Importance of dose and duration of β-lactam therapy in nasopharyngeal colonization with resistant pneumococci

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Antibiotic use greatly influences the nasopharyngeal carriage of drug-resistant Streptococcus pneumoniae and is considered to be one of the most important risk factors for carriage of such organisms. Several studies have shown a reduction in the prevalence of resistant strains following reduced antibiotic consumption. This indicates that it may be possible to reduce resistance rates by changing prescribing patterns. Studies suggest that antibiotics present at low levels tend to select strains with low-level penicillin resistance, that intermediate antibiotic levels may pose the danger of selection of pneumococci with high-level penicillin resistance and that attainment of high levels of antibiotics may reduce the selective pressure for penicillin resistance. High-dose β-lactam (amoxicillin) therapy has been shown to reduce the selection of resistant pneumococci in the nasopharynx. Likewise, short-course antibiotic therapy has reduced colonization by resistant strains. Finally, the effect of the antibiotic appears to differ according to the β-lactam prescribed. Studies suggest that selection by cephalosporins occurs at higher frequencies than that by amoxicillin; this may be explained by the reduced activity of cephalosporins against penicillin-resistant S. pneumoniae.

Introduction

Streptococcus pneumoniae is a leading cause of pneumonia, acute otitis media, meningitis and bacteraemia. During the last decade, there has been a dramatic worldwide increase in antimicrobial resistance among strains of S. pneumoniae. This is generally attributed to the extensive use of antibiotics and the selection pressure they exert on bacterial strains of nasopharyngeal flora.

The human nasopharyngeal flora is established during the first year of life. The nasopharynx is generally colonized by relatively non-pathogenic aerobic and anaerobic organisms, some of which can interfere with the growth of potential pathogens. The human nasopharynx is also the ecological niche of the pneumococcus. The initial step in the pathogenesis of pneumococcal infection is the attachment of the organism to the nasopharynx; colonization precedes infection, but clinical disease occurs in only a small percentage of people who are colonized.

Nasopharyngeal colonization by S. pneumoniae is a dynamic process. Pneumococci are acquired, eliminated and reacquired constantly. Most children are colonized at some time during the first 2 years of life. In one study, the mean age of first acquisition was 6 months, although infants can be colonized as early as shortly after birth. In the same study, the duration of carriage was serotype dependent and inversely correlated with age. Many factors may affect colonization rates, such as age, season, siblings, day care, respiratory illness and antibiotic consumption.

As stated above, extensive antibiotic use has been linked not only to increased rates of nasopharyngeal colonization by S. pneumoniae, but also to carriage of resistant strains. Antibiotic use greatly influences nasopharyngeal carriage of drug-resistant S. pneumoniae and is considered to be one of the most important risk factors for nasopharyngeal carriage of such organisms. To use acute otitis media as an example, when an antibiotic is administered it is targeted to penetrate the middle ear fluid. However, the drug is absorbed and distributed to all compartments of the body, including the nasopharynx. Drug-resistant S. pneumoniae may be selected in this manner and subsequently disseminated.

Several studies have shown a reduction in the prevalence of resistant strains following reduced antibiotic consumption. This indicates that it may be possible to reduce resistance rates by changing prescribing patterns. In this article we review current evidence regarding the importance of antibiotic dose.

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and duration of treatment, as well as the effect of different β-lactams, in the nasopharyngeal colonization rate of drug-resistant *S. pneumoniae*.

**Importance of dose**

The relationship between the dose of antibiotic and selection of antimicrobial resistance depends on the degree of susceptibility of the strain. In theory, any antibiotic can select resistant strains, as long as the local concentration of the drug is below the MIC for the resistant clone. There is little information available about antibiotic levels in the nasopharynx, although antibiotic levels have been shown to be low in salivary secretions during penicillin therapy. Strömberg *et al.* showed that tonsillar concentrations of penicillin were much lower than the corresponding serum concentrations; antibiotic levels in the tonsillar surface fluid were higher than in tonsils, but lower than in serum. As stressed by the authors, since most bacterial infections occur in the extracellular fluid, antibiotic concentrations in this fluid are of more importance than whole tissue levels. High doses of β-lactams will be likely to result in higher concentrations in the nasopharynx than low doses, and therefore eradicate both susceptible and resistant strains. On the other hand, low doses will achieve antibiotic levels that will suppress susceptible strains, but not resistant ones.

