

Tigecycline Evaluation Surveillance Trial (T.E.S.T.) - Global In Vitro Antibacterial Activity against 13,669 Gram-positive and Gram-negative Pathogens

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S. Bouchillon¹, T. Stevens¹, B. Johnson¹, J. Johnson¹, D. Hoban¹, A. Hsiung¹, M. Hackel¹, M. Person¹, M. Dowzicky²

¹International Health Management Associates, Schaumburg, IL, USA
²Wyeth Pharmaceuticals, Collegeville, PA, USA

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

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 species responsible for community and hospital acquired infections. The T.E.S.T. program determined the in vitro activity of tigecycline compared to amikacin, ampicillin, imipenem, cefepime, ceftazidime, ceftriaxone, 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 hospitals in North America, Europe and Asia throughout 2004. **Methods:** A total of 13,669 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 MicroScan and interpreted according to CLSI guidelines. **Results:** Tigecycline's activity was similar to imipenem against most *Enterobacteriaceae*. Tigecycline inhibited ESBL producers with a MIC equal to or less than 2 mcg/ml. Although similar to other classes of broad spectrum antimicrobial agents against non-fermenters, tigecycline was especially active against *Acinetobacter* spp. demonstrating the lowest MIC₉₀ of 1 mcg/ml. Tigecycline successfully inhibited *S. aureus* with a MIC₉₀ of 0.25 mcg/ml regardless of methicillin susceptibility phenotype. Similar results were noticed against enterococci with a tigecycline MIC₉₀ of 0.12 mcg/ml against all strains of enterococci without regard to vancomycin susceptibility. **Conclusion:** Tigecycline's in vitro activity was comparable to or greater than most commonly prescribed antimicrobials against a broad spectrum of aerobic clinical pathogens from a diverse geographical population. The presented data suggest that tigecycline may be an effective therapeutic option against many aerobic Gram-positive and Gram-negative bacteria, including problematic strains with ESBL, VRE and MRSA resistance 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 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*, which are commonly associated with serious nosocomial infections. Similar activity has been observed against *Enterobacteriaceae*, even extended-spectrum β -lactamase and AmpC 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 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 better define the in vitro activity of tigecycline in a large diverse population of clinical isolates collected from hospitals worldwide.

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 - December 2004 from 63 study centers in 15 countries.
- Custom broth microdilution panels were supplied by MicroScan (Dade Behring 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); 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); and imipenem (0.06-16).
- MIC interpretive criteria followed published guidelines established by the NCCLS 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 genus and species by the local laboratory. Each site tested the isolates using broth microdilution.
- 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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Table 1. List of countries and number of investigative sites that contributed to T.E.S.T. program.

Country	Investigative Sites
Canada	1
China	1
France	2
Germany	4
Hungary	1
India	1
Italy	2
Latvia	1
Philippines	1
Poland	1
Spain	1
Switzerland	1
The Netherlands	1
United Kingdom	1
United States	44
Total	63

Table 2. In vitro activity of tigecycline and comparative agents against 7,531 selected strains of *Enterobacteriaceae*.

Organism Name*	Drug*	%SUS	%INT	%RES	MICs (mcg/ml)
<i>E. coli</i> (n=7,531)	Tigecycline	97	2.5	0.5	0.25-1
	Amikacin	95.5	0.7	2	4
	Amox-Clav	60.2	8.5	31.2	>32
	Ampicillin	20.4	6.7	72.9	>32
	Cefepime	95.1	1.3	3.6	<0.5
	Ceftazidime	88.2	2.3	8.5	>8
	Ceftriaxone	95.1	4	4.9	<0.08
	Imipenem	98.6	0.4	1	0.5
	Levofloxacin	95.9	1.8	19.3	0.06
	Minocycline	84.7	7.9	7.4	2
	Pip-Tazo	51.6	2.9	47.2	16

Organism Name*	Drug*	%SUS	%INT	%RES	MICs (mcg/ml)
<i>E. coli</i> (n=1,421)	Tigecycline	98.3	0.1	0.12	0.25
	Amikacin	99.2	0.3	0.5	2
	Amox-Clav	80.4	8.4	11.2	2
	Ampicillin	48.4	1	52.6	>32
	Cefepime	97.1	0.9	2	<0.5
	Ceftazidime	95	1.5	3.5	>8
	Ceftriaxone	98.2	1.4	4.4	<0.08
	Imipenem	99.6	0	0.4	0.25
	Levofloxacin	77.6	2	20.4	0.03
	Minocycline	63.6	9.8	16.6	1
	Pip-Tazo	56.3	1.3	42.4	8

