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Activity of Tigecycline Tested Against Recent *Acinetobacter* spp. Isolates in North American (NA) Hospitals

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ABSTRACT

Background:

Acinetobacter spp. (ASP) is an important nosocomial pathogen with increased resistance (R). We evaluated the activity of tigecycline (TIG), a novel broad-spectrum glycylcycline recently approved for treatment of skin and soft tissue and intra-abdominal infections, and comparator agents against contemporary ASP recovered from patients in NA.

Methods:

Consecutive, non-duplicate bacterial pathogens (prevalence format) were collected from 2003-2005 from patients in 37 NA medical centers. The strains were centrally processed using CLSI reference broth microdilution methods and interpretive criteria. In the absence of ASP TIG breakpoints, those applied to Enterobacteriaceae (≤2 and ≥8 μg/ml for susceptible [S] and R by the US-FDA, respectively) were used for comparison purposes.

Results:

A total of 327 ASP strains were collected, mainly from bacteremia (59%) and pneumonia (30%) cases. Only 2 strains (0.6%) were TIG-R (MIC, 8 μg/ml). TIG ($MIC_{50/90}$, 0.5/2 μg/ml; 90.2% inhibited by ≤2 μg/ml) showed activity comparable to imipenem (IMP; $MIC_{50/90}$, ≤0.5/4 μg/ml; 91.7%S and 4.0% R); only polymyxin B (PB) displayed greater activity (MIC_{90}, ≤1 μg/ml; 100.0% S). Other compounds with activity (≥70% S) included (MIC_{50} [μg/ml]/% S): meropenem (MEM; 1/84), amikacin (AMK; ≤4/78), tobramycin (1/73) and ampicillin/sulbactam (A/S; 4/70). Three strains were S only to PB and TIG (MICs, 1 - 2 μg/ml). The activity of TIG is shown in the table:

Organism (no. tested)	≤0.25	0.5	1	2	4	8
	Cumulative % inhibited at TIG MIC of:					
All ASP (327)	44	56	73	90	>99	100
AMK-R (56)	7	20	50	84	100	-
A/S-R (68)	7	19	44	75	100	-
IMP-R (13)	0	23	54	92	100	-
MDR (11)*	0	18	46	91	100	-

* Strains non-S to AMK, A/S, ceftazidime, ciprofloxacin, IMP and MEM.

Conclusions:

TIG showed excellent in vitro activity against ASP, including strains R to antimicrobials currently used to treat ASP infections, especially MDR strains. TIG seems to represent an important addition to the few remaining parenteral agents active against this emerging pathogen.

INTRODUCTION

Acinetobacter spp. represents a heterogenous group of organisms that are usually commensal, but in the past few decades they have emerged as important opportunistic pathogens. *Acinetobacter* spp. infections are usually restricted to hospital settings, mainly affecting patients in the intensive care unit. These pathogens are capable of causing a range of nosocomial infections, including pneumonia, bacteremia, secondary meningitis, urinary tract infections, and surgical wound infections. *Acinetobacter* spp. are responsible for 2.3% of nosocomial bloodstream infections (varying from 1.4% in North America [NA] to 4.5% in Latin America [LA]) and 4.9% of pneumonias in hospitalized patients (ranging from 2.8% in NA to 8.7% in LA; data from the SENTRY Antimicrobial Surveillance Program).

Acinetobacter spp. isolates have some unique characteristics that favor their persistence in the hospital environment. They usually are resistant to many antimicrobials and spread easily from patient-to-patient. Furthermore, similar to the epidemiology of methicillin-resistant *Staphylococcus aureus,* a few epidemic clones are involved in outbreaks at various institutions.

Tigecycline is the first glycylcycline to be used therapeutically in humans and the first new tetracycline analogue since the release of minocycline over 30 years ago. It has been approved for treatment of complicated skin and soft tissue and intra-abdominal infections. In addition to excellent anti-Gram-positive activity, tigecycline is also one of the very few new antimicrobials with activity against most Enterobacteriaceae species, but also *Acinetobacter* spp. In the present study, we evaluated the activity of tigecycline and comparator agents against contemporary *Acinetobacter* spp. strains recovered from patients in North American medical centers.

