Tigecycline: An Active Antimicrobial Agent against Multidrug-Resistant *Acinetobacter* spp. Isolated in Latin America

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ABSTRACT

Background:

As part of a global surveillance program, the antimicrobial activities of tigecycline (TGC), a novel broad-spectrum glycylcycline, and comparator agents were evaluated against recent isolates collected from patients hospitalized in Latin America (LA) medical centers.

Methods:

Consecutive, non-duplicate *Acinetobacter* spp. (ASP) isolates were collected from Argentina, Brazil, Chile, Mexico and Venezuela between 2003 and 2006. All isolates were processed using CLSI broth microdilution methods and interpretative criteria. Isolates non-susceptible to ampicillin/sulbactam, ceftazidime, cefepime, imipenem, ciprofloxacin, and amikacin were considered multidrug-resistant (MDR) ASP. US-FDA TGC breakpoints for Enterobacteriaceae (≤2 and ≥8 µg/ml for susceptible [S] and resistant [R], respectively) were used for comparison purposes only (Jones et al., JCM 2007; 45:227).

Results:

Among 647 ASP strains tested, 109 (16.8%) were classified as MDR-ASP. Most MDR-ASP strains (65.1%) were collected from bloodstream infections. Argentina contributed with only 101 ASP isolates, but 61.3% of them had the MDR phenotype. In contrast, only 9.4% of Brazilian isolates were MDR-ASP. The activity of TGC was identical in ASP and MDR isolates ($MIC_{50/90}$, 0.5/2 µg/ml). Against MDR-ASP, 97.2% and 100.0% were S to TGC and polymyxin B, respectively. Only 12 (1.9%) ASP showed elevated TGC MIC value (4 µg/ml). The ASP antimicrobial S profile is shown below:

	ASP (n=647)			
	MIC µg/ml		% by category	
Antimicrobial agents	50%	90%	S	R
Tigecycline	0.5	2	98.1	0.0
Amikacin	>32	>32	32.1	62.9
Ampicillin/Sulbactam	16	>16	43.0	42.2
Ceftazidime	>16	>16	23.8	69.4
Cefepime	>16	>16	32.9	51.5
Ciprofloxacin	>4	>4	26.9	73.0
Imipenem	1	>8	78.5	19.9
Polymyxin B	≤1	≤1	99.6	0.4

Conclusions:

TGC showed excellent activity against ASP, including MDR isolates. Given the concern of potential toxicity of polymyxins, TGC emerges as an active alternative agent for ASP infections, especially in geographic regions (LA) where MDR-ASP strains are frequently isolated.

INTRODUCTION

The worldwide emergence of multidrug-resistant (MDR) *Acinetobacter* spp. clinical isolates is of great concern, since it drastically limits therapeutic alternatives. Although carbapenems are potent antimicrobial agents and are usually employed for treatment of serious infections caused by such MDR strains, carbapenemases belonging to ß-lactamase classes B and D have been detected in *Acinetobacter* spp. Moreover, carbapenem resistance may also arise from porin or penicillin-binding protein modifications, reflecting the pathogen's ability to acquire multiple resistance mechanisms.

Increasing resistance trends have been observed among *Acinetobacter* spp. worldwide, prompting for the evaluation of novel compounds as possible therapeutic agents. Tigecycline is the first glycylcycline to be approved by the United States (USA) Food and Drug Administration (FDA) for clinical use. This novel compound has a wide spectrum of activity that includes Gram-positive, Gram-negative, and anaerobic pathogens. In the present study, the activities of tigecycline and selected comparator agents were evaluated against *Acinetobacter* spp. isolated in Latin American medical centers, as part of a global surveillance program.

MATERIALS AND METHODS

Bacterial strains: Consecutive, non-duplicate *Acinetobacter* spp. isolates were collected from patients hospitalized in Latin American medical centers in Argentina, Brazil, Chile, and Mexico in 2003-2006 and in Venezuela in 2003-2004. All isolates were identified at the participating institution by routine methodologies in use at each laboratory. Upon receipt at the monitoring laboratory (JMI Laboratories, North Liberty, IA, USA), isolates were subcultured to ensure viability and purity. Confirmation of species identification was performed with the Vitek system (bioMérieux Vitek, St Louis, MO) or conventional methods, as required.

