Otitis Media—Principles of Judicious Use of Antimicrobial Agents

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ABSTRACT. Otitis media is the leading indication for outpatient antimicrobial use in the United States. Over-diagnosis of and unnecessary prescribing for this condition has contributed to the spread of antimicrobial resistance. A critical step in reducing unnecessary prescribing is to identify the subset of patients who are unlikely to benefit from antibiotics. Conscientiously distinguishing acute otitis media (AOM) from otitis media with effusion (OME), and deferring antibiotics for OME will accom-

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SUPPLEMENT

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Anti-microbials are not indicated for initial treatment. Discussions of shortened courses of antibiotics for AOM and restricted indications for antimicrobial prophylaxis are also presented. Pediatrics 1998;101:165–171; antimicrobial resistance, antimicrobial use, otitis media, upper respiratory infection, antimicrobial therapy, pediatrics, acute otitis media, otitis media with effusion, prophylaxis.

Abbreviation. AHCPR, Agency for Health Care Policy and Research.

**PRINCIPLES**

1. Episodes of otitis media should be classified as acute otitis media (AOM) or otitis media with effusion (OME).
2. Anti-microbials are indicated for treatment of AOM; however, diagnosis requires documented middle ear effusion and signs or symptoms of acute local or systemic illness.
3. Uncomplicated AOM may be treated with a 5- to 7-day course of anti-microbials in certain patients.
4. Anti-microbials are not indicated for initial treatment of OME; treatment may be indicated if effusions persist for 3 months.
5. Persistent middle ear effusion (OME) after therapy for AOM is expected and does not require retreatment.
6. Anti-microbial prophylaxis should be reserved for control of recurrent AOM, defined by 3 distinct and well-documented episodes/6 months or 4 episodes/12 months.

**BACKGROUND AND JUSTIFICATION**

Otitis media consistently leads the list of the most common indications for outpatient anti-microbial use in the United States. In recent years, the number of office visits for otitis media has increased out of proportion to the increase in population size, from 9.9 million visits in 1975 to 24.5 million in 1990. It is not clear why the diagnosis is being made so much more often, although some authorities have suggested an association with increased use of out-of-home child care. Because of its importance as an indication for anti-biotic use, efforts to influence antibiotic prescribing practices have consistently begun by addressing otitis media. As a result of this emphasis, there is a considerable body of literature on which recommendations can be based. The relative efficacy of antibiotic treatment for AOM and OME has been well-defined, the natural history of appropriately treated AOM is understood to include persistent middle ear effusions for several weeks in the majority of children, and the indications for prophylaxis have been evaluated. Yet children continue to routinely receive anti-microbials for OME detected as an incidental finding, for asymptomatic effusions detected only a few weeks after an uncomplicated episode of AOM, and in prophylactic regimens initiated in patients who have not met strict criteria. More work is needed to bring current antibiotic prescribing practices in line with indications available from the considerable body of recent literature on otitis media.

The following guidelines are intended to begin this process by highlighting situations in which antibiotic use may be reduced without compromising patient care.

**EVIDENCE SUPPORTING PRINCIPLES**

### Episodes of Otitis Media Should Be Classified as AOM or OME

Distinguishing each episode of otitis media in this manner leads directly to a management strategy that optimizes treatment for those children who require it, but curtails the use of anti-microbials for children in whom they would not be beneficial. The distinction between these entities is usually clear, but classification of some patients with equivocal otoscopic findings may require careful clinical judgment.

AOM is defined as the presence of fluid in the middle ear in association with signs or symptoms of acute local or systemic illness. Accompanying signs and symptoms may be specific for AOM, such as otalgia or otorrhea; or nonspecific, such as fever. Anti-microbial agents are indicated for this condition, as discussed below.

OME is defined as the presence of fluid in the middle ear in the absence of signs or symptoms of acute infection. Anti-microbials may be appropriately deferred for this group of children, in agreement with recommendations of an expert panel convened by the US Agency for Health Care Policy and Research (AHCPR).

### Anti-microbials Are Indicated for Treatment of AOM

The cumulative evidence from randomized controlled trials in which antibiotic therapy has been compared with no therapy for AOM is persuasive in favoring antibiotic therapy, although the treatment effect is small. Approximately 80% of untreated children have clinical resolution by 7 to 14 days, compared with ~95% of those treated with anti-microbials. Differences among the various anti-microbials in terms of clinical efficacy, if present, are generally too small to be detected. The benefit of anti-microbial treatment is most apparent when pathogenic bacteria are isolated from middle ear fluid, when bacterial eradication is used to assess outcome, or when clinical outcome was assessed at 2 to 3 days, rather than 7 to 14 days.

