

Tigecycline Evaluation Surveillance Trial (T.E.S.T.) - United States In Vitro Antibacterial activity Against Selected Species of Glucose Non-fermenting Organisms

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REVISED ABSTRACT

Background: Glucose non-fermenting Gram-negative rods are known to be highly resistant in hospital settings and have always been a challenge for clinicians and hospital infection control. The degree or type of resistance may be due to several sophisticated mechanisms such as production of broad spectrum beta-lactamases, efflux pumps and altered membrane permeability, inactivating most classes of antimicrobials that are available for treatment including the cephalosporins, carbapenems, aminoglycosides and fluoroquinolones. Tigecycline, a member of a new class of antimicrobials (glycylcyclines), has been shown to have potent expanded broad spectrum activity against most species of *Enterobacteriaceae* and selected species of non-fermenters, as well as Gram positives, atypicals and anaerobes. The T.E.S.T. program determined the in vitro activity of tigecycline compared to amikacin, ampicillin, imipenem, ceftazidime, ceftazidime, ceftriaxone, levofloxacin, minocycline and piperacillin/tazobactam against members of *Acinetobacter* spp. and *Pseudomonas aeruginosa* collected from hospitals in the United States. **Methods:** A total of 1,318 clinical isolates were identified to the species level at each participating site and confirmed by the central laboratory. Isolates were collected throughout 2004. Minimum Inhibitory Concentration (MICs) were determined by the local laboratory using broth microdilution panels and interpreted according to CLSI guidelines. **Results:** Tigecycline was generally less active against *P. aeruginosa* with a MIC₉₀ of >16 mcg/ml. The cephalosporins were inactive against *A. baumannii* (n= 467). Tigecycline showed the lowest MIC₅₀/MIC₉₀ of 0.5/1 mcg/ml against *A. baumannii* compared to amikacin MIC₅₀/MIC₉₀ 4/32, imipenem MIC₅₀/MIC₉₀ 0.5/8 and minocycline MIC₅₀/MIC₉₀ 0.5/8. Similar findings were found in other species of *Acinetobacter* genus. **Conclusion:** The presented data suggest that tigecycline may be an effective therapeutic option against strains of *Acinetobacter* spp. but is not as active against *P. aeruginosa*.

INTRODUCTION

Tigecycline is a novel antimicrobial with an expanded broad-spectrum of activity from a new class of compounds, glycylcyclines. Tigecycline inhibits protein synthesis by binding to the 30S ribosomal subunit. Although it is perceived to be bacteriostatic, its anti-bacterial activity is significant and has shown some bactericidal activity against key targeted pathogens [1,2]. Tigecycline was developed to provide activity against tetracycline and multi-drug-resistant Gram-positive pathogens and has demonstrated significant broad-spectrum activity against aerobic and anaerobic Gram-positive and Gram-negative microorganisms [2-4].

Tigecycline resistance is very infrequent and is also difficult to induce in the laboratory [5, 6] with a selection frequency observed at less than 10⁻⁹ [3, 5, 7]. With the exception of *P. aeruginosa*, tetracycline-resistant bacteria with either tetracycline efflux pumps or ribosomal protective features are sensitive to tigecycline [2-4, 7-11]. The MIC₉₀ values for pseudomonal isolates are generally elevated, in the range of 8-16 mcg/ml due to synergism between outer membrane impermeability and efflux mechanisms [10]. However, tigecycline has shown to be a highly effective against multi-drug resistant *Acinetobacter* spp., particularly *A. baumannii* that are commonly associated with serious nosocomial infections [5].

This study prospectively compared the activity of tigecycline with comparative antimicrobial agents against *Acinetobacter* spp. and *P. aeruginosa* clinical isolates from hospitals across the United States.

