

Tigecycline Evaluation Surveillance Trial (T.E.S.T.) - In Vitro Antibacterial Activity against 9,567 Gram-positive and Gram-negative Pathogens in the United States

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REVISED ABSTRACT

Background: Tigecycline, a member of a new class of antimicrobials (glycylcyclines), has been shown to have potent expanded broad spectrum activity against most commonly encountered Gram-positive and Gram-negative species, including anaerobic pathogens responsible for community and hospital infections. The T.E.S.T. program determined the in vitro activity of tigecycline compared to amikacin, ampicillin, imipenem, ceftazidime, ceftaxime, ceftazidime, ceftazidime, levofloxacin, minocycline and piperacillin/tazobactam against Gram-negative strains in addition to linezolid, penicillin and vancomycin for the Gram-positive species. Isolates were collected from 44 hospitals in the United States throughout 2004. **Methods:** A total of 9,567 clinical isolates were identified to the species level at each participating site and confirmed by the central laboratory. Minimum Inhibitory Concentration (MICs) were determined by the local laboratory using supplied broth microdilution panels from Dade Behring and interpreted according to CLSI guidelines. **Results:** Tigecycline's activity was similar to imipenem against most *Enterobacteriaceae*. Tigecycline inhibited ESBL producers with a MIC₉₀ of 2mcg/ml. Although similar to other classes of broad spectrum antimicrobial agents against non-fermenters, tigecycline was especially active against *Acinetobacter* spp. with the lowest MIC₉₀ of 1 mcg/ml. Tigecycline inhibited *S. aureus* with MIC₉₀ of 0.25 mcg/ml for both MSSA and MRSA isolates. Similar results were noticed against enterococci with a tigecycline MIC₉₀ of 0.12 mcg/mL that remained consistent regardless of vancomycin susceptibility. **Conclusion:** Tigecycline's in vitro activity was comparable or greater than most commonly prescribed antimicrobials against a broad spectrum of aerobic clinical pathogens. The presented data suggest that tigecycline may be an effective therapeutic option against many aerobic Gram-positive and Gram-negative pathogens, including ESBL, VRE and MRSA resistant phenotypes.

INTRODUCTION

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

Tigecycline resistance is very infrequent and is also difficult to select for 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 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 β -lactamase (ESBL) 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 in 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 a large diverse population of clinical isolates collected in hospitals across 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 other defined sources. Only one isolate per patient was accepted.
- 9,567 Clinical isolates were collected and tested between January 2004 – December 2004 from 53 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); piperacillin/tazobactam (0.06-128); levofloxacin (0.008-8); ceftazidime (0.06-64); ceftaxime (0.5-32); ampicillin (0.5-32); amikacin (0.5-64); minocycline (0.5-16); ceftazidime (8-32); tigecycline (0.008-16); and imipenem (0.06-16).

- ESBL activity was confirmed by testing the following antibiotic disks: cefotaxime (30 μ g), cefotaxime/clavulanic acid (30/10 μ g), and ceftazidime (30g), ceftazidime/clavulanic acid (30/10 μ g). Antibiotic disks were manufactured by Oxoid Inc. Ogdensburg, New York. Mueller-Hinton agar used in testing was manufactured by Remel Inc. Lenexa, Kansas.
- An organism is interpreted as producing an ESBL if there is an increase of \geq 5mm in the inhibition zone of the combination disc when compared to that of the cephalosporin alone: cefotaxime/clavulanic acid – cefotaxime \geq 5 mm or ceftazidime/clavulanic acid – ceftazidime \geq 5 mm.
- MIC interpretive criteria followed published guidelines established by the CLSI where applicable [12]. Tigecycline tentative breakpoints (in units of mcg/mL) are defined as susceptible \leq 2; intermediate = 4; and resistant \geq 8.
- Isolates were identified to the genus and species level by the local laboratory. Each site tested the isolates using broth microdilution panels.
- Quality control of broth microdilution panels followed manufacturer's and NCCLS guidelines using the following ATCC strains: *Enterococcus faecalis* ATCC 29212; *Escherichia coli* ATCC 25922; *Haemophilus influenzae* ATCC 49247; *Haemophilus influenzae* ATCC 49766; *Staphylococcus aureus* ATCC 29213; *Streptococcus pneumoniae* ATCC 49619; and *Pseudomonas aeruginosa* ATCC 27853.
- 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. In Vitro Activity of Tigecycline and Comparative Agents against 4,103 Strains of *Enterobacteriaceae*

