Tigecycline for the treatment of multidrug-resistant (including carbapenem-resistant) 

Acinetobacter infections: a review of the scientific evidence

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Objectives: New antibacterial agents are required for the treatment of infections caused by multidrug-resistant (MDR) Acinetobacter spp. Whether tigecycline constitutes an effective treatment option or not, is not well established. We sought to evaluate the available evidence regarding the microbiological activity and clinical effectiveness of tigecycline for MDR (including the subset of carbapenem-resistant) Acinetobacter spp.

Methods: We searched PubMed for relevant articles and extracted/evaluated the available evidence.

Results: We identified 22 microbiological studies reporting data for 2384 Acinetobacter spp. (1906 Acinetobacter baumannii). Susceptibility of at least 90% of the Acinetobacter isolates to tigecycline (with an MIC breakpoint of susceptibility \( \leq 2 \) mg/L) was noted in 9/18 studies reporting data on MDR Acinetobacter and in 7/15 studies reporting specific data on carbapenem-resistant Acinetobacter. In an additional study reporting data for both resistance categories, adequate susceptibility of Acinetobacter spp. was observed by one (broth microdilution) of the methods employed. The effectiveness of tigecycline for MDR Acinetobacter infections was evaluated in eight identified clinical studies, reporting retrospective data regarding 42 severely ill patients, among whom 31 had respiratory tract infection (in 4 cases with secondary bacteraemia) and 4 had bacteraemia. Tigecycline therapy (in combination with other antibiotics in 28 patients) was effective in 32/42 cases. In three cases, resistance to tigecycline developed during treatment.

Conclusions: Tigecycline showed considerable, though not consistent, antimicrobial activity against MDR (including carbapenem-resistant) Acinetobacter spp. However, data to support its clinical use, particularly for ventilator-associated pneumonia or bacteraemia, caused by these pathogens, are still limited.

Keywords: glycylcyclines, imipenem, bloodstream infections, microbial drug resistance, Acinetobacter baumannii

Introduction

Acinetobacter is a genus of non-fermentative Gram-negative cocccobacillary organisms, comprising more than 30 different species. Among these, Acinetobacter baumannii, as well as the genotypically related Acinetobacter genomic species 3 and Acinetobacter genomic species 13TU, are the most pathogenic in humans. These three species along with Acinetobacter calcoaceticus cannot be easily differentiated by many routine laboratory methods and have often been reported in conjunction as the Acinetobacter calcoaceticus–baumannii complex.

Acinetobacter spp. are primarily associated with nosocomial infections in severely ill patients, particularly with ventilator-
Tigecycline

Tigecycline is the first representative of the glycylcycline class of antibacterial agents to be marketed for clinical use. The US Food and Drug Administration (FDA) have approved its use for complicated intra-abdominal and complicated skin and skin structure infections. Chemically, it constitutes the 9-t-butylylcyclamido derivative of minocycline. Regarding its mechanism of action, tigecycline enters bacterial cells through energy-dependent pathways or with passive diffusion, and reversibly binds to the 30S subunit of the ribosome. It acts by blocking the incorporation of transfer RNA into the A site of the ribosome, thus inhibiting protein synthesis.31,32 In comparison with tetracyclines, tigecycline binds to corresponding ribosomal sites with greater affinity, and irrespective of the presence of mutations that confer resistance to tetracyclines.33,34 Furthermore, tigecycline evades tetracycline efflux mechanisms.35

The above-stated properties of tigecycline confer in vitro activity against a wide range of bacterial pathogens, including Gram-positive and Gram-negative aerobic and anaerobic species.32,36–41 Still, some pathogens with clinical significance, such as Pseudomonas aeruginosa and Proteus spp., are not adequately susceptible to tigecycline.42 Regarding A. baumannii, this pathogen has been shown to be susceptible to tigecycline in large-scale microbiological studies.36,43–46 Tigecycline has also shown adequate activity against Acinetobacter species of potential clinical significance other than A. baumannii, such as Acinetobacter junii,47,48 Acinetobacter anitratus,47–50 Acinetobacter calcoaceticus47,48,50 and Acinetobacter lwoffii.47–51

Still, whether tigecycline constitutes a potentially effective treatment option against highly resistant Acinetobacter spp. has not been evaluated in a comprehensive manner.

The objective of this review was to identify and evaluate the available evidence regarding the microbiological activity and clinical effectiveness of tigecycline against multidrug-resistant (MDR) Acinetobacter spp.

