

Tigecycline Evaluation Surveillance Trial (T.E.S.T.) - In Vitro Antibacterial Activity Against Methicillin Resistant and Methicillin Sensitive *Staphylococcus aureus* Isolates

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REVISED ABSTRACT

Background: Resistance of gram positive bacteria continue to be a therapeutic challenge for the clinician. Glycylcyclines are showing the promise of significant activity against many gram-positive pathogens. Tigecycline, a member of this new class of antimicrobials, has shown excellent activity against *Staphylococcus* spp. The *in vitro* activity of tigecycline as compared with those of 9 comparator agents (ampicillin, amoxicillin-clav, imipenem, ceftriaxone, levofloxacin, minocycline, vancomycin, linezolid, piperacillin-tazobactam) against methicillin resistant *Staphylococcus aureus* (MRSA) and methicillin sensitive *Staphylococcus aureus* (MSSA) from multi-national evaluation centers in the T.E.S.T. **Methods:** A total of 710 clinical strains of *Staphylococcus aureus* were identified to the species level at each participating site and confirmed by the central laboratory. Isolates were collected between January 2004 – September 2004. MIC's were determined by the local laboratory using broth microdilution panels from Dade Microscan according to NCCLS guidelines and manufacturer's instructions.

Results: The MICs of tigecycline ranged from 0.03 to 1 for all isolates of *S. aureus*. Tigecycline MIC₉₀ of 0.25 mcg/ml against MSSA was 2 to 4 fold lower than imipenem, minocycline and vancomycin, respectively, and 8 or more fold lower than the remaining comparative agents. Tigecycline MIC₉₀/MIC₅₀ of 0.25/0.5 mcg/ml against MRSA was equal to or better than minocycline and 8/4 fold lower than vancomycin, 16 fold lower than linezolid.

Conclusion: The *in vitro* activity of tigecycline was comparable in all *S. aureus* tested regardless of methicillin phenotype. Tigecycline *in vitro* activity against MRSA was equal to or superior than all antimicrobial agents tested including imipenem, minocycline, linezolid, and vancomycin.

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 MIC₉₀ values 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 [12,13].

This study compared the activity of tigecycline with other agents against methicillin-resistant *Staphylococcus aureus* (MRSA) and methicillin-sensitive *Staphylococcus aureus* (MSSA) from hospitals in Europe and North America.

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 – September 2004 from 20 study centers in 6 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 NCCLS where applicable [14]. Tigecycline tentative breakpoints (in units of mcg/mL) are defined as susceptible ≤ 2 ; intermediate = 4; and resistant ≥ 8 .
- Isolates were identified to genus and species at each site by the local laboratory. Isolates were tested by the local laboratory.
- Organism collection, transport, confirmation of organism identification, as well as, construction and management of a centralized database was coordinated by Laboratories International for Microbiology Studies (LIMS).

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RESULTS

Table 1. In Vitro Activity of Tigecycline and Comparator Agents Against 710 Isolates of *Staphylococcus aureus*

Organism Name	Drug	NCCLS BP*	MIC ₅₀		MIC ₉₀	
			%S	%I	%R	MIC ₉₀
<i>Staphylococcus aureus</i> (n=710)	Tigecycline	2 [†]	100	0	0	0.25
	Amox/Clav	4/2	60.9	0	39.1	2
	Ampicillin	8	9.5	0	90.5	16
	Ceftriaxone	8	54.1	17.1	28.8	8
	Imipenem	4	82.9	2.3	14.6	0.25
	Levofloxacin	2	55.8	6.1	37.8	0.25
<i>Staphylococcus aureus</i> , MSSA (n=401)	Tigecycline	2 [†]	100	0	0	0.12
	Amox/Clav	4/2	87.6	0	12.4	1
	Ampicillin	8	15.7	0	84.3	8
	Ceftriaxone	8	86.9	4.5	8.6	4
	Imipenem	4	94.8	1.9	3	0.25
	Levofloxacin	2	82.8	2.6	14.2	0.12
<i>Staphylococcus aureus</i> , MRSA (n=309)	Tigecycline	2 [†]	100	0	0	0.12
	Amox/Clav	4/2	26.2	0	73.8	8
	Ampicillin	8	1.5	0	98.5	>16
	Ceftriaxone	8	11.7	33.5	54.9	64
	Imipenem	4	67.5	2.9	29.6	1
	Levofloxacin	2	20.9	10.7	68.4	16

* Breakpoints defined by the NCCLS 2003, document M100-S13; Tigecycline tentative breakpoints (in mcg/mL) defined as susceptible ≤ 2 ; intermediate = 4; resistant ≥ 8 MRSA = methicillin-resistant *S. aureus*. MSSA = methicillin-susceptible *S. aureus*.

