Tigecycline Evaluation Surveillance Trial (T.E.S.T.) Program - Global In Vitro Antibacterial Activity against Selected Species of *Enterobacteriaceae*

#P 803

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REVISED ABSTRACT

Background: Rapid increasing resistance in nosocomial pathogens has always been a challenge for clinicians and hospital infection control. 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* as well as Gram positives, atypicals and anaerobes. The T.E.S.T. program determined the in vitro activity of tigecycline compared to amikacin, amoxicillin/clavulanic acid, imipenem, cefepime, ceftazidime, ceftriaxone, levofloxacin, minocycline and piperacillin/tazobactam against members of *Enterobacteriaceae* (mainly *E. coli*, *Klebsiella* spp., *Enterobacter* spp. and *Serratia* spp.) collected from 63 hospitals in North America, Europe and Asia. **Methods:** A total of 7,531 clinical isolates of *Enterobacteriaceae* 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 from Dade MicroScan and interpreted according to CLSI guidelines. **Results:** Tigecycline's activity was equivalent to imipenem presenting a MIC_{50}/MIC_{90} of 0.25/1 mcg/ml against all strains of *Enterobacteriaceae*. In comparison to other antimicrobials tested, the MIC_{90} of 1 mcg/ml for tigecycline was also the lowest being 8 fold lower than commonly prescribed broad spectrum antimicrobials such as ceftriaxone, levofloxacin, and minocycline and 16 fold lower than ceftazidime and piperacillin/tazobactam. The frequency of ESBL production among *K. pneumoniae*, *K. oxytoca*, and *E. coli* was found to be 11.7%, 6%, and 3.3%, respectively. Tigecycline inhibited 97.5% of all ESBL producers at an MIC of 2 mcg/ml. Approximately 20% of *Enterobacter* spp and 9% of *S. marcescens* presented resistance to third generation cephalosporins (ceftazidime and ceftriaxone) suggestive of AmpC-type resistance. Tigecycline inhibited a majority of these isolates with an MIC_{90} of 2 mcg/ml. **Conclusion:** Tigecycline's in vitro activity was comparable to the activity of a broad spectrum antimicrobial, carbapenem (imipenem), and greater than other commonly prescribed broad spectrum agents tested in this study. The presented data suggest that tigecycline may be an effective therapeutic option against both susceptible strains of *Enterobacteriaceae* and drug-resistant strains.

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]. This broad spectrum activity has been demonstrated against gram-negative pathogens, even extended-spectrum ß-lactamase producing *E. coli* and *Klebsiella pneumoniae* [10, 12]. This study was designed to better define tigecycline activity in a large diverse population of clinical isolates.

This study compared the activity of tigecycline with other agents against *Enterobacteriaceae* including *Escherichia coli, Enterobacter cloacae, Enterobacter aerogenes, Klebsiella pneumoniae* and *Serratia marcescens* from hospitals 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.
- *Escherichia coli* and *Klebsiella pneumoniae* were screened and confirmed for ESBL activity according to CLSI guidelines (Table 2A, M100-S14) [13].
- ESBL activity was confirmed by testing the following antibiotic disks: cefotaxime (30 mcg), cefotaxime/clavulanic acid (30/10 mcg), and ceftazidime (30 mcg), ceftazidime/clavulanic acid (30/10 mcg). Antibiotic disks were manufactured by Oxoid Inc. Ogdensburg, New York. Mueller-Hinton agar used in testing was manufactured by Remel Inc. Lenexa, Kansas.
- An organism is interpreted as producing an ESBL if there is an increase of ≥ 5mm in the inhibition zone of the combination disc when compared to that of the cephalosporin alone: cefotaxime/clavulanic acid - cefotaxime ≥ 5 mm or ceftazidime/clavulanic acid - ceftazidime ≥ 5 mm.
- Antimicrobial agents tested with concentrations (expressed in mcg/ml) were: amoxicillin/clavulanic acid (0.12-32); piperacillin/tazobactam (0.06-128); levofloxacin (0.008-8); ceftriaxone (0.06-64); cefepime (0.5-32); amikacin (0.5-64); minocycline (0.5-16); ceftazidime (8-32); tigecycline (0.008-16); imipenem (0.06-16). MIC interpretive criteria followed published guidelines established by the CLSI where applicable [15]. 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 by the local laboratory. Each site tested the isolates using broth microdilution.
- Quality control of antibiotic disks followed manufactures guidelines (Oxoid) using the following ATCC strains: *Klebsiella pneumoniae* ATCC 700603 and *Escherichia coli* ATCC 25922.
- The collection and transportation 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, USA).

