#35E

Tigecycline Evaluation Surveillance Trial (T.E.S.T.) Program - United States In Vitro Antibacterial Activity against Selected Species of Enterococci

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REVISED ABSTRACT

Background: Resistance to glycopeptides in enterococci was first recognized in the late 1980s, and since then has been a major challenge to clinicians and infection control. Tigecycline, a member of a new class of antimicrobials (glycylcyclines), has been shown to have potent expanded broad spectrum activity against most commonly encountered species responsible for community and hospital acquired infections. The T.E.S.T. program determined the in vitro activity of tigecycline compared to vancomycin, linezolid, ampicillin, imipenem, ceftriaxone, levofloxacin, minocycline, penicillin and piperacillin/tazobactam against members of *Enterococcus* spp. collected from 44 hospitals across United States. **Methods:** A total of 525 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 from Dade Behring MicroScan and interpreted according to CLSI guidelines. **Results:** Of 345 *E. faecalis* evaluated, vancomycin resistance was observed in 17 (4.9%) isolates. These isolates were all susceptible to linezolid and tigecycline (using 2 mcg/mL susceptible breakpoint for tigecycline). Tigecycline presented the lowest MIC_{50}/MIC_{90} (0.06/0.12 mcg/ml) among all antimicrobial agents evaluated against *E. faecalis*. As a typical profile of *E. faecalis*, fluoroquinolone (levofloxacin) and tetracycline (minocycline) had limited activities against this species. Among 138 *E. faecium*, 95 (68.8%) were resistant to vancomycin, of which 6 (4.3%) isolates were also resistant to linezolid. Tigecycline also presented the lowest MIC_{50}/MIC_{90} of 0.06/0.12 mcg/ml against all *E. faecium*. **Conclusion:** Tigecycline's in vitro activity was greater than vancomycin, linezolid and levofloxacin against these nosocomial enterococcal strains. The presented data suggest that tigecycline may be an effective therapeutic option against *Enterococcus* spp., including vancomycin-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 and 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 [2-3].

Tigecycline has shown potent activity in animal models infected with selected strains of multi-drug resistant *Enterococcus faecium* and *Enterococcus faecalis* [4, 5] with diverse genotypes van-A, -B and -C [6]. Since current treatment options against vancomycin resistant *Enterococcus* spp. are largely limited to doxycycline, quinupristin/dalfopristin and linezolid, the activity of tigecycline was studied against a large population of enterococci from clinical settings in 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.
- Antimicrobial agents tested with concentrations (expressed in mcg/ml) were: piperacillin/tazobactam (0.25-16); levofloxacin (0.06-32); ceftriaxone (0.03-64); linezolid (0.5-8); minocycline (0.25-8); vancomycin (0.12-32); ampicillin (0.06-16); penicillin (0.06-8); tigecycline (0.008-16); imipenem (0.12-16). MIC interpretive criteria followed published guidelines established by the Clinical and Laboratory Standards Institute (CLSI) where applicable [7]. 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 followed CLSI guidelines using quality contol organism *Enterococcus faecalis* ATCC 29212.
- 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).

ACKNOWLEDGEMENTS

This study was supported by a grant from Wyeth Pharmaceuticals. We gratefully acknowledge contributions to the T.E.S.T. study from the following participating institutions: Laboratory Sciences of Arizona, AZ; Scottsdale Healthcare - Shea, AZ; UCLA Medical Center, CA; Shands Hospital at University of Florida, FL; Jackson Memorial, FL; Bayfront Medical Center, FL; Wellstar Kennestone Hospital, GA; Ochsner Clinic Foundation, LA; LSU HSC - S, LA; University of Maryland Medical Center, MD; University of Michigan Health System, MI; William Beaumont Hospital, MI; New Hanover Regional Medical Center, NC; Wake Forest University Baptist Medical Center, NC; University Hospital - Newark, NJ; The Valley Hospital - Microbiology, NJ; Albany Medical Center Hospital, NY; Montefiore Medical Center, NY; Brookdale Hospital Center, NY; New York Hospital Queens, NY; Columbia Presbyterian Medical Center, NY; Univ. of Rochester Medical Center, NY; Summa Health System, OH; University Hospitals of Cleveland, OH; CompuNet Clinical Laboratories, OH; RML @ SJMC, OK; Memorial Hospital, TN; University of Tennessee Medical Center, TN; Memorial Hermann Hospital, TX; Scott & White Memorial Hospital, TX; LDS Hospital, UT; Hennepin County Medical Center, MN; Stanford University Medical Center, CA; Oregon Medical Laboratories, OR; The Methodist Hospital, TX; Clarian Health Partners, Inc./Methodist Hospital, IN; Charleston Area Medical Center, WV; Marshfield Laboratories, WI; Northside Hospital - Laboratory, GA; Cleveland Clinic Foundation, OH; Inova Fairfax Hospital, VA; Mercy Health Laboratory, PA; Hartford Hospital, CT and Fletcher Allen Health Care, VT

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RESULTS

Table 1. In vitro activity of tigecycline and comparative agents against 138 strains of *Enterococcus faecium*.

