Clinical failures: the tip of the iceberg?

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In pneumococcal meningitis, it is well accepted that resistance in Streptococcus pneumoniae compromises clinical outcome. However, the clinical impact of increasing resistance on community-acquired respiratory tract infections (RTIs) is less clear. Bacteriological eradication should be the aim of antimicrobial therapy. The pharmacodynamics (potency and pharmacokinetics) of an antimicrobial agent against the infecting pathogen can be used to predict the potential for bacterial eradication. Surveillance of clinical isolates from community-acquired RTIs shows that, in many countries, there is a trend towards an increasing prevalence of drug-resistant S. pneumoniae. Results from a number of published clinical trials suggest that resistance has not compromised the clinical efficacy of aminopenicillins when used at the correct dose. However, emerging data indicate that resistance is compromising the efficacy of some other routinely used antimicrobials. There are reports of clinical and bacteriological failure with macrolides and fluoroquinolones in patients with community-acquired pneumonia. Recent retrospective analyses and increasing sporadic reports of clinical failure with these agents may be more representative of the true situation. These reports suggest a need to reassess current empirical therapeutic recommendations for the treatment of community-acquired RTIs.

Key words: antimicrobial agent; bacteriological eradication; community-acquired respiratory tract infections; pneumococcal resistance; treatment failure.

Introduction

Surveillance studies of clinical isolates from community-acquired respiratory tract infections (RTIs) show that the prevalence of resistant pathogens is rising, and that MICs among these resistant isolates are increasing for a range of antimicrobial agents. In recent years, the prevalence of drug-resistant Streptococcus pneumoniae has increased dramatically.

The Alexander Project is an ongoing, worldwide, surveillance study of bacterial resistance in RTI pathogens. Data from the 1997 Alexander Project indicated that the estimated worldwide prevalence of penicillin-resistant S. pneumoniae was 14 1% (1) and was 22% in 1998 (see Craig, 'Introduction', this issue). Within Europe, there is a great deal of variation in the prevalence of penicillin-resistance and, in the U.S.A., susceptibility testing of 1456 strains of S. pneumoniae in 1998 showed that 14-9% were intermediate and 31% resistant to penicillin (2). There has also been a striking increase in macrolide-resistant S. pneumoniae, with a worldwide estimated prevalence of 77-9% (erythromycin MICs ≥ 1 µg ml⁻¹) (3). In Europe, particularly high prevalence rates are seen in the South and, in the U.S.A., the prevalence of macrolide resistance is similar to that of penicillin resistance at 34-3%. In some countries, significant cross-resistance between penicillins and macrolides has been found. For example, in the U.S.A., 5-6% of penicillin-susceptible strains are macrolide-resistant, compared with 47% of intermediate and 75% of resistant isolates (3). The highest prevalences of macrolide resistance are seen currently in South East Asia. For example, a study in 1997 in China found that 75% of pneumococci isolated from children were macrolide resistant whereas only 14% were resistant to penicillin (4).

The emergence of multiple drug-resistant S. pneumoniae (DRSP) has not only complicated the empirical treatment of RTIs, but has also led to increased numbers of treatment failures (5). In the light of such data, clinicians are beginning to show concern about the potential for treatment failure with routinely used agents—β-lactams, macrolides and fluoroquinolones—and to question the relevance of current therapeutic guidelines. Many older antimicrobials (e.g. some macrolides) were recommended before the emergence of resistance in RTI pathogens. As prescribing for community-acquired RTIs is empirical, i.e. with no knowledge of either the infecting pathogen or its susceptibility, therapeutic guidelines must take into account local susceptibility patterns.

