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An Update on Treatment Strategies for Acute Otitis Media

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Goals: To enable the practicing pharmacist in providing pharmaceutical care to patients with acute otitis media (AOM).

LEARNING OBJECTIVES

Following a successful review of this article, the reader should be able to:

1. Describe the epidemiology of AOM.
2. Describe the pathophysiology and microbiology of AOM.
3. Discuss several currently recommended strategies for treatment of AOM.
4. Categorize the advantages and disadvantages of antibacterials currently approved for treatment of AOM.

Abstract: Acute otitis media (AOM) is a common infectious disease in children, especially in the age range of 6 to 24 months. It is associated with an annual cost of $3 to $4 billion to the health care system. AOM is an infection of the middle ear space. Blockage of the Eustachian tube leads to a buildup of fluid in the middle ear, facilitating bacterial growth. The most common bacteria causing AOM are *Streptococcus pneumoniae (S. pneumoniae), Haemophilus influenzae (H.* influenzae), and *Moraxella catarrhalis (M. catarrhalis)*. In recent years, an alarming percentage of *S. pneumoniae* has developed resistance to penicillin and other antibacterials. *S. pneumoniae* has developed resistance to penicillin by alteration of the penicillin binding site, also known as penicillin binding proteins (PBPs). *H. influenzae* and *M. catarrhalis* have also developed resistance to penicillin; however, the mechanism of resistance most often seen in these bacteria is production of β-lactamase, an enzyme that breaks the β-lactam bond of penicillin and other β-lactam antibacterials. Several recent publications have outlined updated treatment strategies for AOM in light of current resistance trends. A Centers for Disease Control (CDC) experts group recommended in 1999 that amoxicillin (standard or high dose) should remain first-line therapy for AOM. This panel, however, only recommended 3 drugs for treatment of AOM unresponsive to amoxicillin: amoxicillin/clavulanate, cefuroxime axetil, and ceftriaxone. Others have published guidelines that include trimethoprim/sulfamethoxazole (TMP/SMX), cefprozil, ceftibuten, cefixime, cefdinir, and cefpodoxime proxetil, in addition to those medications that the CDC working group recommended. Most recent literature suggests that cefaclor, loracarbef, and the macrolides have limited usefulness in AOM and, in most cases, should be avoided.

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NARRATIVE

Acute otitis media (AOM) is the most common cause of physician office visits in children. Pharmacists are an important and readily accessible source of information for AOM patients and their caregivers and, therefore, require a basic understanding of the appropriate management of this common disease. This article will focus on the pathophysiology, epidemiology, etiology, and treatment of AOM. An emphasis will be placed on the wide array of antibacterial treatments approved for AOM in an effort to aid the pharmacist in providing assistance to physicians and patients in recommending appropriate therapy and counseling to patients regarding AOM antibacterial use and potential toxicity.

EPIDEMIOLOGY

AOM is a common cause of infection in infants and small children. It is second only to the common cold in terms of frequency of infection in children.[1] The highest incidence of AOM occurs between 6 to 24 months of age.[2] Approximately 60% of children have at least one episode of AOM within their first year of life and 75% of children will have at least one episode of AOM by age

three.[3] Children make more office visits to physicians because of AOM than any other disease. In 1990, about 24.5 million such office visits were made; by 1999, this number had risen to about 30 million.[4] In the United States, the annual cost for medical and surgical therapy of AOM is estimated to be in the range of $3 billion to $4 billion.[3]

A multitude of studies (table 1) have identified several risk factors for AOM.[5] Children who are in enrolled in daycare centers are more likely to develop AOM. This is likely attributed to an increased exposure to the typical pathogens causing AOM. A higher incidence of AOM is seen in children who are exposed to passive smoke via parents who are smokers. Breast-feeding is protective against AOM for the first 3 to 6 months of the child's life, while bottle-feeding during this time period may increase the incidence of AOM (especially if the child is laying flat while bottle-feeding). Like most other childhood infectious diseases, males are more likely to develop AOM than females.[2] Certain races are at risk for a higher rate of recurrent episodes of AOM, or chronic otitis media, such as Inuit, Native American, and Native Alaskans.[5] Finally, recent studies have indicated that infants with very low birth weight and/or very preterm birth have a higher occurrence of chronic otitis media.

