Treatment of Acute Otitis Media Consensus Recommendations

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Summary: The objective of this paper is to provide consensus recommendations for the management of acute otitis media (AOM) that pediatricians can incorporate into their daily practices. These recommendations were developed during a roundtable meeting that convened clinicians versed in the management of AOM. This meeting was sponsored by an educational grant from SmithKline Beecham Pharmaceuticals. In addition, clinical studies on AOM identified via MEDLINE search were considered in the development of these recommendations. The Drug-Resistant Streptococcus pneumoniae Therapeutic Working Group guidelines for the management of AOM are reviewed in detail. All of the articles identified from the data sources were evaluated and all information deemed relevant was included in this review. AOM is one of the most common infectious diseases affecting infants and children and one of the leading causes of office visits and antibiotic prescriptions for this population. The incidence of AOM has increased during the past 25 years, probably the result of an increased utilization of day care facilities in the United States. The predominant pathogens in AOM include *S. pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*. The high prevalence of drug-resistant *S. pneumoniae* and β-lactamase–producing organisms presents a clinical challenge for practitioners in the selection of empiric antimicrobial therapy. Pharmacokinetic/pharmacodynamic principles should be considered in addition to minimum inhibitory concentrations in selecting antibiotics for AOM. Amoxicillin at conventional or high doses (80–90 mg/kg/day) remains an appropriate choice for first-line therapy for AOM. For patients in whom amoxicillin is unsuccessful, second-line therapy should have demonstrated activity against penicillin-resistant *S. pneumoniae* as well as β-lactamase–producing pathogens. Appropriate options for second-line therapy include high-dose amoxicillin/clavulanate (90 mg/kg/day based on the amoxicillin component) and ceftriaxone. Cefuroxime has been suggested as a second-line agent in the past, but recent surveillance data suggest it may no longer be active against penicillin-resistant strains of *S. pneumoniae*. Tympanocentesis is useful for
Introduction

Acute otitis media (AOM) is the most common bacterial respiratory tract infection in the pediatric population, and it is the most frequent reason for which antibiotics are prescribed to children in the United States. This condition is associated with substantial morbidity and medical costs in infants and young children. Despite the numerous clinical studies on AOM, a great deal of variability exists as to the optimal management for this condition. Acute otitis media is overdiagnosed and antibiotics are prescribed for a substantial proportion of patients in whom they are not beneficial. Because the use of antibiotics has been implicated in the selection and progression of resistance among upper respiratory tract pathogens (i.e., Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis), prescribing of antibiotics for children who do not have bacterial disease carries a risk of resistance without the benefit of an improved clinical outcome. Accordingly, a concerted effort has been established throughout the past few years to promote the judicious use of antibiotics.

A roundtable meeting was recently convened to provide a forum for experts in the fields of infectious disease and pediatrics to discuss the relevant issues and controversies surrounding the management of AOM. The purpose of this meeting was to comprehensively review the management of patients with AOM. This paper will provide a broad review of AOM and summarize the conclusions and recommendations of the roundtable participants.

Epidemiology

Otitis media is one of the most frequently diagnosed infections among children in the United States. The peak incidence occurs during the first 2 years of life, particularly between the ages of 6 and 12 months. Infants are more susceptible to developing AOM compared with older children and adults because of anatomic features unique to this age group (e.g., characteristics of the eustachian tube, such as shortened length, horizontal position, and high compliance). Immunologic factors, including a limited response to antigens and lack of previous exposure to common bacterial and viral pathogens, also may predispose children to episodes of AOM.

Studies in the past decade have reported as much as a fourfold increase in the incidence of OM between 1975 and 1990 (Figure 1). Prospective cohort studies have demonstrated that 60% to 70% of children will experience at least 1 episode of AOM in the first year of life. By age 7, 93% of children will have experienced 1 or more episodes of OM. Further adding to the burden of illness are data that suggest the prevalence of recurrent episodes is also increasing. These trends emphasize the importance of improving the accuracy of diagnosis as well as the treatment of AOM. A higher incidence of OM suggests the need for greater antibiotic use; however, excessive antibiotic use for patients in whom they are not necessary promotes antimicrobial resistance. Thus, the importance of differentiating patients with AOM, who are likely to benefit from antibiotic therapy, from those with otitis media with effusion (OME) cannot be overemphasized.

Certain factors increase the risk for experiencing episodes of AOM or recurrent AOM, including gender (male predominant), ethnic background (Native Amer-
ican or Alaskan and Canadian Inuit), socioeconomic status (inverse relationship), day care attendance (e.g., any setting outside the home where a child regularly spends ≥4 hours per week with at least 2 unrelated children under adult supervision), lack of breast feeding, and exposure to tobacco smoke. In addition, certain factors also predict the likelihood of infection with a resistant pathogen, including prior exposure to antibiotics, day care attendance, time of year, and patient age. A study by Block and colleagues demonstrated the increased risk of developing penicillin-resistant *S. pneumoniae* (PRSP) after a child receives multiple courses of antibiotics. Following antibiotic treatment, the proportion of PRSP increases dramatically and can persist for weeks to months.

