Antibacterial Activity of Tigecycline Against *H. influenzae* and *S. pneumoniae* (2004-06) Global Population - T.E.S.T. Program 2006

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REVISED ABSTRACT

Background: Tigecycline (TIG), a new glycylcycline, 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 comparators against respective gram-positive/negative species. Isolates were collected from 272 hospital sites in 34 countries from 2004 to 2006. **Methods:** A total of 7,473 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*:

	H. influenzae (n=3,570)			*S. pneumoniae* (n=3,903)		
Drug	**%Sus**	**MIC_{50}**	**MIC_{90}**	**%Sus**	**MIC_{50}**	**MIC_{90}**
Tigecycline	na	0.12	0.5	na	0.03	0.25
AmoxClav	99.7	0.5	1	95.3	≤0.03	1
Ceftriaxone	99.9	≤0.06	≤0.06	97.7	≤0.03	1
Levofloxacin	100	0.015	0.03	99.8	0.5	1
Imipenem	100	0.5	1	75.1	≤0.12	0.5
Linezolid	--	--	--	100	≤0.5	1
Penicillin	--	--	--	62.4	≤0.06	2

*na = breakpoints not yet determined at the time of publication.

Overall, 22.1% of *H. influenzae* were beta-lactamase producers and 37.6% of *S. pneumoniae* presented some degree to non-susceptibility to penicillin. Tigecycline demonstrated potent inhibitory activity with MIC_{90} of ≤0.5 mcg/ml and ≤0.25 mcg/ml against beta-lactamase positive *H. influenzae* and penicillin non-susceptible *S. pneumoniae*, respectively. **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 is a broad-spectrum antimicrobial agent and first-in-class of the semisynthetic glycylcyclines to be approved for human use [1]. This synthetic analogue of the minocycline molecule 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 [2, 3]. The development of tigecycline is important in that tigecycline and other glycylcyclines 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 restored 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 [4]. Furthermore, resistance to tigecycline is difficult to produce even in the laboratory.

Previous studies have demonstrated excellent in vitro activity for tigecycline against clinical and laboratory strains of gram-positive and gram-negative bacteria with minimum inhibitory concentrations for the 90th percentile inhibited at or below 2 mcg/ml, including difficult to treat methicillin-resistant *S. aureus* (MRSA), vancomycin-resistant enterococci (VRE) and extended-spectrum beta-lactamase (ESBL) producing *Enterobacteriaceae* [5-9]. This study was undertaken to document the in vitro activity of tigecycline against significant numbers of *H. influenzae* and *S. pneumoniae* collected from laboratories worldwide. This study is part of the larger ongoing global Tigecycline Evaluation and Surveillance Trials (T.E.S.T.) program.

MATERIALS & METHODS

- All isolates were derived from blood, respiratory tract, urine, skin, wound, body fluids and other defined sources. Only one isolate per patient was accepted into the study. Clinical isolates were collected and tested between January 2004 and December 2006 from study centers in worldwide. Isolates were identified to the species level and tested at each site by the participating laboratory.
- Organism collection, transport, confirmation of organism identification, as well as, development and management of a centralized database was 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 site criteria.
- Minimum inhibitory concentrations (MICs) were determined by the CLSI recommended broth microdilution testing method [10]. Tigecycline was supplied by Wyeth Pharmaceuticals (Collegeville, PA, USA). All other agents were supplied by the panel manufacturer, MicroScan (Dade Behring Inc., Sacramento, CA, USA). The following antimicrobial agents were included on the panels with their dilution ranges (expressed in mcg/ml): amoxicillin/clavulanic acid (0.12/0.06-32/16); ampicillin (0.06-16); ceftriaxone (0.06-64); imipenem (0.06-16); linezolid (0.5-8); levofloxacin (0.008-8); minocycline (0.5-16); tigecycline (0.008-16); penicillin (0.06-8); 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 [11] and recent US Food and Drug Administration packaging insert for tigecycline [12], where applicable.
- Quality controls (QC) were performed by each testing site on each day of testing using ATCC control strains *S. aureus* ATCC 29213 and *Enterococcus faecalis* ATCC 29212. Results were included in the analysis only when corresponding QC isolates tested within the acceptable range according to CLSI (2006) guidelines [11].

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RESULTS

The results are listed in the following Tables.

Table 1. In vitro activity of tigecycline and comparative agents against 3,570 *Haemophilus influenzae* categorized by beta-lactamase production.

					MIC (mcg/ml)		
Organisms	**Drug[a]**	**%Sus**	**%Int**	**%Res**	**MIC_{50}**	**MIC_{90}**	**Range**
H. influenzae (n=3,570)	Tigecycline	na	na	na	0.12	0.5	≤0.008 - 2
	AmoxClav	99.7	0	0.3	0.5	1	≤0.12 - >32
	Ampicillin	76.9	2.1	21.1	≤0.5	32	≤0.5 - >32
	Cefepime	99.4	0	0.6	≤0.5	≤0.5	≤0.5 - >32
	Ceftriaxone	99.9	0	0.1	≤0.06	≤0.06	≤0.06 - 32
	Imipenem	100	0	0	0.5	1	≤0.06 - 4
	Levofloxacin	100	0	0	0.015	0.03	≤0.008 - 2
	PipTazo	99.8	0	0.2	≤0.06	≤0.06	≤0.06 - 16
Beta-Lactamase Positive *H. influenzae* (n=788)	Tigecycline	na	na	na	0.12	0.5	≤0.008 - 2
	AmoxClav	98.7	0	1.3	1	2	≤0.12 - >32
	Ampicillin	0	4.6	95.4	32	>32	2 - >32
	Cefepime	98.7	0	1.3	≤0.5	≤0.5	≤0.5 - >32
	Ceftriaxone	99.7	0	0.3	≤0.06	≤0.06	≤0.06 - 32
	Imipenem	100	0	0	0.5	1	≤0.06 - 4
	Levofloxacin	100	0	0	0.015	0.03	≤0.008 - 2
	PipTazo	99.5	0	0.5	≤0.06	≤0.06	≤0.06 - 16