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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 7,531 strains of *Enterobacteriaceae*.

Organism Name	Drug	MICs (mcg/mL) MIC_{50}	MIC_{90}	Range
Enterobacteriaceae (n=7,531)	Tigecycline	0.25	1	0.03-8
	Amikacin	2	4	<0.5->64
	Amox-Clav	8	>32	0.12->32
	Cefepime	≤0.5	2	0.5->32
	Ceftazidime	≤8	16	<8->32
	Ceftriaxone	≤0.06	16	<0.06->64
	Imipenem	0.5	1	0.12->16
	Levofloxacin	0.06	8	<0.008->8
	Minocycline	2	8	<0.5->16
	Pip-Tazo	1	16	<0.06->128

Table 3. In vitro activity of tigecycline and comparators against 7,531 strains of *Enterobacteriaceae* showing frequency distribution and cumulative percent inhibited (%) at each MIC (mcg/ml).

MIC	≤0.008	0.015	0.03	≤0.06	0.06	≤0.12	0.12	0.25	≤0.5	0.5	1	2	4	≤8	8	>8	16	>16	32	>32	64	>64	128	>128
Tigecycline											13		400			1774	1930		2187	723	276	193		35
											0.2		5.5		29	54.7		83.7	93.3	97	99.5		100	
Amikacin														93			2147	3652	1032		147		53		12	46
														29.8	78.3	92					96.6		98.5		99.2		99.4	100
Amox-Clav							1		2				41	296	2044	1168			980		652		514	1834				
							0		0				0.6	4.5	31.7	47.2			60.2		68.8		75.7	100				
Cefepime													6393	2	234	190	196		146		96		76	195				
													84.9	84.9	88.1	90.6	93.2		95.1		96.4		97.4	100				
Ceftazidime																		6617	15		175		185	549				
																		88	88.2		90.5		92.7	100				
Ceftriaxone				4426	3				909	574			291	108	127	111			161		153		145		161	362		
				58.8	58.8				70.9	78.5			82.4	83.8	85.5	87			89.1		91.1		93.1		95.2	100		
Imipenem									10	3667			2797	761	168	36			30		24	48						
									0.1	48.8			85.8	95.9	98.2	98.6			99		99.4	100						
Levofloxacin	31	807	2458		1692				500	350			305	196	130	134			302	626								
	0.4	11.1	43.8		66.2				72.9	77.5			81.6	84.2	85.9	87.7			91.7	100								
Minocycline														1161	6	2038	1903	1272	596		321	234						
														15.4	15.5	42.6	67.8	84.7	92.6		96.9	100						
Pip-Tazo								12				22	155		1073	2675	1850	636	303		195		109		106		126	269
								0.2				0.5	2.5		16.8	52.3	76.8	85.3	89.3		91.9		93.3		94.8		96.4	100

Table 4. In vitro activity of tigecycline and comparative agents against selected representatives of *Enterobacteriaceae.*

