

In Vitro Activity of Tigecycline and 13 Comparators against Pathogens from a Global Population of Intensive Care Patients in 2007

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REVISED ABSTRACT

Objective: Tigecycline is a novel antimicrobial from a new class of compounds, the glycylcyclines, which has been shown to have potent broad spectrum activity against most commonly encountered species responsible for community and hospital acquired infections. The Tigecycline Evaluation Surveillance Trial (TEST), a global longitudinal surveillance study, surveyed the in vitro activity of tigecycline and 13 comparator compounds against pathogens from ICU patients from a global population from 2004-2007. **Methods:** A total of 16,391 clinical isolates from 387 testing sites in 48 countries were evaluated. Minimum Inhibitory Concentration (MICs) were determined by each site using common broth microdilution panels and interpreted according to CLSI and FDA guidelines. **Results:** Results are in the table as follows:

Drug	<i>Enterobacteriaceae</i> (n=7,601)		<i>Acinetobacter</i> spp (n=1,646)	
	MIC ₅₀	MIC ₉₀	MIC ₅₀	MIC ₉₀
Tigecycline	0.5	2	0.5	1
Amikacin	2	8	8	>64
Cefepime	≤0.5	8	16	>32
Imipenem	0.5	1	1	>16
Levofloxacin	0.06	>8	4	>8
Minocycline	2	8	≤0.5	8
PipTazo	2	128	64	>128

Drug	<i>S. aureus</i> (n=1,722)		<i>Enterococcus</i> spp (n=1,252)	
	MIC ₅₀	MIC ₉₀	MIC ₅₀	MIC ₉₀
Tigecycline	0.12	0.25	0.06	0.12
Levofloxacin	0.25	32	16	>32
Linezolid	2	2	2	2
Minocycline	≤0.25	0.5	4	>8
Vancomycin	1	1	1	>32

Conclusion: Tigecycline's in vitro activity was comparable to or greater than most commonly prescribed broad spectrum antimicrobials for all ICU bacterial study strains encountered. Tigecycline's inhibitory activity against *Enterobacteriaceae*, and *Acinetobacter* spp. was comparable to imipenem. Against gram-positive organisms, tigecycline's MIC₅₀ values of ≤0.25mcg/mL suggest that tigecycline may be an effective and reliable therapeutic option against these pathogens in an Intensive Care setting.

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 MIC₉₀ 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 in animal models infected with selected strains of multi-drug resistant *Enterococcus faecium* and *Enterococcus faecalis* [4,5] with diverse genotypes of vanA, vanB and vanC [6].

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 387 hospitals globally from 2004 to 2007. This analysis evaluates the in vitro activity of tigecycline against pathogens commonly isolated from patients in Intensive Care Units.

MATERIALS & METHODS

- For the T.E.S.T program all isolates were derived from blood, respiratory tract, urine (no more than 25% of all isolates), skin, wound, fluids, and other defined sources. Isolates were identified to genus and species by the local laboratory. Each site tested the isolates using broth microdilution. Only one isolate per patient was accepted.
- 16,391 clinical isolates were collected from ICU patients from 2004 to 2007 (387 sites in 48 countries).
- Minimum inhibitory concentrations (MICs) were determined by the CLSI recommended broth microdilution testing method [6]. Tigecycline was supplied by Wyeth Pharmaceuticals (Collegeville, PA, USA). All other agents were supplied by the panel manufacturers, MicroScan (Dade Behring Inc., West Sacramento, CA, USA) and Trek (TREK Diagnostic Systems, Cleveland, OH). The following antimicrobial agents were included on the panels with their dilution ranges (expressed in mcg/ml): amikacin (0.5-64, gram-negative only); amoxicillin/clavulanic acid (0.12/0.06-32/16); ampicillin (0.06-16); cefepime (0.5-32, gram-negative only); ceftazidime (8-32, gram-negative); ceftriaxone (0.06-64); imipenem (0.06-16, MicroScan only); linezolid (0.5-8, gram-positive only); meropenem (0.12-16, TREK only); levofloxacin (0.008-8); minocycline (0.5-16); tigecycline (0.008-16); penicillin (0.06-8, gram-positive only); piperacillin/tazobactam (0.06/4-128/4) and vancomycin (0.12-32, gram-positive only).
- MIC interpretive criteria followed published breakpoints established by the Clinical and Laboratory Standards Institute (CLSI) or the United States of America Food and Drug Administration (FDA) where applicable [13].
- Escherichia coli*, *Klebsiella pneumoniae*, and *Klebsiella oxytoca* were screened for ESBL activity when MIC results for ceftriaxone were >1 mcg/ml using broth microdilution panels. ESBL activity was confirmed using the CLSI (2006) phenotypic confirmatory disk test (Oxoid, Ogdensburg, NY, USA) on Mueller-Hinton agar (Remel Inc., Lenexa, KS, USA) according to CLSI (2006) guidelines. ESBL presence was confirmed by testing the following antibiotic disks: cefotaxime (30-mcg), cefotaxime/clavulanic acid (30/10-mcg), ceftazidime (30-mcg), and ceftazidime/clavulanic acid (30/10-mcg). Antimicrobial disks were manufactured by Oxoid, Inc. (Ogdensburg, NY, USA). Mueller-Hinton agar used in testing was manufactured by Remel, Inc. (Lenexa, KS, USA). An organism was interpreted as containing an ESBL if there was an increase of >5 mm in the inhibition zone of the combination disk when compared to that of the cephalosporin alone.
- Quality control of broth microdilution panels followed manufacturer's and CLSI guidelines using the following ATCC strains where applicable: *Enterococcus faecalis* ATCC 29212; *Escherichia coli* ATCC 25922; *Escherichia coli* ATCC 35218; *Klebsiella pneumoniae* ATCC 700603 (as positive ESBL control); *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, confirmation of identification, and 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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Table 1. In vitro activity of tigecycline and comparator agents against selected gram-negative organisms from ICU's.

