

Evaluation of In Vitro Activity of Tigecycline and Ten Comparators Against Methicillin-Resistant *Staphylococcus aureus* from 38 Countries: TEST Program 2004 - 2006

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REVISED ABSTRACT

Background: Tigecycline (TIG), 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 TIG compared to amoxicillin-clavulanic acid, piperacillin-tazobactam, levofloxacin, ceftriaxone, linezolid (LZD), minocycline (MIN), vancomycin (VAN), ampicillin, penicillin, and imipenem (IMP) against methicillin-resistant *S. aureus* (MRSA) isolates collected from 314 sites in 38 countries between 2004 and 2006. **Methods:** A total of 3,180 clinical isolates of MRSA were identified to the species level at each participating site and confirmed by the central laboratory. Minimum Inhibitory Concentration (MICs) were determined by the local laboratory using supplied broth microdilution panels and interpreted according to CLSI guidelines, except for tigecycline, which used the susceptible breakpoint ≤ 0.5 mcg/ml for *S. aureus* (including MRSA) as defined in the FDA approved package insert. **Results:** The %S for the study drugs with MRSA activity--TIG, VAN, LZD, and MIN--was 100, 100, 100, and 97.6 respectively. There were few significant differences among geographic regions, except for lower activity of MIN in Asia (%S = 81.8) and the Middle East (%S = 13.3) as compared to Europe (97.8%) and North America (99.1%). IMP showed a broad range of MIC₅₀ results, with North America and Europe at the low end (0.5 and 2 mcg/ml, respectively), and all others >16 mcg/ml. TIG inhibited 100% of strains in all regions. MIC_{50/90} (mcg/ml) for TIG, VAN, LZD, and MIN were 0.12/0.25, 1/1, 2/2, and $\leq 0.25/2$, respectively. **Conclusion:** Global susceptibility patterns of MRSA remain fairly consistent. TIG was as potent as VAN and LZD, inhibiting 3,180/3,180 (100%) of the MRSA isolates at their respective breakpoints. TIG's excellent expanded broad spectrum of activity against MRSA should make it a very useful drug in treatment of difficult staphylococcal infections.

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 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 in animal models infected with selected strains of multi-drug resistant *Enterococcus faecium* and *Enterococcus faecalis* [4,5] with diverse genotypes of vanA, vanB and vanC [6].

This study was designed to better define the in vitro activity of tigecycline in methicillin-resistant *Staphylococcus aureus* clinical isolates collected from 314 study centers in 38 countries.

MATERIALS & METHODS

- All isolates were derived from blood, respiratory tract, urine (no more than 25% of all isolates), skin, wound, fluids, and other defined sources. Only one isolate per patient was accepted. Isolates were identified to genus and species by the local laboratory. Each site tested the isolates using broth microdilution.
- Clinical isolates (n=3,180) were collected and tested between January 2004 - December 2006 from 314 study centers in 38 countries.
- 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); ampicillin (0.5-32); piperacillin/tazobactam (0.06-128); levofloxacin (0.008-8); ceftriaxone (0.06-64); linezolid (0.5-8); penicillin (0.06-8); imipenem (0.06-16); minocycline (0.5-16); tigecycline (0.008-16); and vancomycin (0.12-32).
- To be consistent and to be able to compare across regions, MIC interpretive criteria for all drugs except tigecycline followed published guidelines established by the Clinical and Laboratory Standards Institute (CLSI) where applicable [12], regardless of origin of isolates. MIC interpretive criteria for tigecycline followed criteria established by the Food and Drug Administration (FDA, United States, 2005) [13].
- Methicillin phenotype is based upon the susceptibility of *S. aureus* to ceftioxitin, using the disk test according to CLSI document M100-S16 (2006) [12].
- Quality control of broth microdilution panels followed manufacturer's and CLSI guidelines using the following ATCC strains: *Staphylococcus aureus* ATCC 29213 and *Enterococcus faecalis* ATCC 29212.
- The collection and transportation of organisms, 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

Table 1. In vitro activity of tigecycline and comparative agents against 3,180 global clinical isolates of methicillin-resistant *S. aureus*.