PATHOPHYSIOLOGY AND MICROBIOLOGY

Otitis media is a disease of the middle ear. The middle ear is an air-filled cavity that begins at the tympanic membrane and extends to the nasopharynx via the Eustachian tube. The Eustachian tube plays an important role in the normal function of the ear.[2] For example, the Eustachian tube protects the ear from nasopharynx secretions by providing a drainage route. The Eustachian tube lies at a 10-degree angle in infants, while in adults it lies at a 45-degree angle. Accordingly, a decrease in gravitation effects in infants and young children often results in improper nasopharynx secretion drainage. Eventually, improper drainage leads to mucosal congestion and obstruction of the Eustachian tube. Secretions formed by the middle ear mucosa then accumulate behind this obstruction and facilitate the growth of bacteria.

Otitis media is divided into several categories, some of which do not require antibacterial treatment. Therefore, a correct diagnosis is an essential first step for proper use of antibacterials in otitis media. AOM is defined as inflammation of the middle ear accompanied by fluid in the middle ear and the usual signs and symptoms of an acute infection. This typically manifests as a bulging tympanic membrane that is unresponsive to positive pressure when examined by pneumatic otoscopy. The tympanic membrane may be red, but color by itself is not a reliable predictor of AOM.[6] Recurrent otitis media is usually defined as at least 3 episodes of AOM within the last 6 months. If AOM persists after 6 days of therapy or reoccurs a few days after discontinuation of therapy, it is called persistent otitis media. Otitis media with effusion (OME) is defined as the presence of fluid in the middle ear without the usual signs of acute illness (e.g., fever, pain).[7] Unlike AOM, antibiotics are not generally recommended in cases of OME. If the middle ear effusion persists for longer than 6 months (some sources say 3 months) it is termed chronic otitis media.

Approximately 70% of AOM cases are attributed to bacterial infection; the remaining 30% are attributed to infection by viruses and other microorganisms and by

non-infectious causes. Table 2 details the specific bacterial etiology of AOM.

Like many respiratory infections, *S. pneumoniae* is the most common bacterial cause of AOM. The rate of penicillin-resistant *S. pneumoniae* (defined as minimum inhibitory concentration [MIC] > 0.1 μg/mL) has been on a steady increase in the United States.[8] According to the CDC, from 1991 to 1996, there was a greater than 300% increase in penicillin-resistant *S. pneumoniae* rates in the U.S.[9] Resistance to penicillin in *S. pneumoniae* cannot be countered with the addition of a β-lactamase inhibitor to β-lactam therapy. This can be explained by the mechanism of penicillin-resistance in *S. pneumoniae*. Unlike many bacteria, *S. pneumoniae* does not produce β-lactamase. The penicillins bind to and inhibit the function of penicillin-binding proteins, or PBPs. In *S. pneumoniae*, penicillin resistance is attributed to mutation of specific PBPs. This form of resistance has created new challenges in the treatment of AOM, as penicillin-resistant *S. pneumoniae* is often less sensitive to other commonly used β-lactam antibacterials. In addition, *S. pneumoniae* that is highly resistant to penicillin (usually defined as MIC > 2.0 μg/mL) is likely to be resistant to macrolide antibacterials and trimethoprim/sulfamethoxazole (TMP/SMX). The FDA recently approved a heptavalent pneumococcal vaccine (Prevnar®) that provides protection against the 7 most virulent serotypes of *S. pneumoniae*, which cause invasive pneumococcal disease. The benefit of Prevnar® for protection against AOM is, to date, somewhat unclear. Prevnar® decreases the occurrence AOM caused by *S. pneumoniae* (confirmed by culture) by 34%, and it decreases the number of episodes of AOM attributed to a serotype of *S. pneumoniae* present in the vaccine by 57%; however, the total number of AOM cases (regardless of cause) was no different with Prevnar® relative to placebo.[10]

Another common cause of AOM is the gram-negative cocco-bacilli *H. influenzae*, which accounts for approximately 25% of cases. Most of these cases are caused by strains that cannot be typed; however, approximately 10% of otitis media cases caused by *H. influenzae* are caused by the type b strain, and should be preventable by immunization with the *H. influenzae* type b vaccine (HIB). There are multiple mechanisms by which *H. influenzae* can become resistant to antibacterials. Resistance to penicillins is usually because of production of β-lactamase. Therefore, Augmentin®, which contains amoxicillin and the β-lactamase inhibitor clavulanate, may be useful for overcoming this form of resistance. *H. influenzae* can also develop resistance to the penicillins by alteration of several PBPs. While *H. influenzae* is generally sensitive to TMP/SMX, resistance has been reported because of overproduction of the enzyme targeted by trimethoprim (dihydrofolate reductase [DHFR]).