Of these risk factors, day care attendance is playing an increasingly important role. The proportion of US children younger than 5 years of age attending day care has increased substantially during the past decade. Children attending day care have more frequent respiratory infections, more days of illness, more severe illnesses, and increased hospitalization rates for myringotomy and tube placement than children in home care. Because of their increased risk of infection, children in the day care setting are more likely to receive antibiotics at any given time, increasing the possibility of the selection of resistant organisms. A point prevalence survey of more than 1,200 children in child care centers found that 10% were currently receiving antibiotics and that nearly 30% had received antibiotics in the previous month. The increased risk of illnesses associated with these children may extend to their household contacts and to those in intimate contact through nontraditional day care settings (e.g., church nursery, play groups) as well, further compounding the problem. Together, the risk factors for AOM and for infection with resistant pathogens may be used to identify patients who are candidates for preventive measures (e.g., vaccination) or more aggressive antibiotic therapy for cases of AOM (e.g., an agent typically reserved for use as second-line therapy).

Young children (6 months to 4 years) who attend day care and who are frequent sufferers of upper respiratory infections may need to be categorized separately from other children with AOM because of their unique risk circumstances. These patients may require a more tailored approach to therapy, which includes treatment with adjunctive therapies and antibiotics that cover resistant pathogens.

**Consensus Roundtable Summary**

- Based on the available data, it appears that the incidence of AOM is increasing, which is a clinical concern for several reasons. Excessive antibiotic use has contributed to the progression of resistance, and an increasing incidence of AOM suggests the need for greater antibiotic consumption. This
underscores the need to improve the accuracy of the diagnosis of AOM and to avoid the use of antibiotics in children for whom they are unnecessary.

- Certain patient characteristics correlate with an increased risk of experiencing AOM and the risk of infection with a resistant pathogen. Practitioners should be aware of these factors in order to identify patients who would be appropriate candidates for preventive measures and/or more aggressive antimicrobial therapy that is active against resistant pathogens.

**Pathophysiology**

Although the pathogenesis of AOM is multifactorial, disruption of the physiologic function of the eustachian tube (ET) is believed to be an important underlying event (Figure 2). The 3 physiologic functions of the ET with respect to the middle ear include the following: (1) pressure regulation, which balances gas pressure in the middle ear with atmospheric pressure; (2) protection from nasopharyngeal pressure and secretions; and (3) clearance of secretions from the middle ear into the nasopharynx. Impairment of these functions can result in a middle ear effusion, which establishes an environment that is conducive to bacterial growth. If the effusion persists and drainage and aeration are not restored, AOM can ensue. The antecedent event in the majority of cases of AOM is a viral upper respiratory tract infection, which causes inflammation of the mucosa of the upper respiratory tract—including the nasopharynx and ET. Mucosal inflammation causes ET dysfunction, and negative middle ear pressure can develop. Again, if ET function is not restored and bacteria remain in the middle ear cavity, the end result often is AOM. Anatomic abnormalities, including nasal obstruction, palatal dysfunction, or allergies, also may affect ET function, resulting in AOM.

There have been no recent developments to challenge this classic view of the etiology and pathophysiology of AOM. *S. pneumoniae* clearly has been identified as the most frequently occurring pathogen in AOM. This pathogen has received much attention over the past few years because of dramatic increase in the prevalence of antimicrobial resistance. Of the 3 predominant pathogens, *S. pneumoniae* is the least likely to resolve spontaneously without treatment.

**Consensus Roundtable Summary**

- Disruption of ET function is a primary underlying event in the pathogenesis of AOM. Viral upper respiratory tract infection generally is the antecedent event that causes mucosal swelling and ET dysfunction.
- Organisms that colonize the nasopharynx may be aspirated into the middle ear as a result of the ET dysfunction. These organisms, in the milieu of mucosal congestion or middle ear effusion, can proliferate and cause AOM.

![Figure 2](image_url)
Diagnosis

Otitis media is a general term used to describe inflammation of the middle ear. This inflammation may be attributable to an acute infection, resulting in symptoms such as pain, discomfort, and/or fever, or to a chronic condition with or without symptoms. It is important to classify otitis media clinically as either AOM or OME; antibiotics are beneficial for AOM but are not indicated for OME because they are, at most, only minimally effective. However, the distinction between these 2 conditions is subjective and often varies among practitioners. Furthermore, these 2 manifestations of otitis media may be considered segments of a disease continuum. In other words, OME may be the aftermath of AOM, or a new episode of AOM may occur in a patient with established OME.

An accurate diagnosis is imperative to ensure that antimicrobial therapy is prescribed to the appropriate patients, which in turn, increases the likelihood of achieving optimal outcomes and minimizing the impact on resistance. Using stringent diagnostic criteria enables differentiation of patients with AOM from those with OME. Accordingly, a systematic approach should be used in evaluating patients with symptoms of AOM (Figure 3). On pneumatic otoscopy, a diagnosis of OME can be established if there is evidence of middle ear effusion without any signs of acute inflammation that would suggest the presence of infection. The presence of a middle ear effusion is evidenced by tympanic membrane abnormalities (abnormal color, including white, yellow, amber, or blue; opacification other than that due to scarring; and decreased or absent mobility), or by bubbles or air-fluid interfaces. Hearing loss is the predominant symptom associated with OME; however, in infants and children, this symptom can often go unnoticed.

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pain and/or marked redness or distinct fullness or bulging of the tympanic membrane are noted in addition to evidence of middle ear effusion. However, redness alone is a poor indicator of AOM. In infants and young children, unaccustomed tugging or rubbing of the ear may be indicative of ear pain.