Organism Name*	Drug*	%SUS	%INT	%RES	MICs (mcg/ml)
<i>K. pneumoniae</i> (n=1,148)	Tigecycline	94.3	4.9	0.5	2
	Amikacin	97.6	1.3	1.1	2
	Amox-Clav	80.4	8.4	11.2	2
	Ampicillin	3.8	14.9	81.3	>32
	Cefepime	92.2	1.7	6.1	<0.5
	Ceftazidime	85.5	1.8	12.7	>32
	Ceftriaxone	98.8	4.3	8.9	<0.08
	Imipenem	97.2	1.1	1.7	0.5
	Levofloxacin	84.8	1.3	10.3	0.06
	Minocycline	62.3	6.9	10.8	2
	Pip-Tazo	59.2	1.8	37.2	16

Organism Name*	Drug*	%SUS	%INT	%RES	MICs (mcg/ml)
<i>K. oxytoca</i> (n=253)	Tigecycline	98.7	0.4	0.8	2
	Amikacin	98.7	0.4	0.8	2
	Amox-Clav	80.4	8.4	11.2	2
	Ampicillin	5.6	11.6	82.8	>32
	Cefepime	95.7	1.3	3	<0.5
	Ceftazidime	83.6	0.8	15.6	>8
	Ceftriaxone	91.4	5.2	3.4	<0.08
	Imipenem	99.1	0	0.9	0.5
	Levofloxacin	83.6	3	14.3	0.03
	Minocycline	61.4	6.2	2.8	1
	Pip-Tazo	51.9	0.8	47.2	16

Organism Name*	Drug*	%SUS	%INT	%RES	MICs (mcg/ml)
<i>E. coli</i> ESBL producers (n=253)	Tigecycline	92.3	6.6	1.1	0.5
	Amikacin	99.3	0.7	0	2
	Amox-Clav	58.6	4.7	36.7	4
	Ampicillin	27.6	40.3	32.1	16
	Cefepime	92.5	0.5	0.6	<0.2
	Ceftazidime	54.1	9.7	36.2	8
	Ceftriaxone	92.4	0.7	6.9	<0.2
	Ceftriaxone	20.4	20	53.6	64
	Imipenem	98.8	5.6	3.6	0.5
	Levofloxacin	63.8	2.7	33.5	0.1
	Minocycline	65.9	10.2	24	>16
Pip-Tazo	48.6	3	47.2	16	

Organism Name*	Drug*	%SUS	%INT	%RES	MICs (mcg/ml)
<i>K. pneumoniae</i> (n=196)	Tigecycline	92.3	6.6	1.1	0.5
	Amikacin	99.3	0.7	0	2
	Amox-Clav	58.6	4.7	36.7	4
	Ampicillin	27.6	40.3	32.1	16
	Cefepime	92.5	0.5	0.6	<0.2
	Ceftazidime	54.1	9.7	36.2	8
	Ceftriaxone	92.4	0.7	6.9	<0.2
	Ceftriaxone	20.4	20	53.6	64
	Imipenem	98.8	5.6	3.6	0.5
	Levofloxacin	63.8	2.7	33.5	0.1
	Minocycline	65.9	10.2	24	>16
Pip-Tazo	48.6	3	47.2	16	

Organism Name*	Drug*	%SUS	%INT	%RES	MICs (mcg/ml)
<i>E. coli</i> (n=1,81)	Tigecycline	98.6	2	0.8	0.5
	Amikacin	98.6	2.5	0.8	1
	Amox-Clav	7.5	3.3	89.2	>32
	Ampicillin	6.7	4.5	88.8	>32
	Cefepime	95.8	0.8	3.4	<0.5
	Ceftazidime	79.7	5.8	14.5	>32
	Ceftriaxone	92.3	0.7	6.9	<0.2
	Imipenem	98.8	0	1.1	2
	Levofloxacin	82.8	2.7	15	0.06
	Minocycline	80.1	5.8	15.2	2
	Pip-Tazo	58.3	7.8	34.2	8

*Only species with ≥ 20 are represented.
*Breakpoints as defined by NCCLS where available (M100-S14). 2004. Tigecycline breakpoints defined as: susceptible \leq 2; intermediate = 4; and resistant \geq 8.

