Otitis media (OM) is second to the common cold as an infectious cause of disease in infants and children.1 Established risk factors include male gender, Native American or Eskimo descent, pacifier use, larger-group day care settings, exposure to tobacco smoke, and lack of breastfeeding.2 The medical and surgical costs associated with treatment of OM within the US have been estimated at between $3 billion and $4 billion annually.3,4 This review summarizes and highlights recent advances in the treat-
ment and prevention of OM, with an emphasis placed on information reported over the past two years. More detailed background information regarding the etiology, epidemiology, pathophysiology, and pharmacoepidemiology of OM is beyond the scope of this article. Thorough reviews of these topics are available.54-7 The objectives of this article include updating the reader regarding the rationale behind current acute OM (AOM) treatment guidelines, as well as reviewing and ranking alternative medical approaches for the prophylaxis of recurrent OM (rAOM) in a treatment algorithm.

Treatmen of Acute Otitis Media

Streptococcus pneumoniae (pneumococcus) is the most important bacterial cause of AOM, followed closely by nontypable Haemophilus influenzae and Moraxella catarrhalis.8 In recent years, there has been a worldwide increase in strains of pneumococcus that are resistant to penicillins as well as other antibiotics. The National Committee for Clinical Laboratory Standards (NCCLS)9,10 defines breakpoints for susceptible, intermediate-resistant, and resistant pneumococci according to minimum inhibitory concentrations (MICs) of ≤0.06, 0.12–1.0, and ≥2.0 µg/mL (for penicillin G) and <1.0, 1.0–2.0, and >2.0 µg/mL (for amoxicillin), respectively. The increasing resistance of pneumococcus to many of the antibiotics typically used in treating AOM has affected recent treatment guidelines in the US. In 1999, a panel of experts convened by the Centers for Disease Control and Prevention (CDC) recommended new guidelines for treating AOM with antibiotics (Table 1).

FIRST STEP: HIGH-DOSE AMOXICILLIN

The CDC’s expert panel8 advocated amoxicillin as first-line treatment of AOM but recommended increasing the initial dosage used for empiric treatment from 40 to 45 mg/kg/d (usual or standard dose) to 80–90 mg/kg/d (high dose). The rationale behind this recommendation is that, unlike H. influenzae and M. catarrhalis, S. pneumoniae does not produce β-lactamase.2 The mechanism of pneumococcal resistance is alteration in penicillin-binding proteins, a genetic ploy that could theoretically be overcome by simply increasing penicillin/amoxicillin concentrations in the middle ear fluid (MEF). What clinical evidence exists to support such a dosage increase?

Lister et al.11 employed an in vitro pharmacodynamic model to study the killing of three strains each of penicillin-susceptible (MIC ≤0.06 µg/mL), penicillin–intermediate-resistant (MICs 1 strain, 0.25 µg/mL; 2 strains 0.5 µg/mL), and penicillin-resistant (MIC 4 µg/mL) pneumococci. Three different peak amoxicillin concentrations, 3, 6, and 9 µg/mL (achieved every 12 h) and an elimination half-life of 1.6 hours were simulated. Extrapolated from a concentration–time curve, it appeared that the percentages of the dosing interval during which the amoxicillin concentration exceeded the MIC for the susceptible, intermediate-resistant, and resistant pneumococcal isolates were 67%, 47–55%, and 0% (3 µg/mL peak profile); 100%, 70–84%, and 10% (6 µg/mL peak profile); and 100%, 79–88%, and 22% (9 µg/mL peak profile), respectively. These results suggested that peak amoxicillin concentrations of 6 and 9 µg/mL might be sufficient for elimination of penicillin-nonsusceptible pneumococcal strains, especially those of intermediate resistance.

Canafax et al.12 administered a single oral dose of amoxicillin 25 mg/kg (following 2–3 d of standard oral dosing of amoxicillin 13.3 mg/kg/dose every 8 h) to 30 children with AOM. The regular morning dose of 13.3 mg/kg had been withheld prior to administering 25 mg/kg. At least one MEF sample per patient (37 total samples) was collected between 0.5 and four hours after dosing. An MEF concentration mean of approximately 9.5 µg/mL (range, undetectable to 20.6 µg/mL) occurred three hours after 25 mg/kg was administered. The estimated time that the MEF amoxicillin concentrations were above 1.0 and 2.0 µg/mL was approximately four and 2.5 hours (50% and 31% of an 8-h dosing interval), respectively. The MEF amoxicillin penetration tended to be lower in patients with concurrent

<table>
<thead>
<tr>
<th>Antibiotics in Prior Month</th>
<th>Initial Alternative Choices</th>
<th>Clinical Treatment Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>HD amoxicillin*</td>
<td>HD amoxicillin/clavulanate*</td>
</tr>
<tr>
<td></td>
<td>standard-dose amoxicillin</td>
<td>cefuroxime axetil</td>
</tr>
<tr>
<td></td>
<td></td>
<td>im ceftriaxon*</td>
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<td></td>
<td></td>
<td>cefuroxime axetil</td>
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<td></td>
<td></td>
<td>im ceftriaxon*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>clindamycin* or tympanocentesis</td>
</tr>
<tr>
<td>Yes</td>
<td>HD amoxicillin</td>
<td>HD amoxicillin/clavulanate*</td>
</tr>
<tr>
<td></td>
<td>HD amoxicillin/clavulanate</td>
<td>cefuroxime axetil</td>
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<td>cefuroxime axetil</td>
<td>im ceftriaxon*</td>
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<td>im ceftriaxon*</td>
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<tr>
<td></td>
<td></td>
<td>clindamycin* or tympanocentesis</td>
</tr>
</tbody>
</table>

HD = high-dose.

*80–90 mg/kg/d.

*Requires formulation not yet commercially available or two separate prescriptions: amoxicillin/clavulanate (from 6.4 to ~10 mg/kg/d of clavulanate) and amoxicillin to boost the cumulative dosage to 80–90 mg/kg/d.

*50 mg/kg im once daily for three days.

*Not effective against Haemophilus influenzae or Moraxella catarrhalis.
viral infection compared to those without. One weakness of the study was the lack of measurement of baseline amoxicillin concentrations prior to the 25-mg/kg dose. Single doses of amoxicillin 15 mg/kg have generated mean peak values of 3–6 µg/mL.\textsuperscript{11} Using this information, the contribution from a dose of 13.3 mg/kg given at least eight hours earlier is estimated at ≤1 µg/mL according to the 3- and 6-µg/mL peak profiles generated by Lister et al. Another earlier is estimated at a distribution from a dose of 13.3 mg/kg given at least eight hours.

Second, there is a need to eradicate pathogenic bacteria from the middle ear rather than simply produce clinical improvement (clinical improvement alone may reflect the high natural spontaneous cure rate for AOM rather than an antibiotic’s effectiveness). A meta-analysis\textsuperscript{17} of 33 randomized trials involving 5400 children with AOM reported a spontaneous cure rate of 81% (95% CI, 69% to 94%) as part of the natural history of untreated AOM. Antibiotic therapy statistically raised this cure rate by only 13.7% (95% CI, 8.2% to 19.2%). The high spontaneous cure rate for AOM is the reason practitioners in the Netherlands and Scandinavian countries generally first treat AOM in children older than two years of age symptomatically with analgesics alone, reserving antibiotic therapy for patients whose AOM fails to resolve after three to four days.\textsuperscript{18–20} Conclusions about antibiotic efficacy for AOM based solely on either clinical improvement or bacteriologic eradication should be viewed with suspicion since they are not always correlated.\textsuperscript{21,22} Both should be distinct goals of antibiotic therapy for AOM and documented in clinical trials. Comparative trials using only clinical outcome criteria to assess efficacy between antibiotics have generally not demonstrated differences, quite possibly because they lacked adequate sample size or power. Larger sample sizes are necessary to show true clinical differences between two antibiotics, assuming they do exist. For example, assuming a power of 90% and an α of 0.05, one would need to enroll a total of at least 2054 subjects to confirm the suspicion that antibiotic A has 5% greater clinical efficacy than antibiotic B.\textsuperscript{23} The number of subjects required decreases, but only to 473, if a difference in clinical efficacy of 10% is assumed. Adequate funding for larger, solely clinically based outcome studies is usually difficult to obtain. Clinical coupled with bacteriologic outcome criteria may be more sensitive in detecting true differences between antibiotics and more acceptable for the funding agency.

Third, amoxicillin displays a favorable pharmacodynamic profile (i.e., longest time above MIC\textsubscript{90} for DRSP of any commercially available oral antibiotic).\textsuperscript{24} The pharmacodynamic profile of an antibiotic used for AOM is considered its ability to penetrate into and persist in MEF above the MIC of typical AOM bacteria. Antibiotics that exceed the MIC\textsubscript{90} of typical AOM bacteria in MEF for at least 40–50% and 60–70% of the dosing interval have been associated with bacteriologic eradication rates of 80–85% and approaching 100%, respectively. The time that an antibiotic persists at the site of action in a concentration greater than the MIC of a pathogenic organism is a surrogate marker of microbiologic and clinical efficacy that appears appropriate to use in selecting antibiotics that demonstrate concentration-independent killing (e.g., amoxicillin, cephalosporins).

