

Tigecycline In Vitro Activity against Staphylococcus aureus and Enterococcus Strains Resistant To Other Drugs In United States, 2004 - 2006

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J. Johnson¹, D. Hoban¹, B. Johnson¹, R. Badal¹, S. Bouchillon¹, T. Stevens¹, 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

REVISED ABSTRACT

Background: Tigecycline (TIG), a member of a new class of antimicrobials (glycylcyclines), has been shown to have potent activity against many Gram-positive and -negative organisms. The T.E.S.T. program determined the in vitro activity of TIG against *S. aureus* and *enterococci* resistant to 10 commonly prescribed antimicrobials: amoxicillin-clavulanic acid (AUG), piperacillin-tazobactam (PT), levofloxacin (LVX), ceftriaxone (CAX), linezolid (LZD), minocycline (MIN), vancomycin (VAN), ampicillin (AMP), penicillin (P) and imipenem (IMP). Study strains were collected from hospitals in the United States throughout 2004-2006.

Methods: A total of 3,356 clinical isolates (1,271 *enterococci*; 2,085 *S. aureus*) from 99 labs in the United States were identified to the species level at each participating site and confirmed by the central laboratory. Minimum Inhibitory Concentrations (MICs) were determined by the local laboratory using broth microdilution panels. Antimicrobial resistance was interpreted according to CLSI breakpoints with TIG susceptible breakpoints defined as ≤ 0.25 mcg/ml for *enterococci* and ≤ 0.5 mcg/ml for *S. aureus*.

Results: 355/1271 (28%) *enterococci* and 231/2085 (11%) *S. aureus* (including MR + MS strains) were resistant to two or more drug classes. Among the multi-drug resistant (MDR) *enterococci*, resistance rates were LVX 99%, P 88%, AMP 85%, VAN 76%, MIN 11%, and LZD 0%. Resistant rates for MDR *S. aureus* were P 100%, AMP 96%, AUG 59%, LVX 98%, PT 57%, CAX 57%, IMP 59%, MIN 0.4%, LZD 0% and VAN 0%. TIG inhibited 99.4% of the MDR *enterococci* and 94% of the MDR *S. aureus*. MIC₉₀ values for TIG were 0.06 and 0.12 mcg/mL for *enterococci* and *S. aureus*, respectively, against strains with or without resistant determinants.

Conclusion: TIG retained potent activity against *S. aureus* and *enterococci*, inhibiting 99% of all strains at the respective breakpoints. TIG should prove to be a useful empiric agent against these gram-positive pathogens whether they are determined to be resistant to other drugs or not.

INTRODUCTION

Tigecycline is a novel antimicrobial with expanded broad-spectrum activity from a new class of compounds, the 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]. Tigecycline has shown to be a highly effective against multi-resistant *Acinetobacter* spp., particularly *A. baumannii* that are commonly associated with serious nosocomial infections. Similar activity has been observed against *Enterobacteriaceae*, even extended-spectrum beta-lactamase (ESBL) and AmpC producing strains [10]. Tigecycline has demonstrated MIC₉₀ values of ≤ 0.5 mcg/mL against methicillin-resistant *Staphylococcus aureus* (MRSA) and other Gram-positive organisms [2, 4-6]. Tigecycline has shown potent activity against 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].

This study was designed to better define the in vitro activity of tigecycline against *S. aureus* and *Enterococcus* spp isolates

and multi-drug resistant phenotypes collected from study centers representing a diverse population of clinical pathogens.

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.
- 2,085 clinical isolates from 99 centers in the United States were collected and tested from January 2004 to January 2006.
- Custom broth microdilution panels were supplied by MicroScan (Dade MicroScan, Sacramento, CA, USA) with the following antimicrobial agents and concentrations (expressed in mcg/ml): amoxicillin/clavulanic acid (0.12-32); piperacillin/tazobactam (0.06-128); levofloxacin (0.008-8); ceftriaxone (0.06-64); cefepime (0.5-32); ampicillin (0.5-32); amikacin (0.5-64); minocycline (0.5-16); ceftazidime (8-32); tigecycline (0.008-16); and imipenem (0.06-16). MIC interpretive criteria followed published guidelines established by the Clinical and Laboratory Standards Institute (CLSI) where applicable [12]. Tigecycline tentative breakpoints (in units of mcg/mL) are defined susceptible ≤ 0.25 and ≤ 0.5 for *E. faecalis* and *S. aureus*, respectively, in the FDA package insert (Tygacil[®], 2005)[13].
- MIC interpretive criteria followed published guidelines established by the CLSI where applicable [12].
- Isolates were identified to genus and species by the local laboratory. Each site tested the isolates using broth microdilution.
- Quality control of broth microdilution panels followed manufacture's and NCCLS guidelines using the following ATCC strains: *Staphylococcus aureus* ATCC 29213; *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, USA).

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RESULTS

Results of the study are presented in the following tables.