The effects of increased antibiotic resistance are observed first in infections at sites of restricted drug penetration, e.g. meningitis and acute otitis media (AOM) (6). This is because therapeutic concentrations at these sites are more difficult to achieve. In meningitis, for example, increased levels of DRSP have compromised clinical outcomes for the tip of the iceberg?
patients, and this has necessitated changes in the antibiotic regimens used to treat this disease (5,7). Given the current levels of pneumococcal resistance, and the marginal activity of some antimicrobial agents against S. pneumoniae, it would seem likely that treatment failure in community-acquired RTIs will occur more and more commonly.

Pharmacokinetic (PK) and pharmacodynamic (PD) parameters derived from animal and clinical models of infection can be used to predict the bacteriological efficacy of antimicrobial agents. For β-lactams and macrolides, the length of time above MIC is the key parameter; for fluoroquinolones and azalides, it is the AUC₉₀/MIC ratio that is important. These parameters provide a mechanism for determining the potential for clinical efficacy of a particular treatment for a given resistance profile (see Craig, ‘Re-evaluating current antibiotic therapy’, this issue).

Although the results of clinical trials appear to suggest that resistance has not compromised clinical outcome, such trials routinely exclude patients with suspected resistant pathogens. Furthermore, some may have been conducted prior to the current prevalences of pneumococcal resistance. Recent retrospective analyses and increasing sporadic reports of clinical failure due to resistance may reflect just the ‘tip of the iceberg’.

Clinical response alone cannot be used as a measure of antibiotic efficacy, as community-acquired RTIs are associated with a high rate of spontaneous cure, and differences between antimicrobials are therefore masked (8). Cases of clinical failure are more informative, as they are often related to pathogen persistence. Their review may help to shed light on whether current guidelines for the treatment of community-acquired RTIs, such as AOM and pneumonia, need to be re-evaluated.

### Pneumococcal resistance and clinical failure in acute otitis media

Commonly AOM occurs in children, and is generally a mild infection with a high spontaneous recovery rate. The most common pathogens involved in AOM are S. pneumoniae (25-40% of bacterial isolates) and Haemophilus influenzae (20-30% of isolates) (9). In some cases, infections associated with S. pneumoniae can lead to serious complications, such as mastoiditis, bacteremia, meningitis and auditory sequelae (9). Although macrolides are often used to treat AOM, current guidelines recommend amoxicillin for first-line use (5), and no agent has yet shown superiority to amoxicillin/clavulanate in a comparative trial (9). Amoxicillin is highly effective against pneumococci and displays the most favorable pharmacodynamic profile (longest time above MIC) against DRSP of any of the commonly available oral agents (5,10,11).

In vitro susceptibility testing cannot predict clinical efficacy, but bacteriological eradication from middle ear fluid can be measured reliably, using ‘in vivo’ testing with double tympanocentesis. In this technique, a sample of middle ear fluid is taken directly before antibiotic therapy and a second one during therapy. In randomized, comparative trials, this method permits efficacy differentiation between agents on the basis of bacteriological eradication without the need for the large numbers of subjects which would be required to detect differences in clinical efficacy (8). In a study of bacteriological failure in 78 children, treated with either cefaclor or cefuroxime axetil, Dagan et al. estimated that a sample size of around 900 patients (450 per treatment arm) would be required to detect a statistical difference in clinical efficacy at the 5% level (12).

Optimal clinical success in AOM requires bacteriological eradication from middle ear fluid. For example, in a prospective study of 123 children being treated with cefaclor (40 mg kg⁻¹ day⁻¹), azithromycin (10 mg kg⁻¹ day⁻¹) or amoxicillin (50 mg kg⁻¹ day⁻¹), Dagan et al. (13) reported clinical success in 64 of 66 patients (97%) with bacteriological eradication compared with just 36 of 57 patients (63%) with bacteriological failure (P < 0.001). The signs and symptoms of infection also resolved faster in those patients with bacteriological eradication.

Compromised clinical outcomes with certain antimicrobial agents as a result of resistant pathogens have now been described in AOM. In addition, agents with poor penetration into middle ear fluid (e.g. some cephalosporins and macrolides) are unlikely to be able to achieve the therapeutic concentrations required for bacteriological eradication. The effect of resistance on therapy can be investigated by examining differences in the rates of bacteriological eradication between agents against pathogens with different in vitro susceptibilities.