Consensus Roundtable Summary

- There is substantial variability and inconsistency among practitioners, even in clinical trials, in the criteria and modalities used to diagnose AOM.
- Establishing and implementing stringent diagnostic criteria are essential to ensure that antibiotics are prescribed for patients in whom they are necessary. Reducing the use of antibiotics for conditions such as OME may minimize the impact and progression of resistance.
- The diagnostic algorithm provided in this publication, or a similar approach, should be utilized to differentiate AOM from OME.

Microbiology

The major bacterial species isolated from cultures of middle ear fluid have not changed in the past 20 years (Table 1).23,26,27 S. pneumoniae is the most frequently occurring pathogen and is the least likely to resolve without treatment (approximately 20% of cases), compared with other pathogens, such as H. influenzae, which has a spontaneous resolution rate of approximately 50%.28 Other pathogens that are involved less frequently include Group A streptococci, Staphylococcus aureus, and gram-negative organisms such as Pseudomonas aeruginosa.23

Although AOM is generally considered a bacterial infection, viruses usually play a significant role in the etiology and pathogenesis of this condition. Respiratory viruses (e.g., respiratory syncytial virus, parainfluenza virus [types 1, 2, and 3], influenza [types A and B], enterovirus, rhinovirus), generally coinciding with bacterial pathogens, have been identified in most patients with AOM.29-32 Concomitant viral infection causes persistent symptoms despite elimination of bacteria from the middle ear cavity (by antibiotic therapy), or may interfere with the clearance of bacteria despite the use of an antibiotic that is active against the bacterial pathogen.31,33

### Antibiotic Resistant Pathogens

Antibiotic resistance among the predominant pathogens in AOM is an increasing healthcare problem.54 Resistance to antibiotics is associated with a decreased ability to eradicate organisms from the middle ear, which is associated further with a greater likelihood of clinical failure.35 Thus, the high prevalence of resistance underscores the importance of selecting appropriate empiric antimicrobial therapy for patients with AOM.

**Streptococcus pneumoniae**

Before the 1960s, penicillin was the mainstay of treatment for infections caused by *S. pneumoniae*. However, throughout the past few years, resistance to penicillin and other antibiotics among strains of *S. pneumoniae* has become prevalent both in the United States and abroad. Over the past decade, the prevalence of *S. pneumoniae* isolates that are either penicillin-intermediate (i.e., penicillin minimum inhibitory concentrations [MICs] 0.12–1.0 µg/mL) or penicillin-resistant (i.e., MICs ≥2.0 µg/mL) has increased dramatically, with an increase in strains having MICs ≥8 µg/mL as well. From a recent surveillance study,54 29% of *S.
penicillin-resistant and 16% are penicillin-intermediate. Thus, nearly 50% of strains of *S. pneumoniae* can be characterized as being penicillin nonsusceptible.\(^{34}\)

A significant clinical concern is that penicillin-nonsusceptible strains of *S. pneumoniae* are likely to be resistant to other classes of drugs commonly used by practitioners to treat AOM.\(^ {36}\) Multidrug-resistant *S. pneumoniae* is a term used to describe strains with penicillin MICs ≥0.12 µg/mL that also exhibit resistance to at least 2 other classes of antimicrobial agents. The susceptibility of *S. pneumoniae* isolates to penicillin is closely correlated with their susceptibility to other antimicrobials. A 1998 surveillance study\(^ {34}\) of US outpatient respiratory isolates revealed that only 6% of penicillin-susceptible strains are resistant to erythromycin, 1% are resistant to clindamycin, and 14% to trimethoprim-sulfamethoxazole (TMP/SMX). In contrast, among the penicillin-resistant strains, 76% also are resistant to erythromycin, 28% are resistant to clindamycin, and 91% are resistant to trimethoprim-sulfamethoxazole. Overall, 32% of all strains of *S. pneumoniae* are resistant to erythromycin, 10% are resistant to clindamycin, and 43% are resistant to trimethoprim-sulfamethoxazole.\(^ {34}\) Thus, if an isolate of *S. pneumoniae* is resistant to penicillin, it is likely that the isolate will also be resistant to other drugs (i.e., macrolides, trimethoprim-sulfamethoxazole, etc.). Therefore, the strategy of substituting an agent from a different drug class for the treatment of AOM caused by penicillin-nonsusceptible *S. pneumoniae* is not always rational or effective. In fact, despite the current nomenclature (e.g., penicillin-resistant), certain β-lactam antibiotics remain the preferred agents for the treatment of infections caused by resistant strains. The mechanism of resistance to β-lactams among strains of *S. pneumoniae* is alterations in penicillin-binding proteins that result in reduced binding affinity of the β-lactam drug with its target. This mechanism of resistance can be overcome with appropriate pharmacokinetics/pharmacodynamics (PK/PD) (i.e., high-dose amoxicillin therapy). There are multiple mechanisms by which strains of *S. pneumoniae* are resistant to macrolides. One mechanism of resistance (known as MLS resistance) involves alterations in the site on bacterial ribosomes to which macrolides bind to exert an antimicrobial effect. In contrast to β-lactam resistance by *S. pneumoniae* that is mediated through penicillin-binding proteins, MLS resistance to macrolides cannot be overcome with appropriate PK/PD. In addition, it confers cross-resistance to other macrolides and clindamycin. The second mechanism of resistance to macrolides involves the efflux of the drug from the intracellular space. This mechanism confers resistance to other macrolides but not to clindamycin.\(^ {37}\)

