

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, cefepime, 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); cefepime (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 manufacture'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)				
		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	0.12	0.25	<0.5	0.5	1	2	4	<8	8	>8	>16	>32	>64	128	>128
Tigecycline	3	56	116	68	85	142	40	8											
Amikacin	0.6	11.4	33.8	46.9	63.3	90.7	98.5	100											
AmoxClav					9	44	157	151	42	34	41	52.3	95.9	100					
Ampicillin					4	3	4	6	11	33	66	75	65	231					
Cefepime					0.8	1.4	2.1	3.3	5.4	11.8	28.4	42.9	55.4	100					
Ceftazidime									10	2	3	17	51	101	56	276			
Ceftriaxone									1.9	23	29	62	161	357	465	100			
Imipenem									29	36	68	55	47	84	84	115			
Levofloxacin									5.6	12.5	25.7	36.3	45.4	61.6	77.8	100			
Minocycline													241	2	21	39	212		
Pip-Tazo													46.8	47.2	51.3	58.8	100		
Amikacin													82	89	38	37	210		
AmoxClav													1.5	21	48	12	27.8	45	52.3
Ampicillin													164	65	35	48	33	18	20
Cefepime													1	26.1	57.7	70.3	77	95.3	92.7
Ceftazidime													9	13	7	25	59	193	
Ceftriaxone													286	95	48	32	44	11	2
Imipenem													55.2	73.6	82.8	89	97.5	99.6	100
Levofloxacin													0.2	0.6	2.5	19.7	35.3	40.9	42.7
Minocycline																			
Pip-Tazo																			

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	0.12	0.25	<0.5	0.5	1	2	4	<8	8	>8	>16	>32	>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							
AmoxClav						7	35	251	316	127	35	12	9	8					
Ampicillin						0.9	5.2	36.6	76.1	92	96.4	97.9	99	100					
Cefepime							1	2	1	3	12	781							
Ceftazidime								0.1	0.4	0.5	0.9	2.4	100						
Ceftriaxone																			
Imipenem																			
Levofloxacin																			
Minocycline																			
Pip-Tazo																			

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*