The third most common cause of AOM is the gram-negative cocci *M. catarrhalis*. There is a high rate of penicillin and amoxicillin resistance in *M. catarrhalis*; in the U.S. and Europe, more than 75% of strains are now resistant to penicillin and amoxicillin. The most common mechanism for antibacterial resistance in *M. catarrhalis* is production of β-lactamases that are especially reactive to penicillins. On the positive side, recent literature indicates that *M. catarrhalis* currently has a low rate of resistance (< 5% of strains) to cefuroxime axetil, an oral 2nd-generation agent, and cefpodoxime proxetil, an oral 3rd-generation agent.[3]

TREATMENT OF AOM: GENERAL PRINCIPLES

Otitis media needs to be classified as either AOM or OME prior to formulation of a treatment plan. The current recommendation of most experts is that antimicrobial treatment should be withheld in cases of OME.[11]

Even with proper diagnosis, the use of antibacterial treatment in every patient with AOM is debatable because of a less than robust efficacy of antibacterials in resolving AOM compared with no treatment. Indeed, many cases of AOM are self-resolving, and, in light of increasing rates of drug resistance, some physician organizations are advocating not treating uncomplicated AOM with antibacterials. While the benefit of treating AOM with antibacterials is not overwhelming, it is statistically significant. For example, several studies comparing antimicrobial therapy with no therapy in AOM have shown that approximately 80% of untreated children have clinical resolution in 7-14 days, compared with approximately 95% of those children treated with appropriate antimicrobial therapy.[12]

The ideal agent for initial treatment of AOM will have high activity against *S. pneumoniae*, the most common bacterial cause of AOM. Also, the ideal agent for initial therapy will have a relatively narrow antibacterial spectrum (to decrease the risk of bacterial resistance development), will be relatively inexpensive, will achieve adequate middle ear concentrations, and will have a mild adverse effect profile. The ideal agents for cases that fail to respond to initial therapy will be active against penicillin-resistant *S. pneumoniae* and β-lactamase–producing *H. influenzae* and β-lactamase–producing *M. catarrhalis* (the most likely causes of AOM unresponsive to initial treatment).

TREATMENT OF AOM: CURRENT STRATEGIES

In light of increasing bacterial resistance, in 1997, the CDC convened a panel of experts to make recommendations regarding antibacterial treatment of AOM. This panel, named the Drug-resistant *Streptococcus pneumoniae* Therapeutic Working Group, published its guidelines in 1999.[13] Of the multitude of antibacterials approved for treatment of AOM, the CDC working group only recommended 4 agents: amoxicillin, amoxicillin/clavulanate, cefuroxime axetil, and ceftriaxone. Table 3 outlines the treatment guidelines that the CDC working group recommended.

The first question that this panel addressed was whether or not amoxicillin should remain the preferred drug for initial treatment of AOM. The CDC working group concluded that amoxicillin remains the best antibacterial for initial treatment of AOM. There are several reasons for this conclusion. First, 40%-50% of AOM cases are attributed to *S. pneumoniae*, and that no other oral medication has shown to be more active than amoxicillin against this organism (including penicillin-resistant strains). Drug-resistant *S. pneumoniae* is more likely to be a factor if the patient has received prior antibacterial therapy in the past month. Amoxicillin consistently shows higher activity against drug-resistant *S. pneumoniae* than do other commonly prescribed agents for AOM. However, to achieve levels of amoxicillin in the middle ear that will be high enough to overcome drug-resistant *S. pneumoniae*, the dose of amoxicillin should be increased to 80-90 mg/kg/day. While this is not an FDA-approved dose, there is a preponderance of evidence suggesting that amoxicillin is very safe and effective at this higher dose. Another reason supporting

initial use of amoxicillin is that even though many strains of *H. influenzae* and most strains of *M. catarrhalis* are now resistant to amoxicillin via production of β-lactamase, AOM attributed to these organisms is more likely to resolve spontaneously. Therefore, the CDC working group concluded that amoxicillin, either at the normal dose or at the high dose, is appropriate for initial treatment of AOM. For those patients at risk for drug-resistant *S. pneumoniae* (e.g., prior antibacterial use within the past month), the high-dose regimen for amoxicillin should be used as initial therapy.