Methods

Literature review

Medline (1999–1 Mar 2007) was searched through PubMed, using the term ‘tigecycline’ for articles that evaluated the in vitro activity of tigecycline against MDR Acinetobacter spp. or Acinetobacter spp. with other types of clinically significant antimicrobial drug resistance, as well as for articles that evaluated the clinical effectiveness of tigecycline in infections caused by these types of resistant Acinetobacter spp. Multidrug resistance was defined as resistance to two or more classes of agents, among those regarded as potentially effective treatment against Acinetobacter spp., including carbapenems, anti-pseudomonal cephalosporins, anti-pseudomonal penicillins, monobactams, aminoglycosides, tetracyclines, fluoroquinolones, sulbactam and polymyxins. Clinically significant patterns of antimicrobial drug resistance included resistance to colistin or to carbapenems, or the production of either metallo-β-lactamases or other carbapenemases. Isolates with intermediate susceptibility to any of the above agents were classified as resistant, unless otherwise stated. Any study providing data on the susceptibility to tigecycline of Acinetobacter spp. with any of the above-described patterns of resistance, regardless of the primary study objective, as well as any study providing data on the clinical use of tigecycline for the treatment of infections caused by these types of resistant Acinetobacter spp. was included in this review.

Results and discussion

Characteristics of selected studies

Twenty-two different studies including relevant data on the in vitro susceptibilities of MDR Acinetobacter spp. or Acinetobacter spp. with clinically significant resistance were identified.52–74 Data extracted from these studies regarding study design, the characteristics of the Acinetobacter isolates evaluated and their susceptibility to tigecycline are presented in Table 1. Of the 22 overall selected studies, 7 involved isolates originating from the USA,52,55,58,61,66,67,72 6 additional studies involved isolates originating from Asian countries,56,60,63–65,70 whereas 5 and 2 studies involved isolates originating from European countries53,69,71,73,74 and Australia,54,57 respectively. One more study examined isolates from Latin America as well as global isolates,7 and the remaining study examined isolates from both Europe and the USA.58 The microbiological methods used for the determination of the susceptibility of Acinetobacter isolates to tigecycline included dilution methods in 14 studies (broth microdilution in 12;52,53,58,59,61,63,64,66,68,71–73 and agar dilution in 256,74), the Etest (10 studies)54,55,57,60,63,65,67,69,70,74 or the disc diffusion method (4 studies54,57,63,69). It should be noted that more than one of the above methods was used in five of the studies included.54,57,62,69,74

