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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 ≤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 coccobacillary organisms, comprising more than 30 different species.[1] 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.[2–4] 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-

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associated pneumonia and bacteraemia.[5] The frequency of *A. baumannii* nosocomial infections is increasing,[6−10] a fact that may partly be attributed to the ability of these organisms to cause hospital and inter-hospital outbreaks.[11] Mortality in critically ill patients with *Acinetobacter* infections, particularly in those with ventilator-associated pneumonia and bloodstream infections, is high.[12−16]

The management of *A. baumannii* infections can be difficult, due to the increasing number of isolates exhibiting resistance to multiple classes of antibacterial agents.[5,6,13] Agents potentially effective against *A. baumannii* include carbapenems, aminoglycosides (amikacin or gentamicin), tetracyclines (minocycline or doxycycline) and sulbactam.[1,17−20] However, combined resistance to all of the above agents is increasingly being reported.[21−27] Still, extensively resistant *A. baumannii* strains remain generally susceptible to polymyxins (colistin and polymyxin B), a fact that has contributed to the reconsideration and re-introduction of this practically abandoned for decades class of antibacterial agents into clinical practice.[22,28] Yet, the increasing use of polymyxins has the potential to lead to development of bacterial resistance against these agents.[29,30]

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*-butylglycylamido 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 calcoaceticus*[47,48,50] and *Acinetobacter lwoffi*.[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* susceptibility 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 countries[53,69,71,73,74] and Australia,[54,57] respectively. One more study examined isolates from Latin America as well as global isolates,[59] and the remaining study examined isolates from both Europe and the USA.[68] 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 2[56,74]), the Etest (10 studies)[54,55,57,60,63,65,67,69,70,74] or the disc diffusion method (4 studies[54,57,63,69]). 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 1. Microbiological activity of tigecycline against MDR or carbapenem-resistant *Acinetobacter* spp.

Author[ref]	Country; isolate collection period; methods	Scope of study	Number of isolates; resistance characteristics (subpopulations)	Origin of isolates; isolation sites or sites of infection	Relation of isolates to outbreak	n/N, % susceptible (subpopulations)	MIC distribution (mg/L)	MIC$_{50}$ (mg/L)	MIC$_{90}$ (mg/L)
Draghi et al.[52]	USA; NR; broth microdilution	surveillance study	60 *Acinetobacter* spp.; MDR (≥3 agents); (imipenem-resistant: 29)	collected across US regions	NR	55/60, 91.7 (28/29)	0.25–8	1	2
Mezzatesta et al.[53]	Italy; 2003–04; broth microdilution	determination of *in vitro* activity	107 *A. baumannii*; MDR >90%; (meropenem-resistant: 58)	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%)	NR	100/107, 93 (54/58)	0.25–4	2	2
Ratnam et al.[54]	Australia; 2005; Etest (disc diffusion)	determination of *in vitro* activity	10 *A. baumannii*, 1 *A. junii*; resistant to aztreonam, piperacillin/tazobactam, and sulbactam; (colistin-resistant: 1)	first clinical isolates, ICU patients, no more than 1 isolate per week; sputum (82%), blood (18%)	concurrent outbreak	11/11, 100	0.125–2	2	2
Insa et al.[55]	USA; 2003–06; Etest	determination of *in vitro* activity	77 *A. baumannii*; resistant to β-lactams (including carbapenems), sulbactam, aminoglycosides, fluoroquinolones	consecutive non-related clinical isolates; RT (43%), skin and soft tissue (24%), blood (10%), urine (10%)	NR	57/71, 80	0.094–8	NR	NR
Tan and Ng[56]	Singapore; 2004-06; Agar dilution	determination of *in vitro* activity	55 *Acinetobacter* spp.; resistant to ≥2 antibiotic classes	unique isolates from hospitalized patients collected retrospectively	NR	39/55, 71	0.25–16	2	4
Iredell et al.[57]	Australia; 1996–2002; Etest (disc diffusion)	determination of *in vitro* activity	18 *A. baumannii*; MDR; (carbapenem resistant: 14)	12 genotypically distinct strains from 3 hospitals plus multiple isolates of 2 strains, mostly ICU patients	outbreak reported in main hospital	4/18, 22 (0/14)	≤2 to ≥8	≥8	≥8
Hoban et al.[58]	USA; 2004–06; broth microdilution	surveillance study	282 *A. baumannii*; resistant to ≥3 antibiotic classes	unique patient isolates, TEST database, 77% inpatients, 31% ICU patients; RT (37%), blood (21%), urine (16%), integument (15%)	NR	NR	0.12–8	NR	2
Curcio and Fernandez[59]	global isolates Argentina; NR; broth microdilution	comparison of results of Navon-Venezia et al.[60] with those of a surveillance study	631 (55576) *A. baumannii*; resistant to aminoglycosides cephalosporins,	selected from TEST database	NR	600/631, 95 (168/17828/28)	NR	NR	NR

