

# United States In Vitro Antibacterial Activity of Tigecycline against Methicillin Resistant and Methicillin Sensitive *Staphylococcus*

## #33E

## *aureus* Isolates from the Tigecycline Evaluation Surveillance Trial (T.E.S.T.) Program

S. Bouchillon<sup>1</sup>, T. Stevens<sup>1</sup>, B. Johnson<sup>1</sup>, J. Johnson<sup>1</sup>, D. Hoban<sup>1</sup>, A. Hsiung<sup>1</sup>, M. Hackel<sup>1</sup>, M. Person<sup>1</sup>, M. Dowzicky<sup>2</sup>

IHMA, Inc.  
2122 Palmer Dr.  
Schaumburg, IL 60173  
Tel: (847) 303-5003  
Fax: (847) 303-5601  
www.ihmainc.com

<sup>1</sup>International Health Management Associates, Schaumburg, IL, USA

<sup>2</sup>Wyeth Pharmaceuticals, Collegeville, PA, USA

### REVISED ABSTRACT

**Background:** Despite the introduction of new antimicrobials to treat resistant gram-positive bacteria, *Staphylococcus aureus* continues to be a therapeutic challenge for the clinician. Glycylcyclines are showing the promise of significant activity against many Gram-positive pathogens including methicillin-resistant *S. aureus*. Tigecycline, the first glycylcycline to enter clinical trials, has shown excellent activity against *Staphylococcus* spp. This study was initiated to evaluate the in vitro activity of tigecycline as compared with those of 10 comparator agents (ampicillin, penicillin, amoxicillin-clavulanic acid, imipenem, ceftriaxone, levofloxacin, minocycline, vancomycin, linezolid, piperacillin-tazobactam) against *S. aureus* including methicillin-resistant *Staphylococcus aureus* (MRSA) and methicillin-sensitive *Staphylococcus aureus* (MSSA) from 44 US centers in the T.E.S.T program. **Methods:** A total of 914 clinical isolates were identified to the species level at each of participating sites and confirmed by the central laboratory. Isolates were collected throughout 2004. MICs were determined by each participating laboratory using broth microdilution panels from Dade Behring MicroScan. All testing was performed and interpreted according to CLSI guidelines and manufacturer's instructions. **Results:** Among the 914 isolates, 473 (51.7%) were found to be resistant to methicillin (MRSA). Cross resistance of MRSA isolates to imipenem, ceftriaxone, penicillin, ampicillin and piperacillin/tazobactam was observed. A high rate of MRSA non-susceptibility to levofloxacin (76.7%) was demonstrated. No resistance was observed against vancomycin and linezolid. The MICs of tigecycline ranged from 0.015 to 1 mcg/mL for all isolates of *S. aureus*. Tigecycline presented the lowest MIC<sub>50</sub>/MIC<sub>90</sub> of 0.12/0.25 mcg/ml against MRSA isolates, being several folds lower than all the comparator agents. The MSSA isolates showed the expected profile of high resistance to ampicillin and penicillin. MSSA had an unusually high percentage, 18.4%, non-susceptibility to levofloxacin. Tigecycline's MIC<sub>50</sub>/MIC<sub>90</sub> of 0.12/0.12 was also the lowest of all comparators among MSSA isolates. **Conclusion:** The in vitro activity of tigecycline was comparable in all *S. aureus* tested regardless of methicillin susceptibility. Tigecycline's activity against MRSA was equivalent to commonly prescribed agents, linezolid and vancomycin, used for treatment of serious nosocomial infections.

### 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. 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 MIC<sub>90</sub> value of  $\leq 0.5$  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<sub>MAX</sub>) 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 hospitals across 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 and tested between January 2004 - December 2004 from 44 study centers.
- 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  $\leq 2$ ; intermediate = 4; and resistant  $\geq 8$ .
- 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 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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### RESULTS

Table 1. Frequency distribution (n) and cumulative percent inhibition (%) at each MIC (mcg/mL) for tigecycline and comparative agents against 441 methicillin-sensitive *Staphylococcus aureus*.

MIC	0.015	0.03	$\leq 0.06$	0.06	$\leq 0.12$	0.12	$\leq 0.25$	0.25	$\leq 0.5$	0.5	1	2	4	8	>8	16	>16	32	>32	64	>64	
Tigecycline	1	1	86	318	30	4	1															
Amox-Clav	0.2	0.5	20	92.1	98.9	99.8	100															
Ampicillin			1	33	41	116	153	43	9	15	30											
Ceftriaxone			0.2	7.7	17	43.3	78	87.8	89.8	93.2	100											
Imipenem			27	26	7	11	47	43	42	56							64	118				
Levofloxacin			6.1	12	13.6	16.1	26.8	36.5	46	58.7							73.2	100				
Linezolid				1	0.2					11	133	221	19				15	13			4	24
Minocycline				143	246					2.7	32.9	83	87.3				90.7	93.7			94.6	100
Penicillin				32.4	88.2					20	7	6	3	4			3	9				
Pip-Tazo				407	92.3					3	71	307	60									
Vancomycin				0.7	16.8					2	9	8	3	7	5							
				92.3	94.8					7	35	29	40	54	210							
				11	15					16.6	24.5	31.1	40.1	52.4	100							
				18	4.1					146	175	35	14	10	33							
				3	227					37.2	76.9	84.8	88	90.2	92.5	100						
				0.7	52.2					92.7	96.6	97.3	98.9	100								

