Comparative in-vitro activities of MCB3681 and 8 comparators against 200 *Clostridium difficile* isolates with known ribotypes and diverse geographical spread

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Background
Antimicrobial treatments for *C. difficile* infection (CDI) are limited to metronidazole (M), vancomycin (V) and fidaxomycin (FDX). Symptomatic recurrences are common following conventional antimicrobial treatment, therefore further therapeutic options are necessary. MCB3681 is a novel investigational quinolonyl-oxazolidinone antibacterial with good anti-*C. difficile* activity currently being assessed for intravenous treatment of symptomatic recurrences.

We determined in vitro activities of MCB3681 and 8 comparators against *C. difficile* isolates of known PCR ribotypes and diverse geographical spread.

Materials and methods
MICs of MCB3681, M, V, FDX, moxifloxacin (MXF), ciprofloxacin (CIP), clindamycin (CL), tigecycline (TG), linezolid (LZD) were determined for 200 *C. difficile* of prevalent or emerging/multi-resistant ribotypes (RT) sourced across Europe (The ClosER Study, with permission from Astellas Pharma Europe). 8 MICs were determined by Wilkins-Chalgren agar incorporation. CD were designated susceptible (S), intermediate (I) or resistant (R) according to breakpoints established according to CLSI or EUCAST data, where available, or published data.

Results
FDX and MCB3681 were the most active CD treatments tested (geometric means (GM) MIC=0.05 mg/L and 0.12 mg/L, respectively). All CD were MCB3681 susceptible, including those CD with multidrug resistance phenotypes (including MFX-CIP-LZD resistance).

There was no resistance seen for MCB, FDX or TG and V resistance was rare (1.5%).

<table>
<thead>
<tr>
<th>M</th>
<th>V</th>
<th>FDX</th>
<th>MXF</th>
<th>CIP</th>
<th>CL</th>
<th>LZD</th>
<th>MCB3681</th>
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<tbody>
<tr>
<td>GM</td>
<td>0.33</td>
<td>1.02</td>
<td>0.05</td>
<td>5.87</td>
<td>66.27</td>
<td>18.17</td>
<td>0.05</td>
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<tr>
<td>MIC</td>
<td>0.25</td>
<td>1.06</td>
<td>2</td>
<td>64</td>
<td>16</td>
<td>0.06</td>
<td>4</td>
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<tr>
<td>MIC&lt;0.008</td>
<td>1.2</td>
<td>0.125</td>
<td>32</td>
<td>256</td>
<td>128</td>
<td>0.06</td>
<td>8</td>
</tr>
<tr>
<td>%S</td>
<td>99</td>
<td>96</td>
<td>100</td>
<td>50.5</td>
<td>5.5</td>
<td>100</td>
<td>78.9</td>
</tr>
<tr>
<td>%I</td>
<td>1</td>
<td>2.5</td>
<td>-</td>
<td>1</td>
<td>29.5</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>%R</td>
<td>0</td>
<td>1.5</td>
<td>-</td>
<td>48</td>
<td>100</td>
<td>54</td>
<td>-</td>
</tr>
<tr>
<td>range</td>
<td>&lt;0.1</td>
<td>0.004</td>
<td>1-8</td>
<td>&gt;254</td>
<td>&gt;64</td>
<td>&gt;128</td>
<td>&gt;128</td>
</tr>
</tbody>
</table>

Table 1. Susceptibility of 199 *C. difficile* isolates to MCB3681 and 8 comparators

Discussion
MCB3681 had good activity against CD from emerging/pervasive European RTs, superior to M and V, with no evidence of resistance. MCB3681 was slightly (one titration step) less active than FDX. Rashid *et al.* reported similar *C. difficile* susceptibilities to MCB3681 in the range of 0.008-0.5 mg/L. However, MIC<0.008 and MIC>0.25 mg/L, respectively, were slightly higher than those reported previously (0.03 and 0.06 mg/L, respectively) and are similar to those recently described for cadazol, another quinolonyl-oxazolidinone molecule.

Quinolone/oxazolidinone resistance was not associated with increased MCB3681 MICs (Table 3).

Many isolates displaying either both MFX or LZD resistance showed MCB3681 MICs towards the lower (0.008 mg/L), as well as the higher (0.5 mg/L) end of the range observed. Three RT017 and two RT027 isolates showed dual quinolone-oxazolidinone resistant phenotype, and also showed the highest MCB3681 MICs. We previously reported high level chloramphenicol resistance for these isolates. This may indicate the presence of the multidrug resistance gene, cfr. Marín *et al.* reported LZD, chloramphenicol, erythromycin, and CL resistance associated with the presence of cfr in *C. difficile* RT017, 078 and 126 isolates. However, we also found isolates with quinolone-oxazolidinone and chloramphenicol resistance that demonstrated very low MCB3681 MICs (0.008 mg/L). This phenotype may (and possibly cfr gene type) is not linked to increased MCB3681 MICs.

Conclusions
MCB3681 had good activity against CD from emerging/pervasive European RTs, superior to M and V, with no evidence of resistance. The presence of quinolone and/or linezolid resistance did not influence MCB3681 MICs.

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References

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