

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.) in the USA

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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. Tigecycline, the first glycylycine to enter clinical trials, has shown excellent activity against *Staphylococcus* spp. This study evaluated the in vitro activity of tigecycline as compared to 10 comparator agents (ampicillin, amoxicillin-clavulanic acid, imipenem, ceftriaxone, levofloxacin, minocycline, vancomycin, linezolid, penicillin, piperacillin-tazobactam) against *S. aureus* including methicillin-resistant *Staphylococcus aureus* (MRSA) and methicillin-sensitive *Staphylococcus aureus* (MSSA) from 137 US centers in the T.E.S.T. program. **Methods:** A total of 3,723 clinical isolates were identified to the species level at each of participating sites and confirmed by the central laboratory. MICs were determined by each participating laboratory using broth microdilution panels from Dade MicroScan. All testing was performed and interpreted according to NCCLS guidelines and manufacturer's instructions. **Results:** Among the 3,723 isolates, 1,997 (53.6%) were found to be resistant to methicillin (MRSA). No resistance was observed against tigecycline, vancomycin and linezolid. The MICs of tigecycline ranged from 0.008 to 0.5 mcg/mL for all isolates of *S. aureus*, and tigecycline presented the lowest MIC_{50/90} 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. Tigecycline's MIC_{50/90} of 0.12/0.12 was also the lowest among all MSSA isolates. **Conclusion:** The in vitro activity of tigecycline was comparable in all *S. aureus* tested regardless of methicillin phenotype. Tigecycline activity against MRSA was more potent than all antimicrobial agents.

INTRODUCTION

Tigecycline is a novel antimicrobial with expanded broad-spectrum activity from a new class of compounds, the glycylycines. 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]. Tigecycline was developed to provide activity against tetracycline and multi-drug-resistant gram-positive pathogens and has demonstrated significant broad-spectrum activity against aerobic and anaerobic gram-positive and gram-negative microorganisms [2-4].

Tigecycline resistance is very infrequent and is also difficult to induce in the laboratory [5, 6] with a selection frequency observed at less than 10⁻⁹ [3, 5, 7]. With the exception of *P. aeruginosa*, tetracycline-resistant bacteria with either tetracycline efflux pumps or ribosomal protective features are sensitive to tigecycline [2-4, 7-11]. Tigecycline has shown to be a highly effective against multi-resistant *Acinetobacter* spp., particularly *A. baumannii* that are commonly associated with serious nosocomial infections. Similar activity has been observed against *Enterobacteriaceae*, even extended-spectrum beta-lactamase (ESBL) and AmpC producing strains [10]. Tigecycline has demonstrated MIC₉₀ values of \leq 0.5 mcg/ml against methicillin-resistant *Staphylococcus aureus* (MRSA) and other gram-positive organisms [2, 4-6]. Tigecycline has shown potent activity against animal models infected with selected strains of multi-drug resistant *Enterococcus faecium* and *Enterococcus faecalis* [4, 5] with diverse genotypes van-A, -B and -C [6].

This study was designed to better define the in vitro activity of tigecycline in *Staphylococcus aureus* clinical isolates collected from 137 study centers within the 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. Isolates were identified to genus and species by the local laboratory. Each site tested the isolates using broth microdilution.
- Clinical isolates (n=3,723) were collected tested between January 2004 - December 2006 from 137 study centers in the United States.
- Custom broth microdilution panels were supplied by MicroScan (Dade MicroScan, Sacramento, CA, USA) with the following antimicrobial agents and concentrations (expressed in mcg/ml): amoxicillin/clavulanic acid (0.12-32); ampicillin (0.5-32); piperacillin/tazobactam (0.06-128); levofloxacin (0.008-8); ceftriaxone (0.06-64); ceftazidime (8-32); linezolid (0.5-8); penicillin (0.06-8); imipenem (0.06-16); minocycline (0.5-16); tigecycline (0.008-16); and vancomycin (0.12-32).
- MIC interpretive criteria for all drugs except tigecycline followed published guidelines established by the CLSI where applicable [12]. MIC interpretive criteria for tigecycline followed criteria established by the Federal Drug Administration (FDA, United States, 2005) where applicable [13].
- Quality control of broth microdilution panels followed manufacture's and CLSI guidelines using the following ATCC strains: *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, USA).