| Organism Name ^a | Drug ^b | MIC (mcg/mL) | | | | | Organism Name ^a | Drug ^b | MIC (mcg/mL) | | | | |
|-------------------------------------|-------------------|--------------|------|------|-------------------|-------------------|---|-------------------|--------------|------|------|-------------------|-------------------|
| | | %SUS | %INT | %RES | MIC ₅₀ | MIC ₉₀ | | | %SUS | %INT | %RES | MIC ₅₀ | MIC ₉₀ |
| <i>Enterobacteriaceae</i> (n=4,103) | Tigecycline | 96.5 | 2.8 | 0.7 | 0.5 | 1 | ESBL producers (<i>E. coli</i> , <i>K. pneumoniae</i> , <i>K. oxytoca</i>) (n=98) | Tigecycline | 94.9 | 4.1 | 1 | 0.5 | 2 |
| | Amikacin | 99.1 | 0.7 | 0.1 | 2 | 4 | | Amikacin | 91.8 | 8.2 | 0 | 8 | 16 |
| | Amox/Clav | 49.8 | 6.4 | 43.6 | >32 | >32 | | Amox/Clav | 30.6 | 27.6 | 41.8 | 16 | >32 |
| | Ampicillin | 16.7 | 6.6 | 76.7 | >32 | >32 | | Ampicillin | 0 | 2 | 98 | >32 | >32 |
| | Cefepime | 96.6 | 1 | 2.4 | \leq 0.5 | 1 | | Cefepime | 61.2 | 5.1 | 33.7 | 8 | >32 |
| | Ceftazidime | 87.5 | 2.2 | 10.2 | \leq 8 | 32 | | Ceftazidime | 10.2 | 3.1 | 86.7 | >32 | >32 |
| | Ceftaxime | 90.3 | 4.3 | 5.4 | \leq 0.06 | 8 | | Ceftaxime | 27.6 | 29.6 | 42.9 | 32 | >64 |
| | Imipenem | 87.3 | 0.6 | 1.1 | 0.5 | 1 | | Imipenem | 82.7 | 11.2 | 6.1 | 0.5 | 8 |
| | Levofloxacin | 98.4 | 1.8 | 10.8 | 0.06 | 8 | | Levofloxacin | 23.5 | 6.1 | 70.4 | >8 | >8 |
| | Minocycline | 86.4 | 6.7 | 6.9 | 2 | 8 | | Minocycline | 72.4 | 9.2 | 18.4 | 4 | 16 |
| | Pip-Tazo | 91.4 | 3.5 | 5.1 | 2 | 16 | | Pip-Tazo | 57.1 | 5.1 | 37.8 | 16 | >128 |
| <i>E. coli</i> (n=1,240) | Tigecycline | 99.9 | 0.1 | 0 | 0.12 | 0.25 | <i>E. aerogenes</i> (n=334) | Tigecycline | 95.8 | 3.6 | 0.6 | 0.5 | 1 |
| | Amikacin | 99.5 | 0.4 | 0.1 | 2 | 4 | | Amikacin | 98.8 | 1.2 | 0 | 2 | 4 |
| | Amox/Clav | 75.6 | 13.2 | 11.2 | 4 | 32 | | Amox/Clav | 6.3 | 3.3 | 90.4 | >32 | >32 |
| | Ampicillin | 46.1 | 13.3 | 52.6 | >32 | >32 | | Ampicillin | 5.1 | 4.5 | 90.4 | >32 | >32 |
| | Cefepime | 98.7 | 0.3 | 1 | \leq 0.5 | \leq 0.5 | | Cefepime | 97.6 | 1.5 | 0.9 | \leq 0.5 | 1 |
| | Ceftazidime | 94.7 | 1.4 | 4 | \leq 8 | \leq 8 | | Ceftazidime | 84.1 | 5.4 | 10.5 | \leq 8 | 32 |
| | Ceftaxime | 95.9 | 1.8 | 2.3 | \leq 0.06 | 0.25 | | Ceftaxime | 92.4 | 5.1 | 1.5 | 0.12 | 8 |
| | Imipenem | 99.7 | 0 | 0.3 | 0.25 | 0.5 | | Imipenem | 98.8 | 0 | 1.2 | 1 | 2 |