In the clinical setting, bacterial populations in the human microflora are exposed to a wide range of antibiotic concentrations after each dose of the drug. Basically, a combination of two kinds of antibiotic pressure can be identified: (i) repeated cycles of brief, high (super-MIC) concentrations of the antibiotic; and (ii) an extended period of drug clearance during which the antibiotic concentration nears, and may actually drop below, the MIC value. Moreillon & Tomasz recreated these two kinds of antibiotic pressure separately. The former (i.e. >MIC<5MIC cycles) selected for mutants with defective lysis without changing the MIC. On the other hand, reconstruction of the second type of drug pressure (i.e. prolonged exposure to nearly constant concentration of the antibiotic very close to the MIC) selected for resistant mutants with increased MICs.

Negri *et al.* evaluated the selective pressure of exposure to different concentrations of β-lactams. They demonstrated that exposure of *S. pneumoniae* with different penicillin susceptibilities to low concentrations of β-lactams eliminated the susceptible population and increased the low-level and high-level resistant populations, whereas exposure to high concentrations of β-lactams decreased the number of resistant bacteria because of the reduced number of low-level resistant populations. These results suggest that antibiotics present at low levels tend to select strains with low-level penicillin resistance, that those with intermediate levels may pose the danger of selection of pneumococci with high-level penicillin resistance and that attainment of high levels of antibiotics may reduce the emergence of penicillin resistance.

For amoxicillin, resistant mutants can be selected if the serum level is ≤4 × MIC and for cephalosporins, selection occurs at ≤16 × MIC. Sifaoui *et al.* estimated the frequencies of one-step mutations leading to resistance using different β-lactams as selectors. Many of the mutants were selected with concentrations of only ≤4 × MIC. This suggests that the higher the concentration of antibiotic, the lower will be the chance to select for spontaneous mutants.

Guillemot *et al.* tested the hypothesis that the emergence of penicillin-resistant *S. pneumoniae* was related to the daily dose and duration of β-lactam use. Children were studied to determine whether they were pharyngeal carriers of *S. pneumoniae* and, if present, whether it was penicillin resistant; oral β-lactam usage and the dose and duration of treatment were explored as well. All children who had taken a low dose had strains with penicillin MICs > 0.1 mg/L; in contrast, all isolates from children who had taken a high dose had a penicillin MIC < 0.1 mg/L. Furthermore, among *S. pneumoniae* carriers, a low daily dose was associated with an increased risk of penicillin-resistant *S. pneumoniae* carriage. In this study, the number of daily doses was not found to be associated significantly with a risk of penicillin-resistant *S. pneumoniae* carriage (although the small sample sizes make it difficult to show a statistically significant difference).

Recently, Schrag *et al.* evaluated the clinical and microbiological efficacy of short-course, high-dose antibiotic therapy to reduce the selection of resistant pneumococci. At day 28, the risk of penicillin-resistant *S. pneumoniae* carriage was significantly lower in the short-course, high-dose group. Additionally, in contrast to a standard-course group, children in the short-course, high-dose group did not have a higher risk of penicillin-resistant pneumococci carriage at day 28 compared with day 0. When the analysis was limited to pneumococcal carriers, the risk of penicillin-resistant *S. pneumoniae* carriage at the day 28 visit was also significantly lower in the short-course, high-dose group. Moreover, the MIC50 for the pneumococcal isolates in the short-course, high-dose group was lower than for those in the standard-course group.