Characteristics of the included Acinetobacter isolates

In the 22 studies included in this review, a total of 2384 Acinetobacter isolates with multiple drug resistance or other type of clinically significant resistance were evaluated for susceptibility to tigecycline. The great majority of these isolates were identified as A. baumannii (79.9%), whereas more than 10.4% of the total number of isolates were identified as members of the A. calcoaceticus–baumannii complex, which
<table>
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<th>Author</th>
<th>Country; isolate collection period; methods</th>
<th>Scope of study</th>
<th>Number of isolates; resistance characteristics (subpopulations)</th>
<th>Origin of isolates; isolation sites or sites of infection</th>
<th>Relation of isolates to outbreak</th>
<th>n/N, % susceptible (subpopulations)</th>
<th>MIC distribution (mg/L)</th>
<th>MIC\textsubscript{50} (mg/L)</th>
<th>MIC\textsubscript{90} (mg/L)</th>
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<tr>
<td>Draghi et al.\textsuperscript{52}</td>
<td>USA; NR; broth microdilution</td>
<td>surveillance study</td>
<td>60 \textit{Acinetobacter} spp.; MDR (≥3 agents); (imipenem-resistant: 29)</td>
<td>collected across US regions</td>
<td>NR</td>
<td>55/60, 91.7 (28/29)</td>
<td>0.25–8</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Mezzatesta et al.\textsuperscript{53}</td>
<td>Italy; 2003–04; broth microdilution</td>
<td>determination of \textit{in vitro} activity</td>
<td>107 \textit{A. baumannii}; MDR &gt;90%; (meropenem-resistant: 58)</td>
<td>first patient isolates, from 9/45 laboratories in a surveillance study; bloodstream and lower RT infections (77%); complicated skin and skin structure infections (14%); intra-abdominal infections (3%); urinary catheters (7%)</td>
<td>NR</td>
<td>100/107, 93 (54/58)</td>
<td>0.25–4</td>
<td>2</td>
<td>2</td>
</tr>
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<td>Ratnam et al.\textsuperscript{54}</td>
<td>Australia; 2005; Etest (disc diffusion)</td>
<td>determination of \textit{in vitro} activity</td>
<td>10 \textit{A. baumannii}, 1 \textit{A. junii}; resistant to aztreonam, piperacillin/tazobactam, and sulbactam; (colistin-resistant: 1)</td>
<td>first clinical isolates, ICU patients, no more than 1 isolate per week; sputum (82%), blood (18%)</td>
<td>concurrent outbreak</td>
<td>11/11, 100</td>
<td>0.125–2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Insa et al.\textsuperscript{55}</td>
<td>USA; 2003–06; Etest</td>
<td>determination of \textit{in vitro} activity</td>
<td>77 \textit{A. baumannii}; resistant to β-lactams (including carbapenems), sulbactam, aminoglycosides, fluoroquinolones</td>
<td>consecutive non-related clinical isolates; RT (43%); skin and soft tissue (24%), blood (10%), urine (10%)</td>
<td>NR</td>
<td>57/71, 80</td>
<td>0.094–8</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Tan and Ng\textsuperscript{56}</td>
<td>Singapore; 2004-06; Agar dilution</td>
<td>determination of \textit{in vitro} activity</td>
<td>55 \textit{Acinetobacter} spp.; resistant to ≥2 antibiotic classes</td>
<td>unique isolates from hospitalized patients collected retrospectively</td>
<td>NR</td>
<td>39/55, 71</td>
<td>0.25–16</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Iredell et al.\textsuperscript{57}</td>
<td>Australia; 1996–2002; Etest (disc diffusion)</td>
<td>determination of \textit{in vitro} activity</td>
<td>18 \textit{A. baumannii}; MDR; (carbapenem resistant: 14)</td>
<td>12 genotypically distinct strains from 3 hospitals plus multiple isolates of 2 strains, mostly ICU patients</td>
<td>outbreak reported in main hospital</td>
<td>4/18, 22 (0/14)</td>
<td>≤2 to ≥8</td>
<td>≥8</td>
<td>≥8</td>
</tr>
<tr>
<td>Hoban et al.\textsuperscript{58}</td>
<td>USA; 2004–06; broth microdilution</td>
<td>surveillance study</td>
<td>282 \textit{A. baumannii}; resistant to ≥3 antibiotic classes</td>
<td>unique patient isolates, TEST database, 77% inpatients, 31% ICU patients; RT (37%), blood (21%), urine (16%), integument (15%) selected from TEST database</td>
<td>NR</td>
<td>NR</td>
<td>0.12–8</td>
<td>NR</td>
<td>2</td>
</tr>
<tr>
<td>Curcio and Fernandez\textsuperscript{59}</td>
<td>global isolates Argentina; NR; broth microdilution</td>
<td>comparison of results of Navon-Venezia et al.\textsuperscript{60} with those of a surveillance study</td>
<td>631 (55576) \textit{A. baumannii}; resistant to aminoglycosides cephalosporins,</td>
<td></td>
<td>NR</td>
<td>600/631, 95 (168/17828/28)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
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</table>

