Amoxicillin Treatment Regimens for Acute Otitis Media and the Impact
On Penicillin-Resistant *Streptococcus pneumoniae*

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Abstract

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With increasing prevalence of penicillin-resistant *Streptococcus pneumoniae*, treatment of acute otitis media is becoming more complicated. Current standards of antibiotic treatment are being questioned as some research indicates that low dose amoxicillin (50 mg/kg/day) and a long treatment duration (longer than 5 days) may encourage the proliferation of resistant strains. The amoxicillin dose must be sufficiently high to reach the minimum inhibitory concentration of resistant strains and the duration of treatment should be reduced to avoid a prolonged antibiotic selective environment. A dose of 75-90 mg/kg/day, to a maximum of 2-3gm in 24 hours, for 5 days is recommended for treatment of acute otitis media in children older than 2 years.
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**Introduction**

As the pathogens that cause acute otitis media (AOM) in children become more resistant to antibiotic therapy, there has been an increased awareness of the drawbacks resulting from the liberal use of antibiotics. AOM is the most common reason for antibiotic prescriptions in the U.S. (Kozyrskyj et al., 1998). Antibiotic use results in proliferation of resistant strains through the selective pressure of the antibiotic on the bacteria over time. The purpose of this paper is to review the literature to determine the best prescribing practice for preventing antibiotic resistance while effectively treating patients with AOM. The question is: what method of treatment reduces the selective pressure and prevents penicillin-resistant *Streptococcus pneumoniae* (PRSp) from being selected? It is common practice to place emphasis on the importance of taking the complete course of antibiotics for the full 10 to 14 days, regardless of improved symptoms. This may not be necessary for AOM because it is generally an opportunistic infection of normal flora from the nasopharynx by bacteria such as *Streptococcus pneumoniae*, *Haemophilus influenza*, or *Moraxella catarrhalis* (Jawetz et al., 1989). The goal of therapy for AOM is to eliminate the bacteria from the middle ear fluid only, not entirely from the body. The dosage of amoxicillin and the duration of treatment necessary to effectively eradicate these pathogens from the middle ear fluid without selecting resistant strains has been examined.
Statement of the Problem

Prevalence of Antibiotic Usage for AOM

Kozyrskyj et al. (1998) state the following:

Before age 7 years, 65% to 95% of children will have experienced one or more episodes of AOM. Acute otitis media is the most common indication for antibiotic prescribing in the United States; over 90% of children with AOM will be treated with a 10-day course of antibiotics (p.1736).

Despite the knowledge the health care provider has of increasing antibiotic resistance, and an understanding of the repercussions of this, antibiotics for AOM continue to be dispensed at a high rate. “In 1990, one or more drugs-mainly antimicrobials-were prescribed at more than 80% of the estimated 24.5 million visits to physicians’ offices for otitis media” (Paradise, 1997, p. 1640). It is widely thought that antibiotic treatment will shorten an episode, prevent complications, and reduce the likelihood of recurrent episodes. However, existing research offers no compelling evidence of this outcome (Froom et al., 1997).

Physicians report pressures to prescribe unnecessary antibiotics from parents, however most parents do not acknowledge that they pressure their physician (Dowell, Marcy, Phillips, Gerber & Schwartz, 1998). Generally, it is agreed that antibiotics are indicated to treat AOM, however there are inconsistencies in what signs and symptoms are diagnostic. A survey of 165 pediatricians reported 147 different criteria for AOM (Dowell et al., 1998). Many pediatricians are using antibiotics to treat otitis media with effusion (OME) however, the majority of cases can be deferred without treatment while
OME resolves spontaneously (Dowell et al., 1998). Persistent middle ear effusion after treatment for 6 weeks or more is expected and does not require re-treatment (Dowell et al., 1998).

