

Revised Abstract

Background: Tigecycline (TIG), a new glycylyccline, 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 gram-positive/negative species. Isolates for the overall T.E.S.T program were collected from 1016 hospital sites in 53 countries from 2004 to 2008. **Methods:** A total of 9,627 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*:

	<i>H. influenzae</i> (6,976)				<i>S. pneumoniae</i> (2,651)			
	%SUS	%INT	%RES	MIC ₉₀	%S	%I	%R	MIC ₉₀
Tigecycline	na	na	na	0.5	na	na	na	0.12
Amox/Clav	99.7	0.0	0.3	1	94.0	3.6	2.4	2
Ampicillin	76.8	2.6	20.6	32	0.0	0.0	0.0	2
Cefepime	99.3	0.0	0.7	<0.5	na	na	na	na
Cefazidime	na	na	na	<8	na	na	na	na
Ceftriaxone	100.0	0.0	0.0	<0.06	93.3	4.9	1.9	1
Levofloxacin	100.0	0.0	0.0	0.03	99.2	0.3	0.5	1
Minocycline	25.5	0.2	0.3	1	na	na	na	<0.25
Pip/Tazo	99.8	0.0	0.2	<0.06	na	na	na	<0.25

* na = breakpoints not available.

Overall, 21.7% of *H. influenzae* were β-lactamase producers and 35.9% of *S. pneumoniae* presented resistance to penicillin. Tigecycline demonstrated potent inhibitory activity with an MIC₉₀ of ≤ 0.5mg/L against β-lactamase positive *H. influenzae* and penicillin non-susceptible *S. pneumoniae*. **Conclusions:** Tigecycline showed excellent inhibitory activity against *H. influenzae* and *S. pneumoniae* regardless of the presence of β-lactamase or penicillin-resistance mechanisms. The results of this study suggest that tigecycline may be a 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 glycylycclines. This synthetic analogue of the tetracyclines exhibits 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 glycylycclines 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 90th percentile inhibited at or below 2 mg/L, including difficult to treat methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE), and extended-spectrum β-lactamase (ESBL) producing *Enterobacteriaceae* [4-6]. This study was undertaken to document the *in vitro* activity of tigecycline against *S. pneumoniae* and *H. influenzae*, including penicillin non-susceptible and β-lactamase positive strains. This study is part of the ongoing global Tigecycline Evaluation and Surveillance Trial (T.E.S.T.) program with isolates collected from 1016 hospital sites in 53 countries from 2004 to 2008.

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 2008. Isolates were identified to the species level and tested at each site by the participating laboratory.
- All organisms were deemed clinically significant by local participant criteria. Isolate inclusion was independent of medical history, antimicrobial use, age, or gender.
- 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.
- MIC interpretive criteria followed published guidelines defined by EUCAST, where available (<http://www.srga.org/eucastw/MICTAB/index.html>, 2009); CLSI breakpoints were used where EUCAST not available. [12].
- 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 mg/L): 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); imipenem (0.06-16); linezolid (0.5-8); levofloxacin (0.008-8); meropenem (0.06-16); 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 [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 *E. coli* ATCC 35218; *H. influenzae* ATCC 49766; *H. influenzae* ATCC 49247; and *S. pneumoniae* ATCC 49619. Results were included in the analysis only when corresponding QC isolates tested within the acceptable range according to CLSI (2009) guidelines [8].

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Acknowledgements

We gratefully acknowledge the contributions of the investigators, laboratory personnel, and all members of the Tigecycline Evaluation Study Trials program group. This study was sponsored by a grant from Wyeth Pharmaceuticals.

Results

The results are listed in the following tables.