For the majority of antibiotics, pneumococcal resistance is rarely the result of single point mutations; in contrast, resistance is acquired either by transformation or transfer via conjugative transposons. Despite being an uncommon mechanism, however, the emergence of pneumococcal resistance due to single point mutation can be enhanced by low antibiotic dosing. In the case of the fluoroquinolones, the mutation prevention concentration (MPC) is defined as the lowest drug concentration that prevents the growth of resistant mutants from very large inocula. For *S. pneumoniae*, the MPCs have varied between 4 × and 7 × MIC. Resistant mutants are selected only in the concentration range between the MIC and the MPC. Below the MIC, no mutant will be
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enriched because selective pressure is absent; above the MPC, the emergence of resistance is much less frequent because a double mutation is required for growth. Zhao & Drlica designated the concentration range between MIC and MPC as the mutant selection window. A regimen of high doses may help to minimize the length of time that the antibiotic concentration is in the mutant selection window. All these data suggest that the emergence by selection of antibiotic-resistant bacterial populations may occur only at certain antibiotic concentrations, the so-called selective antibiotic concentration.

Importance of the length of treatment

Like high-dose therapy, short-course antibiotic therapy has been proposed as an intervention to reduce selection and spread of resistant pneumococci. One advantage of shortened therapy is a reduced impact on commensal flora; since resident nasopharyngeal flora such as viridans streptococci and anaerobic streptococci can antagonize colonization with S. pneumoniae, their elimination may enhance pneumococcal attachment to the mucosa. Secondly, reducing the length of therapy minimizes exposure of bacteria to antibiotics and therefore reduces the opportunity for the emergence of resistance. Other advantages of short-course therapy are reduced economic costs, and theoretically at least, the improvement of compliance, and fewer side effects.

Nasrin et al. examined the relationship between use of antibiotics and nasal carriage of resistant S. pneumoniae. The percentages of penicillin-resistant isolates were similar in the group that had no β-lactam use and the group that had only a relatively short course of β-lactam, but this percentage increased as the number of days of use increased beyond 7. Using a logistic regression model adjusted for the effect of clustering within children, they found that for each additional day of use in the preceding 6 months, the odds of a child carrying a penicillin-resistant pneumococcus increased by 4%.

In a study mentioned previously, Guillemot et al. found that long-duration therapy (>5 days) with β-lactams was associated with an increased risk of carrying penicillin-resistant S. pneumoniae.

Antibiotic prophylaxis, the paradigm of long-term antibiotic therapy, has been shown to fail to eliminate pneumococci from the nasopharynx and to predispose to selection of resistant mutants. In one study, the rate of recovery of penicillin-resistant S. pneumoniae increased only among patients who received amoxicillin prophylaxis; resistant strains were recovered from a quarter of the children receiving at least 5 months of amoxicillin prophylaxis (versus none before therapy). The number of penicillin-resistant pneumococcal isolates declined gradually over 5 months after prophylaxis was discontinued. Furthermore, although antimicrobial treatment may temporarily reduce the carriage rates, the rates increase again once antibiotics are stopped and may be even higher than that without antimicrobial treatment.

Differences between different β-lactam antibiotics

The effect of antibiotic treatment appears to differ according to the drug prescribed. When certain β-lactams are used, adequate bactericidal concentrations may not be achieved in the nasopharynx, thereby creating a selective environment that favours bacterial variants with reduced susceptibility. The drugs with highest in vitro potency against S. pneumoniae induce a drastic fall in the carriage of penicillin-susceptible pneumococci, thereby increasing the proportion of penicillin-resistant pneumococci carried after treatment. Thus, antibiotics differ in their effects on nasopharyngeal carriage of both susceptible and resistant organisms; for example, co-amoxiclav has been shown repeatedly to reduce the carriage of resistant and susceptible pneumococci, whereas other drugs have shown little effect on the carriage of either. Even a drug that kills resistant organisms can nevertheless exert selection in favour of resistance, if it is more effective against susceptible organisms.

A comparison of several β-lactam agents shows that all oral cephalosporins achieve a serum concentration above the MIC for penicillin-susceptible S. pneumoniae for at least 50% of the dosing interval. However, of the oral β-lactam agents, only amoxicillin maintains a serum concentration above the MIC for at least 40% of the dosing interval for both intermediate and penicillin-resistant pneumococci.