**The Problem of Antibiotic Resistance**

Antibiotic resistance complicates treatment as the emergence of multiple drug resistance in *Mycobacterium tuberculosis, Streptococcus pneumoniae, and Staphylococcus aureas* has made many antibiotics ineffective (Cohen, 1992). *Streptococcus pneumoniae* is a major cause of community acquired pneumoniae, meningitis and AOM. It accounts for over one million deaths each year around the world in children less than 5 years of age (Guillemot et al., 1998). Cohen et al. (1997) found that after antibiotic treatment for AOM there was an increased rate of resistant *S. pneumoniae* carriage and subsequent transfer of this resistant strain among children in schools and daycare. A study by Wilson and Guiney (1992) found in two patients *Klebsiella pneumonia* and *Escherichia coli* that contained the same type of plasmid that coded for TMP/SMX resistance. This finding suggests that in vivo transfer of this plasmid occurred during TMP/SMX prophylactic therapy from the *E. coli* to the *K. pneumonia*. Bacteria can transfer their genes for antibiotic resistance to other bacterial species (Knudson, 1998).

Multiple antibiotics are available but pharmaceutical companies are limited in their capacity to continue to develop new antibiotics to combat resistant strains (Knudson, 1998).

**Background**

**Methods of Antibiotic Resistance**
The exchange of genetic material between bacteria can occur through the exchange of DNA or plasmids (extrachromosomal DNA), resulting in the spread of resistance to other bacterial species (Neu, 1992). Antibiotics can be made inactive by bacteria destroying the drug, bacteria preventing the antibiotic from gaining access to the cell, or alteration of the antibiotic binding site (Neu, 1992).

Much of the penicillin resistance of *Streptococcus pneumoniae* involves the development of altered penicillin binding proteins (PBP) with a decreased affinity for beta-lactam antibiotics (Neu, 1992). The presence of penicillin-intermediate or penicillin-resistant strains of pneumococci does not appear to be a contraindication for the use of amoxicillin (Jacobs, 1996). PRSp is relative and can usually be overcome with higher doses. Virtually all amoxicillin resistant pneumococci have minimum inhibitory concentrations (MICs) between 2 and 4 μg/ml and these levels can be reached with amoxicillin dosed at 75 mg/kg/day. (Canafax et al., 1998). Barone (1996) states the maximum amoxicillin dose for a pediatric patient should be 2-3 grams in 24 hours.

**Antibiotic Use and Resistance Selection**

*Streptococcus pneumoniae* inhabiting the nasopharynx are of many subspecies with different antibiotic susceptibility levels (Negri, Morosini, Loza & Baquero, 1994). Clinical experience suggests a relationship between the use of antibiotics and the selection of resistant bacterial subtypes (Baquero, Negri, Morosini & Blazquez, 1998). Doone, Klespies & Sabella (1997) conducted a case controlled study with 69 patients with systemic pneumococcal infections. The purpose was to identify risk factors that may differentiate children who develop systemic infection with PRSp from those who develop penicillin susceptible pneumococcal infections. They found that when compared
with the control group, patients with PRSp isolates were significantly more likely to have received a course of antibiotics for treatment of an ear infection within one month of developing PRSp infection.

An important question is whether the use of antibiotics promotes bacterial evolution. Multiple studies have shown a link between antibiotic use and the development of resistant organisms. This is thought to be due to selective pressure, in which antibiotics create an environment that allows bacteria to express their differences in fitness to survive the antibiotic influence (Baquero et al., 1998). Organisms resistant to the antibiotic were resistant before the antibiotic was used but were not able to differentially proliferate (Baquero et al., 1998).

Dagan et al. (1998) report that after 3-4 days of antibiotic treatment half the penicillin-susceptible strains were eradicated from the nasopharynx but the penicillin-nonsusceptible pneumococci were not eradicated by the beta-lactam. This demonstrates a selection towards resistant organisms within a short period of time.

Negri et al. (1994) demonstrated antibiotic selective pressures on populations of *Streptococcus pneumoniae* after 4 hours. This time reflects the period during which the MIC is considered to be surpassed after a single administration of amoxicillin. After this time an expression of the resistant population can be seen.

Ekdahl et al. (1997) did a study on the duration of PRSp carriage. Nasopharyngeal samples were obtained at consultation for clinical infection. All detected carriers of PRSp were followed by means of weekly nasopharyngeal cultures. Median duration of carriage in 678 individuals was 19 days with a range of 3-267 days. It was longest in children less than one year (median 30 days) and shortest in adults (median 14 days).
PRSp spontaneously disappeared from the nasopharynx within 4 weeks of detection in 68%, within 8 weeks in 87%, and within 12 weeks in 94% of the individuals.