Susceptibility testing: *Acinetobacter* spp. isolates were tested against tigegycline and comparator agents by broth microdilution methods using fresh Mueller-Hinton broth, as described by the Clinical and Laboratory Standards Institute (CLSI M7-A7, 2006). Susceptibility results were interpreted according to CLSI document M100-S17 (2007) for all comparison agents. USA-FDA tigecycline breakpoints for Enterobacteriaceae (≤2 and ≥8 µg/ml for susceptible and resistant, respectively) were used for comparison purposes only (Jones et al., 2007). Isolates non-susceptible to ampicillin/sulbactam (MIC, ≥16 µg/ml), ceftazidime (MIC, ≥16 µg/ml), cefepime (MIC, ≥16 µg/ml), imipenem (MIC, ≥8 µg/ml), ciprofloxacin (MIC, ≥2 µg/ml), and amikacin (MIC, ≥32 µg/ml), were considered MDR. Concurrent quality control was performed using the following organisms: *Escherichia coli* ATCC 25922, *Pseudomonas aeruginosa* ATCC 27853 and *Staphylococcus aureus* ATCC 29213.

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RESULTS

- A total of 647 *Acinetobacter* spp. isolates were collected from Latin American medical centers. Most of these strains (71.6%) were isolated between 2005 and 2006.

Table 1. Antimicrobial activity of tigecycline and comparator agents tested against *Acinetobacter* spp. collected from Latin American medical centers (2003-2006).

	Acinetobacter spp.			
	MIC µg/ml		% by category	
Organism group/antimicrobial agent	50%	90%	Susceptible[a]	Resistant[a]
All strains (647)				
Tigecycline	0.5	2	98.1[b]	0.0[b]
Amikacin	>32	>32	32.1	62.9
Ampicillin/Sulbactam	16	>16	43.0	42.2
Ceftazidime	>16	>16	23.8	69.4
Cefepime	>16	>16	32.9	51.5
Ciprofloxacin	>4	>4	26.9	73.0
Imipenem	1	>8	78.5	19.9
Polymyxin B	≤1	≤1	99.6	0.4
Multidrug-resistant strains (109)[c]				
Tigecycline	0.5	2	97.2[b]	0.0[b]
Amikacin	>32	>32	0.0	95.4
Ampicillin/Sulbactam	>16	>16	0.0	81.7
Ceftazidime	>16	>16	0.0	91.7
Cefepime	>16	>16	0.0	81.7
Ciprofloxacin	>4	>4	0.0	100.0
Imipenem	>8	>8	0.0	94.5
Polymyxin	≤1	≤1	100.0	0.0

a. Criteria as published by the CLSI [2007].
b. Tigecycline USA-FDA breakpoints approved for Enterobacteriaceae (≤2 and ≥8 µg/ml for susceptible and resistant, respectively) were used for comparison purposes only (Jones et al., 2007).
c. Isolates non-susceptible to ampicillin/sulbactam, ceftazidime, cefepime, imipenem, ciprofloxacin, and amikacin were considered multidrug-resistant.

- Brazilian medical centers contributed the highest number of *Acinetobacters* (349; 53.9%) followed by Chile (111; 17.2%), Argentina (101; 15.6%), Mexico (78; 12.1%) and Venezuela (8; 1.2%).
- Bloodstream (396 strains; 61.2%) was the most common body site of infection, followed by lower respiratory tract (178 strains; 27.5%) and skin and soft tissue (38 strains; 5.9%).
- One hundred and nine isolates (16.8%) were classified as MDR, mostly recovered from bloodstream infections (71; 65.1%).
- Although Brazilian medical centers contributed the highest number of strains (349), most of the MDR isolates (62; 56.9%) were collected from medical centers located in Argentina.
- Tigecycline ($MIC_{50/90}$, 0.5/2 µg/ml; 98.2% susceptible) showed potency and spectrum similar to that of polymyxin B ($MIC_{50/90}$, ≤1/≤1 µg/ml; 99.6% susceptible; Table 1).
- Against MDR strains, tigecycline (97.2% susceptible) and polymyxin B (100.0% susceptible) were the most active compounds tested (Tables 1 and 2).

Table 2. Tigecycline MIC distributions of *Acinetobacter* spp. strains with various resistance phenotypes collected in Latin American medical centers (2003-2006).

