

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

S. Bouchillon¹, T. Stevens¹, B. Johnson¹, J. Johnson¹, D. Hoban¹, A. Hsiung¹, M. Hackel¹, M. Person¹, M. Dowzicky²

¹International Health Management Associates, Schaumburg, IL, USA

²Wyeth Pharmaceuticals, Collegeville, PA, USA

IHMA, Inc.
2122 Palmer Dr.
Schaumburg, IL 60173
Tel: (847) 303-5003
Fax: (847) 303-5601
www.ihmainc.com

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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 63 hospitals in 15 countries. **Methods:** A total of 816 clinical isolates of *Enterococcus* spp. 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 559 *E. faecalis* evaluated, resistance to vancomycin was observed in 22 (3.9%) isolates. These isolates were all susceptible to tigecycline (using 2 mcg/mL susceptible breakpoint for tigecycline). Tigecycline presented the lowest MIC₅₀/MIC₉₀ (0.12/0.12 mcg/ml) among all antimicrobial agents evaluated. Among 211 *E. faecium*, 98 (46.4%) were resistant to vancomycin, of which seven isolates also showed some degree of resistance to linezolid. Tigecycline presented the lowest MIC₅₀/MIC₉₀ of 0.06/0.12 mcg/ml against VRE *E. faecium*. **Conclusion:** Tigecycline's in vitro activity was greater than vancomycin, linezolid and levofloxacin against these enterococcal nosocomial pathogens. The presented data suggest that tigecycline may be an effective and reliable 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 prospectively studied against a large geographically diverse population of enterococci in clinical settings.

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.
- 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.
- Quality control followed CLSI guidelines using quality control 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).

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Results are shown in the following tables.

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 211 strains of *Enterococcus faecium*.

Organism Name	Drug ¹	MICs (mcg/mL)					
		%SUS	%INT	%RES	MIC ₅₀	MIC ₉₀	
<i>Enterococcus faecium</i> (n=211)	Tigecycline	100	0	0	0.06	0.12	
	Ampicillin	20.9	0	79.1	>16	>16	
	Ceftriaxone	ra	ra	ra	>64	>64	
	Imipenem	ra	ra	ra	>16	>16	
	Levofloxacin	15.6	14	83	>32	>32	
	Linezolid	94.3	24	33	2	2	
	Minocycline	67.3	20.9	11.8	0.5	0.8	
	Pip-Tazo	ra	ra	ra	>16	>16	
	Penicillin	15.2	0	84.8	>8	>8	
	Vancomycin	52.4	0.9	46.7	1	>2	

¹ Breakpoints as defined by NCCLS where applicable (M100-S14), 2004. na = not applicable. Tigecycline breakpoints defined as: susceptible ≤2; intermediate = 4; and resistant ≥8

RESULTS

Table 3. In vitro activity of tigecycline and comparative agents against 98 strains of vancomycin resistant *Enterococcus faecium*.

Organism Name	Drug ¹	MICs (mcg/mL)					
		%SUS	%INT	%RES	MIC ₅₀	MIC ₉₀	
<i>Enterococcus faecium</i> VRE (n=98)	Tigecycline	100	0	0	0.06	0.06	
	Ampicillin	2	0	98	>16	>16	
	Ceftriaxone	na	na	na	>64	>64	
	Imipenem	na	na	na	>16	>16	
	Levofloxacin	1	0	99	>32	>32	
	Linezolid	92.9	3	4.1	2	2	
	Minocycline	62.2	28.6	9.2	4	8	
	Pip-Tazo	ra	ra	ra	>16	>16	
	Penicillin	0	0	100	>8	>8	
	Vancomycin	0	0	100	>32	>32	

¹ 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 211 *Enterococcus faecium*.

Organism Name	Drug ¹	MICs (mcg/mL)										
		%SUS	%INT	%RES	MIC ₅₀	MIC ₉₀						
<i>Enterococcus faecalis</i> (n=559)	Tigecycline	100	0	0	0.12	0.12						
	Ampicillin	97.3	0	2.7	1	2						
	Ceftriaxone	na	na	na	>64	>64						
	Imipenem	na	na	na	1	2						
	Levofloxacin	57.4	1.1	41.5	1	>32						
	Linezolid	97.9	1.6	0.5	2	2						
	Minocycline	39.6	44.7	15.7	8	>8						
	Pip-Tazo	na	na	na	2	8						
	Penicillin	95.9	0	4.1	2	4						
	Vancomycin	95.5	0.5	4	1	2						

¹ 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 5. Frequency distribution (n) and cumulative percent inhibition (%) at each MIC (mcg/ml) for tigecycline and comparative agents against 98 strains of vancomycin resistant *Enterococcus faecium*.