Various studies have used double tympanocentesis to evaluate whether bacteriological and clinical outcomes are compromised by pneumococcal resistance. The earliest of these assessed clinical outcome during oral cephalosporin therapy—either cefuroxime axetil, 30 mg kg⁻¹ day⁻¹, or cefaclor, 40 mg kg⁻¹ day⁻¹—for penicillin-intermediate S. pneumoniae infection (12). Among the 78 isolates of S. pneumoniae, 31 (40%) were penicillin intermediate (MIC 0.125-1.0 μg ml⁻¹). Overall, the bacteriological failure rate was 3 of 47 (6%) patients with susceptible pneumococci and 11 of 31 (35%) patients with penicillin-intermediate pneumococci (P < 0.001). The bacteriological failure rates for each agent were found to be directly proportional to the penicillin MIC. Although both drugs were equally effective against susceptible pneumococci, results were better for cefuroxime axetil than for cefaclor for those pneumococci with intermediate resistance, at failure rates of 22% versus 58%, respectively. A minor increase of MIC to penicillin to the 0.125–0.25 μg ml⁻¹ range did not appear to affect the response to cefuroxime axetil but seriously impaired the response to cefaclor. The investigators also showed that clinical outcome was compromised where resistant pathogens were present. Clinical failure was observed in 9 of 14 patients (64%) with bacteriological failure versus 10 of 32 (19%) patients with bacteriological eradication (P = 0.003).

Similarly, a comparison of the bacteriological efficacies of the azalide, azithromycin (10 mg kg⁻¹ o.d. daily for 3 days) and cefaclor (40 mg kg⁻¹ day⁻¹ t.d. for 10 days) also found that clinical outcome was compromised when
resistant pathogens were present (14). For both agents, there was a clear correlation between the persistence of *S. pneumoniae* and increased drug MICs. For azithromycin, there were no bacteriological failures among patients with macrolide-susceptible pneumococci (MIC ≤ 0.06 µg ml⁻¹), but all patients with macrolide-resistant pneumococci (MIC ≥ 32 µg ml⁻¹) experienced bacteriological failure. In the cefaclor group, bacteriological failure was observed in 3 of 14 (21%) patients infected with strains of *S. pneumoniae* with cefaclor MICs < 0.5 µg ml⁻¹, and in 13 of 19 (68%) patients with strains of *S. pneumoniae* with cefaclor MICs ≥ 0.5 µg ml⁻¹ (P = 0.05).

A subsequent study involving 238 children with AOM provided more evidence of clinical failure with the macrolide azithromycin (15). This compared the bacteriological and clinical efficacies of a standard dose of amoxicillin/clavulanate (45/6.4 mg kg⁻¹ day⁻¹ b.d. for 10 days) and azithromycin (10 mg kg⁻¹ on day 1, followed by 5 mg kg⁻¹ day⁻¹ for 4 days). Interestingly, there was a high prevalence of penicillin-non-susceptible (59%) and macrolide-resistant (24%) *S. pneumoniae* isolates in the study group. While bacteriological success was clearly related to MIC for azithromycin, there was no relationship between bacteriological outcome and MIC for amoxicillin/clavulanate at the MICs encountered in this study (Fig. 1). Amoxicillin/clavulanate was highly effective in eradicating *S. pneumoniae* isolates including two strains with penicillin MICs of > 2 µg ml⁻¹. Overall, amoxicillin/clavulanate led to a higher rate of *S. pneumoniae* eradication than azithromycin (90% versus 68%, NS).

