

Tigecycline Evaluation Surveillance Trial (T.E.S.T.) Program - Global 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 63 hospitals in North America, Europe and Asia. **Methods:** A total of 1,964 non-fermenting 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 supplied broth microdilution panels and interpreted according to CLSI guidelines. **Results:** The cephalosporins were ineffective towards *A. baumannii* (n=674). Tigecycline showed the lowest MICs against *A. baumannii* with a MIC₅₀/MIC₉₀ of 0.25/1 mcg/ml in comparison to amikacin, 78.8% inhibition MIC₅₀/MIC₉₀ 4/64, imipenem, 84.1% MIC₅₀/MIC₉₀ 0.5/8 and minocycline, 83.3% MIC₅₀/MIC₉₀ 0.5/8. Similar findings were found in other species of the *Acinetobacter* genus. Tigecycline was not as active than comparators against *P. aeruginosa* with a MIC₉₀ of >16 mcg/ml. **Conclusion:** The presented data suggest that tigecycline may be an effective therapeutic option against strains of *Acinetobacter* spp., but is inactive 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 pseudomonas 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 been shown to be 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 in vitro activity of tigecycline with comparative antimicrobial agents against *Acinetobacter* spp. and *P. aeruginosa* from a geographically diverse clinical populations worldwide.

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 63 study centers in 15 countries.
- 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. List of countries and number of investigative sites that contributed to T.E.S.T. program.

Country	Investigative Sites
Canada	1
China	1
France	2
Germany	4
Hungary	1
India	1
Italy	2
Latvia	1
Philippines	1
Poland	1
Spain	1
Switzerland	1
The Netherlands	1
United Kingdom	1
United States	44
Total	63

Table 2. In vitro activity of tigecycline and comparative agents against 1,964 strains of *P. aeruginosa* and *Acinetobacter* spp. combined.

Organism Name	Drug	MICs (mcg/mL)		
		MIC ₅₀	MIC ₉₀	Range
<i>P. aeruginosa</i> and <i>Acinetobacter</i> spp. (n=1,964)	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	1	>8	≤0.008 - >8
	Minocycline	4	>16	≤0.5 - >16
	Pip-Tazo	4	>128	≤0.06 - >128

Table 3. In vitro activity of tigecycline and comparative agents against selected Gram-negative non-fermenters.

Organism Name	Drug*	MICs (mcg/mL)															
		%SUS	%INT	%RES	MIC ₅₀	MIC ₉₀	1	2	4	8	16	32	64	128	>128		
<i>Acinetobacter</i> spp. (n=783)	Tigecycline	98.7	1.3	0	0.25	1											
	Amikacin	81.4	6.9	11.7	4	64											
	Amox-Clav	na	na	na	32	>32											
	Ampicillin	na	na	na	32	>32											
	Cefepime	52.9	15.4	31.7	8	>32											
	Ceftazidime	52.6	5.8	41.6	≤8	>32											
	Ceftriaxone	33.6	23.1	43.3	16	>64											
	Imipenem	86.3	5.1	8.6	0.5	8											
	Levofloxacin	53.9	6.1	40	1	>8											
	Minocycline	89.8	7.8	2.4	≤0.5	8											
Pip-Tazo	74.2	0	25.8	8	>128												
<i>A. baumannii</i> (n=674)	Tigecycline	98.5	1.5	0	0.25	1											
	Amikacin	78.8	7.8	13.4	4	64											
	Amox-Clav	na	na	na	32	>32											
	Ampicillin	na	na	na	>32	>32											
	Cefepime	46.7	17.2	36.1	16	>32											
	Ceftazidime	47.3	5.7	47	16	>32											
	Ceftriaxone	27.3	23.3	49.4	32	>64											
	Imipenem	84.1	5.9	10	0.5	8											
	Levofloxacin	47.6	6.8	45.6	4	>8											
	Minocycline	88.3	8.9	2.8	≤0.5	8											
Pip-Tazo	70.6	0	29.4	16	>128												
<i>P. aeruginosa</i> (n=1,181)	Tigecycline	4.9	10.7	84.4	8	>16											
	Amikacin	95	1.9	3.1	4	8											
	Amox-Clav	na	na	na	>32	>32											
	Ampicillin	na	na	na	>32	>32											
	Cefepime	74	13.8	12.2	4	32											
	Ceftazidime	78.5	7.4	14.1	<8	32											
	Ceftriaxone	13.5	14.3	72.1	>64	>64											
	Imipenem	81.1	8.2	10.7	1	16											
	Levofloxacin	62.8	6.6	30.6	1	>8											
	Minocycline	4.7	11.6	83.7	>16	>16											
Pip-Tazo	87.4	0	12.6	4	128												

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

Table 4. In vitro activity of tigecycline and comparators against 783 *Acinetobacter* spp. showing cumulative percent inhibited (%) at each MIC (mcg/ml).

MIC	MICs (mcg/mL)															
	≤0.008	0.015	0.03	≤0.06	0.06	0.12	0.12	0.25	≤0.5	0.5	1	2	4	8	16	>16
Tigecycline	5	1	15	102	189	126	118	172	45	10						
Amikacin	0.6	0.8	2.7	15.7	39.8	55.9	71	93	98.7	100						
Amox-Clav					35		83	236	196		49	38	54	42	50	
Ampicillin					4.5		17	10	20	53	123	123	103	321		
Cefepime					0.6	1.7	3.8	5.1	7.7	14.4	30.1	45.8	59	100		
Ceftazidime							23	11	9	32	78	149	90	388		
Ceftriaxone							2.9	4.4	5.5	9.6	19.6	38.7	50.3	100		
Imipenem							64	54	111	91	94	121	115	133		
Levofloxacin							8.2	15.1	29.2	40.9	52.9	68.3	83	100		
Minocycline											408	2	45	88	256	
Pip-Tazo											52.4	52.6	58.4	67.1	100	
Imipenem							10	1.3	1.4	2	4	8.2	16.3	33.6	50.1	56.7
Levofloxacin							0.5	12	227	242	96	43	52	40	39	28
Minocycline							0.1	1	3.8	24	40.6	45.2	47.1	50.4	53.9	60
Pip-Tazo											472	132	57	42	61	16
											63.3	77.1	84.4	89.8	97.6	99.6
											195	30	28	63	43	46
											28.7	32.3	36.1	39.3	44.3	49.8
											55.3	61.2	67	74.2	84.5	100

Table 5. In vitro activity of tigecycline and comparators against 1,181 *Pseudomonas aeruginosa* showing cumulative percent inhibited (%) at each MIC (mcg/ml).