

# The Activity of Tigecycline and Comparators Against Fastidious Pathogens from the Tigecycline Evaluation Surveillance Trial (T.E.S.T.) Program from Asia and the Pacific Rim



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## Revised Abstract

**Objectives:** Tigecycline is a novel glycolcycline, which has been shown to have potent activity against organisms with either ribosomal protection or active efflux. Tigecycline has shown excellent in vitro activity against fastidious isolates. The T.E.S.T. program determined the activity of tigecycline as compared to those of comparative agents against *Streptococcus pneumoniae*, *Streptococcus agalactiae* and *Haemophilus influenzae* from hospital-based investigative centers in Asia. **Methods:** A total of 1,595 clinical isolates were identified to the species level at each participating site and confirmed by the central laboratory. Isolates were collected from 2004-2008 from centers across Asia and the Pacific Rim. MIC's of tigecycline and comparator antimicrobial agents were determined by the local laboratory using broth microdilution panels from Siemens according to CLSI guidelines and manufacturer's instructions. **Results:** Tigecycline had a MIC<sub>90</sub> of ≤1.0 µg/mL against all the fastidious organisms tested. Of *S. pneumoniae*, 47.7% were non-susceptible to penicillin (I+R). Twenty one percent (26.9%) of *H. influenzae* were β-lactamase producers. Tigecycline had a MIC<sub>90</sub> of 0.06 µg/ml against all *S. pneumoniae*, 0.12 mcg/ml against *S. agalactiae*, and 1.0 µg/ml against β-lactamase positive *H. influenzae*. **Conclusions:** Tigecycline's activity is comparable to all of most commonly prescribed and broad spectrum antimicrobial agents evaluated in this study. The results indicate that tigecycline is an effective in vitro against the fastidious isolates, regardless of penicillin susceptibility or β-lactamase production. Tigecycline may serve as an effective alternative therapeutic option for infections caused by fastidious species.

## Introduction

Tigecycline is a novel antimicrobial with expanded broad-spectrum activity from a new class of compounds, the glycolcyclines. Tigecycline inhibits protein synthesis by binding to the 30S ribosomal subunit. Although it is perceived to be bacteriostatic, it 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, 7-9]. Tigecycline has demonstrated MIC<sub>90</sub> values of <0.5 µg/mL against *Streptococcus pneumoniae*, *Streptococcus pyogenes* and other Gram-positive organisms [2, 4-6]. Tigecycline has shown potent activity against non-enterobacteriaceae Gram-negative aerobes such as *Haemophilus influenzae* with MIC<sub>90</sub>s values of 0.25 µg/mL regardless of β-lactamase activity.

This study was designed to better define the in vitro activity of tigecycline in a limited number of fastidious clinical isolates collected from a diverse population in 10 Asian and Pacific Rim countries.

## Materials & Methods

- All isolates were derived from blood, genitourinary, respiratory tract and other sources. Only one isolate per patient was accepted.
- There were 1,595 clinical isolates were collected tested between January 2004 – December 2008 from 75 study centers in Australia, China, Hong Kong, India, Indonesia, Korea, Pakistan, Philippines, Singapore and Taiwan.
- Custom broth microdilution panels were supplied by MicroScan (Dade MicroScan, Sacramento, CA, USA) with the following antimicrobial agents and concentrations (expressed in µg/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).
- 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 manufacture's and CLSI guidelines using the following ATCC strains: *Haemophilus influenzae* ATCC 49247; *Haemophilus influenzae* ATCC 49766; and *Streptococcus pneumoniae* ATCC 49619.
- 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, USA).

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## Results

Table 1. In vitro Activity of Tigecycline and 10 Comparators against 605 Strains of *Haemophilus influenzae* from Asia and the Pacific Rim Characterized by Beta-lactamase Activity.

