

# Global In Vitro Antibacterial Activity of Tigecycline against Methicillin Resistant and Methicillin Sensitive *Staphylococcus aureus* Isolates from the Tigecycline Evaluation Surveillance Trial (T.E.S.T.) Program

#P 802

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## REVISED ABSTRACT

**Background:** Resistant, *Staphylococcus aureus* and other resistant gram-positive bacteria, continue to be a therapeutic challenge for the clinician. Despite the introduction of new antimicrobials glycolcyclines are showing the promise of significant activity against many gram-positive pathogens including methicillin-resistant *S. aureus*. Tigecycline, the first glycolcycline 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 the T.E.S.T. program evaluation centers worldwide. **Methods:** A total of 1,381 clinical isolates were identified to the species level at each of 63 sites in 15 countries and confirmed by the central laboratory. Isolates were collected between January 2004 and December 2004. MICs were determined by each participating laboratory using custom broth microdilution panels supplied from Dade Behring MicroScan. All testing was performed according to CLSI guidelines and manufacturer's instructions. **Results:** Among the 1,381 isolates, 617 (44.7%) were found to be resistant to methicillin (MRSA). Besides the cross resistance of MRSA isolates to imipenem, ceftriaxone, penicillin, ampicillin and piperacillin/tazobactam, most of MRSA isolates were also non-susceptible to levofloxacin. The MICs of tigecycline ranged from 0.06 to 1 mcg/mL for all isolates of *S. aureus*. Tigecycline's MIC<sub>50</sub>/MIC<sub>90</sub> of 0.12/0.12 mcg/mL, respectively, against MSSA was the lowest than the comparative agents. Tigecycline's MIC<sub>50</sub>/MIC<sub>90</sub> of 0.12/0.25 mcg/mL, respectively, against MRSA was 8/4 fold lower than vancomycin, 2/4 fold lower than minocycline and 16 fold lower than linezolid. All isolates of *S. aureus* were inhibited by tigecycline at a MIC of 1 mcg/mL, regardless of methicillin phenotype. **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, for the treatment of serious nosocomial infections.

## INTRODUCTION

Tigecycline is a novel antimicrobial with an expanded broad-spectrum of activity from a new class of compounds, glycolcyclines. 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 worldwide.

## 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 - December 2004 from 63 study centers in 15 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  $\leq 2$ ; 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 was 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: List of countries and number of investigative sites that contributed to T.E.S.T. program.

Country	Investigative Sites
Canada	1
China	1
France	2
Germany	4
Hungary	1
India	1
Italy	2
Latvia	1
Philippines	1
Poland	1
Spain	1
Switzerland	1
The Netherlands	1
United Kingdom	1
United States	44
<b>Total</b>	<b>63</b>

Table 2: In vitro activity of tigecycline and comparator agents against 1,381 isolates of *Staphylococcus aureus*.

Organism Name (n=1,381)	Drug <sup>a</sup>	%S	%I	%R	MICs (mcg/mL)	
					MIC <sub>50</sub>	MIC <sub>90</sub>
<i>Staphylococcus aureus</i>	Tigecycline	100	0	0	0.12	0.25
	Amox-Clav	69	0	31	1	>8
	Ampicillin	9.9	0	90.1	16	>16
	Ceftriaxone	57.8	21	21.2	4	>64
	Imipenem	88	1.8	10.2	0.25	16
	Levofloxacin	58.4	8.5	33.1	0.25	>32
	Linezolid	100	0	0	2	4
<i>Staphylococcus aureus</i> , MSSA (n=764)	Minocycline	98.7	1	0.3	$\leq 0.25$	0.5
	Pip-Tazo	70.1	0	29.9	2	>16
	Penicillin	8.7	0	91.3	>8	>8
	Vancomycin	100	0	0	1	1
	Tigecycline	100	0	0	0.12	0.12
	Amox-Clav	93.5	0	6.5	1	2
	Ampicillin	17	0	83	4	>16
Ceftriaxone	91.6	4.1	4.3	4	8	
Imipenem	97.4	0.8	1.8	0.25	0.25	
Levofloxacin	86.1	2.5	11.4	0.12	8	
Linezolid	100	0	0	2	4	
Minocycline	99.1	0.8	0.1	$\leq 0.25$	0.5	
Pip-Tazo	93.7	0	6.3	1	4	
Penicillin	14.8	0	85.2	8	>8	
Vancomycin	100	0	0	0.5	1	