Continued
### Table 1. Continued

<table>
<thead>
<tr>
<th>Author ref</th>
<th>Country; isolate collection period; methods</th>
<th>Scope of study</th>
<th>Number of isolates; resistance characteristics (subpopulations)</th>
<th>Origin of isolates; isolation sites or sites of infection</th>
<th>Relation of isolates to outbreak</th>
<th>MIC ((\text{mg/L})) distribution</th>
<th>(\text{MIC}_{50} (\text{mg/L}))</th>
<th>(\text{MIC}_{90} (\text{mg/L}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Navon-Venezia et al.</td>
<td>Israel; 2003; Etest</td>
<td>determination of \textit{in vitro} activity</td>
<td>82 \textit{A. baumannii}; resistant to (\geq 3) antibiotic classes; (imipenem-resistant: 22)</td>
<td>consecutive unique patient isolates; wound (44%), RT (39%), blood (9%), urine (7%), CSF (1%)</td>
<td>outbreak, 19 genotypically distinct isolates outbreak, 25 genotypically distinct isolates</td>
<td>18/82, 22 (1/22)</td>
<td>1–128</td>
<td>16</td>
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<tr>
<td>Scheetz et al.</td>
<td>USA; 2001–05; broth microdilution</td>
<td>determination of \textit{in vitro} activity</td>
<td>93 \textit{A. baumannii}; carbapenem-intermediate or -resistant</td>
<td>unique patient isolates per calendar year</td>
<td></td>
<td>88/93, 95</td>
<td>NR</td>
<td>1</td>
</tr>
<tr>
<td>Thamilkitkul et al.</td>
<td>Thailand; 2002–05; broth microdilution, disc diffusion, Etest</td>
<td>determination of \textit{in vitro} activity</td>
<td>148 \textit{A. baumannii}; resistant to all (\beta)-lactams, aminoglycosides and fluoroquinolones</td>
<td>unique isolates from hospitalized infected patients</td>
<td></td>
<td>NR</td>
<td>144/148, 97 by broth microdilution; 107/148, 72 by Etest; 66/148, 44 by disc diffusion</td>
<td>11–26 mm inhibition zone diameter</td>
</tr>
<tr>
<td>Song et al.</td>
<td>Korea; 2002–06; broth microdilution</td>
<td>determination of \textit{in vitro} activity</td>
<td>43 \textit{A. baumannii}; carbapenem-resistant</td>
<td>unique isolates randomly selected from ICU patients</td>
<td></td>
<td>NR</td>
<td>24/43, 56</td>
<td>1–4</td>
</tr>
<tr>
<td>Akcam et al.</td>
<td>Turkey; 2000–04; Etest</td>
<td>determination of \textit{in vitro} activity</td>
<td>74 \textit{A. baumannii}; resistant (\geq 2) antibiotic classes; (carbapenem-resistant: 13)</td>
<td>randomly selected isolates from hospitalized patients</td>
<td></td>
<td>NR</td>
<td>74/74, 100 (13/13)</td>
<td>(\geq 0.0125) to (\leq 0.064)</td>
</tr>
<tr>
<td>Halstead et al.</td>
<td>USA; 2004–05; broth microdilution</td>
<td>surveillance study</td>
<td>249 \textit{A. calcoaceticus–baumannii} complex; resistant to (\geq 3) antibiotic classes</td>
<td>TEST database, 76 centres, infected patients, nosocomial strains</td>
<td></td>
<td>NR</td>
<td>NR</td>
<td>0.12–4</td>
</tr>
<tr>
<td>Sands et al.</td>
<td>USA; recent; Etest</td>
<td>determination of \textit{in vitro} activity</td>
<td>19 \textit{A. baumannii}; MDR</td>
<td>RT (47%), urine (32%), blood (10%), wound (10.5%)</td>
<td></td>
<td>NR</td>
<td>11/19, 58</td>
<td>NR</td>
</tr>
<tr>
<td>Seifert et al.</td>
<td>Europe and USA; 1990–2003; broth microdilution</td>
<td>determination of \textit{in vitro} activity</td>
<td>215 \textit{A. baumannii}; MDR; (imipenem-resistant: 7, colistin-resistant: 6)</td>
<td>epidemiologically characterized isolates representing different sporadic or outbreak strain types</td>
<td></td>
<td>NR</td>
<td>183/215, 85 (6/7, 6/6)</td>
<td>(\leq 0.06) to (\geq 32)</td>
</tr>
<tr>
<td>Author(s)</td>
<td>Country</td>
<td>Year</td>
<td>Methodology</td>
<td>Isolates</td>
<td>Outcomes</td>
<td>Multicity</td>
<td>Clones</td>
<td></td>
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<tr>
<td>Bogaerts et al.</td>
<td>Belgium</td>
<td>2004–05</td>
<td>Disc diffusion (susceptibility testing), Etest (MICs)</td>
<td>17 A. baumannii; resistant to all β-lactams, ciprofloxacin, amikacin; OXA-58 positive; borderline susceptible to colistin</td>
<td>ICU patients (71%), infected patients (71%); RT (76%), blood (12%), wound (12%)</td>
<td>outbreak strains belonging to a single clone</td>
<td>17/17, 100</td>
<td></td>
</tr>
<tr>
<td>Vahaboglu et al.</td>
<td>Turkey</td>
<td>2003</td>
<td>Determination of prevalence of subgroups of carbapenemases</td>
<td>10 A. baumannii; MDR carbapenem-resistant (OXA-51 and OXA-58 positive)</td>
<td>selected among consecutive, non-replicate clinical isolates from 7 hospitals, ICU patients unique patient isolates from 17 hospitals; bronchial secretions (56%), pus (23%), blood (13%), other sources (8%)</td>
<td>isolates exhibiting different phenotypes</td>
<td>0/10, 0</td>
<td></td>
</tr>
<tr>
<td>Souli et al.</td>
<td>Greece</td>
<td>2003–05</td>
<td>Broth microdilution</td>
<td>100 A. baumannii; resistant to ≥2 antibiotic classes; (imipenem-resistant: 94, colistin-resistant: 3)</td>
<td>NR</td>
<td>99/100, 99 (3/3)</td>
<td>0.12–4 0.5 1</td>
<td></td>
</tr>
<tr>
<td>Lolans et al.</td>
<td>USA</td>
<td>2005</td>
<td>Broth microdilution</td>
<td>42 A. baumannii; imipenem-resistant (OXA-40 positive)</td>
<td>first submitted isolates from 9 centres; sputum (24%), wound (19%), catheter tips (12%), blood (10%), urine (7%), environmental (14%)</td>
<td>multicity outbreak, 97% of isolates belonged to a single clone</td>
<td>9/42, 21</td>
<td></td>
</tr>
<tr>
<td>Pachon-Ibanez et al.</td>
<td>Spain</td>
<td>NR</td>
<td>Broth microdilution</td>
<td>38 A. baumannii; Imipenem-resistant</td>
<td>NR</td>
<td>34/38, 89</td>
<td>NR</td>
<td></td>
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<tr>
<td>Henwood et al.</td>
<td>United Kingdom</td>
<td>2000</td>
<td>Surveillance study</td>
<td>13 Acinetobacter spp.; MDR carbapenem-resistant</td>
<td>consecutive, unique patient isolates from 54 laboratories, patients in burns unit (46%), ICU (23%), general medical ward (23%)</td>
<td>NR</td>
<td>11/13, 85</td>
<td></td>
</tr>
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</table>