The aminopenicillins have been regarded as being disproportionately responsible for selecting penicillin-resistant S. pneumoniae, although it is possible that other antibiotics (e.g. cephalosporins, macrolides and co-trimoxazole) are equally or more important than aminopenicillins in promoting penicillin-resistant pneumococci. In one study performed in Iceland, co-trimoxazole (OR = 13.14) and erythromycin (OR = 12.16) selected twice as many penicillin-resistant S. pneumoniae as β-lactams (OR = 6) in children who had received three or more courses of treatment.

Several studies have shown a connection between cephalosporins and penicillin-resistant S. pneumoniae. These studies suggest that selection by cephalosporins occurs at higher frequencies than that by amoxicillin; this may be explained by their reduced activities against penicillin-resistant S. pneumoniae. Cohen et al. evaluated the effects of ceftriaxone and co-amoxiclav on S. pneumoniae carriage. For patients colonized with S. pneumoniae, the percentage of resistant strains was higher with co-amoxiclav, whereas the number of children who carried penicillin-resistant pneumococci was higher with ceftriaxone. This is the result of a more dramatic decrease in carriage of penicillin-susceptible strains for co-amoxiclav. The chances of a child carrying penicillin-
resistant S. pneumoniae did not increase after treatment. In another study\textsuperscript{24} comparing cefpodoxime with co-amoxiclav, the same authors found that the reduction of carriage of S. pneumoniae was significantly more important for co-amoxiclav.

Dagan \textit{et al.}\textsuperscript{25} found that, after 4 days of treatment, penicillin-susceptible pneumococci had disappeared almost totally in children treated with cefuroxime, whereas cefaclor had almost no effect on the nasopharyngeal carriage of penicillin-susceptible S. pneumoniae.

In an \textit{in vitro} study, Sifaoui \textit{et al.}\textsuperscript{11} found that extended-spectrum cephalosporins (cefpodoxime, cefuroxime, cefixime, cefotaxime and ceftriaxone) showed higher frequencies of selection and different profiles of resistance than those observed with aminopenicillins, with a larger increase in the MICs.

Dabernat \textit{et al.}\textsuperscript{26} studied the effect of either cefixime or co-amoxiclav on the nasopharyngeal carriage of S. pneumoniae. At the end of treatment, the number of children carrying S. pneumoniae was significantly lower in the co-amoxiclav group than in the cefixime group; however, the percentage of penicillin-resistant pneumococci was significantly lower in the cefixime group. In other words, patients treated with aminopenicillins were less likely to carry S. pneumoniae, but if they did, then the strain carried was more likely to be penicillin resistant.

### Conclusions

The dramatic increase in resistance rates for S. pneumoniae may pose a challenge for the treatment of such infections in the future. Epidemiological studies have repeatedly identified recent antibiotic use as the strongest risk factor for the carriage and spread of resistant pneumococci. In this article we have evaluated proposed interventions to reduce the spread of resistant pneumococci, particularly modifications of antibiotic treatment regimens. Interpreting these results, it must be taken into account that MICs must be considered with reference to the concentration of antimicrobial achieved at the site of infection. Since this article focuses on nasopharyngeal carriage, it must be kept in mind that most articles refer to serum concentrations, since information on nasopharyngeal antibiotic concentrations is sparse.

Finally, it should be mentioned that vaccination strategies offer the simplest approach to controlling drug-resistant S. pneumoniae. Conjugate vaccines aimed at the paediatric serotypes may provide a useful tool for the reduction of nasopharyngeal carriage and limit the spread of resistant pneumococci. The great majority of penicillin-resistant strains belong to serogroups 6, 9, 14, 19 and 23. The conjugate vaccines developed to date, which include serotypes representing the above listed serogroups, may be helpful in preventing the carriage and spread of resistant S. pneumoniae.\textsuperscript{27,28}

### References


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