Evidence to support the rationale that bacterial eradication in respiratory tract infection is an important aim of antimicrobial therapy

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Clinical outcome is dependent upon antibiotic-mediated bacterial eradication in a number of infections. However, in respiratory tract infections, the need for bacterial eradication has been controversial. Clinical data are now available that support the need for active bacterial eradication in otitis media. This may also be the case for other respiratory tract infections. An increase in antimicrobial resistance reduces the probability of achieving eradication. Conversely, failure to eradicate bacteria may promote the emergence and dissemination of antimicrobial-resistant clones. Pharmacokinetic/pharmacodynamic parameters can be used to predict the bacteriological efficacy of antimicrobial therapy. In conclusion, the aim of antimicrobial therapy in respiratory tract infections should be the eradication of the infecting organism.

Introduction

The classic definition of antibacterial chemotherapy is the treatment of an infectious disease with chemical agents to aid in the eradication of the infecting pathogen. Active bacterial eradication is recognized as a requirement for clinical efficacy in a variety of infections, including endocarditis, meningitis, osteomyelitis and infections in neutropenic patients. There is now clinical evidence that eradication is also necessary in achieving optimal clinical success in respiratory tract infections (RTIs), such as sinusitis and otitis media.

The prevalence of resistant strains of the common RTI pathogens is increasing. The estimated worldwide prevalence of penicillin-resistant Streptococcus pneumoniae (PRSP) was 14.1% in 1997, but much higher prevalences (30–40%) are seen in some regions, notably southern Europe (France and Spain) and southeast Asia (exceeding 70%). Resistance to other agents, such as macrolides, chloramphenicol, co-trimoxazole and tetracyclines, is also increasingly common. In particular, macrolide resistance in S. pneumoniae has increased dramatically in many countries over the last 10 years. The estimated worldwide prevalence of macrolide-resistant S. pneumoniae was 22% in 1997 and was considerably higher in some areas, exceeding penicillin resistance in many countries. In the case of Haemophilus influenzae and Moraxella catarrhalis, the worldwide prevalence of β-lactamase-producing isolates was 13 and 92%, respectively, with a wide geographical variability in the prevalence of β-lactamase production by H. influenzae isolates.

The effect of increasing degrees of antibiotic resistance is always seen first in infections at sites where penetration of the antibiotic is restricted, and therapeutic concentrations are consequently more difficult to achieve. The increased prevalence of penicillin-resistant and macrolide-resistant strains of S. pneumoniae is, for example, reflected in the changes in the antibiotic regimens used to treat infections such as bacterial meningitis. Increasing antimicrobial resistance could also impede eradication of pathogens in RTIs treated with standard drug regimens. Studies of the relationship between bacteriological cure and clinical out-
come would help establish the importance of bacteriological eradication in treating RTIs.

The spread of resistant clones throughout a population may also be exacerbated by the failure to eradicate bacteria. If eradication does not succeed, the resistant clones will lead the process of recolonization of the mucosal membranes after discontinuation of therapy. In this way, the resistant populations will increase in absolute number, and this within-host proliferation will have consequences for the between-host transmission of resistant clones. Thus, a negative spiral develops where resistant clones spread, making eradication more difficult and in turn leading to the further spread of the clone. It is important, then, to consider the patient in the wider community and the implications of the continuing carriage of resistant organisms when making the choice of antibiotic in an individual case.

Pharmacokinetic/pharmacodynamic (PK/PD) parameters can be used to predict the potential for bacterial eradication with antimicrobial therapy. The validity of these parameters is supported by both animal and clinical studies.

This paper discusses the clinical importance of bacterial eradication, the increasing prevalence of antibiotic resistance and its effect on bacterial eradication of key respiratory tract pathogens.

Clinical impact of bacteriological eradication in otitis media

Otitis media is the most common reason for antibiotic prescribing in young children and infants, so it is not surprising that there has been an increase in the prevalence of antibiotic resistance in the main causative pathogens. The approach of providing antibiotic therapy in cases of suspected otitis media with mild or non-specific symptoms and some middle ear effusion will result in unnecessary prescribing. In those patients in whom treatment is warranted, the role of antibiotics in otitis media is to eradicate the causative organism from the middle ear. It is also highly advisable to achieve eradication from the nasopharynx in order to prevent recolonization. To do this, the antibiotic must be active in vitro against the causative organism and must penetrate into middle-ear fluid at sufficient concentrations. It should also be noted that spontaneous bacterial eradication is high in otitis media. For example, Howie & Ploussard observed spontaneous eradication rates of 18% for S. pneumoniae and 48% for H. influenzae.

