

REVISED ABSTRACT

**Background:** Tigecycline (TIG), a new glycylicycline, has been shown to have potent 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 TIG and 10 comparators against gram positive/negative species. Isolates for the overall T.E.S.T. program were collected from 205 hospital sites in 30 countries from 2004 to 2006. **Methods:** A total of 5,084 clinically significant respiratory isolates collected worldwide were analyzed in this survey. The isolates were identified to the species level at the participating sites and confirmed by the central laboratory. MICs were determined by each site using supplied broth microdilution panels and interpreted according to CLSI guidelines. **Results:** Activities of tigecycline and comparator antimicrobials are shown in the table below<sup>1</sup>:

	<i>H. influenzae</i> (2,433)				<i>S. pneumoniae</i> (2,651)			
	%SUS	%INT	%RES	MIC <sub>90</sub>	%S	%I	%R	MIC <sub>90</sub>
Tigecycline	na	na	na	0.5	na	na	na	0.5
Ceftriaxone	99.8	-	0.2	≤0.06	97.8	1.3	0.9	1
Levofloxacin	100	-	-	0.03	99.9	0.1	-	1
Minocycline	na	na	na	1	na	na	na	4
Amox/Clav	99.8	-	0.2	1	94.8	3.2	2	2
Penicillin	-	-	-	-	61	26.8	11.3	2
Pip/Tazo	99.8	-	0.2	≤0.06	na	na	na	2
Linezolid	-	-	-	-	100	-	-	1
Vancomycin	-	-	-	-	100	-	-	0.5

<sup>1</sup>na = breakpoints not available.

Overall, 23.3% of *H. influenzae* were beta-lactamase producers and 38.1% of *S. pneumoniae* presented some degree of non-susceptibility to penicillin. Tigecycline demonstrated potent inhibitory activity with an MIC<sub>90</sub> of ≤0.5mcg/ml against beta-lactamase positive *H. influenzae* and penicillin non-susceptible *S. pneumoniae*. **Conclusion:** Tigecycline showed excellent inhibitory activity against *H. influenzae* and *S. pneumoniae* regardless of the presence of beta-lactamase or penicillin-resistance mechanisms. The results of this study suggest that tigecycline may be a reliable therapeutic option for the treatment of respiratory infections due to these species.

INTRODUCTION

Tigecycline (formerly GAR-936) is a member of a new class of antimicrobial agents, the glycylicyclines. This synthetic analogue of the tetracyclines exhibits significant antibacterial activity that is both bacteriostatic and, in certain instances, bactericidal with killing activity that is as much as fourfold better than vancomycin and daptomycin [1, 2]. The development of tigecycline is important in that tigecycline and other glycylicyclines are active against bacterial strains carrying either or both of the two major forms of tetracycline resistance: efflux and ribosomal protection. Certain substituents at the 9-position of the tetracycline molecule restore activity against bacteria harboring genes encoding either or both efflux and ribosomal protection. A single chemical modification of tigecycline overcomes the two molecularly distinct forms of resistance while maintaining activity against susceptible gram-positive, gram-negative, aerobic, and anaerobic bacteria [3].

Previous studies have demonstrated excellent in vitro activity for tigecycline against clinical and laboratory strains of gram-positive and -negative bacteria with minimum inhibitory concentrations for the 90<sup>th</sup> percentile inhibited at or below 2 mcg/ml, including difficult to treat methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *enterococci* (VRE), and extended-spectrum beta-lactamase (ESBL) producing *Enterobacteriaceae* [4-6]. This study was undertaken to document the in vitro activity of tigecycline against significant numbers of clinical pathogens collected from a large geographically diverse population over three years time. This study is part of the ongoing global Tigecycline Evaluation and Surveillance Trials (T.E.S.T.) program.