Organism Name	Drug[a]	%SUS	%INT	%RES	MICs (mcg/mL) MIC_{50}	MIC_{90}
Enterococcus faecium (n=138)	Tigecycline	100	0	0	0.06	0.12
	Ampicillin	15.2	0	84.8	>16	>16
	Ceftriaxone	na	na	na	>64	>64
	Imipenem	na	na	na	>16	>16
	Levofloxacin	6.5	0.7	92.8	>32	>32
	Linezolid	93.5	1.4	5.1	2	2
	Minocycline	65.9	25.4	8.7	0.5	8
	Pip-Tazo	na	na	na	>16	>16
	Penicillin	10.1	0	89.9	>8	>8
	Vancomycin	29.7	1.4	68.9	>32	>32

[a]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 2. In vitro activity of tigecycline and comparative agents against 95 strains of vancomycin-resistant *Enterococcus faecium*.

Organism Name	Drug[a]	%SUS	%INT	%RES	MICs (mcg/mL) MIC_{50}	MIC_{90}
Enterococcus faecium (n=95)	Tigecycline	100	0	0	0.06	0.06
	Ampicillin	2.1	0	97.9	>16	>16
	Ceftriaxone	na	na	na	>64	>64
	Imipenem	na	na	na	>16	>16
	Levofloxacin	0	0	100	>32	>32
	Linezolid	93.7	2.1	4.2	2	2
	Minocycline	62.1	29.5	8.4	4	8
	Pip-Tazo	na	na	na	>16	>16
	Penicillin	0	0	100	>8	>8
	Vancomycin	0	0	100	>32	>32

[a]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 3. Frequency distribution (n) and cumulative percent inhibition (%) at each MIC (mcg/ml) for tigecycline and comparative agents against 138 *Enterococcus faecium*.

MIC	0.015	0.03	<0.06	0.06	0.12	<0.25	0.25	0.5	1	2	4	8	>8	16	>16	32	>32	64	>64
Tigecycline	2	61		57	17		1												
	1.4	45.7		87	99.3		100												
Ampicillin			1						1	11	4	1	3		1	116			
			0.7						1.4	9.4	12.3	13	15.2		15.9	100			
Ceftriaxone											2				1		2		6	127
											1.4				2.2		3.6		8	100
Imipenem									2	4	5	3	1			123			
									1.4	4.3	8	10.1	10.9			100			
Levofloxacin									2	4	3	1	2		3		16	107	
									1.4	4.3	6.5	7.2	8.7		10.9		22.5	100	
Linezolid										44	85	2	3	4					
										31.9	93.5	94.9	97.1	100					
Minocycline						63		6			2	20	35	12					
						45.7		50			51.4	65.9	91.3	100					
Penicillin										6	8			124					
										4.3	10.1			100					
Pip-Tazo									1	5	1	3		4	124				
									0.7	4.3	5.1	7.2		10.1	100				
Vancomycin							1	18	21	1		1		1		2	93		
							0.7	13.8	29	29.7		30.4		31.2		32.6	100		

Table 5. In vitro activity of tigecycline and comparative agents against 345 strains of *Enterococcus faecalis*.

Organism Name	Drug[a]	%SUS	%INT	%RES	MICs (mcg/mL) MIC_{50}	MIC_{90}
Enterococcus faecalis (n=345)	Tigecycline	100	0	0	0.06	0.12
	Ampicillin	96.5	0	3.5	1	2
	Ceftriaxone	na	na	na	>64	>64
	Imipenem	na	na	na	1	2
	Levofloxacin	52.5	1.1	46.4	2	>32
	Linezolid	98.6	0.8	0.6	2	2
	Minocycline	39.1	46.7	14.2	8	>8
	Pip-Tazo	na	na	na	2	4
	Penicillin	95.7	0	4.3	2	4
	Vancomycin	94.2	0.9	4.9	1	2

[a]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 6. In vitro activity of tigecycline and comparative agents against 17 strains of vancomycin-resistant *Enterococcus faecalis*.