These considerations have been investigated in clinical studies of otitis media using the double-tymanocentesis method. This in vitro susceptibility test involves taking a culture from the middle-ear fluid by tympanocentesis before treatment and a second one 3–5 days after the initiation of treatment. This technique can thus be used to compare the bacteriological efficacies of different antibiotics, determine in vivo MIC breakpoints and demonstrate clinical correlates of bacterial eradication.

The effect of bacteriological failure on clinical failure has been investigated in 206 children with otitis media using the double-tymanocentesis method. Of 123 culture-positive, evaluable children before treatment, 57 (46%) were culture positive on day 4–5 of antibiotic therapy and 66 (54%) showed bacteriological eradication. Among the 57 children who were culture positive at day 4–5, there were 21 clinical failures (37%) at day 10 of the study. In comparison, of the 66 children that were culture negative on day 4–5, only two (3%) were clinical failures at day 10. Thus, 91% of clinical failures at day 10 (21/23) were culture positive on day 4–5. Whilst clinical success was clearly maximized (97%) through bacterial eradication, some 63% of bacteriological failures at day 4–5 were clinically cured by day 10. This means that if clinical outcome alone is used to measure drug efficacy, differences between drugs are more difficult to quantify.

The relationship between bacteriological and clinical efficacy was investigated in more detail using a symptom severity scale in 68 children. This included the patient’s temperature, irritability, ear tugging, redness and bulging of the ear drum on day 4–5. The score range for each parameter was 0–3, with a maximum score (maximum severity) of 15. On day 1, before antibiotic treatment, the mean (± s.d.) severity score was 9.5 ± 1.6. On day 4–5, 35 children were culture positive and 33 culture negative with mean severity scores of 3.9 and 2.4, respectively (P < 0.01). Four culture-positive children (11%) had a severity score of =1 (P < 0.004), whereas 15 culture-negative children (45%) had a severity score of =1 (P < 0.004). Hence, bacteriological eradication on day 4–5 was associated with children who felt and looked better. Almost all children improved clinically between days 1 and 4–5, however, irrespective of bacteriological eradication. Some children failed clinically by day 10, though this was less likely if bacteriological eradication had been achieved.

In otitis media, there is evidence that bacteriological success contributes to improved clinical outcomes. However, clinical efficacy does not always indicate bacteriological efficacy, making it difficult to distinguish between antimicrobials on clinical outcome alone. This effect has been termed the ‘Pollyanna phenomenon’ by Marchant et al. It indicates that when bacteriological success is 100% in otitis media, clinical success will also be high (89%), though not 100%, owing to cases with a non-bacterial aetiology that have not completely resolved. However, when bacteriological success is low (27%), clinical success will still be fairly good (74%). Thus, discrimination between ‘good’ and ‘bad’ antimicrobials on clinical outcome alone would require extremely large clinical trials.

This has been illustrated by Dagan et al. in a study of bacteriological failures in 161 children treated with cefaclor or cefuroxime axetil. In children who were culture positive before treatment, bacteriological failure rates were 32% for cefaclor and 15% for cefuroxime axetil. In this case, 100 patients per treatment arm would be required to show a
significant difference. When children who were culture negative before treatment were included, the bacteriological failure rate was 12 and 23%, respectively. At these rates, approximately 400 patients would be required to demonstrate a statistically significant difference. As only one-third of bacteriological failures are clinical failures, the clinical failure rates for all patients were predicted as 4 and 9% for cefuroxime axetil and cefaclor, respectively. Using clinical efficacy alone, a sample size of around 900 patients (450 per treatment arm) would be required to show a statistically significant difference at the 5% level. Few clinical studies in otitis media include this many children and statistically significant differences in clinical outcome are, therefore, rarely seen.

The difference between clinical success rates for cefaclor and cefuroxime axetil in this study (91% and 96%) might initially be considered insignificant. However, in the USA there are over 20 million episodes of acute otitis media every year. A 5% increase in clinical failures thus represents more than a million more failures per year. These clinical failures also result in increased morbidity and an increased risk of the selection and spread of resistance. Clinical studies should, therefore, be designed to detect subtle differences between antibiotics even if differences in overall clinical outcome do not appear to be significant.

The effect of antibiotic resistance on bacterial eradication in otitis media

Bacterial eradication of β-lactamase-positive H. influenzae

Three studies investigating the eradication of H. influenzae from middle-ear fluid in otitis media have illustrated the effect of β-lactamase production on the bacteriological efficacy of amoxycillin (references 11 and 12 and R. Dagan, unpublished results). For β-lactamase-negative H. influenzae, respective eradication rates of 100, 70 and 79% were observed, compared with 37, 34 and 40% for β-lactamase-positive isolates. As the eradication rates for β-lactamase-positive isolates were similar to spontaneous eradication rates observed for H. influenzae, the effect of amoxycillin was equivalent to placebo against these isolates. Similarly, in a comparison of amoxycillin and cefuroxime axetil in 238 patients with otitis media, amoxycillin displayed low activity, with 60% persistence of β-lactamase-producing strains of H. influenzae. Cefuroxime axetil was more effective, eradicating 85% of all H. influenzae. Against β-lactamase-negative strains, 79% were eradicated with amoxycillin treatment, again illustrating the effect of β-lactamase production on the efficacy of this agent.