MATERIALS & METHODS

- All isolates were derived from blood, respiratory tract, urine (no more than 25% of all isolates), skin, wound, fluids and few other defined sources. Only one isolate per patient was accepted.
- Clinical isolates were collected tested between January 2004 - December 2004 from 44 study centers in the United States.
- Custom broth microdilution panels were supplied by MicroScan (Dade Behring, Sacramento, CA, USA) with the following antimicrobial agents and concentrations (expressed in mcg/ml): amoxicillin/clavulanic acid (0.12-32); piperacillin/tazobactam (0.06-128); levofloxacin (0.008-8); ceftriaxone (0.06-64); ceftazidime (0.5-32); ampicillin (0.5-32); amikacin (0.5-64); minocycline (0.5-16); ceftazidime (8-32); tigecycline (0.008-16); and imipenem (0.06-16).
- MIC interpretive criteria followed published guidelines established by the Clinical and Laboratory Standards Institute where applicable [12]. Tigecycline tentative breakpoints (in units of mcg/mL) are defined as susceptible ≤ 2; intermediate = 4; and resistant ≥ 8.
- Isolates were identified to genus and species at each site by the local laboratory. Isolates were tested by the local laboratory.
- Quality control of broth microdilution panels followed manufacturer's and CLSI guidelines using the following ATCC strains: *Pseudomonas aeruginosa* ATCC 27853 and *Escherichia coli* ATCC 25922.
- The collection and transporting of organisms and the confirmation of identification, as well as, construction and management of a centralized database were conducted and coordinated by Laboratories International for Microbiology Studies (LIMS), a subsidiary of International Health Management Associates, Inc. (IHMA, Schaumburg, IL).

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RESULTS

Table 1. In vitro activity of tigecycline and comparative agents against 1,318 strains of *P. aeruginosa* and *Acinetobacter* spp. combined.

Organism Name	Drug ^a	MICs (mcg/mL)		
		MIC ₅₀	MIC ₉₀	Range
<i>P. aeruginosa</i> and <i>Acinetobacter</i> spp. (n=1,318)	Tigecycline	1	16	≤0.008 - >16
	Amikacin	4	32	≤0.5 - >64
	Amox-Clav	>32	>32	≤0.12 - >32
	Ampicillin	>32	>32	≤0.5 - >32
	Cefepime	8	>32	≤0.5 - >32
	Ceftazidime	8	>32	≤8 - >32
	Ceftriaxone	64	>64	≤0.06 - >64
Imipenem	1	8	≤0.06 - >16	
Levofloxacin	2	>8	≤0.008 - >8	
Minocycline	4	>16	≤0.5 - >16	
Pip-Tazo	8	>128	≤0.06 - >128	

^aBreakpoints as defined by NCCLS where available (M100-S14), 2004. na = not available. Tigecycline breakpoints defined as: susceptible ≤ 2; intermediate = 4; and resistant ≥ 8.

Table 2. In vitro activity of tigecycline and comparative agents against 1,318 selected gram-negative non-fermenters.

Organism Name	Drug ^a	%SUS %INT %RES MICs (mcg/mL)				
		%SUS	%INT	%RES	MIC ₅₀ MIC ₉₀	
<i>Acinetobacter</i> spp. (n=518)	Tigecycline	98.5	1.5	0	0.5	1
	Amikacin	84.4	7.9	7.7	4	32
	Amox-Clav	na	na	na	32	>32
	Ampicillin	na	na	na	>32	>32
	Cefepime	45.4	16.2	38.4	16	>32
	Ceftazidime	47.2	4.1	48.7	16	>32
	Ceftriaxone	27.8	24.5	47.7	32	>64
	Imipenem	86.3	6.4	7.3	0.5	8
	Levofloxacin	46.5	5	48.5	4	>8
	Minocycline	89	8.5	2.5	≤0.5	8
Pip-Tazo	72.4	0	27.6	8	>128	

<i>A. baumannii</i> (n=467)	Tigecycline	98.3	1.7	0	0.5	1
	Amikacin	82.9	8.7	8.4	4	32
	Amox-Clav	na	na	na	32	>32
	Ampicillin	na	na	na	>32	>32
	Cefepime	40.9	17.6	41.5	16	>32
	Ceftazidime	44	3.2	52.8	32	>32
	Ceftriaxone	24	24.2	51.8	64	>64
	Imipenem	84.8	7.1	8.1	0.5	8
	Levofloxacin	42.2	5.1	52.7	8	>8
	Minocycline	88	9.2	2.8	≤0.5	8
Pip-Tazo	70	0	30	16	>128	
<i>P. aeruginosa</i> (n=800)	Tigecycline	4.8	10.1	85.1	8	>16
	Amikacin	96.4	1.5	2.1	4	8
	Amox-Clav	na	na	na	>32	>32
	Ampicillin	na	na	na	>32	>32
	Cefepime	74.5	13.9	11.6	4	32
	Ceftazidime	81.4	5.2	13.4	≤8	32
	Ceftriaxone	14.1	15.8	70.1	>64	>64
	Imipenem	82.1	8.5	9.4	1	8
	Levofloxacin	61.8	7.1	31.1	1	>8
	Minocycline	4.4	10.2	85.4	>16	>16
Pip-Tazo	86.6	0	13.4	4	128	