Finally, amoxicillin has traditionally been a well-tolerated antibiotic, even at high dosages. No difference was detected in adverse effects among 274 children, aged three to 10 years, randomly allocated to receive either amoxicillin 125 mg three times daily for seven days or 750 mg twice daily for two days.\textsuperscript{25} Although no weights were reported...
for these patients, it is likely that some children receiving the higher dosage may have been taking approximately 75–100 mg/kg/d, assuming an average weight range of 15–20 kg for children three to six years old. Only one case of diarrhea was reported out of 43 infants and children with OM who received amoxicillin 150 mg/kg/d.26

SECOND-STEP: WHEN AMOXICILLIN INITIALLY FAILS

What is the recommended second-line therapy for AOM when high-dose amoxicillin appears to have failed? Controversy exists regarding recommendations made by various authors for antibiotics to treat AOM refractory to high-dose amoxicillin.8,15,27-29 The main controversy dwells on the need to provide coverage for DRSP if high-dose amoxicillin has already been prescribed. The traditional strategy has been to prescribe an oral antibiotic that is effective against β-lactamase–producing bacteria (but not necessarily DRSP), is dosed infrequently (usually once to twice daily), is low cost, and has acceptable palatability. However, some practitioners believe that this strategy may not be optimal in the present era of increasing prevalence of DRSP. Two bacteriologic studies30,31 highlight this dilemma.

Gehanno et al.8 identified S. pneumoniae in 67 of 170 bacterial isolates (39.4%) taken from 126 AOM patients in the Paris region who had failed prior oral antibiotics. The most frequently prescribed prior antibiotic was amoxicillin/clavulanate in 43% of cases. Reduced susceptibility to penicillin (MIC ≥0.125 µg/mL) was present in 52 of the pneumococcal isolates (77.6%).

Similarly, in Washington, DC, pneumococcus has been found to be responsible for approximately one-third of the bacterial isolates cultured from the MEF of children not responding to other oral antibiotics. Antibiotic resistance among these pneumococcal isolates was >60%.31 The CDC panel of experts8 believed that empirically prescribed second-line antibiotics should be effective against not only β-lactamase–producing H. influenzae and M. catarrhalis, but also DRSP. One exception to this dual-coverage guideline would be a culture of the MEF in which a single pathogenic bacteria was identified. In this case, antibiotic therapy could be definitively narrowed (as opposed to broad empiric therapy). For example, clindamycin is not effective against H. influenzae or M. catarrhalis, but is potentially very useful for culture-confirmed pneumococcal AOM, especially when caused by penicillin-resistant S. pneumoniae (PRSP).

The additional requirement for effectiveness against both DRSP and β-lactamase–producing bacteria is extremely limiting. Only three of the 16 systemic antibiotics presently approved by the FDA for OM32 are acceptable according to the CDC’s expert panel.8 The other systemic antibiotics (i.e., amoxicillin, trimethoprim/sulfamethoxazole [TMP/SMX], erythromycin/sulfisoxazole, azithromycin, clarithromycin, cefixime, cefetabuten, cefdinir, loracarbef, cefprozil, cefpodoxime, cefaclor, cepalexin) were not endorsed because of limited data showing these agents capable of eradicating DRSP from the middle ear and/or little β-lactamase coverage. The three antibiotics recommended by the expert panel include high-dose amoxicillin/clavulanate (presently requires additional prescription of amoxicillin to boost the dose to 80–90 mg/kg/d while limiting the clavulanate to ≤10 mg/kg/d), cefuroxime axetil, and intramuscular ceftriaxone (Table 1).

Amoxicillin/clavulanate 40 mg/kg/d in three divided doses has been suggested34 as the best oral antibiotic available for maximizing the time in which the concentration remains greater than the MIC (T > MIC) for the full spectrum of AOM bacteria (i.e., S. pneumoniae, H. influenzae, M. catarrhalis). The T > MIC for DRSP is increased by supplementing this usual dose of amoxicillin/clavulanate with a second prescription for additional amoxicillin. In the future, high-dose amoxicillin/clavulanate (90/6.4 mg/kg/d, twice daily) will likely be commercially available to facilitate adherence to and coverage of both β-lactamase–producing bacteria and DRSP.33

Cohen et al.34 found no difference in efficacy between a 10-day course of high-dose amoxicillin/clavulanate (80/10 mg/kg/d divided in 3 doses daily) and a single dose of ceftriaxone (50 mg/kg im) in the treatment of newly diagnosed patients with AOM in France (an area with a high rate of PRSP isolated from patients with AOM, >50% as of 1995). A weakness of the study is that tympanocentesis was not done to identify MEF bacteria, although culture and sensitivity tests using samples from nasopharyngeal swabs were performed prior to treatment and on days 12–14 to study the effect of treatment on bacterial carriage. No difference existed in the carriage of S. pneumoniae, M. catarrhalis, and H. influenzae between the two groups prior to treatment. The reduction of S. pneumoniae and M. catarrhalis carriage at days 12–14 was significantly greater for the amoxicillin/clavulanate group compared with the ceftriaxone group (42.6% vs. 14.9% and 47% vs. 12.9% reductions, respectively; p < 0.0001 for both). Amoxicillin/clavulanate has a high acquisition cost compared with older, low-cost antibiotics (i.e., amoxicillin, TMP/SMX, erythromycin/sulfisoxazole [Table 2]).35 Although diarrhea was a major problem with the original formulations of amoxicillin/clavulanate (4:1 ratio), the newer formulations (7:1) have substantially lessened this problem.36 The next generation of amoxicillin/clavulanate formulations (14:1) should maintain a similar reduced incidence of gastrointestinal problems since they should contain a similar amount of clavulanate per dose as the 7:1 formulations.33

Cefuroxime axetil was included as a viable second-line antibiotic by the CDC’s expert panel due primarily to one prospective study of children with pneumococcal AOM. Gehanno et al.37 treated 84 children with AOM with cefuroxime axetil 30 mg/kg/d in two divided doses for eight days. Treatment failure, defined as persistent signs of infection for >10 days (fever, otoscopic abnormalities, pain), occurred in three of 42 penicillin-susceptible (7%, MIC <0.1 µg/mL), one of 10 intermediate-resistant (10%, MIC 0.1–1.0 µg/mL), and eight of 32 highly resistant (25%, MIC ≥2.0 µg/mL) pneumococcal isolates. The failure to repeat tympanocentesis to verify bacteriologic eradication
and lack of a comparison/control group were methodologic weaknesses of this study.

In a double-blind taste comparison of 22 antimicrobial suspensions,\textsuperscript{38} cefuroxime axetil as well as oxacillin, dicloxacillin, cefpodoxime, and erythromycin/sulfisoxazole, were judged as having the worst aftertastes, which the authors believed could potentially jeopardize compliance. Cefuroxime also has a high acquisition cost relative to older, low-cost antibiotics (Table 2).\textsuperscript{38} When coverage of both \( \beta \)-lactamase-positive \( H. \text{influenzae} \) and DRSP is necessary, we recommend high-dose amoxicillin/clavulanate rather than cefuroxime (Table 3).\textsuperscript{38,39} Our selection is based on greater palatability; similar cost, even with the additional amoxicillin prescription (Table 2); and higher pharmacodynamic profile of amoxicillin against DRSP.\textsuperscript{24,35,38} The most recent commercially available amoxicillin/clavulanate formulations (7:1) should be prescribed at an amoxicillin/clavulanate dosage of 45/6.4 mg/kg/d; additional amoxicillin should be prescribed to boost the cumulative dosage to 80–90 mg/kg/d. Occasionally, some patients or caregivers find it too difficult to administer two antibiotics at the same time. In these cases, cefuroxime axetil is an appropriate choice.

Controversy exists as to what place the oral antibiotics excluded by the CDC’s expert panel\textsuperscript{a} should hold in AOM therapy. TMP/SMX has long been beneficial for treating AOM due to its twice-daily dosing schedule, lack of admixture requirement for the suspension, low cost (Table 2), and broad effectiveness against most middle ear pathogens.\textsuperscript{35} Recently, however, 11.9\% of all isolates of \( S. \text{pneumoniae} \) were found to be resistant to TMP/SMX (13.4\% and 40.4\% TMP/SMX resistance for penicillin intermediate- and highly resistant pneumococcal isolates, respectively).\textsuperscript{40} Even isolates of \( H. \text{influenzae} \) have been found to be resistant to TMP/SMX in up to 9\% of cases.\textsuperscript{41} Despite the concerns raised by results of in vitro studies, we are not aware of any randomized, comparative trial that demonstrates TMP/SMX to have less clinical and bacteriologic effectiveness than another antibiotic for initial treatment of AOM. In addition, no randomized, comparative trials of any antibiotics have been published addressing the treatment of AOM initially unresponsive to high-dose amoxicillin. Given the lack of comparison with other antibiotics and trends toward greater in vitro resistance, it is probably appropriate to reserve the use of TMP/SMX to special AOM situations, such as initial treatment of AOM in amoxicillin-allergic/intolerant patients who lack risk factors for DRSP (antibiotic use in the preceding month, age <2 y, day care attendance, recent hospitalization, infection during the late winter or spring), AOM refractory to at least a three-day regimen of high-dose amoxicillin where adherence was good or complete, and situations when high acquisition cost of the antibiotic is likely to result in the caregiver not filling the prescription.\textsuperscript{42}

Although AOM has traditionally been treated with a 10-day course of antibiotics, the evidence to support this dura-