Continued

Table 1. *Continued*

Author[ref]	Country; isolate collection period; methods	Scope of study	Number of isolates; resistance characteristics (subpopulations)	Origin of isolates; isolation sites or sites of infection	Relation of isolates to outbreak	n/N, % susceptible (subpopulations)	MIC distribution (mg/L)	MIC$_{50}$ (mg/L)	MIC$_{90}$ (mg/L)
			fluoroquinolones; (imipenem non-susceptible: 17828)						
Navon-Venezia et al.[60]	Israel; 2003; Etest	determination of *in vitro* activity	82 *A. baumannii*; resistant to ≥3 antibiotic classes; (imipenem-resistant: 22)	consecutive unique patient isolates; wound (44%), RT (39%), blood (9%), urine (7%), CSF (1%)	outbreak, 19 genotypically distinct isolates	18/82, 22 (1/22)	1–128	16	32
Scheetz et al.[61]	USA; 2001–05; broth micro dilution	determination of *in vitro* activity	93 *A. baumannii*; carbapenem-intermediate or -resistant	unique patient isolates per calendar year	outbreak, 25 genotypically distinct isolates	88/93, 95	NR	1	2
Thamlikitkul et al.[62a]; Tiengrim et al.[63a]	Thailand; 2002–05; broth microdilution, disc diffusion, Etest	determination of *in vitro* activity	148 *A. baumannii*; resistant to all β-lactams, aminoglycosides and fluoroquinolones	unique isolates from hospitalized infected patients	NR	144/148, 97 by broth microdilution; 107/148, 72 by Etest; 66/148, 44 by disc diffusion	11–26 mm inhibition zone diameter	0.5 (broth microdilution) 2 (Etest)	1 (broth microdilution) 4 (Etest)
Song et al.[64]	Korea; 2002–06; broth microdilution	determination of *in vitro* activity	43 *A. baumannii*; carbapenem-resistant	unique isolates randomly selected from ICU patients	NR	24/43, 56	1–4	2	4
Akcam et al.[65]	Turkey; 2000–04; Etest	determination of *in vitro* activity	74 *A. baumannii*; resistant ≥2 antibiotic classes; (carbapenem-resistant: 13)	randomly selected isolates from hospitalized patients	NR	74/74, 100 (13/13)	≥0.0125 to ≤2	≤0.064	≤0.19
Halstead et al.[66]	USA; 2004–05; broth microdilution	surveillance study	249 *A. calcoaceticus–baumannii* complex; resistant to ≥3 antibiotic classes	TEST database, 76 centres, infected patients, nosocomial strains	NR	NR	0.12–4	NR	2
Sands et al.[67]	USA; recent; Etest	determination of *in vitro* activity	19 *A. baumannii*; MDR	RT (47%), urine (32%), blood (10%), wound (10.5%)	NR	11/19, 58	NR	NR	NR
Seifert et al.[68]	Europe and USA; 1990–2003; broth microdilution	determination of *in vitro* activity	215 *A. baumannii*; MDR; (imipenem-resistant: 7, colistin-resistant: 6)	epidemiologically characterized isolates representing different sporadic or outbreak strain types	NR	183/215, 85 (6/7, 6/6)	≤0.06 to ≥32	0.5	4

Study	Country; year; method	Study aim	Isolates	Source/patients	Clonality				
Bogaerts et al.[69]	Belgium; 2004–05; disc diffusion (susceptibility testing), Etest (MICs)	analysis of carbapenem-resistance mechanisms	17 A. baumannii; resistant to all β-lactams, ciprofloxacin, amikacin; OXA-58 positive; borderline susceptible to colistin	ICU patients (71%), infected patients (71%); RT (76%), blood (12%), wound (12%)	outbreak strains belonging to a single clone	17/17, 100	NR	NR	NR
Vahaboglu et al.[70]	Turkey; 2003; Etest	determination of prevalence of subgroups of carbapenemases	10 A. baumannii; MDR carbapenem-resistant (OXA-51 and OXA-58 positive)	selected among consecutive, non-replicate clinical isolates from 7 hospitals, ICU patients	isolates exhibiting different phenotypes	0/10, 0	4	4	4
Souli et al.[71]	Greece; 2003–05; broth microdilution	determination of in vitro activity	100 A. baumannii; resistant to ≥2 antibiotic classes; (imipenem-resistant: 94, colistin-resistant: 3)	unique patient isolates from 17 hospitals; bronchial secretions (56%), pus (23%), blood (13%), other sources (8%)	NR	99/100, 99 (3/3)	0.12–4	0.5	1
Lolans et al.[72]	USA; 2005; broth microdilution	analysis of carbapenem-resistance mechanisms	42 A. baumannii; imipenem-resistant (OXA-40 positive)	first submitted isolates from 9 centres; sputum (24%), wound (19%), catheter tips (12%), blood (10%), urine (7%), environmental (14%)	multicity outbreak, 97% of isolates belonged to a single clone	9/42, 21	2–8	4	4
Pachon-Ibanez et al.[73]	Spain; NR; broth microdilution	determination of in vitro activity	38 A. baumannii; Imipenem-resistant	blood	isolates belonging predominantly to two clones	≥34/38, 89	NR	NR	NR
Henwood et al.[74]	United Kingdom; 2000; agar dilution (Etest confirmatory)	surveillance study	13 Acinetobacter spp.; MDR carbapenem-resistant	consecutive, unique patient isolates from 54 laboratories, patients in burns unit (46%), ICU (23%), general medical ward (23%)	NR	11/13, 85	NR	NR	NR

