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Pseudomonas aeruginosa and *Acinetobacter* Isolates from Latin American Hospitals The Activity of Tigecycline and Comparators in the T.E.S.T. Program 2004 - 2008

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Revised Abstract

Background: The Tigecycline Evaluation Surveillance Trial (T.E.S.T.) program is a longitudinal global surveillance prospective report of tigecycline and comparator *in vitro* activity from 2004 through 2008. This study evaluates trends in susceptibility over time of *Acinetobacter* species and *Pseudomonas aeruginosa* in Latin American countries. **Methods:** More than 2,696 clinical isolates were collected from 149 cumulative investigative sites in 12 Latin American countries. Clinical isolates were identified to the species level at each participating site and confirmed by the central laboratory. Minimum Inhibitory Concentrations (MICs) were determined by the local laboratory using supplied broth microdilution panels and interpreted according to CLSI guidelines. **Results:** $MIC_{50/90}$ values by antimicrobial and species by year are as follows:

	Acinetobacter spp		*Pseudomonas aeruginosa*	
	2004	2008	2004	2008
n=	54	381	59	558
Tigecycline	0.5/1	0.5/2	8/>16	8/>16
Amikacin	64/>64	>64/>64	4/>64	4/64
Cefepime	32/>32	32/>32	8/32	8/>32
Ceftazidime	>32/>32	>32/>32	≤8/>32	≤8/>32
Ceftriaxone	>64/>64	>64/>64	64/>64	>64/>64
Imipenem	>16/>16	ID	1/16	ID
Meropenem	ID	16/>16	ID	2/>16
Levofloxacin	8/>8	>8/>8	>8/>8	2/>8
Minocycline	≤0.5/1	1/16	na	na
PipTazo	>128/>128	>128/>128	4/128	16/>128

ID = Insufficient Data; na = not applicable.

Conclusions: Although the MIC_{50} of tigecycline against *Acinetobacter* spp. essentially remained the same over the five year period, it exhibited a one dilution higher MIC_{90} since 2004 in Latin America. The minocycline $MIC_{50/90}$ increased from 2004 to 2008 for *Acinetobacter* spp. In addition, the MIC_{50} of levofloxacin against *P. aeruginosa* decreased in the same time period. The results for the other antimicrobials remained constant during this period.

Introduction

While tigecycline was designed to avert resistance due to tetracycline efflux pumps and ribosomal protective features [1, 2], the MIC_{90} values for *Pseudomonas aeruginosa* isolates are generally in the range of 8-16 mcg/ml, seemingly due to chromosomally encoded multidrug efflux pumps [9,10]. However, tigecycline has been shown to be highly active against multi-drug resistant *Acinetobacter* spp., particularly *A. baumannii* that are commonly associated with serious nosocomial infections [3-5].

This study evaluates the *in vitro* activity of tigecycline and comparative antimicrobial agents against *Acinetobacter* spp. and *P. aeruginosa* isolated in labs from Latin America countries. This study is part of the Tigecycline Evaluation and Surveillance Trial (TEST), a global surveillance program, which has monitored the *in vitro* activity of tigecycline and comparator agents since 2004.

Materials & Methods

- All isolates were derived from blood, respiratory tract, urine (no more than 25% of all isolates), skin, wound, body fluids, and other defined sources. Only one isolate per patient was accepted into the study. Clinical isolates were collected and tested between 2004 and 2008 from 149 cumulative study centers (50% participated in multiple years) in 12 Latin America countries (Argentina, Brazil, Chile, Colombia, Guatemala, Honduras, Jamaica, Mexico, Nicaragua, Panama, Puerto Rico, Venezuela). Isolates were identified to the species level and tested at each site by the participating laboratory.
- MIC interpretive criteria followed published breakpoints established by CLSI where applicable [6]; No breakpoints have yet been established for tigecycline against either *Acinetobacter* or *Pseudomonas* species [6].
- Minimum inhibitory concentrations were determined by the CLSI recommended broth microdilution testing method [7] and instructions from the custom panel manufacturers, MicroScan® (Siemens Medical Solutions Diagnostics, West Sacramento, CA, USA) or Sensititre® (TREK Diagnostic Systems, Cleveland, OH, USA). The following antimicrobial agents were included on the panels with their dilution ranges (expressed in mcg/ml): amikacin (0.5-64); amoxicillin/clavulanic acid (0.12/0.06-32/16); ampicillin (0.5-32); cefepime (0.5-32); ceftriaxone (0.06-64); ceftazidime (8-32); imipenem (0.06-16); levofloxacin (0.008-8); meropenem (0.06-16); minocycline (0.5-16); tigecycline (0.008-16); piperacillin/tazobactam (0.06/4-128/4).
- Quality controls (QC) were performed by each testing site on each day of testing using the following ATCC control strains: *E. coli* ATCC 25922; *E. coli* ATCC 35218 and *Pseudomonas aeruginosa* ATCC 27853. Results were included in the analysis only when corresponding QC isolates tested within the acceptable range according to CLSI (2009) guidelines [6].