Organism Name	Drug[a]	%SUS	%INT	%RES	MICs (mcg/mL) MIC_{50}	MIC_{90}
Enterococcus faecalis (n=17)	Tigecycline	100	0	0	0.06	0.12
	Ampicillin	58.8	0	41.2	2	>16
	Ceftriaxone	na	na	na	>64	>64
	Imipenem	na	na	na	4	>16
	Levofloxacin	5.9	0	94.1	>32	>32
	Linezolid	100	0	0	2	2
	Minocycline	41.1	47.1	11.8	8	>8
	Pip-Tazo	na	na	na	4	>16
	Penicillin	52.9	0	47.1	8	>8
	Vancomycin	0	0	100	>32	>32

[a]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. Frequency distribution (n) and cumulative percent inhibition (%) at each MIC (mcg/ml) for tigecycline and comparative agents against 95 strains of vancomycin resistant *Enterococcus faecium*.

MIC	0.015	0.03	0.06	0.12	<0.25	0.5	1	2	4	8	>8	16	>16	32	>32	>64
Tigecycline	1	44	42	8												
	1.1	47.4	91.6	100												
Ampicillin							1		1		1	92				
							1.1		2.1		3.2	100				
Ceftriaxone																95
																100
Imipenem									1		94					
									1.1		100					
Levofloxacin										2		13	80			
										2.1		15.8	100			
Linezolid							27	62	2	1	3					
							28.4	93.7	95.8	96.8	100					
Minocycline					43	1		2	13	28	8					
					45.3	46.3		48.4	62.1	91.6	100					
Penicillin											95					
											100					
Pip-Tazo												95				
												100				
Vancomycin														2	93	
														2.1	100	

Table 7. Frequency distribution (n) and cumulative percent inhibition (%) at each MIC (mcg/ml) for tigecycline and comparative agents against 345 *Enterococcus faecalis*.

	0.015	0.03	<0.06	0.06	0.12	<0.25	0.25	<0.5	0.5	1	2	4	8	>8	16	>16	32	>32	64	>64
Tigecycline	2	18		159	148		17		1											
	0.6	5.8		51.9	94.8		99.7		100											
Ampicillin					1		2		95	209	22	2	2		3	9				
					0.3		0.9		28.4	89	95.4	95.9	96.5		97.4	100				
Ceftriaxone										1	1		2		13		24		45	259
										0.3	0.6		1.2		4.9		11.9		24.9	100
Imipenem							6		117	187	19	2	1		2	11				
							1.7		35.7	89.9	95.4	95.9	96.2		96.8	100				
Levofloxacin			1						52	113	15	4	3		24		53	80		
			0.3						15.4	48.1	52.5	53.6	54.5		61.4		76.8	100		
Linezolid								7		122	211	3	1	1						
								2		37.4	98.6	99.4	99.7	100						
Minocycline						80			8	3	9	35	161	49						
						23.2			25.5	26.4	29	39.1	85.8	100						
Penicillin									3	27	234	61	5	15						
									0.9	8.7	76.5	94.2	95.7	100						
Pip-Tazo									3	34	214	68	10		1	15				
									0.9	10.7	72.8	92.5	95.4		95.7	100				
Vancomycin									26	219	79	1	3				3	14		
									7.5	71	93.9	94.2	95.1				95.9	100		

Table 8. In vitro activity of tigecycline and comparative agents against 17 strains of vancomycin-resistant *Enterococcus faecalis*.

	0.03	0.06	<0.12	<0.25	0.25	<0.5	0.5	1	2	4	8	>8	16	>16	32	>32	64	>64
Tigecycline	3	8	5		1													
	17.6	64.7	94.1		100													
Ampicillin						3	5	1	1				7					
						17.6	47.1	52.9	58.8				100					
Ceftriaxone																	1	16
																	5.9	100
Imipenem						4	3	1	1			1	7					
						23.5	41.2	47.1	52.9			58.8	100					
Levofloxacin								1								7	9	
								5.9								47.1	100	
Linezolid				1		5	11											
				5.9		35.3	100											
Minocycline			3		1		2	1	8	2								
			17.6		23.5		35.3	41.2	88.2	100								
Penicillin					1	4	3	1	8									
					5.9	29.4	47.1	52.9	100									
Pip-Tazo					1	7	1						8					
					5.9	47.1	52.9						100					
Vancomycin															3	14		
															17.6	100		

CONCLUSIONS

- Tigecycline had the lowest MIC_{90}, 0.12 mcg/mL, of all comparative agents against all study strains of *Enterococcus faecium* and *Enterococcus faecalis*.
- Tigecycline MIC_{90}s were more than 16 fold lower than linezolid, minocycline or levofloxacin against vancomycin-resistant *Enterococcus faecium* and *Enterococcus faecalis*.
- Tigecycline exhibits potent in vitro activity against *Enterococcus faecium* and *Enterococcus faecalis* regardless of vancomycin phenotype.