aRepresent 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.[66] Regarding the resistance characteristics of the *Acinetobacter* isolates included in this review, data regarding MDR isolates were reported in 18 studies,[52–60,63,65–71,74] 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.[62]

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.[68] 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.[52,53,59,61,68,69,71] 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,[62] 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 intermediately susceptible to colistin (colistin MIC of 3 mg/L). All of these isolates were found to be susceptible to tigecycline.[69]

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

Author[ref]; type of study	Type of infection (no. patients)	Patient characteristics	Type of pathogens; resistance characteristics	Co-administered antibiotics (no. patients)	Treatment outcomes
Anthony et al.[79]; retrospective case series	VAP (3), VAP with empyema (2), tracheobronchitis (1), mediastinitis/secondary bacteraemia (1), UTI (1), cellulitis (1), diabetic ulcer/osteomyelitis (1)	47–86y, females: 6, various comorbidities	*A. baumannii*; MDR (resistant ≥3 antibiotic classes); 4/9 (44%) tigecycline-susceptible, 5/9 (56%) tigecycline-intermediate	cefepime (1), amikacin + colistin (1), inhaled colistin (1), tobramycin (1), inhaled tobramycin (1), levofloxacin (1), none (3)	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
Schafer and Mangino[80]; case report	probable osteomyelitis following open femur fracture	55y male	*A. baumannii*; MDR, sensitive to tobramycin, intermediate to imipenem; coagulase-negative *Staphylococcus*	vancomycin	cure
Wadi and Al Rub[81]; case report	meningitis secondary to cranial injury and lumbar shunt infection	26y male	*A. calcoaceticus*; MDR	none	cure
Schafer et al.[82]; retrospective case series	VAP (19), VAP with bacteraemia (3), bacteraemia (3)	25 critically ill patients (60% surgical)	*A. baumannii*; MDR (resistant ≥2 antibiotics from ≥2 classes); 13/20 (65%) tigecycline-susceptible, 6/20 (30%) tigecycline-intermediate, 1/20 (5%) tigecycline-resistant	imipenem (9), imipenem + nebulized colistin (3), imipenem + iv colistin (1), nebulized colistin (6), iv colistin (1), none (5)	resolution 21/25 (84%); recurrence in 3 patients with VAP; microbial eradication in 12/15 (80%); emergence of resistance in 1 patient
Curcio et al.[83]; case reports	VAP (2)	71y male, 71y female; ICU	*Acinetobacter* spp.; MDR, colistin-susceptible	none reported	improvement
Reid et al.[84]; case report	urinary tract infection	53y female; kidney and liver transplantation	*A. baumannii*; MDR, tigecycline MIC 1.5 mg/L	none reported	development of pneumonia, paraspinal abscess and osteomyelitis, with tigecycline-resistant *A. baumannii*
Leclerc et al.[85]; case report	pulmonary infection—septic shock	18y female	*A. baumannii*; MDR, sensitive to co-trimoxazole, colistin, tigecycline MIC 0.75 mg/L	piperacillin–tazobactam, co-trimoxazole	cure
Taccone et al.[86]; case report	complicated intra-abdominal infection—septic shock	25y male; ICU	*A. baumannii*; MDR, colistin-susceptible, tigecycline MIC 2 mg/L	meropenem, colistin	improvement

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 potentially 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 intermediately susceptible 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.[55,74] 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_{90}

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.[54,57,92,93] 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]

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.[61,67,96]

Conclusions

Tigecycline has shown considerable *in vitro* activity against MDR (including carbapenem-resistant) *Acinetobacter* spp. at a provisional MIC breakpoint of susceptibility 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.

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