An Evidence Based Guideline to Treat Otitis Media in Children:

Solution for the Child, Parent, or Mankind?

By: Brian Molenda

Despite the numerous publications concerning the frequency, risk factors, and drug selection of antibiotics to treat otitis media, this disease state continues to generate controversy. The healthcare provider is expected to construct an accurate clinical diagnosis, select the most appropriate antibiotic when needed, and occasionally have the courage to walk away from a screaming child or frustrated parent without doing anything. The latter act may be the most beneficial, although hardest to perform.

The development of bacterial resistance caused by the inaccurate diagnosis of otitis media and overly prescribed antibiotics is a major health concern. This evidence based guideline’s objective is to describe the pathophysiology, diagnosis, treatment options, and explore the relationship between otitis media and bacterial resistance. This information intends to help direct healthcare providers choose the most appropriate choice of treatment, along with educating them on emerging resistance issues. Lastly, this paper will explore the ethical dilemma of potentially dispensing unnecessary antibiotics to a child in the face of emerging bacterial resistance issues.

Otitis media is a term to describe an inflammation of the middle ear, with classification dependent upon clinical presentation. Generally, there are three major classifications which include acute otitis media, otitis media with effusion, and chronic purulent media. Acute otitis media (AOM) is the rapid onset of signs and symptoms (e.g. otalgia, hearing loss, and fever) of the middle ear. Otitis media with effusion (OME or accumulation of liquid in the middle ear cavity) differs from AOM in that the signs and symptoms of an acute infection are absent, or asymptomatic. The tympanic membrane’s opacity makes the type of effusion (serous, mucous) difficult to determine. Chronic purulent media is characterized by chronic inflammation of the middle ear and otitis media without effusion, and is the least prevalent of the three types.1

The middle ear is an air-filled cavity that begins at the tympanic membrane and extends to the nasopharynx via the eustachian tube. In adults, the eustachian tube lies at a 45-degree angle to the horizontal plane, and at a 10-degree angle in infants. Its primary functions with respect to the middle ear are to regulate atmospheric pressure between both sides of the tympanic membrane, protect against nasopharyngeal secretions, and drain secretions from the middle ear into the nasopharynx. In infants, this difference in angles causes improper drainage of the middle ear as a result of decreased gravitational effects on the
eustacian tube. In addition, the muscle responsible for eustachian tube opening, the tensor veli palatine, is less efficient. These deficiencies cause the reflux transudation of liquid in the middle ear and proliferation of bacteria in these secretions, resulting in acute otitis media.1

The most frequent diagnosis in infants and children who visit physicians because of illness is acute otitis media (AOM).2 Moreover, before age 7 years, 65% to 95% of children will have experienced 1 or more episodes of AOM.3 It has been estimated that more than $3.5 billion dollars is spent annually on managing AOM in the United States.4 However, these impressive numbers also result in similar, more alarming statistics with regards to antibiotic resistance. For example, the pathogens and rates of resistance in AOM have changed so frequently that data before 19935 is not reflective of the current situation. In the 1980’s, H. influenza was the most common pathogen isolated in patients who failed to respond to initial treatment of AOM.6 Currently, this distinction belongs to S. pneumoniae, particularly penicillin-resistant strains.7,8,9 S. pneumoniae causes approximately 7 million cases of otitis media annually in the United States.10 The second and third most frequently cultured pathogens are H. influenza and Moraxella catarrhalis, respectively. Of concern, in the 1990’s, the percentage of S. pneumoniae strains found to demonstrate a reduced susceptibility to amoxicillin ranged from 30% to 60% in the United States.11 Moreover, the proportion of ß-lactamase producing H. influenza and M. catarrhalis strains in AOM has nearly tripled, with resistance going from 15% to 55% for H. influenza to nearly 100% for M. catarrhalis. With the three most prevalent bacterial causes of AOM expressing increasingly significant bacterial resistance, the following guidelines have been developed. Each guideline is followed by a summary of relevant clinical data, and concludes in a degree of level of evidence and recommendation, as defined by Tables 1 and 2, respectively.