Although penicillin-resistant strains have been isolated from all age groups, the highest proportion of resistant strains is collected from children aged 2 years and younger. In addition, resistant strains are most likely to be isolated from the middle ear (approximately 55% of all *S. pneumoniae* isolates), sinus (approximately 53% of all *S. pneumoniae* isolates), and nasopharyngeal specimens (approximately 48% of all *S. pneumoniae* isolates).\(^ {34}\) Clinicians should be aware that the prevalence of resistance in these studies might be overestimated because the majority of these cultures were obtained from children in whom treatment had failed. However, if these trends are accurate, it is cause for concern because AOM is a condition that primarily affects children ≤2 years old. The increased prevalence of resistance among pathogens causing AOM has not only complicated the choice of empiric treatment for AOM, it has also led to an increase in treatment failure.\(^ {15,38,39}\)

**Haemophilus influenzae**

β-Lactamase production among strains of *H. influenzae* has increased steadily throughout the past 2 decades. Presently, approximately 30% to 35% of *H. influenzae* strains produce β-lactamas, and a higher proportion can be found in the New England states.\(^ {34,40}\) Unlike *S. pneumoniae*, the administration of higher doses of β-lactam antibiotics is not effective in overcoming the actions of β-lactamas. However, infections caused by these strains generally can be overcome by the addition of a β-lactamase inhibitor (e.g., clavulanic acid) or by using a β-lactamase–stable antibiotic (e.g., cefixime, cefpodoxime, cefdinir).

As a class, the macrolides have limited baseline activity against *H. influenzae* compared with *S. pneumoniae*. It takes a 100-fold higher concentration of macrolide to inhibit a strain of *H. influenzae* compared with a strain of *S. pneumoniae*. Some agents may have poor activity in vivo despite demonstrated in vitro susceptibility due to unfavorable PK/PD properties.\(^ {41}\)

**Moraxella catarrhalis**

Virtually all strains of *M. catarrhalis* are β-lactamase producers. Recent surveillance study data\(^ {34}\) demonstrated that 98% of
M. catarrhalis strains produce β-lactamases. As with H. influenzae, the addition of a β-lactamase inhibitor is effective in overcoming this mechanism of resistance. All isolates of M. catarrhalis in the 1998 surveillance study were susceptible to amoxicillin/clavulanate, macrolides/azalides, cefixime, and doxycycline. There also was 100% susceptibility to ciprofloxacin and ofloxacin; these agents are not approved for use in children, however. Significant resistance was observed to other cephalosporins (i.e., loracarbef, cefaclor, cefprozil) and TMP/SMX.

Consensus Roundtable Summary

- The microbiology of AOM has not changed significantly within the past 30 years, with respect to the pathogens involved; however, resistance has become more prevalent among these pathogens.

- Resistance to common antimicrobial agents among strains of S. pneumoniae is alarmingly substantial and may be increasing. The prevalence of S. pneumoniae strains that are nonsusceptible to penicillin is approximately 45%. Pneumococcal resistance is also prevalent among other classes: 32% of all strains of S. pneumoniae are resistant to erythromycin, 10% are resistant to clindamycin, 43% are resistant to trimethoprim-sulfamethoxazole, and 22% are resistant to doxycycline. The rate of resistance to these classes among strains that are already resistant to penicillin is even greater.

- Penicillin resistance does not confer resistance to all β-lactams because this mechanism of resistance (penicillin-binding proteins) can be overcome by using agents with appropriate PK/PD properties.

- β-Lactamase production is highly prevalent among strains of H. influenzae and M. catarrhalis. This mechanism of resistance to β-lactam antibiotics can be overcome by the addition of a β-lactamase inhibitor (e.g., amoxicillin/clavulanate) or by using an agent that is stable to the action of β-lactamases (e.g., cefixime, cefpodoxime, cefdinir).

Pharmacokinetic/Pharmacodynamic Parameters

The goal of antimicrobial therapy is to provide an adequate concentration at the site of infection for a period of time sufficient to eradicate bacterial pathogens. Antimicrobial activity against a particular pathogen is frequently assessed based on MICs, and the National Committee for Clinical Laboratory Standards (NCCLS) has historically evaluated MIC data in the determination of susceptibility breakpoints. Although MIC data provide information about the potency of a drug against a given pathogen, they do not account for the mechanism of antimicrobial activity or “postantibiotic” effects.

A new approach to assessing in vitro antimicrobial activity has been proposed based on PK/PD parameters. Pharmacokinetic parameters characterize absorption, distribution, metabolism, and elimination of drugs, whereas pharmacodynamic parameters characterize the interactions of the drug within the body with respect to time, including the mechanism of antimicrobial activity. Nicolau et al. in 1995, suggested that the PK/PD characteristics of antibiotics may be a better means of predicting clinical outcome as compared with MIC data. The PK/PD parameters have been correlated with antibiotic efficacy studies in animal models and, more importantly, in children with AOM.