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**Table 2. Selected Antibiotic Suspension Costs**

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Daily Dose (mg/kg/d)</th>
<th>Dollar Cost (optimal patient weights where no wastage occurs)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>0–5</td>
</tr>
<tr>
<td>Low cost</td>
<td></td>
<td>Weight Range (kg)</td>
</tr>
<tr>
<td>amoxicillin, HD (generic)</td>
<td>90</td>
<td>1.94 (4.2)</td>
</tr>
<tr>
<td>amoxicillin, SD (generic)</td>
<td>45</td>
<td>2.25 (4.4)</td>
</tr>
<tr>
<td>ery-sulf (generic)</td>
<td>50 (ery)</td>
<td>7.46</td>
</tr>
<tr>
<td>TMP/SMX (generic)</td>
<td>8 (TMP)</td>
<td>1.38 (3)</td>
</tr>
<tr>
<td>Moderate/high cost</td>
<td></td>
<td></td>
</tr>
<tr>
<td>amoxicillin/clavulanate, HD\textsuperscript{d}</td>
<td>90/6.4</td>
<td>18.80 (4.4)</td>
</tr>
<tr>
<td>amoxicillin/clavulanate, SD</td>
<td>45/6.4</td>
<td>16.55 (4.4)</td>
</tr>
<tr>
<td>azithromycin</td>
<td>10 (loading dose), then 5 once daily for 4 d</td>
<td>27.74</td>
</tr>
<tr>
<td>cefaclor (generic)</td>
<td>40</td>
<td>10.13 (4.7)</td>
</tr>
<tr>
<td>cefdinir</td>
<td>14</td>
<td>33.26</td>
</tr>
<tr>
<td>cefixime</td>
<td>8</td>
<td>32.85</td>
</tr>
<tr>
<td>cefpodoxime proxetil</td>
<td>10</td>
<td>18.11</td>
</tr>
<tr>
<td>cefprozil</td>
<td>30</td>
<td>15.26 (4.2)</td>
</tr>
<tr>
<td>cefixime</td>
<td>10</td>
<td>27.17</td>
</tr>
<tr>
<td>cefuroxime axetil</td>
<td>30</td>
<td>15.07 (3.3)</td>
</tr>
<tr>
<td>clarithromycin</td>
<td>15</td>
<td>16.13</td>
</tr>
<tr>
<td>loracarbef</td>
<td>30</td>
<td>15.07 (3.3)</td>
</tr>
</tbody>
</table>

\( \text{ery-sulf} = \text{erythromycin–sulfisoxazole} ; \text{HD} = \text{high dose} ; \text{SD} = \text{standard dose} ; \text{TMP/SMX} = \text{trimethoprim/sulfamethoxazole} .\)

\textsuperscript{a} Costs for treating infants and children within various weight ranges in 5-kg increments up to 20 kg, and ≥20 kg.

\textsuperscript{b} Average wholesale price (brand) or federal upper limit price (generic)\textsuperscript{6} for 10-day regimen at listed dose (azithromycin 5 d).

\textsuperscript{d} Dollar cost plus the optimal patient weight in parentheses (i.e., weight where no wastage occurs when given at listed dose for 10 d); dollar cost listed alone indicates the closest larger bottle size with the least wastage.

\textsuperscript{4} Requires two prescriptions, amoxicillin/clavulanate plus amoxicillin; lack of wastage based on amoxicillin/clavulanate.
tion is practically nonexistent and is probably more an extrapolation from the 10-day penicillin regimen used to treat streptococcal pharyngitis. A meta-analysis of 32 randomized, controlled trials of the treatment of AOM in children with antibiotics of different durations suggested the efficacy of a five-day course of antibiotic. Dowell et al. recommended that uncomplicated AOM (i.e., absence of perforated tympanic membrane, underlying medical conditions, chronic/recurrent OM) may be treated with a five-day course of antibiotics in children two years of age or older. Theoretical advantages to this shortened regimen include a reduction in selective pressure favoring resistant bacteria and greater adherence to therapy. We support the use of the five-day oral antibiotic regimen (high-dose amoxicillin included) for the initial treatment of uncomplicated AOM in children at least two years old. However, if the AOM fails to clear with the initial regimen, subsequent oral regimens should be ≥10 days long until resolution occurs (exception: azithromycin requires only 5 d of treatment). If the initial antibiotic chosen to treat AOM is standard-dose amoxicillin or TMP/SMX and symptomatic improvement (e.g., decreased ear pain, irritability, fever, sleeplessness, anorexia) together with a reduction in tympanic membrane inflammation, redness, bulging, and/or otorrhea have not occurred by day 3, resistant β-lactamase-producing H. influenzae and/or pneumococcus should be suspected. In this case, the second-step antibiotic chosen should cover both types of bacteria.

Disadvantages of the older macrolide/sulfonamide combination product erythromycin/sulfisoxazole include its requirement for dosing three to four times per day, potential for gastrointestinal upset, and unpleasant taste. As with TMP/SMX, the incidence of in vitro resistance of pneumococcus to erythromycin has increased in recent years. Advantages of erythromycin/sulfisoxazole for AOM include low cost and coverage of comorbid infections caused by atypical bacteria (e.g., Mycoplasma or Chlamydia pneumoniae). Neither erythromycin/sulfisoxazole, clarithromycin, nor azithromycin were recommended by the CDC’s expert panel due to concerns of resistance to pneumococcus (~10% of isolates), substantial cross-resistance with β-lactams, and the inability to overcome pneumococcal resistance by increasing the dosage. Other authors have expressed concern about potentially inadequate extracellular MEF concentrations of erythromycin, clarithromycin, and azithromycin to treat H. influenzae and have not recommended them as second-line agents for treatment of refractory AOM. Although these antibiotics concentrate intracel-

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### Table 3. Recommended Antibiotics for Treating AOM in Childrena

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Step 1</th>
<th>Step 2*</th>
<th>Step 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preferred</td>
<td>HD amoxicillin (80–90 mg/kg/d) or SD amoxicillin (40 mg/kg/d)*</td>
<td>TMP/SMX</td>
<td>HD amoxicillin/clavulanate* ceptraxone* or tympanocentesis</td>
</tr>
<tr>
<td>Alternative(s)</td>
<td>SD amoxicillin/clavulanate cefdinir* cepdinir* cefprozil* or cefuroxone axetil*</td>
<td>cefdinir* cefuroxime axetil*</td>
<td></td>
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<tr>
<td></td>
<td>-lactamase–positive H. influenzae and DRSP.</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Covers β-lactamase–positive Haemophilus influenzae.</td>
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<tr>
<td></td>
<td>Acceptable if low risk of DRSP (see text); failure of this antibiotic as the initial treatment of AOM warrants treatment with a second-step antibiotic that covers both β-lactamase–positive H. influenzae and DRSP.</td>
<td></td>
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<tr>
<td></td>
<td>Presently requires patient/caregiver adherence to the concomitant administration of amoxicillin/clavulanate (45/6.4 mg/kg/d) and amoxicillin to boost the cumulative dose to 80–90 mg/kg/d.</td>
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<tr>
<td></td>
<td>Three-dose regimen (50 mg/kg im once daily for 3 d).</td>
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<tr>
<td></td>
<td>Not clinically investigated for refractory AOM, although it possesses in vitro activity similar to that of cefpodoxime proxetil.</td>
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<tr>
<td></td>
<td>Taste may jeopardize compliance.</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Although questionable in vitro activity against β-lactamase–producing H. influenzae, no difference in clinical efficacy was seen in one study with AOM patients harboring β-lactamase–positive and –negative H. influenzae.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Reserve for possible comorbid atypical bacterial infections (prescribe ery-sulf, clarithromycin, or azithromycin) or concerns of caregiver/patient adherence (prescribe azithromycin).</td>
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</tr>
</tbody>
</table>

AOM = acute otitis media; DRSP = drug-resistant *Streptococcus pneumoniae*; ery-sulf = erythromycin–sulfisoxazole; HD = high dose; SD = standard dose; TMP/SMX = trimethoprim/sulfamethoxazole.

*Steps 2 and 3 indicated for clinical treatment failure after three days of antibiotic from prior step. Clinical treatment failure defined as lack of clinical improvement in signs and symptoms (e.g., ear pain, irritability, fever, sleeplessness, anorexia) together with tympanic membrane findings of inflammation, redness, bulging, or otitis.

*Steps 2 and 3 indicated for clinical treatment failure after three days of antibiotic from prior step. Clinical treatment failure defined as lack of clinical improvement in signs and symptoms (e.g., ear pain, irritability, fever, sleeplessness, anorexia) together with tympanic membrane findings of inflammation, redness, bulging, or otitis.

*Steps 2 and 3 indicated for clinical treatment failure after three days of antibiotic from prior step. Clinical treatment failure defined as lack of clinical improvement in signs and symptoms (e.g., ear pain, irritability, fever, sleeplessness, anorexia) together with tympanic membrane findings of inflammation, redness, bulging, or otitis.

*Steps 2 and 3 indicated for clinical treatment failure after three days of antibiotic from prior step. Clinical treatment failure defined as lack of clinical improvement in signs and symptoms (e.g., ear pain, irritability, fever, sleeplessness, anorexia) together with tympanic membrane findings of inflammation, redness, bulging, or otitis.