[a] Interpretive criteria as defined by CLSI, M100-S16 (2006), where applicable [10]; na=not available; Breakpoints are undefined for tigecycline against this species at the time of this publication.

Figure 1. Cumulative percents inhibited (%) of tigecycline and comparative agents against 3,570 *Haemophilus influenzae* at each MIC (mcg/mL).

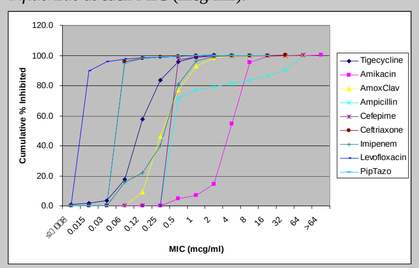
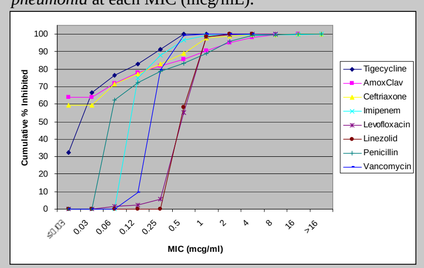


Table 2. In vitro activity of tigecycline and comparative agents against 3,903 *Streptococcus pneumoniae* categorized by penicillin susceptibility.

					MIC (mcg/ml)		
Organisms	**Drug[a]**	**%Sus**	**%Int**	**%Res**	**MIC_{50}**	**MIC_{90}**	**Range**
S. pneumoniae (n=3,903)	Tigecycline	na	na	na	0.03	0.25	≤0.008 - 0.5
	AmoxClav	95.3	2.8	1.9	≤0.03	1	≤0.03 - >8
	Ceftriaxone	97.7	1.3	1	≤0.03	1	≤0.03 - >64
	Imipenem	75.1	21.5	3.4	≤0.12	0.5	≤0.12 - >16
	Levofloxacin	99.8	0.2	0	0.5	1	≤0.06 - 4
	Linezolid	100	0	0	≤0.5	1	≤0.5 - 2
	Penicillin	62.4	26.7	10.9	≤0.06	2	≤0.06 - >8
	Vancomycin	99.9	0	0.1	0.25	0.5	≤0.12 - 2
Penicillin-Susceptible *S. pneumoniae* (n=2,437)	Tigecycline	na	na	na	0.03	0.5	≤0.008 - 0.5
	AmoxClav	100	0	0	≤0.03	≤0.03	≤0.03 - 0.5
	Ceftriaxone	100	0	0	≤0.03	≤0.03	≤0.03 - 1
	Imipenem	99.9	0.1	0	≤0.12	≤0.12	≤0.12 - 1
	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
Penicillin-Intermediate *S. pneumoniae* (PISP) (n=1,042)	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	1.1	0.4	0.12	0.5	≤0.03 - 4
	Imipenem	45.8	51.4	2.8	0.25	0.5	≤0.12 - >16
	Levofloxacin	99.7	0.3	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
Penicillin-Resistant *S. pneumoniae* (n=424)	Tigecycline	na	na	na	0.03	0.25	≤0.008 - 0.5
	AmoxClav	58.5	23.8	17.7	2	8	≤0.03 - >8
	Ceftriaxone	82.5	9.2	8.3	1	2	0.25 - >64
	Imipenem	1.2	73.9	24.9	0.5	1	≤0.12 - >16
	Levofloxacin	99.3	0.7	0	1	1	0.25 - 4
	Linezolid	100	0	0	≤0.5	1	≤0.5 - 2
	Penicillin	0	0	100	2	4	2 - >8
	Vancomycin	99.5	0	0.5	0.25	0.5	≤0.12 - 2

[a] Interpretive criteria as defined by CLSI, M100-S16 (2006), where applicable [10]; na=not available; Breakpoints are undefined for tigecycline against this species at the time of this publication.

Figure 2. Cumulative percents inhibited (%) of tigecycline and comparative agents against 3,903 *Streptococcus pneumonia* at each MIC (mcg/mL).



CONCLUSIONS

- Tigecycline demonstrated potent in vitro activity against *H. influenzae* and *S. pneumoniae* in this surveillance study of clinical isolates worldwide.
- Tigecycline MIC_{50} and MIC^{90} values of 0.12 and 0.5 mcg/ml, respectively, against *H. influenzae* were not affected in the presence of beta-lactamase.
- Tigecycline MIC_{50} and MIC_{90} values of 0.03 and 0.25 mcg/ml, respectively, against *S. pneumoniae* remained constant against all isolates and was unaffected by the penicillin-resistant phenotype.
- The in vitro activity of tigecycline in this study suggests that tigecycline is highly active against all study strains of *H. influenzae* and *S. pneumoniae* and may be an effective treatment option for these clinical pathogens.