Though there were significant differences in bacteriological eradication between the two agents in this study, this translated into only a modest difference in clinical success between amoxicillin/clavulanate compared with azithromycin (86% versus 80%, NS). This illustrates the effect of the high spontaneous resolution rate seen in AOM – termed the ‘Pollyanna Phenomenon’ by Marchant et al. (8) – which masks differences between highly active and less active antimicrobials. The clinical difference may seem small, but given the number of episodes of AOM, even a small increase in clinical failure rates due to the spread of resistant organisms can translate into a significant increase in the number of failures. For example, there are about 20 million episodes of AOM per year in the U.S.A. A 6% difference in failure rates therefore translates into 1.2 million additional failures per year. It is more difficult to estimate the impact of the increased risk of selection and spread of resistant isolates. Thus, clinical studies should aim to detect differences between antimicrobials, rather than comparing clinical success rates.

### Pneumococcal resistance and clinical failure in pneumonia

Community-acquired pneumonia (CAP) remains one of the leading causes of morbidity and mortality (6). It is a common cause of hospitalization in adults, and places a heavy burden on health services. *S. pneumoniae* is the most frequently isolated pathogen in CAP, and is associated with more severe disease than other causative pathogens, such as *H. influenzae* and others (6). For these reasons, *S. pneumoniae* must be viewed as the pivotal pathogen for determining empirical treatment of pneumonia in the community.

#### β-LACTAM THERAPY

As a group, β-lactam antimicrobials have good penetration into the lung, and penicillin is still the drug of choice for CAP due to its excellent activity against *S. pneumoniae*. According to a report by the Drug-resistant *Streptococcus pneumoniae* Therapeutic Working Group (6), patients with *S. pneumoniae* pneumonia caused either by penicillin-susceptible (<0.06 µg ml⁻¹) or -intermediate (0.1–1 µg ml⁻¹) isolates respond well to standard doses of β-lactam antimicrobial agents. There are conflicting data, however, on the outcome of β-lactam treatment for pneumonia caused by pneumococcal strains with penicillin MICs in the resistant range (≥2 µg ml⁻¹).

One of the problems in evaluating the available data is variability in the classifications used for *S. pneumoniae* penicillin resistance. In a study carried out in 1995, Pallarès et al. (16) found that, during treatment with either benzylpenicillin or ampicillin, patients they had defined as having penicillin-resistant *S. pneumoniae* infection (MIC ≥ 0.12 µg ml⁻¹) had an increased risk of mortality compared with patients infected with susceptible (≤0.06 µg ml⁻¹) isolates (38% versus 24%, respectively, P = 0.001). Once these data were controlled for independent predictors of mortality, however, the risk of mortality was found to be similar whether patients were infected with ‘resistant’ *S. pneumoniae* or not (25% versus 19%, respectively, NS). This may be due to the fact that most of the isolates in the study had penicillin MICs that would now be considered as being of intermediate resistance (1 µg ml⁻¹). Only one isolate had a MIC that would currently be classified as resistant (≥2 µg ml⁻¹). Another study (17), in patients with pneumococcal bacteremia, indicated that infection with penicillin-resistant

![Fig. 1. Effect of resistance to penicillin and macrolides on the efficacy of amoxicillin/clavulanate and azithromycin (15).](image-url)
S. pneumoniae (MIC $\geq 2 \mu g \text{ ml}^{-1}$) was indeed independently associated with mortality. However, more than half of the patients in the study also had documented HIV infection, which makes it difficult to draw any conclusions about the impact of resistance per se in the general population. In addition, very few patients in this study received penicillin, most having been treated with vancomycin and/or ceftiraxone.

High-level penicillin resistance has been associated with increased mortality. Feikin et al. (18) showed that pneumonia patients infected with high-level penicillin-resistant S. pneumoniae (MIC $\geq 4 \mu g \text{ ml}^{-1}$) were 7-1 times more likely to have a poor clinical outcome than patients infected with penicillin-susceptible isolates. However, there was only a small number of patients with penicillin MICs as high as 4 $\mu g \text{ ml}^{-1}$, prohibiting statistical analysis; furthermore, the antibiotic regimens used during treatment were not made clear. It is, therefore, difficult to know whether patients were given appropriate treatment. Additionally, no adjustments were made for disease severity.