The CDC working group also addressed what alternative agents should be used when amoxicillin therapy fails. Therapy failure is defined as persistence of clinical signs and symptoms of acute infection after 3 days of therapy. The ideal drug for treatment of AOM that does not respond to amoxicillin would have shown consistent activity against penicillin-resistant *S. pneumoniae* and β-lactamase–producing strains of *H. influenzae* and *M. catarrhalis*. While no single oral medication fits all of these parameters, the CDC working group identified 3 agents that it found were superior to all others for treatment of amoxicillin-resistant AOM: high-dose amoxicillin therapy using amoxicillin/clavulanate (requires either the 7:1 or 14:1 amoxicillin:clavulanate formulation), cefuroxime axetil, and IM ceftriaxone. However, there are clear disadvantages for each of these 3 agents recommended by the CDC working group (described below in the section reviewing individual drugs and drug classes that are used in AOM treatment). Two additional agents, cefprozil and cefpodoxime (oral 3rd-generation cephalosporins) were also highly considered, but were not endorsed because of limited clinical data supporting their use for AOM because of drug resistance to *S. pneumoniae*. Clindamycin, a lincomycin with activity against gram-positive aerobes and gram-positive and gram-negative anaerobes, is recommended by the CDC working group as an option for treatment of AOM because of drug-resistant *S. pneumoniae*. However, clindamycin is not active against *H. influenzae* or *M. catarrhalis*, and should be used only if *S. pneumoniae* is confirmed by culture.

In a recent publication, Erramouspe and Heyneman offer a similar approach to the CDC expert group with several appropriate modifications.[1] Recognizing that the CDC expert group has been criticized for not giving greater consideration to recommending a second step approach to AOM initially resistant to amoxicillin that focuses on β-lactamase production alone, the authors argue that several other antibacterials are worth advocating in this situation. For patients that have been adherent to an adequate regimen of initial amoxicillin therapy, treatment failure is very likely to be because of β-lactamase–producing strains of *H. influenzae* or *M. catarrhalis*. In this case, TMP/SMX may be an appropriate agent for treatment of AOM unresponsive to amoxicillin. TMP/SMX can be given twice daily, and has a low acquisition cost. While resistance has risen, TMP/SMX still maintains relatively high activity against both *H. influenzae* and *M. catarrhalis*. On the other hand, TMP/SMX would not be an appropriate choice if the patient has risk factors for drug-resistant *S. pneumoniae*, lives in an area that is known to have a high rate of *H. influenzae* that is resistant to TMP/SMX, or if patient compliance is a major concern (TMP/SMX is associated with poor palatability). Erramouspe and Heyneman give several other alternatives for second-line treatment of AOM unresponsive to amoxicillin, but with less preference relative to TMP/SMX

because of higher acquisition cost and/or lack of good evidence indicating that these agents reach high enough middle ear concentrations. These alternatives include azithromycin, clarithromycin, erythromycin /sulfisoxazole, cefdinir, cefpodoxime, cefixime, ceftibuten and IM ceftriaxone. Finally, the authors conclude their discussion of second-line therapy for AOM unresponsive to amoxicillin by stating that cefaclor and loracarbef should not be recommended because of a high rate of resistance, a position that is confirmed in most AOM treatment guidelines. The recommendations suggested by Erramouspe and Heyneman are summarized in table 4.

TREATMENT OF AOM: REVIEW OF COMMONLY USED ANTI-BACTERIALS

Amoxicillin

As described above, there continues to be overwhelming support for amoxicillin as the treatment of choice for initial, non-recurring AOM. Standard-dose amoxicillin (40-45 mg/kg/day) is highly effective for treatment of AOM attributed to penicillin-sensitive *S. pneumoniae*. High-dose amoxicillin (80-90 mg/kg/day) is effective for AOM for penicillin-intermediate strains of *S. pneumoniae* and is often effective for AOM from penicillin-resistant strains of *S. pneumoniae*. Indeed, no other antibacterial has been proven superior for treatment of AOM owing to *S. pneumoniae* if appropriate amoxicillin dosing is used.[13] Amoxicillin-resistant AOM infections are typically caused by β-lactamase–producing strains of *H. influenzae* and, to a lesser extent, β-lactamase–producing *M. catarrhalis*. In these situations, alternative therapy targeting β-lactamase–producing *H. influenzae* must be used.

