Breakthrough pneumococcal bacteraemia in patients treated with clarithromycin or oral β-lactams

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The incidence of penicillin- and erythromycin-resistant strains of Streptococcus pneumoniae has increased considerably in Belgium. The medical charts of all patients with pneumococcal bacteraemia who were admitted to hospital over a period of 3 years (n = 136) were reviewed to identify treatment failure of outpatient antibiotic therapy. Twelve patients had received antibiotics for at least 48 h prior to admission. Four treatment failures received clarithromycin as pre-hospitalization therapy, and S. pneumoniae from all four patients were highly resistant to macrolides. Five patients failed on co-amoxiclav, whereas their S. pneumoniae were highly resistant to macrolides. This observation suggests that macrolide resistance is clinically relevant and leads to treatment failure, whereas suboptimal dosing may explain breakthrough pneumococcal bacteraemia in β-lactam-treated patients.

Keywords: S. pneumoniae, breakthrough bacteraemia, macrolides, β-lactams

Introduction

Streptococcus pneumoniae is one of the most common bacterial pathogens in childhood bacteraemia and bacterial infections of the respiratory tract, such as pneumonia, otitis media and sinusitis. Worldwide it is the leading cause of community-acquired pneumonia, accounting for at least 25–30% of all cases, and for two-thirds of all bacteraemic pneumonia. Despite appropriate antimicrobial therapy and intensive medical care, the overall case-fatality rate for pneumococcal bacteraemia is 16–36% among adults. Patients at highest risk for invasive pneumococcal disease include children younger than 2 years, adults older than 65 years, alcoholics, patients with asplenia, or diabetes mellitus, or who are long-term users of systemic corticosteroids, patients with chronic diseases, such as cardiovascular, lung or liver disease, or those who are immunosuppressed.¹

Since the 1960s, pneumococcal infection therapy has become difficult, as a result of the emergence and spread of bacterial resistance to penicillin and other β-lactams, as well as to a number of other antimicrobials, such as macrolides, chloramphenicol and tetracyclines. This is an epidemiological problem of worldwide concern.² In Belgium, rates of penicillin resistance increased from <5% before 1994 to 17.6% in 2000. Thirty-six per cent of invasive clinical isolates of S. pneumoniae, and 81.7% of penicillin-non-susceptible pneumococci, are resistant to erythromycin.³

Macrolide resistance in S. pneumoniae is usually mediated by one of two mechanisms: activity of ribosomal methylases encoded by ermAM genes, which results in strains being resistant to all macrolides, azalides and clindamycin (MLS B phenotype), and drug efflux encoded by mef genes, which confers resistance to 14-membered macrolides and azalides, but does not affect the response to 16-membered macrolides or clindamycin (M phenotype). Importantly, macrolide resistance conferred by ermAM is typically high-grade (i.e. erythromycin MIC > 64 mg/L), whereas efflux mutations result in much lower erythromycin MICs (1–32 mg/L).⁴ In Belgium, >90% of the erythromycin-resistant pneumococci have the ermAM gene and express MLS B phenotype resistance. These results are in contrast to reports from Canada, USA and Japan, where the M phenotype is the most common resistance phenotype.⁵

Although data specifically evaluating the impact of macrolide resistance on clinical outcomes are sparse, clinical
failures with macrolides, followed by successful resolution with another antimicrobial, strongly suggests clinical significance. More data are available regarding the clinical relevance of penicillin resistance among pneumococci. Adequately dosed penicillin treatment of pneumococcal pneumonia remains effective when the MIC is ≤ 2 mg/L. Recent articles, however, cited higher mortality rates, or suppurative complications, for patients with bacteraemic pneumococcal pneumonias, when isolates displayed high-level resistance to cefotaxime (MIC ≥ 2 mg/L) or penicillin (MIC ≥ 4 mg/L). 7

The aim of this study was to investigate antibiotic resistance as a possible cause of breakthrough pneumococcal bacteraemia.

Materials and methods

All adult patients with S. pneumoniae bacteraemia, confirmed by positive blood cultures, and hospitalized between January 1998 and December 2000 at the University Hospital Leuven, were included in this study. The medical charts were retrospectively reviewed by means of a standardized protocol.