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RESULTS

The results are listed in the following tables:

Table 1. In vitro activity of tigecycline and comparative agents against 3,723 clinical isolates of *Staphylococcus aureus*.*

| Organism / Phenotype | Drug | %Sus | %Int | %Res | MIC (mcg/mL) | |
|---|--------------|------|------|------|-------------------|-------------------|
| | | | | | MIC ₅₀ | MIC ₉₀ |
| <i>Staphylococcus aureus</i> (n=3,723) | Tigecycline | 100 | a | a | 0.12 | 0.25 |
| | AmoxClav | 61.2 | 0 | 38.8 | 2 | >8 |
| | Ampicillin | 9.1 | 0 | 90.9 | 16 | >16 |
| | Ceftriaxone | 52.2 | 28.5 | 19.3 | 8 | >64 |
| | Imipenem | 91.6 | 2.1 | 6.3 | 0.25 | 4 |
| | Levofloxacin | 55.7 | 2.7 | 41.6 | 0.25 | >32 |
| | Linezolid | 100 | a | a | 2 | 2 |
| | Minocycline | 99.2 | 0.7 | 0.1 | \leq 0.25 | \leq 0.25 |
| | Penicillin | 8 | 0 | 92 | >8 | >8 |
| | PipTazo | 66.7 | 0 | 33.3 | 4 | >16 |
| Vancomycin | 100 | 0 | 0 | 0.5 | 1 | |
| Methicillin-Resistant [†] <i>Staphylococcus aureus</i> (n=1,997) | Tigecycline | 100 | a | a | 0.12 | 0.25 |
| | AmoxClav | 27.6 | 0 | 72.4 | 8 | >8 |
| | Ampicillin | 0 | 0 | 100 | >16 | >16 |
| | Ceftriaxone | 11.5 | 52.6 | 36 | 32 | >64 |
| | Imipenem | 84.5 | 3.9 | 11.6 | 0.5 | 16 |
| | Levofloxacin | 21.5 | 2.9 | 75.7 | 8 | >32 |
| | Linezolid | 100 | a | a | 2 | 2 |
| | Minocycline | 99.1 | 0.8 | 0.1 | \leq 0.25 | 0.5 |
| | Penicillin | 0 | 0 | 100 | >8 | >8 |
| | PipTazo | 38 | 0 | 62 | 16 | >16 |
| Vancomycin | 100 | 0 | 0 | 1 | 1 | |
| Methicillin-Susceptible [‡] <i>Staphylococcus aureus</i> (n=1,726) | Tigecycline | 100 | a | a | 0.12 | 0.12 |
| | AmoxClav | 100 | 0 | 0 | 1 | 2 |
| | Ampicillin | 19.6 | 0 | 80.4 | 4 | >16 |
| | Ceftriaxone | 99.3 | 0.6 | 0.1 | 2 | 4 |
| | Imipenem | 100 | 0 | 0 | \leq 0.12 | 0.25 |
| | Levofloxacin | 95.4 | 2.4 | 2.2 | 0.12 | 0.25 |
| | Linezolid | 100 | a | a | 2 | 2 |
| | Minocycline | 99.4 | 0.6 | 0 | \leq 0.25 | \leq 0.25 |
| | Penicillin | 17.3 | 0 | 82.7 | 8 | >8 |
| | PipTazo | 100 | 0 | 0 | 0.5 | 1 |
| Vancomycin | 100 | 0 | 0 | 0.5 | 1 | |

* Susceptibilities are defined in CLSI document M100-S16 (2006) where applicable. Tigecycline breakpoints are defined in FDA package insert (Tygacil[®], 2005) as susceptible \leq 0.5 mcg/mL.

^a The absence of resistance precludes the assignment of intermediate and resistant breakpoints.

[‡] Methicillin phenotype is based upon the susceptibility of *S. aureus* to cefoxitin disk according to CLSI document M100-S16 (2006).