Table 1. System Used for Defining Levels of Evidence in Otitis Media Treatment

<table>
<thead>
<tr>
<th>Level of Evidence</th>
<th>Definition</th>
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<tbody>
<tr>
<td>I</td>
<td>Randomized clinical trials or meta-analyses</td>
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<tr>
<td>II</td>
<td>A single randomized trial or nonrandomized studies</td>
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<tr>
<td>III</td>
<td>Expert opinion, case studies, or standard of care</td>
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Table 2. System for Defining Levels of Recommendation in Otitis Media Treatment

<table>
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<th>Level of Evidence</th>
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A There is evidence that the treatment is effective, convenient, safe, and cost effective.
B There is conflicting evidence about the efficacy, convenience, safety, and cost-effectiveness of the treatment.
C There is little evidence for use.

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 avoids the use of antimicrobials for children in whom they would not be beneficial. The distinction between these entities is usually clear, however, some patients with equivocal otoscopic findings may require careful clinical judgement. AOM is defined as presence of fluid in the middle ear in association with signs or symptoms of acute local or systemic illness, which is an indication for antimicrobials. However, the diagnosis of AOM is still under scrutiny. Different practitioners use various criteria to define AOM. For example, a survey of 165 pediatricians reported 147 different sets of criteria for the diagnosis of AOM. Furthermore, in clinical trials, a review of 26 trials revealed 18 different sets of criteria. A standard set of symptomatic criteria for definitive classification of AOM is needed.

There has been sufficient data, however, to establish the presence of middle ear effusion. Pneumatic otoscopy should be used to assess four principal characteristics of the tympanic membrane: position, color, translucency, and mobility. Visual otoscopy alone is discouraged because mobility of the tympanic membrane is very difficult to assess. More advanced diagnostic methods such as tympanometry and acoustic reflectometry can aid in establishing fluid content, along with repetition and visual comparison by the examiner.

There are various opinions regarding which signs and symptoms of acute or local illness are sufficient to satisfy the diagnosis of AOM with middle ear effusion. Clinical data include the presence of local signs (e.g. 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 is not necessarily attributable to AOM in the absence of other symptoms. Fever may be indicative of AOM, although in the absence of other findings, it 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. Thus, differentiation between AOM and OME is necessary to decide if the selection and duration of antibiotics is necessary. (Recommendation: Level IA)
In the United States, AOM traditionally has been treated with a 10-day course of antimicrobials. Surprisingly, 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. In addition, 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, and have reported satisfactory results. Most of these trials, however, were conducted in Europe, which may have different standards of care. For example, one of the studies compared Penicillin V for 2 days versus 7 days for AOM, an antibiotic not normally used in the United States for AOM. However, a trial conducted in the U.S. reported no difference in outcome among 59 patients who received 5 days of cefaclor (90% success) compared with 64 patients who received 10 days of cefaclor (92% success). This study, however, did have limited power due to the low number of patients and a clinically significant difference could not be detected. Another recent trial including 719 patients reported a 5 day course of cefuroxime axetil was equivalent to 10 days of either cefuroxime axetil or amoxicillin/clavulanate. There are even some reports that a single dose of ceftriaxone, which only provides therapeutic middle ear concentrations of antibiotic for 3-5 days, is equally effective as a 10 day course of amoxicillin or trimethoprim-sulfamethoxazole. Although this shorter course therapy evidence may be limited, evidence to support 10 to 14 day courses is almost nonexistent.

There are many theoretical advantages to shortening the duration of therapy to 5-7 days for AOM. One of the major reasons would be an anticipative reduction in the selective pressure favoring resistant organisms, both in the community and in the individual patient. Ironically, the shorter course of therapy may realistically be the actual dispensing practices of parents who fail to complete the 10 day course. In addition, if the course of treatment was reduced to 5 or 7 days, an anticipated increase in compliance would be expected.