Organism Name	Drug ¹	MICs (mcg/mL)										
		%SUS	%INT	%RES	MIC ₅₀	MIC ₉₀						
<i>Enterococcus faecalis</i> VRE (n=98)	Tigecycline	100	0	0	0.06	0.12						
	Ampicillin	63.6	0	36.4	1	>16						
	Ceftriaxone	na	na	na	>64	>64						
	Imipenem	na	na	na	1	>16						
	Levofloxacin	4.5	0	95.5	32	>32						
	Linezolid	95.5	0	4.5	2	2						
	Minocycline	45.5	40.9	13.6	8	>8						
	Pip-Tazo	na	na	na	2	>16						
	Penicillin	59.1	0	40.9	4	>8						
	Vancomycin	0	0	100	>32	>32						

Table 6. In vitro activity of tigecycline and comparative agents against 559 strains of *Enterococcus faecalis*.

Organism Name	Drug ¹	MICs (mcg/mL)					
		%SUS	%INT	%RES	MIC ₅₀	MIC ₉₀	
<i>Enterococcus faecalis</i> (n=559)	Tigecycline	100	0	0	0.12	0.12	
	Ampicillin	97.3	0	2.7	1	2	
	Ceftriaxone	na	na	na	>64	>64	
	Imipenem	na	na	na	1	2	
	Levofloxacin	57.4	1.1	41.5	1	>32	
	Linezolid	97.9	1.6	0.5	2	2	
	Minocycline	39.6	44.7	15.7	8	>8	
	Pip-Tazo	na	na	na	2	8	
	Penicillin	95.9	0	4.1	2	4	
	Vancomycin	95.5	0.5	4	1	2	

¹ 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 7. In vitro activity of tigecycline and comparative agents against 22 strains of vancomycin-resistant *Enterococcus faecalis*.

Organism Name	Drug ¹	MICs (mcg/mL)					
		%SUS	%INT	%RES	MIC ₅₀	MIC ₉₀	
<i>Enterococcus faecalis</i> VRE (n=22)	Tigecycline	100	0	0	0.06	0.12	
	Ampicillin	63.6	0	36.4	1	>16	
	Ceftriaxone	na	na	na	>64	>64	
	Imipenem	na	na	na	1	>16	
	Levofloxacin	4.5	0	95.5	32	>32	
	Linezolid	95.5	0	4.5	2	2	
	Minocycline	45.5	40.9	13.6	8	>8	
	Pip-Tazo	na	na	na	2	>16	
	Penicillin	59.1	0	40.9	4	>8	
	Vancomycin	0	0	100	>32	>32	

¹ 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 8. Frequency distribution (n) and cumulative percent inhibition (%) at each MIC (mcg/ml) for tigecycline and comparative agents against 559 *Enterococcus faecalis*.

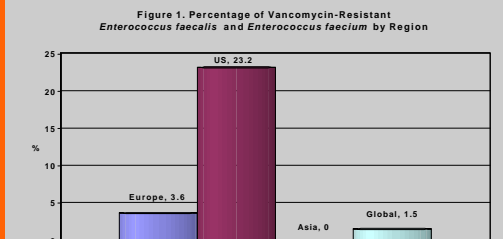
Organism Name	Drug ¹	MICs (mcg/mL)										
		%SUS	%INT	%RES	MIC ₅₀	MIC ₉₀						
<i>Enterococcus faecalis</i> (n=559)	Tigecycline	100	0	0	0.12	0.12						
	Ampicillin	97.3	0	2.7	1	2						
	Ceftriaxone	na	na	na	>64	>64						
	Imipenem	na	na	na	1	2						
	Levofloxacin	57.4	1.1	41.5	1	>32						
	Linezolid	97.9	1.6	0.5	2	2						
	Minocycline	39.6	44.7	15.7	8	>8						
	Pip-Tazo	na	na	na	2	8						
	Penicillin	95.9	0	4.1	2	4						
	Vancomycin	95.5	0.5	4	1	2						

¹ 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 9. In vitro activity of tigecycline and comparative agents against 22 strains of vancomycin-resistant *Enterococcus faecalis*.

Organism Name	Drug ¹	MICs (mcg/mL)					
		%SUS	%INT	%RES	MIC ₅₀	MIC ₉₀	
<i>Enterococcus faecalis</i> VRE (n=22)	Tigecycline	100	0	0	0.06	0.12	
	Ampicillin	63.6	0	36.4	1	>16	
	Ceftriaxone	na	na	na	>64	>64	
	Imipenem	na	na	na	1	>16	
	Levofloxacin	4.5	0	95.5	32	>32	
	Linezolid	95.5	0	4.5	2	2	
	Minocycline	45.5	40.9	13.6	8	>8	
	Pip-Tazo	na	na	na	2	>16	
	Penicillin	59.1	0	40.9	4	>8	
	Vancomycin	0	0	100	>32	>32	

Figure 1. Percentage of Vancomycin-Resistant *Enterococcus faecalis* and *Enterococcus faecium* by Region



CONCLUSIONS

- Tigecycline had the lowest MIC₉₀, 0.12 mcg/mL, of all comparative agents against both *Enterococcus faecium* and *Enterococcus faecalis* regardless of vancomycin phenotype.
- Tigecycline MIC₉₀s were several folds lower than linezolid, minocycline and 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.