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ularly, the inflammatory cells in which they concentrate may be delivered in large amounts to the site of infection/inflammation (e.g., the inner ear).45

A recommendation has been made that macrolide/azalide antibiotics be considered for AOM refractory to amoxicillin.45 Clarithromycin and azithromycin have moderate patient acquisition cost; azithromycin is especially competitively priced for children weighing ≥20 kg (Table 2).38 Azithromycin has other advantages over erythromycin/sulfisoxazole and clarithromycin, that is, an extended half-life (30–60 h), permitting once-daily dosing for five days, relative lack of association with significant drug interactions, and better taste.38 Due to concern for inducing resistant H. influenzae and, especially, pneumococcal isolates from macrolide/azalide antibiotic overuse, we recommend that erythromycin/sulfisoxazole, clarithromycin, and azithromycin be reserved for situations when, despite good or complete adherence to high-dose amoxicillin, treatment failure has occurred, and either coverage of atypical bacteria for a comorbid infection is necessary or concerns of adherence by the patient/caregiver dictate that oral therapy for a short duration is warranted (azithromycin is recommended in this instance).

Loracarbef, cefaclor, and cefprozil have excellent tastes and may be administered, conveniently, twice daily.38 However, these antibiotics have acquisition costs in the moderate (cefaclor) to high range (Table 2).38 Among the three antibiotics, cefprozil appears to have the most in vitro activity against DRSP, with one noncomparative, open-label trial suggesting clinical effectiveness for children with persistent and recurrent AOM. Pichichero et al.39 treated AOM in 262 children aged six months to 12 years with cefprozil 30 mg/kg/d in two divided doses for 10 days. Eighteen percent of the children had persistent AOM (i.e., antibiotic used ≤7 d before study entry); 37% had recurrent AOM (i.e., ≥4 episodes/12 mo or ≥3 episodes/6 mo immediately preceding study entry). All children underwent tympanocentesis and had pretreatment cultures of the MEF performed. Subsequently, the clinical signs and symptoms of AOM were assessed by one telephone contact (days 3–6) and during two return visits (days 11–15 and 28–40).

Single and multiple bacterial pathogens were identified in 57% and 11% of the MEF samples, respectively. Satisfactory clinical responses in the children occurred in 13 of 14 with M. catarrhalis (93%), 56 of 75 with H. influenzae (75%), and 70 of 93 with S. pneumoniae (75%). There was no difference in the clinical success of patients harboring β-lactamase–positive (30/42, 71%) and β-lactamase–negative (26/33, 79%) H. influenzae. The clinical response rates for patients infected with penicillin-susceptible (MIC ≤0.06 µg/mL; 39/50, 78%), –intermediate-resistant (MIC 0.1–1 µg/mL; 11/12, 92%), and -resistant (MIC ≥2 µg/mL; 21/31, 68%) S. pneumoniae were similar to those reported from France by Gehanno et al.37 who used cefuroxime axetil to treat DRSP AOM. Both studies failed to include a comparison/control group and repeat tympanocentesis after completion of therapy.

A major concern when using loracarbef, cefaclor, and cefprozil for AOM refractory to high-dose amoxicillin is their in vitro coverage of H. influenzae. A recent US surveillance study of the activity of oral antibiotics against pneumococcus and H. influenzae used pharmacodynamically derived breakpoints to determine susceptibilities. For the β-lactams tested, the breakpoints for susceptibilities were based on drug concentrations in serum that maintained serum concentrations greater than the bacteria’s MIC for 40–50% of the dosing interval. It has not been determined whether this new susceptibility testing method should someday replace the method presently used by the NCCLS.9,10 Out of 1676 clinical isolates of untypable H. influenzae (41.6% of the isolates produced β-lactamase), the percentages of isolates reported susceptible to cefaclor, loracarbef, and cefprozil were 2%, 9%, and 14%, respectively, compared with 57%, 78%, 98%, and 100% for amoxicillin, cefuroxime, amoxicillin/clavulanate, and cefixime, respectively. Among 1476 strains of S. pneumoniae, over half (50.4%) were resistant, with roughly two-thirds of these (64.5%) displaying high-level resistance. The overall susceptibilities of all S. pneumoniae isolates were 11% (loracarbef), 22% (cefaclor), 52% (cefixime), 63% (cefprozil and cefuroxime), 69% (azithromycin and clarithromycin), and 94% (amoxicillin and amoxicillin/clavulanate).

This study highlights a disturbing trend — the increased resistance of key pathogens of AOM to antibiotics extensively used in the past for treating this infection. At present, the use of cefaclor and loracarbef for AOM refractory to high-dose amoxicillin seems difficult to support, unless sensitive bacteria have been identified. Cefprozil might be used in refractory patients whose adherence to high-dose amoxicillin was poor or incomplete, since the clinical response rate for DRSP appears similar to that of cefuroxime axetil.37,39 In addition, despite questionable in vitro susceptibility, the clinical response rate for β-lactamase–producing H. influenzae to cefprozil has not been proven to differ from β-lactamase–negative H. influenzae.38,46

The CDC’s expert panel report has been criticized for not giving greater consideration to advocating a second-step approach to AOM initially refractory to amoxicillin, which concentrates on β-lactamase–producing bacteria alone.28 Use of this approach assumes that good adherence to an adequate regimen of amoxicillin has occurred as the initial AOM step and, therefore, β-lactamase–producing H. influenzae or M. catarrhalis are the most likely bacteria to have persisted. TMP/SMX seems the most cost-effective choice with this approach unless palatability and/or adverse effects preclude its use, or the community in which the patient lives has a high incidence of resistance of H. influenzae to TMP/SMX. In vitro resistance rates to TMP/SMX of only 9.0% for H. influenzae and 6.5% for M. catarrhalis have been reported.47,48 Oral antibiotics considered as acceptable alternatives to TMP/SMX, albeit with greater acquisition costs, include standard-dose amoxicillin/clavulanate (45 mg/kg/d), cefuroxime, azithromycin, clarithromycin, erythromycin/sulfisoxazole, cefdinir, cef-
ixime, cefpodoxime, and cefditiben (Table 2). The last four antibiotics (third-generation cephalosporins) may be given once daily, have high acquisition costs (Table 2), and, with one exception (cefpodoxime), good taste.

Cefpodoxime and cefdinir have similar in vitro antibacterial activity to organisms including penicillin-susceptible and –intermediate-resistant *S. pneumoniae*, although neither antibiotic has been extensively evaluated in children with refractory AOM due to DRSP. Cefixime and cefditiben are less active against pneumococci, especially DRSP, than cefpodoxime and cefdinir.

**THIRD-STEP: CEFTRIAXONE AND TYMPOANOCENTESIS**

Presently, ceftriaxone is FDA-approved as only a single-dose regimen for the treatment of AOM. Studies of treatment with single-dose ceftriaxone are limited to patients with new AOM. The CDC panel of experts believed that this duration may not be sufficient to treat refractory AOM due to PRSP and advocated a three-day regimen of ceftriaxone (50 mg/kg/dose im once daily for 3 d). Three studies have investigated this regimen in patients who initially failed oral antibiotic therapy; however, comparison with the single-dose regimen occurred in only one of these studies.

Leibovitz et al. prospectively studied 92 pediatric patients with AOM who did not respond to treatment with either amoxicillin, amoxicillin/clavulanate, or cefaclor. MEF was collected prior to beginning the three-day ceftriaxone regimen and again on days 4 to 10. Among bacteria isolates recovered from the MEF, eradication occurred in 54 (100%) *H. influenzae*, 13 (100%) penicillin-susceptible pneumococcus, 28 of 34 (82%) penicillin–intermediate-resistant pneumococcus (MIC 0.1–1.0 µg/mL), one of two (50%) *M. catarrhalis*, and two (100%) *S. pyogenes* with treatment. Although all isolates of pneumococcus were susceptible to ceftriaxone (MIC <0.5 µg/mL), four cases of bacteriologic failure (defined by a positive culture on days 4–10) and two cases of relapse (defined as a recurrence of the same organism before the end of follow-up of 17 ± 2 d) occurred. All four patients who experienced bacteriologic failure of pneumococcus showed clinical improvement at three to five days and clinical cure at 10–12 days occurred in 88.9% of patients with PRSP. Ceftriaxone regimen (p = 0.009). Both group A and B patients were followed until day 30 ± 2 with no apparent difference evident in clinical (8 and 7 cases) and bacteriologic (6 and 4 cases, all with new pathogens) relapses, respectively. In conclusion, the three-day regimen was significantly superior to the one-day regimen in eradicating DRSP from the MEF of patients with nonresponsive AOM.

