

# In Vitro Study to Determine the Activity of Tigecycline as Compared to Nine Comparator Antimicrobials Against Various Species of *Enterobacteriaceae* from the Tigecycline Evaluation Surveillance Trial (T.E.S.T)

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T. Stevens<sup>1</sup>, B. Johnson<sup>1</sup>, J. Johnson<sup>1</sup>, S. Bouchillon<sup>1</sup>, D. Hoban<sup>1</sup>, C. Gaylord<sup>1</sup>, M. McCarthy<sup>1</sup>, M. Dowzicky<sup>2</sup>

IHMA, Inc.  
2122 Palmer Dr.  
Schaumburg, IL 60173  
Tel: (847) 303-5003  
Fax: (847) 303-5601  
www.ihmainc.com

<sup>1</sup>International Health Management Associates, Schaumburg, IL, USA

<sup>2</sup>Wyeth Pharmaceuticals, Collegeville, PA, USA

## REVISED ABSTRACT

**Background:** Tigecycline (GAR-936), a member of a new class of antimicrobials (glycylcyclines), has been shown to have potent activity against most species of *Enterobacteriaceae*. The T.E.S.T. determined the in vitro activity of tigecycline compared to amikacin, amoxicillin/clav, ampicillin, imipenem, cefepime, ceftazidime, ceftriaxone, minocycline, piperacillin/tazobactam and levofloxacin against *Escherichia coli*, *Klebsiella spp.*, *Enterobacter spp.*, and other species of *Enterobacteriaceae* from multi-national hospitals from North America, Europe, Asia, and Latin America. **Methods:** A total of 3,204 clinical isolates were identified to the species level at each participating site and confirmed by the central laboratory. Isolates were collected between January 2004 – November 2004. MIC's were determined by the local laboratory using broth microdilution panels from Dade Microscan according to NCCLS guidelines and manufacturer's instructions. **Results:** Tigecycline demonstrated a MIC<sub>50</sub> / MIC<sub>90</sub> of 0.25/1 mcg/ml against all strains of *Enterobacteriaceae* that was equivalent to imipenem. The MIC<sub>90</sub> of 1 for tigecycline was 8 fold lower than levofloxacin and ≥16 fold lower than amoxicillin-clavulanic acid, ceftazidime, ceftriaxone and piperacillin-tazobactam. Tigecycline inhibited >97% of all *E. coli* and *K. pneumoniae* ESBL producers at a MIC of 2 mcg/ml. **Conclusion:** Tigecycline is an effective antimicrobial agent against the selected *Enterobacteriaceae* in this study with low MICs against both ESBL and non-ESBL producing strains.

## INTRODUCTION

Tigecycline is a novel antimicrobial with an expanded broad-spectrum of activity from a new class of compounds, 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<sup>-9</sup> [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]. The MIC<sub>90</sub> values for pseudomonas isolates are generally elevated, in the range of 8-16 mcg/ml [10, 12]. The pharmacokinetics of parenteral tigecycline is linear with a mean half-life of 36 hours and a maximum serum concentration (C<sub>MAX</sub>) of a 300mg dose infused over 1 hour of 2.8 mcg/ml [13,14].

This study compared the activity of tigecycline with other agents against *Enterobacteriaceae* including *Escherichia coli*, *Enterobacter cloacae*, *Enterobacter aerogenes* and *Klebsiella pneumoniae* from hospitals throughout Europe and North America.

## 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.
- Clinical isolates were collected tested between January 2004 - November 2004 from 20 study centers in 6 countries.
- Antimicrobial agents tested with concentrations (expressed in mcg/ml) were: Amoxicillin/clavulanic acid (0.12-32); Piperacillin/tazobactam (0.06-128); Levofloxacin (0.008-8); Ceftriaxone (0.06-64); Cefepime (0.5-32); Ampicillin (0.5-32); Amikacin (0.5-64); Minocycline (0.5-16); Ceftazidime (8-32); Tigecycline (0.008-16); Imipenem (0.06-16). MIC interpretive criteria followed published guidelines established by the NCCLS where applicable [15]. Tigecycline tentative breakpoints (in units of mcg/mL) are defined as susceptible ≤ 2; intermediate = 4; and resistant ≥ 8.
- Isolates were identified to genus and species at each site by the local laboratory. Isolates were tested by the local laboratory.
- Organism collection, transport, confirmation of organism identification, as well as, construction and management of a centralized database was coordinated by Laboratories International for Microbiology Studies (LIMS).