<i>Staphylococcus aureus</i> , MRSA (n=617)	Tigecycline	100	0	0	0.12	0.25
Amox-Clav	37.4	0	62.6	8	>8	
Ampicillin	1.1	0	98.9	>16	>16	
Ceftriaxone	14.9	42.1	43	32	>64	
Imipenem	75.9	3.2	20.9	0.5	>16	
Levofloxacin	22.9	16.3	60.8	8	>32	
Linezolid	100	0	0	2	4	
Minocycline	98.2	1.3	0.5	$\leq 0.25$	1	
Pip-Tazo	39.5	0	60.5	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  $\geq 8$

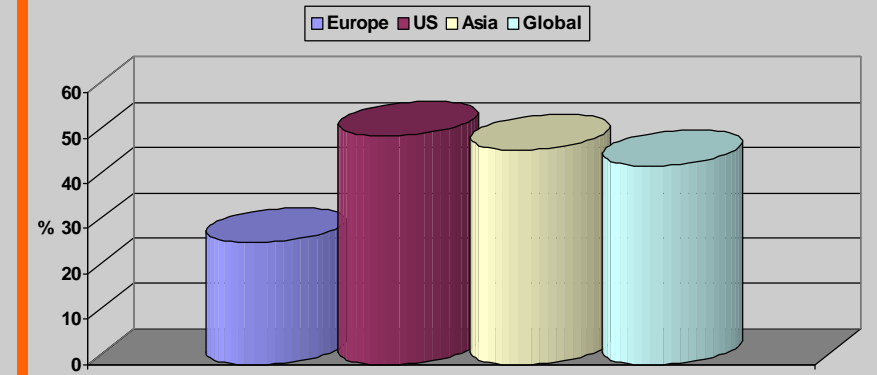
Table 3: Frequency distribution (n) and cumulative percent inhibition (%) at each MIC (mcg/mL) for tigecycline and comparative agents against 764 methicillin-sensitive *Staphylococcus aureus*.

MIC	$\leq 0.008$	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	1	149	543	62	6	1															
Amox-Clav	0.1	0.3	0.4	19.9	91	99.1	99.9	100															
Ampicillin	57	53	20	41	70	70	84	94	102	173													
Ceftriaxone	7.5	14.4	17	22.4	31.5	40.7	51.7	64	77.4	100													
Imipenem	2	2	31	289	353	23	18	13	4	29													
Levofloxacin	122	39	367	123	91.8	94.8	96.1	97.4	98.2	98.7	100												
Linezolid	16	64	80.1	80.1	83.5	84.6	86.1	88.6	91.6	94.5	97	100											
Minocycline						0.9	18.1	85.5	100														
Penicillin	94	28	19	89.7	89.7	95.7	97.8	99.1	99.9	100													
Pip-Tazo	12.3	14.8	18.5	23	30.1	36.3	46.4	57.9	100														
Vancomycin						5	380	356	19	4													
						0.7	50.4	97	99.5	100													

Table 4. Frequency distribution (n) and cumulative percent inhibition (%) at each MIC (mcg/mL) for tigecycline and comparative agents against 617 methicillin-resistant *Staphylococcus aureus*.

MIC	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	2	94	401	98	17	5																	
Amox-Clav	0.3	15.6	80.6	96.4	99.2	100																	
Ampicillin	3	3	1	5	13	11	34	63	142	342													
Ceftriaxone	0.5	1	1.1	1.9	4.1	5.8	11.3	21.6	44.6	100													
Imipenem					1	8	15	12	55	166	94	36	229										
Levofloxacin	11	74	32	6	2	16	101	75	97	75	128												
Linezolid	1.8	13.8	19	19.9	20.3	22.9	39.2	51.4	67.1	79.3	100												
Minocycline						10	106	427	74														
Penicillin	6	1	83.6	89.6	90.4	93.7	98.2	99.5	100														
Pip-Tazo	1	1.1	1.6	2.9	4.2	5.8	10.5	18.3	100														
Vancomycin				4	6	15	19	36	80	90	112	261											
				0.5	36.8	94.2	99.4	100															

Figure 1. Frequency distribution of MRSA by region.



## CONCLUSIONS

- Tigecycline inhibited the growth of all *Staphylococcus aureus* at a MIC  $\leq 1$  mcg/ml in all regions and labs without regard to methicillin phenotype.
- Tigecycline demonstrates greater in vitro activity against MSSA and MRSA than levofloxacin, imipenem and the  $\beta$ -lactam antimicrobials.
- Tigecycline demonstrates in vitro activity comparable to commonly prescribed antimicrobial agents, linezolid and vancomycin, currently used for the treatment of serious staphylococcal nosocomial infections.
- Tigecycline appears to be promising agent in the treatment of methicillin sensitive and methicillin resistant *Staphylococcus aureus*.