Table 2. Frequency Distribution (n) and Cumulative Percent Inhibition (%) at each MIC (mcg/mL) for Tigecycline and Comparative Agents Against 401 Methicillin-sensitive *Staphylococcus aureus*.

	MIC (mcg/mL) – n / Cumulative % – (MIC ₅₀)												
	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	>64
Tigecycline	1	84	272	34	9	1							
Amox/Clav	0.4	21.3	89.1	97.4	99.6	100							
Ampicillin	29	26	9	15	31	31	26	44	55	135			
Ceftriaxone	7.1	13.5	15.7	19.5	27.3	35.2	41.6	52.4	66.3	100			
Imipenem		113	236	15	5	8	3	8	5	8			
Levofloxacin		28.5	87.6	91.4	92.5	94.4	95.1	97	98.1	100			
Linezolid		13.9	60.7	76.4	80.5	80.9	83.1	85.8	88.8	91.4	94.4	100	
Minocycline					0.4	16.5	89.1	100					
Pip/Tazo					326	55	11	8	1				
Vancomycin					81.3	95.1	97.8	97.8	99.6	100			

Figure 1. In Vitro Activity of Tigecycline and Comparators Against 401 MSSA Showing Cumulative Percent Inhibited (%) at Each MIC (mcg/ml)

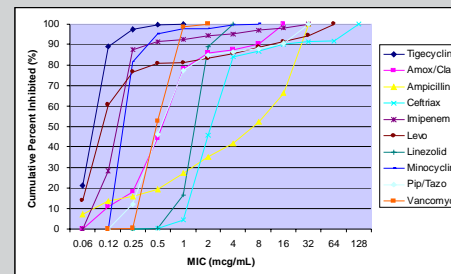
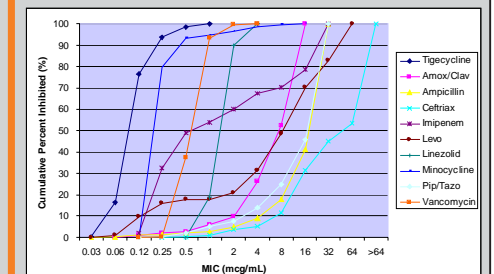


Table 3. Frequency Distribution (n) and Cumulative Percent Inhibition (%) at each MIC (mcg/mL) for Tigecycline and Comparative Agents Against 309 Methicillin-resistant *Staphylococcus aureus*.

	MIC (mcg/mL) – n / Cumulative % – (MIC ₅₀)												
	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	>64
Tigecycline	1	49	187	52	15	5							
Amox/Clav	0.5	16.5	76.7	93.7	98.5	100							
Ampicillin	1	3	1	3	6	14	27	72	182				
Ceftriaxone	0.5	1.5	1.9	2.9	4.9	9.2	18	41.3	100				
Imipenem		6	94	51	15	20	23	9	25	66			
Levofloxacin	3	27	20	6	9	33	52	68	39	52			
Linezolid	1	9.7	16	18	20.9	31.6	48.5	70.4	83	100			
Minocycline						58	219	32					
Pip/Tazo						79.6	93.2	94.7	96.6	98.5	99.5	100	
Vancomycin					0.5	1.9	5.3	7.8	14.1	24.8	45.6	100	

Figure 2. In Vitro Activity of Tigecycline and Comparators Against 309 MRSA Showing Cumulative Percent Inhibited (%) at Each MIC (mcg/ml)



CONCLUSIONS

- Tigecycline inhibited the growth of all MSSA and MRSA at a MIC ≤ 1 mcg/ml.
- Tigecycline demonstrates *in vitro* activity comparable to or better than both vancomycin and linezolid against all MSSA and MRSA.
- Tigecycline demonstrates greater *in vitro* activity against MSSA and MRSA than levofloxacin, imipenem and the β -lactam antimicrobials.
- Tigecycline appears to be promising agent in the treatment of methicillin sensitive and methicillin resistant *Staphylococcus aureus*.