Table 2. Frequency distribution (n) and cumulative percent inhibition (%) at each MIC (mcg/mL) for tigecycline and comparative agents against 473 methicillin-resistant *Staphylococcus aureus*.

MIC	$\leq 0.06$	0.06	$\leq 0.12$	0.12	$\leq 0.25$	0.25	$\leq 0.5$	0.5	1	2	4	8	>8	16	>16	32	>32	64	>64		
Tigecycline	76	327	52	14	4																
Amox-Clav	16.1	85.2	96.2	99.2	100																
Ampicillin	3	2	6	12	41	107	141	161													
Ceftriaxone	0.6	0.8	1.1	1.5	3.2	4.4	10.1	21.8													
Imipenem					0.6	3	4	13.3													
Levofloxacin					14	33	21	29	16	24	46										
Linezolid					5	14	71	85.2													
Minocycline					20.3	23.3	38.3	46.3													
Penicillin					2	75	332	64													
Pip-Tazo					0.4	16.3	86.5	100													
Vancomycin					15	4	7	11	3	1											
					94.5	95.3	96.8	99.2	99.8	100											
					5	6	6	23	39	388											
					2.3	3.6	4.9	9.7	18	100											
					6	11	23	61	75	106	188										
					1.9	4.2	9.1	22	37.8	60.3	100										
					2	180	270	18	2	1											
					0.4	38.5	95.6	99.4	99.8	100											

Table 3. In vitro activity of tigecycline and comparator agents against 914 isolates of *Staphylococcus aureus*.

Organism Name	Drug <sup>a</sup>	%S	%I	%R	MICs (mcg/mL)	
					MIC <sub>50</sub>	MIC <sub>90</sub>
<i>Staphylococcus aureus</i> (n=914)	Tigecycline	100	0	0	0.12	0.25
	Amox-Clav	63	0	37	2	>8
	Ampicillin	7.1	0	92.9	16	>16
	Ceftriaxone	49.9	27.7	22.4	16	>64
	Imipenem	89.1	2.1	8.8	0.25	8
	Levofloxacin	52.4	8.6	39	2	>32
	Linezolid	100	0	0	2	4
	Minocycline	99	0.9	0.1	$\leq 0.25$	$\leq 0.25$
	Pip-Tazo	64.1	0	35.9	4	>16
	Penicillin	6.6	0	93.4	>8	>8
<i>Staphylococcus aureus</i> , MSSA (n=441)	Vancomycin	100	0	0	1	1
	Tigecycline	100	0	0	0.12	0.12
	Amox-Clav	89.8	0	10.2	1	8
	Ampicillin	13.6	0	86.4	8	>16
	Ceftriaxone	87.3	6.3	6.4	4	16
	Imipenem	96.4	0.9	2.7	0.25	0.5
	Levofloxacin	81.6	2.3	16.1	0.12	16
	Linezolid	100	0	0	2	4
	Minocycline	98.9	1.1	0	$\leq 0.25$	$\leq 0.25$
	Pip-Tazo	90.2	0	9.8	1	8
<i>Staphylococcus aureus</i> , MRSA (n=473)	Penicillin	12.5	0	87.5	8	>8
	Vancomycin	100	0	0	0.5	1
	Tigecycline	100	0	0	0.12	0.25
	Amox-Clav	36.2	0	63.8	8	>8
	Ampicillin	1.1	0	98.9	>16	>16
	Ceftriaxone	13.3	48.2	38.5	32	>64
	Imipenem	81.8	3.4	14.8	0.5	16
	Levofloxacin	23.3	15	61.7	16	>32
	Linezolid	100	0	0	2	4
	Minocycline	99.2	0.6	0.2	$\leq 0.25$	$\leq 0.25$
Pip-Tazo	37.8	0	62.2	16	>16	
Penicillin	1.1	0	98.9	>8	>8	
Vancomycin	100	0	0	1	1	

<sup>a</sup>Breakpoints as defined by NCCLS (M100-S14), 2004. Tigecycline breakpoints defined as: susceptible  $\leq 2$ ; intermediate = 4; and resistant