**In vitro activity of tigecycline against multidrug-resistant Acinetobacter baumannii**

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Sir,

*Acinetobacter baumannii* has emerged as a leading nosocomial pathogen, particularly in intensive care units (ICUs), where several outbreaks have been described.1

Treatment of severe *A. baumannii* infection represents a difficult clinical challenge due to the propensity of this organism to acquire antimicrobial resistance, resulting in the emergence of multi- and pan-resistant clones.1,2 There are few therapeutic options to combat multidrug-resistant (MDR) *A. baumannii*.1

Tigecycline, a new semi-synthetic tetracycline, has provided hope for the treatment of bacterial infections.2 Literature data on the *in vitro* activity of tigecycline against MDR *A. baumannii* shows variable susceptibility,3–7 likely resulting from different susceptibility testing methods and high clonal correlation among epidemic strains. Indeed, early studies have reported excellent *in vitro* activity of tigecycline against isolates of the *A. baumannii* complex (MIC90 2 mg/L).3 However, *A. baumannii* isolates showing reduced susceptibility to tigecycline (MIC50 32 mg/L) have recently been identified,4 posing the risk for selection and spreading of resistance in this notoriously adaptable species. Therefore, we investigated the *in vitro* activity of tigecycline against a collection of 80 presumed MDR *A. baumannii* isolates and compared the activity between tigecycline and 17 other antimicrobials, including three tetracyclines.

*A. baumannii* primary isolates were obtained between January 2004 and June 2005 from ICU patients cared for in six general hospitals of the Rome (Italy) urban area. None of the patients had undergone previous treatment with tigecycline. Bacteria were identified by the Vitek II system (bioMérieux, Marcy l’Étoile, France) and Amplified Ribosomal DNA Restriction Analysis.1 Although all isolates had been provided as MDR by collaborating centres, antimicrobial susceptibility testing was re-assessed using ampicillin/sulbactam, piperacillin, piperacillin/tazobactam, ceftazidime, aztreonam, imipenem, meropenem, amikacin, gentamicin, ciprofloxacin, levofloxacin, trimethoprim/sulfamethoxazole, colistin, tetracycline, doxycycline, minocycline and tigecycline. For all drugs, except colistin, doxycycline, minocycline and tigecycline, susceptibility tests were performed by the Vitek II ID-GNB and AST-GN09 cards. Doxycycline and minocycline susceptibility was determined by the disc diffusion method. Tigecycline and colistin susceptibility was determined by the broth microdilution method, according to the CLSI guidelines. The US FDA breakpoints approved for Enterobacteriaceae were applied to define tigecycline susceptibility (≤2 mg/L susceptibility; ≥8 mg/L resistance). Colistin susceptibility was interpreted according to Gales et al. The MDR phenotype was defined as diminished susceptibility to more than one of the following five drug classes: antipseudomonal cephalosporins, antipseudomonal carbapenems, β-lactam/β-lactamase inhibitor combinations, antipseudomonal fluoroquinolones and aminoglycosides.9

The *in vitro* activity of individual antimicrobial agents against *A. baumannii* clinical isolates is summarized in Table 1. Seventy-eight isolates were definitively defined as MDR. The most common phenotype (≥90% of the isolates) was resistant to piperacillin, piperacillin/tazobactam, ceftazidime, aztreonam, ciprofloxacin and levofloxacin. Individual resistance to imipenem, amikacin, trimethoprim/sulfamethoxazole and tetracycline was observed in 70% to 86.2% of the isolates. Approximately 50% of the *A. baumannii* isolates were resistant to gentamicin and 22.5% to ampicillin/sulbactam. A high level of carbapenem resistance was observed, with 77.5% and 81.3% of isolates resistant to imipenem and meropenem, respectively.

Concerning tigecycline, 27.5% of the isolates were nonsusceptible, including 23.7% intermediate and 3.7% fully resistant isolates. The MIC50 and MIC90 values were 2 and 4 mg/L, respectively, with a unimodal distribution of tigecycline MICs in the 0.125–8 mg/L range. These findings are in the middle-upper range of previously reported tigecycline resistance data.3–7 Notably, the only isolate resistant to colistin was susceptible to tigecycline.

Recent data on the activity of tetracyclines against *A. baumannii* are conflicting. In large surveys from the UK, the USA, Germany and Italy, the frequency of *A. baumannii* isolates resistant to tigecycline, minocycline and doxycycline varied in the ranges 4% to 6%, 0% to 18% and 6% to 44%, respectively, in association with high overall rates of resistance to tetracycline.3,5–7 Conversely, a study conducted in Israel showed that 66% and 37% of the MDR *A. baumannii* isolates were resistant to tigecycline and minocycline, respectively.4 Here, we report that 3 (3.8%), 13 (16.3%) and 69 (86.3%) out of the 80 presumed MDR *A. baumannii* isolates were resistant to minocycline, doxycycline and tigecycline, respectively. Taking into account non-susceptible isolates (intermediate and fully resistant), the relative activities of tetracyclines were minocycline > tigecycline ≈ doxycycline > tetracycline, with an overall decreased susceptibility to tigecycline among *A. baumannii* isolates resistant to other tetracyclines. In fact, all isolates susceptible to minocycline, doxycycline and tigecycline were highly susceptible to tigecycline (MIC range 0.125–1 mg/L), whereas only 6 of 16 (37.5%) isolates non-susceptible to the three tetracyclines were susceptible to tigecycline (MIC range
Table 1. Distribution of antimicrobial susceptibilities for *Acinetobacter baumannii* isolates (n = 80).

<table>
<thead>
<tr>
<th>Antimicrobial</th>
<th>Resistance breakpoint of antimicrobial (mg/L)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>SAM</td>
</tr>
<tr>
<td></td>
<td>≤ 0.125</td>
</tr>
<tr>
<td>No. of resistant (%)</td>
<td>&lt; 25</td>
</tr>
<tr>
<td>No. of intermediate (%)</td>
<td>&gt; 1.2</td>
</tr>
<tr>
<td>No. of susceptible (%)</td>
<td>&lt; 25</td>
</tr>
</tbody>
</table>

SAM, ampicillin/sulbactam; PIP, piperacillin; TZP, piperacillin/tazobactam; FEP, cefepime; CAZ, ceftazidime; ATM, aztreonam; IPM, imipenem; MEM, meropenem; AMK, amikacin; GEN, gentamicin; CIP, ciprofloxacin; LVX, levofloxacin; SXT, trimethoprim/sulfamethoxazole; TIG, tigecycline; TET, tetracycline; DOX, doxycycline; MIN, minocycline; COL, colistin; NA, not applicable.

0.125–2 mg/L). It should be pointed out, however, that the *in vitro* superiority of minocycline among tetracyclines has limited clinical implications due to the unavailability of intravenous minocycline formulations.

In conclusion, tigecycline resistance among MDR *Acinetobacter baumannii* isolates that had not previously been exposed to the drug is worrying, given the paucity of antibiotic options available to clinicians to combat these bacteria. When treating patients with severe infections caused by MDR *Acinetobacter baumannii*, *in vitro* susceptibility to tigecycline should be assessed preventively.

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Transparency declarations

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