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Multi Drug Resistant (MDR) S. aureus Are Susceptible to Tigecycline: T.E.S.T Program - United States Surveillance

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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 glycylcycline 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**: 68 hospital sites in the United States between 2004 - 2005 collected 1,484 clinically significant *S. aureus* and 105 MDR *S. aureus*. MICs were performed as specified by CLSI at each site. **Results**: MIC_{90} of tigecycline and comparators to MDR groups 0 - 5 are shown in the table. **Conclusions**: Tigecycline in comparison to 10 relevant comparators exhibited the lowest MIC_{90} to *S. aureus* isolated worldwide irrespective of MDR phenotype and multiple drug class resistance.

	MDR Group[1] (N) MIC$_{90}$				
	0 (82)	1 (833)	2 (463)	3 (102)	4 (4)
Tigecycline	0.12	0.12	0.25	0.5	1
Amox/Clav	0.25	8	>8	>8	>8
Ampicillin	0.12	>16	>16	>16	>16
Ceftriaxone	4	32	>64	>64	>64
Imipenem	0.25	0.5	4	>16	>16
n	0.25	4	>32	>32	32
Linezolid	4	2	4	2	4
Minocycline	≤0.25	≤0.25	0.5	2	>8
Penicillin	0.12	>8	>8	>8	>8
Pip-tazo	0.5	16	>16	>16	>16
Vancomycin	1	1	1	1	2

[1]Resistant to 0, 1, 2, 3, or 4 drug classes

INTRODUCTION

Tigecycline (formerly GAR-936) is a member of a new class of antimicrobial agents, the glycylcyclines. This synthetic analogue of the tetracyclines exhibits significant antibacterial activity that is both bacteriostatic and, in certain instances, bactericidal with killing activity that is as much as fourfold better than vancomycin and daptomycin [1, 2]. The development of tigecycline is important in that it and other glycylcyclines are active against bacterial strains carrying either or both of the two major forms of tetracycline resistance: efflux and ribosomal protection. Certain substituents at the 9-position of the tetracycline molecule restored activity against bacteria harboring genes encoding either or both efflux and ribosomal protection. A single chemical modification of tigecycline overcomes the two molecularly distinct forms of resistance while maintaining activity against susceptible gram-positive, gram-negative, aerobic, and anaerobic bacteria [3]. Furthermore, resistance to tigecycline is difficult to produce even in the laboratory.

Previous studies have demonstrated excellent in vitro activity for tigecycline against clinical and laboratory strains of Gram-positive and -negative bacteria with minimum inhibitory concentrations for the 90th percentile inhibited at or below 2 mcg/mL, including difficult to treat methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE) and extended-spectrum beta-lactamase (ESBL) producing *Enterobacteriaceae* [4-7]. Faced with ever-increasing rates of methicillin resistance and multi-drug resistance among staphylococci-both hospital- and community-acquired-as well as the recent appearance of diminished susceptibility to vancomycin, the need for new effective anti-MRSA drugs remains. This study was undertaken to document the in vitro activity of tigecycline against a significant number of multi-drug resistant MRSA from large diverse population within the United States. This study is part of the larger ongoing global Tigecycline Evaluation and Surveillance Trials (T.E.S.T.) program.

MATERIALS & METHODS

- All isolates were derived from blood, respiratory tract, urine, skin, wound, body fluids and other defined sources. Only one isolate per patient was accepted into the study. Clinical isolates were collected and tested between January 2004 - July 2005 from 68 sites in the United States. Isolates were identified to the species level and tested at each site by the participating laboratory.
- Organism collection, transport, confirmation of organism identification, and development and management of a centralized database were coordinated by Laboratories International for Microbiology Studies (LIMS), a division of International Health Management Associates, Inc. located in Schaumburg, IL, USA.
- All organisms were deemed clinically significant by local participant criteria. Isolate inclusion was independent of medical history, antimicrobial use, age or gender. All sites identified each study isolate utilizing local laboratory site criteria.