### Diagnosis of AOM

Although there is general agreement that anti-microbials are indicated for AOM, there is no such agreement on how to establish the diagnosis. Specific criteria for the diagnosis have been notoriously difficult to validate or standardize, perhaps reflecting the diversity of criteria used in practice and in clinical trials. For example, a survey of 165 pediatricians reported 147 different sets of criteria for the diagnosis of AOM. Furthermore, in clinical trials in which standardization is even more essential, 18 different sets of criteria were used in 26 trials.

Agreement can be reached on the essential steps in...
establishing the presence of middle ear effusion, without which the diagnosis of AOM cannot be supported. In rare circumstances, the practitioner may observe signs of acute inflammation in the hours before fluid accumulates in the middle ear cavity. Pneumatic otoscopy should be used to assess four principal characteristics of the tympanic membrane: position, color, translucency, and mobility. The use of visual otoscopy alone is discouraged because of the inability to assess the mobility of the tympanic membrane. Newer diagnostic tools such as tympanometry and acoustic reflectometry can aid in establishing the presence of fluid and in validating the examiner’s skills through repeated use and comparison with visual observation.

Agreement may be more difficult on which signs and symptoms of acute local or systemic illness are sufficient to establish the diagnosis of AOM in conjunction with middle ear effusion. The diagnosis can be established by the presence of local signs such as otorrhea with evidence of middle ear origin, a bulging tympanic membrane that has cloudy or yellow fluid visible behind it or is distinctly red, or local symptoms such as ear pain. Ear-pulling in the absence of other symptoms is not necessarily attributable to AOM. Fever may be indicative of AOM, although in the absence of any other findings, such as ear pain or a red or bulging tympanic membrane, fever often may be unrelated to middle ear effusion. Other signs and symptoms such as rhinorrhea, cough, irritability, headache, anorexia, vomiting, or diarrhea may be present but are not specific for AOM. Although viral upper respiratory infections frequently precede or accompany AOM, the presence of rhinorrhea or other nonspecific signs or symptoms of upper respiratory infection alone is not adequate to differentiate AOM from OME. These nonspecific symptoms usually reflect an underlying or preceding viral illness and do not resolve as rapidly after appropriate antibiotic therapy as do fever and ear pain.

Uncomplicated AOM May Be Treated With a 5- to 7-Day Course of Antimicrobials in Certain Patients

In the United States, AOM traditionally has been treated with a 10-day course of antimicrobials. There are few controlled data to support such a practice, which seems to have been carried over from the recommendations for 10 days of penicillin for streptococcal pharyngitis. Although physicians prescribe 10-day courses, children often fail to complete them.

A number of randomized trials have compared shorter courses of antimicrobial therapy, ranging from 2 to 7 days, with more traditional courses and have reported satisfactory results. Most of the trials were conducted in Europe, where differences in standard care are such that the results may not be easily applicable in the United States. One comparison was of 2 days versus 7 days of penicillin V, an antibiotic not often recommended or used to treat AOM in the United States. Two of the trials enrolled only children >3 years of age, although most antibiotic failures are reported in those <18 months. A trial from the United States reported no difference in outcome among 59 children who received 5 days of cefaclor (90% success) compared with 64 who received 10 days of cefaclor (92% success). However, this study, like those cited previously, may not have had the statistical power to detect a clinically significant difference. A recent trial including 719 patients reported that the efficacy of 5 days of cefuroxime axetil was equivalent to 10 days of either cefuroxime or amoxicillin/clavulanate. Perhaps more persuasive are reports that a single dose of ceftriaxone, which produces therapeutic middle ear concentrations of antibiotic for only 3 to 5 days, is equally effective as a 10-day course of amoxicillin or trimethoprim-sulfamethoxazole. In any case, although the evidence to support shorter courses of antimicrobials is not optimal, the evidence to support 10 to 14 days of antimicrobials is practically nonexistent. In parts of Europe, deferring antimicrobial therapy unless symptoms persist for >2 days or treating with 5 to 7 days of antimicrobials is the standard of care, and cure rates between 66% and 92% have been recorded among children treated only with analgesics and observation.