The CDC’s expert panel suggested that ceftriaxone might be used as second-line treatment for AOM initially refractory to high-dose amoxicillin. We believe that ceftriaxone regimens are probably better reserved as third-line treatment when both first- and second-line oral antibiotics have failed unless the risk of nonadherence to a five- to 10-day course of oral antibiotic appears very likely. Widespread use of ceftriaxone for mild infections such as AOM has the potential to select for resistant isolates, which could compromise ceftriaxone’s utility for moderate to severe infections. The three-day intramuscular ceftriaxone regimen has been shown to have superior bacteriologic eradication compared with the single-dose regimen. Ceftriaxone regimens that employ less-frequent dosing (e.g., every other day or every third day) or cumulative dosages (i.e., <3) may be just as effective but have not been evaluated. Two factors suggest that such regimens might be equally efficacious: concentration-independent killing of bacteria by cephalosporins, and high concentrations of ceftriaxone that are achievable and persist in MEF for extended periods. In one study, the maximum ceftri-
axone MEF concentration (35 μg/mL) from a single 50-
mg/kg intramuscular dose given to children with chronic
middle-ear effusion occurred 24 hours later and was
35–580 times higher than the MIC₉₀ for the three major
bacteria causing AOM, including PRSP. The estimated
half-life in the MEF was 25 hours, and the T > MIC₉₀ varied
between 100 and >200 hours depending on the bacte-
ria. Therefore, it might be possible to achieve the same lev-
el of bacterial eradication with fewer doses administered
over a more prolonged period. The effect on adherence of
ceftriaxone regimens employing fewer doses administered
less frequently also needs to be investigated. Until addi-
tional studies are done, the three-day ceftriaxone regimen
should generally be considered the preferred empiric third-
line treatment if tympanocentesis is not done.

The CDC’s expert panel⁸ suggested a diagnostic tympa-
nocentesis be done when treatment failures occur in pa-
tients who have recently received multiple courses of an-
tibiotics. Tympanocentesis is not a new or unique pro-
dure.⁷ It is our opinion that, presently, few primary care
physicians have been adequately trained to perform tym-
nocentesis. This lack of skilled training is probably the
result of decades when the standard practice to counteract
most AOM failures has been to treat empirically with a
different antibiotic rather than perform tympanocentesis.
Even manufacturers of antibiotics for AOM have voiced
difficulties in finding physicians willing to perform tympa-
nocentesis on children participating in studies.⁹ Undoubt-
edly, some physicians will remain reluctant to view tympa-
nocentesis as necessary. Physician concerns regarding
tympanocentesis may include the time and costs required
to perform it and the attendant bacteriologic studies, care-
giver/patient acceptance, liability in the event of a bad out-
come, and lost clientele should they choose to refer pa-
tients for tympanocentesis. Despite these concerns, we rec-
ommend tympanocentesis as a viable third-line option and
encourage physicians to improve their skills in this area.

In summary, we recommend high-dose amoxicillin for
initial empiric treatment of AOM in patients at risk of
DRSP (Table 3).¹⁰ If patient risk factors for DRSP appear
low, standard-dose amoxicillin or TMP/SMX are also ap-
propriate for initial therapy, although symptomatic failure
with either of these two regimens should warrant coverage
of both β-lactamase–positive H. influenzae and DRSP with
the next antibiotic prescribed. If failure occurs after three
days of good or complete adherence to high-dose amox-
icillin, β-lactamase–positive H. influenzae seems the most
likely organism, and we recommend TMP/SMX for treat-
ment. If there is a reason to avoid TMP/SMX in this situ-
ation, appropriate alternatives include standard-dose amoxicillin/clavulanate, oral third-generation cephalosporins, ce-
furoxime axetil, erythromycin/sulfisoxazole, azithromycin,
or clarithromycin. Poor or incomplete adherence to and
failure of high-dose amoxicillin as a first-step antibiotic
should prompt coverage for both β-lactamase–positive H.
influenzae and DRSP. We prefer high-dose amoxicillin/
clavulanate, provided the patient/caregiver can adhere to
the administration of two antibiotics at the same time. If
adherence seems to be a potential problem, cefdinir, cefpo-
doxime proxetil, cefprozil, or cefuroxime axetil can be
considered. We do not recommend loracarbef or cefaclor
for empiric treatment of AOM due to the array of antibiot-
ic alternatives available that have superior in vitro activity
and pharmacodynamic profiles. The three-day intramuscu-
lar ceftriaxone regimen is the preferred empiric third-step
choice. However, tympanocentesis-directed antibiotic ther-
apy is also appropriate at this point, and we advocate its
use although we suspect that, at present, few physicians
feel comfortable performing it. Given the present risks and
difficulties associated with treating AOM, renewed efforts
at prevention appear warranted.

**Prevention of Otitis Media**

**ANTIBIOTICS**

rAOM has been defined as three or more distinct
episodes of AOM in a six-month period, or four occur-
rences within a single year.⁵⁹ Prevention of rAOM is unar-
guageable superior to treatment after the fact, particularly
when the possible sequelae of hearing loss and potential
long-range learning disabilities are considered.⁶⁰,⁶¹ Continuous
 antimicrobial prophylaxis for rAOM has generally
been considered efficacious. The most commonly recom-
ended regimens have included oral amoxicillin 20 mg/kg/d
or sulfisoxazole 35–75 mg/kg/d given either once daily at
bedtime or in two divided doses.⁵⁸,⁶³

Several reports⁶⁴–⁶⁷ assessing prophylactic antibiotic effi-
cacy in children with rAOM have documented a two- to
threelfold reduction in AOM recurrences compared with
placebo. One study⁶⁸ reported no statistical difference in
recurrences between treatment and placebo groups, despite
use of amoxicillin 20 mg/kg/d. A 1993 meta-analysis of
nine studies⁶⁹ found an overall reduction of 0.11 AOM
episodes per patient per month (95% CI 0.03 to 0.19) at-
tributable to prophylactic antibiotic use. Considering the
outer ranges of the 95% CI reported, this suggests that the
prophylactic use of antibiotics could, on average, reduce
yearly occurrences of AOM by approximately 0.4–2.3
episodes per child.

These unimpressive results must be considered in light
of the documented emergence of DRSP. Baquero et al.⁷⁰
reported a clear and direct correlation between annual
aminopenicillin use and the incidence of S. pneumoniae re-
sistance. A recent Canadian study⁷¹ noted an increasing
prevalence of pneumococci with reduced susceptibility to
fluoroquinolones and postulated that this increase has oc-
curred secondary to selective pressure from increased use
of this antibiotic class. The use of prophylactic antibiotics
has been documented as a risk factor for nasopharyngeal
carriage of DRSP (p < 0.001).⁷² A meta-analysis⁷³ reported
that antibiotic use increases the risk of nasopharyngeal car-
riage of DRSP two- to fivefold. The importance of increas-
ing pneumococcal resistance patterns is highlighted by the
fact that penicillin-resistant species are, more often than
not, resistant to multiple antibiotics and β-lactams includ-
Compelling evidence of the dangers of prophylactic antibiotic overuse has been reported recently. In this study, nasopharyngeal cultures were obtained from children taking daily or every-other-day oral TMP/SMX prophylaxis for at least six weeks and were compared with those from children taking no antibiotics. While the overall S. pneumoniae colonization rate was similar in the two groups, increased resistance to penicillin and multiple antibiotics was identified more frequently in the prophylaxis group (82% vs. 7% for penicillin resistance, p value NR; 82% vs. 0% for multiple-drug resistance, p = 0.00001, respectively).

Overuse of antibiotics for AOM, rAOM, and OM with effusion is postulated to act as a natural selective pressure toward resistance. The use of strict criteria for patient selection has been advocated before prophylactic antibiotics are administered.

Given that >90% of AOM cases are preceded by a respiratory tract infection, intermittent dosing of prophylactic antibiotics seems rational. The evidence supporting intermittent versus continuous prophylaxis is equivocal, however. One study comparing oral administration of azithromycin 5 or 10 mg/kg/wk with amoxicillin 20 mg/kg/d over a six-month period reported that the recurrence rate with azithromycin 10 mg/kg/wk was significantly lower (p < 0.05) than with amoxicillin. Treatment with azithromycin 5 mg/kg/wk was terminated early, however, due to a high AOM recurrence rate (55.5%). The only head-to-head comparison of continuous versus intermittent AOM prophylaxis in children with rAOM compared oral amoxicillin 10 mg/kg/dose given twice daily either continuously for four months or at the first sign of an upper respiratory tract infection and continued for two weeks. Continuous amoxicillin therapy was found to be superior to intermittent prophylaxis. Seventy-three percent of the continuous prophylaxis group had no AOM episodes; 52% of the intermittent prophylaxis group remained free of recurrences (p value NR). Two groups of investigators compared intermittent prophylaxis in OM-prone children with placebo. Prellner et al. reported a 50% decrease (p = 0.025) in AOM recurrences compared with placebo when children were given prophylaxis with penicillin V 25 mg/kg twice daily for 10 days initiated at the first sign of a respiratory tract infection. Another group of investigators, using a similar study design, failed to show a statistical difference in AOM recurrences when comparing administration of placebo with amoxicillin/clavulanic acid 20 mg/kg orally given twice daily for seven days at the first appearance of symptoms of respiratory tract infection. Low sample size (n = 104) and shorter treatment time (7 vs. 10 d) may have contributed to the lack of observed effect in the latter study.