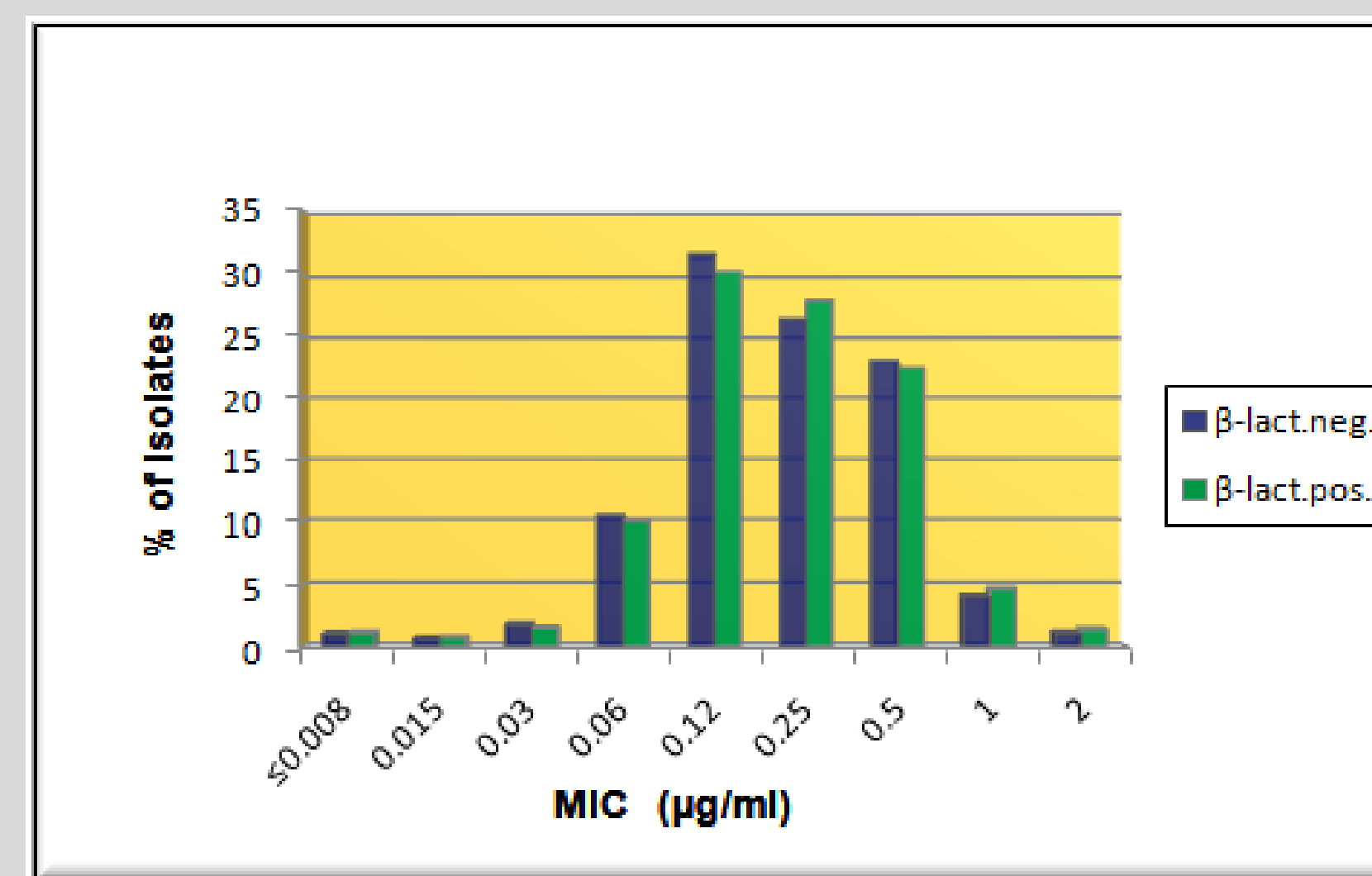
Table 1. *In vitro* activity of tigecycline and comparative agents against 6,976 *H. influenzae* isolates.

