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

Several new recommendations could influence treatment choices

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)
APPLIED EVIDENCE

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.

How acute otitis media develops

Nasal congestion/mucus due to URI allergy

<table>
<thead>
<tr>
<th>Neutral position of TM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retracted, no MEE</td>
</tr>
<tr>
<td>Clear/cloudy fluid</td>
</tr>
<tr>
<td>Retracted, no MEE</td>
</tr>
</tbody>
</table>

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.

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. Although various definitions of AOM have been proposed, all agree that AOM is a diagnosis based on visualization of the tympanic membrane.

published recommendations for the management of AOM in 1999. 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. The AAFP and AAP published a new guideline in 2004.
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It is crucial to distinguish between AOM and otitis media with effusion, which is not treated with antimicrobials.

**FIGURE 2**

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

- Antibiotic treatment with amoxicillin, TMP-SMX, or macrolides within prior month

  - NO
  - YES

  **NOT RECOMMENDED**
  - Amoxicillin, TMP-SMX, erythromycin-sulfisoxazole, azithromycin, clarithromycin

  **Risk factor analysis**

- **No risk factors**
  - Amoxicillin 45 mg/kg (maximum 1.5 g/d) or Amoxicillin 90 mg/kg (maximum 3 g/d)
  - If severely penicillin-allergic: TMP-SMX or Erythromycin-sulfisoxazole or Azithromycin or Clarithromycin

- **High risk for penicillin-resistant S pneumoniae**
  - Amoxicillin 90 mg/kg or Amoxicillin/clavulanate 90 mg/kg or Cefdinir or Cefpodoxime or Cefprozil or Cefuroxime

- **High risk for β-lactamase-positive H influenza, or M catarrhalis**
  - Amoxicillin/clavulanate 45 mg/kg or Cefdinir or Cefixime or Cefpodoxime or Cefprozil or Cefitibuten or Cefuroxime

- **High risk for penicillin-resistant S pneumoniae and β-lactamase-positive H influenza, or M catarrhalis**
  - Amoxicillin 90 mg/kg or Amoxicillin/clavulanate 90 mg/kg or Cefdinir or Cefpodoxime or Cefprozil or Cefuroxime

**Failure**

Ceftriaxone or alternative oral agent with similar activity

Failure → Typanocentesis

**FAST TRACK**

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

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

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.16 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.2,3

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.

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,6 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 CDC2 and Clinical Advisory Committee3 guidelines were published, the Agency for Healthcare Research and Quality (AHRQ) report13 was released; it suggested most episodes of AOM resolve without the use of antimicrobials.
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The AAP/AAFP guidelines viewed compliance as important in selecting an antimicrobial for children. Therefore, the AAP/AAFP guideline 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 did not agree with the often quoted 70% to 80% spontaneous resolution. The Clinical Advisory Committee and Wald 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, and because children who receive only symptomatic treatment have consistently higher failure rates than those treated with antimicrobials.

How compliance factors influence treatment outcomes. The CDC guidelines 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 and the AAP/AAFP guideline viewed these compliance factors as important in selecting an appropriate antimicrobial for children.

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 severe allergies.

### Table 1: Consistency of guidelines for acute otitis media

<table>
<thead>
<tr>
<th>All recommend as first-line</th>
<th>Amoxicillin, mostly at 80–90 mg/kg/d</th>
</tr>
</thead>
<tbody>
<tr>
<td>All recommend as second-line</td>
<td>Amoxicillin/clavulanate, mostly “ES” 80–90 mg/kg/d</td>
</tr>
</tbody>
</table>
| 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 | Azithromycin  
Clarithromycin  
Trimethoprim/sulfamethoxazole  
Erythromycin/sulfisoxazole  
Cefaclor  
Loracarbef  
Cefixime  
Ceftibuten  
Clindamycin |

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.
No guidelines recommend trimethoprim/sulfamethoxazole (TMP/SMX) or azithromycin as a 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).

**Fast Track**

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

<table>
<thead>
<tr>
<th>Antibiotics in Prior Month?</th>
<th>Day 0</th>
<th>Clinically Defined Treatment Failure on Day 3</th>
<th>Clinically Defined Treatment Failure on Day 10–28</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>High-dose amoxicillin; or usual-dose amoxicillin</td>
<td>High-dose amoxicillin; clavulanate; or cefuroxime axetil; or IM ceftriaxone</td>
<td>Same as day 3</td>
</tr>
<tr>
<td>Yes</td>
<td>High-dose amoxicillin; or high-dose amoxicillin; clavulanate; or cefuroxime axetil</td>
<td>IM ceftriaxone; or clindamycin; tympanocentesis</td>
<td>High-dose amoxicillin; clavulanate; or cefuroxime axetil; or IM ceftriaxone; tympanocentesis</td>
</tr>
</tbody>
</table>

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*.

**Recommendations from a clinical advisory committee**

A clinical advisory committee made recommendations focused on the medical management of persistent and recurrent AOM. 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
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

<table>
<thead>
<tr>
<th>AGE</th>
<th>CERTAIN DIAGNOSIS</th>
<th>UNCERTAIN DIAGNOSIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Under 6 months</td>
<td>Antibacterial therapy</td>
<td>Antibacterial therapy</td>
</tr>
<tr>
<td>6 months to 2 years</td>
<td>Antibacterial therapy</td>
<td>Antibacterial therapy if severe illness. Observation option* if non-severe illness.</td>
</tr>
<tr>
<td>2 years or older</td>
<td>Antibacterial therapy if severe illness. Observation option* if non-severe illness</td>
<td>Observation option*</td>
</tr>
</tbody>
</table>

*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.

Modiﬁed from the New York State Department of Health and the New York Region Otitis Project Committee20,21

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

# AAP/AAFP guideline details
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# 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
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. 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.

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.

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 and Hoberman et al. In the work by Dagan, eradication of S pneumoniae by azithromycin was slower than with amoxicillin/clavulanate, and slower eradication impacts clinical outcomes. But more important, Dagan et al showed that azithromycin was no more effective than placebo in eradicating H influenzae.

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. 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.

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 and a meta-analysis, 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.

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%. 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. 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 pneumoniae—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.

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. Telithromycin has shown promising results in studies of AOM treatment.

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