MACROLIDE THERAPY

In the clinical setting, treatment failure in CAP due to macrolide resistance in S. pneumoniae was first reported in 1992 during erythromycin therapy (19). Needle aspiration of the lung, from the two patients involved, revealed erythromycin-resistant pneumococci (MIC $> 8 \mu g \text{ ml}^{-1}$). The patients responded successfully to $\beta$-lactam therapy. To date, a center at the Hospital de Mutua de Terrassa, in Barcelona, Spain (20), has documented 18 cases of treatment failure on therapy with macrolides (azithromycin, erythromycin, clarithromycin and josamycin) in patients with pneumococcal pneumonia, all of whom were subsequently treated effectively with $\beta$-lactams (Table 1). Nine patients from Barcelona, Spain, and three from Providence, U.S.A., developed bacteremia with a macrolide-resistant S. pneumoniae while receiving a macrolide. All patients had pneumonia except for one who had no identifiable site of infection. Five were children (all from Barcelona) and seven were adults. Three had received erythromycin, four azithromycin, three clarithromycin and two josamycin for a median of 3 days prior to detection of bacteremia. All the isolates from Barcelona had the erm gene. One isolate from Providence had the mef gene.

These data are supported by a study by Kelley et al. in patients admitted to hospital with pneumococcal bacteremia (21). Of 41 patients admitted, four had previously been treated with either azithromycin or clarithromycin for 3–5 days as outpatients. All four of these clinical failures had strains of pneumococci with low-level macrolide resistance (erythromycin MICs 8–16 $\mu g \text{ ml}^{-1}$). Although the mechanism of resistance was not directly tested, all four of the erythromycin-resistant strains were susceptible to clindamycin (21). These data suggest that low-level macrolide resistance due to the mefE gene may also be associated with clinical failure. Studies in an animal model of pneumococcal pneumonia also show failure with azithromycin (22). Animals were infected intrabronchially to produce pneumonia, and therapy with oral agents was initiated 24 hours later. Azithromycin was shown to be ineffective against strains of S. pneumoniae resistant to both penicillin and macrolides (Fig. 2).

There are two key mechanisms of macrolide resistance in S. pneumoniae. The first of these results from mutations in the ermB gene, which alters the ribosomes of S. pneumoniae in such a way that macrolides can no longer affect them (23). This produces very high levels of resistance, for example azithromycin and erythromycin MIC$_{90}$ $> 32 \mu g \text{ ml}^{-1}$ and clarithromycin MIC$_{90}$ $> 128 \mu g \text{ ml}^{-1}$. Clinically, in the presence of ermB mutations in S. pneumoniae, it is not possible to increase the serum macrolide concentration high enough to overcome these resistant organisms. Mutations in the mefE gene—encoding a macrolide efflux pump—produce low-level macrolide resistance (24). Whether the concentrations at the site of infection achieved clinically with macrolides are

<table>
<thead>
<tr>
<th>Macrolide</th>
<th>Days treated</th>
<th>Type of infection</th>
<th>Outcome</th>
</tr>
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<tbody>
<tr>
<td>Erythromycin</td>
<td>3</td>
<td>Pneumonia</td>
<td>Cured (penicillin)</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>8</td>
<td>Pneumonia</td>
<td>Cured (penicillin)</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>4</td>
<td>Pneumonia</td>
<td>Cured (cefotaxime)</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>5</td>
<td>Pneumonia</td>
<td>Cured (amoxicillin)</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>2X2</td>
<td>Pneumonia</td>
<td>Cured (penicillin)</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>2</td>
<td>Pneumonia</td>
<td>Cured (ceftriaxone)</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>2</td>
<td>Pneumonia</td>
<td>Cured (ceftriaxone)</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>3</td>
<td>Pneumonia</td>
<td>Cured (ceftriaxone)</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>3</td>
<td>Pneumonia + empyema</td>
<td>Cured (ceftriaxone)</td>
</tr>
<tr>
<td>Josamycin</td>
<td>2</td>
<td>Pneumonia</td>
<td>Cured (ceftriaxone)</td>
</tr>
<tr>
<td>Josamycin</td>
<td>4</td>
<td>Bacteremia</td>
<td>Cured (amoxicillin/clavulanate)</td>
</tr>
</tbody>
</table>
PNEUMOCOCCAL RESISTANCE AND CLINICAL OUTCOMES