Organism Name	Drug	n	%SUS ^a	%INT	%RES	MIC (mg/L)		MIC range (mg/L)	
						MIC ₉₀	MIC ₅₀	Low	High
<i>H. influenzae</i>	Tigecycline	6,976	na	na	na	0.25	0.5	<0.008	2
	Amikacin	6,975	na	na	na	4	8	<0.5	>64
	Amox/Clav	6,976	99.7	0.0	0.3	0.5	1	<0.12	>32
	Ampicillin	6,976	76.8	2.6	20.6	<0.5	32	<0.5	>32
	Cefepime	6,976	99.3	0.0	0.7	<0.5	<0.5	<0.5	>32
	Cefazidime	6,968	na	na	na	<8	<8	<8	16
	Ceftriaxone	6,976	100.0	0.0	0.0	<0.06	<0.06	<0.06	32
	Imipenem	3,497	100.0	0.0	0.0	0.5	1	<0.06	4
	Levofloxacin	6,975	100.0	0.0	0.0	0.015	0.03	<0.008	2
	Meropenem	3,479	100.0	0.0	0.0	<0.06	0.25	<0.06	1
	Minocycline	6,976	25.5	0.2	0.3	<0.5	1	<0.5	>16
	Pip/Tazo	6,976	99.8	0.0	0.2	<0.06	<0.06	<0.06	16
<i>H. influenzae</i> β-lactamase negative	Tigecycline	5,461	na	na	na	0.25	0.5	<0.008	2
	Amikacin	5,461	na	na	na	4	8	<0.5	>64
	Amox/Clav	5,461	100.0	0.0	0.0	0.25	1	<0.12	32
	Ampicillin	5,461	98.2	1.8	0.0	<0.5	<0.5	<0.5	2
	Cefepime	5,461	99.4	0.0	0.6	<0.5	<0.5	<0.5	32
	Cefazidime	5,455	na	na	na	<8	<8	<8	16
	Ceftriaxone	5,461	100.0	0.0	0.0	<0.06	<0.06	<0.06	2
	Imipenem	2,728	100.0	0.0	0.0	0.5	1	<0.06	4
	Levofloxacin	5,461	100.0	0.0	0.0	0.015	0.03	<0.008	2
	Meropenem	2,733	100.0	0.0	0.0	<0.06	0.25	<0.06	1
	Minocycline	5,461	25.9	0.2	0.3	<0.5	1	<0.5	>16
	Pip/Tazo	5,461	99.9	0.0	0.1	<0.06	<0.06	<0.06	4
<i>H. influenzae</i> β-lactamase positive	Tigecycline	1,515	na	na	na	0.25	0.5	<0.008	2
	Amikacin	1,514	na	na	na	4	8	<0.5	>64
	Amox/Clav	1,515	98.8	0.0	1.2	1	2	<0.12	>32
	Ampicillin	1,515	0.0	5.2	94.8	32	>32	2	>32
	Cefepime	1,515	98.8	0.0	1.2	<0.5	<0.5	<0.5	>32
	Cefazidime	1,513	na	na	na	<8	<8	<8	16
	Ceftriaxone	1,515	99.9	0.0	0.1	<0.06	<0.06	<0.06	32
	Imipenem	769	100.0	0.0	0.0	0.5	1	<0.06	4
	Levofloxacin	1,515	100.0	0.0	0.0	0.015	0.03	<0.008	2
	Meropenem	746	100.0	0.0	0.0	<0.06	0.25	<0.06	0.5
	Minocycline	1,515	24.3	0.4	0.4	<0.5	1	<0.5	>16
	Pip/Tazo	1,515	99.7	0.0	0.3	<0.06	<0.06	<0.06	16

na = breakpoints not available.

* Breakpoints as defined by EUCAST, where available, 2009; CLSI breakpoints were used where EUCAST not available. na = not available; breakpoints not defined.

Figure 1: *In vitro* activity of tigecycline against 5,461 β-lactamase negative and 1,515 β-lactamase positive *H. influenzae* strains.



