

Tigecycline Evaluation Surveillance Trial (T.E.S.T.) – In Vitro Antibacterial Activity Against Selected Species of Non-Glucose Fermenting Gram-negative Rods – United States Data, 2004-2008

GN052

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Revised Abstract

Objectives: Non-glucose fermenting gram negative rods are known to be highly resistant in hospital settings and have always been a challenge for clinicians and hospital infection control. Tigecycline has been shown to have potent in vitro activity against most species of Enterobacteriaceae and selected species of non-fermenters. The T.E.S.T. program determined the in vitro activity of tigecycline compared to amikacin, imipenem, meropenem, cefepime, ceftazidime, ceftriaxone, levofloxacin, minocycline and piperacillin/tazobactam against members of *Acinetobacter* spp. and *Pseudomonas aeruginosa* collected from hospitals in the United States. **Methods:** A total of 9,907 clinical isolates were collected from 2004 through 2008 and Minimum Inhibitory Concentrations (MICs) were determined by broth microdilution panels using fresh broth and interpreted according to CLSI guidelines. **Results:** The MIC₅₀/MIC₉₀ of tigecycline to *Acinetobacter* spp. and *P. aeruginosa* was 0.5/1 mcg/ml and 8/>16 mcg/ml. Ceftazidime and cefepime remained active against a majority of isolates inhibiting 50% of the *Acinetobacter* and approximately 80% of *P. aeruginosa* isolates, respectively. Tigecycline showed the lowest MIC₅₀/MIC₉₀ of 0.5/1 mcg/ml against *Acinetobacter* species (n=3,426), compared to amikacin MIC₅₀/MIC₉₀ 4/64, imipenem MIC₅₀/MIC₉₀ 0.5/16 and minocycline MIC₅₀/MIC₉₀ ≤0.5/8. Performance of tigecycline was unaffected against multi-resistant isolates of *A. baumannii* with similar findings observed in other species of *Acinetobacter*. Tigecycline was ineffective against *P. aeruginosa*. **Conclusions:** The presented data suggest that tigecycline may be a potential therapeutic option against commonly encountered nosocomial *Acinetobacter* spp. and multi-drug resistant strains regardless of degree or type of resistance

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. Isolates were identified to genus and species at each site by the local laboratory. Isolates were tested by the local laboratory. Only one isolate per patient was accepted.
- Clinical isolates were collected and tested between January 2004 and December 2008 from 460 study centers in the United States.
- Custom broth microdilution panels were supplied by MicroScan (Dade Behring Inc., Sacramento, CA, USA) with the following antimicrobial agents and concentrations (expressed in mcg/ml): piperacillin/tazobactam (0.06-128); levofloxacin (0.008-8); ceftriaxone (0.06-64); cefepime (0.5-32); amikacin (0.5-64); minocycline (0.5-16); ceftazidime (8-32); tigecycline (0.008- 16); imipenem (0.06-16); and meropenem (0.12-16).
- MIC interpretive criteria followed published guidelines established by the Clinical and Laboratory Standards Institute where applicable [12]. Tigecycline tentative breakpoints (expressed in mcg/ml) are defined as susceptible ≤2; intermediate = 4; and resistant ≥8 for comparative purposes only as no breakpoints are yet defined for tigecycline against *Acinetobacter* and *Pseudomonas* species.
- Quality control of broth microdilution panels followed manufacturer's and CLSI guidelines using the following ATCC strains: *P. aeruginosa* ATCC 27853 and *Escherichia coli* ATCC 25922.
- The collection and transporting 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

Results are shown in the following tables.

Table 1. In vitro activity of tigecycline and comparative agents against 9,907 selected Gram-negative non-fermenters.

| | | MIC (mcg/ml) | | % Sus ¹ | % Int | % Res |
|--|--------------|-------------------|-------------------|--------------------|-------|-------|
| | | MIC ₅₀ | MIC ₉₀ | | | |
| <i>Acinetobacter</i> spp* (n=3,834) | Tigecycline | 0.5 | 1 | 97.7 | 2.0 | 0.3 |
| | Amikacin | 4 | 64 | 81.6 | 6.3 | 12.1 |
| | Cefepime | 8 | >32 | 50.0 | 13.4 | 36.5 |
| | Ceftazidime | 16 | >32 | 49.6 | 5.3 | 45.1 |
| | Ceftriaxone | 32 | >64 | 31.1 | 24.9 | 43.9 |
| | Imipenem | 0.5 | 16 | 87.1 | 2.5 | 10.4 |
| | Meropenem | 1 | >16 | 67.6 | 3.7 | 28.7 |
| | Levofloxacin | 2 | >8 | 50.8 | 5.9 | 43.2 |
| | Minocycline | ≤0.5 | 8 | 87.7 | 8.6 | 3.7 |
| | PipTazo | 8 | >128 | 58.0 | 14.6 | 27.4 |
| <i>Pseudomonas aeruginosa</i> (n=6,073) | Tigecycline | 8 | >16 | 6.4 | 15.2 | 78.4 |
| | Amikacin | 4 | 8 | 97.0 | 1.3 | 1.7 |
| | Cefepime | 4 | 16 | 78.0 | 12.3 | 9.6 |
| | Ceftazidime | ≤8 | 32 | 83.1 | 5.9 | 11.1 |
| | Ceftriaxone | 32 | >64 | 17.8 | 36.8 | 45.4 |
| | Imipenem | 1 | 8 | 84.9 | 7.4 | 7.7 |
| | Levofloxacin | 1 | >8 | 63.7 | 7.1 | 29.1 |
| | Meropenem | 1 | 8 | 82.8 | 7.7 | 9.5 |
| | Minocycline | >16 | >16 | na | na | na |
| | PipTazo | 4 | 128 | 89.7 | 0.0 | 10.3 |

