

Tigecycline Evaluation Surveillance Trial (T.E.S.T.) Program - Antibacterial Activity Against Enterococcus species from Asia and the Pacific Rim - 2008

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Revised Abstract

Objectives: Resistance to β -lactams and glycopeptides in enterococci was first recognized in the late 1980s, and since then has been a major challenge to clinicians and infection control. Tigecycline, the representative member of a new class of antimicrobials, glycyclines, has been shown to have potent activity against most commonly encountered species responsible for community and hospital 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 selected *Enterococcus* species collected from hospitals across Asia and the Pacific Rim. **Methods:** A total of 852 clinical isolates were identified to the species level at each participating site and confirmed by the central laboratory. Isolates were collected throughout 2004-2008. Minimum Inhibitory Concentration (MICs) were determined by the local laboratory using broth microdilution panels and interpreted according to CLSI guidelines. **Results:** 66/769 (8.6%) (*E. faecalis* and *E. faecium*) vancomycin resistance strains were observed in the isolates tested. Overall, tigecycline presented the lowest MIC₅₀/MIC₉₀ (0.12/0.25 mcg/mL) of all antimicrobial agents evaluated. Levofloxacin and minocycline had limited activities against *E. faecalis*. A high level of resistance to levofloxacin and minocycline was observed in *E. faecium* with non-susceptibility rates of 93.4% and 23.7%, respectively. Tigecycline presented the lowest MIC₅₀/MIC₉₀ of 0.06/0.12 mcg/mL against this species. **Conclusions:** Tigecycline's low MIC₅₀/MIC₉₀ values suggest that tigecycline may be an effective and reliable therapeutic option against nosocomial infections of enterococci.

Introduction

Tigecycline is a novel antimicrobial with an expanded broad-spectrum of activity from a new class of compounds, glycyclines. Tigecycline inhibits protein synthesis by binding to the 30S ribosomal subunit and although it is perceived to be bacteriostatic, it 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 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 2008 from 75 study centers in Australia, China, Hong Kong, India, Indonesia, Korea, Pakistan, Philippines, Singapore, and Taiwan.
- ❖ Antimicrobial agents tested with concentrations (expressed in mcg/ml) were: 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); and tigecycline (0.008-16). MIC interpretive criteria followed published guidelines established by the Clinical and Laboratory Standards Institute (CLSI) where applicable [7]. Tigecycline breakpoints were approved by United States Federal Drug Administration (FDA) as susceptible ≤ 0.25 mcg/ml for vancomycin-susceptible *E. faecalis* only [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 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

Results are shown in the following tables.

Table 1. In vitro activity of tigecycline and comparative agents against 852 strains of enterococci.

Organism	Drug	mcg/ml		%Sus	%Int	%Res
		MIC ₅₀	MIC ₉₀			
<i>Enterococcus</i> spp ^a (n=852)	Tigecycline	0.12	0.25	99.9	0	0.1
	Ampicillin	1	>16	70.9	0	29.1
	Ceftriaxone	>64	>64	3.3	0	96.7
	Levofloxacin	16	>32	38.3	0	61.7
	Linezolid	2	2	100	0	0
	Minocycline	8	>8	43.9	32.5	23.6
	Penicillin	4	>8	70.4	0	29.6
	Vancomycin	1	4	91.4	0.7	7.9
<i>E. faecalis</i> (n=511)	Tigecycline	0.12	0.25	100	0	0
	Ampicillin	1	2	100	0	0
	Ceftriaxone	>64	>64	3.5	0	96.5
	Levofloxacin	1	>32	56	0	44
	Linezolid	2	2	100	0	0
	Minocycline	8	>8	28.4	41.3	30.3
	Penicillin	2	4	99.4	0	0.6
	Vancomycin	1	2	99	0.4	0.6
<i>E. faecium</i> (n=258)	Tigecycline	0.06	0.12	100	0	0
	Ampicillin	>16	>16	14	0	86
	Ceftriaxone	>64	>64	2.7	0	97.3
	Levofloxacin	>32	>32	6.6	0	93.4
	Linezolid	2	2	100	0	0
	Minocycline	≤ 0.25	8	76.4	14	9.7
	Penicillin	>8	>8	16.7	0	83.3
	Vancomycin	1	>32	75.2	0.4	24.4