Certainly, there are theoretic advantages to decreasing the duration of therapy to 5 to 7 days for uncomplicated AOM. One would anticipate a reduction in selective pressure favoring resistant organisms, both in the community and in the individual patient. In fact, shorter courses may reflect more realistically the actual dispensing practices of parents and make it more likely that the medications are given as prescribed.

Although the available data support the use of short-course therapy for older children with mild AOM, such treatment has not been well-evaluated in children with severe or complicated AOM. Ten or more days of antimicrobials may be necessary for those children who present with perforation of the tympanic membrane. In addition, the trials assessing efficacy of shorter courses generally excluded patients at higher risk for treatment failure, such as those with underlying medical conditions and those with chronic or recurrent otitis media. Data supporting short courses of therapy in such patients are therefore lacking, and short-course therapy for these patients cannot be recommended until more data become available.

Short-course therapy also may not be appropriate for younger children. Children <15 months to 2 years of age are at increased risk for treatment failure, even with conventional dosing. The eight trials of short-course therapy reviewed above enrolled ~250 children <18 months of age, but most did not analyze the success of therapy separately for this group. Recently, a randomized trial comparing 5 days with 10 days of amoxicillin/clavulanate documented significant differences favoring the 10-day regimen among children <2 years of age. In the absence of additional data testing the efficacy of short course treatment in this age group, it seems prudent to restrict short-course therapy to children <2 years of age.
Antimicrobials Are Not Indicated for Initial Treatment of OME

Recent comprehensive reviews of the literature have been conducted and an expert panel of the US AHCPR has addressed the issue of antibiotic treatment for OME. Results of these analyses indicate that in the majority of cases, antimicrobial therapy can be deferred safely while OME resolves spontaneously, and that antimicrobials are effective at resolving effusion in only a minority of cases.

Three metaanalyses of published trials of antibiotic therapy for OME have concluded that there is a small but statistically significant effect on short-term resolution. Most of these trials enrolled children with documented middle ear effusion but no recent history of AOM. No beneficial effect of therapy was seen in those studies that included children with illnesses characterized by a high natural cure rate, such as children with effusion after a recent episode of AOM. Approximately 65% of all cases of OME will resolve within 3 months without antibiotic therapy, as will 90% of the subset of OME that immediately follows a diagnosed episode of AOM. Although the overall difference in the rate of short-term resolution between treated and untreated children in the metaanalyses was statistically significant, about seven children would have to be treated with antimicrobials for one to benefit. Of greater importance, however, is that there was no significant difference in the incidence of OME when assessed >1 month after treatment was completed, whether placebo or antibiotic therapy was used. These findings have prompted many experts to recommend that middle ear effusion in the absence of AOM should not be treated with antimicrobials at all.

Guidelines for the diagnosis and treatment of OME have been published recently by an expert panel convened by the US AHCPR and endorsed by the American Academy of Pediatrics, the American Academy of Family Physicians, and the American Academy of Otolaryngology–Head and Neck Surgery. For initial treatment of OME, the panel endorsed either of two options with similar long-term outcomes: observation with no therapy or antibiotic therapy.

With the accumulation of evidence that antibiotic use increases the risk for both colonization and invasive disease with penicillin-resistant Streptococcus pneumoniae, observation without antibiotic therapy now appears to be the preferred option. For the practicing physician faced with a well-appearing child with a middle ear effusion, considerations of risks and benefits to that individual child appropriately outweigh concerns about the emergence of antimicrobial resistance in the community as a whole. Thus, the observation that children treated with a course of antimicrobials are at increased risk to become carriers of nonsusceptible pneumococci as a result of that treatment, and that carriers of resistant strains are more likely to fail antibiotic therapy, must take precedence over the sometimes marginal benefits of antibiotic therapy for that child.

The AHCPR guidelines recommend antibiotic therapy or bilateral myringotomy with insertion of tympanotomy tubes for patients in whom bilateral effusion has been documented to persist for 3 months and is accompanied by significant bilateral hearing loss. This approach is reasonable, because persistent middle ear effusions in infancy have been associated in some studies with deficits in cognitive function and school achievement at age 7 years, although this has not been a consistent finding, and recent evidence indicates that cognitive deficits, if present, may be related more to diminished maternal responsiveness secondary to the hearing loss than to the hearing loss per se.