Susceptibility to penicillin G (oxacillin 1 μg disc), tetracycline, erythromycin and ofloxacin was tested by the standardized disc diffusion test on Mueller–Hinton agar containing 5% horse blood, according to the recommendations of the NCCLS. On strains with oxacillin inhibition zones of <20 mm, MICs of penicillin and cefotaxime were determined by Etest (AB Biodisk, Solna, Sweden). MICs of erythromycin and clindamycin were determined for all erythromycin-resistant isolates with the same methodology. MICs of amoxicillin were determined for strains from patients with breakthrough bacteraemia on amoxicillin therapy, and MICs of cefaclor for strains isolated from patients on oral cephalosporin therapy. NCCLS criteria were used to categorize isolates as susceptible, intermediate or resistant to the different antibiotics.

Results

From 1998 to 2000, 136 patients with pneumococcal bacteraemia were hospitalized. Sixty-one per cent were male. Analysis of the age distribution showed that > 44% were patients older than 70 years. The overall mortality rate during hospitalization was 22.8%; however, this increased strongly with age in patients older than 70 years (36.6%).

Predisposing underlying medical conditions were chronic cardiovascular disease (37.5%), chronic pulmonary disease (34.6%), malignancy (32.4%), long-term use of systemic corticosteroids (18.4%), diabetes mellitus (13.2%), chronic renal failure (11.0%), liver disease (9.6%), congenital immunodeficiency or HIV (4.4%). Fifteen per cent of the patients had no obvious predisposing factors.

Diagnosis based on presenting symptoms at admission were pneumonia (78%), upper respiratory tract infections (6%), bronchitis (5%), abdominal infections (3%) or catheter-related infections (2%). One patient had cellulitis and another an overwhelming post-splenectomy infection. Five per cent of the patients presented with fever of unknown origin.

Overall, 14 of the 136 pneumococci (10.3%) were non-susceptible to penicillin (MIC > 0.1 mg/L), and 33 (24.3%) to erythromycin (MIC ≥ 1 mg/L). Ten of the 14 pneumococci, with reduced susceptibility to penicillin, showed intermediate resistance; three had an MIC of 2 mg/L and one of 4 mg/L. Seven of these 14 pneumococci showed intermediate resistance to cefotaxime (MIC 0.5–2 mg/L), and in all seven isolates the MICs of cefotaxime were lower than those of penicillin. Only two of 33 erythromycin-resistant S. pneumoniae had a low-grade erythromycin resistance (erythromycin MIC 32 mg/L) and both were clindamycin susceptible (clindamycin MIC 0.12 mg/L). The remaining 31 were highly resistant to erythromycin and clindamycin.

Only 12 of the 136 patients had received several days worth of antibiotics at therapeutic doses, the last dose within 24 h before admission to hospital. Therapies consisted of: co-amoxiclav (five patients), clarithromycin (four patients), cefadroxil (two patients) and cefaclor (one patient). Sex, age, underlying diseases and antibiotic therapy prior to hospitalization are shown in Table 1. The four patients on clarithromycin therapy received the drug at a dosage of 500 mg twice daily for 3–14 days. Pneumococci isolated from blood cultures of these four patients were susceptible to penicillin, but highly resistant to erythromycin (MICs ≥ 256 mg/L) and clindamycin.

In contrast, all five pneumococci isolated from patients under therapy with co-amoxiclav were very susceptible to penicillin (MIC 0.008–0.016 mg/L) and amoxicillin (MIC 0.008–0.016 mg/L). The isolate from the one treated with cefaclor was very susceptible to penicillin (MIC 0.012 mg/L) and cefaclor (MIC 0.19 mg/L). The isolates from the two patients treated with cefadroxil had penicillin MICs of 1 mg/L and cefaclor MICs of 64 mg/L. Patient 11 had been receiving maintenance therapy with cefadroxil for > 6 months after a prosthetic valve endocarditis.

Table 2 gives data on the subsequent antibiotherapy during hospitalization, and on the outcome of the patients. All 12 patients were empirically treated with high doses of β-lactam antibiotics. Ten of the 12 patients received penicillin G intravenously, or a third-generation cephalosporin, which are the standard regimens for the empirical therapy of community-acquired pneumonia. For two patients, the ceftriaxone therapy was combined with clarithromycin. The outcome was favourable for nine of the 12 patients; discharge was possible after a mean stay of 7 days (range 2–10 days).