This shorter duration of therapy is supportive for mild AOM, and may not necessarily be recommended or evaluated in children with severe or complicated AOM. For example, children with a ruptured tympanic membrane may require the use of a 10 or more day course of antibiotics. Moreover, many of the trials that studied the shorter course of duration generally excluded high risk children, such as those with chronic or recurrent otitis media. In this population, the data is limited and a short course therapy may not be recommended.

Short-course therapy may not be appropriate for younger children as well. Children <15 months to 2 years of age are at an increased risk for treatment failure, even with conventional dosing. Of the eight trials that used a short course therapy, approximately 250 of the children were <18 months of age, although success rates of therapy were not analyzed. Yet another trial compared
5 days with 10 days of amoxicillin/clavulanate resulted in significant differences favoring the 10 day regimen among children <2 years of age. In light of the absence of data testing the efficacy of short course treatment in this age group, short-course therapy should be restricted to children >2 years of age. (Recommendation: Level IB)

A review of three published meta-analyses of antibiotic therapy for OME have determined that there is a small, but statistically significant effect on short-term resolution. The children in most of these trials who had documented middle ear effusion had no recent history of AOM. If a child had recently been diagnosed with AOM, along with middle ear effusion, no beneficial effect of antimicrobials was seen.

According to one study, nearly 65% of all cases of OME will resolve within 3 months without antibiotic therapy, as well as 90% of OME that follows a diagnosed episode of AOM. With regard to overall therapy duration and impact, about seven children would have to be treated with antimicrobials for one to benefit. Moreover, there was no significant difference in the incidence of OME when assessed >1 month after treatment was completed, whether placebo or antimicrobial therapy was used. This data has many experts recommending that middle ear effusion in the absence of AOM should not be treated with antimicrobials.

This sentiment is echoed by the accumulation of evidence that antibiotic use increases the risk for both colonization and invasive disease with penicillin-resistant Streptococcus pneumoniae. As will be discussed later in the paper, the decision of the practitioner to prescribe antimicrobial therapy to a well-appearing child with middle ear effusion will be based on the risks and benefits of such therapy. One major issue will include an increased risk of these children to become carriers of no susceptible pneumococci, with resultant resistant strains developing.

There are some cases in which antibiotic therapy is necessary to prevent future problems. Specifically, the AHCPR (Agency for Health Care Policy and Research) guidelines have recommended therapy or bilateral myringotomy with insertion of tympanotomy tubes for patients whom bilateral effusion has been documented to persist for 3 months and is accompanied by significant bilateral hearing loss. This recommendation is reasonable due to a study indicating a correlation between persistent middle ear effusions in infancy and deficits in cognitive function and school achievement at age 7 years old. In addition, 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. This panel estimated that 25-35% of all diagnoses of otitis media would fit the criteria of OME. If deferred treatment of antimicrobials in this group were to occur,
approximately 6 to 8 million courses of unnecessary antibiotic therapy could be avoided each year. (Recommendation: Level IB)

Appropriately treated AOM is for middle ear effusion to persist for weeks to months, which is a natural history of the disease. This fact may not necessarily be well known by physicians who reexamine ears soon after therapy is completed. Moreover, 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.\(^\text{33,34,35}\) More importantly, when middle ear fluid is detected in asymptomatic children at follow-up visits for AOM, additional courses of antimicrobials is generally unnecessary.\(^\text{36}\) Thus, educating clinicians that persistent effusions are part of the expected course of AOM and therefore additional antimicrobial therapy is not warranted.

