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**In vitro activity of tigecycline against carbapenem-susceptible and -resistant isolates of *Klebsiella* spp. and *Enterobacter* spp.**

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Sir,

Carbapenems are often the last active antibiotics for serious infections caused by Gram-negative opportunistic pathogens. Resistance is still extremely rare among Enterobacteriaceae, but is increasingly detected in isolates of *Klebsiella* and *Enterobacter* in the UK. In a few cases it is mediated by class A or B carbapenemases, but more often results from combinations of a β-lactamase [often a CTX-M extended-spectrum β-lactamase (ESBL) in *Klebsiella* or an AmpC enzyme in *Enterobacter*] acting together with impermeability and/or increased efflux. Among the three available carbapenems, ertapenem is most affected and, hence, is also the best indicator. The public health importance of this resistance type, which prompted the UK’s first National Resistance Alert in December 2005 (http://www.hpa.org.uk/infections/topics_az/antimicrobial_resistance/alert.htm), reflects the limited options for treating serious infections caused by such multiresistant isolates: many of which are susceptible only to polymyxins among established antibiotics.

Tigecycline is a new glycylcycline with broad-spectrum activity, including against most Enterobacteriaceae except Proteaeae. Previously, we noted a trend toward decreased susceptibility to tigecycline among ESBL-producing *Klebsiella* spp. and AmpC-producing *Enterobacter* spp. collected in a survey of cephalosporin-resistant isolates from south-east England, with a raised modal MIC for the *Klebsiella* spp. and with increased ‘trails’ of resistant isolates among both genera. Here we investigated whether this pattern was general for ESBL and AmpC-producing isolates of *Klebsiella* and *Enterobacter* submitted from across the UK; we also assessed whether the *in vitro* activity of tigecycline was further reduced against those isolates with the permeability and efflux changes that, acting in concert with an ESBL or AmpC enzyme, can confer carbapenem resistance.

Eight hundred and sixty-nine clinical isolates of *Klebsiella* spp. (n = 540) and *Enterobacter* spp. (n = 329) were included. These had been referred to the Antibiotic Resistance Monitoring and Reference Laboratory from UK clinical laboratories between June 2004 and July 2006 on the basis of resistance, mainly to cephalosporins. The isolates included 89 *Klebsiella* spp. and 65 *Enterobacter* spp. that were resistant to ertapenem (MIC > 2 mg/L). Among ertapenem-resistant isolates, 7 *Klebsiella* spp. and 21 *Enterobacter* spp. were also resistant to imipenem; 19 *Klebsiella* spp. and 15 *Enterobacter* spp. also to meropenem. Even when not considered resistant, MICs of the latter carbapenems for these ertapenem-resistant isolates were above the modal values for the genera. Among referred carbapenem-susceptible isolates, 240 (91%) *Enterobacter* spp. and 380 (84%) *Klebsiella* spp. were resistant to cephalosporins, defined here as cefotaxime MIC > 1 mg/L.

Tigecycline was supplied as powder of known potency by the manufacturer (Wyeth Pharmaceuticals, Taplow, UK). MICs were determined and interpreted in accordance with BSAC and European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints; values ≤ 1 mg/L indicate susceptibility for Enterobacteriaceae and those > 2 mg/L indicate resistance (http://www.bsac.org.uk). Statistical comparisons were performed using Fisher’s exact test (http://www.graphpad.com/quickcalc/contingency2.cfm).

MIC distributions of tigecycline for referred carbapenem-susceptible and -resistant isolates are shown in Table 1, together with EUCAST data for susceptible wild-type populations (http://www.srga.org/eucastwt/WT_EUCAST.htm) and data from the BSAC Bacteraemia Surveillance for 2002–2004 (http://www.bsac.org.uk). Among *Klebsiella* spp., the modal MIC was 0.5 mg/L for referred carbapenem-resistant isolates and for the BSAC and EUCAST datasets, but was raised to 1 mg/L for referred carbapenem-susceptible isolates; the reason for this requires further investigation. The modal MIC for all groups of *Enterobacter* spp. was 0.5 mg/L (Table 1).