Three patients, all older than 80 years, died within the first 3 days of their hospitalization.
**Breakthrough pneumococcal bacteraemia**

**Table 1.** Patients with breakthrough pneumococcal bacteraemia: data prior to hospitalization

<table>
<thead>
<tr>
<th>Number</th>
<th>Sex</th>
<th>Age</th>
<th>Underlying diseases</th>
<th>Reason for antibiotic treatment</th>
<th>Failed therapy</th>
<th>Antibiotics</th>
<th>Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>77</td>
<td>COPD, mitral valve insufficiency</td>
<td>exacerbation bronchitis</td>
<td>CLR</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>27</td>
<td>none</td>
<td>upper respiratory tract infection</td>
<td>CLR</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>44</td>
<td>liver cirrhosis</td>
<td>acute bronchitis</td>
<td>CLR</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>95</td>
<td>chronic renal failure</td>
<td>bronchopneumonia</td>
<td>CLR</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>54</td>
<td>COPD, chronic corticosteroid</td>
<td>exacerbation bronchitis</td>
<td>AMC</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>28</td>
<td>none</td>
<td>flu-like symptoms</td>
<td>AMC</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>36</td>
<td>none</td>
<td>bronchopneumonia</td>
<td>AMC</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>32</td>
<td>none</td>
<td>bronchopneumonia</td>
<td>AMC</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>52</td>
<td>none</td>
<td>acute bronchitis</td>
<td>AMC</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>M</td>
<td>65</td>
<td>COPD, chronic corticosteroid</td>
<td>exacerbation bronchitis</td>
<td>CEC</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>M</td>
<td>83</td>
<td>prosthetic heart valve</td>
<td>bronchopneumonia</td>
<td>CFR</td>
<td>190</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>F</td>
<td>85</td>
<td>none</td>
<td>bronchopneumonia</td>
<td>CFR</td>
<td>16</td>
<td></td>
</tr>
</tbody>
</table>

CLR, clarithromycin 500 mg twice a day; AMC, co-amoxiclav 500/125 mg twice a day; CEC, cefaclor 250 mg three times a day; CFR, cefadroxil 500 mg twice a day. COPD, chronic obstructive pulmonary disease.

**Table 2.** Patients with breakthrough bacteraemia: data after admission

<table>
<thead>
<tr>
<th>Number</th>
<th>Sex</th>
<th>Age</th>
<th>Antibiotics</th>
<th>Dosage/day</th>
<th>Days</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>77</td>
<td>AMC</td>
<td>4 × 1 g iv</td>
<td>10</td>
<td>favourable</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>27</td>
<td>PEN</td>
<td>6 × 2.10^6 IU iv</td>
<td>10</td>
<td>favourable</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>44</td>
<td>CRO</td>
<td>1 × 2 g iv</td>
<td>10</td>
<td>favourable</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>95</td>
<td>CXM</td>
<td>3 × 750 mg iv</td>
<td>3</td>
<td>died</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>54</td>
<td>PEN</td>
<td>6 × 2.10^6 IU iv</td>
<td>5</td>
<td>favourable</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>28</td>
<td>AMC</td>
<td>4 × 1 g iv</td>
<td>4</td>
<td>favourable</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>36</td>
<td>PEN</td>
<td>6 × 2.10^6 IU iv</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>32</td>
<td>CRO</td>
<td>1 × 2 g iv</td>
<td>3</td>
<td>favourable</td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>52</td>
<td>PEN</td>
<td>6 × 2.10^6 IU iv</td>
<td>7</td>
<td>favourable</td>
</tr>
<tr>
<td>10</td>
<td>M</td>
<td>65</td>
<td>CLR</td>
<td>2 × 500 mg by mouth</td>
<td>10</td>
<td>favourable</td>
</tr>
<tr>
<td>11</td>
<td>M</td>
<td>83</td>
<td>CLR</td>
<td>2 × 500 mg by mouth</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>F</td>
<td>85</td>
<td>TZP</td>
<td>3 × 4 g iv</td>
<td>9</td>
<td>favourable</td>
</tr>
<tr>
<td>13</td>
<td>M</td>
<td>52</td>
<td>CRO</td>
<td>1 × 2 g iv</td>
<td>1</td>
<td>died</td>
</tr>
<tr>
<td>14</td>
<td>F</td>
<td>85</td>
<td>CTX</td>
<td>2 × 2 g iv</td>
<td>3</td>
<td>died</td>
</tr>
<tr>
<td>15</td>
<td>F</td>
<td>85</td>
<td>GEN</td>
<td>1 × 240 mg iv</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>

AMC, co-amoxiclav; CXM, cefuroxime; GEN, gentamicin; PEN, penicillin; CLR, clarithromycin; CRO, ceftriaxone; TZP, piperacillin/tazobactam; CTX, cefotaxime.