*Represent the same study. NR, non-reported; MDR, multidrug-resistant; ICU, intensive care unit; MIC, minimum inhibitory concentration; RT, respiratory tract; TEST, tigecycline evaluation and surveillance trial.
are perceived to represent mainly *A. baumannii* isolates. Regarding the resistance characteristics of the *Acinetobacter* isolates included in this review, data regarding MDR isolates were reported in 18 studies,\(^{52-60,63,66-71}\) among which 11 studies reported data on carbapenem-resistant isolates as well.\(^{52,53,55,59,60,63,68-71,74}\) The remaining 4 of the 22 studies included reported data exclusively on the subset of carbapenem-resistant isolates.\(^{61,64,72,73}\) The activity of tigecycline against colistin-resistant *Acinetobacter* spp. isolates was additionally reported in 4 among the 22 studies included.\(^{54,68,71,74}\)

**Interpretative criteria**

The interpretation of the findings of the *in vitro* susceptibility studies regarding the antimicrobial activity of tigecycline against *Acinetobacter* spp. is hampered by the lack of universally accepted interpretative MIC breakpoints. The FDA and the European Committee on Antimicrobial Susceptibility Testing (EUCAST) have issued interpretative breakpoints of susceptibility for tigecycline, though for categories of pathogens other than *Acinetobacter* spp. The breakpoints referring to Enterobacteriaceae have been used as provisional breakpoints for *Acinetobacter* spp. in most relevant studies. However, the respective recommendations issued by the FDA and the EUCAST differ. Specifically, the FDA-approved MIC breakpoints for susceptibility and resistance are ≤2 and ≥8 mg/L, respectively, whereas the corresponding EUCAST breakpoints are ≤1 and >2 mg/L,\(^{75}\) respectively.

It should be mentioned that the British Society for Antimicrobial Chemotherapy (BSAC) has adopted the EUCAST Enterobacteriaceae MIC breakpoints for application to *Acinetobacter* spp.\(^{76}\) The BSAC also elaborated breakpoints for susceptibility of *Acinetobacter* spp. to tigecycline, pertinent to the BSAC disc diffusion method, in correspondence to the MIC breakpoints. The BSAC disc breakpoints are ≤19 mm and ≥24 mm for resistance and susceptibility, respectively.\(^{77}\) These criteria are stricter than the corresponding FDA approved tigecycline disc breakpoints for Enterobacteriaceae (resistance ≤14 mm and susceptibility ≥19 mm).

The great majority of the 22 different studies identified in this review, which evaluated the microbiological activity of tigecycline against MDR *Acinetobacter* spp., reported susceptibility data relevant to an MIC breakpoint of ≤2 mg/L or a corresponding disc breakpoint. In the studies that did not directly provide such data, the susceptibility rate of *Acinetobacter* isolates to tigecycline with regard to the above provisional breakpoint was inferred by the consideration of MIC distribution data.

**Susceptibility of MDR *Acinetobacter* to tigecycline**

We considered susceptibility of at least 90% (which is a commonly used threshold) of the total number of *Acinetobacter* spp. isolates to tigecycline to denote adequate microbiological activity of this agent against *Acinetobacter* spp.\(^{78}\) Respectively, adequate activity of tigecycline against MDR *Acinetobacter* was noted in 9 of the 18 studies that reported specific relevant data.\(^{52-54,58,59,65,66,69,71}\) Inadequate activity of tigecycline against MDR *Acinetobacter* spp. was noted in eight studies.\(^{55-57,60,67-68,70,74}\) The remaining study showed adequate activity of tigecycline against MDR *Acinetobacter* spp. by the broth microdilution method, though not with the Etest or the disc diffusion method.\(^{52}\)

Regarding the studies that reported relevant data for at least 100 MDR *Acinetobacter* spp. isolates, five of the seven studies showed adequate activity of tigecycline,\(^{53,58,59,66,71}\) whereas one study showed adequate activity by one of the testing methods employed\(^{62}\) and one study showed activity of tigecycline against 85% of the isolates.\(^{58}\) It should be noted that the three largest of the studies included in this review\(^{58,59,66}\) were performed as part of the tigecycline evaluation and surveillance trial (TEST) programme, which is a global multicentre surveillance study aiming to assess the activity of tigecycline against a range of clinically important pathogens and is funded by the branding company of this drug.