Antimicrobial Susceptibility Testing

- Minimum inhibitory concentrations (MICs) were determined by the CLSI recommended broth microdilution testing method [8]. Tigecycline was supplied by Wyeth Pharmaceuticals (Collegeville, PA, USA). All other agents were supplied by the panel manufacturer, MicroScan (Dade Behring Inc., West Sacramento, CA, USA). The following antimicrobial agents and dilution ranges (expressed in terms of mcg/mL) were included on the panels: amoxicillin/clavulanic acid (0.12/0.06-32/16); ampicillin (0.06-16,); ceftriaxone (0.06-64); imipenem (0.06-16); linezolid (0.5-8); levofloxacin (0.008-8); minocycline (0.5-16); tigecycline (0.008-16); penicillin (0.06-8); piperacillin/tazobactam (0.06/4-128/4) and vancomycin (0.12-32). MIC interpretive criteria followed published guidelines established by the Clinical and Laboratory Standards Institute [9] and the recent US Food and Drug Administration package insert for tigecycline [10], where applicable.
- Quality controls (QC) were performed by each testing site on each day of testing using the corresponding ATCC control strains: *S. aureus* ATCC 29213 and *Enterococcus faecalis* ATCC 29212. Results were included in the analysis only when corresponding QC isolates tested within the acceptable range according to CLSI (2005) guidelines [9].

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RESULTS

The results are shown in the following tables.

Table 1. In vitro Activity of Tigecycline and Comparative Antimicrobial Agents against 1,484 *Staphylococcus aureus* Isolates from the United States

Organism (N)	Drug	MIC (mcg/mL) MIC$_{50}$	MIC$_{90}$	Range	%Sus [a]
S. aureus (n=1484)	Tigecycline	0.12	0.25	015 - 4	99.6
	AmoxClav	4	>8	≤03 - 32	59.2
	Ampicillin	16	>16	≤06 - >32	7
	Ceftriaxone	16	>64	0.12 - >64	45.4
	Imipenem	0.25	4	≤0.12 - >16	90.2
	Levofloxacin	1	>32	≤06 - >32	52.6
	Linezolid	2	4	≤0.5 - 4	100
	Minocycline	≤0.25	0.5	≤0.25 - >8	99.3
	Penicillin	>8	>8	≤06 - 16	6.1
	PipTazo	4	>16	≤0.25 - 128	63.1
	Vancomycin	1	1	≤0.12 - 4	100

[a]Interpretive criteria as defined by CLSI document M100-S15 (2005); tigecycline susceptible breakpoint is according to FDA package insert (2005) [10].

Table 2. In Vitro Activity of Tigecycline and Comparators at each Multi-Drug Resistant Group for 1484 *Staphylococcus aureus* from the United States

Drug	MIC (mcg/mL)	Multi-drug Resistant Groups* Group 0 (n=82)	Group 1 (n=833)	Group 2 (n=463)	Group 3 (n=102)	Group 4 (n=4)
Tigecycline	MIC$_{50}$	0.12	0.12	0.12	0.12	1
	MIC$_{90}$	0.12	0.12	0.25	0.5	1
AmoxClav	MIC$_{50}$	0.12	1	8	>8	>8
	MIC$_{90}$	0.25	8	>8	>8	>8
Ampicillin	MIC$_{50}$	≤0.06	16	16	>16	16
	MIC$_{90}$	0.12	>16	>16	>16	>16
Ceftriaxone	MIC$_{50}$	2	4	32	>64	>64
	MIC$_{90}$	4	32	>64	>64	>64
Imipenem	MIC$_{50}$	0.25	0.25	0.5	>16	16
	MIC$_{90}$	0.25	0.5	4	>16	>16
Levofloxacin	MIC$_{50}$	0.12	0.12	32	32	16
	MIC$_{90}$	0.25	4	>32	>32	32
Linezolid	MIC$_{50}$	2	2	2	2	2
	MIC$_{90}$	4	2	4	2	4
Minocycline	MIC$_{50}$	≤0.25	≤0.25	≤0.25	≤0.25	1
	MIC$_{90}$	≤0.25	≤0.25	0.5	2	>8
Penicillin	MIC$_{50}$	≤0.06	>8	>8	>8	>8
	MIC$_{90}$	0.12	>8	>8	>8	>8
Pip-tazo	MIC$_{50}$	0.5	1	16	>16	>16
	MIC$_{90}$	0.5	16	>16	>16	>16
Vancomycin	MIC$_{50}$	0.5	0.5	1	1	1
	MIC$_{90}$	1	1	1	1	2