Organism Name	Drug[a]	%SUS	%INT	%RES	MICs (mcg/mL) MIC_{50}	MIC_{90}
Enterobacter aerogenes (n=359)	Tigecycline	96.4	3	0.6	0.5	1
	Amikacin	96.9	2.5	0.6	2	4
	Amox/Clav	7.5	3.3	89.2	>32	>32
	Cefepime	95.8	0.8	3.4	≤0.5	2
	Ceftazidime	79.7	5.8	14.5	≤8	>32
	Ceftriaxone	88.6	6.7	4.7	0.12	16
	Imipenem	98.9	0	1.1	1	2
	Levofloxacin	92.8	2.2	5	0.06	1
	Minocycline	89.1	5.8	5.1	2	8
	Pip-Tazo	88.3	7.5	4.2	2	32
Enterobacter cloacae (n=966)	Tigecycline	94.4	4.2	1.4	0.5	2
	Amikacin	98.8	0.3	0.9	2	2
	Amox/Clav	4	1.6	94.4	>32	>32
	Cefepime	94.8	1.3	3.9	≤0.5	4
	Ceftazidime	74.4	5.2	20.4	≤8	>32
	Ceftriaxone	77.7	8.7	13.6	0.25	64
	Imipenem	99	0.1	0.9	0.5	1
	Levofloxacin	92.8	1.5	5.7	0.06	2
	Minocycline	85.7	7.2	7.1	2	8
	Pip-Tazo	82	9	9	2	64
Escherichia coli (n=1,421)	Tigecycline	99.9	0.1	0	0.12	0.25
	Amikacin	99.2	0.3	0.5	2	4
	Amox/Clav	76.7	14	9.3	4	16
	Cefepime	97.1	0.9	2	≤0.5	≤0.5
	Ceftazidime	95	1.5	3.5	≤8	≤8
	Ceftriaxone	94.2	1.4	4.4	≤0.06	0.25
	Imipenem	99.6	0	0.4	0.25	0.5
	Levofloxacin	77.6	2	20.4	0.03	>8
	Minocycline	83.6	9.8	6.6	1	8
	Pip-Tazo	96.3	1.3	2.4	1	4
Klebsiella pneumoniae (n=1,148)	Tigecycline	94.3	4.9	0.8	0.5	2
	Amikacin	97.6	1.3	1.1	2	8
	Amox/Clav	80.4	8.4	11.2	2	32
	Cefepime	92.2	1.7	6.1	≤0.5	4
	Ceftazidime	85.5	1.8	12.7	≤8	>32
	Ceftriaxone	86.8	4.3	8.9	≤0.06	32
	Imipenem	97.2	1.1	1.7	0.5	1
	Levofloxacin	88.4	1.3	10.3	0.06	8
	Minocycline	82.3	6.9	10.8	2	16
	Pip-Tazo	90.7	1.8	7.5	2	16
Klebsiella oxytoca (n=233)	Tigecycline	98.3	1.7	0	0.25	1
	Amikacin	98.7	0.4	0.9	2	4
	Amox/Clav	85.8	4.7	9.5	2	16
	Cefepime	95.7	1.3	3	≤0.5	1
	Ceftazidime	93.6	0.8	5.6	≤8	≤8
	Ceftriaxone	91.4	5.2	3.4	≤0.06	8
	Imipenem	99.1	0	0.9	0.25	0.5
	Levofloxacin	93.6	3	3.4	0.03	1
	Minocycline	91.4	6	2.6	1	4
	Pip-Tazo	91	0.8	8.2	1	8
Serratia marcescens (n=534)	Tigecycline	96.8	2.8	0.4	1	2
	Amikacin	99.3	0.1	0.6	2	4
	Amox/Clav	2.8	2.2	95	>32	>32
	Cefepime	96.6	1.1	2.3	≤0.5	1
	Ceftazidime	91.2	2.4	6.4	≤8	≤8
	Ceftriaxone	91.6	3.7	4.7	0.25	8
	Imipenem	98.5	0.4	1.1	0.5	2
	Levofloxacin	95.3	1.3	3.4	0.12	1
	Minocycline	90.4	6.6	3	4	4
	Pip-Tazo	94.9	2.6	2.5	1	8

[a] Breakpoints as defined by NCCLS (M100-S14), 2004. Tigecycline breakpoints defined as: susceptible ≤ 2; intermediate = 4; and resistant ≥ 8

Table 5. In vitro activity of tigecycline and comparative agents against extended-spectrum beta-lactamase producing *Enterobacteriaceae.*