**Susceptibility of carbapenem-resistant *Acinetobacter* to tigecycline**

Adequate activity of tigecycline against carbapenem-resistant *Acinetobacter* spp. was noted in 7 of the 15 studies that reported specific relevant data.\(^{52,53,59,61,68,69,73}\) In an additional study, at least 89% of the imipenem-resistant isolates, as we inferred from relevant data provided, were susceptible to tigecycline.\(^{73}\) Inadequate activity of tigecycline against carbapenem-resistant *Acinetobacter* spp. was noted in six studies,\(^{55,60,64,70,72,74}\) whereas in the remaining study,\(^{62}\) the determination of susceptibility of *Acinetobacter* spp. to tigecycline varied considerably depending on the method employed.

Regarding the studies that evaluated the susceptibility of at least 100 carbapenem-resistant *Acinetobacter* isolates to tigecycline, one of the two relevant studies showed adequate activity of tigecycline,\(^{59}\) whereas in the other one,\(^{52}\) susceptibility data differed considerably depending on the method employed.

**Susceptibility of colistin-resistant *Acinetobacter* to tigecycline**

In three studies included in this review, the susceptibility of 10 colistin-resistant *Acinetobacter* spp. to tigecycline was reported.\(^{54,68,71}\) All but one of these isolates were susceptible to tigecycline. An additional study evaluated the susceptibility to tigecycline of 17 isolates belonging to the same clone that were initially susceptible to colistin (colistin MIC of 3 mg/L). All of these isolates were found to be susceptible to tigecycline.\(^{59}\)

**Clinical effectiveness of tigecycline for infections caused by MDR *Acinetobacter***

Eight studies regarding the clinical effectiveness of tigecycline for the treatment of patients with infections caused by MDR *Acinetobacter* spp. or *Acinetobacter* spp. with clinically significant resistance were identified.\(^{79-86}\) Data extracted from these studies are presented in Table 2.

In total, the eight studies included present the cases of 42 unique patients with infections caused by MDR *Acinetobacter* spp. (identified as *A. baumannii* in all but three patients\(^{81,83}\)) that were treated with tigecycline. The main types of infections described were respiratory tract infections (mainly ventilator-associated pneumonia) in 31 of the 42 (74%) patients (with
### Table 2. Clinical effectiveness of tigecycline for MDR *Acinetobacter* spp. infections

<table>
<thead>
<tr>
<th>Author et al.</th>
<th>Type of study</th>
<th>Type of infection (no. patients)</th>
<th>Patient characteristics</th>
<th>Type of pathogens; resistance characteristics</th>
<th>Co-administered antibiotics (no. patients)</th>
<th>Treatment outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anthony et al.</td>
<td>retrospective case series</td>
<td>VAP (3), VAP with empyema (2), tracheobronchitis (1), mediastinitis/secondary bacteraemia (1), UTI (1), cellulitis (1), diabetic ulcer/ osteomyelitis (1)</td>
<td>47–86y, females: 6, various comorbidities</td>
<td><em>A. baumannii</em>: MDR (resistant ≥3 antibiotic classes); 4/9 (44%) tigecycline-susceptible, 5/9 (56%) tigecycline-intermediate</td>
<td>cefepime (1), amikacin + colistin (1), imipenem (1), imipenem + iv colistin (1), levofloxacin (1), none (3)</td>
<td>positive clinical response 5/10 (50%), uncertain in 1/10 (10%); survival 6/10 (60%), all deaths were related to infection with tigecycline-intermediate pathogens; microbiological response in 3/4 (75%); emergence of resistance in 1 patient</td>
</tr>
<tr>
<td>Schafer and Mangino</td>
<td>case report</td>
<td>probable osteomyelitis following open femur fracture</td>
<td>55y male</td>
<td><em>A. baumannii</em>: MDR, sensitive to tobramycin, intermediate to imipenem; coagulase-negative <em>Staphylococcus</em></td>
<td>vancomycin</td>
<td>cure</td>
</tr>
<tr>
<td>Wadi and Al Rub</td>
<td>case report</td>
<td>meningitis secondary to cranial injury and lumbar shunt infection</td>
<td>26y male</td>
<td><em>A. calcoaceticus</em>: MDR</td>
<td>none</td>
<td>cure</td>
</tr>
<tr>
<td>Schafer et al.</td>
<td>retrospective case series</td>
<td>VAP (19), VAP with bacteraemia (3), bacteraemia (3)</td>
<td>25 critically ill patients (60% surgical)</td>
<td><em>A. baumannii</em>: MDR (resistant ≥2 antibiotics from ≥2 classes); 13/20 (65%) tigecycline-susceptible, 6/20 (30%) tigecycline-intermediate, 1/20 (5%) tigecycline-resistant</td>
<td>imipenem (9), imipenem + nebulized colistin (3), imipenem + iv colistin (1), nebulized colistin (6), iv colistin (1), none (5)</td>
<td>resolution 21/25 (84%); recurrence in 3 patients with VAP; microbial eradication in 12/15 (80%); emergence of resistance in 1 patient</td>
</tr>
<tr>
<td>Curcio et al.</td>
<td>case reports</td>
<td>VAP (2)</td>
<td>71y male, 71y female; ICU</td>
<td><em>Acinetobacter</em> spp.: MDR, colistin-susceptible</td>
<td>none reported</td>
<td>improvement</td>
</tr>
<tr>
<td>Reid et al.</td>
<td>case report</td>
<td>urinary tract infection</td>
<td>53y female; kidney and liver transplantation</td>
<td><em>A. baumannii</em>: MDR, tigecycline MIC 1.5 mg/L</td>
<td>none reported</td>
<td>development of pneumonia, paraspinal abscess and osteomyelitis, with tigecycline-resistant <em>A. baumannii</em></td>
</tr>
<tr>
<td>Leclerc et al.</td>
<td>case report</td>
<td>pulmonary infection—septic shock</td>
<td>18y female</td>
<td><em>A. baumannii</em>: MDR, sensitive to co-trimoxazole, colistin, tigecycline MIC 0.75 mg/L</td>
<td>piperacillin–tazobactam, co-trimoxazole</td>
<td>cure</td>
</tr>
<tr>
<td>Taccone et al.</td>
<td>case report</td>
<td>complicated intra-abdominal infection—septic shock</td>
<td>25y male; ICU</td>
<td><em>A. baumannii</em>: MDR, colistin-susceptible, tigecycline MIC 2 mg/L</td>
<td>meropenem, colistin</td>
<td>improvement</td>
</tr>
</tbody>
</table>