Controversy exists regarding the origin of antibiotic resistance and whether it is induced by some interaction with the drug or whether mutants arise independently of the drug. Joklik, Willett, Amos & Wilfer (1992) state that it has been established that drug resistance rises by a random mutation and occurs independently of antibiotic use. This mutation results in an altered susceptibility to the drug with the drug serving only as the selective agent favoring the survival of resistant organisms over sensitive ones (Joklik et al., 1992). Random genetic drift, where random fluctuations in bacteria characteristics allow it to survive, have been largely unconsidered as a factor in the evolution of antibiotic resistance (Baquero et al., 1998).

**Streptococcus pneumoniae Resistance to Amoxicillin**

*Streptococcus pneumoniae* are defined as resistant based on the MIC to amoxicillin. "Amoxicillin breakpoints for susceptible, intermediate, and resistant pneumococci are <1, 1.0 to 2.0 and >2.0 µg/ml respectively. Virtually all amoxicillin-resistant pneumococci have MICs between 2 and 4 µg/ml" (Canafax et al., 1998, p.153). The standard amoxicillin dose of 40 mg/kg/day does not reach this MIC. *Streptococcus pneumoniae* is found in 35-50% of AOM cases in the U.S. and 17-42% are reported to be penicillin resistant (Jacobs, 1996). The incidence of penicillin-resistant *Streptococcus pneumoniae* in reports from Spain, Hungary, and South Africa show rates of 40-70% (Doone et al., 1997). Over the course of a decade in France, the frequency of penicillin-resistant *Streptococcus pneumoniae* isolates increased from 0.5% in 1984 to 32% in 1994 (Guillemot et al., 1998). With the numbers of increasingly resistant strains growing
current amoxicillin dosing standards will not eradicate the intermediate and resistant PRS$p$ strains. If the antibiotic concentration reaching the infected middle ear is below the MIC for the infecting bacteria, treatment failure or chronic OM with effusion is likely to result. This challenge warrants higher antibiotic doses than currently used to avoid insufficient middle ear fluid antibiotic concentrations and the proliferation of resistant pneumococcci (Canafax et al., 1998).

**Amoxicillin Dose and Duration of Treatment**

Guillemot et al. (1998) did a study to analyze the relationship between PRS$p$ pharyngeal carriage and characteristics of beta-lactam use. They did an observational study of 941 children, 3 to 6 years old, from 20 randomly sampled schools in France. Their findings indicated that low daily doses of amoxicillin, defined as 50 mg/kg/day in three divided doses, was associated with an increased risk of PRS$p$ carriage. In contrast, PRS$p$ was never identified with high doses of amoxicillin at 80 to 100 mg/kg/day in three divided doses. A long duration of treatment, defined as longer than 5 days, with amoxicillin increased the risk of PRS$p$ carriage. The rate of PRS$p$ carriage in low dose with long duration was different than in high dose with short duration, 8.0% and 0.0% respectively. Theses researchers state that the relationship between dosage, duration, antibiotic treatment and PRS$p$ has been suggested in cases where resistance occurs with antibiotic prophylaxis; but has never been previously proven in clinical studies.

**Amoxicillin Dose**

Canafax et al. (1998) conducted a controlled experimental study with 34 children in Texas age 3 months to 5 years with AOM. The purpose was to determine middle ear fluid (MEF) penetration with amoxicillin. Tympanocentesis was performed on the MEF
after the subject was given a single dose of amoxicillin that was 25 mg/kg, this is approximately double the current standard dose of 13.3 mg/kg. The middle ear fluid concentrations of amoxicillin 4 hours after dosing averaged at 2.7 μg/ml in viral only infection, 4.1 μg/ml in bacterial/viral infected and 5.7 μg/ml in bacterial only infection. There were not controls for MEF without infection. Amoxicillin-resistant pneumococci have MICs between 2 and 4 μg/ml. About 59% of the subjects receiving a 25 mg/kg dose of amoxicillin had concentrations exceeding 2 μg/ml, which is high enough to eradicate resistant strains. Researchers suggest that 90% of pneumococcal AOM infections can be successfully treated with an amoxicillin dosing regimen of 75 mg/kg/day in three divided doses.

