

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 MIC₅₀/MIC₉₀ (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 MIC₅₀/MIC₉₀ 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 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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REFERENCES

- Sum, P.E. and P. Petersen, Synthesis and structure-activity relationship of novel glycylcycline derivatives leading to the discovery of GAR-936. *Bioorg Med Chem Lett*, 1999, 9(10): p. 1459-62.
- Abbanat, D., M. Macielag, and K. Bush, Novel antibacterial agents for the treatment of serious Gram-positive infections. *Expert Opin Investig Drugs*, 2003, 12(3): p. 379-99.
- Gales, A.C. and R.N. Jones, Antimicrobial activity and spectrum of the new glycylcycline, GAR-936 tested against 1,203 recent clinical bacterial isolates. *Diagn Microbiol Infect Dis*, 2000, 36(1): p. 19-36.
- Mercier, R.C., C. Kennedy, and C. Meadows, Antimicrobial activity of tigecycline (GAR-936) against *Enterococcus faecium* and *Staphylococcus aureus* used alone and in combination. *Pharmacotherapy*, 2002, 22(12): p. 1517-23.
- Murphy, T.M., et al., Therapeutic efficacy of GAR-936, a novel glycylcycline, in a rat model of experimental endocarditis. *Antimicrob Agents Chemother*, 2000, 44(11): p. 3022-7.
- Patel, R., et al., In vitro activity of GAR-936 against vancomycin-resistant enterococci, methicillin-resistant *Staphylococcus aureus* and penicillin-resistant *Streptococcus pneumoniae*. *Diagn Microbiol Infect Dis*, 2000, 38(3): p. 177-9.
- National Committee for Clinical Laboratory Standards (NCCLS). Performance Standards for Antimicrobial Susceptibility Testing; Fourteenth Informational Supplement. NCCLS document M100-S14. Wayne, PA, 2004.

RESULTS

Results are shown in the following tables.

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
<i>Enterococcus faecium</i> (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

^aBreakpoints 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
<i>Enterococcus faecium</i> (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

^aBreakpoints 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	MICs (mcg/mL)																			
	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															
Ampicillin	1.4	45.7	87	99.3	100			1	11	4	1	3		1	116					
Ceftriaxone										2				1	2			6	127	
Imipenem										1.4				2	2			3.6	8	100
Levofloxacin										2	4	5	3	1					123	
Linezolid										1.4	4.3	6.5	7.2	8.7					10.9	16
Minocycline										44	85	2	3	4					100	107
Penicillin										63	6	2	20	35	12					107
Pip-Tazo										45.7	50		51.4	65.9	91.3	100				100
Vancomycin																				124
																				100
																				124
																				100
																				93
																				100
																				93
																				100

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	MICs (mcg/mL)																			
	0.015	0.03	0.06	0.12	<0.25	0.5	1	2	4	8	>8	16	>16	32	>32	64	>64			
Tigecycline	1	44	42	8																
Ampicillin	1.1	47.4	91.6	100																
Ceftriaxone																				95
Imipenem																				100
Levofloxacin																				95
Linezolid																				80
Minocycline																				100
Penicillin																				100
Pip-Tazo																				95
Vancomycin																				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
<i>Enterococcus faecalis</i> (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

^aBreakpoints 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
<i>Enterococcus faecalis</i> (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

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

MIC	MICs (mcg/mL)																			
	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														
Ampicillin	0.6	5.8	51.9	94.8	99.7	100														
Ceftriaxone																				95
Imipenem																				100
Levofloxacin																				100
Linezolid																				80
Minocycline																				100
Penicillin																				