VAP, ventilator-associated pneumonia; ICU, intensive care unit; MIC, minimum inhibitory concentration; MDR, multidrug-resistant.
associated bacteraemia in 4 of these patients), as well as primary or secondary bacteraemia in an additional 4 patients. It should be noted that most of the patients included were critically ill, and also that tigecycline was administered in combination with other potently active antimicrobials against Acinetobacter spp. in the great majority of the patients included (66.7%).

A favourable clinical course was observed in 32 of the overall 42 patients included (76%). However, some points of concern regarding the clinical utility of tigecycline in infections caused by MDR Acinetobacter spp. may arise. First, in the two case series included in this review, the susceptibility rate to tigecycline of MDR A. baumannii isolates recovered from infected patients was 59%. Infection with intermediate susceptibility strains was associated with worse prognosis in one of the relevant studies.79 Furthermore, tigecycline was ineffective in microbiologically clearing A. baumannii bacteraemia in one case,79 and recurrence of ventilator-associated pneumonia was observed in three patients (one of whom had two recurrences), though re-treatment was successful.82 Last but not least, in 3 of the overall 42 patients included, A. baumannii strains resistant to tigecycline emerged after tigecycline therapy was instituted, and this was associated with clinical failure in 2 of the 3 cases.79,82,84 Development of resistance of MDR A. baumannii to tigecycline after treatment with this drug has also been observed in a study presented as a conference abstract.87 Specifically, among 12 ICU patients treated with tigecycline for MDR A. baumannii infections, 1 patient developed a tigecycline-resistant strain, which was associated with an adverse clinical course.87 Of note, the mortality rate of the 12 patients treated with tigecycline (of whom 7 received tigecycline monotherapy) was 50%.87 Moreover, breakthrough bacteraemia with tigecycline-resistant MDR A. baumannii strains has been reported in two patients receiving tigecycline therapy for other indications.88 Whether tigecycline resistance emerged after the exposure of A. baumannii strains to this agent could not be adequately documented, though.