We support the criteria for antibiotic prophylaxis proposed by Paradise. Patients should meet the basic criteria for rAOM (at least 3 episodes of AOM during the preceding 6 mo or at least 4 occurrences within the preceding year). Some authors have cautioned against the use of sulfonamides for AOM prophylaxis on the basis of increased risk of severe cutaneous eruptions, blood dyscrasias, and hemolytic anemia in patients with glucose-6-phosphate deficiency. However, Gutman reviewed 14 studies using TMP/SMX in children and found that, of 2061 children treated for seven to 10 days, three (0.15%) discontinued therapy because of an adverse drug reaction, and all three reactions (rash, vomiting, leukopenia) subsided upon discontinuation. Current data confirm that serious hematologic, hepatic, and cutaneous reactions to sulfonamides are rare in children, and compare reasonably with the adverse effect profiles of many other antibiotics. Sulfisoxazole seems a rational first choice given its lengthy and convincing safety record, availability in liquid form, and some rather convincing data suggesting that, compared with amoxicillin, sulfisoxazole may be less likely to promote nasopharyngeal colonization with DRSP or β-lactamase-producing bacteria. Amoxicillin is a good alternative for patients allergic to sulfonamides. Azithromycin may be considered for prophylaxis in patients with sulfonamide allergies and a pathogen known to be resistant to amoxicillin or for patients allergic to both sulfonamides and β-lactams.

Intermittent dosing, although not proven superior to continuous prophylaxis, has nevertheless been documented to decrease recurrences of AOM by 50% and should be less likely to promote the selection and spread of resistant bacteria. Continuous antibiotic prophylaxis would probably also result in poor compliance when compared with intermittent prophylaxis, although this remains to be proven. The dosage recommended for antibiotic prophylaxis is generally half the usual therapeutic dosage and is given once daily, preferably at bedtime. We advocate a 10-day duration of prophylactic antibiotic therapy, regardless of the antibiotic chosen, based on the inferior results achieved in one study using the shorter course. Due to the nature of β-lactam resistance of pneumococci (alterations in penicillin-binding proteins that may be overcome by elevated β-lactam concentrations), the dosage of amoxicillin should depend on local prevalence of DRSP. If local resistance is low, we advocate the use of amoxicillin 20 mg/kg given orally at bedtime for 10 days, initiated at the first sign of a respiratory tract infection. If local pneumococcal resistance levels are known to be high, a dosage increase to 40 mg/kg/d for 10 days seems rational (this is still half the current recommended empiric therapy for AOM). Breakthrough episodes of AOM require an alternative antibiotic regimen. For example, if a child has been treat-
ed prophylactically at the first sign of a respiratory tract infection for at least three days and still has signs and symptoms of AOM (fever, fussiness, otalgia), it seems rational to recommend switching to a therapeutic dosage of an antibiotic with documented efficacy against DRSP and β-lactamase–producing *H. influenzae* and *M. catarrhalis*, such as high-dose amoxicillin/clavulanic acid, cefuroxime axetil, cefprozil, cefpodoximeproxetil, or cefdinir. Sulfonamides are not generally recommended after antibiotic treatment failure, due to diminished levels of TMP/SMX sensitivity reported in areas with a high prevalence of penicillin-resistant pneumococcus. When choosing an antibiotic, consideration should be given to knowledge of local levels of resistance as well as the patient’s risk factors and prior experience with antibiotics. Day care attendance, temperature >38 °C with signs of otalgia, age less than two years, and prior antibiotic therapy with erythromycin/sulfisoxazole have been documented as independently predictive risk factors for PRSP.

**SURGICAL OPTIONS**

Myringotomy and tympanostomy tube placement have been proposed as reasonable alternatives to repeated courses of antibiotics. Data comparing the efficacy of myringotomy or tympanostomy tube placement with chemoprophylaxis are sparse and equivocal; myringotomy has no demonstrable influence on the course of AOM. An increased incidence of retraction or atrophy of the tympanic membrane has been noted in patients who received myringotomy when compared with placebo controls. Gonzalez et al. compared tympanostomy tube insertion with sulfisoxazole 500–1000 mg given orally twice daily or placebo in 65 children with rAOM. These authors reported that tympanostomy tube placement significantly reduced treatment failures when compared with placebo (23% vs. 60%, respectively; p < 0.02). The sulfisoxazole prophylaxis group reported 38% treatment failures, but this was not significantly different from either the tympanostomy tube group or the placebo group. It is important to note that these results were confounded by inclusion of 18 patients (27.7%) who had OM with effusion. In a larger trial, tympanostomy tube insertion was compared with amoxicillin 20 mg/kg/d or placebo in 264 children aged seven to 35 months. This study used stricter rAOM inclusion criteria, excluding all patients with OM with effusion. Both tube placement and chemoprophylaxis proved superior to placebo for the prevention of AOM recurrences (p < 0.001 for tympanostomy tubes and p = 0.03 for amoxicillin, respectively). Due to a 3.9% incidence of persistent tympanic membrane perforations in the tympanostomy tube group, however, these authors advocated amoxicillin prophylaxis over tympanostomy tube insertion for rAOM prevention. We believe the inherent risks of anesthesia and eardrum perforation, atrophy, or retraction, as well as the lack of convincing clinical evidence, relegate myringotomy and tympanostomy tube placement as last-line therapy for rAOM prevention.

**ALTERNATIVE MEDICAL APPROACHES**

Concern regarding the spread of antimicrobial resistance has spurred interest in alternative medical approaches to AOM prevention, including the use of oligosaccharides and xylitol. In an interesting study, oligosaccharides administered intranasally prevented pneumococcal colonization of the nasopharynx of infant rats. The authors posited that oligosaccharides act as ligand homologs to inhibit adherence — the first step in the pneumococcal pathogenic process. If these results prove similar in human trials, oligosaccharides may be an innovative, easily administered agent for the prevention of AOM.

Xylitol, a sugar substitute, has been widely used in Europe for the prevention of *Streptococcus mutans*–mediated dental caries. While the mechanism is not clearly understood, xylitol 5% has been demonstrated in vitro to inhibit both the growth and epithelial cell adhesion of *S. pneumoniae*. Based on this information, Uhari et al. conducted two well-designed clinical trials investigating the usefulness of this compound in the prevention of AOM in young children attending day care centers. In the first trial, xylitol gum chewed five times daily (total 8.4 g/d) was well tolerated and achieved a 42% reduction in AOM episodes compared with sucrose-containing placebo gum (p < 0.04). The efficacy of xylitol was remarkably diminished in subjects who were noncompliant with the regimen, suggesting a dose-dependent effect. The second trial used a similar design to determine the efficacy of 8.4–10 g/d of xylitol gum, lozenges, or syrup (the latter dosage forms were included because gum is not appropriate for use in children <5 y old). The syrup and gum formulations of xylitol resulted in reductions in AOM recurrences of approximately 30% (p < 0.006) and 40% (p < 0.012), respectively, compared with placebo. Differences in AOM episodes between the lozenge formulation and placebo were not statistically significant. Lack of widespread availability (gum containing the requisite amount of xylitol is not commercially available in the US) and dosing five times a day will certainly limit the clinical usefulness of xylitol. However, further trials are certainly justified to document safety in children and to determine whether less frequent dosing, perhaps with dosage formulations containing higher concentrations of xylitol, could make this form of AOM prevention practical.

**VACCINE STRATEGIES**

*S. pneumoniae* is the most common bacterial cause of AOM; thus, it seems rational to expect that administration of a pneumococcal vaccine would reduce the incidence of AOM in children. However, the 23-valent unconjugated pneumococcal vaccine is a polysaccharide, which requires a T cell–independent antibody response in order to invoke immunity, a pathway that does not mature until the child is approximately two years old. Unfortunately, this is the population with the highest incidence and prevalence of AOM. Not surprisingly, administration of unconjugated
pneumococcal vaccine to infants has not been shown to decrease the incidence of OM.101

The concept of conjugating a polysaccharide vaccine to a protein carrier molecule to enhance immunogenicity has been proven successful with the Haemophilus influenzae B (Hib) vaccine. Current strategies have included conjugating seven to 11 of the 90 naturally occurring capsular S. pneumoniae polysaccharides to diphtheria or tetanus toxoid proteins or to other immunogenic proteins. The heptavalent conjugate vaccines promote immunity against 52–81% of invasive pneumococcal diseases in children, including 58% of the serotypes causing AOM.102-104 Five different formulations of heptavalent pneumococcal conjugate vaccines are currently undergoing Phase II or III clinical evaluations. Prevnar (a heptavalent pneumococcal vaccine conjugated to a nontoxic mutant diphtheria toxin CRM197) has recently become the first conjugate pneumococcal vaccine to obtain FDA approval for use in infants and young children.105 Wyeth-Ayerst Laboratories plans to pursue approval for 9- and 11-valent pneumococcal formulations.105

Considerable evidence exists in support of both the safety and immunogenicity of conjugate pneumococcal vaccines in children.106-108 Dagan et al.109 documented reduction of pneumococcal nasopharyngeal carriage by three- to fivefold compared with placebo in infants after immunization with tetravalent pneumococcal vaccines conjugated to tetanus or diphtheria toxoids (p = 0.014 and p = 0.001, respectively).

Data confirming the efficacy of conjugate pneumococcal vaccines in preventing AOM recurrences was published recently by the Kaiser-Permanente Vaccine Study Center.110 In this double-blind, multicenter trial, 37,868 healthy infants were randomized to receive either Prevnar or meningococcus type C CRM197 conjugate at two, four, six, and 12–15 months of age. The trial was terminated prematurely and unblinded on interim analysis when 97.4% efficacy was established for the prevention of invasive pneumococcal disease in children who were administered Prevnar (95% CI 82.7% to 99.9%; p < 0.0001). Compared with the meningococcal vaccine, Prevnar was 7.0% effective overall in the prevention of OM episodes (95% CI 4.1% to 9.7%; p value NR). The vaccine’s efficacy in preventing OM episodes increased from 9.3% to 22.8% as the frequency of OM episodes increased from three to five per six-month time period. Infants who received Prevnar were 20.1% less likely to require tympanostomy tube placement than the control group (95% CI 1.5% to 35.2%; p value NR).

