

In Vitro Activity Tigecycline and 10 Broad Spectrum Comparators against Multi-Drug Resistant *Staphylococcus aureus*: A Multi-nation Evaluation

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REVISED ABSTRACT

Background: Worldwide *S. aureus* are increasingly displaying resistance to multiple drug classes (MDR). Therapeutic options to MDR *S. aureus* phenotypes are limited. Tigecycline, a new glycylicycline offers the potential of enhanced activity against MDR *S. aureus*. The tigecycline evaluation surveillance trial (T.E.S.T.) evaluated the activity of tigecycline and comparators to MDR *S. aureus* isolated worldwide. **Methods:** 150 hospital sites in 27 countries between 2004-2006 collected 3,228 clinically significant *S. aureus*. MICs were determined at each site using broth microdilution panels and results interpreted as specified by CLSI at each site. **Results:** MIC₉₀ of tigecycline and comparators to MDR groups 0 - 4 are shown in the table:

	MDR Group (N) / MIC ₉₀ (mcg/mL)					
	Group 0 (n=233)	Group 1 (n=1688)	Group 2 (n=689)	Group 3 (n=359)	Group 4 (n=256)	Group 5 (n=3)
Tigecycline	0.12	0.12	0.25	0.25	0.5	0.5
AmoxClav	0.25	4	8	>8	>8	>8
Ampicillin	0.12	>16	>16	>16	>16	>16
Ceftriaxone	4	16	32	>64	>64	>64
Penicillin	0.25	0.5	0.5	8	>16	>16
PipTazo	0.25	0.5	>32	>32	>32	>32
Imipenem	4	4	4	4	2	4
Levofloxacin	<0.25	<0.25	0.5	2	8	>8
Linezolid	0.12	>8	>8	>8	>8	>8
Minocycline	0.5	8	>16	>16	>16	>16
Vancomycin	1	1	1	1	2	2

*Resistant to 0, 1, 2, 3, 4 or 5 different drug classes.

Conclusion: Tigecycline exhibited the lowest MIC₉₀ of all study agents against *S. aureus* strains worldwide in spite of a 2- to 4-fold increase in MIC₉₀ values against *S. aureus* resistant to two or more drug classes. Tigecycline MIC values remained at or below its susceptible breakpoint of 0.5 mcg/mL for all *S. aureus*.

INTRODUCTION

Tigecycline is the first novel antimicrobial with an expanded broad-spectrum of activity from a new class of compounds, glycylicyclines. 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].

While developed to provide activity against tetracycline- and multi-drug-resistant gram-positive pathogens, it has been demonstrated to possess significant broad-spectrum activity against aerobic and anaerobic gram-positive and gram-negative microorganisms [1,3-5]. Tigecycline MIC₉₀ value of <0.5 mcg/ml have been demonstrated against methicillin-resistant *Staphylococcus aureus* (MRSA) [2, 4-6].

Tigecycline resistance is very infrequent and difficult to induce in the laboratory [7, 8] with a selection frequency observed at less than 10⁻⁹ [2, 3, 7]. Most tetracycline-resistant bacteria with either tetracycline efflux pumps or ribosomal protective features are sensitive to tigecycline [1-4, 6, 9-11]. The pharmacokinetics of parenteral tigecycline is linear with an unusually long half-life of 36 hours and a maximum serum concentration (C_{MAX}) of a 300 mg dose infused over 1 hour of 2.8 mcg/ml [12].

This study compared the activity of tigecycline with other agents against methicillin-resistant *Staphylococcus aureus* (MRSA) and methicillin-sensitive *Staphylococcus aureus* (MSSA) from a geographically diverse global population.

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 - January 2006 from 150 study centers in 27 countries.
- Antimicrobial agents tested with concentrations (expressed in mcg/ml) were: amoxicillin/clavulanic acid (0.03-8); 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 [13]. Tigecycline tentative breakpoints (in units of mcg/mL) are defined as susceptible ≤0.5 by the FDA in the Wyeth product insert (Tygacil[®], 2005).
- Isolates were identified to genus and species by the local laboratory. Each site tested the isolates using broth microdilution. All MRSA and MSSA were confirmed by the central laboratory using oxacillin disk test (Oxoid).
- Quality control followed CLSI guidelines using quality control organism *Staphylococcus aureus* ATCC 29213.
- The collection and transporting 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

Table 1. In vitro (mcg/mL) Activity of Tigecycline and Comparators against 3,228 Strains of *Staphylococcus aureus* from a Multi-Center, Multi-National Population.