| | Levofloxacin | 77.3 | 1.7 | 2.1 | 0.03 | >8 | | Levofloxacin | 94.9 | 2.4 | 2.7 | 0.06 | 0.5 |
| | Minocycline | 85.5 | 8.1 | 6.4 | 1 | 8 | | Minocycline | 91 | 4.2 | 4.8 | 2 | 4 |
| | Pip-Tazo | 96 | 1.8 | 2.3 | 1 | 4 | | Pip-Tazo | 89.5 | 6.9 | 3.6 | 2 | 32 |
| <i>K. pneumoniae</i> (n=1,024) | Tigecycline | 94.6 | 4.5 | 0.9 | 0.5 | 2 | <i>E. cloacae</i> (n=795) | Tigecycline | 93.6 | 4.3 | 2.1 | 0.5 | 2 |
| | Amikacin | 98 | 1.8 | 0.2 | 2 | 4 | | Amikacin | 99.4 | 0.4 | 0.3 | 2 | 4 |
| | Amox/Clav | 85.2 | 5.7 | 9.2 | 2 | 16 | | Amox/Clav | 3.6 | 1.8 | 94.6 | >32 | >32 |
| | Ampicillin | 31.1 | 17 | 79.9 | >32 | >32 | | Ampicillin | 4.3 | 3 | 92.7 | >32 | >32 |
| | Cefepime | 94.4 | 0.7 | 4.9 | \leq 0.5 | 2 | | Cefepime | 95.2 | 1.8 | 3 | \leq 0.5 | 4 |
| | Ceftazidime | 87.9 | 1.2 | 10.9 | \leq 8 | >32 | | Ceftazidime | 75.5 | 3.6 | 20.9 | \leq 8 | >32 |
| | Ceftaxime | 91 | 3.3 | 5.7 | \leq 0.06 | 8 | | Ceftaxime | 78.5 | 8.8 | 12.7 | 0.25 | 64 |
| | Imipenem | 96.1 | 1.8 | 2.1 | 0.5 | 1 | | Imipenem | 98.7 | 0.1 | 1.1 | 0.5 | 1 |
| | Levofloxacin | 88.6 | 1.1 | 10.4 | 0.06 | 8 | | Levofloxacin | 91.6 | 2.5 | 5.9 | 0.06 | 2 |
| | Minocycline | 84.6 | 6.4 | 9 | 2 | 8 | | Minocycline | 85.2 | 6.4 | 8.4 | 2 | 8 |
| | Pip-Tazo | 91.3 | 1.1 | 7.6 | 2 | 16 | | Pip-Tazo | 82.9 | 8.8 | 8.3 | 2 | 64 |
| <i>K. oxytoca</i> (n=173) | Tigecycline | 98.8 | 1.2 | 0 | 0.25 | 1 | <i>S. marcescens</i> (n=467) | Tigecycline | 96.8 | 3 | 0.2 | 1 | 1 |
| | Amikacin | 100 | 0 | 0 | 2 | 4 | | Amikacin | 100 | 0 | 0 | 2 | 4 |
| | Amox/Clav | 86.1 | 4 | 9.8 | 2 | 16 | | Amox/Clav | 2.4 | 1.1 | 96.6 | >32 | >32 |
| | Ampicillin | 2.9 | 8.7 | 88.4 | >32 | >32 | | Ampicillin | 2.4 | 3.6 | 94 | >32 | >32 |
| | Cefepime | 100 | 0 | 0 | \leq 0.5 | 1 | | Cefepime | 96.8 | 1.5 | 1.7 | \leq 0.5 | 1 |
| | Ceftazidime | 92.5 | 0.6 | 6.9 | \leq 8 | 78 | | Ceftazidime | 91 | 3 | 6 | \leq 8 | \leq 8 |
| | Ceftaxime | 94.2 | 5.2 | 0.6 | \leq 0.06 | 4 | | Ceftaxime | 92.7 | 3.4 | 3.9 | 0.25 | 4 |
| | Imipenem | 99.4 | 0 | 0.6 | 0.5 | 0.5 | | Imipenem | 98.7 | 0.4 | 0.9 | 1 | 2 |
| | Levofloxacin | 94.8 | 3.5 | 1.7 | 0.03 | 1 | | Levofloxacin | 96.1 | 1.3 | 2.6 | 0.12 | 1 |
| | Minocycline | 93.1 | 5.8 | 1.2 | 1 | 4 | | Minocycline | 89.9 | 5.8 | 4.3 | 4 | 8 |
| | Pip-Tazo | 92.5 | 0.6 | 6.9 | 1 | 8 | | Pip-Tazo | 95.7 | 2.6 | 1.7 | 1 | 8 |