Region	Drug	%SUS ¹	%INT	%RES	MIC (mcg/ml)		MIC range (mcg/ml)	
					MIC ₅₀	MIC ₉₀	Low	High
Global	Tigecycline ²	100	0	100	0.12	0.25	0.015	0.5
	AmoxClav	0	0	100	8	>8	0.25	>8
	Ampicillin	0	0	100	>16	>16	0.5	>16
	Ceftriaxone	0	0	100	32	>64	0.12	>64
	Imipenem	0	0	100	0.5	>16	≤ 0.12	>16
	Levofloxacin	21.5	5.6	72.9	8	>32	≤ 0.06	>32
	Linezolid	100	0	100	2	2	≤ 0.5	4
	Minocycline	97.8	2.3	0.2	≤ 0.25	2	≤ 0.25	>8
	Penicillin	0	0	100	>8	>8	0.25	>8
	PipTazo	36.3	0	63.7	16	>16	≤ 0.25	>16
	Vancomycin	100	0	100	1	1	0.25	2

¹ Susceptibility as defined in CLSI document M100-S16 (2006) where applicable. Tigecycline breakpoints are defined in FDA package insert (Tygacil[®], 2005) as susceptible (≤ 0.5 mcg/ml [13]). All beta-lactams are resistant to MRSA as defined by CLSI [12].

² The absence of resistance precludes the assignment of intermediate and resistant breakpoints.

Table 2. In vitro activity of tigecycline and comparative agents against 3,180 clinical isolates of methicillin-resistant *S. aureus*, by region.