Antimicrobials frequently used for the treatment of AOM can be grouped into 2 categories based on the mechanism of antimicrobial killing in vivo: concentration- and time-dependent. β-lactams, erythromycin, and clarithromycin exhibit time-dependent killing (Figure 4). Thus, a serum concentration that achieves this goal can be used as the PK/PD susceptibility breakpoint of the organism. The rate or extent of bacterial killing does not increase when the drug concentration is increased further (i.e., it is the time that the concentration exceeds the MIC rather than the absolute concentration). Azithromycin currently is the only agent commonly used for the treatment of AOM with a concentration-dependent mechanism of antimicrobial activity. Fluoroquinolones also have a concentration-dependent mechanism; however, these agents currently are not approved for use in children. For these agents, the PK/PD parameter that correlates with clinical outcome is the ratio between the area under the concentration-versus-time curve (AUC)
Treatment of Otitis Media

Consensus Roundtable Summary

- The incorporation of PK/PD parameters with in vitro activity (i.e., MIC data) may be a better predictor of in vivo antimicrobial efficacy than using MIC data alone.
- Two major PK/PD models of bacterial killing—time-dependent and concentration-dependent—can be used to predict the efficacy of most oral antibiotics.
- For time-dependent antibiotics, the PK/PD target is a concentration above the MIC for more than 40% to 50% of the dosing interval.
- For concentration-dependent antibiotics, the PK/PD target is estimated to be an AUC/MIC ratio of 25 to 30.
- According to PK/PD breakpoints, amoxicillin/clavulanate is the only oral agent approved for use in AOM that is active against >90% of strains of the predominant pathogens in AOM.

Management

As described above, the eradication of the infecting pathogen by an antibiotic is dependent on the time that concentrations at the site of infection exceed the MIC, or on the AUC/MIC ratio. Antibiotic selection for AOM, however, should be based not only on in vitro activity against common pathogens but also on studies demonstrating bacteriologic outcomes. Resistant pathogens are more difficult to eradicate from the middle ear cavity, and bacteriologic persistence is associated with clinical failure. Because AOM is extremely prevalent in the United States, with an estimated 19 million episodes per year, the use of an antibiotic with a slightly higher efficacy is warranted.

and the MIC (Figure 5). Achieving an AUC/MIC ratio of >25 to 30 with these agents is thought to correlate with efficacy. The NCCLS recently reevaluated the susceptibility breakpoints for certain β-lactams used to treat respiratory tract infections caused by S. pneumoniae and updated them based on microbiologic, animal, PK/PD, and clinical outcome data. The relative activities (based on PK/PD profile) of various antibiotics commonly used for AOM are listed in Table 2.

Figure 4. Pharmacodynamic concept: Time>MIC. Schematic representation of the pharmacokinetic profile of time-dependent antimicrobial agents (adapted with permission).

Figure 5. Pharmacodynamic concept: AUC:MIC ratio. Schematic representation of the pharmacokinetic profile of concentration-dependent antimicrobial agents (adapted with permission).
bacteriologic success rate translates to a significant number of clinical successes.

Studies of early treatment failure revealed that organisms could not be isolated in a significant proportion of children who underwent tympanocentesis (30%–50%), despite signs and symptoms of AOM.26,27 Of the organisms isolated, 20% were resistant to the antibiotic most recently received. These findings suggest that persistence of clinical symptoms may result from viral infection, inadequate concentrations of antibiotic in the middle ear, noncompliance with therapy, or by a resistant pathogen. However, these studies were conducted before the current era of pneumococcal resistance. A 1998 study from Israel51 demonstrated that, of children who were recently treated with antibiotics or who were failing antibiotic treatment, \textit{S. pneumoniae} was the most common isolate recovered. In patients who had not received previous treatment, \textit{H. influenzae} was the most common pathogen isolated.

For recently treated children, the MICs for \textit{S. pneumoniae} isolates against penicillin, cefaclor, and cefuroxime were significantly higher than the MICs in those who had not recently been treated. The MICs for strains of \textit{H. influenzae} were not different between groups. The authors concluded that pneumococcus is more prevalent in AOM following recent antibiotic exposure, and the MICs for \textit{S. pneumoniae} isolates of the commonly used β-lactam drugs are significantly higher in this setting.

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<td><strong>RELATIVE ANTIMICROBIAL ACTIVITY BASED ON PHARMACODYNAMIC BREAKPOINTS</strong>(^*)34,46</td>
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\(^*\)For β-lactams and macrolides: \(T>MIC>40\%\) of the dosing interval; for fluoroquinolones: 24-hr AUC/MIC ratio >100–125 for \textit{H. influenzae} and >30–50 for \textit{S. pneumoniae}.

\(^†\)80–90 mg/kg/day based on the amoxicillin component in 2 divided doses.

Amox/clav = amoxicillin/clavulanate; I = intermediate to penicillin; R = resistant to penicillin; S = susceptible to penicillin. 4 = adequate pharmacodynamic profile using conventional dosing in patients with normal renal and hepatic function; ± = borderline pharmacodynamic profile using conventional dosing in patients with normal renal and hepatic function.
Choice of Antimicrobial Agent

With a plethora of agents from which to select for the treatment of AOM, one of the most significant clinical questions is “Which agents are best?” Although *in vitro* data are available for these agents, this may not always be an adequate surrogate marker for *in vivo* activity and clinical efficacy. Unfortunately, many of the clinical trials with antibiotics for AOM were designed to demonstrate equivalency for FDA approval, not necessarily to demonstrate superiority. Because these studies use clinical outcomes and modest sample sizes, antibiotics with limited activity appear to be equivalent to those with excellent antibacterial activity. This tendency for poor drugs to appear better than they really are is referred to as the “Pollyanna phenomenon.” The result is that some clinicians prescribe inferior antibiotics and some of these children remain symptomatic when they might otherwise have become asymptomatic with more effective therapy.