^a Interpretive criteria as defined by CLSI, M100-S18 (2008), where applicable. Tigecycline FDA breakpoints for enterococci are approved for vancomycin-susceptible *E. faecalis* only; susceptibilities for all other enterococci are entered for comparison purposes only [10].

Table 2. In vitro activity of tigecycline and comparative agents against 66 strains of vancomycin-resistant enterococci (VRE).

Organism	Drug	mcg/ml		%Sus	%Int	%Res
		MIC ₅₀	MIC ₉₀			
All VRE's (n=66)	Tigecycline	0.06	0.25	100	0	0
	Ampicillin	>16	>16	4.5	0	95.5
	Ceftriaxone	>64	>64	0	0	100
	Levofloxacin	>32	>32	0	0	100
	Linezolid	2	2	100	0	0
	Minocycline	≤ 0.25	>8	80.3	9.1	10.6
	Penicillin	>8	>8	7.6	0	92.4
	Vancomycin	>32	>32	0	0	100

^b Breakpoints as defined by CLSI where applicable (M100-S18), 2008; na = not applicable. Tigecycline breakpoints are defined by FDA (Tygacil[®], 2005), as susceptible ≤ 0.25 mcg/ml for vancomycin-susceptible *E. faecalis* only; are applied to all enterococci for comparative purposes only.

Table 3. Frequency distribution (n) and cumulative percent inhibition (%) at each MIC (mcg/ml) for tigecycline and comparative agents against 852 *Enterococcus* species.

N	MIC (mcg/ml)													
	≤ 0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	≥ 64
Tigecycline	3	4	88	234	366	156	1							
	0.4	0.8	11.2	38.6	81.6	99.9	100.0							
Ampicillin				2	6	10	98	365	91	19	13	21	227	
				0.2	0.9	2.1	13.6	56.5	67.1	69.4	70.9	73.4	100.0	
Ceftriaxone				3	1	1	8	5	10	5	12	14	25	28
				0.4	0.5	0.6	1.5	2.1	3.3	3.9	5.3	6.9	9.9	13.1
Levofloxacin				1	1	5	83	236	53	20	20	42	152	239
				0.1	0.2	0.8	10.6	38.3	44.5	46.8	49.2	54.1	71.9	100.0
Linezolid							19	287	507	39				
							2.2	35.9	95.4	100.0				
Minocycline						240	20	10	32	72	277	201		
						28.2	30.5	31.7	35.4	43.9	76.4	100.0		
Penicillin				4	1	4	20	40	262	205	64	252		
				0.5	0.6	1.1	3.4	8.1	38.8	62.9	70.4	100.0		
Vancomycin						6	18	110	453	163	29	6	1	59
						0.7	2.8	15.7	68.9	88.0	91.4	92.1	92.3	93.1

Conclusions

- ❖ Tigecycline had the lowest MIC₉₀ of all comparative study drugs against both *Enterococcus faecalis* (0.25 mcg/ml) and *Enterococcus faecium* (0.12 mcg/ml).
- ❖ Vancomycin-resistant enterococci rate was a fairly low 8.6% for the Asia/Pacific Rim region.
- ❖ Tigecycline's MIC₉₀ of 0.25 mcg/mL ranged from 8-fold to more 16-fold lower than vancomycin, and linezolid and 64-to 128-fold lower than ampicillin, minocycline and levofloxacin against all strains of enterococci.
- ❖ Tigecycline exhibits potent in vitro activity against *Enterococcus faecium* and *Enterococcus faecalis* but continued testing is warranted to document tigecycline activity against vancomycin-resistant strains in this geographic region.