Table 1. In vitro Susceptibilities of Tigecycline and Comparators against 3,356 *Enterococci* and *Staphylococcus aureus* from a Multi-center, Multi-national Population.

Organism	Drug	Percent (%) Susceptible*	Percent (%) Intermediate	Percent (%) Resistant	MIC (mcg/mL)	
					MIC ₅₀	MIC ₉₀
<i>Enterococcus</i> Spp. (n=1271)	Tigecycline	99.5	0	0.5	0.06	0.12
	Ampicillin	75.8	0	24.2	1	>16
	Levofloxacin	44.1	1.2	54.7	16	>32
	Linezolid	97.7	2.3	0	2	2
	Minocycline	52.4	38.5	9.1	4	8
	Penicillin	75.1	0	24.9	2	>8
<i>S. aureus</i> (n=2085)	Vancomycin	77.6	0.9	21.5	1	>32
	Tigecycline	98.8	0	1.2	0.12	0.25
	AmoxClav	63	0	37	2	>8
	Ampicillin	8.1	0	91.9	16	>16
	Ceftriaxone	49.4	30.5	20.1	16	>64
	Imipenem	91.4	1.9	6.8	0.25	4
	Levofloxacin	51.5	2.5	46	0.5	>32
	Linezolid	100	0	0	2	4
	Minocycline	99.2	0.7	0	≤ 0.25	0.5
	Penicillin	6.7	0	93.3	>8	>8
PipTazo	66.9	0	33.1	4	>16	
Vancomycin	100	0	0	1	1	

*Interpretive criteria are defined by CLSI document M100-S15 (2005); Tigecycline breakpoints defined by FDA package insert (Tygacil[®], 2005) with susceptible ≤ 0.5 mcg/mL for *S. aureus* and ≤ 0.25 mcg/mL for *E. faecalis*. Tigecycline breakpoints for *E. faecalis* have been expanded to include all *enterococci* for comparison purposes only.

Table 2. In vitro Susceptibilities of Tigecycline and Comparators against 586 Multi-drug Resistant *Enterococci* and *Staphylococcus aureus*.*

Organism	Drug	Percent (%) Susceptible**	Percent (%) Intermediate	Percent (%) Resistant	MIC (mcg/mL)	
					MIC ₅₀	MIC ₉₀
Multi-drug Resistant <i>Enterococcus</i> spp (n=355)	Tigecycline	99.4	0	0.6	0.06	0.12
	Ampicillin	14.6	0	85.4	>16	>16
	Levofloxacin	0	0.3	99.7	>32	>32
	Linezolid	97.2	2.8	0	2	2
	Minocycline	65.4	23.9	10.7	2	>8
	Penicillin	12.1	0	87.9	>8	>8
Multi-drug Resistant <i>S. aureus</i> (n=231)	Vancomycin	23.9	0.3	75.8	>32	>32
	Tigecycline	93.5	0	6.5	0.12	0.5
	AmoxClav	40.7	0	59.3	>8	>8
	Ampicillin	3.9	0	96.1	>16	>16
	Ceftriaxone	26.8	16	57.1	>64	>64
	Imipenem	40.7	0	59.3	16	>16
	Levofloxacin	2.2	0	97.8	16	>32
	Linezolid	100	0	0	2	4
	Minocycline	92.3	7.3	0.4	≤ 0.25	2
	Penicillin	0	0	100	>8	>8
PipTazo	43.3	0	56.7	>16	>16	
Vancomycin	100	0	0	1	1	

*Multi-drug resistant is defined as any strain that is resistant to two or more drug classes; *S. aureus* isolates contain methicillin-susceptible and methicillin-resistant strains.

**Interpretive criteria are defined by CLSI document M100-S15 (2005); Tigecycline breakpoints defined by FDA package insert (Tygacil[®], 2005) with susceptible ≤ 0.5 mcg/mL for *S. aureus* and ≤ 0.25 mcg/mL for *E. faecalis*. Tigecycline breakpoints for *E. faecalis* have been expanded to include all *enterococci* for comparison purposes only.

CONCLUSIONS

- Tigecycline had the lowest MIC₉₀, 0.12 mcg/mL, of all comparative agents against all *Enterococcus* species.
- Tigecycline MIC₉₀ values were at least 16- to 512-fold lower than linezolid, minocycline, levofloxacin and vancomycin against all *enterococci* without regard to resistant constituents.
- Tigecycline exhibits activity in vitro comparable to linezolid against multi-drug resistant enterococci and *S. aureus*.
- Tigecycline inhibited the growth of 99% of all *S. aureus* at a MIC value of 0.5 mcg/mL, comparable to the activity of linezolid and vancomycin.
- Tigecycline demonstrates in vitro activity comparable to commonly prescribed antimicrobial agents, linezolid and vancomycin, currently used for the treatment of serious staphylococcal and enterococcal nosocomial infections.