Further considerations

The accumulated evidence identified in this review reveals that tigecycline has considerable microbiological activity against MDR Acinetobacter spp. including carbapenem-resistant Acinetobacter spp. However, the finding in an appreciable proportion of the studies included that the activity of tigecycline was not optimal suggests that the recent introduction of tigecycline in clinical practice may not constitute a definitive solution to the problem of growing antimicrobial drug resistance in Acinetobacter spp., particularly in A. baumannii. Nonetheless, the utility of tigecycline should not be disregarded, since other antimicrobial agents, with the exception of polymyxins, are not reliably active against carbapenem-resistant A. baumannii isolates.61,64,89

It should also be mentioned that the susceptibility rates reported herein may prove to be a serious overestimation of the antimicrobial activity of tigecycline against MDR Acinetobacter spp., if the more conservative BSAC breakpoints of susceptibility (≤ 1 mg/L), compared with those used for the purposes of this review (≤ 2 mg/L), become widely accepted.35,74 This can be inferred by the observation that in many of the studies included in this review that showed adequate in vitro activity of tigecycline against MDR Acinetobacter isolates, the MIC value was equal to 2 mg/L and exceeded the BSAC breakpoint of susceptibility (Table 1).52–54,58,61,66

The use of a clinical MIC breakpoint of susceptibility to tigecycline of ≤2 mg/L for Acinetobacter spp. raises some concerns when pharmacokinetic/pharmacodynamic parameters are considered, particularly regarding bloodstream infections. The antimicrobial activity of tigecycline against A. baumannii has been shown to be maximal at concentrations near the MIC.53,61 For serious infections, such as bloodstream infections, the attainment of maximal antimicrobial activity is essential. However, the steady-state peak concentration of tigecycline in serum after intravenous administration of multiple 50 mg doses has been measured to be 0.62–0.72 mg/L.90,91 Therefore, treatment with tigecycline at the standard dosing regimen for bloodstream infections caused by A. baumannii strains with an MIC near the provisional breakpoint of ≤2 mg/L may be suboptimal. Exposure to relatively low antibiotic concentrations may also promote the development of drug resistance. This may relate to the clinical reports of cases of development of resistance during tigecycline therapy for MDR A. baumannii infections that are described in this review.

It should also be mentioned that the determination of the microbiological activity of tigecycline may vary with the use of different methods. The use of the disc diffusion method has been associated with lower susceptibility rates of A. baumannii isolates to tigecycline when compared with the broth microdilution method or the Etest, in various studies.34,57,92,93 Accordingly, the use of less-strict zone diameter criteria for the determination of the susceptibility of Acinetobacter spp. to tigecycline, compared with those approved by the FDA for Enterobacteriaceae, has been proposed as more appropriate.92 Nevertheless, these findings have not been corroborated with the use of the BSAC disc diffusion method.77

Regarding the clinical evidence for the clinical use of tigecycline in the treatment of MDR Acinetobacter spp. infections, available data identified in this review should be considered preliminary. Although the overall clinical response rates in the identified reports seem favourable, safe conclusions cannot be drawn due to the small number of patients included and the co-administration of various antimicrobial agents along with tigecycline. Some points of concern raised indicate that clinicians should cautiously interpret the in vitro activity of tigecycline into presumed in vivo effectiveness in the case of use of this agent for off-label indications. Yet, tigecycline is expected to be used off-label in clinical practice, since it may be the only available active agent in certain cases of MDR Acinetobacter infections.94 The accumulated clinical experience may be one source of evidence, particularly in the form of well-designed studies comparing the outcomes of tigecycline-treated patients with patients that received other, established antimicrobial agents. However, randomized controlled trials should provide more concrete evidence. Notably, a double-blind, randomized, clinical trial comparing tigecycline versus imipenem/cilastatin for nosocomial pneumonia has been conducted under the sponsorship of the branding company of tigecycline (ClinicalTrials.gov identifier: NCT00080496). The company stated in a press release regarding the preliminary findings of this trial that clinical cure rates were inferior for tigecycline when compared with imipenem/cilastatin in the subset of patients with ventilator-associated pneumonia.95
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In routine clinical practice, tigecycline is expected to be frequently used in combination regimens for the off-label treatment of severe infections. It should be mentioned that synergy studies have revealed an indifferent effect of tigecycline in combinations with carbapenems, cephalosporins, fluoroquinolones, aminoglycosides, ampicillin/sulbactam, rifampicin and polymyxins, against MDR or carbapenem-resistant Acinetobacter spp. 

Conclusions

Tigecycline has shown considerable in vitro activity against MDR (including carbapenem-resistant) Acinetobacter spp. at a provisional MIC breakpoint of ≤2 mg/L. However, the activity of tigecycline is not universally consistent, and relevant findings could be affected if a more conservative breakpoint is adopted. Data regarding the clinical use of tigecycline, for the treatment of patients with infections caused by MDR Acinetobacter spp., are scarce and are confounded by the use of tigecycline in combination regimens. The potential development of resistance to tigecycline during the course of therapy is of concern. Further evidence derived from well-designed studies on the clinical use of tigecycline for infections caused by MDR Acinetobacter spp. is warranted, considering the increasing resistance rates of these pathogens to commonly used antibacterial agents.

Transparency declarations

None to declare.

References

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66. Halstead DC, Abid J, Dowzicky MJ. Antimicrobial susceptibility among Acinetobacter calcoaceticus–baumannii complex and