Children tolerate amoxicillin well, and it is one of the safest antimicrobials available. Even though the high-dose amoxicillin regimen is not FDA-approved, there is an overwhelming body of literature supporting the safety of this dose in children. Adverse effects include GI distress, allergic rash, and a non-allergic "ampicillin rash." The non-allergic rash occurs in about 10% of patients; however, the time to onset of rash is typically longer than that of a true allergic reaction.

Amoxicillin/Clavulanate

The combination of the β-lactamase inhibitor clavulanic acid with amoxicillin in the product Augmentin® extends the spectrum of amoxicillin to most β-lactamase–producing strains of *H. influenzae* and *M. catarrhalis*. This combination is useful for AOM that is unresponsive to amoxicillin, and is one of the agents recommended by the CDC expert group for this purpose. The original formulation consists of a 4:1 ratio of amoxicillin to clavulanate; this formulation is dosed 3 times daily. Two additional Augmentin® formulations, a 7:1 formulation, and the recently approved 14:1 (Augmentin ES-600®) formulation, allow for twice daily dosing for treatment of AOM. Amoxicillin/clavulanate given twice daily for treatment of AOM is effective, improves compliance, and decreases the severity of clavulanate-related adverse effects owing to the overall lower daily dose of clavulanic acid. Because of the different ratios of amoxicillin to clavulanate in these products, care must be taken not to substitute one formulation for the other. If the recommended high dose of amoxicillin is to be given as amoxicillin/clavulanate, then the new 14:1 formulation is preferable, as it minimizes clavulanate intake and adverse effects.

Because of the presence of clavulanic acid, this combination is not tolerated as well as amoxicillin alone. Diarrhea is a common adverse effect of amoxicillin/clavulanate. Although the severity of diarrhea with the 7:1 formulations is decreased, the overall incidence remains the same. As with amoxicillin, both an allergic and non-allergic rash may occur. Patients with a history of an allergic to response to any penicillin should not receive amoxicillin/clavulanate.

Cephalosporins

The cephalosporins are β-lactam antibacterials that are divided into 3 (occasionally 4) generations for convenience. As a general rule, higher generation cephalosporins have greater gram-negative coverage and a longer half-life, allowing for qd or bid dosing. As a drug class, the cephalosporins are less susceptible to β-lactamase degradation than the penicillins (excluding the penicillinase-resistant penicillins). At present there are 10 cephalosporins marketed in the U.S. with an indication for treatment of AOM.

The 1st-generation cephalosporins indicated for AOM are cephalexin (Keflex®) and cephradine (Velosef®). These cephalosporins have reasonable coverage of *Streptococcus* spp., but their coverage of *H. influenzae* and *M catarrhalis* is poor to nonexistent. Therefore, using a 1st-generation cephalosporin for the treatment of AOM is no longer recommended.

The 2nd-generation cephalosporins indicated for AOM are cefaclor (Ceclor®), loracarbef (Lorabid®), cefprozil (Cefzil®), and cefuroxime axetil (Ceftin®). Cefaclor has been used successfully for over 20 years for AOM. However, recent bacterial resistance trends have called into question whether cefaclor is an appropriate choice for empirical treatment of AOM. Cefaclor has been associated with serum-like sickness in approximately 0.5% of patients. Studies have demonstrated that cefuroxime axetil, when compared with amoxicillin / clavulanate, is as or more effective for AOM. Also, cefuroxime axetil may be superior to amoxicillin/clavulanate because of its lower incidence of GI adverse effects. However, the poor taste of cefuroxime axetil suspension may limit its use in some patients.[14] While past studies have shown loracarbef to be as efficacious as amoxicillin/clavulanate for AOM and to have superior activity against *H. influenzae* than cefaclor, recent data demonstrate that the resistance of middle ear pathogens to loracarbef is high enough to no longer justify its routine use in AOM.[13] Cefprozil is 2-8 times more potent against streptococci than cefaclor, but is less active against β-lactamase–producing *H. influenzae* and *M. catarrhalis* than amoxicillin/clavulanate.[3] Several studies have determined cefprozil to be equivalent to amoxicillin/clavulanate, cefaclor, and cefixime for AOM. In summary, cefprozil and cefuroxime axetil are the 2nd-generation cephalosporins that are potentially useful for AOM but have failed to respond to amoxicillin; loracarbef and cefaclor are the 2nd-generation cephalosporins that should be avoided for treatment of AOM.