**Discussion**

The main conclusion of this study is that breakthrough bacteraemia with pneumococci, in patients on macrolide treatment, was associated with macrolide resistance, whereas following treatment with co-amoxiclav it was not associated with penicillin or amoxicillin resistance. This observation strongly suggests that macrolide resistance is clinically relevant and leads to treatment failure. Since penicillin resistance is obviously not the reason for treatment failure in co-amoxiclav-treated patients, other mechanisms explaining breakthrough pneumococcal bacteraemia must be explored. Dosing
Macrolide resistance among strains of *S. pneumoniae* has escalated dramatically within past decades worldwide. The European Antimicrobial Resistance Surveillance System (EARSS), an international surveillance programme organized by the European Commission, tracks resistance rates from multiple laboratories in Europe. EARSS has shown marked variability in rates of macrolide resistance of invasive *S. pneumoniae* between 21 European countries, ranging from 2.1% to 39%. The highest rates of erythromycin resistance (>20%) were observed in Italy, Belgium, Spain and Luxembourg.

In Belgium, macrolide resistance in invasive pneumococcal isolates increased from 6.7% in 1987 to 21.5% in 1993 and 37% in 2001. Three serogroups/serotypes (19, 14 and 6) accounted for 80% of macrolide-resistant isolates, consistent with clonal spread. Extensive use of macrolides in our country may have contributed to the high rate of macrolide resistance.

Studies in Finland and Spain found that resistance to macrolides correlated highly significantly with overall macrolide use, and particularly with once-a-day macrolide consumption.

The dominant mechanism of erythromycin resistance in Belgium is the methylation of a highly conserved region of the peptidyl transferase loop of the 23S mRNA, encoded by the *erm* AM gene. This gene is usually carried on conjugative transposons that may facilitate rapid dissemination of erythromycin resistance.

Although we did not assess the mechanism of erythromycin resistance of the four pneumococci isolated from blood cultures of patients with clarithromycin outpatient therapy, the fact that they were all highly resistant to erythromycin, and resistant to clindamycin, suggests the MLSB phenotype.

For treating pneumonia, antibiotic levels in extracellular fluid, where *S. pneumoniae* is located, are important. Concentrations of clarithromycin in extracellular tissue fluids are in equilibrium with concentrations in serum. The four patients described in this study all received conventional dosing of clarithromycin (500 mg twice a day). The expected mean peak serum concentration in the steady state achieved after five doses with this dosage is 2–3 mg/L. It is obvious that the mean serum concentrations of clarithromycin are lower than the MIC of clarithromycin for *S. pneumoniae* with MLSB phenotype resistance, and that the failure of the outpatient therapy with breakthrough bacteraemia was probably due to the resistance to macrolides. Because culture samples were taken after patients had been treated for several days with clarithromycin, it is unclear whether the resistant strains were present as the primary aetiology, or whether they emerged because of the selective effect of clarithromycin.

Data specifically evaluating the impact of macrolide resistance on clinical outcome are sparse. Dagan *et al.* investigated the effect of macrolide resistance in *S. pneumoniae* on bactericidal eradication in otitis media. They illustrated that azithromycin had an effect similar to that of placebo against macrolide-resistant *S. pneumoniae*. Kelley *et al.* described four patients treated with azithromycin or clarithromycin, who presented with breakthrough bacteraemia caused by erythromycin-resistant pneumococci, although the four isolates exhibited low-level resistance to erythromycin. Fogarty *et al.* described three patients who received 3–5 days of orally administered azithromycin and were subsequently admitted with a bacteraemic pneumonia caused by macrolide-resistant pneumococci. Lonks *et al.* conducted a matched case–control study of patients with bacteraemic pneumococcal infection at three US centres and one Spanish centre. Their data show that development of breakthrough bacteraemia, during macrolide or azithromycin therapy, is more likely to occur among patients infected with an erythromycin-resistant pneumococcus. Their study also demonstrated that low-level, as well as high-level, resistance caused therapy failure. Interestingly, all 18 patients responded to the β-lactam antibiotics received in hospital.

Relatively few patients are treated with macrolides alone, and there is frequent use of empirical therapy for lower respiratory tract infections, in the absence of microbiological and susceptibility data. This results in unsolved problems when evaluating the impact of macrolide resistance on outcome.

The patients pre-treated with cefadroxil had strains with intermediate resistance to penicillin and high resistance to cefaclor (MIC 64 mg/L). Cefadroxil was not available for testing, but the MIC distribution is similar to that of cefaclor. Failure in these cases may be attributed to cephaplarin resistance.