Seikel, Shelton, & McCracken (1998) did a study with 27 children age 1 to 130 months. MEF concentrations were drawn after administration of 45 mg/kg amoxicillin. Concentrations of amoxicillin exceeded 1.0 μg/ml in 90% and 4.0 μg/ml in 40%. Researchers suggest that 90 mg/kg in two divided doses should be effective against about two-thirds of intermediate resistant pneumococcal strains and one-third of resistant strains causing AOM.

Negri et al. (1994) studied the effects of different antibiotic concentration on mixed cultures of susceptible and resistant bacteria. Four *S. pneumoniae* strains with MICs to penicillin of 0.015, 0.5, 1, and 2 μg/ml were used. These mixed colonies with different MICs were incubated with amoxicillin for 4 hours. This time reflects the period in which the MIC of the more susceptible population was considered to be achieved after a single administration of the drug. In general, the findings suggested that antibiotics presented at lower levels tend to select *S. pneumoniae* strains with low level penicillin-
resistance, intermediate levels of antibiotic concentration may select pneumococci with high level penicillin resistance. Attainment of sufficiently high levels of active antibiotic may overcome pressure selecting for resistance by eradicating even resistant strains of *Streptococcus pneumoniae*.

**Duration of Treatment**

Kozyrskyj et al. (1998) conducted a meta-analysis of 32 randomized controlled trials of antibiotic treatment of acute otitis media in children 4 weeks to 18 years. The purpose was to determine whether outcomes were comparable in children treated with antibiotics for less than 7 days vs. 7 days or more. Their findings suggested that by 30 days following initiation of therapy a 10 day course of amoxicillin compared to a 5 day course in terms of clinical outcomes. The failure rate for the 5 day course was 2.3% higher than for the 10 day course. This translates into 44 children requiring treatment with a 10 day course to prevent 1 failure following a 5 day antibiotic course. Comparisons of treatment outcome over a 3-month period revealed no significant differences between the 2 treatment regimens.

Cohen, Levy, Boucherat, Langue & Rocque (1998) 4 to 30 months old, comparing the efficacy between short (3 to 5 days) and standard (7 to 10 days) antibiotic regimens for children less than 2 years. The children received either 10 days of 80 mg/kg/day amoxicillin/10 mg/kg/day clavulanate in three divided doses or 5 days of the same regimen followed by 5 days of placebo. These researchers suggested that at the evaluation period of 12-14 days after the onset of treatment a 5 day regimen does not have clinical outcomes as good as the 10 day regimen in children less that two years of age (Cohen et al., 1998).
Dagan et al. (1997) studied 123 children 3 to 24 months with positive MEF cultures. Amoxicillin 50 mg/kg/day was initiated and 72 to 96 hours later a second culture was obtained. Clinical failure was observed at the end of treatment in 37% of patients with positive MEF cultures versus 3% failure in those that had bacterial eradication after 3-4 days of treatment.

Froom et al. (1997) found that penicillin concentrations of the MEF decreased by 70% after the second day of treatment compared with the first day, suggesting that penetration depends on inflammation. Treatment for more than a few days might have little local effect on antimicrobial penetrance of the MEF.