The oral, 3rd-generation cephalosporins indicated for AOM are cefpodoxime proxetil (Vantin®), ceftibuten (Cedax®), cefdinir (Omnicef®), and cefixime (Suprax®). Cefixime has excellent activity against β-lactamase–producing *H. influenzae* and *M. catarrhalis* but has significantly weaker activity against *S. pneumoniae* than amoxicillin. Therefore, cefixime may be a good choice for AOM unresponsive to

agents with high activity against *S. pneumoniae*, as these cases of AOM are likely attributed to *H. influenzae* or *M. catarrhalis*. Ceftibuten is similar to cefixime in terms of bacterial coverage and efficacy. Studies have shown it to be as effective for AOM as cefaclor and cefprozil.[3] In general, cefixime and ceftibuten should not be used for initial treatment of AOM, but should be reserved for cases likely caused by β-lactamase–producing *H. influenzae* and *M. catarrhalis*. Cefpodoxime proxetil has higher activity against *S. pneumoniae* than cefixime, and has been shown to be significantly more effective for AOM than both cefixime and amoxicillin clavulanate. Cefdinir is the latest addition to the cephalosporin family, and has a spectrum of activity and efficacy similar to cefpodoxime proxetil. When administered with iron products, cefdinir may bind iron, decreasing oral absorption of both agents. Cefdinir may cause reddening of the feces when administered to infants receiving formula high in iron. Overall, the oral 3rd-generation cephalosporins should be reserved for AOM that doesn't respond to first-line therapy, and is likely caused by β-lactamase–producing *H. influenzae* or *M. catarrhalis*. Of the 3rd-generation agents, cefpodoxime proxetil and cefdinir may be superior to ceftibuten and cefixime for the treatment of AOM because of their excellent *H. influenzae* and *M. catarrhalis* activity and their higher activity, relative to cefixime and ceftibuten, against *S. pneumoniae*.[15]

Ceftriaxone (Rocephin®), a parenteral, 3rd-generation cephalosporin with a relatively long half-life of 6-8 hours, was recently approved as a single-dose treatment for AOM. Ceftriaxone has been proven to be as effective as 14 days of amoxicillin for AOM; however, its use is limited by the necessity of an IM injection. In addition, up to 3 doses (50 mg/kg/day) may be necessary for appropriate treatment of AOM caused by drug-resistant *S. pneumoniae*.[1] Compliance with the second and third IM doses of ceftriaxone has been called in question; however, in certain situations, such as noncompliance or children with malabsorption syndromes, ceftriaxone IM as a single-dose treatment for AOM may be useful.

Trimethoprim/Sulfamethoxazole

The CDC expert group did not recommend TMP/SMX for any stage of AOM treatment. However, there are obvious situations in which TMP/SMX may be a useful alternative therapy to amoxicillin. For patients allergic to penicillin and who cannot take amoxicillin, TMP/SMX is an inexpensive, useful alternative for the treatment of AOM.[1] The activity of TMP/SMX is especially potent against *H. influenzae*; however, coverage of group A streptococci is relatively poor and pneumococcal resistance is increasing.[16] When the patient has been compliant with initial high-dose amoxicillin, yet does not have resolution of AOM symptoms, then further treatment with TMP/SMX may be an inexpensive and effective therapy. It is important to remember that the dose of TMP/SMX, when calculated by body weight, is determined based on trimethoprim content.

Adverse effects of TMP/SMX are usually minor and localized to the GI tract. Because of the sulfonamide component there is a risk of hematologic and dermatologic complications and allergic reactions. Patient compliance with TMP/SMX may be decreased from the poor taste of the oral suspension.