Azithromycin has better in vitro activity against H. influenzae than erythromycin and clarithromycin and is not affected by β-lactamase production. It also has a long serum half-life and good penetration into tissues. However, Dagan et al. found that 24 of 34 H. influenzae isolates (71%) persisted after azithromycin therapy, similar to the effect of placebo, despite good penetration into the middle ear. These results were confirmed in two comparative studies. In a comparison of azithromycin and cefaclor in 138 patients with acute otitis media, 53% (16/30) of patients treated with azithromycin and 52% (13/25) treated with cefaclor experienced bacteriological failure. New infections with H. influenzae were detected during treatment in 15% (5/33) of patients in the azithromycin group, even though all the strains isolated were susceptible to azithromycin according to current NCCLS breakpoints (MICs ≤ 4.0 mg/L and MIC50 1.0 mg/L). Similarly, in a comparison of azithromycin and co-amoxiclav in acute otitis media, eradication of H. influenzae was achieved in 33% (13/33) of patients receiving azithromycin compared with 87% (26/30) of those receiving co-amoxiclav.

These results appear puzzling at first, but can be explained by the fact that azithromycin concentrates intracellularly, in this case in the inflammatory cells in the middle-ear fluid. Extracellular concentrations on the other hand remain relatively low, as reflected in the low concentrations achieved in serum. As H. influenzae is an extracellular pathogen, the extracellular azithromycin concentrations to which isolates were exposed in this study were insufficient for bacteriological eradication. As all new macrolides concentrate intracellularly, this evidence suggests that they are inappropriate for the treatment of otitis media due to H. influenzae. Using the clinical evidence outlined above, combined with pharmacodynamic modelling, Dagan and others suggest that the current NCCLS breakpoints for azithromycin for H. influenzae be changed from 1 to 0.12 mg/L, to reflect the impact of pharmacodynamics on the in vivo activity of this agent in otitis media (W. A. Craig, unpublished results).

Bacterial eradication of penicillin- and macrolide-resistant S. pneumoniae

The effect of penicillin resistance in S. pneumoniae on antimicrobial bacteriological efficacy has also been investigated in otitis media by Dagan et al. (Figure 1). In this study, the bacteriological failure rates of the oral cephalosporins cefaclor and cefuroxime axetil were each <10% against penicillin-susceptible isolates. Cefuroxime axetil also maintained failure rates of <10% against S. pneumoniae with intermediate susceptibility to penicillin (MICs 0.125–0.25 mg/L by Etest). However, against pneumococci with a higher level of penicillin resistance (MICs 0.38–1.0 mg/L), bacteriological failure rates increased to 50% for cefuroxime axetil and 80% for cefaclor. The results for cefaclor for pneumococci with the higher penicillin MIC range are equivalent to those seen with placebo.

As this study included only small numbers of patients, particularly those with highly resistant isolates of S. pneu-
Resistant isolates of the key respiratory pathogens \textit{S. pneumoniae}, \textit{H. influenzae} and \textit{M. catarrhalis} have become increasingly prevalent in the last 10 years. The Alexander Project\textsuperscript{1} is an ongoing, international surveillance study that uses centralized standard methods, allowing geographical and temporal changes in resistance patterns to be investigated. It is a valuable database for studying the evolution of resistance patterns in RTI pathogens.

\section*{Resistance in \textit{S. pneumoniae}}

There is currently a worldwide pandemic of penicillin resistance among clinical isolates of \textit{S. pneumoniae} (Table I).\textsuperscript{1} Southern and eastern European countries, Mexico and the USA are ‘hot spots’ for penicillin-resistant pneumococci (PRP). The highest prevalences are found in Korea and Hong Kong.\textsuperscript{13,12} In contrast, the Czech Republic, Germany and the Scandinavian countries have low prevalences of resistance, despite their proximity to countries with high prevalences, such as Hungary and Slovakia. The prevalence of penicillin resistance in pneumococci has risen steeply over the past 6 years in some countries, for example the USA (from 15 to 35\% in New York), whereas in others, such as Spain and France, it has stabilized at around 50\%.\textsuperscript{1}