A complexity arises differentiating 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 the acute disease. However, this distinction can be made by noting if the effusion is accompanied by a new onset of local or systemic signs or symptoms of infection, such as fever or persistent ear pain. If so, AOM is diagnosed and a course of antimicrobials is administered. Conversely, if a child has middle ear effusion with a diagnosed episode of AOM in the previous 2 to 3 months, but no signs of an acute illness or is nonspecific, then a second course of antimicrobials would not be warranted. Thus, the administration of antimicrobials should be administered to those children with both middle ear effusion and a new onset of local or systemic illness, or with bilateral effusions accompanied by documented hearing loss > 3 months. (Recommendation: Level IB)

Although continuous prophylactic antimicrobials has been documented, the decrease in frequency of recurrent episodes is minor.\(^\text{28}\) Because of the potential consequences of the emergence of additional resistant pneumococci, along with its limited benefit, many experts recommend against using antibiotic prophylaxis for children with recurrent AOM.\(^\text{13}\) On the other hand, others have argued that prophylaxis remains a valuable therapeutic option for children with recurrent AOM and it’s role in therapy should not be discounted.\(^\text{37}\)

Clinical trials treating children with low dose antibiotic therapy compared with placebo have shown a lower incidence of AOM in the treated group, whether the antibiotic was erythromycin\(^\text{38}\), trimethoprim-sulfamethoxazole\(^\text{39}\), amoxicillin\(^\text{40}\), or sulfisoxazole\(^\text{41,42}\). The summary of this meta-analysis resulted in concluding that antibiotic treatment resulted in an average decrease in approximately one episode of AOM per year. The treatment group tended to be greater when sulfisoxazole was used, when the population studied had a high rate of recurrences, or when treatment was continued for <6 months.
The specific population that was identified may provide guidance as to the type of patient that may benefit from prophylaxis. Moreover, the strict criteria used may limit its use to those likely to have frequent recurrences. Consensus for prophylaxis has been three or more distinct and well documented episodes of AOM in the preceding 6 months or four episodes in the preceding year. High risk patients for recurrent or severe disease most likely to benefit included children <2 years of age and those in out of home daycare. Conversely, other eligible children may be poor candidates for prophylaxis due to decreased compliance, estimated to be approximately 50% in one inner city population.

Different scheduling for antimicrobial prophylaxis have been attempted, although none have been found to be as consistently beneficial as that of continuous. Intermittent antimicrobial prophylaxis at the onset of upper respiratory infection has yield mixed clinical results. In addition, prophylactic trimethoprim-sulfamethoxazole in conjunction with prednisone after tympanostomy tube insertion decreased the short term rate of AOM recurrence and no overall long term benefit. In comparing antibiotic prophylaxis and tympanostomy tube insertion, one study advocated antimicrobial prophylaxis in 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 prophylaxis therapy must be weighed against the risk of increasing bacterial resistance. There is evidence that even short term antimicrobial use is associated with an increased risk of nasopharyngeal resistant pneumococci; along with an increased percentage of children with β-lactamase producing organisms in middle ear effusions. Of note, the rate of colonization with resistant strains returned to baseline levels several months after discontinuation of the prophylaxis.

There are also other means by which AOM recurrences can be reduced. These include eliminating smoking in the home, reducing day care attendance, avoiding wintertime infections, and eliminating pacifiers. In addition, pneumococcal vaccines may be beneficial along with decreased incidence of recurrent AOM with increasing age of the child.