The success of Prevnar in preventing invasive pneumococcal disease was tempered by its relatively unimpressive 7% overall efficacy in the prevention of OM. While the Kaiser-Permanente study110 provides some indication that the conjugate pneumococcal vaccine’s efficacy may be greater in pediatric patients with rAOM, early termination of the study prevented collection of further data that would have assisted in a cost–benefit analysis and identification of patients most likely to benefit from Prevnar. The high cost of the conjugate pneumococcal vaccine (~$300 for the 4-injection series) has sparked debate concerning the establishment of administration guidelines. The CDC’s Advisory Committee on Immunization Practices (ACIP) Vaccines for Children Program recently recommended the use of Prevnar for all infants and children at least six weeks of age through 59 months old.111 This resolution identified children at highest risk, as those with sickle cell disease or anatomic asplenia, chronic illnesses, immunocompromising conditions, or HIV infection. Groups at moderate risk were identified as toddlers 24–35 months old, children of African-American, Native American, and Alaskan Native descent, and children 35–59 months of age who attend out-of-home child care. The American Academy of Pediatrics (AAP) has released a policy statement112 recommending pneumococcal conjugate vaccination for all children ≤23 months of age. This statement also recommends vaccination for all children 24–59 months of age at high risk for invasive pneumococcal disease.

The prospect of effective immunization for the prevention of OM is especially promising for treatment of rAOM, because these children often have lower concentrations of immunoglobulin (Ig) G against certain pneumococcal antigens.113 In a study performed by Breukels et al.,114 five children with rAOM and a poor IgG response were immunized with heptavalent conjugated pneumococcal vaccine, followed by injection of the 23-valent polysaccharide vaccine six months later. The unconjugated booster response was dramatic, resulting in an 11.5- to 163-fold increase in IgG2 antipolysaccharide antibody titers. Hopefully, larger studies will clearly delineate the role of the 23-valent unconjugated pneumococcal product, if any, as a booster vaccine in rAOM.

Some rather dramatic enhancements in mouse T cell reactivity to pneumococcal antigens have been reported,115 using heat shock proteins as highly immunogenic conjugate molecules. Another animal study116 noted successful oral immunization of mice with an S. pneumoniae polysaccharide conjugate vaccine in enterically coated microparticle form. Further research identifying alternative dosage forms as well as the best protein for polysaccharide conjugation is certainly on the horizon.

The role of respiratory viruses in the etiology of AOM has been highlighted by two recent reports.117,118 Heikkinen et al.117 reported MEF prevalence rates of 74%, 52%, and 42% for respiratory syncytial, parainfluenza, and influenza viruses, respectively, isolated from children with AOM. Some children in this study had concomitant bacterial and viral infections; all eight of the children with positive S. pneumoniae cultures also had influenza virus in their MEF. Pitkaranta et al.118 used a reverse transcription polymerase chain reaction assay to detect viral RNA in nasal aspires and middle ear effusions from children with AOM, and found evidence of infection by human rhinovirus, respiratory syncytial virus, and human coronavirus in 35%, 28%, and 17% of patients, respectively. Overall, 48% of middle ear effusion samples showed evidence of viral RNA.
Three trials\textsuperscript{119-124} have been conducted assessing the efficacy of influenza vaccine in reduction of AOM episodes in children. All three trials reported overall reductions in AOM incidence from 30–36\% compared with placebo (2 studies\textsuperscript{126,121} reported p values ≤0.02; 1 study\textsuperscript{119} did not report a p value). Not surprisingly, Clements et al.\textsuperscript{120} discovered that the greatest protection against AOM occurred during flu season. The report by Belshe et al.\textsuperscript{131} is particularly interesting because the influenza vaccine was administered intranasally; this dosage form may become preferable to intramuscular injection in the pediatric population.

Influenza vaccine has not traditionally been considered part of the prophylaxis guidelines for rAOM. However, given substantial evidence for viral etiology and pathogenesis of AOM,\textsuperscript{122} documented immunization efficacy in reducing AOM recurrences, and established safety of influenza vaccine in the pediatric population,\textsuperscript{123} it seems rational to consider viral immunization yearly (in October–November) in addition to the conjugate pneumococcal vaccine for children with severe, documented rAOM that worsens in the winter months.\textsuperscript{32} White et al.\textsuperscript{124} recently estimated a net cost savings of $35 per child who was vaccinated in a group-based vaccination scenario. These cost savings were derived primarily from averted indirect costs (e.g., missed work). Prevention of potential episodes of OM was not included in the calculations, a factor that would certainly increase the estimated dollar savings. Further research and development of vaccines against respiratory syncytial virus and parainfluenzae virus are needed.

Summary

We support the CDC’s expert panel\textsuperscript{4} guideline to initially treat children with AOM who are at risk of DRSP with high-dose amoxicillin (standard-dose amoxicillin is acceptable in the absence of risk factors for DRSP). In the event of failure and poor or incomplete adherence, we recommend switching from high-dose amoxicillin to second-step antibiotics that include coverage of both DRSP and β-lactamase–producing bacteria. In this situation, we recommend high-dose amoxicillin/clavulanate, provided that adherence to the concurrent administration of two separate preparations would not be too difficult for the patient or caregiver to achieve. TMP/SMX is our preferred second-step antibiotic if adherence to at least three days of high-dose amoxicillin appeared to be good or complete. The three-day regimen of intramuscular ceftriaxone should be reserved for third-step therapy unless nonadherence to a 10-day course of oral antibiotic seems likely. The three-day ceftriaxone regimen employs less frequent dosing and cumulative dosages. Tympanocentesis-directed antibiotic therapy is also appropriate, and we support its use as a third-step management option; however, there are few physicians who feel comfortable performing tympanocentesis. Efforts to prevent rAOM seem more consequential when one considers the difficulties in changing the treatment of refractory AOM from a largely empiric approach to a more definitive approach involving the increased frequency of use of tympanocentesis.

As healthcare providers, we have been trained and pressured to cure disease with drugs. The concept of disease prevention is often presented last in our pharmaceutical care paradigm, when it actually is the most powerful weapon in our therapeutic armamentarium. In this era of reduced sensitivity to existing antibiotics, it is essential to realize that antimicrobial prophylaxis of rAOM is not the only option. The potential short-term benefits of prophylactic antibiotic use must continuously be weighed against the risks of furtherance and spread of antibiotic resistance.\textsuperscript{42} Practicality may dictate a stepwise approach to rAOM prevention and therapy (Table 4).\textsuperscript{125-129}

Established modifiable risk factors for AOM include lack of breast feeding,\textsuperscript{125,126} exposure to environmental smoke,\textsuperscript{126,127} pacifier use,\textsuperscript{124,128} and day care in large group settings.\textsuperscript{126,129} We consider the nonpharmacologic risk factor reduction approach to be first line.

<table>
<thead>
<tr>
<th>Table 4. Algorithm for Prevention of AOM*</th>
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<tr>
<td>First line environmental modifications</td>
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<tr>
<td>encourage breast feeding for at least 3 mo\textsuperscript{125,126}</td>
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<tr>
<td>reduce exposure to environmental smoke\textsuperscript{126,127}</td>
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<tr>
<td>minimize pacifier use\textsuperscript{136,128}</td>
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<tr>
<td>discourage child care in large group settings\textsuperscript{126,129}</td>
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<tr>
<td>Second line immunizations</td>
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<tr>
<td>conjugate pneumococcal vaccine\textsuperscript{a}</td>
</tr>
<tr>
<td>influenza vaccine for children ≥6 mo old\textsuperscript{b}</td>
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<tr>
<td>pneumococcal vaccine for children ≥2 y old\textsuperscript{c}</td>
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<tr>
<td>Third line drug therapy</td>
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<tr>
<td>xylitol gum or syrup\textsuperscript{d}</td>
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<tr>
<td>intermittent antibiotic prophylaxis\textsuperscript{e}</td>
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<tr>
<td>Fourth line surgical interventions</td>
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<tr>
<td>myringotomy/tympanostomy tube placement</td>
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<td>adenoidectomy</td>
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AOM = acute otitis media.

\textsuperscript{a}Indicated for all children less than two years old. Conjugate pneumococcal vaccine is also indicated for children under the age of five years with sickle cell anemia, HIV, or chronic diseases, or who are immunocompromised, as well as for children of African-American, Native American, or Alaskan Native descent. Administration should be considered in children under age five with recurrent otitis media, those who are socially or economically disadvantaged, and those who participate in large group day care.

\textsuperscript{b}Consider in cases of severe recurrent acute otitis media, which historically occur or worsen in the winter/early spring months. Use the split (subvirion or purified surface antigen) vaccine, not the whole virus vaccine in children younger than 12 years.

\textsuperscript{c}Use only if conjugate vaccine not available.

\textsuperscript{d}Not available in the US.