The prevalence of macrolide-resistant \textit{S. pneumoniae} has increased dramatically in most centres involved in the Alexander Project since 1992 and in many countries now surpasses penicillin resistance (Table I).\textsuperscript{1,26,27} Because of the local spread of multi-resistant clones, a relationship has been suggested between the prevalence of resistance to macrolides and penicillin,\textsuperscript{26} although the correlation is not absolute. In some countries, such as South Africa or in some parts of the USA, the prevalence of penicillin resistance is high and the prevalence of macrolide resistance is low, whereas in Belgium or Italy, resistance to macrolides by far surpasses penicillin resistance.\textsuperscript{26}
Bacterial eradication in RTI

Resistance in H. influenzae

Alexander Project data from 1992–1997 indicate that the prevalence of β-lactamase production appears to have reached a steady state in some countries, such as France and the USA, but may be as high as 35% in some areas.1,28 Although use of a vaccine against H. influenzae serotype b (the most virulent serotype) may decrease the importance of this strain, resistant, non-typeable strains remain clinically significant community-acquired respiratory tract pathogens.

Resistance in M. catarrhalis

Most (50–80%) isolates of M. catarrhalis isolated during the Alexander Project in 1992 produced β-lactamase.28 However, this had increased further, to 90–100%, in the participating centres by 1997.1 Resistance to other (non-β-lactam) antibiotic classes was stable in M. catarrhalis (as it was in H. influenzae).

Factors influencing the spread of antibiotic resistance

Data from the Alexander Project show that the countries with a high prevalence of β-lactamase-producing H. influenzae also have a high prevalence of penicillin-resistant S. pneumoniae, suggesting a ‘resistance syndrome’ of bacterial respiratory tract pathogens.1,28 Under a high intensity of antibiotic selection, the emergence and spread of resistance in RTI pathogens continues to evolve and the dissemination of resistant bacteria is a global issue. The eradication of bacteria, not only from the site of infection, but also from the nasopharynx, prevents the spread of resistant strains throughout the community. Other factors, for example the overall consumption of antibiotics, the duration of antibiotic therapy and compliance with medication, will also influence the development and spread of resistance.

Nasopharyngeal carriage and clonal spread

Antibiotic-resistant isolates of S. pneumoniae are often resistant to more than one antibiotic class and clonal spread of specific serotypes is seen throughout the world. The spread of resistant clones has been the subject of many investigations. Recently, Yagupsky et al.29 examined the spread of a 23F clone of S. pneumoniae between two groups of children in a daycare centre in southern Israel linked by siblings attending both groups. The clone was first isolated in a single child, reached the second group after about 1 month and disseminated until it was widespread through-

### Table I. Worldwide penicillin and macrolide resistance in 2036 isolates of S. pneumoniae from the 1997 Alexander Project

<table>
<thead>
<tr>
<th>Country</th>
<th>Intermediate penicillin resistance</th>
<th>High-level penicillin resistance</th>
<th>Macrolide resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>France</td>
<td>20</td>
<td>29</td>
<td>46</td>
</tr>
<tr>
<td>Germany</td>
<td>15</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Italy</td>
<td>4</td>
<td>3</td>
<td>30</td>
</tr>
<tr>
<td>Spain</td>
<td>17</td>
<td>35</td>
<td>33</td>
</tr>
<tr>
<td>UK</td>
<td>6</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Belgium</td>
<td>4</td>
<td>6</td>
<td>31</td>
</tr>
<tr>
<td>Czech Republic</td>
<td>2</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Slovak Republic</td>
<td>10</td>
<td>16</td>
<td>13</td>
</tr>
<tr>
<td>Poland</td>
<td>5</td>
<td>9</td>
<td>14</td>
</tr>
<tr>
<td>Switzerland</td>
<td>6</td>
<td>4</td>
<td>16</td>
</tr>
<tr>
<td>Eire</td>
<td>10</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>Portugal</td>
<td>4</td>
<td>17</td>
<td>4</td>
</tr>
<tr>
<td>USA (five centres)</td>
<td>13–17</td>
<td>11–37</td>
<td>12–21</td>
</tr>
<tr>
<td>Brazil</td>
<td>14</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Hong Kong</td>
<td>5</td>
<td>52</td>
<td>78</td>
</tr>
<tr>
<td>Mexico</td>
<td>13</td>
<td>37</td>
<td>16</td>
</tr>
<tr>
<td>South Arabia</td>
<td>42</td>
<td>6</td>
<td>16</td>
</tr>
<tr>
<td>South Africa</td>
<td>26</td>
<td>5</td>
<td>8</td>
</tr>
</tbody>
</table>

*Penicillin resistance was defined as: intermediate (MIC 0.12–1.0 mg/L) and high-level (MIC > 1.0 mg/L). Macrolide resistance was defined as erythromycin MIC ≥ 1 mg/L.*
R. Dagan et al.