References

1. Visalli MA, Murphy E, Projan SJ, Bradford PA. *AcrAB multidrug efflux pump is associated with reduced levels of susceptibility to tigecycline (GAR-936) in Proteus mirabilis*. Antimicrob Agents Chemother 2003;47:665-9
2. Dean CR, Visalli MA, Projan SJ, et al. *Efflux-mediated resistance to tigecycline (GAR-936) in Pseudomonas aeruginosa PAO1*. AntimicroAgenChemother2003;47:972-8
3. Henwood, C.J., et al., *Antibiotic resistance among clinical isolates of Acinetobacter in the UK, and in vitro evaluation of tigecycline (GAR-936).* J Antimicrob Chemother, 2002. **49**(3): p. 479-87.
4. Hoban DJ, Bouchillon SK, Dowzicky MJ. *Antimicrobial susceptibility of extended-spectrum beta-lactamase producers and multidrug-resistant Acinetobacter baumannii throughout the United States and comparative in vitro activity of tigecycline, a new glycylcycline antimicrobial*. Diagn Microbiol Infect Dis 2007;57:423-8
5. Taccone FS, Rodriguez-Villalobos H, De Backer D, et al. *Successful treatment of septic shock due to pan-resistant Acinetobacter baumannii using combined antimicrobial therapy including tigecycline*. Eur J Clin Microbiol Infect Dis 2006;25:257-60
6. CLSI, 2009. *Performance Standards for Antimicrobial Susceptibility Testing; Fourteenth Informational Supplement*. CLSI document M100-S19. Clinical and Laboratory Standards Institute (CLSI), Wayne, PA 19087-1898 USA.
7. CLSI, 2008. *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standard—Seventh Edition*, in *Document M7-A7*. Clinical and Laboratory Standards Institute (CLSI), Wayne, PA 19087-1898 USA.

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Results

Table 1. *In vitro* activity of tigecycline and comparators against 2,696 isolates of non-fermenting gram-negative bacteria collected in Latin America from 2004 through 2008.

Drug	N=	%Sus [a]	%Int	%Res	MIC (mcg/ml) MIC_{50}	MIC (mcg/ml) MIC_{90}
***Acinetobacter* spp.** [a]						
Tigecycline	1,113	na	na	na	0.5	2
Amikacin	1,113	33.7	12.1	54.2	64	>64
Cefepime	1,113	28.2	14.4	57.4	32	>32
Ceftazidime	1,113	20.1	8.7	71.2	>32	>32
Ceftriaxone	1,113	14.4	11.1	74.6	>64	>64
Imipenem*	314	62.7	4.1	33.1	1	>16
Meropenem*	799	38.7	6.6	54.7	16	>16
Levofloxacin	1,113	24.5	11.9	63.5	8	>8
Minocycline	1,113	89.9	5	5	≤0.5	8
PipTazo	1,113	22.8	11.3	65.9	>128	>128
Pseudomonas aeruginosa						
Tigecycline	1,583	na	na	na	8	>16
Amikacin	1,583	71.8	8.1	20	4	64
Cefepime	1,583	60.5	15.3	24.2	8	>32
Ceftazidime	1,583	60.2	11.1	28.7	≤8	>32
Ceftriaxone	1,583	11.9	23.8	64.2	>64	>64
Imipenem*	447	66.2	15	18.8	1	16
Meropenem*	1,136	66.3	8.8	24.9	2	>16
Levofloxacin	1,583	52.4	5.6	42	2	>8
PipTazo	1,583	76.8	0	23.2	16	>128

[a] Interpretive criteria are defined by CLSI document M100-S19 (2009). na = breakpoints not available.
[b] Acinetobacter spp is comprised of *A. baumannii* (1009), *A. lwoffii* (46), *Acinetobacter*, non-speciated (33), *A. calcoaceticus* (23), and *A. haemolyticus* (2).
* Meropenem replaced imipenem in 2006.