	Cumulative % inhibited at MIC (µg/ml):							MIC (µg/ml)	
Resistance phenotype (no. tested/% of total)	≤0.06	0.12	0.25	0.5	1	2	4	50%	90%
All strains (647/100%)	2.8	14.5	32.3	61.5	83.3	98.1	100.0	0.5	2
Ampicillin/sulbactam-resistant (273/42.2%)	-	2.6	17.9	58.2	81.3	97.8	100.0	0.5	2
Imipenem-resistant (129/19.9%)	-	4.7	27.1	61.2	81.4	97.7	100.0	0.5	2
MDR (109/16.8%)[a]	-	0.9	22.9	56.9	78.0	97.2	100.0	0.5	2

a. Isolates non-susceptible to ampicillin/sulbactam, ceftazidime, cefepime, imipenem, ciprofloxacin, and amikacin were considered multidrug-resistant.

Table 3. Characteristics of 12 *Acinetobacter* spp. isolates showing reduced susceptibility (MIC, 4 µg/ml) to tigecycline collected in Latin American medical centers (2003-2006).

Species	Year of isolation	Body site of infection	Country	Co-resistance phenotype
A. baumannii	2004	Skin/soft tissue	Brazil	Amikacin, cefepime, ceftazidime, ciprofloxacin
A. anitratus	2004	Bloodstream	Venezuela	Ampicillin/sulbactam
A. baumannii	2004	Respiratory tract	Argentina	Amikacin, ampicillin/sulbactam, cefepime, ceftazidime, ciprofloxacin
A. baumannii	2004	Bloodstream	Brazil	Amikacin, cefepime, ceftazidime, ciprofloxacin
A. baumannii	2005	Bloodstream	Brazil	Cefepime, ceftazidime, ciprofloxacin
A. baumannii	2005	Bloodstream	Argentina	Amikacin, ampicillin/sulbactam, cefepime, ceftazidime, ciprofloxacin, imipenem, meropenem
A. baumannii	2006	Bloodstream	Brazil	Amikacin, cefepime, ceftazidime, ciprofloxacin
A. baumannii	2006	Bloodstream	Brazil	None
A. baumannii	2006	Bloodstream	Brazil	Ampicillin/sulbactam, cefepime, ceftazidime, ciprofloxacin
A. baumannii	2006	Bloodstream	Brazil	Amikacin, ampicillin/sulbactam, cefepime, ceftazidime, ciprofloxacin, imipenem, meropenem
A. baumannii	2006	Respiratory tract	Argentina	Amikacin, ampicillin/sulbactam, cefepime, ceftazidime, ciprofloxacin, imipenem, meropenem
A. baumannii	2006	Respiratory tract	Brazil	Amikacin, cefepime, ceftazidime, ciprofloxacin

- Only 12 of 647 (1.9%) *Acinetobacter* spp. strains showed elevated tigecycline MIC values, all at 4 µg/ml (intermediate according to the breakpoints established for Enterobacteriaceae). Eight of these isolates (66.7%) were detected in Brazilian medical centers (Table 3 and Figure 1).

Figure 1. The circles represent the cities, where the 12 *Acinetobacter* spp. isolates exhibiting reduced susceptibility to tigecycline (MIC, 4 µg/ml) were isolated. The strains were collected from: São Paulo (3 isolates), Brasília (1 isolate), Florianópolis (2 isolates), and Porto Alegre (2 isolates), in Brazil; Caracas (1 isolate) in Venezuela; and Buenos Aires (2 isolates) and Rosario (1 isolate) in Argentina.

CONCLUSIONS

- Tigecycline showed excellent in vitro activity against *Acinetobacter* spp. isolated in Latin American medical centers, including MDR strains.
- The majority (56.9%) of MDR strains were isolated in Argentina, which contributed only 15.6% of strains. The elevated number of MDR *Acinetobacter* spp. strains in Argentina may reflect clonal dissemination within participant medical centers.
- Only 12 (1.9%) isolates were non-susceptible to tigecycline, and each strain was only one doubling dilution (4 µg/ml) above the susceptible breakpoint established by the USA-FDA for Enterobacteriaceae.
- Tigecycline appears to be a possible alternative therapeutic agent for treatment of infections caused by *Acinetobacter* spp., especially in geographic regions where this pathogen exhibits high rates of resistance to multiple antimicrobials.