MATERIALS & METHODS

- All isolates were derived from the respiratory tract. Only one isolate per patient was accepted into the study. Clinical isolates were collected and tested worldwide from 2004 to 2006. Isolates were identified to the species level and tested at each site by the participating laboratory.
- Organism collection, transport, confirmation of organism identification, and development and management of a centralized database, were coordinated by Laboratories International for Microbiology Studies (LIMS), a division of International Health Management Associates, Inc. located in Schaumburg, IL, USA.
- All organisms were deemed clinically significant by local participant criteria. Isolate inclusion was independent of medical history, antimicrobial use, age, or gender. All sites identified each study isolate utilizing local laboratory criteria.
- Minimum inhibitory concentrations (MICs) were determined by the CLSI recommended broth microdilution testing method [7]. Tigecycline was supplied by Wyeth Pharmaceuticals (Collegeville, PA, USA). All other agents were supplied by the panel manufacturer, MicroScan (Dade Behring Inc., West Sacramento, CA, 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, gram-negative panel, and 0.06-16, gram-positive panel); cefepime (0.5-32); ceftriaxone (0.06-64); ceftazidime (8-32); imipenem (0.06-16); linezolid (0.5-8); levofloxacin (0.008-8); minocycline (0.5-16); tigecycline (0.008-16); piperacillin/tazobactam (0.06/4-128/4) and vancomycin (0.12-32). MIC interpretive criteria followed published guidelines established by the Clinical and Laboratory Standards Institute [8] and the recent US Food and Drug Administration package insert for tigecycline [9], where applicable.
- Quality controls (QC) were performed by each testing site on each day of testing using the corresponding ATCC control strains: *E. coli* ATCC 25922; *E. coli* ATCC 35218; *H. influenzae* ATCC 49766; *H. influenzae* ATCC 49247; *S. aureus* ATCC 29213; *Pseudomonas aeruginosa* ATCC 27853; *Enterococcus faecalis* ATCC 29212 and *S. pneumoniae* ATCC 49619. Results were included in the analysis only when corresponding QC isolates tested within the acceptable range according to CLSI (2006) guidelines [8].

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RESULTS

The results are listed in the following tables.

Table 1. In vitro activity of tigecycline and comparative agents against 2,433 *H. influenzae* isolates.

Organism Name	Drug	n	%SUS <sup>a</sup>	%INT	%RES	MIC (mcg/ml)		MIC range (mcg/ml)	
						MIC <sub>50</sub>	MIC <sub>90</sub>	Low	High
<i>H. influenzae</i>	Tigecycline	2,433	na	na	na	0.12	0.5	≤0.008	2
	AmoxClav	2,433	99.8	0	0.2	0.5	1	≤0.12	>32
	Ampicillin	2,433	75.6	2.1	22.3	≤0.5	>32	≤0.5	>32
	Cefepime	2,433	98.9	0	1.1	≤0.5	≤0.5	≤0.5	>32
	Ceftriaxone	2,433	99.8	0	0.2	≤0.06	≤0.06	≤0.06	>64
	Imipenem	2,433	100	0	0	0.5	1	≤0.06	4
	Levofloxacin	2,433	100	0	0	0.015	0.03	≤0.008	2
	Meropenem	90	100	0	0	≤0.06	0.12	≤0.06	0.5
	Pip/Tazo	2,433	99.8	0	0.2	≤0.06	≤0.06	≤0.06	16
	<i>H. influenzae</i> beta-lactamase negative	Tigecycline	1,867	na	na	na	0.12	0.5	≤0.008
AmoxClav		1,867	100	0	0	0.25	1	≤0.12	4
Ampicillin		1,867	98.5	1.4	0.1	≤0.5	≤0.5	≤0.5	16
Cefepime		1,867	99	0	1	≤0.5	≤0.5	≤0.5	32
Ceftriaxone		1,867	99.8	0	0.2	≤0.06	≤0.06	≤0.06	16
Imipenem		1,867	100	0	0	0.5	1	≤0.06	4
Levofloxacin		1,867	100	0	0	0.015	0.03	≤0.008	2
Meropenem		57	100	0	0	≤0.06	0.12	≤0.06	0.5
Pip/Tazo		1,867	99.9	0	0.1	≤0.06	≤0.06	≤0.06	2
<i>H. influenzae</i> beta-lactamase positive		Tigecycline	566	na	na	na	0.12	0.5	≤0.008
	AmoxClav	566	99.1	0	0.9	1	2	≤0.12	>32
	Ampicillin	566	0	4.4	95.6	32	>32	2	>32
	Cefepime	566	98.6	0	1.4	≤0.5	≤0.5	≤0.5	>32
	Ceftriaxone	566	99.6	0	0.4	≤0.06	≤0.06	≤0.06	>64
	Imipenem	566	100	0	0	0.5	1	≤0.06	4
	Levofloxacin	566	100	0	0	0.015	0.03	≤0.008	2
	Meropenem	33	100	0	0	≤0.06	≤0.06	≤0.06	0.12
	Pip/Tazo	566	99.3	0	0.7	≤0.06	≤0.06	≤0.06	16

