# In Vitro Activity of Tigecycline Against In-patient and Out-patient Enterobacteriaceae Collected From Australia - T.E.S.T. Program 2006

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## REVISED ABSTRACT

**Background:** Tigecycline, a member of a new class of antimicrobials (glycylcyclines), has been shown to have potent broad spectrum activity against community and hospital acquired infections. The T.E.S.T. program determined the in vitro activity of tigecycline compared to most commonly prescribed broad spectrum antimicrobials against gram-negative and gram-positive species collected from 3 investigative sites in Australia from 2005 to 2006. **Methods:** A total of 241 clinical *Enterobacteriaceae* isolates from Australia were identified to the species level and confirmed by the central laboratory. Minimum Inhibitory Concentration (MICs) were determined by each site using broth microdilution panels and interpreted according to CLSI guidelines. **Results:** Cumulative data results are in the table as follows, with individual species data to be presented:

| | *Enterobacteriaceae* | | | |
|---|---|---|---|---|
| | In patients (n=173) | | Out patients (n=68) | |
| | %S | $MIC_{90}$ | %S | $MIC_{90}$ |
| Tigecycline* | 96.5 | 1 | 100 | 1 |
| Amikacin | 100 | 4 | 100 | 4 |
| Cefepime | 98.3 | 2 | 100 | ≤0.5 |
| Ceftazidime | 80.9 | 32 | 95.6 | ≤8 |
| Imipenem | 100 | 1 | 100 | 1 |
| Levofloxacin | 98.3 | 0.25 | 100 | 0.12 |
| Minocycline | 90.2 | 4 | 94.1 | 4 |
| PipTazo | 84.4 | 64 | 92.6 | 4 |

*Tigecycline susceptibility ≤2 mcg/mL (Tygacil®, FDA package insert, 2005)

**Conclusion:** Tigecycline's in vitro activity was comparable to or greater than most commonly prescribed broad spectrum antimicrobials without any categorical susceptibility change between In- and Out-patient bacterial study strains. Tigecycline in vitro activity was comparable to most of the study broad spectrum antimicrobials. The presented data suggest that tigecycline may be an effective and reliable therapeutic option against nosocomial or community enteric pathogens.

## 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 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 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 $MIC_{90}$ values of <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 communicate clinical laboratory in vitro experience with activity of tigecycline in a limited numberagainst isolates collected from three medical centers in Australia.

## 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.
- 500 clinical isolates were collected tested between January 2005 - December 2006 from three study centers from Australia. Of these, 241 had designations of In-Patient and Out-patient locations.
- 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 (0.03-32); piperacillin/tazobactam (0.06-128); levofloxacin (0.008-32); ceftriaxone (0.03-64); cefepime (0.5-32); ampicillin (0.06-32); amikacin (0.5-64); minocycline (0.25-16); ceftazidime (8-32); tigecycline (0.008-16); and imipenem (0.06-16).
- MIC interpretive criteria followed published guidelines established by the CLSI where applicable [12]. MIC interpretive criteria for Tigecycline followed published guidelines established by the FDA where applicable [13].
- Quality control of broth microdilution panels followed manufacturer's and CLSI guidelines using the following ATCC strains: *E. coli* ATCC 25922; *K. pneumoniae* ATCC 700603; 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, USA).

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## RESULTS

The results of this study are presented in the following tables:

Table 1. Gram-negative antibiogram for tigecycline and 10 comparators with $MIC_{90}$ (mcg/mL) and percent susceptible (%) against 251 selected *Enterobacteriaceae*.

| | | $MIC_{90}$ in mcg/mL (% Susceptible)* | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Organisms** | **N=** | **Tige** | **Amik** | **Cefep** | **Ceftaz** | **Imip** | **Levo** | **PipTazo** |
| *Enterobacteriaceae* † | 251 | 1(97.6) | 4(100) | 2(98.4) | 32(84.9) | 1(100) | 0.25(98.8) | 64(86.5) |
| *E. aerogenes* | 26 | 0.5(96.2) | 2(100) | ≤0.5(100) | 32(65.4) | 1(100) | 0.12(100) | 32(88.5) |
| *E. cloacae* | 48 | 1(95.8) | 4(100) | 8(93.8) | >32(52.1) | 1(100) | 0.5(97.9) | 64(58.3) |
| *E. gergoviae* | 1 | 0.5(100) | 1(100) | 8(100) | >32(0) | 0.5(100) | 0.12(100) | 128(0) |
| *E. coli* | 75 | 0.25(100) | 8(100) | ≤0.5(100) | ≤8(98.7) | 0.5(100) | 0.06(98.7) | 2(97.3) |
| *K. oxytoca* | 29 | 0.5(100) | 2(100) | 2(100) | ≤8(96.6) | 0.5(100) | 0.12(100) | >128(75.9) |
| *K. pneumoniae* | 42 | 1(97.6) | 2(100) | ≤0.5(97.6) | ≤8(95.2) | 0.5(100) | 0.25(97.6) | 4(97.6) |
| *K. pneumoniae*, ESBL | 1 | 1(100) | 4(100) | >32(0) | 16(0) | 0.25(100) | >8(0) | 8(100) |
| *S. marcescens* | 29 | 2(96.6) | 8(100) | ≤0.5(100) | ≤8(96.6) | 2(100) | 0.5(100) | 4(100) |
| *S. odorifera* | 1 | 4(0) | 2(100) | ≤0.5(100) | ≤8(100) | 0.5(100) | 0.12(100) | 2(100) |