In general, outcomes in clinical trials involving patients with AOM are based on the following: (1) Infectious Disease Society of America criteria, in which outcomes are defined by symptomatic response alone with no regard to specific tympanic membrane findings; (2) more stringent criteria, in which success is based on resolution of symptoms and otoscopic findings of acute inflammation; or (3) studies that determine bacteriologic outcome.

Double tympanocentesis (or double “tap”) studies have been used to demonstrate *in vivo* activity. In this type of study, tympanocentesis is performed before antibiotic therapy and again during therapy, typically 4 to 6 days later. Bacteriologic studies performed in the late 1960s determined that the ultimate test of an antibiotic is its ability to eradicate organisms from the site of infection. Since then, double tympanocentesis is the method that is most often used in clinical trials to determine bacteriologic outcome.

In studies employing the double-tap design, the relationship between clinical and bacteriologic outcomes has been examined. Dagan and colleagues conducted a study that correlated bacteriologic outcome with clinical outcome in 123 children with AOM. Patients underwent tympanocentesis on Day 0 and again after 3 to 4 days of antibiotics (e.g., Days 4 to 5). Of the 57 children who had positive cultures on Days 4 to 5 (i.e., bacteriologic failure), approximately two thirds achieved clinical cure. Of the 66 patients who had negative cultures on Days 4 to 5 (i.e., bacteriologic cure), nearly 100% achieved a clinical cure (Figure 6). The results of this study indicate that clinical success is more likely when bacteriologic cure is achieved.

![Figure 6. Clinical versus bacteriologic outcome (reprinted, with permission).](image)
The fact that patients improve symptomatically over time despite persistent positive cultures is the primary factor of the “Pollyanna phenomenon.” An antibiotic with little or no bacteriologic efficacy (e.g., placebo) will appear to be effective clinically. Agents that are the least effective will achieve a significant clinical cure because of spontaneous resolution and the improvement in symptoms that occurs over time in the natural course of AOM. Also, antibiotics with excellent bacteriologic activity may appear to have decreased clinical efficacy. The most effective antibiotic will achieve a clinical cure in only 90% of cases because of other factors such as viral infection or host immune response. Therefore, it may seem insignificant to differentiate between antibiotics with only small differences in clinical cure rates. However, clinicians should bear in mind that even seemingly insignificant differences in clinical cure rates could have a tremendous impact on healthcare because of the high prevalence of the condition. Furthermore, for patients who are failing antibiotic therapy, it is important to select alternative agents that can eradicate pathogens from the middle ear, including those that are resistant.

Although academicians tend to focus on double tympanocentesis studies, pediatricians often do not recognize their relevance in clinical practice. This concentration solely on clinical outcomes, however, may lead to the perpetual use of ineffective drugs. Practitioners are urged to consider the results of studies demonstrating bacteriologic efficacy when selecting empiric antimicrobial agents for their patients.

**Antibiotic Recommendations**

The Drug-Resistant Streptococcus pneumoniae (DRSP) Therapeutic Working Group was convened by the Centers for Disease Control and Prevention (CDC) in 1996 to address the high prevalence of DRSP in community-acquired infections. The first initiative of the Group was to provide consensus recommendations for the management of AOM and the surveillance of DRSP. The Group was also concerned that most physicians prescribe antibiotics based on convenience and taste rather than efficacy. Therefore, part of the effort was to point out which agents were most active against the predominant pathogens.

The Group evaluated the appropriateness of amoxicillin as the preferred initial agent for AOM. It was concluded that amoxicillin at conventional doses (40–45 mg/kg) or higher doses...
Thus, the causative strains are 385, or tympanocentesis is indicated. If they fail amoxicillin. Early treatment failures (i.e., on Days 0–3) are most likely to be viral in origin (and hence not truly treatment failures); however, there is an increasing prevalence of β-lactamase-producing organisms and drug-resistant S. pneumoniae causing early treatment failures. Late treatment failures are likely the result of infection with a new organism; however, it is more likely to be a resistant pathogen because prior antibiotic treatment often promotes persistence or new colonization of the nasopharynx by resistant pathogens. For these patients, the second-line agents should be selected based on activity against β-lactamase-producing organisms and resistant pneumococci. The selection of appropriate agents was based on concentrations found in middle ear fluid and outcomes in clinical studies—nor merely the MICs of the organisms. If a patient without previous antibiotic exposure in the past month fails therapy on Day 3 or on Days 10 to 20, high-dose amoxicillin/clavulanate, cefuroxime, or ceftriaxone is recommended. High-dose amoxicillin/clavulanate consists of 40 to 45 mg/kg/day amoxicillin/clavulanate plus 40 to 45 mg/kg/day amoxicillin for a total of 80 to 90 mg/kg/day based on the amoxicillin component. If a patient with antibiotic exposure in the previous month fails therapy on Day 3, IM ceftriaxone, clindamycin (not active against H. influenzae or M. catarrhalis), or tympanocentesis is recommended. Accordingly, clindamycin treatment should be reserved for patients known to have episodes of AOM caused by resistant S. pneumoniae. If they have failed therapy on Days 10 to 28, high-dose amoxicillin/clavulanate, cefuroxime, IM ceftriaxone, or tympanocentesis is recommended.