na = breakpoints not available.

<sup>a</sup>Interpretive criteria as defined by CLSI, M100-S16 (2006), where available.

Table 2. In vitro activity of tigecycline and comparative agents against 2,651 *S. pneumoniae* isolates.

Organism Name	Drug	%SUS <sup>a</sup>	%INT	%RES	MIC (mcg/ml)		MIC range (mcg/ml)		
					MIC <sub>50</sub>	MIC <sub>90</sub>	Low	High	
<i>S. pneumoniae</i> (n<2,651)	Tigecycline	na	na	na	0.03	0.5	≤0.008	1	
	AmoxClav	94.8	3.2	2	≤0.03	2	≤0.03	8	
	Ceftriaxone	97.8	1.3	0.9	≤0.03	1	≤0.03	16	
	Imipenem	63.8	33.1	3.1	≤0.12	0.5	≤0.12	>16	
	Levofloxacin	99.9	0.1	0	0.5	1	≤0.06	4	
	Linezolid	100	0	0	≤0.5	1	≤0.5	2	
	Penicillin	61.9	26.8	11.3	≤0.06	2	≤0.06	>8	
	Vancomycin	100	0	0	0.25	0.5	≤0.12	1	
	<i>S. pneumoniae</i> (PSSP) (n<1,640)	Tigecycline	na	na	na	0.03	0.5	≤0.008	1
		AmoxClav	100	0	0	≤0.03	≤0.03	≤0.03	1
Ceftriaxone		100	0	0	≤0.03	≤0.03	≤0.03	1	
Imipenem		86.4	13.6	0.1	≤0.12	0.25	≤0.12	>16	
Levofloxacin		99.9	0.1	0	0.5	1	≤0.06	4	
Linezolid		100	0	0	≤0.5	1	≤0.5	2	
Penicillin		100	0	0	≤0.06	≤0.06	≤0.06	<0.06	
Vancomycin		100	0	0	0.25	0.5	≤0.12	1	
<i>S. pneumoniae</i> (PISP) (n<711)		Tigecycline	na	na	na	0.03	0.25	≤0.008	0.5
		AmoxClav	99.2	0.7	0.1	0.12	1	≤0.03	8
	Ceftriaxone	98.6	1.3	0.1	0.12	0.5	≤0.03	4	
	Imipenem	38.2	59.3	2.5	0.25	0.5	≤0.12	>16	
	Levofloxacin	99.9	0.1	0	0.5	1	≤0.06	4	
	Linezolid	100	0	0	≤0.5	1	≤0.5	2	
	Penicillin	0	100	0	0.25	1	0.12	1	
	Vancomycin	100	0	0	0.25	0.5	≤0.12	1	
	<i>S. pneumoniae</i> (PRSP) (n<300)	Tigecycline	na	na	na	0.03	0.25	≤0.008	1
		AmoxClav	56	26.7	17.3	2	8	≤0.03	8
Ceftriaxone		84.7	8.3	7	1	2	≤0.03	16	
Imipenem		1	78.1	20.9	0.5	1	≤0.12	>16	
Levofloxacin		99.7	0.3	0	0.5	1	0.25	4	
Linezolid		100	0	0	≤0.5	1	≤0.5	2	
Penicillin		0	0	100	2	4	2	>8	
Vancomycin		100	0	0	0.25	0.5	≤0.12	1	

na = breakpoints not available.