MATERIALS AND METHODS

Bacterial Strains: The isolates were consecutively collected and only one strain per patient was included in the study (prevalence mode format). Thirty-seven medical centers located in the United States and Canada participated in the study and the isolates were collected from January 2003 to December 2005. The sites of infection included the bloodstream, respiratory tract (mainly in hospitalized patients), skin and soft tissue and urinary tract.

Antimicrobial Susceptibility Testing: Strains were tested for susceptibility against tigecycline and comparator antimicrobials using validated, dry-form broth microdilution panels with cation-adjusted Mueller-Hinton medium (TREK Diagnostics Inc., Cleveland, OH) according to Clinical and Laboratory Standards Institute (CLSI, formerly NCCLS) guidelines. Results were interpreted as specified by the M100-S16 CLSI document (2006). For tigecycline, Enterobacteriaceae breakpoints approved by the USA Federal Drug Administration (US-FDA) were used for comparison purposes, i.e. ≤2 μg/ml for susceptibility and ≥8 for resistance.

SELECTED REFERENCES

1. Clinical and Laboratory Standards Institute. (2006). *Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically, 7th ed. Approved Standard M7-A7*. Wayne, PA: CLSI, 2006.

2. Clinical and Laboratory Standards Institute. (2006). *Performance standards for antimicrobial susceptibility testing, 16th informational supplement M100-S16.* Wayne, PA: CLSI.

3. Gales AC, Jones RN, Forward KR, Linares J, Sader HS, Verhoef J (2001). Emerging importance of multidrug-resistant *Acinetobacter* species and *Stenotrophomonas maltophilia* as pathogens in seriously ill patients: geographic patterns, epidemiological features, and trends in the SENTRY Antimicrobial Surveillance Program (1997-1999). *Clin Infect Dis* 32 Suppl 2: S104-113.

4. Livermore DM (2005). Tigecycline: What is it, and where should it be used? *J Antimicrob Chemother* 56: 611-614.

5. Pachon-Ibanez ME, Jimenez-Mejias ME, Pichardo C, Llanos AC, Pachon J (2004). Activity of tigecycline (GAR-936) against *Acinetobacter baumannii* strains, including those resistant to imipenem. *Antimicrob Agents Chemother* 48: 4479-4481.

6. Rice LB (2006). Challenges in identifying new antimicrobial agents effective for treating infections with *Acinetobacter baumannii* and *Pseudomonas aeruginosa*. *Clin Infect Dis* 43 Suppl 2: S100-105.

7. Tygacil Package Insert (2005). Philadelphia (PA): Wyeth Pharmaceuticals Inc. (June, 2005).

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RESULTS

- Tigecycline (MIC_{50}, 0.5 μg/ml; MIC_{90}, 2 μg/ml; 90.2% susceptible) showed potency and percentage susceptibility similar to that of imipenem (MIC_{50}, ≤0.5 μg/ml; MIC_{90}, 4 μg/ml; 91.7% susceptible). Only 2 strains (0.6%) were resistant (MIC, ≥8 μg/ml) to tigecycline (Tables 1 and 2).
- The activity of tigecycline was most similar to that of imipenem against *Acinetobacter* spp. strains resistant to amikacin (83.9% susceptible to tigecycline and 85.7% susceptible to imipenem) or to ampicillin/sulbactam (75.0% and 73.5% susceptible, respectively; Table 1).
- Imipenem-resistant strains exhibited high rates of resistance to all antimicrobials tested except tigecycline (MIC_{90}, 2 μg/ml; 92.3% susceptible) and polymyxin B (MIC_{90}, ≤1 μg/ml; 100.0% susceptible; Table 1)
- Tigecycline was highly active against multidrug-resistant (MDR) strains (MIC_{90}, 2 μg/ml; 90.9% susceptible) with no tigecycline resistant strains detected among these isolates (Tables 1 and 2).

Table 1. Antimicrobial activity of tigecycline and comparator agents tested against *Acinetobacter* spp. strains with various antimicrobial resistance phenotypes collected in 37 North American medical centers.