Organism	n	%S*	%I*	%R*	MIC ₅₀	MIC ₉₀
<i>Enterobacteriaceae</i>						
Tigecycline	7,601	95.8	3.4	0.9	0.5	2
Amikacin	7,601	97.1	1.4	1.6	2	8
AmoxClav	7,601	39.3	7.6	5.3	32	>32
Ampicillin	7,601	9.1	6	84.8	>32	>32
Cefepime	7,601	90.8	2.5	6.7	<0.5	8
Ceftazidime	7,601	78.8	3.8	17.5	≤8	>32
Ceftriaxone	7,601	79.5	6.6	13.9	0.12	64
Imipenem	5,403	99.5	0.2	0.4	0.5	1
Levofloxacin	7,601	82.8	2.7	14.6	0.06	>8
Meropenem	2,198	96.7	0.9	2.4	≤0.06	0.5
Minocycline	7,601	81.9	8.4	9.7	2	8
PipTazo	7,601	82.4	7.2	10.3	2	128
<i>E. coli</i> ^a						
Tigecycline	1,727	100	0	0	0.12	0.5
Amikacin	1,727	98	1	1	2	8
AmoxClav	1,727	67	17.7	15.3	8	32
Ampicillin	1,623	33.3	1.1	65.6	>32	>32
Cefepime	1,727	93	1.8	5.2	<0.5	4
Ceftazidime	1,727	91.6	2.4	6	≤8	≤8
Ceftriaxone	1,727	89.6	2	8.5	<0.06	16
Imipenem	1,249	99.7	0	0.3	0.25	0.5
Levofloxacin	1,727	70.8	2.5	26.7	0.03	>8
Meropenem	478	99	0.4	0.6	≤0.06	0.12
Minocycline	1,727	81.9	7.7	10.4	1	16
PipTazo	1,727	91.6	3.2	5.2	1	16
<i>Klebsiella</i> spp. ^b						
Tigecycline	2,418	94.6	4.4	1	0.5	2
Amikacin	2,418	95.6	1.9	2.5	2	8
AmoxClav	2,418	72.5	8.9	18.7	4	32
Ampicillin	2,418	0.7	11.7	87.6	>32	>32
Cefepime	2,418	86.8	3	10.3	<0.5	32
Ceftazidime	2,418	79.2	2.9	18	≤8	>32
Ceftriaxone	2,418	79.7	5	15.3	<0.06	>64
Imipenem	1,694	99.1	0.4	0.5	0.25	0.5
Levofloxacin	2,418	82.9	2.7	14.4	0.06	>8
Meropenem	724	94.1	1.4	4.6	≤0.06	0.5
Minocycline	2,418	80.6	8	11.4	2	16
PipTazo	2,418	82.2	3.9	13.9	2	>128
ESBL-producers ^c						
Tigecycline	524	93.3	5	1.7	0.5	2
Amikacin	524	84	8.4	7.6	8	32
AmoxClav	524	21.9	30	48.1	16	>32
Ampicillin	524	0.8	0.2	99	>32	>32
Cefepime	524	43.7	10.3	46	16	>32
Ceftazidime	524	19.5	9.4	71.2	>32	>32
Ceftriaxone	524	16.6	17.2	66.2	32	32
Imipenem	364	97.8	1.6	0.5	0.5	1
Levofloxacin	524	35.5	6.1	58.4	8	>8
Meropenem	160	85.6	3.8	10.6	0.12	16
Minocycline	524	63.2	10.9	26	4	>16
PipTazo	524	53.4	11.3	35.3	16	>128
<i>Enterobacter</i> spp.						
Tigecycline	2,390	94	4.6	1.5	0.5	2
Amikacin	2,390	98.3	0.8	0.9	2	4
AmoxClav	2,390	2.6	1.7	95.7	>32	>32
Ampicillin	2,390	1	4.5	94.5	>32	>32
Cefepime	2,390	91.5	3	5.5	≤0.5	8
Ceftazidime	2,390	63.3	6.4	30.3	<8	>32
Ceftriaxone	2,390	68	12.4	19.6	0.5	>64
Imipenem	1,696	99.7	0.1	0.2	0.5	1
Levofloxacin	2,390	86	3.1	11	0.06	8
Meropenem	694	97.4	0.9	1.7	≤0.06	0.5
Minocycline	2,390	80.4	9.2	10.4	2	16
PipTazo	2,390	72	14.5	13.5	2	128
<i>Acinetobacter</i> spp.						
Tigecycline	1,646	na	na	na	0.5	1
Amikacin	1,646	64.2	9	26.8	8	>64
Cefepime	1,646	38.8	16.6	44.7	16	>32
Ceftriaxone	1,646	19.8	22.4	57.8	>64	>64
Imipenem	1,178	75.1	3.3	21.6	1	>16
Levofloxacin	1,646	40.3	11.7	47.9	4	>8
Meropenem	468	55.3	5.6	39.1	4	>16
Minocycline	1,646	87.9	8	4.1	≤0.5	8
PipTazo	1,646	42.9	15.4	41.7	64	>128
<i>P. aeruginosa</i>						
Tigecycline	2,190	na	na	na	8	>16
Amikacin	2,190	91.6	3.1	5.4	4	16
Cefepime	2,190	68.5	15.1	16.4	8	32
Ceftazidime	2,190	72.6	8.7	18.7	≤8	>32
Ceftriaxone	2,190	12.4	29.8	57.9	64	>64
Imipenem	1,547	74.5	12	13.5	1	16
Levofloxacin	2,190	59.5	6.6	33.9	1	>8
Meropenem	643	70.5	9.6	19.9	2	>16
Minocycline	2,190	4.3	15.1	80.6	>16	>16
PipTazo	2,190	83.8	0	16.2	8	128