The only indication to receive antibiotic prophylaxis is with recurrent AOM among children with three or more well-documented episodes in the preceding 6 months or four or more in the preceding year. If initiated, the duration of therapy should last no longer than 6 months due to decreased effectiveness and increased risk of bacterial resistance development. The agent of choice is either sulfisoxazole or amoxicillin, with sulfisoxazole being more widely used in most clinical trials and appears to be more efficacious at preventing recurrences. (Recommendation: Level IB)
At first thought, one may not consider the administration of antibiotics for otitis media to be an ethically related decision. However, this notion can quickly gain momentum by understanding that only specific clinical criteria (see Guidelines above) recommend antibiotic use, and that many clinicians choose to purposely ignore such information. Moreover, not only is this act of dispensing increasing the risk of resistance in the individual, but in the general community as well. This resistance is becoming increasingly greater as infectious disease departments all across the country try to solve the aminoglycoside and penicillin-resistant enterococci from developing. A similar path is taking form with the emergence of vancomycin-resistant enterococci. The experts’ options are becoming limited as new antibiotics are slow to progress to market. The patients that are the most susceptible are the ones in the most severe health state – the elderly and those in the hospital with immunodeficiency. Is this emerging dilemma the result of a failure to act in a Utilitarian manner, in which the best interests of society as a whole considered? Or was it the result of an act of deontology, in which each child’s health was of foremost concern at the time of diagnosis and no regard to the consequences were considered? A deeper analysis is warranted.

Assuming the prescriber is aware of this increased bacterial resistance trend, then according to utilitarian theory, “One ought to act so that the consequences of one’s act will produce the greatest possible total welfare across all members of the population.” Acknowledging that most children’s otitis media will self resolve, is it correct to withhold the antibiotics for the sake of the at-risk community members? Is it the prescriber’s duty to care about all members of the population, especially when a life is at risk as opposed to symptomatic inconvenience? Or should the prescriber have autonomy for the child, in which symptomatic relief may occur 2 days earlier? The child has a right to feel better, but at what cost? The utilitarian theory would suggest that the consequences of withholding the antibiotics may improve the lives of the many, and that the greater good would benefit from the few children that are temporarily ill.

Conversely, perhaps the most significant concept to understand about the deontological system of thought is that their moral principles are completely separated from any consequences which may be the result of the principle. Thus, if the morally right thing is to relieve the child’s otitis media, then that should be the act that is undertaken. The problem lies with the consequences of such an act (or the increase in resistant bacteria in this case), which is not considered. Thus, there is an inherent dilemma of having two moral choices to choose from, and not knowing which to choose. The logical decision would be to choose the “lesser of the two evils”. However, the deontological theory doesn’t allow this “gray” area, where the morality of an action is questionable. It is a system based on absolutes, founded upon a divine command.

Before we can choose which kind of act is right, perhaps we need to define what is “right”. Emannuel Kant summarized this ration of thought by
stating "If we know what to do and we know enough to do it, that is what should be done". His ethical work centered around the search for and establishment of the supreme principle of morality. In Kant's view, the sole feature that gives an action moral worth is not the outcome that is achieved by the action, but the motive that is behind the action. Thus, choosing not to dispense the antibiotic may not be the wrong choice, if our motive is morally guided. The end result of decreased antibacterial resistance, Kant may argue, is not even necessarily the end result of decreased antibacterial dispensing. Hoping to achieve some particular end, no matter how beneficial it may seem, is not purely and unconditionally good. Conversely, choosing to administer the antibiotic is not necessarily the wrong choice, if the motive behind it is morally guided. Kant believes we have a freedom to make a rational decision based upon reason. The decision, Kant believes, should be derived from the only intrinsic good - 'good will'. We might be tempted to think that the motivation that makes an action good is having a positive goal-to make people happy (pain relief), or to provide some benefit (decrease resistance). Kant believes this is not the right type of motive. Simply, Kant believes fortunes can be misspent, or intended beneficial acts can actually cause harm. It is not the effect or even the intended effect that bestows moral character on an action; it is the morally guided will that adds a moral dimension to one's act.51

Kant's beliefs, as can be extrapolated, contradict those of utilitarianism. These opposing philosophical differences are the moral fibers that connect ethics and medicine. The problem arises when a fiber becomes loose, causing a disentanglement of the finely woven fabric we know as integrity. The decision then becomes how to repair this fabric, or do we just throw it away? The answer may lie somewhere in between, and whether or not the fiber is part of a blanket. The same very blanket that keeps you warm so you can sleep well at night.
References


