin)

Sources: Steele et al 2001;[33] Ruff et al 1991;[34] Demers et al 1994.[35]

FAST TRACK

The heptavalent pneumococcal conjugate vaccine may be more beneficial for chldren with AOM than initially calculated

ACKNOWLEDGMENTS

Dr Pichichero has received grants/research support from Abbott Laboratories, Aventis, Bristol-Myers Squibb, GlaxoSmithKline, and Johnson & Johnson; he has served as a consultant to Abbott, Aventis, and GlaxoSmithKline. Dr Evans has received grants/research support from Abbott Laboratories, Bristol-Myers Squibb, GlaxoSmithKline, and Johnson & Johnson.

REFERENCES

1. Pelton SI. Otitis media. In: *Principles and Practice of Pediatric Infectious Diseases,* Long SS, et al, eds. Philadelphia, Pa: Churchill Livingstone; 2003: chap 27.
2. Dowell SF, Butler JC, Giebink GS. Acute otitis media: management and surveillance in an era of pneumo-

coccal resistance. *Nurse Pract* 1999; 24(10 Suppl): 1–9.

3. Pichichero ME, Reiner SA, Brook I, et al. Controversies in the medical management of persistent and recurrent otitis media. *Ann Otol Rhinol Laryngol* 2000; 109:2–12.
4. American Academy of Pediatrics Subcommittee on Management of Acute Otitis Media. Clinical practice guideline: Diagnosis and management of acute otitis media. *Pediatrics* 2004; 113:1451–1466.
5. Heikkinen T, Ruuskanen O. Signs and symptoms predicting acute otitis media. *Arch Pediatr Adolesc Med* 1995; 149:26–29.
6. Kontiokari T, Koivunen P, Niemala M, Pokka T, Uhari M. Symptoms of acute otitis media. *Pediatr Infect Dis J* 1998; 17:676–679.
7. Pichichero ME. Acute otitis media: Part I. Improving diagnostic accuracy. *Am Fam Physician* 2000; 61:2051–2056.
8. Casey JR, Pichichero ME. Changes in frequency and pathogens causing acute otitis media in 1995–2003. *Ped Infect Dis J* 2004; 23:824–828.
9. Barnett ED, Klein JO. The problem of resistant bacteria for the management of acute otitis media. *Pediatr Clin North Am* 1995; 42:509–517.
10. Doern GV, Pfaller MA, Kugler K, Freeman J, Jones RN. Prevalence of antimicrobial resistance among respiratory tract isolates of Streptococcus pneumoniae in North America: 1997 results from the SENTRY antimicrobial surveillance program. *Clin Infect Dis* 1998; 27:764–770.
11. Doern GV, Jones RN, Pfaller MA, Kugler K. Haemophilus influenzae and Moraxella catarrhalis from patients with community-acquired respiratory tract infections: antibacterial susceptibility patterns from the SENTRY antibacterial surveillance program (United States and Canada, 1997). *J Antimicrob Chemother* 1999; 43:385–389.
12. Pichichero ME. Acute otitis media: Part II. Treatment in an era of increasing antibiotic resistance. *Am Fam Phys* 2000; 61: 2410–2416.
13. Marcy M, Takata GS, Shekelle P, et al. Management of acute otitis media. Evidence report/technology assessment no. 15. AHRQ Publication No. 01-E010. Rockville, Md: Agency for Healthcare Research and Quality; 2001.
14. Wald ER. Acute otitis media: more trouble with the evidence. *Pediatr Infect Dis J* 2003; 22:103–104.
15. Wandstrat TL, Kaplan B. Pharmacoeconomic impact of factors affecting compliance with antibiotic regimens in the treatment of acute otitis media. *Pediatr Infect Dis J* 1997; 16(Suppl):S27–S29.
16. Block SL, McCarty JM, Hedrick JA, et al. Comparative safety and efficacy of cefdinir vs amoxicillin/clavulanate for treatment of suppurative acute otitis media in children. *Pediatr Infect Dis J* 2000; 19(Suppl): S159–S165.
17. Block SL, Hedrick JA, Kratzer J, Nemeth MA, Tack KJ. Five-day twice daily cefdinir therapy for acute otitis media: Microbiologic and clinical efficacy. *Pediatr Infect Dis J* 2000; 19(Suppl): S153–S158.