Figure 2. Impact of antibiotic treatment on nasopharyngeal carriage and spread of penicillin-susceptible and penicillin-resistant *S. pneumoniae* for amoxicillin/clavulanate versus (a) ceftriaxone and (b) cefixime.30 Black bars, before treatment; grey bars, after treatment.

out both groups. Factors influencing the introduction and dissemination of this resistant clone in the patient group were travel and daycare. In particular, failure of antibiotic therapy to eliminate or reduce the persistence and spread of the clone was identified as a contributing factor to clonal spread. In different settings, however, different factors may be important.

The nasopharyngeal bacterial population is an important reservoir of infection, carriage and spread of pathogenic bacteria, including antibiotic-resistant clones. Antibiotic therapy should not only be active against both susceptible and resistant strains at concentrations achievable at the site of infection, but also reduce the prevalence of carriage to minimize the potential for the selection and spread of resistant clones. This may require high doses of antibiotics for antibiotic-resistant strains. A reduction in the duration of therapy, without compromising bacteriological efficacy, may also help to prevent the emergence and spread of resistance.

Dabernat et al.30 compared the effect of co-amoxiclav, which has high activity against PRSP with that of cefixime, which has poor activity against these strains. Co-amoxiclav reduced nasopharyngeal carriage of penicillin-susceptible *S. pneumoniae* from 65 subjects before treatment to four after treatment (by approximately 90%) and of PRSP from 42 subjects to 17 (by about 60%). In comparison, results for cefixime showed a 30% decrease in penicillin-susceptible isolates (from 69 to 47) but there was no impact on the carriage of resistant strains (Figure 2).30

Appropriate antibiotic therapy can therefore decrease the incidence of nasopharyngeal carriage, including the numbers of patients carrying resistant pneumococci. Conversely, inappropriate therapy has been implicated in increased carriage of PRSP.31 In a study of children in Iceland, the odds ratio (OR) for the carriage of PRSP after three or more courses of antibiotic was 13 for co-trimoxazole and 12 for erythromycin, compared with 6 for β-lactams. For one or two courses of antibiotics, the ORs were 7–8 for all three classes of antibiotic. Thus, in this community, repeated use of co-trimoxazole and erythromycin appear to be more potent selectors of PRSP than use of β-lactams. Furthermore, when consumption of co-trimoxazole and erythromycin in Iceland was reduced by 30% (from 1990), this coincided with a reduction in the prevalence of PRSP (mainly the predominant type 6B multi-resistant clone), from a peak of 20% in 1992 to 13% in 1997.32 During this time, there was no change (<10%) in the consumption of β-lactams.
Bacterial eradication in RTI

The *S. pneumoniae* clone in Iceland was multiply resistant to a number of agents. Where this is the case, other antibiotic classes, including macrolides, may select for carriage of PRSP more effectively than β-lactams. For example, the use of co-trimoxazole has been shown to be more efficient at selecting pneumococcal penicillin resistance than various β-lactams.33 Any of the antibiotics to which the organism is resistant could select for resistance to all of them. It is therefore important to use an antibiotic with the greatest potential for eradicating the multi-resistant clones, thus preventing spread within the community.

Antibiotic prescribing and the development of resistance

It has long been suspected that the worldwide increase in antibiotic resistance is related to patterns of antibiotic use. Some researchers have looked for a correlation between the prevalence of antibiotic resistance and prescribing habits. In Italy and Spain, an increase in the prevalence of macrolide-resistant *Streptococcus pyogenes* has been shown to correlate with macrolide usage.34,35 A similar trend has been observed in Finland.36 The relationship between antibiotic use and resistance in many cases is not, however, as simple as it might at first appear. For example, analysis of Alexander Project data revealed a correlation between the use of long-acting macrolides (azithromycin and clarithromycin) and the prevalence of macrolide-resistant *S. pneumoniae* (Figure 3).1,26 No such correlation was seen with short-acting macrolides. Though this does not necessarily indicate causality, it was suggested by the investigators that differences in potency and pharmacokinetics could account for the varying potentials of different antibiotics to select resistant bacterial clones.26 An alternative explanation may be that the relationship is a result of a threshold in the selective intensity of the total amount of macrolides used in a particular community, i.e. the launch of the new macrolides has contributed to an overall increase in macrolide use, which has pushed macrolide consumption over the critical threshold, resulting in an increase in resistance that is apparently related only to the new agents.