Macrolides

Erythromycin combined with sulfisoxazole (Pediazole®) and clarithromycin (Biaxin®)

are macrolide products approved for treatment of AOM. In addition, one macrolide-like product, azithromycin (Zithromax®), is also approved for AOM. However, there is no clear evidence that the macrolides have any benefit over high-dose amoxicillin for the treatment of drug-resistant *S. pneumoniae*. In fact, because of current trends in antibacterial resistance, there is a high likelihood that AOM that is resistant to amoxicillin will also be resistant to macrolide therapy.[13] Unlike amoxicillin and other β-lactams, *S. pneumoniae* resistance to the macrolides usually cannot be overcome with higher doses.

Erythromycin/sulfisoxazole has been used for patients who do not respond to amoxicillin; however, the high rate of GI distress, poor palatability, and high dosing frequency associated with this combination makes it a less attractive alternative than other agents. In addition, many *H. influenzae* strains are now resistant to erythromycin. On the other hand, if amoxicillin cannot be used or is ineffective, erythromycin/sulfisoxazole is one of the few inexpensive alternatives available.

Clarithromycin and its active metabolite 14-hydroxy-clarithromycin are both active against common AOM organisms; because of this additive effect, clarithromycin may be dosed bid. Clarithromycin has been proven as effective as amoxicillin, amoxicillin/clavulanate, and cefaclor, and presents an attractive alternative when β-lactam therapy cannot be used or is ineffective. For some patients, compliance for 10 days of therapy may be difficult because of the poor aftertaste of the suspension. Parents of children receiving clarithromycin suspension should be advised not to store the product in the refrigerator.

Azithromycin is a macrolide with an exceptionally long half-life (70-80 hrs), and can be conveniently dosed qd. Unlike any other oral medication for AOM, azithromycin is approved for just 5 days of therapy, as the long half-life provides 10 days of therapeutic blood levels with 5 days of drug therapy. Like clarithromycin, azithromycin has been proven as effective as amoxicillin and amoxicillin/clavulanate for AOM. Children tolerate Azithromycin well, and the suspension has an improved taste relative to clarithromycin suspension. It is recommended that azithromycin suspension be taken on an empty stomach; azithromycin tablets may be taken without regard to food. For patients with compliance difficulties, azithromycin presents an attractive alternative to other antibacterials.

SUMMARY

There is a large selection of antibacterials currently approved for the treatment of AOM. In most cases, amoxicillin remains the drug of choice for initial treatment of AOM; in children at risk for drug-resistant *S. pneumoniae*, the higher dose of amoxicillin (80-90 mg/kg/day) should be the initial amoxicillin dose. In cases of amoxicillin failure, there are multiple alternatives available presenting a challenge to the pharmacist in terms of therapy recommendation and patient counseling. According to the CDC expert group, amoxicillin/clavulanate, cefuroxime axetil, and IM ceftriaxone are the only antibacterials that can be relied upon for treatment of AOM that don't respond to initial standard or high-dose amoxicillin therapy. However, other clinicians feel that there is a valid role for older, cheaper antiinfectives, such as trimethoprim/sulfamethoxazole, for either initial or alternative therapy of AOM. Therefore, when choosing AOM therapy, it may be appropriately modified for patient-specific factors, such as past antibacterial exposure, risk for drug-resistant *S. pneumoniae*, history of compliance, and medication cost. The informed pharmacist will be empowered to intervene on the patient's behalf when an alternative therapy is necessary for the treatment of AOM.

Table 1: Factors that Increase or Decrease the Risk of Otitis Media

Increased Risk of Otitis Media	Decreased Risk of Otitis Media
• Daycare visits • Passive smoking • Male sex • Inuit, Native American, Native Alaskan race • Bottle-feeding, especially if child is on back	• Female sex • Breast-feeding (decreased occurrence of chronic otitis media in first 3-6 months of life)

Table 2: Bacterial Pathogens Isolated from Middle Ear Fluid in Children with Acute Otitis Media[2]

Microorganism	Percent
S. pneumoniae	39
H. influenzae	27
M. catarrhalis	10
Other (e.g., *S. aureus*, group A streptococcus)	13
None or nonpathogenic bacteria	28

Table 3: CDC Expert Group Recommendations for AOM Treatment[13]