Limit of detection

Fig. 2. Bacterial kill for various antimicrobials in an animal model of pneumonia (penicillin- and macrolide-resistant strain). GEM: gemifloxacin; CIP: ciprofloxacin; GRP: grepafloxacin; LEV: levofloxacin; TRV: trovafloxacin; AMX/CA: amoxicillin/clavulanate; CXM: cefuroxime; AZI: azithromycin; ○: rats killed at 96 h; error bars represent mean and standard deviation. Reproduced with permission (22).

sufficient to eradicate \textit{S. pneumoniae} with the \textit{mefE} mutation is a point of debate. Although preliminary data suggest that low-level macrolide resistance does result in clinical failure (21), more clinical data are required to resolve this question.

**FLUOROQUINOLONE THERAPY**

The prevalence of fluoroquinolone resistance is currently low, though a recent study has found levels to be increasing, possibly as a result of selective pressure due to increased quinolone use (25). Cases of treatment failure during therapy with the older fluoroquinolones are well documented. Persistence of pathogens, superinfection, distant spread and \textit{in vivo} selection of resistant strains have all been reported—particularly for ciprofloxacin (26–29).

Despite a relatively broad spectrum of activity, older fluoroquinolones (e.g. ofloxacin, ciprofloxacin and norfloxacin) have poor activity against Gram-positive pathogens, including \textit{S. pneumoniae}. Although ciprofloxacin has had some success in treating RTIs, it is not thought to be appropriate for the treatment of CAP (30,31). Perhaps this is not surprising, given that ciprofloxacin has marginal activity against \textit{S. pneumoniae} (32). The MIC concentrations for ciprofloxacin against \textit{S. pneumoniae} range from 1 to 4 \(\mu\text{g ml}^{-1}\), whereas peak serum levels of ciprofloxacin, after a dose of 500 mg b.d., are around 2-5 \(\mu\text{g ml}^{-1}\) (33).

One case of treatment failure and \textit{in vivo} selection of resistant strains after ciprofloxacin therapy was described by Perez-Trallero et al. (26). This involved an elderly male patient hospitalized for CAP due to \textit{S. pneumoniae} serotype 3 strain. This is a serotype that seldom shows resistance to antibiotics. Initial treatment was with ciprofloxacin, 200 mg intravenously, every 12 hours, followed by 500 mg orally, every 12 hours. The patient responded well and was discharged after 4 weeks. Ten days after the end of treatment, he was re-admitted to hospital suffering from empyema. Culture revealed an \textit{S. pneumoniae} strain with the same serotype and susceptibility to non-quinolone agents as previously, except this time it had reduced susceptibility to ciprofloxacin and other quinolones (Table 2). The patient went on to respond well to amoxicillin.

Likewise, there is already some evidence of clinical failure in CAP with levofloxacin therapy due to resistant organisms (34).

The newer fluoroquinolones (moxifloxacin, gatifloxacin and gemifloxacin) have increased degrees of potency against a wider range of Gram-positive pathogens than older members of the class and have improved pharmacokinetics (22,35). Some of these agents may, therefore, have increased potential in the treatment of CAP of pneumococcal etiology. Of these, gemifloxacin is the most active of the new oral fluoroquinolones with potent \textit{in vivo} activity against both penicillin- and macrolide-resistant strains of \textit{S. pneumoniae} (MIC \(\leq 0.03 \mu\text{g ml}^{-1}\)) (22). Gemifloxacin has been shown to be as effective as amoxicillin/clavulanate in eradicating a penicillin/macrolide-resistant \textit{S. pneumoniae} in an experimental pneumococcal lung infection model (22).