Antibiotic dosage

Evidence of the mechanisms driving antibiotic resistance in vivo is limited. Fundamental parameters, such as the dose, frequency and duration required to select resistant strains, have yet to be adequately defined. However, it has been suggested that sub-optimal dosage of antibiotics, caused by either inadequate prescribing or a failure to comply with medication, and a long duration of dosage may promote the spread of antibiotic-resistant bacterial clones.26 A study including 16 children carrying PRSP supports this hypothesis.37 Ten of the 16 patients had received antibiotic treatment of low dose and long duration. An OR of 3 [95% confidence interval (CI) 1.1–8.3] for carriage of PRSP was associated with oral β-lactam therapy in the past 30 days (*P* = 0.03). When the dose was below average, however, there was a statistically significant increase in the OR to 5.9 (95% CI 2.1–16.7, *P* = 0.002). A significant increase in the OR was also seen when treatment duration was >5 days (OR 3.5, 95% CI 1.3–9.8, *P* = 0.02). More studies are required to confirm these findings and to determine the optimal duration of treatment, but when making therapeutic decisions one should consider the possibility of resistance selection.

Pharmacokinetics/pharmacodynamics as predictors of bacterial eradication

There has been increasing interest in the use of PK/PD parameters in the prediction of bacteriological and clinical efficacy.38 In animal studies with β-lactams and macrolides, high survival rates (>90%) are seen if serum drug concentrations exceed the MIC for approximately 40–50% of the dosing interval.39 The dosing regimen (unit dose and frequency) is the most important determinant of this. For fluoroquinolones and azalides, the ratio of the area under the time–concentration curve (AUC) to the MIC correlates more closely with efficacy for these agents. The total amount of drug administered is therefore the critical determinant of efficacy.40 Twenty-four hour AUC/MIC ratios of ≥25–30 have been shown to result in high success rates in immunocompetent animals infected with *S. pneumoniae*.16,40,41 This is equivalent to a mean antibiotic

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**Figure 3.** Correlation between prescribing of old (short-acting) (■, dashed line) and new (long-acting) (■, solid line) macrolide antibiotics and macrolide resistance in *S. pneumoniae*. Reproduced from reference 26 with permission of the Journal of Chemotherapy.

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concentration in serum approximately equal to the MIC for the whole 24 h dosing period.

Clinical studies support the PK/PD requirements derived from animal models. In patients with otitis media or sinusitis, clinical data confirm that a time above MIC of around 40% for penicillins and 50% for cephalosporins achieves high bacteriological cure (eradication) rates (Figure 4).\textsuperscript{19} For the macrolides, conventional dosing of erythromycin and clarithromycin against macrolide-susceptible \textit{S. pneumoniae} gave a time above MIC of 88–100% and bacteriological cure rates of 93–100%.\textsuperscript{19} In contrast, against typical strains of \textit{H. influenzae}, even peak serum concentrations frequently did not exceed the MIC and the corresponding bacteriological cure rates were 15–20%.\textsuperscript{19,42,43} Against isolates with decreased antibiotic susceptibility, antibacterial agents may no longer achieve the necessary PK/PD parameters predictive of bacteriological eradication. For example, in the case of the azalide azithromycin, the AUC/MIC ratio is the most important PK/PD parameter. In otitis media treated with azithromycin, a high bacteriological cure rate (100%) is seen against macrolide-susceptible \textit{S. pneumoniae}, for which the AUC/MIC ratio is $<0.4$ and the bacteriological cure rate is no better than that with placebo.\textsuperscript{13} In addition, the AUC/MIC against \textit{H. influenzae} is 1.5 for azithromycin and the corresponding bacteriological cure rate is also similar to that of placebo.\textsuperscript{14}

In summary, PK/PD parameters predict that many common dosage regimens of antibiotic therapy will not achieve bacteriological eradication. This is supported by clinical evidence. Co-amoxiclav and ceftriaxone have the highest potential for bacteriological eradication across the bacterial spectrum in otitis media and should be considered as first-line therapy in this indication.

**Achieving bacterial eradication: the effect of penicillin resistance on the treatment of meningitis, pneumococcal pneumonia and bacteraemia**

Active bacterial eradication is a strategy aimed at optimizing the treatment of infection while minimizing the risk of selection, carriage and spread of resistant strains. However, therapeutic choice becomes more limited as multi-resistant strains become more prevalent. Thus, local susceptibility patterns must also be considered when choosing antimicrobial therapy. Another important concern is based on the possible increase in the MICs for the penicillin-resistant strains (for instance to MICs of 64–128 mg/L). This could severely compromise the success of current therapeutic strategies, even in RTIs. An alert system for the early detection of such strains is highly advisable, in order to stop their spread with maximal efficacy. Conversely, the current absence of these strains may suggest that the biological cost associated with the high mutational load in such organisms could be a self-limiting factor in their spread.

