Treatment of Gram-positive bone and joint infection: authors’ response

Elizabeth S. R. Darley* and Alasdair P. MacGowan

Bristol Centre for Antimicrobial Research and Evaluation, Southmead Hospital, Westbury-on-Trym, Bristol BS10 5NB, UK

Keywords: osteomyelitis, bone infections, joint infections, antibiotics, Gram-positive

*Corresponding author. Tel: +44-117-9595651; Fax: +44-117-9593154; E-mail: Elizabeth.Darley@north-bristol.swest.nhs.uk

Sir,

We have noted with interest the points made by Frippiat et al.1 and make the following comments.

We have not stated that the newer quinolones should not be considered for treatment of Gram-positive bone and joint infections. We agree that this group of antibiotics offers an attractive alternative to standard parenteral therapy because of their potency against Gram-positive pathogens and good bioavailability, but caution that the safety of the newer quinolones in long-term use is not yet established. There is a lack of clinical experience and data regarding long-term outcome with these agents treating chronic infections in man, compared with older fluoroquinolones. Quinolone resistance is increasing; the development of resistance to the new fluoroquinolones in Gram-positive organisms has been reported in a pharmacodynamic study,2 and Frippiat et al.3 also refer to a clinical case where resistance developed in one of seven of their patients treated for Gram-positive prosthetic joint infection. In agreement with Frippiat et al., our advice to clinicians is that until there are more clinical data available, the addition of a second antibiotic (often rifampicin) should be considered when using a quinolone to treat deep infection, over a prolonged duration.

The optimum dose of rifampicin for use as a second agent in treatment of orthopaedic infection has not been identified, although bone penetration studies have suggested that 600 mg twice daily will give optimal bone concentrations when compared with 300 mg twice daily or 600 mg daily.3 We usually recommend a dose between 300–600 mg twice daily, depending on the size of the patient and the causal pathogen. This dose is comparable to the dose of 10–20 mg/kg/day suggested by Frippiat et al.1

Finally, we agree that whereas linezolid is an attractive option for oral treatment of MRSA and other multi-resistant Gram-positive infection, it is not recommended for use in chronic infection, such as osteomyelitis, due to the lack of safety data when used for >28 days.4 We have not yet encountered optic neuropathy in association with prolonged linezolid treatment, but have observed thrombocytopenia in some patients, a recognized side effect,5 and advise clinicians to monitor full blood count weekly when prescribing linezolid for both inpatients and outpatients.

References

performed by the microdilution method with cation-adjusted Mueller–Hinton broth (Oxoid, Basingstoke, UK) according to the recommendations of the NCCLS. A disc-diffusion test, with 2-mercaptoethanesulfonic acid as an MBL inhibitor, was used to screen for MBL producers, as described by Arakawa et al. Whole cell DNA from *P. aeruginosa* prepared by a rapid alkaline lysis procedure was used as template in PCR assays. Primers for PCR were designed based on all MBLs published in GenBank and were: bla*IMP*, 5′-CTG CCK CAG GAG MGK CTT T-3′ and 5′-AAC CAG TTT TGC YTT ACY AT-3′; bla*VI*M, 5′-CTT TAC CAG ATT GGY CAT GG-3′ and 5′-CGG YAG RCC GTG CCC SGG AAC-3′. The amplicons were purified with PCR Clean Up Kits (Roche Molecular Biochemicals, Mannheim, Germany) and were sequenced on an ABI PRISM 377 Sequencer Analyzer (Applied Biosystems, Foster City, CA, USA). Genomic DNA for PFGE analysis was digested overnight with 10 U of *SpeI* (New England Biolabs, Beverly, MA, USA). The samples were electrophoresed with the Pulsaphor Plus System (Amersham Pharmacia Biotech) at 200 V for 30 h, with pulse times in the range 5–30 s.

Seven of 24 isolates of *P. aeruginosa* resistant to imipenem showed potentiation of cefazidime by 2-mercaptoethanesulfonic acid, suggesting the production of MBL. Characteristics of these isolates are listed in Table 1. All seven were resistant to imipenem, piperacillin, cefotaxime, cefazolin, cefalothin, cefoxitin and cefazolin. Their susceptibilities to aztreonam and ciprofloxacin varied.

All seven isolates positive by the screening test gave PCR amplicons using primers specific for *bla*IMP* alleles; the remaining 17 isolates were negative. None of the 24 isolates contained *bla*VI*M alleles. The PFGE patterns of the IMP-producing isolates were identical, suggesting nosocomial spread of the strain. Sequence analysis revealed that the *bla*IMP* allele of this strain differed from *bla*IMP*1* (GenBank AY168635) by replacements of T → C, T → C and C → T at nucleotides 87, 171 and 394 of the structural gene, respectively. These mutations were all silent, so the strain produced IMP-1 enzyme. This is the first report of IMP-1 MBL in China. The carbapenem-resistant phenotype of the 17 *P. aeruginosa* that lacked *bla*IMP* and *bla*VI*M genes probably resulted from the loss of the outer membrane protein OprD, or up-regulation of the MexAB-OprM efflux pump.

Rasmussen & Bush predicted that an increase in MBL-producing organisms was inevitable, given the more frequent use of carbapenems. Our studies indicate the urgent need for action to prevent further spread of MBL-producing organisms. Previous experience indicates that once resistant bacteria become widespread they cannot be controlled. Our first task is to detect MBL producers among clinical isolates. Although the NCCLS does not currently recommend procedures for detection, a disc-diffusion test, as used here, is a simple method for screening for MBL producers. Laboratories in China and in other countries with carbapenem-resistant organisms should screen for MBL-producing isolates to determine their clinical impact and to prevent further spread.

### Acknowledgements

We are grateful to Yu Yun-song (Department of Infectious Diseases, NO.1 Affiliated Hospital, College of Medicine, Zhejiang University, Hangzhou, China) for his generous provision of the *bla*IMP*-positive control strain and technical assistance.

### References


**Table 1. Susceptibilities of *Pseudomonas aeruginosa* carrying MBL genes**

<table>
<thead>
<tr>
<th>Strain</th>
<th>Department</th>
<th>Specimen</th>
<th>MIC (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>PIP</td>
</tr>
<tr>
<td>75653</td>
<td>ICU</td>
<td>sputum</td>
<td>&gt;128</td>
</tr>
<tr>
<td>60164</td>
<td>ICU</td>
<td>sputum</td>
<td>&gt;128</td>
</tr>
<tr>
<td>76407</td>
<td>respiratory</td>
<td>sputum</td>
<td>&gt;128</td>
</tr>
<tr>
<td>58936</td>
<td>ICU</td>
<td>sputum</td>
<td>&gt;128</td>
</tr>
<tr>
<td>68819</td>
<td>ICU</td>
<td>sputum</td>
<td>&gt;128</td>
</tr>
<tr>
<td>59622</td>
<td>ICU</td>
<td>sputum</td>
<td>&gt;128</td>
</tr>
<tr>
<td>69409</td>
<td>respiratory</td>
<td>sputum</td>
<td>&gt;128</td>
</tr>
</tbody>
</table>

PPI, piperacillin; CAZ, ceftazidime; CTX, cefotaxime; CFZ, cefazolin; CEF, cefalothin; FOX, cefoxitin; ATM, aztreonam; IPM, imipenem; GEN, gentamicin; CIP, ciprofloxacin.