* Susceptibility defined by CLSI document M100-S16 (2006), where available.
† All *Enterobacter*, *Escherichia*, *Klebsiella* and *Serratia* combined.

Table 2. In vitro activity of tigecycline and comparators against selected *Enterobacteriaceae* for in-patient vs out-patient populations*

| | | In-Patient | | | | Out-Patient | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Organism** | **Drug** | **%Sus** | **%Res** | **Mean MIC** | **$MIC_{90}$** | **%Sus** | **%Res** | **Mean MIC** | **$MIC_{90}$** | **p-Value†** |
| *Enterobacter aerogenes* (n=IP 20; n=OP 5) | Tigecycline | 95 | 0 | 0.7 | 2 | 100 | 0 | 0.4 | 0.5 | 0.4501 |
| | Amikacin | 100 | 0 | 1.65 | 2 | 100 | 0 | 1.6 | 2 | 0.89 |
| | Cefepime | 100 | 0 | 0.549 | 1 | 100 | 0 | 0.499 | ≤0.5 | 0.4819 |
| | Ceftazidime | 60 | 15 | 13.6 | 32 | 80 | 20 | 12.799 | 32 | 0.8611 |
| | Imipenem | 100 | 0 | 0.687 | 1 | 100 | 0 | 0.8 | 1 | 0.457 |
| | Levofloxacin | 100 | 0 | 0.054 | 0.06 | 100 | 0 | 0.066 | 0.12 | 0.6402 |
| | PipTazo | 90 | 0 | 9.25 | 16 | 80 | 0 | 14 | 64 | 0.5193 |
| *Enterobacter cloacae* (n=IP 35; n=OP 11) | Tigecycline | 95 | 4.5 | 1.021 | 1 | 100 | 0 | 0.681 | 1 | 0.536 |
| | Amikacin | 100 | 0 | 1.857 | 2 | 100 | 0 | 1.727 | 2 | 0.7613 |
| | Cefepime | 94.3 | 5.7 | 3.185 | 4 | 100 | 0 | 1.363 | 2 | 0.4251 |
| | Ceftazidime | 45.7 | 42.9 | 19.2 | >32 | 81.8 | 18.2 | 12.366 | 32 | 0.0824 |
| | Imipenem | 100 | 0 | 0.55 | 1 | 100 | 0 | 0.727 | 1 | 0.247 |
| | Levofloxacin | 97.1 | 2.9 | 0.328 | 0.5 | 100 | 0 | 0.169 | 0.5 | 0.7011 |
| | PipTazo | 54.3 | 8.6 | 32.228 | 64 | 81.8 | 9.1 | 16.136 | 32 | 0.2356 |
| *Escherichia coli* (n=IP 43; n=OP 29) | Tigecycline | 100 | 0 | 0.174 | 0.25 | 100 | 0 | 0.153 | 0.25 | 0.2516 |
| | Amikacin | 100 | 0 | 3.023 | 4 | 100 | 0 | 3.034 | 8 | 0.9811 |
| | Cefepime | 100 | 0 | 0.581 | ≤0.5 | 100 | 0 | 0.499 | ≤0.5 | 0.4154 |
| | Ceftazidime | 97.7 | 2.3 | 8.558 | ≤8 | 100 | 0 | 7.999 | ≤8 | 0.4154 |
| | Imipenem | 100 | 0 | 0.279 | 0.5 | 100 | 0 | 0.301 | 0.5 | 0.4207 |
| | Levofloxacin | 97.7 | 2.3 | 0.253 | 0.25 | 100 | 0 | 0.035 | 0.06 | 0.3396 |
| | PipTazo | 95.3 | 4.7 | 7.331 | 4 | 100 | 0 | 1.198 | 2 | 0.2267 |
| *Klebsiella oxytoca* (n=IP 20; n=OP 9) | Tigecycline | 100 | 0 | 0.412 | 0.5 | 100 | 0 | 0.277 | 0.5 | 0.3484 |
| | Amikacin | 100 | 0 | 1.65 | 2 | 100 | 0 | 1.666 | 2 | 0.9519 |
| | Cefepime | 100 | 0 | 0.949 | 2 | 100 | 0 | 0.888 | 4 | 0.9228 |
| | Ceftazidime | 95 | 0 | 8.399 | ≤8 | 100 | 0 | 7.999 | ≤8 | 0.5123 |
| | Imipenem | 100 | 0 | 0.387 | 0.5 | 100 | 0 | 0.333 | 1 | 0.5248 |
| | Levofloxacin | 100 | 0 | 0.15 | 0.25 | 100 | 0 | 0.03 | 0.03 | 0.4235 |
| | PipTazo | 75 | 25 | 33.02 | >128 | 77.8 | 22.2 | 29.278 | >128 | 0.8693 |
| *Klebsiella pneumoniae* (n=IP 30; n=OP 10) | Tigecycline | 96.7 | 0 | 0.783 | 1 | 100 | 0 | 0.575 | 1 | 0.3986 |
| | Amikacin | 100 | 0 | 1.333 | 2 | 100 | 0 | 1.2 | 2 | 0.62 |
| | Cefepime | 96.7 | 3.3 | 1.549 | ≤0.5 | 100 | 0 | 0.499 | ≤0.5 | 0.5705 |
| | Ceftazidime | 93.3 | 0 | 8.533 | ≤8 | 100 | 0 | 7.999 | ≤8 | 0.4152 |
| | Imipenem | 100 | 0 | 0.325 | 0.5 | 100 | 0 | 0.3 | 0.5 | 0.5517 |
| | Levofloxacin | 96.7 | 3.3 | 0.406 | 0.25 | 100 | 0 | 0.092 | 0.25 | 0.5088 |
| | PipTazo | 96.7 | 0 | 4.066 | 4 | 100 | 0 | 2.3 | 2 | 0.6332 |
| *Serratia marcescens* (n=IP 23; n=OP 4) | Tigecycline | 95.7 | 0 | 1.369 | 2 | 100 | 0 | 1 | 1 | 0.3364 |
| | Amikacin | 100 | 0 | 4.347 | 8 | 100 | 0 | 1.5 | 2 | 0.1677 |
| | Cefepime | 100 | 0 | 0.847 | ≤0.5 | 100 | 0 | 0.499 | ≤0.5 | 0.6651 |
| | Ceftazidime | 95.7 | 4.3 | 9.043 | ≤8 | 100 | 0 | 7.999 | ≤8 | 0.6851 |
| | Imipenem | 100 | 0 | 0.875 | 2 | 100 | 0 | 0.666 | 1 | 0.5229 |
| | Levofloxacin | 100 | 0 | 0.192 | 0.5 | 100 | 0 | 0.06 | 0.12 | 0.1042 |
| | PipTazo | 100 | 0 | 2.913 | 4 | 100 | 0 | 1.25 | 2 | 0.341 |

