The possibility of change for in vitro susceptibility of Cryptococcus spp. in the future justifies the need for further systematic studies using standardized techniques. This is particularly valid for azoles, as their period of clinical and therapeutic use is still very short.

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Transparency declarations

None to declare.

References


In vitro activity of ceftobiprole against clinical isolates of Pseudomonas aeruginosa obtained from Canadian intensive care unit (ICU) patients as part of the CAN-ICU Study

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Keywords: antimicrobial resistance, susceptibility, cefepime

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Sir,

In recent years, Pseudomonas aeruginosa isolates resistant to multiple classes of antimicrobial agents have become
increasingly common.1 Several mechanisms may contribute to antimicrobial resistance among P. aeruginosa, including the production of a chromosomally encoded AmpC β-lactamase.1 Ceftobiprole (BAL9141), an investigational pyrrolidinone cephalosporin, is reported to have activity against a broad spectrum of clinically important Gram-negative bacteria including P. aeruginosa.2 Additionally, in vitro studies have demonstrated that ceftobiprole is hydrolysed very slowly by AmpC cephalosporinases.3 The purpose of this report was to describe the in vitro activity of ceftobiprole versus 419 clinical isolates of P. aeruginosa obtained from patients in an intensive care unit (ICU) setting. Ceftepime was used as a comparator antimicrobial agent.

From September 2005 to June 2006, inclusive, P. aeruginosa isolates were collected as part of the Canadian National Intensive Care Unit (CAN-ICU) Study. The CAN-ICU Study included 19 medical centres from all regions of Canada with active ICUs. Each centre submitted a maximum of 300 consecutive pathogens isolated from blood, urine, tissue/wound and respiratory specimens (one pathogen per cultured site per patient) of ICU patients. Centres were requested to only obtain ‘clinically important’ specimens from patients with a presumed infectious disease. Surveillance swabs, eye, ear, nose and throat swabs were excluded, as were anaerobic bacteria and fungi. Isolates were shipped to the reference laboratory (Health Sciences Centre, Winnipeg, MB, Canada) on Amies charcoal swabs, subcultured onto appropriate media and stocked in skimmed milk at −80°C until MIC testing was performed. The in vitro activities of ceftobiprole and ceftepime were determined by microbroth dilution in accordance with the CLSI guidelines.4,5 MIC interpretive standards for ceftepime were defined according to CLSI breakpoints.5 At present, susceptibility breakpoints for ceftobiprole do not exist.

In total, 419 isolates of P. aeruginosa were collected as part of the CAN-ICU Study. The breakdown of these 419 isolates by specimen source was as follows: respiratory (69.0%), wound (12.4%), urine (10.7%) and blood (7.9%). The MIC distributions of ceftobiprole and ceftepime for the isolates were very similar (Table 1). At an antimicrobial concentration of ≤8 mg/L, 74.7% and 78.7% of our isolates would be inhibited by ceftobiprole and ceftepime, respectively. The MIC50 and MIC90 values of ceftepime were 4 and 32 mg/L. The corresponding MIC50 and MIC90 values of ceftobiprole were 4 and 16 mg/L. The MIC distributions of ceftobiprole and ceftepime were comparable, regardless of specimen source. Cross-resistance between ceftobiprole and ceftepime was observed. Of 43 ceftepime-resistant isolates (MIC ≥ 32 mg/L), only 3 (7.0%) had an MIC of ceftobiprole of ≤8 mg/L. Similarly, only 6 of 40 isolates (15%) with a ceftobiprole MIC of ≥32 mg/L were susceptible to ceftepime.

In agreement with our results, previous studies have reported similar in vitro activity between ceftobiprole and ceftepime when evaluated against P. aeruginosa.2,6 A recent study by Pillar et al.2 documented a lower modal MIC of ceftepime in comparison with ceftobiprole against P. aeruginosa isolates (1 mg/L versus 2 mg/L). However, the MIC50 and MIC90 values were identical (4 and 16 mg/L, respectively) for both antimicrobials.2 Our data demonstrate a high degree of cross-resistance between ceftobiprole and ceftepime. Hebeisen et al.6 have previously described the finding of cross-resistance between ceftazidime, ceftipime and ceftobiprole. These investigators reported the activity of ceftobiprole against 17 ceftazidime-non-susceptible P. aeruginosa isolates (MIC50 of 16 mg/L and MIC90 of >64 mg/L for ceftazidime). The MIC50 and MIC90 values of ceftobiprole against these isolates were 16 and >64 mg/L, respectively.6 The corresponding MIC50 and MIC90 values of ceftepime versus the ceftazidime-non-susceptible isolates were 32 and 32 mg/L.6 Cross-resistance has also been described in a study by Pillar et al.2, where the MIC50/MIC90 values of ceftobiprole against 491 ceftazidime-susceptible and 130 ceftazidime-non-susceptible P. aeruginosa isolates were 2/8 and 16/32 mg/L, respectively.

