Significance of macrolide resistance in Streptococcus pneumoniae

Eric L. Nuerberger and William R. Bishai

Center for Tuberculosis Research, Division of Infectious Diseases, Johns Hopkins University School of Medicine, 424 North Bond Street, Baltimore, MD 21231, USA

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Sir,

We wish to comment on the paper by Van Kerkhoven et al., 1 to dispel certain misconceptions that may arise from a cursory review of their study. The authors present a 3 year retrospective chart review of patients hospitalized with pneumococcal bacteraemia at a single hospital. Of the 136 patients identified, 14 (10.3%) and 33 (24.3%) had isolates non-susceptible to penicillin and erythromycin, respectively. Of the erythromycin-resistant isolates, 94% had an MLSB-resistance phenotype and high-level erythromycin resistance (MIC > 64 mg/L). Further analysis was limited to 12 patients who received β-lactam therapy before admission and combination therapy with a β-lactam plus a macrolide or, alternatively, with a fluoroquinolone, until culture and susceptibility results were available. Although these cases were used to illustrate failure of the antibiotic, the outcomes may have been preventable with better medical decision-making.

Most importantly, because macrolide resistance among pneumococci in Belgium is dominated by the erm(B)-mediated mechanism, the study does not shed light on whether efflux-mediated resistance is clinically relevant. In their discussion, the authors cite a study by Lonks et al.2 as demonstrating that both low-level (that is, efflux-mediated) as well as high-level macrolide resistance is responsible for therapeutic failure. That study, however, included only one patient isolate with an MIC < 16 mg/L, a value more reflective of low-level resistance. In fact, there is no convincing evidence that such low-level macrolide resistance increases the risk of macrolide failure. On the other hand, recent evidence from animal models suggests that isolates with MICs up to 8 mg/L may respond to clarithromycin.3 Such evidence is supported by the concentrations of drug achievable in the alveolar epithelial lining fluid and lung parenchyma of healthy human volunteers.4 This unresolved conundrum has important implications in North America, where efflux mechanisms account for 61–85% of macrolide-resistant isolates.5 In other words, if pneumococci with MICs ≤ 8 mg/L are actually treatable with clarithromycin, then clinically significant macrolide resistance occurs in <10% of invasive pneumococcal isolates.

Finally, we are reluctant to accept that the inadequate pharmacokinetics of co-amoxiclav 500/125 mg twice daily was responsible for treatment failures in five non-elderly patients infected with fully susceptible organisms, and with little apparent co-morbidity. Even this dosage exceeds well-accepted pharmacodynamic parameters predictive of efficacy (for example, serum concentrations >MIC for >50% of the dosing interval).6 If marginal pharmacokinetics were the issue, organisms with reduced susceptibility to β-lactams should be over-represented among breakthrough infections. Whereas we are in full agreement with the authors that all antimicrobials should be prescribed for maximal effectiveness rather than convenience, the failures on co-amoxiclav therapy point out the inadequacies of anecdotal reports of treatment failure. The fact is that treatment of bacteraemic pneumococcal pneumonia fails sometimes, whether due to inherent bacterial virulence, or issues related to the host or antibiotic regimen. This possibility makes anecdotes less meaningful. As a result, the collective literature leaves us in no position to determine whether efflux-mediated macrolide resistance in pneumococci is clinically relevant.

References

The reason for failure after macrolide therapy was resistance, which was not unexpected with regard to the large predominance of MLSB-type macrolide resistance. That not low-level resistance to macrolides inevitably leads to failure is a strong supposition is unlikely in patients whose infection resulted in admission to hospital.

Our conclusions are straightforward: (1) empiric treatment with cephalosporins or co-amoxiclav on a twice-daily basis is not safe for patients at risk for invasive pneumococcal infections; (2) macrolide therapy is not a good alternative in Belgium because of the high-level resistance to this class of antibiotics.


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Reply

J. Verhaegen*1, W. Peetemans2 and L. Verbist1

Department of 1Microbiology and 2Internal Medicine, University Hospitals Leuven, Department of Microbiology, B-3000 Leuven, Belgium

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*Corresponding author. Tel: +32-16-347073; Fax: +32-16-347931; E-mail: jan.verhaegen@uz.kuleuven.ac.be

Sir,

Our study is retrospective but not anecdotal. Our starting question was: what is the reason behind the failure of initial therapy in patients with invasive pneumococcal infection? In order to give any therapy a fair chance, our cut-off point was treatment for more than 48 h, which left us with 12 patients remaining out of 136 with proven pneumococcal bacteremia. The reason for failure after macrolide therapy was resistance, which was not unexpected with regard to the large percentage of high-level resistance (MLS\textsubscript{B}) in Belgium. Whether or not low-level resistance to macrolides inevitably leads to failure is not an issue in our country, or in other European countries with a strong predominance of MLS\textsubscript{B}-type macrolide resistance. That matter is covered by other investigators. Surveillance studies in the USA and Canada show a gradual increase in pneumococcal macrolide resistance, reaching levels up to 40% in certain areas. Taking into account a prevalence of MLS\textsubscript{B}-type resistance of 15%–39%, as cited by the authors, it seems appropriate to survey closely the evolution and type of macrolide resistance among pneumococci in these countries.

The surprising fact was that failures after oral \(\beta\)-lactam therapy on a twice-daily basis apparently were not as a result of resistance to penicillin. All patients further treated with high doses of \(\beta\)-lactams recovered quickly, with the exception of three patients (all over 80 years) for whom therapeutic doses were too late. We do not agree with Nuernberger & Bishai that the outcomes of the three patients who died may have been preventable with better medical decision making or combination therapy. These patients were very old and died within 3 days of admission, despite treatment with adequate dosages of \(\beta\)-lactam antibiotics to which the causative organisms were susceptible. A case-fatality rate of three out of 12 patients (25%) is similar to the overall case-fatality rate of 22.8% observed for all patients with pneumococcal bacteremia, and to case-fatality rates reported in the literature. The advantage of combination treatment of a \(\beta\)-lactam antibiotic plus a macrolide for treatment of community-acquired pneumococci in hospitalized patients or bacteremic pneumococcal pneumonia, although widely accepted in the USA and Canada, remains highly controversial in Europe. There are conflicting data regarding the presence and pathogenic role of atypical bacteria in community-acquired pneumonia, and the effect on outcome of omitting treatment for these microbes.

The most likely reason for initial failure of oral \(\beta\)-lactam therapy is insufficient antibiotic levels (in time/concentration), either because the doses were too low and/or the interval between doses was too long, or because the patients were not taking the drugs. The latter supposition is unlikely in patients whose infection resulted in admission to hospital.

Our conclusions are straightforward: (1) empiric treatment with cephalosporins or co-amoxiclav on a twice-daily basis is not safe for patients at risk for invasive pneumococcal infections; (2) macrolide therapy is not a good alternative in Belgium because of the high-level resistance to this class of antibiotics.

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