Antimicrobial (no. tested)	MIC_{50}	MIC_{90}	% Susceptible[a]	% Resistant[a]
All strains (327)				
Tigecycline	0.5	2	90.2	0.6
Ceftazidime	16	>16	47.4	46.2
Imipenem	≤0.5	4	91.7	4.0
Ampicillin/sulbactam	4	>16	70.0	20.8
Ciprofloxacin	>4	>4	47.1	51.4
Levofloxacin	2	>4	50.8	44.0
Amikacin	4	>32	78.3	17.1
Gentamicin	≤2	>8	54.4	42.2
Polymyxin B	≤1	≤1	100.0	0.0
Amikacin-resistant (56)				
Tigecycline	1	4	83.9	0.0
Ceftazidime	>16	>16	5.4	89.3
Imipenem	≤0.5	8	85.7	5.4
Ampicillin/sulbactam	16	>32	48.2	33.9
Ciprofloxacin	>4	>4	0.0	100.0
Levofloxacin	>4	>4	0.0	87.5
Gentamicin	>8	>8	5.4	92.9
Polymyxin B	≤1	≤1	100.0	0.0
Ampicillin/sulbactam-resistant (68)				
Tigecycline	2	4	75.0	0.0
Ceftazidime	>16	>16	7.4	89.7
Imipenem	2	>8	73.5	13.2
Ciprofloxacin	>4	>4	10.3	89.7
Levofloxacin	>4	>4	11.8	85.3
Amikacin	8	>32	61.8	27.9
Gentamicin	>8	>8	11.8	88.2
Polymyxin B	≤1	≤1	100.0	0.0
Imipenem-resistant (13)				
Tigecycline	1	2	92.3	0.0
Ceftazidime	>16	>16	0.0	92.3
Ampicillin/sulbactam	>32	>32	23.1	69.2
Ciprofloxacin	>4	>4	7.7	92.3
Levofloxacin	>4	>4	7.7	84.6
Amikacin	32	>32	38.5	23.1
Gentamicin	>8	>8	0.0	92.3
Polymyxin B	≤1	≤1	100.0	0.0
MDR[b] (11)				
Tigecycline	2	2	90.9	0.0
Ceftazidime	>16	>16	0.0	100.0
Imipenem	>8	>8	0.0	54.5
Ampicillin/sulbactam	>16	>16	0.0	100.0
Ciprofloxacin	>4	>4	0.0	100.0
Levofloxacin	>4	>4	0.0	100.0
Amikacin	32	>32	0.0	45.5
Gentamicin	>8	>8	0.0	100.0
Polymyxin B	≤1	≤1	100.0	0.0

a. According to breakpoints established by CLSI (2006). Tigecycline US-FDA breakpoints approved for Enterobacteriaceae (≤2 μg/ml) were applied for *Acinetobacter* spp. for comparison purposes only.
b. Isolates non-susceptible to amikacin, ampicillin/sulbactam, ceftazidime, ciprofloxacin, and imipenem.

Table 2. Tigecycline MIC distributions of *Acinetobacter* spp. strains with various antimicrobial susceptibility patterns.

Resistance phenotype (no. tested)	≤0.03	0.06	0.12	0.25	0.5	1	2	4	8
	No. of isolates (cumulative %) inhibited at MIC (μg/ml) of:								
All strains (327)	1 (0.3)	19 (6.1)	64 (25.7)	60 (44.0)	40 (56.3)	53 (72.5)	58 (90.2)	30 (99.4)	2 (100.0)
Amikacin-resistant (56)	-	-	1 (1.8)	3 (7.1)	7 (19.6)	17 (50.0)	19 (83.9)	9 (100.0)	-
Ampicillin/sulbactam-resistant (68)	-	2 (2.9)	2 (5.9)	1 (7.4)	8 (19.1)	17 (44.1)	21 (75.0)	17 (100.0)	-
Imipenem-resistant (13)	-	-	-	-	3 (23.1)	4 (53.8)	5 (92.3)	1 (100.0)	-
MDR[a] (11)	-	-	-	-	2 (19.2)	3 (45.5)	5 (90.9)	1 (100.0)	-

a. Isolates non-susceptible to amikacin, ampicillin/sulbactam, ceftazidime, ciprofloxacin, and imipenem.

CONCLUSIONS

- Tigecycline demonstrated excellent in vitro activity against *Acinetobacter* spp. strains, including strains resistant to antimicrobials currently used to treat *Acinetobacter* spp. infections, especially multidrug-resistant strains.
- Only tigecycline and polymyxin B showed consistent activity against imipenem-resistant *Acinetobacter* spp. strains.
- Resistance to other antimicrobial agents did not adversely influence tigecycline activity against *Acinetobacter* spp.
- Tigecycline represents an important addition to the limited number of antimicrobial agents active against this emerging, often resistant pathogen.