Organism Name*	Drug*	%SUS	%INT	%RES	MICs (mcg/ml)
<i>E. coli</i> (n=21)	Tigecycline	95.2	4.8	0	0.25-1
	Amikacin	100	0	0	1-8
	Amox-Clav	42.8	0	57.1	>32
	Ampicillin	19	4.8	76.2	>32
	Cefepime	100	0	0	<0.5
	Ceftazidime	66.7	4.7	28.6	>8
	Ceftriaxone	71.4	9.5	19.1	0.25-64
	Imipenem	95.2	4.8	0	0.5
	Levofloxacin	82.7	0	14.3	0.12-8
	Minocycline	75.2	14.3	9.5	2
	Pip-Tazo	50.5	4.7	4.8	2-8

Organism Name*	Drug*	%SUS	%INT	%RES	MICs (mcg/ml)
<i>E. coli</i> (n=966)	Tigecycline	94.4	4.2	1.4	0.12-2
	Amikacin	98.3	0.3	0.9	2-2
	Amox-Clav	4	1.6	94.4	>32
	Ampicillin	5.4	3.4	91.2	>32
	Cefepime	94.9	1.3	3.9	<0.5
	Ceftazidime	74.4	5.2	20.4	>8
	Ceftriaxone	77.7	8.7	13.6	0.25-64
	Imipenem	99	0.1	0.9	0.5
	Levofloxacin	92.8	1.5	5.7	0.06-2
	Minocycline	85.7	7.1	7	2-8
	Pip-Tazo	52	2	47	8-64

Organism Name*	Drug*	%SUS	%INT	%RES	MICs (mcg/ml)
<i>S. aureus</i> (n=617)	Tigecycline	96.8	2.8	0.4	1-2
	Amikacin	99.3	0.1	0.6	4
	Amox-Clav	2.8	2.2	95	>32
	Ampicillin	3.4	1.5	95.1	>32
	Cefepime	96.6	1.3	2.3	<0.5
	Ceftazidime	96.2	1.2	2.4	>8
	Ceftriaxone	91.6	3.7	4.7	0.25-8
	Imipenem	98.5	0.4	1	0.5
	Levofloxacin	95.3	1.9	2.4	0.12-1
	Minocycline	90.4	6.6	3	4-4
	Pip-Tazo	49.8	2.8	47.2	8-16

Organism Name*	Drug*	%SUS	%INT	%RES	MICs (mcg/ml)
<i>S. pneumoniae</i> (n=234)	Tigecycline	98.7	1.3	0	0.25-4
	Amikacin	98.7	1.3	0	0.25-4
	Amox-Clav	98.7	1.3	0	0.25-4
	Ampicillin	98.7	1.3	0	0.25-4
	Cefepime	98.7	1.3	0	0.25-4
	Ceftazidime	98.7	1.3	0	0.25-4
	Ceftriaxone	98.7	1.3	0	0.25-4
	Imipenem	98.7	1.3	0	0.25-4
	Levofloxacin	98.7	1.3	0	0.25-4
	Minocycline	98.7	1.3	0	0.25-4
	Pip-Tazo	98.7	1.3	0	0.25-4

Organism Name*	Drug*	%SUS	%INT	%RES	MICs (mcg/ml)
<i>Acinetobacter baumannii</i> (n=21)	Tigecycline	98.1	0.5	0.38	1
	Amikacin	98.1	0.5	0.38	1
	Amox-Clav	98.1	0.5	0.38	1
	Ampicillin	98.1	0.5	0.38	1
	Cefepime	98.1	0.5	0.38	1
	Ceftazidime	98.1	0.5	0.38	1
	Ceftriaxone	98.1	0.5	0.38	1
	Imipenem	98.1	0.5	0.38	1
	Levofloxacin	98.1	0.5	0.38	1
	Minocycline	98.1	0.5	0.38	1
	Pip-Tazo	98.1	0.5	0.38	1

Organism Name*	Drug*	%SUS	%INT	%RES	MICs (mcg/ml)
<i>Acinetobacter baumannii</i> (n=4)	Tigecycline	98.1	0.5	0.38	1
	Amikacin	98.1	0.5	0.38	1
	Amox-Clav	98.1	0.5	0.38	1
	Ampicillin	98.1			