Table 2. *In vitro* activity (MIC_{90} / % Susceptibility) of tigecycline and comparators against 1,113 isolates of *Acinetobacter* species collected in Latin America from 2004 through 2008.

Drug MIC_{90}/%Sus	2004 (n=54)	2005 (n=139)	2006 (n=257)	2007 (n=282)	2008 (n=381)	P-Value [b]
Tigecycline	1/na	1/na	2/na	2/na	2/na	0.0134
Amikacin	>64/11.1	>64/30.2	>64/42.4	>64/27.7	>64/36.7	<0.001
Cefepime	>32/7.4	>32/21.6	>32/30.7	>32/22	>32/36.5	<0.001
Ceftazidime	>32/3.7	>32/15.8	>32/24.1	>32/14.2	>32/25.7	<0.001
Ceftriaxone	>64/0	>64/4.3	>64/13.2	>64/11	>64/23.4	<0.001
Imipenem*	>16/35.8	>16/70.8	>16/65.3	ID	ID	<0.001
Meropenem*	ID	ID	>16/42.1	>16/34	>16/40.9	0.8382
Levofloxacin	>8/5.6	>8/14.4	>8/26.5	>8/20.6	>8/32.5	<0.001
Minocycline	1/98.1	2/99.3	4/92.2	4/94.3	16/80.6	<0.001
PipTazo	>128/3.7	>128/17.3	>128/23.7	>128/17.7	>128/30.7	<0.001

[a] Interpretive criteria are defined by CLSI document M100-S19 (2009). na = breakpoints not available. ID = Insufficient data.
* Meropenem replaced imipenem in 2006.
[b] P-value calculated using Fisher's Exact Test compares %Sus from 2004 to 2008. Imipenem and meropenem compare 1st and last year of use. P-values <0.05 are significant.

Table 3. *In vitro* activity (MIC_{90} / % Susceptibility) of tigecycline and comparators against 1,583 isolates of *Pseudomonas aeruginosa* collected in Latin America from 2004 through 2008.

Drug MIC_{90}/%Sus	2004 (n=59)	2005 (n=172)	2006 (n=422)	2007 (n=372)	2008 (n=558)	P-Value [b]
Tigecycline	>16/na	>16/na	>16/na	>16/na	>16/na	0.3868
Amikacin	>64/76.3	64/69.2	64/75.6	>64/66.7	64/72.8	0.6447
Cefepime	32/64.4	>32/56.4	>32/64	>32/55.6	>32/62	0.7786
Ceftazidime	>32/64.4	>32/57.6	>32/62.8	>32/59.7	>32/59	0.4863
Ceftriaxone	>64/27.1	>64/14	>64/10.4	>64/12.1	>64/10.8	0.001
Imipenem*	16/71.4	16/66.3	>16/64.9	ID	ID	0.4299
Meropenem*	ID	ID	>16/65	>16/65.1	>16/67.7	0.4842
Levofloxacin	>8/44.1	>8/48.3	>8/52.4	>8/51.3	>8/55.2	0.1302
PipTazo	128/79.7	128/87.8	>128/78.4	>128/70.2	>128/76.2	0.6299

[a] Interpretive criteria are defined by CLSI document M100-S19 (2009). na = breakpoints not available. ID = Insufficient data.
* Meropenem replaced imipenem in 2006.
[b] P-value calculated using Fisher's Exact Test compares %Sus from 2004 to 2008. Imipenem and meropenem compare 1st and last year of use. P-values <0.05 are significant.

Conclusions

- Tigecycline demonstrated a one dilution higher shift in MIC_{90} values against *Acinetobacter* spp. from Latin America over the five year study period compared to its pre-marketing baseline (p<0.05).
- Tigecycline's MIC_{90} of ≤2 mcg/mL against *Acinetobacter* spp. for the years 2004 to 2008 was the lowest among all broad spectrum antimicrobials tested. Tigecycline's limited activity against *P. aeruginosa* is similar to tetracyclines and their analog derivatives.
- Only meropenem had no change in activity against *Acinetobacter* since its introduction to the study in 2006 (p>0.05). Most of the other study drugs had significant increases in *in vitro* activity against *Acinetobacter* species (p<0.001), however, only minocycline (90% susceptible) had a percent susceptible rate above 65%.
- The *in vitro* activity of tigecycline against *Acinetobacter* spp in this study suggests that tigecycline may be an option for the treatment of this serious nosocomial pathogen.