*Species include: *A. baumannii* (3426), *A. baumannii* (277), *A. non-speciated* (85), *A. anitratus* (23), *A. junii* (19), *A. calcoaceticus* (16), *A. haemolyticus* (7), *A. johnsonii* (1).
¹ Interpretive criteria as defined by CLSI, document M100-S18 (2008), where applicable [12]; Tigecycline breakpoints defined as susceptible ≤2 mcg/ml, intermediate = 4 mcg/ml, resistant ≥8 mcg/ml for comparative purposes only, na breakpoints not established for this species.

Table 2. In vitro activity of tigecycline and comparators against 3,834 *Acinetobacter* species* showing cumulative percent inhibited (%) at each MIC (mcg/ml).

| MIC | N | ≤0.008 | 0.015 | 0.03 | 0.06 | 0.12 | 0.25 | 0.5 | 1 | 2 | 4 | 8 | 16 | 32 | 64 | 128 | ≥256 |
|--------------|----|--------|-------|------|------|------|------|-----|-----|----|----|----|----|----|----|-----|------|
| Tigecycline | 30 | 7 | 46 | 387 | 811 | 554 | 768 | 870 | 291 | 78 | 12 | 12 | 12 | 12 | 12 | 12 | 12 |
| Amikacin | | | | | | | | | | | | | | | | | |
| Cefepime | | | | | | | | | | | | | | | | | |
| Ceftazidime | | | | | | | | | | | | | | | | | |
| Ceftriaxone | | | | | | | | | | | | | | | | | |
| Imipenem | | | | | | | | | | | | | | | | | |
| Levofloxacin | | | | | | | | | | | | | | | | | |
| Meropenem | | | | | | | | | | | | | | | | | |
| Minocycline | | | | | | | | | | | | | | | | | |
| PipTazo | | | | | | | | | | | | | | | | | |

*Species include: *A. baumannii* (3426), *A. baumannii* (277), *A. non-speciated* (85), *A. anitratus* (23), *A. junii* (19), *A. calcoaceticus* (16), *A. haemolyticus* (7), *A. johnsonii* (1).

Table 3. In vitro activity of tigecycline and comparators against 6,073 *Pseudomonas aeruginosa* showing cumulative percent inhibited (%) at each MIC (mcg/ml).

| MIC | N | ≤0.008 | 0.015 | 0.03 | 0.06 | 0.12 | 0.25 | 0.5 | 1 | 2 | 4 | 8 | 16 | 32 | 64 | 128 | ≥256 |
|--------------|----|--------|-------|------|------|------|------|-----|-----|-----|------|------|-----|----|----|-----|------|
| Tigecycline | 10 | 1 | 1 | 3 | 14 | 19 | 53 | 83 | 205 | 924 | 2255 | 1708 | 797 | | | | |
| Amikacin | | | | | | | | | | | | | | | | | |
| Cefepime | | | | | | | | | | | | | | | | | |
| Ceftazidime | | | | | | | | | | | | | | | | | |
| Ceftriaxone | | | | | | | | | | | | | | | | | |
| Imipenem | | | | | | | | | | | | | | | | | |
| Levofloxacin | | | | | | | | | | | | | | | | | |
| Meropenem | | | | | | | | | | | | | | | | | |
| Minocycline | | | | | | | | | | | | | | | | | |
| PipTazo | | | | | | | | | | | | | | | | | |

Conclusions

- Tigecycline inhibited 97.7% of *Acinetobacter* species tested in vitro at an MIC of 2 mcg/ml.
- Tigecycline's MIC₉₀ of 1 mcg/ml against *Acinetobacter* species was the lowest among all broad spectrum antimicrobials tested.
- With the exception of imipenem, amikacin, and minocycline, all commonly prescribed broad spectrum antimicrobials evaluated in this study (cefepime, ceftazidime, levofloxacin, and piperacillin/tazobactam) had limited activity against the *Acinetobacter* species.
- Tigecycline's limited activity against *P. aeruginosa* is similar to that of tetracyclines and their analog derivatives.
- Tigecycline's in vitro activity in this study suggests that it may be a therapeutic option for the treatment of infections caused by *Acinetobacter* species.