**Meningitis**

The effect of increased antimicrobial resistance is seen most dramatically in meningitis. This is because of the large differences seen between serum concentrations and those in cerebrospinal fluid, which make the required PK/PD parameters more difficult to achieve. A 1992 study of pneumococcal meningitis treated with penicillin and chloram-phenicol\textsuperscript{2} illustrates the impact of resistance on outcome. Adverse clinical outcome (death, severe CNS deficit or the need for a change in antibiotic treatment) was experienced in 14 of 43 patients (33%) infected with penicillin-susceptible pneumococci, compared with 20 of 25 patients (80%) infected with penicillin-resistant strains.\textsuperscript{2}

**Pneumonia and bacteraemia**

In RTIs, penetration of $\beta$-lactam antibiotics into lung tissue is generally good and serum concentrations are thus very similar to those at the site of infection. Also, pneumococcal resistance to $\beta$-lactams is not absolute, and increased doses can achieve the required PK/PD parameters for even the most resistant strains. High-dose penicillins can therefore eradicate multi-resistant \textit{S. pneumoniae} in pneumonia. For penicillin, intravenous bolus dose results in serum concentrations above the MICs for penicillin-susceptible and penicillin-intermediate isolates ($\leq 1$ mg/L) for $\leq 6$ h after administration (Figure 5). The highest intravenous dose (5 million units of penicillin) achieves serum con-
penicillin-resistant strains (Figure 5). Fortunately, pneumonia caused by highly penicillin-resistant meningitis with high-dose parenteral agents for the management of pneumonia caused by penicillin-susceptible strains for every 6 h will give serum concentrations above the MIC for approximately 20 mg/L in serum for the whole dosing interval. This is above the MIC for all S. pneumoniae, including penicillin-resistant strains (Figure 5). Fortunately, pneumococci with penicillin MICs of \( \geq 4 \) mg/L are still relatively rare, emphasizing the importance of minimizing the spread of these strains.

High doses of penicillin are often used in the management of pneumonia. Bolus doses of 4 million units given every 6 h will give serum concentrations above the MIC for highly penicillin-resistant strains for \( \geq 50\% \) of the dosing interval (3 h).

PK/PD data predict that there should be no clinical failures when treating pneumonia or bacteraemia (not meningitis) with high-dose parenteral \( \beta \)-lactams, even for infections caused by highly penicillin-resistant S. pneumoniae. This is supported by clinical data. Friedland & Klugman compared mortality in children with penicillin-susceptible (\( n = 124 \)) and -resistant (\( n = 83 \)) pneumococcal bacteraemia treated with intravenous penicillin or ampicillin. There was no significant difference between the two groups, with mortality rates of 11 and 14\%, respectively. However, it is possible that there were differences in more sensitive clinical signs and symptoms between the groups.

Friedland further investigated the clinical response in these children. There were no differences in clinical parameters, such as the duration of fever or respiratory distress and oxygen requirements between children with penicillin-resistant and penicillin-susceptible S. pneumoniae.

The efficacy of high-dose penicillin in the treatment of pneumonia caused by PRSP has been confirmed in a number of studies in both children and adults (Table II). A South Korean study included children with pneumococcal pneumonia treated with penicillin 150 000–200 000 units/kg/day or cefotaxime 100 mg/kg/day. In the penicillin-treated group, there was a trend for decreased clinical success rates with increasing resistance to penicillin. However, clinical outcome was found to be closely related to the initial diagnosis. In children initially diagnosed as ‘critical’, clinical success at 72 h was 52\% and mortality 17\%, compared with 92\% and 0\% in those initially diagnosed as non-critical (Table II). In conclusion, initial clinical condition was predictive of clinical response and mortality, and there was no clear relationship between outcome and the penicillin resistance of the infecting organism.

These conclusions were confirmed by Deeks et al. in Uruguay and Argentina. This study included 75 children with pneumonia, treated with penicillin 150 000–200 000 units/kg/day or intravenous ampicillin. In the 52 patients infected with penicillin-susceptible S. pneumoniae the clinical success rate was 67\%, compared with 78\% in 23 patients infected with highly penicillin-resistant strains (penicillin MICs \( \geq 2 \) mg/L). There were no significant differences in mortality between the two groups. Similarly, in Boston, Silverstein et al. found no difference in mortality or duration of hospital stay for patients with pneumonia caused by penicillin-susceptible or penicillin-resistant strains of S. pneumoniae. Infection due to cephalosporin-resistant S. pneumoniae did not affect mortality, but patients infected with these strains spent longer in hospital and had more lumbar punctures performed. However, this may have been due to increased vigilance by medical staff once a cephalosporin-resistant strain was identified.