^a Only species with n \geq 20 are represented.

^b Breakpoints as defined by NCCLS where available (M100-S14), 2004. Tigecycline breakpoints defined as: susceptible \leq 2; intermediate = 4; and resistant \geq 8.

Table 2. In Vitro Activity of Tigecycline and Comparative Agents against 1,665 *Acinetobacter* spp and *Pseudomonas aeruginosa*

| Organism Name ^a | Drug ^b | MIC (mcg/mL) | | | | |
|----------------------------------|-------------------|--------------|------|------|-------------------|-------------------|
| | | %SUS | %INT | %RES | MIC ₅₀ | MIC ₉₀ |
| <i>Acinetobacter</i> spp (n=684) | Tigecycline | 98.8 | 1.2 | 0 | 0.5 | 1 |
| | Amikacin | 85.2 | 7.2 | 7.6 | 4 | 32 |
| | Amox/Clav | na | na | na | 32 | >32 |
| | Ampicillin | na | na | na | >32 | >32 |
| | Cefepime | 46.3 | 15.4 | 38.3 | 16 | >32 |
| | Ceftazidime | 47.4 | 13.8 | 48.8 | 16 | >32 |
| | Ceftaxime | 29.4 | 22.8 | 47.8 | 32 | >64 |
| | Imipenem | 87.8 | 5.9 | 6.3 | 0.5 | 8 |
| | Levofloxacin | 48 | 5.1 | 46.9 | 4 | >8 |
| | Minocycline | 90.2 | 7.6 | 2.2 | \leq 0.5 | 4 |
| | Pip-Tazo | 73.1 | 0 | 26.9 | 8 | >128 |
| <i>A. baumannii</i> (n=617) | Tigecycline | 98.7 | 1.3 | 0 | 0.5 | 1 |
| | Amikacin | 84.7 | 7.8 | 7.5 | 4 | 32 |
| | Amox/Clav | na | na | na | 32 | >32 |
| | Ampicillin | na | na | na | >32 | >32 |
| | Cefepime | 43.8 | 16.5 | 39.7 | 16 | >32 |
| | Ceftazidime | 46 | 3.1 | 50.9 | 32 | >32 |
| | Ceftaxime | 26.7 | 23 | 50.2 | 64 | >64 |
| | Imipenem | 87 | 6 | 7 | 0.5 | 8 |
| | Levofloxacin | 45.4 | 5.3 | 49.3 | 4 | >8 |
| | Minocycline | 89.3 | 8.3 | 2.4 | \leq 0.5 | 8 |
| | Pip-Tazo | 72.6 | 0 | 27.4 | 8 | >128 |
| <i>A. calcoaceticus</i> (n=15) | Tigecycline | 100 | 0 | 0 | 0.25 | 2 |
| | Amikacin | 93.3 | 0 | 6.7 | 2 | 8 |
| | Amox/Clav | na | na | na | 32 | >32 |
| | Ampicillin | na | na | na | 32 | >32 |
| | Cefepime | 60 | 13.3 | 26.7 | 8 | >32 |
| | Ceftazidime | 66.7 | 13.3 | 20 | \leq 8 | >32 |
| | Ceftaxime | 26.7 | 46.7 | 26.7 | 16 | >64 |
| | Imipenem | 100 | 0 | 0 | 0.5 | 1 |
| | Levofloxacin | 66.7 | 0 | 33.3 | 0.12 | >8 |
| | Minocycline | 93.3 | 6.7 | 0 | \leq 0.5 | 2 |
| | Pip-Tazo | 86.7 | 0 | 13.3 | 4 | 128 |
| <i>A. hydrophilus</i> (n=37) | Tigecycline | | | | | |