* Susceptibilities defined by CLSI document M100-S16 (2006), where available. Tigecycline breakpoints defined in FDA package insert (Tygacil®, 2005).
† Oneway ANOVA.

## CONCLUSIONS

- Tigecycline inhibited 97.6% of all *Enterobacteriaceae* tested in vitro at a $MIC_{90}$ of 1 mcg/mL. Tigecycline's $MIC_{90}$ of 1 mcg/mL was equivalent to imipenem and 2- to 64-fold better than the beta-lactams and beta-lactam/beta-lactamase inhibitor combinations. Only levofloxacin had a lower $MIC_{90}$ at 0.25 mcg/mL against all *Enterobacteriaceae* tested.
- Tigecycline activity exhibited small, but statistically significant (p-value <0.5), increases in mean MIC values for in-patient compared to out-patient *Enterobacteriaceae* study species. Similar increases in mean MIC values were seen in two or more study species for cefepime, ceftazidime, imipenem, levofloxacin and piperacillin-tazobactam. Tigecycline inhibited between 95% and 100% of all study species at or below its susceptibility breakpoint of 2 mcg/mL regardless of the source location, in-patient or out-patient, of the causative pathogen.
- The in vitro activity of tigecycline in this study suggests that tigecycline is an effective agent with excellent antimicrobial activity in this single clinical laboratory against common gram-negative nosocomial and community acquired pathogens.