Organism(N)	Drug	Percent (%)			MIC (mcg/mL)	
		SUS	INT	RES	MIC ₅₀	MIC ₉₀
<i>Staphylococcus aureus</i> (n=3228)	Tigecycline	99.9	0.1	0	0.12	0.25
	AmoxClav	69	0	31	1	>8
	Ampicillin	9.7	0	90.3	16	>16
	Ceftriaxone	57.8	22.4	19.8	4	>64
	Imipenem	89.8	1.5	8.8	0.25	8
	Levofloxacin	58	2.1	39.8	0.25	32
	Linezolid	100	0	0	2	4
	Minocycline	98.3	1.6	0.1	≤0.25	0.5
	Penicillin	8	0	92	>8	>8
	PipTazo	71.7	0	28.3	1	>16
<i>Staphylococcus aureus</i> , Methicillin-Susceptible * (n=1775)	Tigecycline	100	0	0	0.12	0.25
	AmoxClav	99.5	0	0.5	1	2
	Ampicillin	17.1	0	82.9	4	>16
	Ceftriaxone	97.2	2.4	0.4	4	4
	Imipenem	99.5	0	0.5	0.25	0.25
	Levofloxacin	89.5	1.5	9	0.12	2
	Linezolid	100	0	0	2	4
	Minocycline	99.4	0.6	0.1	≤0.25	0.5
	Penicillin	14.1	0	85.9	8	>8
	PipTazo	99.8	0	0.2	1	2
<i>Staphylococcus aureus</i> , Methicillin-Resistant * (n=1453)	Tigecycline	99.9	0.1	0	0.12	0.25
	AmoxClav	31.7	0	68.3	8	>8
	Ampicillin	0.6	0	99.4	>16	>16
	Ceftriaxone	9.8	46.8	43.4	32	>64
	Imipenem	77.8	3.2	18.9	0.5	>16
	Levofloxacin	19.5	3	77.5	8	>32
	Linezolid	100	0	0	2	2
	Minocycline	96.9	2.9	0.2	≤0.25	2
	Penicillin	0.4	0	99.6	>8	>8
	PipTazo	37.3	0	62.7	16	>16
<i>Staphylococcus aureus</i> , Methicillin-Resistant * (n=1160)	Tigecycline	99.9	0.1	0	0.12	0.25
	AmoxClav	69	0	31	1	>8
	Ampicillin	9.7	0	90.3	16	>16
	Ceftriaxone	57.8	22.4	19.8	4	>64
	Imipenem	89.8	1.5	8.8	0.25	8
	Levofloxacin	58	2.1	39.8	0.25	32
	Linezolid	100	0	0	2	4
	Minocycline	98.3	1.6	0.1	≤0.25	0.5
	Penicillin	8	0	92	>8	>8
	PipTazo	71.7	0	28.3	1	>16
<i>Staphylococcus aureus</i> , Methicillin-Resistant * (n=1160)	Tigecycline	99.9	0.1	0	0.12	0.25
	AmoxClav	31.7	0	68.3	8	>8
	Ampicillin	0.6	0	99.4	>16	>16
	Ceftriaxone	9.8	46.8	43.4	32	>64
	Imipenem	77.8	3.2	18.9	0.5	>16
	Levofloxacin	19.5	3	77.5	8	>32
	Linezolid	100	0	0	2	2
	Minocycline	96.9	2.9	0.2	≤0.25	2
	Penicillin	0.4	0	99.6	>8	>8
	PipTazo	37.3	0	62.7	16	>16
<i>Staphylococcus aureus</i> , Methicillin-Resistant * (n=1160)	Tigecycline	99.9	0.1	0	0.12	0.25
	AmoxClav	31.7	0	68.3	8	>8
	Ampicillin	0.6	0	99.4	>16	>16
	Ceftriaxone	9.8	46.8	43.4	32	>64
	Imipenem	77.8	3.2	18.9	0.5	>16
	Levofloxacin	19.5	3	77.5	8	>32
	Linezolid	100	0	0	2	2
	Minocycline	96.9	2.9	0.2	≤0.25	2
	Penicillin	0.4	0	99.6	>8	>8
	PipTazo	37.3	0	62.7	16	>16

*Methicillin susceptibility is determined by oxacillin disk susceptibility as outlined by CLSI in document M100-S15, 2005.