* Includes 130 ESBL-producing *E. coli* strains.
* Includes 377 *K. pneumoniae* and 17 *K. oxytoca* ESBL producing strains.
* ESBL-producing *E. coli*, *K. pneumoniae* and *K. oxytoca*.
* Interpretive criteria as defined by CLSI; na = not available. Species with n's <20 were omitted from individual analysis but included as part of any aggregate totals.

RESULTS

Table 2. In vitro activity of tigecycline and comparator agents against selected gram-positive organisms from ICU's.

Organism	n	%S*	%I*	%R*	MIC ₅₀	MIC ₉₀
<i>S. aureus</i> (MS)						
Tigecycline	876	100	0	0	0.12	0.25
AmoxClav	876	100	0	0	1	2
Ampicillin	876	18.5	0	81.5	4	>16
Ceftriaxone	876	99	1	0	2	4
Imipenem	587	99.8	0.2	0	<0.12	0.25
Levofloxacin	876	95.8	1.9	2.3	0.12	0.25
Linezolid	876	100	0	0	2	4
Meropenem	289	100	0	0	≤0.12	0.25
Minocycline	876	99.8	0.2	0	<0.25	<0.25
Penicillin	876	15.6	0	84.4	8	>8
PipTazo	876	100	0	0	1	1
Vancomycin	876	100	0	0	0.5	1
<i>S. aureus</i> (MR) ^a						
Tigecycline	846	100	0	0	0.12	0.25
AmoxClav	846	0	0	100	>8	>8
Ampicillin	846	0	0	100	>	