Our data show that breakthrough bacteraemia during therapy with co-amoxiclav was not associated with penicillin resistance. β-Lactam antibiotics are time-dependent drugs, with the time above MIC being the outcome predictor. In animal studies, high survival rates (>90%) are seen if serum drug concentrations exceed the MIC for at least 40% of the dosing interval for penicillins, and at least 50% of the dosing interval for cephalosporins. For orally administered amoxicillin, as well for other parenteral β-lactams, a serum concentration above the MIC for at least 40–50% of the dosing interval for intermediate penicillin resistant pneumococci is maintained. The average serum levels 6 h after an oral dose of co-amoxiclav are between 0.5 and 0.6 mg/L, i.e. 40 times higher than the observed MICs (0.008–0.016 mg/L) for the five breakthrough strains for at least 75% of the time between two dosing intervals (500 mg twice a day). The question then arises, is even a 75% time above MIC sufficient for successful treatment of pneumococcal pneumonia? For infections caused by highly resistant pneumococci (penicillin MIC > 1 mg/L;
Breakthrough pneumococcal bacteraemia

cefotaxime MIC > 2 mg/L), β-lactam therapy may lead to
treatment failure. Recent publications cited higher mortality
to these drugs, or supportive complications, for patients with bac-
teraemic pneumococcal pneumonias when isolates dis-
played high-level resistance to cefotaxime or penicillin.⁷,¹⁹,²⁰
Although the pneumococcal isolates from the five patients in
our retrospective study who received co-amoxiclav as pre-
hospitalization therapy were very susceptible to penicillin
(MIC 0.008–0.016 mg/L) and amoxicillin (MIC 0.008–
0.016 mg/L), a breakthrough bacteraemia could not be
avoided. Apart from the resistance issue, treatment failure can
occur because an antibiotic is either not taken or not absorbed,
or not prescribed in the proper dose or dosing interval. Host
factors and co-morbidities, as well as virulence character-
istics of the infecting micro-organisms, may also contribute
to treatment failure. Analysis of patients’ records shows it
unlikely that treatment failures occur solely because of lack of
compliance or poor absorption, but it cannot be excluded.
Underlying pathology is also an unlikely cause, since only
one of the five patients who received co-amoxiclav was a
chronic obstructive pulmonary disease (COPD) patient on
corticosteroid therapy, whereas the other four presented with-
out predisposing medical conditions. Our data suggest that
the cause of the breakthrough bacteraemia in these patients
was underdosing. Co-amoxiclav (500/125 mg twice a day)
may not achieve the necessary PK/PD parameters predictive
for bacteriological eradication in cases of pneumococcal
pneumonia. Underdosing was likely in the patient treated
with cefaclor (3 × 250 mg). In the early days of antibiotic
therapy, a dosing interval of four to six times the half-life time
was a rule of thumb in the treatment of patients with serious
infections. Meanwhile, pharmaceutical companies have pro-
gressively downscaled the number of daily administrations
of oral penicillins and cephalosporins (with a half-life time of
∼1 h) from four to three and finally to two administrations a
day, officially for reasons of ‘compliance’, but corresponding
with the arrival and the competitive pressure of newer anti-
biotics with a longer half-life time (doxycycline, fluoro-
quinoles, neo-macrolides). Subsequently, this was justified
by animal studies, showing that even for antibiotics with a
short half-life time, and depending for their activity on time
above MIC (β-lactams), 40–50% of the dosing interval
was sufficient to obtain success in at least 90% of the animals. This
parameter has never been verified under controlled condi-
tions in patients with severe pneumococcal infections, and it
remains questionable whether this time lapse is sufficient for
the treatment of invasive pneumococcal infections in patients
where antibiotic activity really matters, and a 100% success
rate is the goal.

The newer macrolides are well-established anti-infective
agents and have been considered superior to erythromycin in
microbiological activity and clinical efficacy. The most
recent guidelines from the Infectious Diseases Society of
America, and the American Thoracic Society, advocate either
a macrolide, a respiratory fluoroquinolone or doxycycline, for
empirical treatment of outpatients with community-acquired
pneumonia who lack significant comorbidities.²¹,²² The
usefulness of macrolides, as first-line or indeed second-line
empirical monotherapy for this indication, is becoming
questionable in Belgium, since resistance of S. pneumoniae
to macrolides, and of the MLSB phenotype, is now very common.
It would appear prudent to suggest that macrolides should
only be used in patients when an atypical pneumonia is the
most likely diagnosis.

Penicillins are still the drugs of choice for treating pneumo-
coccal infections. However, it is time to abandon minimal
antibiotic regimens and aim for adequate dosage and dosing
intervals. This may not only contribute to clinical success but
also limit the emergence of resistance.²³

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