Amoxicillin/clavulanate (especially with higher doses of the amoxicillin component) and ceftriaxone, the 2 agents recommended by the Group, may be more active than other available agents against penicillin-resistant pneumococci and β-lactamase-producing pathogens. Although approved for use in AOM as a single-dose injection, the Group recommended a ceftriaxone regimen that includes administering an initial dose with a second and third dose given if the patient does not improve clinically and symptomatically. The Group emphasized that the clinical experience with IM ceftriaxone is much more limited compared to oral agents and that it may be advisable to reserve injectable cephalosporin therapy for use in severe infections only.

Although the CDC recommendations are helpful in guiding antibiotic therapy for AOM, there are several limitations. First, the prevalence of resistance to β-lactams, macrolides, and other antibiotics among strains of S. pneumoniae has changed since the publication of the CDC recommendations. In light of more recent antimicrobial surveillance data, the inclusion of cefuroxime as a second-line agent may no longer be appropriate. Data from these studies demonstrate that cefuroxime may not provide adequate activity against penicillin-resistant strains of S. pneumoniae. Specifically, only approximately 64% of S. pneumoniae strains are currently susceptible to cefuroxime. A 1998 by Dagan and colleagues evaluated the effect of cefuroxime on nasopharyngeal pneumococcal carriage within 3 to 4 days after initiation of treatment in AOM. The results demonstrated that while cefuroxime was effective in clearing penicillin-susceptible strains of pneumococci, it did not reduce the carriage of penicillin-resistant isolates of S. pneumoniae.
Another limitation of the CDC recommendations is that they do not address the management of patients with a true allergy to β-lactam antibiotics. For these patients, treatment alternatives include azithromycin, clindamycin (for those in whom H. influenzae and M. catarrhalis can be ruled out), and erythromycin/sulfisoxazole.

**Tympanocentesis**

Tympanocentesis, which was recommended by the Group for patients who fail therapy, can be beneficial in identifying the causative pathogen. A secondary benefit of tympanocentesis is the relief of pressure in the middle ear cavity and promoting the drainage of the middle ear effusion. More extensive drainage of the middle ear effusion via myringotomy was the standard treatment for AOM in the preantibiotic and early antibiotic eras but fell out of favor with the widespread use of antibiotics. With the increasing prevalence of resistant pathogens causing AOM in recent years, there has been an increased incidence of refractory AOM, leading to a renewed role for tympanocentesis in the management of patients with AOM.

Tympanocenteses are painful, but there may also be some relief of earache by relieving the pressure behind the bulging eardrum; however, performing the procedure solely for the purpose of relieving pain warrants careful consideration. Options for pain management and sedation before tympanocentesis include acetaminophen with codeine for younger children with an additional dose of acetaminophen to achieve a total dose of 20 mg/kg and midazolam in combination with ibuprofen for older children. The oral form of midazolam may be administered as a one-time dose of 0.7 mg/kg (not to exceed 18 mg). The use of midazolam may increase the costs if it falls under medications used for conscious sedation. Some institutions categorize midazolam as a conscious sedation agent; some do not. Other options for pain control include an 8% tetracaine solution applied with a Pope Otowick. Less favorable options include a phenol applicator, EMLA cream, lidocaine injections, and iontophoresis with lidocaine. The procedure generally is safe and without complications when performed by an experienced clinician. Morbidities associated with tympanocentesis are very unlikely; the most frequent include excessive bleeding or leakage of blood and pus after procedure. Potential risks include ossicular disruption, chronic perforation, permanent hearing loss, and facial nerve paralysis; however, these complications remain hypothetical. The risks associated with this procedure depend primarily on the experience of the clinician.

Consensus Roundtable Summary

- Bacterial eradication is associated with greater clinical success. The selection of an antibiotic should be based on bacteriologic outcome data as well as in vitro activity against the suspected pathogen(s).
- It is important to identify patients at risk for infection with resistant pathogens to ensure that appropriate antimicrobial therapy is selected.
- The DRSP Therapeutic Working Group guidelines for antibiotic selection in AOM provide adequate recommendations. Amoxicillin remains an appropriate choice as first-line therapy. Second-line agents should provide activity against penicillin-resistant S. pneumoniae and β-lactamase-producing pathogens (e.g., high-dose amoxicillin/clavulanate and ceftriaxone).
- Tympanocentesis is beneficial for both diagnosis and adjunctive treatment of AOM. Practitioners should familiarize themselves with the role of this procedure in the management of AOM. Tympanocentesis is frequently used in clinical trials to demonstrate bacterial eradication.

**Vaccination**

Because of the prevalence of AOM and the burden of illness (in terms of healthcare expenditures and morbidity) associated with this condition, preventive measures (i.e., vaccination) are an attractive option. The vaccines that have shown promise for preventing episodes of AOM include the influenza vaccine and the pneumococcal conjugate vaccine. Previous studies have suggested that the influenza vaccine is effective in reducing episodes of AOM during the influenza season or during times when viral respiratory illness is present. However, a recent trial in children aged 6–24 months found no effect in OM-related morbidity.