\textsuperscript{e}Only if three or more episodes in six months or four or more episodes in 12 months. Consider sooner in children who are immunocompromised or who have concurrent disease states exacerbated by recurrent acute otitis media (e.g., diabetes, asthma). Therapy should begin at the first sign of an upper respiratory tract infection and continue for 10 days.
At present, immunization with pneumococcal conjugate vaccine holds the most hope for control of recurrent pneumococcal AOM. We support the use of this vaccine per ACIP guidelines for the prevention of rAOM, with consideration given to the use of influenza vaccine for cases of rAOM, which historically worsen during the flu season (Table 4).

Sulfisoxazole prophylaxis should be reserved for children who are immunocompromised, have concurrent disease states exacerbated by AOM, and for children with three or more documented episodes of AOM in six months or at least four occurrences in 12 months despite conjugate pneumococcal and influenza vaccination. Therapy should be intermittent, beginning at the first sign of an upper respiratory tract infection and continued for 10 days. Alternative prophylactic agents for children who have sulfonamide allergies or who harbor resistant organisms include amoxicillin and azithromycin.

The potential for psychological trauma, invasive nature, and risks of anesthesia relegate myringotomy, tympanostomy tubes, and adenopectomy to last-line therapies for rAOM.

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60. Sniadack DH, Schwartz B, Lipman H, Bogaerts J, Butler JC, Dagan R,
**RÉSUMÉ**

**OBJECTIF :** Revoir et résumer les nouvelles tendances et progrès dans le traitement et la prévention de l’otite moyenne.

**SOURCE DE DONNÉES :** Une recherche informatisée MEDLINE (janvier 1996 à mars 2000) a été réalisée pour identifier les articles pertinents. Les références de ces articles ont aussi été révisés si jugées d’intérêt.

**SÉLECTION DES ÉTUDES ET EXTRACTION DES DONNÉES :** Les articles de langue anglaise concernant le traitement et la prévention de l’otite moyenne aiguë (OMA) ont été inclus. Les articles se concentrant exclusivement sur l’otite moyenne avec effusion ou l’otite sèche et l’otite moyenne chronique avec suppuration ont été exclus. Les informations concernant la prévention et le traitement médicamenteux ont été revues, avec accent porté sur les progrès réalisés les deux dernières années.

**RÉSUMÉ :** Récemment, un panel d’experts recommandait l’utilisation de seulement trois des 16 antibiotiques systémiques approuvés par l’Administration des Drogues et Alimentaires (FDA) pour le traitement de l’OMA : l’amoxicilline, le céfuroxime axetil, et le céftriaxone. Des controverses existent sur l’importance de la sélection des facteurs clés utilisés par le panel d’experts dans la détermination des antibiotiques à recommander dans l’algorithme de traitement c’est à dire les données in vitro, les profils pharmacodynamiques et la nécessité de couvrir les organismes résistants à la médication tel que le Strep-tococcus pneumoniae à chaque étape du traitement empirique. Des facteurs additionnels de sélection des patients et des antibiotiques utiles pour individualiser la thérapie incluent l’efficacité clinique, les effets adverses, la fréquence et la durée de l’administration, le coût, et les ramifications si une résistance bactérienne se développe à l’antibiotique choisi. Un algorithme de traitement à trois paliers pour les OMA réfractaires composé d’amoxicilline, de triméthoprim-sulfaméthoxazole ou de doses élevées d’amoxicilline/acide clavulinique (en fonction de la dose antérieure et de l’adhésion à l’amoxicilline), le céftriaxone ou une tympanocentèse à l’étape 1, 2 et 3, respectivement, apparaît rationnel et coût-efficace. La récente recrudescence dans la résistance antimicrobienne est soulignée et des recommandations sont présentées pour le traitement et la prévention des OMA récurrentes (OMAR).

**CONCLUSIONS :** L’amoxicilline demeure l’antibiotique de choix pour le traitement empirique initial de l’OMA même si la dose traditionnelle devrait être augmentée chez les patients à risque d’un Strep-tococcus pneumoniae résistant au médicament. Dans les cas réfractaires aux hautes doses d’amoxicilline, le triméthoprim/sulfaméthoxazole devrait être prescrit si l’adhésion semble bonne et complète, ou de hautes doses d’amoxicilline/acide clavulinique si l’adhésion était incomplète ou questionnable. Le céftriaxone devrait être réservé en troisième ligne. L’augmentation de la prévalence des résistances médicamenteuses face au Strep-tococcus pneumoniae met l’accent sur l’importance de développer des approches médicales alternatives pour la prévention de l’OM, de même que l’usage judicieux d’antibiotiques dans des cas établis. Le retrait des facteurs de risque modifiables devrait être une première ligne de thérapie pour la prévention de l’OMAR. Nous supportons l’utilisation du vaccin antipneumococcique conjugué selon les guides d’utilisation de l’ACIP pour la prévention de l’OMAR et considérons l’utilisation du vaccin contre l’influenza pour les cas d’OMAR avec histoire de déterioration pendant la saison des grippes. Une prophylaxie au sulfaméthoxazole devrait être réservé aux enfants immunocompris, avec des pathologies concomitantes exacerbées par l’OMA et pour les enfants qui rencontrent les critères d’OMA malgré une vaccination antipneumococcique et contre l’influenza. La thérapie doit être intermittente débutant aux premiers signes d’une infection respiratoire haute et doit être poursuivie pour une période de 10 jours. La nature invasive et les risques de l’anesthésie relèvent la myringotomie, les tubes de tympanostomie, et l’adenoidectomie comme thérapies de derniers recours pour l’OMAR.

Chantal Guévrémont

**Fuentes de información :** Se hizo una búsqueda en el sistema de búsqueda de información MEDLINE de enero del 1996 a marzo del 2000 para identificar los artículos relevantes. Las referencias de dichos artículos también se revisaron si se juzgaban importantes.

**Extracción de datos :** Se incluyeron artículos de la literatura primaria y de revisión en el idioma inglés enfocándose en la prevención y tratamiento de otitis media aguda (OMA). Se excluyeron estudios cuyo foco exclusivo era otitis media con efusión o seroso u otitis media crónica supurativa. Se revisó la información concerniente a la prevención y terapia con fármacos con énfasis en los avances hechos en los últimos dos años.

**Síntesis :** Recientemente un panel de expertos del Centro para el Control y Prevención de Enfermedades (CDC) recomendó el uso de solo tres de 16 antibióticos sistémicos aprobados por la Administración de Drogas y Alimentos (ADA). Estos son amoxicilin, cefuroxime axetil, y ceftriaxone. Existe una controversia de la importancia de los factores de selección claves utilizados por el panel de expertos para determinar cuál antibiótico recomendar en un algoritmo de dos pasos, la interpretación de datos de pruebas in vitro, perfiles farmacodinámicos, y la necesidad de cobertura para Estreptococcus pneumoniae resistente a fármacos en todos los pasos del tratamiento empírico. Algunos factores útiles para la selección antibiótica de acuerdo a las individualidad del paciente y el tipo de infección incluyen: eficacia clínica, efectos adversos, frecuencia de la dosis y duración del tratamiento, sabor, costo, infecciones concomitantes, y consecuencias del desarrollo de resistencia con el antibiótico escogido. Otra consideración importante al seleccionar la terapia es el historial de adherencia a la terapia por parte del paciente y los que le cuidan (especialmente si ha habido falla de la terapia). Un algoritmo de tres pasos para OMA refractaria que emplea amoxicillín, trimetroprim-sulfametoxazole o amoxicillín-clavulanato en dosis altas (dependiendo de la dosis anterior y adherencia al amoxicillín), y ceftriaxone o timpanoontesis en los pasos 1, 2 y 3, respectivamente, parece una estrategia racional y costo-efectiva. Se enfatiza el surgimiento reciente de resistencia antimicrobiana, y se presentan recomendaciones para la prevención y tratamiento de OMA recurrente.

**Conclusiones :** Amoxicillín permanece como el antibiótico de elección inicial empírico, aunque la dosis debe ser mayor que la tradicional en los pacientes en riesgo de adquirir Estreptococcus pneumoniae resistente a fármacos. En casos refractarios a dosis altas de amoxicillín donde la adherencia al tratamiento se considera buena, se debe prescribir trimetroprin/sulfametoxazol. Si la adherencia al tratamiento fue incompleta o cuestionable, se recomienda amoxicillín-clavulanate en dosis altas. Se debe reservar ceftriaxone como un agente de tercera línea. El aumento en la prevalencia de cepas de Estreptococcus pneumoniae resistentes a medicamento enfatiza la importancia de estrategias alternas para la prevención de otitis media así como el uso juicioso de antibióticos. La primera línea de terapia debe ser la remoción de factores de riesgo modificables para prevenir OMA recurrente. Aportamos el uso de la vacuna conjugada de pneumocooco según las guías del Comité Consultor para Prácticas de Inmunización del CDC para la prevención del OMA recurrente, y que se considere la vacuna de influenza para los casos de OMA recurrente que históricamente empeoran durante la época del flu. La profilaxis con sulfisoxazole debe reservarse para niños inmunocomprometidos que tienen condiciones que se exacerban por OMA y para aquellos niños que retienen los criterios de OMA recurrente aún después de ser vacunados contra influenza y pneumocooco. La terapia con sulfisoxazole debe ser intermitente, comenzando el tratamiento al detectar las primeras señales de infección respiratoria superior y debe continuar por un período de 10 días. La naturaleza invasiva y riesgos de la anestesia relejan la myringotomía, los tubos de timpanostomía, y la adenoidectomía a considerarse las terapias de última opción para OMA recurrente.

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