**TABLE 2. Clinical selection of quinolone-resistant pneumococci in a patient with pneumococcal pneumonia treated with ciprofloxacin (200 mg i.v., every 12 h, followed by 500 mg orally, every 12 h, for 4 weeks). Reproduced with permission (26)**

<table>
<thead>
<tr>
<th>Antimicrobial agent</th>
<th>MIC ((\mu\text{g ml}^{-1}))</th>
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<tbody>
<tr>
<td></td>
<td>First admission</td>
</tr>
<tr>
<td>Penicillin</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>&lt;0.25</td>
</tr>
<tr>
<td>Cotrimoxazole</td>
<td>&lt;0.5/9-5</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>&lt;0.5</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>2</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>1</td>
</tr>
<tr>
<td>Norfloxacin</td>
<td>4</td>
</tr>
<tr>
<td>Ofloxacin</td>
<td>1</td>
</tr>
</tbody>
</table>

Implications of treatment failures for clinical practice

This paper indicates that resistance does have an impact on clinical outcomes in RTI where therapy is sub-optimal. Current levels of resistance clearly compromise the efficacy of some oral cephalosporins (e.g. cefaclor) in AOM and of macrolides (e.g. azithromycin) in both AOM and CAP. Older fluoroquinolones (ciprofloxacin and ofloxacin) have
marginal activity against *S. pneumoniae* and may select for resistant isolates (26). Although quinolone resistance is currently rare, there is already some evidence of clinical failure in CAP with the new fluoroquinolones, levofloxacin, due to resistant organisms (35). There now appears to be a need to reassess appropriate antimicrobial use for empirical treatment in the community.

Some β-lactam antimicrobials, i.e. the aminopenicillins (e.g. amoxicillin/clavulanate), continue to demonstrate high levels of clinical efficacy in AOM and pneumonia, despite increasing levels of pneumococcal resistance. Most cases of CAP caused by non-susceptible isolates of *S. pneumoniae* are likely to respond to high doses of aminopenicillins, though treatment failures with standard doses may occur at higher levels of resistance (>4 µg ml⁻¹). Pharmacodynamic studies show that a time above MIC of about 40% is predictive of bacteriological efficacy for β-lactams. Thus, an increased dose of aminopenicillin, which achieves a sufficient serum concentration, is likely to ensure continued efficacy against isolates currently defined as being fully penicillin resistant (36). For example, use of the high-dose formulation of amoxicillin/clavulanate (14:1 90/6.4 mg kg⁻¹ day⁻¹) in an *in vivo* model of pneumonia showed that efficacy was maintained against *S. pneumoniae* with MICs to amoxicillin of 4 µg ml⁻¹ (37).

Currently, the level of penicillin resistance in *S. pneumoniae* appears to be fairly stable (MICs of 2–4 µg ml⁻¹). However, in 1997, clinical isolates of *S. pneumoniae* with amoxicillin MICs of >4 µg ml⁻¹ were found in 29 patients from different cities across France—18 isolates had amoxicillin MICs of 8 µg ml⁻¹ (38). Fortunately, such findings are rare, though continued surveillance is required to detect such high level resistant pathogens early.

In summary, for the empirical treatment of community-acquired RTI, if infection with penicillin- or macrolide-resistant *S. pneumoniae* is suspected, adequate dosing with an aminopenicillin (e.g. amoxicillin/clavulanate) or one of the newer more potent fluoroquinolones is likely to achieve bacterial eradication and therefore increase the potential for maximum clinical cure and minimized selection and spread of resistance.

**References**