Organism (n)	Drug *	%Sus	%Int	%Res	MIC (mcg/ml)		
					MIC <sub>50</sub>	MIC <sub>90</sub>	Range
<i>H. influenzae</i> (n=605)	Tigecycline	n/a	na	na	0.25	0.5	<0.008 / 2
	Amox-Clav	100.0	0.0	0.0	0.5	1	<0.12 / 2
	Ampicillin	77.5	8.5	14.1	<0.5	16	<0.5 / >32
	Cefepime	98.6	0.0	1.4	<0.5	<0.5	<0.5 / 4
	Ceftazidime	0.0	0.0	100.0	<8	<8	<8 / 16
	Ceftriaxone	100.0	0.0	0.0	<0.06	<0.06	<0.06 / 1
	Imipenem	98.6	0.0	1.4	0.5	1	<0.06 / 8
	Levofloxacin	98.6	0.0	1.4	0.015	0.12	<0.008 / 8
	Minocycline	na	na	na	<0.5	1	<0.5 / 1
	Pip-Tazo	100.0	0.0	0.0	<0.06	0.12	<0.06 / 0.5
Beta-lactamase Negative	Tigecycline	na	na	na	0.25	0.5	0.008 / 2
	Amox-Clav	100.0	0.0	0.0	0.5	1	<0.12 / 2
	Ampicillin	94.6	5.4	0.0	<0.5	1	<0.5 / 2
	Cefepime	98.2	0.0	1.8	<0.5	<0.5	<0.5 / 4
	Ceftazidime	0.0	0.0	100.0	<8	<8	<8 / 16
	Ceftriaxone	100.0	0.0	0.0	<0.06	0.25	<0.06 / 1
	Imipenem	98.2	0.0	1.8	0.5	1	0.12 / 8
	Levofloxacin	98.2	0.0	1.8	0.015	0.25	<0.008 / 8
	Minocycline	na	na	na	<0.5	1	<0.5 / 1
	Pip-Tazo	100.0	0.0	0.0	<0.06	0.12	<0.06 / 0.5
Beta-lactamase Positive	Tigecycline	na	na	na	0.25	0.5	<0.008 / 2
	Amox-Clav	100.0	0.0	0.0	1	1	<0.12 / 2
	Ampicillin	13.3	20.0	66.7	16	>32	<0.5 / >32
	Cefepime	100.0	0.0	0.0	<0.5	<0.5	<0.5 / >0.5
	Ceftazidime	0.0	0.0	100.0	<8	<8	<8 / >8
	Ceftriaxone	100.0	0.0	0.0	<0.06	<0.06	<0.06 / >0.06
	Imipenem	100.0	0.0	0.0	0.5	1	<0.06 / 1
	Levofloxacin	100.0	0.0	0.0	0.015	0.015	<0.008 / 0.5
	Minocycline	na	na	na	<0.5	1	<0.5 / 1
	Pip-Tazo	100.0	0.0	0.0	<0.06	<0.06	<0.06 / >0.06

\*Breakpoints as defined by CLSI where available (M100-S16), 2008. na = CLSI breakpoints not available.

Table 2. Frequency Distribution and Cumulative Percents Inhibited for Tigecycline and Comparative Agents against 605 Strains of *Haemophilus influenzae*.

MIC N	MIC (µg/ml)															
	<0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	≥64		
Tigecycline	9	2	5	45	128	160	224	31	1	2	4	8	16	32	64	≥64
AmoxClav	5.8	28.9	63.0	81.8	85.5	99.7	99.8	100.0								
Ampicillin	380	44	29	5	13	21	33	80								
Cefepime	591	8	5	1												
Ceftazidime	97.7	99.0	99.8	100.0					603	2						
Ceftriaxone	576	13	5	5	5	1										
Imipenem	66	26	26	75	28	4										
Levofloxacin	151	362	44	16	9	6	10	3	4							
Meropenem	25.0	84.8	92.1	94.7	98.2	97.2	98.8	99.3	100.0							
Minocycline	57.1	84.5	97.4	100.0						378	179	40	5	3		
PipTazo	578	21	4	1	1											
	95.5	99.0	99.7	99.8	100.0											

Table 3. In vitro Activity of Tigecycline and 10 Comparators against 537 Strains of *Streptococcus pneumoniae* and 453 Strains of *Streptococcus agalactiae* from Asia and the Pacific Rim.