Region	Drug	%SUS ¹	%INT	%RES	MIC (mcg/ml)		MIC range (mcg/ml)	
					MIC ₅₀	MIC ₉₀	Low	High
Africa (n=38)	Tigecycline ²	100	0	100	0.12	0.5	0.06	0.5
	AmoxClav	0	0	100	>8	>8	0.5	>8
	Ampicillin	0	0	100	>16	>16	1	>16
	Ceftriaxone	0	0	100	>64	>64	2	>64
	Imipenem	0	0	100	16	>16	≤ 0.12	>16
	Levofloxacin	31.6	5.3	63.2	4	8	0.12	>32
	Linezolid	100	0	100	2	2	≤ 0.5	4
	Minocycline	97.4	2.6	0	2	4	≤ 0.25	8
	Penicillin	0	0	100	>8	>8	1	>8
	PipTazo	0	0	100	>16	>16	0.5	>16
	Vancomycin	100	0	100	1	1	0.5	2
Asia/Pacific Rim (n=176)	Tigecycline ²	100	0	100	0.25	0.5	0.03	0.5
	AmoxClav	0	0	100	>8	>8	0.25	>8
	Ampicillin	0	0	100	>16	>16	0.5	>16
	Ceftriaxone	0	0	100	>64	>64	1	>64
	Imipenem	0	0	100	>16	>16	≤ 0.12	>16
	Levofloxacin	26.1	4	69.9	8	>32	≤ 0.06	>32
	Linezolid	100	0	100	2	2	≤ 0.5	4
	Minocycline	81.8	17.6	0.6	2	8	≤ 0.25	>8
	Penicillin	0	0	100	>8	>8	0.5	>8
	PipTazo	0	0	100	>16	>16	≤ 0.25	>16
	Vancomycin	100	0	100	1	1	0.25	2
Europe (n=407)	Tigecycline ²	100	0	100	0.12	0.25	0.03	0.5
	AmoxClav	0	0	100	>8	>8	0.25	>8
	Ampicillin	0	0	100	>16	>16	0.5	>16
	Ceftriaxone	0	0	100	>64	>64	1	>64
	Imipenem	0	0	100	2	>16	≤ 0.12	>16
	Levofloxacin	14.7	5.2	80.1	8	32	≤ 0.06	>32
	Linezolid	100	0	100	2	2	≤ 0.5	4
	Minocycline	97.8	2.2	0	≤ 0.25	4	≤ 0.25	8
	Penicillin	0	0	100	>8	>8	0.25	>8
	PipTazo	0	0	100	>16	>16	≤ 0.25	>16
	Vancomycin	100	0	100	1	1	0.25	2
Latin America (n=208)	Tigecycline ²	100	0	100	0.12	0.25	0.06	0.5
	AmoxClav	0	0	100	>8	>8	1	>8
	Ampicillin	0	0	100	>16	>16	2	>16
	Ceftriaxone	0	0	100	>64	>64	4	>64
	Imipenem	0	0	100	>16	>16	≤ 0.12	>16
	Levofloxacin	15.9	18.8	65.4	4	16	≤ 0.06	>32
	Linezolid	100	0	100	2	2	≤ 0.5	4
	Minocycline	99	1	0	≤ 0.25	2	≤ 0.25	8
	Penicillin	0	0	100	>8	>8	2	>8
	PipTazo	0	0	100	>16	>16	1	>16
	Vancomycin	100	0	100	1	1	0.25	2
Middle East (n=15)	Tigecycline ²	100	0	100	0.5	0.5	0.12	0.5
	AmoxClav	0	0	100	>8	>8	0.5	>8
	Ampicillin	0	0	100	>16	>16	1	>16
	Ceftriaxone	0	0	100	>64	>64	>64	>64
	Imipenem	0	0	100	>16	>16	≤ 0.12	>16
	Levofloxacin	13.3	0	86.7	8	16	0.25	16
	Linezolid	100	0	100	2	4	1	4
	Minocycline	13.3	80	6.7	8	8	2	>8
	Penicillin	0	0	100	>8	>8	2	>8
	PipTazo	0	0	100	>16	>16	2	>16
	Vancomycin	100	0	100	1	1	0.5	2
North America (n=2,336)	Tigecycline ²	100	0	100	0.12	0.25	0.015	0.5
	AmoxClav	0	0	100	8	>8	0.25	>8
	Ampicillin	0	0	100	>16	>16	0.5	>16
	Ceftriaxone	0	0	100	32	>64	0.12	>64
	Imipenem	0	0	100	0.5	16	≤ 0.12	>16
	Levofloxacin	22.7	4.6	72.7	8	>32	≤ 0.06	>32
	Linezolid	100	0	100	2	2	≤ 0.5	4
	Minocycline	99.1	0.7	0.1	≤ 0.25	0.5	≤ 0.25	>8
	Penicillin	0	0	100	>8	>8	0.25	>8
	PipTazo	0	0	100	>16	>16	≤ 0.25	>16
	Vancomycin	100	0	100	1	1	0.25	2

¹ Susceptibility as defined in CLSI document M100-S16 (2006) where applicable. Tigecycline breakpoints are defined in FDA package insert (Tygacil[®], 2005) as susceptible (≤ 0.5 mcg/ml [13]). All beta-lactams are resistant to MRSA as defined by CLSI [12].

² The absence of resistance precludes the assignment of intermediate and resistant breakpoints.

Table 3. In vitro activity of tigecycline and comparators against global isolates of methicillin-resistant *S. aureus* (n=3,180) showing frequency distribution (n) and cumulative percent inhibited (%) at each MIC (mcg/ml), with MIC₉₀ highlighted in yellow.

MIC	n	% Inhibited																					
		0.015	0.03	≤ 0.06	0.06	≤ 0.12	0.12	≤ 0.25	0.25	≤ 0.05	0.5	1	2	4	8	>8	16	>16	32	>32	64	>64	
Tigecycline	1	13	462	2084	484	137	100																
AmoxClav	6	32	80	204	554	1051	1254																
Ampicillin	0.2	1.2	3.7	10.1	27.5	60.6	100																
Ceftriaxone	0.5	1.6	3.7	7.4	16.9	37.1	100																
Imipenem	0.1	0.4	1.7	3.6	12.9																		