[*]MDR Groups are defined as resistant to 0, 1, 2, 3 or 4 different drug classes

Table 3. In vitro Activity of Tigecycline and Comparative Antimicrobial Agents against 105 Multi-drug Resistant,* Methicillin-Resistant *Staphylococcus aureus* Isolates from the United States

Organism (N)	Drug	MIC (mcg/mL) MIC$_{50}$	MIC$_{90}$	Range	%Sus [a]
S. aureus (MRSA) (n=105)	Tigecycline	0.5	0.03	0.03 - 1	97.1
	AmoxClav	>8	8	8 - 32	0
	Ampicillin	>16	4	4 - >32	0
	Ceftriaxone	>64	16	16 - >64	0
	Imipenem	>16	16	16 - >16	0
	Levofloxacin	>32	8	8 - >32	0
	Linezolid	2	≤0.5	≤0.5 - 4	100
	Minocycline	2	≤0.25	≤0.25 - >8	98.1
	Penicillin	>8	8	8 - >8	0
	Pip-tazo	>16	8	8 - 128	0
	Vancomycin	2	0.5	0.5 - 2	100

*Multi-drug resistant MRSA is defined as any *S. aureus* resistant to oxacillin and 2 or more drug classes other than a beta-lactam.
[a]Interpretive criteria as defined by CLSI document M100-S15 (2005); tigecycline susceptible breakpoint is according to FDA package insert (2005) [10].

Table 4. Frequency Distribution (n) and Cumulative Percent Inhibited (%) at each MIC (mcg/mL) for Tigecycline and Comparators for 105 Multi-Drug Resistant,* Methicillin-Resistant *Staphylococcus aureus* from the United States

	MIC(mcg/mL)												
n/Cum%	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128
Tigecycline	1	8	50	32	11	3							
	1	8.6	56.2	86.7	97.1	100							
AmoxClav									5	99	1		
									4.8	99	100		
Ampicillin								1	3	16	84	1	
								1	3.8	19	99	100	
Ceftriaxone										1	3	1	100
										1	3.8	4.8	100
Imipenem										32	73		
										30.5	100		
Levofloxacin									8	32	33	32	
									7.6	38.1	69.5	100	
Linezolid					1	24	70	10					
					1	23.8	90.5	100					
Minocycline				68	16	6	8	5	1	1			
				64.8	80	85.7	93.3	98.1	99	100			
Penicillin									4	101			
									3.8	100			
Pip-tazo									1	3	100		1
									1	3.8	99		100
Vancomycin					28	65	12						
					26.7	88.6	100						

*Multi-drug resistant MRSA is defined as any *S. aureus* resistant to oxacillin and 2 or more drug classes other than a beta-lactam.

CONCLUSIONS

- Tigecycline had the lowest in vitro MIC_{90} of all study drugs against all strains of *Staphylococcus aureus* and at 0.25 mcg/mL this value was comparable to minocycline and 4- to 16-fold lower than imipenem, linezolid and vancomycin. At CLSI breakpoints all *Staphylococcus aureus* were susceptible to linezolid and vancomycin. Using the FDA breakpoint of ≤0.5 mcg/mL, 99.6% *S. aureus* were susceptible to tigecycline.
- Tigecycline inhibited 97.1% of multi-drug resistant MRSA at 0.5 mcg/mL and 100% of multi-drug resistant MRSA at 1 mcg/mL.
- The MIC_{50} and MIC_{90} values of all study drugs increased as the number of drugs resistant classes against *S. aureus* increased. Tigecycline remained effective although resistance to 2 drug classes increased the tigecycline MIC_{90} by 2-fold, 3 classes 4-fold and resistance to 4 classes increased it by 8-fold.
- The in vitro activity or tigecycline was equivalent to minocycline, linezolid and vancomycin against multi-drug resistant MRSA resistant to 2 or more drug classes.
- The in vitro activity of tigecycline in this study suggests that tigecycline is a potent antimicrobial agent that may be beneficial in the treatment of infections due to drug resistant and multi-drug resistant *Staphylococcus aureus*.