^aBreakpoints as defined by NCCLS where available (M100-S14), 2004. na = not available. Tigecycline breakpoints defined as: susceptible ≤ 2; intermediate = 4; and resistant ≥ 8.

Table 3. In vitro activity of tigecycline and comparators against 518 *Acinetobacter* spp. showing cumulative percent inhibited (%) at each MIC (mcg/ml).

MIC	≤0.008	0.015	0.03	≤0.06	0.06	0.12	0.25	≤0.5	0.5	1	2	4	≤8	8	>8	>16	32	>32	64	>64	128	>128	
Tigecycline	3	56	116	68	95	142	40	8															
Amikacin	0.6	11.4	33.8	46.9	63.3	90.7	98.5	100	42	34	41	19	21										
Amox-Clav	4	3	1.7	10.2	40.5	69.7	77.8	84.4	92.3	95.9	100												
Ampicillin	2.1	3.3	5.4	11.8	28.4	42.9	56.4	100															
Cefepime	1.9	2.3	2.9	6.2	16.1	35.7	46.5	100															
Ceftazidime	29	36	68	55	47	84	84	115															
Ceftriaxone	7	1.4	2	1.4	2.1	3	14	37	82	89	38	37	210										
Imipenem	0.4	1	26.1	57.7	70.3	77	86.3	92.7	96.1	100													
Levofloxacin	1	2	10	89	81	29	9	13	7	26	58	193											
Minocycline	0.2	0.6	2.5	19.7	35.3	40.9	42.7	45.2	46.5	51.5	62.7	100											
Pip-Tazo	112	17	18	20	15	27	30	28	29	34	45	62	81										

Table 4. In vitro activity of tigecycline and comparators against 800 *Pseudomonas aeruginosa* showing cumulative percent inhibited (%) at each MIC (mcg/ml).

MIC	≤0.008	0.015	0.03	≤0.06	0.06	0.12	0.25	≤0.5	0.5	1	2	4	≤8	8	>8	>16	32	>32	64	>64	128	>128	
Tigecycline	1	4	6	9	18	81	284	258	139														
Amikacin	0.1	0.6	1.4	2.5	4.8	14.9	50.4	82.6	100														
Amox-Clav	7	35	251	316	127	35	12	9	8														
Ampicillin	0.9	5.2	36.6	76.1	92	96.4	97.9	100															
Cefepime	1	1	2	1	3	12	781																
Ceftazidime	0.1	0.1	0.4	0.5	0.9	2.4	100																
Ceftriaxone	2	0.2	0.4	0.5	1.1	2.1	5.4	14.1	21.4	29.9	38.1	100											
Imipenem	1	1	3	4	6	51	202	134	92	57	53	196											
Levofloxacin	0.1	0.2	0.6	1.1	1.9	8.2	33.5	50.3	61.8	68.9	75.5	100											
Minocycline	1	1	7	9	18	82	183	500															
Pip-Tazo	3	6	0.1	11	17	162	237	112	74	42	29	44	63										

CONCLUSIONS

- Tigecycline inhibited 98.5% of *Acinetobacter* spp. tested in vitro at an MIC of 2 mcg/mL.
- Tigecycline's MIC₉₀ of 1 mcg/mL against *Acinetobacter* spp. was the lowest among all broad spectrum antimicrobials tested.
- With the exception of imipenem, amikacin, and minocycline, all broad spectrum antimicrobials commonly prescribed evaluated in this study (cefepime, ceftazidime, levofloxacin and piperacillin/tazobactam) had limited activity against *A. baumannii*.
- Tigecycline's limited activity against *P. aeruginosa* is similar to tetracyclines and their analog derivatives.
- The in vitro activity of tigecycline in this study suggests that tigecycline is a promising compound in the treatment of serious nosocomial infections caused by *Acinetobacter* spp.