No significant difference in mortality has been found in adults with pneumococcal pneumonia between patients infected with penicillin-susceptible and -resistant strains in Spain, France and the USA (Table II). A total of 883 patients infected with penicillin-susceptible and 265 with -resistant pneumococci are included in these studies. Although in some reports, patients with infections due to PRSP have a longer duration of hospital stay, this may have been due to a poorer basal clinical status, which was unrelated to pneumonia.

\( \beta \)-Lactams are therefore recommended as first-line therapy for penicillin-resistant pneumococcal pneumonia. High-dose penicillins or cefuroxime are appropriate parenteral agents for the management of pneumonia caused by strains with penicillin MICs of \( \leq 2 \) mg/L. Parenteral therapy with ceftriaxone or cefotaxime should also be
R. Dagan et al.

Table II. Clinical efficacy of high-dose penicillin or ampicillin against pneumococcal pneumonia caused by penicillin-susceptible (PSSP), penicillin-intermediate (PISP) and penicillin-resistant (PRSP) S. pneumoniae

<table>
<thead>
<tr>
<th>Location/reference</th>
<th>No. of patients</th>
<th>Clinical response</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Children</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seoul, South Korea</td>
<td>47 PSSP</td>
<td>83% success at 72 h (2.5% mortality)</td>
</tr>
<tr>
<td></td>
<td>14 PISP</td>
<td>86% success at 72 h (7.1% mortality)</td>
</tr>
<tr>
<td></td>
<td>18 PRSP</td>
<td>67% success at 72 h (11% mortality)</td>
</tr>
<tr>
<td></td>
<td>not initially critical</td>
<td>92% success at 72 h (0% mortality)</td>
</tr>
<tr>
<td></td>
<td>initially critical</td>
<td>52% success at 72 h (17% mortality)</td>
</tr>
<tr>
<td>Uruguay and Argentina</td>
<td>52 PSSP</td>
<td>67% success</td>
</tr>
<tr>
<td></td>
<td>23 PRSP (MIC ( \geq 2 ) mg/L)</td>
<td>78% success (no significant difference in mortality)</td>
</tr>
<tr>
<td>Boston, MA, USA</td>
<td>674 PSSP, 52 PRSP</td>
<td>no difference in mortality or hospital stay</td>
</tr>
<tr>
<td></td>
<td>694 CSSP, 20 CRSP</td>
<td>no difference in mortality, but increased number of lumbar punctures and duration of hospital stay</td>
</tr>
<tr>
<td><strong>Adults</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Omaha, NB, USA</td>
<td>100 PSSP, 41 PRSP</td>
<td>no difference in mortality; hospital stay 11.9 and 10.3 days, respectively</td>
</tr>
<tr>
<td>Columbus, OH, USA</td>
<td>460 PSSP, 39 PRSP</td>
<td>mortality, 19% and 21%, respectively; hospital stay, 15.8 and 12.2 days, respectively</td>
</tr>
<tr>
<td>Toulouse, France</td>
<td>323 PSSP, 40 PRSP</td>
<td>no difference in mortality</td>
</tr>
<tr>
<td>Barcelona, Spain</td>
<td>145 PRSP, 359 others</td>
<td>no difference in mortality</td>
</tr>
</tbody>
</table>

CSSP, cephalosporin-susceptible S. pneumoniae; CRSP, cephalosporin-resistant S. pneumoniae.

considered where MICs are \( \geq 4 \) mg/L, although high doses of penicillin should be effective. Alternatively, one of the newer fluoroquinolones with enhanced activity against Gram-positive bacteria may be effective, although these are only available for use in adults. \( \beta \)-Lactams are also still the treatment of choice in empirical oral therapy (i.e. for community-acquired pneumonia).

Conclusions

The prevalence of antimicrobial resistance in the key respiratory tract pathogens continues to increase in many countries. In the case of S. pneumoniae, this is primarily due to the spread of multi-resistant clones. In some countries, the prevalence of macrolide resistance among S. pneumoniae has increased markedly in recent years and is now higher than that of penicillin resistance. The patterns of resistance continue to change and antimicrobials that are effective today may be ineffective against resistant pathogens tomorrow.

PK/PD parameters can be used to predict the bacteriological efficacy of antimicrobial agents and local susceptibility patterns should be taken into account.

A goal of antimicrobial therapy should be to reduce the emergence and spread of resistant bacteria. Continued nasopharyngeal carriage appears to be an important factor in the dissemination of resistant clones. Antimicrobial therapy should therefore optimize the potential for bacteriological eradication from both the infection site and the nasopharynx in RTI.

As the pressures of resistance continue to become manifest in clinical failures, the question of bacterial eradication is likely to become an increasingly important one to ask when prescribing antibiotic therapy in RTI.

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References

Bacterial eradication in RTI