Organism Name	Drug[a]	%SUS	%INT	%RES	MICs (mcg/mL)[1] MIC_{50}	MIC_{90}
Escherichia coli , ESBL (n=47)	Tigecycline	100	0	0	0.25	0.5
	Amikacin	95.7	0	4.3	4	16
	Amox-Clav	23.4	51.1	25.5	16	32
	Cefepime	48.9	14.9	36.2	16	>32
	Ceftazidime	36.2	21.2	42.6	16	>32
	Ceftriaxone	14.9	17	68.1	>64	>64
	Imipenem	100	0	0	0.25	0.5
	Levofloxacin	23.4	2.1	74.5	>8	>8
	Minocycline	68.1	14.9	17	4	16
	Pip-Tazo	89.4	2.1	8.5	4	64
Klebsiella pneumoniae , ESBL (n=135)	Tigecycline	90.4	8.1	1.5	0.5	2
	Amikacin	88.1	5.9	6	8	32
	Amox-Clav	28.1	37.8	34.1	16	>32
	Cefepime	56.3	8.1	35.6	8	>32
	Ceftazidime	17	4.4	78.6	>32	>32
	Ceftriaxone	23.7	25.2	51.1	64	>64
	Imipenem	86.7	8.1	5.2	0.5	8
	Levofloxacin	44.4	2.2	53.4	8	>8
	Minocycline	65.2	8.9	25.9	4	>16
	Pip-Tazo	61.5	7.4	31.1	8	>128
Klebsiella oxytoca , ESBL (n=14)	Tigecycline	85.7	14.3	0	0.5	4
	Amikacin	78.6	7.1	14.3	2	>64
	Amox-Clav	35.7	28.6	35.7	16	32
	Cefepime	50	7.1	42.9	8	>32
	Ceftazidime	28.6	7.1	64.3	>32	>32
	Ceftriaxone	7.1	64.3	28.6	16	>64
	Imipenem	100	0	0	0.5	1
	Levofloxacin	64.3	21.4	14.3	1	>8
	Minocycline	64.3	7.1	28.6	4	16
	Pip-Tazo	64.3	0	35.7	8	>128
All ESBL producers *E. coli*, *K. pneumoniae* and *K. oxytoca* (n=196)	Tigecycline	92.3	6.6	1.1	0.5	2
	Amikacin	89.3	4.6	6.1	8	32
	Amox-Clav	27.6	40.3	32.1	16	>32
	Cefepime	54.1	9	36.2	8	>32
	Ceftazidime	22.4	8.7	68.9	>32	>32
	Ceftriaxone	20.4	26	53.6	64	>64
	Imipenem	90.8	5.6	3.6	0.5	1
	Levofloxacin	40.8	3.6	55.6	8	>8
	Minocycline	65.8	10.2	24	4	>16
	Pip-Tazo	66.4	5.6	28	8	>128

[a] Breakpoints as defined by NCCLS (M100-S14), 2004. Tigecycline breakpoints defined as: susceptible ≤ 2; intermediate = 4; and resistant ≥ 8

Table 6. In vitro activity of tigecycline and comparators against 196 strains of ESBL producing *E. coli*, *K. pneumoniae* and *K. oxytoca* showing frequency distribution and cumulative percent inhibited (%) at each MIC (mcg/ml).

MIC	0.015	0.03	0.06	0.12	0.25	≤0.5	0.5	1	2	4	≤8	8	>8	16	>16	32	>32	64	>64	128	>128
Tigecycline				1	22	41		61	37	19	13		2								
				0.5	11.7	32.7		63.8	82.7	92.3	99		100								
Amikacin							2		26	43	26		40		38		9		1	11	
							1		14.3	36.2	49.5		69.9		89.3		93.9		94.4	100	
Amox-Clav										1	11		42		79		82	31			
										0.5	6.1		27.6		68		96.2	100			
Cefepime						13		14	19	34			26		19		13	58			
						6.6		13.8	23.5	40.8			54.1		63.8		70.4	100			
Ceftazidime													43		17		28	109			
													21.9		22.4		31.1	44.4	100		
Ceftriaxone				1	2		2	2	4	8			25		24	81					
				0.5	1.5		2.6	3.6	5.6	9.7			20.4		33.7		46.4	58.7	100		
Imipenem							89		72	17			11		5	2					
							45.4		82.1	90.8			96.4		99	100					
Levofloxacin	1	8	16	7	7		13	15	13	7			3	1							
	0.5	4.6	12.8	16.3	19.9		26.5	34.2	40.8	44.4			55.1	100							
Minocycline						4		25	42	56			20		25	22					
						2		14.8	36.2	65.8			76		88.8	100					
Pip-Tazo							1	12	42	37			25		17		8	3	9	42	
							0.5	6.6	28.1	46.9			99.7		68.4		72.4	74	78.6	100	

CONCLUSIONS

- Tigecycline inhibited 97% of all *Enterobacteriaceae* tested in vitro at an MIC of 2 mcg/mL.
- Tigecycline's MIC_{90} of 1 mcg/mL was equivalent to imipenem and 8 to 64 fold better than the beta-lactams, beta-lactam/beta-lactamase inhibitor combinations and levofloxacin against all *Enterobacteriaceae* tested.
- Tigecycline demonstrated potent in vitro activity against both ESBL and non-ESBL producing *E. coli*, *K. pneumoniae* and *K. oxytoca*.
- Tigecycline demonstrated potent in vitro activity against both AmpC and non-AmpC producing *Enterobacter* spp. and *S. marcescens*.
- The in vitro activity of tigecycline in this study suggests that tigecycline is a promising compound in the treatment of gram-negative infections caused by selected *Enterobacteriaceae*.