18. Hedrick HA, Sher LD, Schwartz RH, Pierce PF. Cefprozil verus high dose amoxicillin/clavulanate in children with acute otitis media. *Clin Ther* 2001; 23:193–204.
19. Van Dyk JC, Terespolsky SA, Meyer CS, Can Niekerk CH, Klugman KP. Penetration of cefpodoxime into middle ear fluid in pediatric patients with acute otitis media. *Pediatr Infect Dis J* 1997; 16:79–81.
20. Craig WA, Andes D. Pharmacokinetics and pharmacodynamics of antibiotics in otitis media. *Ped Infect Dis J* 1996; 15:255–259.
21. Jacobs MR, Bajaksouzian S, Zilles A, et al. Susceptibilities of *Streptococcus pneumoniae* and *Haemophilus influenzae* to 10 oral antimicrobial agents based on pharmacodynamic parameters: 1997 US Surveilance Study. *Antimicrob Agents Chemother* 1999; 43:1901–1908.
22. Dagan R, Johnson CE, Mc Linn S. Bacteriologic and clinical efficacy of amoxicillin/clavulanate vs. azithromycin in acute otitis media. *Pediatr Infect Dis J* 2000; 20:829–837.
23. Hoberman A. Extra-strength amoxicillin-clavulanate (A/C-ES) vs. azithromycin (AZI) for acute otitis media (AOM) in children. 43rd Interscience Conference on Antimicrobial Agents and Chemotherapy 2003; Session 88 G-459.
24. Dagan R, Leibovitz E, Greenberg D, et al. Early eradication of pathogens from middle ear fluid during antibiotic treatment of acute otitis media is associated with improved clinical outcome. *Pediatr Infect Dis J* 1998; 17:776–782.
25. Howie VM. Eradication of bacterial pathogens from middle ear infection. *Clin Infect Dis* 1992; 14(Suppl 2):209–210.
26. Pichichero ME, Cohen R. Shortened course of antibiotic therapy for acute otitis media, sinusitis, and tonsillopharyngitis. *Pediatr Infect Dis J* 1997; 16:680–685.
27. Kozyrskyj AL, Hildes-Ripstein E, Longstaffe SEA, et al. Treatment of acute otitis media with a shortened course of antibiotics: A meta-analysis. *JAMA* 1998; 279:1736–1742.
28. Pichichero ME. Dynamics of antibiotic prescribing for children. *JAMA* 2002; 287:23.
29. Black S, Shinefield H, Fireman B. Efficacy, safety and the immunogenicity of heptavalent pneumococcal conjugate vaccine in children. *Pediatr Infect Dis J* 2000; 19:187–195.
30. Eskola J, Kilpi T, Palmu A, et al. Efficacy of a pneumococcal conjugate vaccine against acute otitis media. *N Engl J Med* 2001; 344:403–409.
31. Yee CL, Duffy C, Gerbino PG, Stryker S, Noel GJ. Tendon or joint disorders in children after treatment with fluoroquinolones or azithromycin. *Ped Infect Dis J* 2002; 21:525–529.
32. Ackerman G, Rodloff AC. Drugs of the 21st century: Telithromycin (HMR 3647)—the first ketolide. *J Antimicrob Chemother* 2003; 51:497–511.
33. Steele RW, Thomas MP, Begue RE. Compliance issues related to the selection of antibiotic suspensions for children. *Pediatr Infect Dis J* 2001; 20:1–5.
34. Ruff ME, Schotik DA, Bass JW. Antimicrobial drug suspensions: A blind comparison of taste of fourteen common pediatric drugs. *Pediatr Infect Dis J* 1991; 10:30–33.
35. Demers DM, Chan DS, Bass JW. Antimicrobial drug suspensions: A blinded comparison of taste of twelve common pediatric drugs including cefixime, cefpodoxime, cefprozil, and loracarbef. *Pediatr Infect Dis J* 1994; 13:87–89.

DRUG BRAND NAMES

Amoxicillin/clavulanate • Augmentin
Azithromycin • Zithromax
Cefdinir • Omnicef
Cefixime • Suprax
Cefpodoxime • Vantin
Cefprozil • Cefzil
Ceftriaxone • Rocephin
Cefuroxime • Ceftin
Clarithromycin • Biaxin
Erythromycin-sulfisoxazole • Eryzole, Pediazole
Gatifloxacin • Tequin
Levofloxacin • Levaquin
Loracarbef • Lorabid
Telithromycin • Ketek
TMP-SMZ • Bactrim, Cotrim, Septra, Sulfatrim