The AHCPR panel defined a patient with OME as a child between 1 and 3 years of age with effusion present 6 weeks after an acute episode of otitis media, with no apparent symptoms, and with no underlying medical condition. The panel estimated that 25% to 35% of all diagnoses of otitis media would fit the criteria of OME. Were antimicrobials deferred for this group of children alone, 6 to 8 million courses of unnecessary antibiotic therapy could be avoided each year.

Persistent Middle Ear Effusion After Therapy for AOM Is Expected and Does Not Require Retreatment

The natural history of appropriately treated AOM is for middle ear effusion to persist for weeks to months, a fact that may not be recognized clearly by physicians who reexamine ears soon after therapy is completed. Approximately 70% of children will have fluid in the middle ear at 2 weeks, 50% at 1 month, 20% at 2 months, and 10% at 3 months, despite appropriate antibiotic therapy. Thus, when middle ear fluid is detected in asymptomatic children at follow-up visits for AOM, administering additional courses of antimicrobials is generally unnecessary. An important step in reducing the burden of unnecessary antibiotic treatment for otitis media is the recognition that persistent effusions are part of the expected course of AOM and do not warrant therapy.

It may appear difficult to distinguish the child who has a persistent middle ear effusion as part of the natural course of appropriately treated AOM from the child who has a new effusion as part of a second episode of acute disease, but this distinction can be made by using the same criteria listed above to distinguish AOM from OME. When the effusion is accompanied by new onset of local or systemic signs or symptoms of infection, such as fever or persistent ear pain, AOM is diagnosed and a course of antimicrobials is administered. On the other hand, middle ear effusion in a child who has had an episode of AOM in the previous 2 to 3 months and in whom signs of acute illness are absent or nonspecific, such as rhinorrhea alone, would not warrant a second course of antimicrobials. Irrespective of the recent history of middle ear disease, the administration of a course of antimicrobials should be recommended only for those children with both middle ear effusion and new onset of local or systemic illness, or with bilateral effusions accompanied by documented hearing loss for ≥3 months, as discussed above.
Antibiotic Prophylaxis Should Be Reserved for Control of Recurrent AOM

The efficacy of continuous prophylactic antimicrobials for the control of recurrent AOM is well-established, although the decrease in frequency of recurrent episodes is small. Nevertheless, because of the potential consequences of emergence of additional resistant pneumococci, a recommendation that antibiotic prophylaxis for AOM be avoided whenever possible has been made. Others have argued that prophylaxis remains a valuable therapeutic option for children with recurrent AOM and should not be dismissed so readily.

Trials in which children treated with daily low-dose antibiotic therapy were compared with those given placebo have consistently documented a lower incidence of AOM in the treated group, whether the antibiotic used was erythromycin, amoxicillin, trimethoprim-sulfamethoxazole, or sulfisoxazole. A metaanalysis summarizing these results concluded that antibiotic treatment resulted in an average decrease in the number of episodes of AOM of 0.11 episode per patient per month, or slightly more than one episode per year. The treatment effect tended to be greater when sulfisoxazole was used, when treatment was continued for <6 months, or when the population studied had a high rate of recurrences.

This last point is important because it indicates that the type of patient selected for prophylaxis will determine the utility of the prophylactic regimen. The benefit of prophylaxis will be greatest if strict criteria for initiating prophylaxis are used and its use limited to those who are likely to have frequent recurrences. The most consistent criterion for prophylaxis in the published trials has been three or more distinct and well-documented episodes of AOM in the preceding 6 months or four episodes in the preceding year. Patients at high risk for severe or recurrent disease who are most likely to benefit from prophylaxis include those <2 years of age, those in out-of-home child care, and Native American children. On the other hand, some otherwise eligible children may be poor candidates for prophylaxis because of their decreased likelihood of compliance with the regimen, which was <50% in one inner-city population.

Alternative approaches to antimicrobial prophylaxis for otitis media using different schedules have been attempted, but none have been as consistently beneficial as continuous prophylaxis as outlined above. Intermittent prophylaxis using antimicrobials administered at the onset of signs of upper respiratory infection was found to be beneficial in preventing recurrent AOM in one study, but not another, and was significantly less effective than continuous prophylaxis when the two methods were compared. Prophylactic trimethoprim-sulfamethoxazole in conjunction with prensione after tympanostomy tube insertion decreased the short-term rate of tube extrusion, but there was no beneficial effect on the rate of AOM recurrence and no overall long-term benefit. An attempt at antibiotic prophylaxis rather than tympanostomy tube insertion has been advocated in one study of children with long-standing OME and hearing loss, but surgically treated patients had a lower rate of treatment failure and better short-term hearing than those on prophylaxis.