**Discussion**

The theory of antibiotic dose and duration of therapy having an impact on resistance has been suggested. The only study measuring both of these factors is by Guillemot et al. (1998). Unfortunately, the results of this study are concluded based on pharyngeal swabs taken only after antibiotic therapy. The study would have more power had a swab been taken before and after treatment to get an accurate measure of resistance developed from antibiotic treatment. Guillemot et al. (1998) also only studied children 3 to 6 years limiting the applicability of these findings to that age group. The study by Canafax et al. (1998) is a well designed study that clearly shows that AOM is more effectively treated with higher doses than the current U.S. standard. However, this study does not consider the role of the duration of therapy and the impact it has on resistance. Seikel et al. (1998) also demonstrated the effectiveness of high dose amoxicillin; but no recommendations for treatment duration are made. Negri et al. (1994) suggested that higher doses of amoxicillin are necessary to prevent the selection of PRS∅ and that
selection of the resistant strains begins after just four hours of treatment. Kozyrskyj et al. (1998) found in their meta-analysis that clinical results following a 5 day treatment compared with clinical results following a 10 day treatment duration at a three month evaluation period. Kozyrskyj et al. (1998) do not discuss dosage; but include children 4 weeks to 18 years of age. Cohen et al. (1998) recommend children less than 2 years not be treated with the short duration regimen. Their study was well designed with large numbers but the evaluation periods were done at 12-14 days after beginning therapy regardless of the duration. The individuals who received 10 days of antibiotic probably were not yet showing signs and symptoms of failure as the group that had ended treatment after 5 days may have been.

**Recommendations for Practice**

It is the responsibility of health care providers to adequately treat AOM as well as to use antibiotics judiciously to prevent the promotion of antibiotic resistance. Clinical studies indicate the current amoxicillin dose of 40 mg/kg/day in three divided doses is not reaching the MIC for intermediate and resistant strains of PRSp. To prevent resistant strains from being selected amoxicillin dosed at 70-90 mg/kg/day in three divided doses is necessary. An antibiotic environment allows resistant strains to survive and proliferate. A long duration of treatment prolongs the antibiotic selective pressures. There is sufficient evidence to suggest that a treatment duration of 5 days with amoxicillin dosed at 75-90 mg/kg/day in three divided doses, with a maximum dose of 2-3 grams in 24 hours, is clinically effective for treatment of AOM. Excluded from this recommendation is the child less that two years, those that have chronic OM, a perforation, or chronic health problem.
Doone et al. (1997) indicated an increased chance of an infection caused by PRSp if there had been treatment with antibiotics in the previous month. Ekdahl et al. (1997) indicated a spontaneous return to penicillin susceptible strains in the nasopharynx after 12 weeks in 94%. These findings may be considered when prescribing antibiotics for AOM that has been treated with antibiotics in the previous 3 months.

**Recommendations for Future Research**

Numerous questions remain unanswered regarding antibiotic use and selection of resistance. More randomized controlled studies are needed to evaluate how the antibiotic dose and treatment duration influence selective pressure and proliferation of resistant strains. There is a large gap in the literature regarding the effectiveness of antibiotics at a high dose for a shortened duration in AOM in children less than 2 years. This group is a major consumer of antibiotics and resistance is prevalent, unfortunately they are often excluded from studies. Also of interest would be the evaluation of whether antibiotic treatment for opportunistic infections from normal flora require the same antibiotic therapy as nosocomial infections. In the case of nosocomial infections the pathogens are transient in the body and the goal of treatment is to eradicate them. Thus, treatment requires antibiotics until pathogens are eliminated. Since the pathogen an opportunistic infection is a part of the normal flora it is not eradicated and the treatment duration may not need to be as long as currently recommended. It would be interesting to study the clinical effectiveness of using antibiotics only until symptoms resolve for an opportunistic infection. This would minimize selective pressure and may have a significant impact on the proliferation of resistant strains. This approach runs counter to
the current trend to counsel patients to finish the prescribed duration of antibiotics regardless of symptom resolution.

**Conclusion**

PRSp is a growing problem and is complicating treatment for AOM. Presently, research is looking at ways to effectively treat AOM while preventing the promotion of PRSp strains. What effective method of treatment reduces the selective pressure and prevents PRSp from being selected? Health care providers continue to be taught that the best way to keep resistance at bay is to prescribe a low dose and long course of antibiotics to treat AOM. This standard of care may not be based on present theory that PRSp has a higher MIC than the current dosage is able to reach, and that *Streptococcus pneumoniae* is likely to not be eradicated even with an extended treatment duration. A better approach to treating AOM may be a higher dose over a shorter period of time. Research is indicating that this is clinically effective in children older than two years, and seems to reduce antibiotic selective pressures. However, more randomized controlled trials are needed to confirm this hypothesis.
References