Pneumococcal vaccination has the potential to impact the prevalence and morbidity associated with otitis media caused by S. pneumoniae. The pneumococcal polysaccharide vaccine, which has been available since 1979, is effective at preventing invasive pneumococcal disease in adults. In infants and young children—the population at greatest risk for AOM—however, it has proved to be poorly immunogenic. The development of conjugate vaccine technology, however, has allowed for increased immunogenicity in this population. A heptavalent
pneumococcal conjugate vaccine, which contains the 7 serotypes of pneumococci that are responsible for the majority of disease, has recently been licensed in the United States for the prevention of invasive pneumococcal disease in young children. Studies evaluating the efficacy of the vaccine have demonstrated significant reductions in invasive pneumococcal disease. Reductions in otitis media episodes, office visits, severity, and tympanostomy tube insertion were also observed, although less dramatically. Owing to the widespread prevalence of otitis media, however, even minor reductions in episodes and office visits can result in substantial reductions in healthcare utilization and expenditures.

Most strains of penicillin-resistant *S. pneumoniae* are the serotypes that are included in the vaccine; however, a few resistant strains are serotypes not included in the vaccine. Consequently, drug-resistant serotypes will still be prevalent with use of the vaccine. Studies of the effect of pneumococcal vaccines on nasopharyngeal carriage suggest that there is an increase in colonization with nonvaccine serotypes in vaccinated patients. The clinical impact this will have on the carriage and spread of resistant strains of *S. pneumoniae* remains to be fully elucidated. The DRSP Therapeutic Working Group guidelines for AOM were published in 1999 and developed in 1997. The pneumococcal vaccine was not available at that time, and thus, was not included as part of their recommendations. This agent is licensed for universal immunization of infants younger than 2 years, and practitioners should also consider using the pneumococcal conjugate vaccine for appropriate older patient groups with recurrent AOM.

**Consensus Roundtable Summary**

- The pneumococcal conjugate vaccine appears to be safe and effective in the prevention of pneumococcal disease, particularly invasive disease.
- Patients at high risk for the development of AOM and, especially, those at increased risk for infection with DRSP, should be considered as candidates for pneumococcal vaccine.

**Summary of Consensus Recommendations**

The high prevalence of antimicrobial resistance among the predominant pathogens is a significant clinical concern and challenge in the treatment of AOM. Based on clinical experience, available data, and the expert guidelines developed by the DRSP Therapeutic Working Group, the consensus roundtable panel established the following recommendations for practitioners for the management of AOM:

- Strict criteria for diagnosis help to ensure an accurate diagnosis and thus identify appropriate patients for antimicrobial therapy. Practitioners should use risk factors to identify patients at high risk for developing AOM and/or infection with resistant pathogens, implement preventive measures (e.g., vaccination) when appropriate, and initiate antibiotics with greater activity against penicillin-resistant *S. pneumoniae* and β-lactamase–producing pathogens if acute infection should occur.
- Evaluation of antimicrobial efficacy based on PK/PD parameters is a more reliable method for predicting in vivo efficacy than using MIC data in the absence of bacteriologic outcome data. The only oral antimicrobial agent indicated for use in pediatrics that has activity against >90% of strains of the 3 major pathogens in AOM according to PK/PD breakpoints is amoxicillin/clavulanate.
- The guidelines developed by the DRSP Therapeutic Working Group provide adequate recommendations for the treatment of AOM. However, the guidelines were developed several years ago and practitioners should consider the current rates of resistance to some of the agents in their recommendations when selecting antimicrobial therapy.
- Amoxicillin, especially at higher doses (80–90 mg/kg/day divided in 2 daily doses), still is recommended as first-line therapy. If a patient has received antibiotics within the past month, there is an increased risk for infection with penicillin-resistant *S. pneumoniae*, as well as β-lactamase–producing strains of *H. influenzae* and *M. catarrhalis*; thus, initial treatment with high-dose amoxicillin/clavulanate should be considered.
- Factors to consider in determining the risk of infection with DRSP should include age of the patient (failure increases with age ≤2 years), time of year (e.g., winter, spring), day care attendance (e.g., any setting outside the home where a child regularly spends ≥4 hours per week with at least 2 unrelated children under adult supervision), and recent exposure to antibiotics (i.e., within the past 3 months).
- Amoxicillin/clavulanate (especially with higher doses of the amoxicillin component) and ceftriaxone are the 2 agents recommended by the Group that have superior activity against both highly resistant pneumo-
coci and β-lactamase-producing strains of *H. influenzae*. The DRSP Therapeutic Working Group indicated that clinical experience with IM ceftriaxone is much more limited compared to oral agents and that it may be advisable to reserve injectable cephalosporin therapy for use in severe infections only.

• Tymanocentesis is encouraged as a beneficial procedure for the clinical management of the patient. Benefits of tymanocentesis include obtaining an accurate diagnosis, identifying the causative organism, and relieving pain.

• The pneumococcal vaccine may provide an effective means of reducing AOM episodes, office visits, recurrent AOM, and tympanostomy tube insertion. It is recommended for universal immunization of infants younger than 2 years and it should be considered for appropriate patients, particularly those at high risk of infection with resistant pneumococci.

REFERENCES