Organism (n)	Drug *	%Sus	%Int	%Res	MIC (µg/mL)		
					MIC <sub>50</sub>	MIC <sub>90</sub>	Range
<i>S. pneumoniae</i> (n=537)	Tigecycline	na	na	na	0.03	0.06	<0.008 / 0.25
	Amox-Clav	98.8	1.2	0.0	<0.03	0.5	<0.03 / 4
	Ampicillin	na	na	na	<0.06	1	<0.06 / >16
	Ceftriaxone	100.0	0.0	0.0	<0.03	0.5	<0.03 / 1
	Imipenem	69.1	29.6	1.2	<0.12	0.25	<0.12 / 2
	Levofloxacin	97.5	1.2	1.2	0.5	1	<0.06 / 8
	Linezolid	100.0	0.0	0.0	<0.5	1	<0.5 / 2
	Minocycline	na	na	na	1	8	<0.25 / >8
	Penicillin	69.1	23.5	7.4	<0.06	1	<0.06 / >8
	Pip-Tazo	na	na	na	<0.25	1	<0.25 / 8
Vancomycin	97.5	0.0	2.5	0.25	0.5	<0.12 / 0.5	
<i>S. pneumoniae</i> Penicillin-Susceptible (n=281)	Tigecycline	na	na	na	0.03	0.06	<0.008 / 0.25
	Amox-Clav	100.0	0.0	0.0	<0.03	<0.03	<0.03 / 0.06
	Ampicillin	na	na	na	<0.06	<0.06	<0.06 / 0.12
	Ceftriaxone	100.0	0.0	0.0	<0.03	<0.03	<0.03 / 0.12
	Imipenem	94.6	5.4	0.0	<0.12	<0.12	<0.12 / 0.25
	Levofloxacin	100.0	0.0	0.0	0.5	1	<0.06 / 1
	Linezolid	100.0	0.0	0.0	<0.5	1	<0.5 / 1
	Minocycline	na	na	na	<0.25	8	<0.25 / >8
	Penicillin	100.0	0.0	0.0	<0.06	<0.06	<0.06 / >0.06
	Pip-Tazo	na	na	na	<0.25	<0.25	<0.25 / >0.25
Penicillin-Intermediate <i>S. pneumoniae</i> (n=121)	Tigecycline	na	na	na	0.03	0.06	<0.008 / 0.25
	Amox-Clav	100.0	0.0	0.0	0.25	1	<0.03 / 1
	Ampicillin	na	na	na	0.25	2	<0.06 / 2
	Ceftriaxone	100.0	0.0	0.0	0.12	1	<0.03 / 1
	Imipenem	15.8	84.2	0.0	0.25	0.5	<0.12 / 0.5
	Levofloxacin	100.0	0.0	0.0	0.5	1	0.5 / 2
	Linezolid	100.0	0.0	0.0	<0.5	1	<0.5 / 1
	Minocycline	na	na	na	4	>8	<0.25 / >8
	Penicillin	0.0	100.0	0.0	0.25	1	0.12 / 1
	Pip-Tazo	na	na	na	<0.25	2	<0.25 / 2
<i>S. agalactiae</i> (n=453)	Tigecycline	98.9	na	na	0.12	2	<0.008 / 2
	Amox-Clav	na	na	na	0.03	0.12	<0.008 / 1
	Ampicillin	94.9	0.0	5.1	0.12	0.25	<0.06 / 1
	Ceftriaxone	92.3	0.0	7.7	0.06	0.25	<0.03 / >64
	Imipenem	na	na	na	0.25	0.5	<0.12 / 1
	Levofloxacin	87.2	0.0	12.8	0.5	8	0.5 / 16
	Linezolid	100.0	0.0	0.0	1	1	<0.5 / 2
	Minocycline	na	na	na	8	>8	<0.25 / >8
	Penicillin	94.9	0.0	5.1	<0.06	0.12	<0.06 / 4
	Pip-Tazo	na	na	na	<0.25	0.5	<0.25 / 4
Vancomycin	100.0	0.0	0.0	0.5	0.5	0.25 / 1	

\*Breakpoints as defined by CLSI where available (M100-S16), 2008. na = CLSI breakpoints not available.

Table 4. Frequency Distribution and Cumulative Percents Inhibited for Tigecycline and Comparative Agents against 537 Strains of *Streptococcus pneumoniae*.

MIC N	MIC (µg/ml)															
	<0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	≥64	
Tigecycline	30	173	205	85	42	2	2	5	1	2	4	8	16	32	64	≥64
AmoxClav	5.6	37.8	76.0	91.8	99.6	100.0										
Ampicillin	292	23	25	22	26	57	49	25	17	1						
Ceftriaxone	54.4	58.7	63.3	67.4	72.3	82.9	92.0	96.6	99.8	100.0						
Imipen																