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## RESULTS

Table 1. *In Vitro* activity of Tigecycline and comparative agents against 3,204 strains of *Enterobacteriaceae*

Organism Name	Drug	MIC (mcg/mL)		
		MIC <sub>50</sub>	MIC <sub>90</sub>	Range
<i>Enterobacteriaceae</i> (n=3,204)				
	Tigecycline	0.25	1	0.03 - 16
	Amikacin	2	4	<0.5 - >64
	Amox/Clav	8	>32	0.5 - >32
	Ampicillin	>32	>32	<0.5 - >32
	Cefepime	<0.5	2	<0.5 - >32
	Ceftazidime	<8	16	<8 - >32
	Ceftriaxone	<0.06	8	<0.06 - >64
	Imipenem	0.5	1	0.12 - >16
	Levofloxacin	0.06	8	<0.008 - >8
	Minocycline	2	8	<0.5 - >16
	Pip/Tazo	1	16	<0.06 - >128

Table 2. *In Vitro* activity of Tigecycline and comparative agents against major representatives of *Enterobacteriaceae*

Organism Name	Drug	%SUS	%INT	%RES	MIC (mcg/mL)	
					MIC <sub>50</sub>	MIC <sub>90</sub>
<i>Enterobacter aerogenes</i> (n=163)						
	Tigecycline	97.6	0.9	1.5	0.5	1
	Amikacin	100.0	0.0	0.0	2	4
	Amox/Clav	10.0	3.1	86.9	>32	>32
	Ampicillin	5.5	4.9	89.6	>32	>32
	Cefepime	97.5	1.2	1.2	0.5	1
	Ceftazidime	84.7	4.3	11.0	8	32
	Ceftriaxone	92.6	4.3	3.1	0.12	4
	Imipenem	99.4	0.0	0.6	1	2
	Levofloxacin	92.0	3.1	4.9	0.06	1
	Minocycline	90.8	5.5	3.7	2	4
	Pip/Tazo	87.1	7.4	5.5	2	32
<i>Enterobacter cloacae</i> (n=397)						
	Tigecycline	93.0	5.1	1.9	0.5	2
	Amikacin	99.2	0.0	0.8	2	2
	Amox/Clav	3.0	1.0	96.0	>32	>32
	Ampicillin	5.0	2.3	92.7	>32	>32
	Cefepime	93.2	2.8	4.0	0.5	4
	Ceftazidime	70.3	6.5	23.2	8	>32
	Ceftriaxone	75.1	10.6	14.4	0.25	64
	Imipenem	99.0	0.0	1.0	0.5	1
	Levofloxacin	90.7	2.3	7.0	0.06	2
	Minocycline	85.9	5.8	8.3	2	8
	Pip/Tazo	79.6	11.1	9.3	2	64

<i>Escherichia coli</i> (n=645)					
	Tigecycline	100.0	0.0	0.0	0.12 - 0.25
	Amikacin	98.8	0.5	0.8	2 - 4
	Amox/Clav	77.1	13.9	8.7	4 - 16
	Ampicillin	48.8	0.8	50.4	>32 - >32
	Cefepime	97.5	0.6	1.9	<0.5 - <0.5
	Ceftazidime	94.9	1.7	3.4	8 - 8
	Ceftriaxone	94.6	1.6	3.9	0.06 - 0.5
	Imipenem	99.8	0.0	0.2	0.25 - 0.5
	Levofloxacin	76.6	1.6	21.9	0.03 - >8
	Minocycline	83.1	8.8	8.1	1 - 8
	Pip/Tazo	95.7	1.2	3.1	1 - 4
<i>Klebsiella pneumoniae</i> (n=484)					
	Tigecycline	95.2	3.6	1.2	0.5 - 2
	Amikacin	98.6	0.8	0.6	2 - 4
	Amox/Clav	86.7	6.9	6.3	2 - 16
	Ampicillin	3.7	16.7	79.5	>32 - >32
	Cefepime	95.9	1.0	3.1	0.5 - 2
	Ceftazidime	86.4	2.3	11.4	8 - 32
	Ceftriaxone	90.5	5.0	4.5	0.06 - 8
	Imipenem	98.6	0.4	1.0	0.5 - 1
	Levofloxacin	88.8	2.1	9.1	0.06 - 4
	Minocycline	83.5	5.6	11.0	2 - 16
	Pip/Tazo	93.2	1.4	5.4	2 - 8
<i>Klebsiella oxytoca</i> (n=101)					
	Tigecycline	98.9	0.0	1.1	0.25 - 0.5
	Amikacin	99.0	1.0	0.0	2 - 4
	Amox/Clav	82.3	7.6	10.1	2 - 32
	Ampicillin	4.0	9.9	86.1	>32 - >32
	Cefepime	96.0	0.0	4.0	0.5 - 4
	Ceftazidime	91.1	1.0	7.9	8 - 8
	Ceftriaxone	89.1	8.9	2.0	0.06 - 16
	Imipenem	99.0	0.0	1.0	0.5 - 0.5
	Levofloxacin	96.0	4.0	0.0	0.03 - 0.5
	Minocycline	94.0	3.0	5.1	1 - 4
	Pip/Tazo	89.1	1.0	9.9	1 - 64

## CONCLUSIONS

- Tigecycline inhibited 97% of all *Enterobacteriaceae* tested *in vitro* at an MIC of 2 mcg/mL.
- Tigecycline's MIC<sub>90</sub> of 1 mcg/mL was equivalent to imipenem and 8 to 64 fold better than the beta-lactams, beta-lactam/beta-lactamase inhibitor combinations and levofloxacin against all *Enterobacteriaceae* tested.
- Tigecycline demonstrated potent *in vitro* activity against both ESBL and non-ESBL producing *E. coli* and *K. pneumoniae* and *K. oxytoca*.
- The *in vitro* activity of tigecycline in this study suggests that tigecycline is a promising compound in the treatment of Gram-negative infections caused by selected *Enterobacteriaceae*.