Among referred carbapenem-susceptible *Enterobacter* spp. isolates, 205 (78%) were susceptible to tigecycline, 35 (13%) were fully resistant, and 24 (9%) had intermediate susceptibility. No differential was seen between the tigecycline susceptibility of these carbapenem-susceptible isolates and isolates in the BSAC dataset (P = 0.37). However, referred carbapenem-resistant *Enterobacter* spp. isolates were less often susceptible to tigecycline (32/65, 49%; P < 0.0001); with 20 (31%) fully resistant, and 13 (20%) intermediate. In contrast, there was no significant difference in the proportions of tigecycline-susceptible *Klebsiella* spp. isolates among referred carbapenem-susceptible (303/451; 67%) and carbapenem-resistant isolates (54/89; 60%) (P = 0.27). However, tigecycline non-susceptibility (MICs ≥ 2 mg/L) was more frequent in both groups when compared with BSAC bacteraemia isolates (P < 0.0001).

Among new agents, tigecycline is unique in having good activity against Gram-negative bacteria in general. However, these data support the observation that many cephalosporin-resistant (i.e. mostly ESBL-producing) *Klebsiella* spp. isolates require slightly raised tigecycline MICs but refute the hypothesis that further rises occur in this genus contingent on the
uptake and efflux changes associated with carbapenem resistance. In contrast, carbapenem-resistant Enterobacter spp. isolates were more likely to show reduced tigecycline susceptibility than carbapenem-susceptible isolates, even when the latter were resistant to cephalosporins. These differences between Enterobacter spp. and Klebsiella spp. remain to be explained. Non-carbapenemase-mediated carbapenem resistance in Klebsiella spp. is associated with porin loss along with ESBLs; the mechanisms in Enterobacter spp. are less clear although AmpC enzyme activity has a role. Porin loss may arise via mutations in porin genes or via changes at global regulatory loci, with the latter also able to affect efflux pumps. Acquired resistance to tigecycline in the Enterobacteriaceae can also involve efflux through up-regulation of intrinsic pumps or mutations in acquired pumps, and has also been associated with changes at a regulatory locus. There is therefore potential for such mechanisms to confer reduced susceptibility to both carbapenems and tigecycline. The mechanisms of reduced tigecycline susceptibility and resistance in cephalosporin-resistant Klebsiella spp. and in carbapenem-resistant Enterobacter spp. are now under investigation.

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References


Table 1. Distribution of tigecycline MICs (modes are shown in bold font) for ertapenem-susceptible (ETP-S) and ertapenem-resistant (ETP-R) isolates of Klebsiella spp. (n = 540) and Enterobacter spp. (n = 329) in comparison with isolates in the EUCAST and BSAC bacteraemia databases

<table>
<thead>
<tr>
<th>Genus</th>
<th>MIC (mg/L)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>≤0.25</td>
</tr>
<tr>
<td><strong>Klebsiella spp.</strong></td>
<td></td>
</tr>
<tr>
<td>ETP-S (n = 451)</td>
<td>60</td>
</tr>
<tr>
<td>ETP-R (n = 89)</td>
<td>12</td>
</tr>
<tr>
<td>EUCAST (n = 1076)</td>
<td>253</td>
</tr>
<tr>
<td>BSAC (n = 737)</td>
<td><strong>86</strong></td>
</tr>
<tr>
<td><strong>Enterobacter spp.</strong></td>
<td></td>
</tr>
<tr>
<td>ETP-S (n = 264)</td>
<td>18</td>
</tr>
<tr>
<td>ETP-R (n = 65)</td>
<td>5</td>
</tr>
<tr>
<td>EUCAST (n = 781)</td>
<td>168</td>
</tr>
<tr>
<td>BSAC (n = 630)</td>
<td>50</td>
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