The benefit of any form of prophylactic therapy must be weighed against the risk of promoting antibiotic resistance. Evidence that even short courses of antimicrobial therapy are associated with an increased risk of nasopharyngeal carriage as well as of invasive disease with resistant bacteria has been reviewed above and elsewhere. In addition, there is specific evidence that antibiotic prophylaxis increases the likelihood of nasopharyngeal colonization with resistant pneumococci and the proportion of children with β-lactamase-producing organisms in middle ear effusions. This effect is seen among children given amoxicillin prophylaxis, but not among those given sulfisoxazole. Importantly, the rate of colonization with resistant strains returned to baseline levels several months after prophylaxis was discontinued.

Other interventions that may decrease the incidence of recurrent AOM without the risks of antibiotic prophylaxis include eliminating smoking in the home, reducing day care attendance, eliminating pacifiers, and giving influenza vaccine. Insertion of tympanostomy tubes has been demonstrated to be an effective means of reducing the frequency of recurrent AOM and may be a reasonable alternative to antimicrobial prophylaxis in selected children. Conjugate pneumococcal vaccines may provide an important alternative in the future. Parents should also be reassured that the incidence of recurrent AOM appears to decrease with increasing age of the child.

Control of recurrent AOM among children with three or more well-documented and separate episodes in the preceding 6 months or four or more episodes in the preceding 12 months is the only indication for which evidence of the beneficial effects of antibiotic prophylaxis has been consistent and persuasive. Because of the potential consequences of promoting resistant bacteria to both the patient and the community, prophylaxis should not be initiated for other indications. When initiated, the duration of prophylactic therapy should be no more than 6 months, because longer courses are less effective and may be more likely to promote colonization with resistant bacteria. Either sulfisoxazole or amoxicillin is the agent of choice; cephalosporins have not been demonstrated to be effective. Sulfisoxazole has been used in the majority of controlled trials of prophylaxis, appears to be more efficacious at preventing recurrences than the other agents, and may be less likely than amoxicillin to promote colonization with β-lactamase-producing bacteria or resistant pneumococci.

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Pharyngitis—Principles of Judicious Use of Antimicrobial Agents

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ABSTRACT. Accurate diagnosis of group A streptococcal pharyngitis and appropriate antimicrobial therapy are important, particularly to prevent nonsuppurative sequelae such as rheumatic fever. Most episodes of sore throat, however, are caused by viral agents. Clinical findings cannot reliably differentiate streptococcal from viral pharyngitis and most physicians tend to overestimate the probability of a streptococcal infection based on history and physical examination alone. Therefore, diagnosis should be based on results of a throat culture or an antigen-detection test with pending results of a culture is discouraged because treatment often continues despite a negative test result. Other bacterial causes of pharyngitis are uncommon and often can be diagnosed based on nonpharyngeal findings. Penicillin remains the drug of choice for streptococcal pharyngitis because of its effectiveness, relatively narrow spectrum, and low cost. No group A streptococci are resistant to β-lactam antibiotics. High rates of resistance to macrolides has been documented in several areas; in Finland, decreased national rates of macrolide use led to a decline in the proportion of macrolide-resistant group A streptococci. Pediatrics 1998;101:171–174; group A Streptococcus, pharyngitis, diagnosis, antimicrobial therapy.

PRINCIPLES

1. Diagnosis of group A streptococcal pharyngitis should be made based on results of appropriate laboratory tests in conjunction with clinical and epidemiologic findings.

2. Antimicrobial therapy should not be given to a child with pharyngitis in the absence of diagnosed group A streptococcal or other bacterial infection.

3. A penicillin remains the drug of choice for treating group A streptococcal pharyngitis.

BACKGROUND AND JUSTIFICATION

Sore throat is one of the most common complaints in pediatrics, resulting in millions of physician office visits each year. Group A Streptococcus (S. pyogenes), the leading bacterial cause of pharyngitis, accounts for ~15% of all cases. Diagnosis and treatment of streptococcal pharyngitis are important because antimicrobial therapy initiated within 9 days of onset is effective in preventing acute rheumatic fever. In addition, treatment of group A streptococcal infection may prevent supplicative complications, lead to more rapid resolution of illness, and prevent the spread of infection. Nevertheless, because most episodes of sore throat are caused...
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