In summary, ceftobiprole and ceftepime demonstrated comparable in vitro activity against P. aeruginosa clinical isolates from Canadian ICUs and cross-resistance between these agents was common. Whether ceftobiprole will be clinically useful in the treatment of serious infections caused by P. aeruginosa remains to be determined.

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**Table 1. Distribution of ceftepime and ceftobiprole MICs (mg/L) for 419 P. aeruginosa clinical isolates**

<table>
<thead>
<tr>
<th>Antimicrobial</th>
<th>Number of isolates susceptible at MIC (cumulative % of all isolates tested)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Cefepime</td>
<td>57 (13.6)</td>
</tr>
<tr>
<td>Ceftobiprole</td>
<td>42 (10.0)</td>
</tr>
</tbody>
</table>
Cape Breton Regional Hospital, Sydney, NS (K. McVarish); University of Alberta Hospitals, Edmonton, AB (Dr R. Rennie); Vancouver Hospital, Vancouver, BC (Dr D. Roscoe); Regina General Hospital, Regina, SK (Dr E. Thomas); and St John Regional Hospital, St John, NB (Y. Yaschuk).

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Susceptibility of 71 French isolates of Francisella tularensis subsp. holarctica to eight antibiotics and accuracy of the Etest® method

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Keywords: method comparison, minimum inhibition concentration, tularaemia

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Sir, Francisella tularensis subsp. holarctica causes tularaemia, which affects a large range of vertebrates, including humans and other mammals.1 This facultative intracellular bacterium is highly infectious and causes life-threatening infections, especially when transmitted via the respiratory route. In France, 20 to 25 cases in humans are reported to the national health authorities each year.2 This bacterium is naturally resistant to penicillins and cephalosporins, but is susceptible to many other antibiotics including aminoglycosides, chloramphenicol, tetracyclines, rifampicin and fluoroquinolones.3–6

In this study, we aimed to determine the in vitro antibiotic susceptibility of a representative panel of 71 French F. tularensis subsp. holarctica strains by the agar dilution method and to evaluate the accuracy of the Etest® method (AB Biodisk, Sweden) using supplemented Mueller–Hinton II reference medium (Becton Dickinson, France) or supplemented chocolate medium (Becton Dickinson).

Seventy-one isolates of F. tularensis subsp. holarctica were collected from human or animal samples in France between 1996 and 2005 by the French National Reference Centre for Tularaemia (AFSSA/LERPAZ). The isolates were selected to include those obtained from diverse geographical areas of France [Table S1, available as Supplementary data at JAC Online (http://jac.oxfordjournals.org/)]. MICs were determined for eight antibiotics by the broth microdilution and the agar dilution methods using Mueller–Hinton II medium supplemented with 2% IsoVitalex™ to satisfy the in vitro growth requirements of Francisella. MICs were read after 48 h of incubation in ambient air to comply with the recommendations of the CLSI. For antibiotics for which specific breakpoints have been established, strains were classified as susceptible or non-susceptible. In the absence of specific breakpoint data, CLSI general interpretative standards were used.

We first determined MICs by the broth microdilution method, but this method did not give reproducible results, except for gentamicin, ciprofloxacin and doxycycline. It was difficult to determine the MIC due to a regrowth phenomenon, which does not depend on the bactericidal or bacteriostatic activity of the antibiotic. Due to these technical difficulties, we therefore used the agar dilution method.

Consistent with the results of previous studies,3,5,6 100% of our isolates were susceptible to gentamicin (MIC 0.03–0.5 mg/L) and streptomycin (MIC < 0.5–1 mg/L). As streptomycin is rarely used in France, gentamicin remains the first-line antibiotic for the treatment of tularaemia. All isolates were also susceptible to doxycycline (MIC 0.125–1 mg/L), ciprofloxacin (MIC 0.015–0.03 mg/L), nalidixic acid (MIC 0.06–2 mg/L) and chloramphenicol (MIC 0.25–2 mg/L). Fluoroquinolones and doxycycline are now considered as treatment options and are the recommended antibiotics for post-exposure prophylaxis in...