Conclusions

- Overall, 30.2% of *H. influenzae* were β-lactamase producers and 47.7% of *S. pneumoniae* presented resistance to penicillin.
- Tigecycline showed excellent *in vitro* activity against *H. influenzae* and *S. pneumoniae* regardless of the presence of β-lactamase or penicillin-resistance mechanisms.
- Tigecycline's MIC₉₀ of 0.12 mg/L against penicillin non-susceptible *S. pneumoniae* was the lowest among all study antimicrobials.
- The results of this study suggest that tigecycline may be a therapeutic option for the treatment of respiratory infections due to these species.

Table 2. *In vitro* activity of tigecycline and comparative agents against 6,946 *S. pneumoniae* isolates.

Organism Name	Drug	n	%SUS ^a	%INT	%RES	MIC (mg/L)		MIC range (mg/L)	
						MIC ₉₀	MIC ₅₀	Low	High
<i>S. pneumoniae</i> (PSSP) (n=6,946)	Tigecycline	na	na	na	na	0.03	0.12	<0.008	na
	Amoxiclav	66.0	3.6	2.4	<0.03	2	<0.03	94.6	
	Ampicillin	0.0	0.0	0.0	<0.06	2	<0.06	0.0	
	Azithromycin	66.0	0.4	31.6	0.12	>64	<0.03	48.0	
	Ceftioxone	69.3	4.9	1.9	<0.03	1	<0.03	93.3	
	Chloramphenicol	66.3	0.6	31.1	0.03	>64	<0.03	48.3	
	Clindamycin	66.0	0.3	16.7	0.06	>64	<0.03	83.0	
	Erythromycin	67.7	0.3	11.8	0.12	64	<0.03	67.7	
	Imipenem	56.9	19.9	3.2	<0.12	0.3	<0.12	36.9	
	Levofloxacin	69.2	0.3	0.5	0.5	1	<0.06	99.2	
	Linezolid	100.0	0.0	0.0	<0.5	1	<0.5	100.0	
	Meropenem	76.8	2.3	20.9	0.12	1	<0.12	76.8	
	Minocycline	na	na	na	<0.25	4	<0.25	na	
	Penicillin	61.1	25.2	13.7	<0.06	2	<0.06	61.1	
Pip/Tazo	na	na	na	<0.25	2	<0.25	na		
Vancomycin	100.0	0.0	0.0	0.25	0.5	<0.12	100.0		
<i>S. pneumoniae</i> (PISP) (n=4,244)	Tigecycline	na	na	na	na	0.03	0.12	<0.008	1
	Amoxiclav	100.0	0.0	0.0	<0.03	<0.03	<0.03	0.5	
	Ampicillin	0.0	0.0	0.0	<0.06	<0.06	<0.06	>16	
	Azithromycin	64.4	0.4	15.2	0.12	32	<0.03	>64	
	Ceftioxone	100.0	0.0	0.0	<0.03	<0.03	<0.03	1	
	Chloramphenicol	64.8	0.2	15.0	0.03	3	<0.03	>64	
	Clindamycin	61.6	0.3	6.1	0.06	0.12	<0.03	>64	
	Erythromycin	63.9	0.3	15.6	0.12	16	<0.03	>64	
	Imipenem	69.6	0.3	0.1	<0.12	<0.12	<0.12	1	
	Levofloxacin	99.6	0.2	0.2	0.5	1	<0.06	>32	
	Linezolid	100.0	0.0	0.0	<0.5	1	<0.5	2	
	Meropenem	99.7	0.0	0.3	<0.12	<0.12	<0.12	0.5	
	Minocycline	na	na	na	<0.25	0.5	<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	4		
Vancomycin	100.0	0.0	0.0	0.25	0.5	<0.12	2		
<i>S. pneumoniae</i> (PRSP) (n=1,751)	Tigecycline	na	na	na	na	0.03	0.12	<0.008	1
	Amoxiclav	65.1	0.3	0.1	0.12	1	<0.03	8	
	Ampicillin	na	na	na	0.25	2	<0.06	8	
	Azithromycin	66.8	0.7	32.4	2	>64	<0.03	>64	
	Ceftioxone	67.4	2.0	0.6	0.12	0.5	<0.03	16	
	Chloramphenicol	47.3	0						