Table 2. Frequency distribution (n) and cumulative percent inhibited (%) in vitro activity of tigecycline and comparative agents against 3,723 *S. aureus*.

| N / Cum% | MIC (mcg/mL) | | | | | | | | | | | | | | |
|--------------|--------------|-------|------|------|------|------|-----|---|---|---|---|----|----|----|-----|
| | \leq 0.008 | 0.015 | 0.03 | 0.06 | 0.12 | 0.25 | 0.5 | 1 | 2 | 4 | 8 | 16 | 32 | 64 | >64 |
| Tigecycline | 13 | 3 | 28 | 656 | 2626 | 320 | 77 | | | | | | | | |
| AmoxClav | 0.3 | 0.4 | 1.2 | 18.8 | 89.3 | 97.9 | 100 | | | | | | | | |
| Ampicillin | | | | | | | | | | | | | | | |
| Ceftriaxone | | | | | | | | | | | | | | | |
| Imipenem | | | | | | | | | | | | | | | |
| Levofloxacin | | | | | | | | | | | | | | | |
| Linezolid | | | | | | | | | | | | | | | |
| Minocycline | | | | | | | | | | | | | | | |
| Penicillin | | | | | | | | | | | | | | | |
| PipTazo | | | | | | | | | | | | | | | |
| Vancomycin | | | | | | | | | | | | | | | |

Table 3. Frequency distribution (n) and cumulative percent inhibited (%) in vitro activity of tigecycline and comparative agents against 1,997 methicillin-resistant *S. aureus*.

| N / Cum% | MIC (mcg/mL) | | | | | | | | | | | | | | |
|--------------|--------------|------|------|------|------|-----|---|---|---|---|----|----|----|-----|--|
| | 0.015 | 0.03 | 0.06 | 0.12 | 0.25 | 0.5 | 1 | 2 | 4 | 8 | 16 | 32 | 64 | >64 | |
| Tigecycline | 1 | 7 | 289 | 1406 | 227 | 67 | | | | | | | | | |
| AmoxClav | | | | | | | | | | | | | | | |
| Ampicillin | | | | | | | | | | | | | | | |
| Ceftriaxone | | | | | | | | | | | | | | | |
| Imipenem | | | | | | | | | | | | | | | |
| Levofloxacin | | | | | | | | | | | | | | | |
| Linezolid | | | | | | | | | | | | | | | |
| Minocycline | | | | | | | | | | | | | | | |
| Penicillin | | | | | | | | | | | | | | | |
| PipTazo | | | | | | | | | | | | | | | |
| Vancomycin | | | | | | | | | | | | | | | |

Table 4. Frequency distribution (n) and cumulative percent inhibited (%) in vitro activity of tigecycline and comparative agents against 1,726 methicillin-susceptible *S. aureus*.

| N / Cum% | MIC (mcg/mL) | | | | | | | | | | | | | | |
|--------------|--------------|-------|------|------|------|------|-----|---|---|---|---|----|----|----|-----|
| | \leq 0.008 | 0.015 | 0.03 | 0.06 | 0.12 | 0.25 | 0.5 | 1 | 2 | 4 | 8 | 16 | 32 | 64 | >64 |
| Tigecycline | 13 | 21 | 367 | 1220 | 93 | 10 | | | | | | | | | |
| AmoxClav | 0.8 | 0.9 | 2.1 | 23.3 | 94 | 99.4 | 100 | | | | | | | | |
| Ampicillin | | | | | | | | | | | | | | | |
| Ceftriaxone | | | | | | | | | | | | | | | |
| Imipenem | | | | | | | | | | | | | | | |
| Levofloxacin | | | | | | | | | | | | | | | |
| Linezolid | | | | | | | | | | | | | | | |
| Minocycline | | | | | | | | | | | | | | | |
| Penicillin | | | | | | | | | | | | | | | |
| PipTazo | | | | | | | | | | | | | | | |
| Vancomycin | | | | | | | | | | | | | | | |

CONCLUSIONS

- Tigecycline inhibited 100% of all *Staphylococcus aureus* at or below 0.5 mcg/mL and 100% of MRSA and MSSA isolates at or below 0.5 mcg/mL.
- The in vitro activities of tigecycline, amoxicillin-clavulanic acid, ceftriaxone, minocycline, imipenem, linezolid, piperacillin-tazobactam and vancomycin were equivalent against MSSA. Only tigecycline, linezolid, minocycline and vancomycin remained more than 99% active against MRSA.
- The in vitro activity of tigecycline in this study suggests that tigecycline should be seriously considered for the treatment of *S. aureus* including both methicillin-resistant and -susceptible phenotypes.