Antibiotics in Prior Month	Day 0	Treatment Failure on Day 3	Treatment Failure on Days 10-28
No	High-dose amoxicillin; standard-dose amoxicillin	High-dose amoxicillin-clavulanate; cefuroxime axetil; IM ceftriaxone	Same as day 3
Yes	High-dose amoxicillin; high-dose amoxicillin-clavulanate; cefuroxime axetil	IM ceftriaxone; clindamycin; tympanocentesis	High-dose amoxicillin-clavulanate; cefuroxime axetil; IM ceftriaxone; tympanocentesis

Table 4: Alternative Recommendations for AOM Treatment[1]

STEP 1		STEP 2a Adherence to Step 1 HD Amoxicillin	STEP 3a	
Treatment		**Good/Complete[c]**	**Poor/Incomplete[c]**	
Preferred	HD Amoxicillin or SD Amoxicillin[b]	TMP/SMX	HD Amoxicillin/ Clavulanate	Ceftriaxone[e] Tympanocentesis
Alternative(s)	TMP/SMX[b]	SD Amoxicillin/Clavulanate Cefdinir Cefixime Cefpodoxime proxetil Ceftibuten Cefuroxime axetil Azithromycin Clarithromycin Erythromycin/Sulfisoxazole	Cefdinir Cefpodoxime proxetil Cefproxil Cefuroxime axetil	

[a] Steps 2 & 3 indicated for treatment failure after 3 days of Step 1 therapy
[b] Acceptable if patient is low risk for drug-resistant *S. pneumoniae*
[c] Therapies chosen for coverage of β-lactamase–producing *H. influenzae*
[d] Therapies chosen for coverage of β-lactamase–producing *H. influenzae* and drug-resistant *S. pneumoniae*
[e] Three-dose regimen (IM 50 mg/kg once daily for 3 days)

Table 5: Commonly Used Antibacterials for Treatment of AOM

Antibacterial		Dose	Comments
Generic	**Trade**		
Amoxicillin	Amoxil®, Trimox®, Wymox®	40-45 mg/kg/day (STD dose) q8h or 80-90 mg/kg/day (high dose) q8-12h[1]	DOC for non-recurring AOM; Inexpensive; 10% patients have non-allergic rash
Amoxicillin/ Clavulanate	Augmentin®	45 mg/kg/day given q12h 40 mg/kg/day given q8h 80-90 mg/kg/day given q8-12h (high dose)	High incidence of GI effects; Take with food
	Augmentin®-ES 600	90 mg/kg/day given q12h	
Cefaclor	Ceclor®	40 mg/kg/day given q8-12h	Serum-like sickness reported in 0.5% of patients; Avoid antacids; High- resistance rates
Loracarbef	Lorabid®	30 mg/kg/day given q12h	High-resistance rates
Cefprozil	Cefzil®	30 mg/kg/day given q12h	
Cefuroxime axetil	Ceftin®	30 mg/kg/day given q12h	Take with food; Capsules & suspension not equivalent; Poor taste
Cefixime	Suprax®	8 mg/kg/day given q12-24h	
Cefpodoxime proxetil	Vantin®	10 mg/kg/day given q12-24h	Take with food; Avoid antacids
Ceftibuten	Cedax®	9 mg/kg/day given q24h	Take on empty stomach
Cefdinir	Omnicef®	14 mg/kg/day given q12-24h	Binds to iron – avoid concomitant intake of products high in iron; Avoid antacids
Ceftriaxone	Rocephin®	50 mg/kg IM once (3 doses may be necessary for drug-resistant AOM)	May increase bleeding time
Clarithromycin	Biaxin®	15 mg/kg/day given q12h	Poor taste; Do not refrigerate suspension
Azithromycin	Zithromax®	Day 1: 10mg/kg once Days 2 -5: 5 mg/kg q24h	Take suspension on empty stomach; Tablets may be taken with food
Erythromycin/Sulfisoxazole	Pediazole®	50 mg/kg/day erythromycin given q6h	High incidence of GI effects; Poor taste
TMP/SMX	Bactrim® Septra®	8-10mg/kg/day trimethoprim given q12h	Rare hematologic & dermatologic effects; Photosensitivity may occur; Poor taste

[1] Currently recommended dose is higher than FDA-approved dose for AOM

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