<sup>a</sup>Interpretive criteria as defined by CLSI, M100-S16 (2006), where available.

Figure 1: In vitro activity of tigecycline against 1,867 beta-lactamase negative and 566 beta-lactamase positive *H. influenzae* strains.

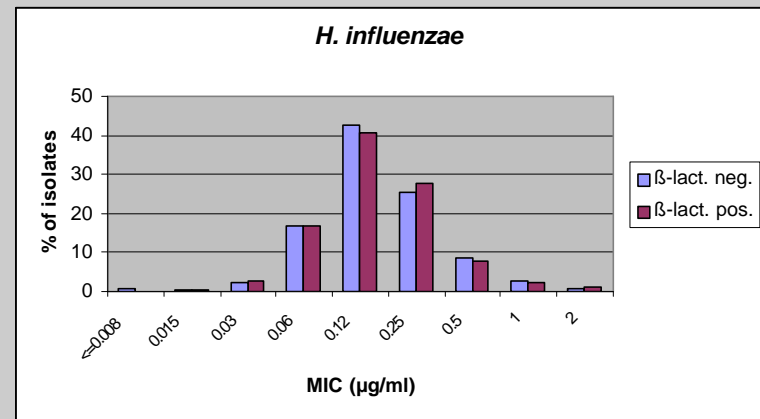
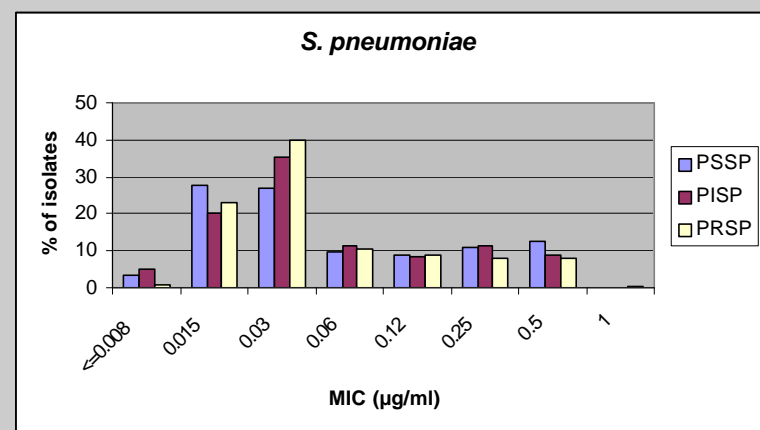


Figure 2: In vitro activity of tigecycline against 1,640 penicillin-susceptible (PSSP), 711 penicillin-intermediate (PISP) and 300 penicillin-resistant (PRSP) *S. pneumoniae* strains.



CONCLUSIONS

- Overall, 23.3% of *H. influenzae* were beta-lactamase producers and 38.1% of *S. pneumoniae* presented some degree to non-susceptibility to penicillin.
- Tigecycline showed excellent in vitro activity against *H. influenzae* and *S. pneumoniae* regardless of the presence of beta-lactamase or penicillin-resistance mechanisms.

- Tigecycline's MIC<sub>90</sub> of 0.25mcg/ml against penicillin non-susceptible *S. pneumoniae* was the lowest among all study antimicrobials.
- The results of this study suggest that tigecycline may be a reliable therapeutic option for the treatment of respiratory infections due to these species.