Table 2. In vitro (mcg/mL) Activity of Tigecycline and Comparators against 1,160 Multi-drug Resistant, Methicillin-Resistant *Staphylococcus aureus*.*

Organism(N)	Drug	Percent (%)			MIC (mcg/mL)	
		SUS	INT	RES	MIC ₅₀	MIC ₉₀
Multi-drug Resistant, Methicillin-Resistant	Tigecycline	99.9	0.1	0	0.12	0.25
<i>Staphylococcus aureus</i> (n=1160)	AmoxClav	69	0	31	1	>8
	Ampicillin	9.7	0	90.3	16	>16
	Ceftriaxone	57.8	22.4	19.8	4	>64
	Imipenem	89.8	1.5	8.8	0.25	8
	Levofloxacin	58	2.1	39.8	0.25	32
	Linezolid	100	0	0	2	4
	Minocycline	98.3	1.6	0.1	≤0.25	0.5
	Penicillin	8	0	92	>8	>8
	PipTazo	71.7	0	28.3	1	>16
	Vancomycin	100	0	0	1	1

*Multi-drug resistant, methicillin-resistant *S. aureus* are defined as any isolate resistant to oxacillin and resistant to one or more drug classes other than a beta-lactam.

Table 3. In vitro Activity (mcg/mL) of Tigecycline and Comparators at each Grouping of Resistant Drug Classes for 3,228 Isolates of *Staphylococcus aureus*.

Drug	(mcg/mL)	Resistant Drug Class Group (n)					
		Group 0 (n=233)	Group 1 (n=1688)	Group 2 (n=689)	Group 3 (n=359)	Group 4 (n=256)	Group 5 (n=3)
		Tigecycline	MIC ₅₀	0.12	0.12	0.12	0.12
	MIC ₉₀	0.12	0.12	0.25	0.25	0.5	0.5
AmoxClav	MIC ₅₀	0.12	1	4	>8	>8	>8
	MIC ₉₀	0.25	4	8	>8	>8	>8
Ampicillin	MIC ₅₀	0.12	8	16	>16	>16	>16
	MIC ₉₀	0.12	>16	>16	>16	>16	>16
Ceftriaxone	MIC ₅₀	2	4	16	>64	>64	>64
	MIC ₉₀	4	16	32	>64	>64	>64
Imipenem	MIC ₅₀	0.25	0.25	0.25	2	>16	>16
	MIC ₉₀	0.25	0.5	0.5	8	>16	>16
Levofloxacin	MIC ₅₀	0.12	0.12	16	16	16	8
	MIC ₉₀	0.25	0.5	>32	>32	>32	>32
Linezolid	MIC ₅₀	2	2	2	2	2	2
	MIC ₉₀	4	4	4	4	2	4
Minocycline	MIC ₅₀	≤0.25	≤0.25	≤0.25	≤0.25	0.5	>8
	MIC ₉₀	≤0.25	≤0.25	0.5	2	8	>8
Penicillin	MIC ₅₀	≤0.06	>8	>8	>8	>8	>8
	MIC ₉₀	0.12	>8	>8	>8	>8	>8
PipTazo	MIC ₅₀	0.5	1	8	>16	>16	>16
	MIC ₉₀	0.5	8	>16	>16	>16	>16
Vancomycin	MIC ₅₀	0.5	0.5	1	1	1	1
	MIC ₉₀	1	1	1	1	2	2

CONCLUSIONS

- Tigecycline inhibited 99.9% of all *Staphylococcus aureus* at its susceptible breakpoint of <0.5 mcg/mL.
- Tigecycline activity in vitro was comparable to linezolid and vancomycin against all *S. aureus* without regard to methicillin phenotype and demonstrates greater in vitro activity against MRSA than levofloxacin, imipenem and the beta-lactam antimicrobials.
- Tigecycline exhibited the lowest MIC₉₀ of all study agents against *S. aureus* strains worldwide in spite of a 2- to 4-fold increase in MIC₉₀ values against *S. aureus* resistant to two or more drug classes.
- Tigecycline demonstrated potent in vitro activity comparable to linezolid and vancomycin against multi-drug resistant-methicillin-resistant *Staphylococcus aureus*.
- Tigecycline appears to be promising agent in the treatment of *Staphylococcus aureus* including strains with multiple resistant determinants.