

Global Study to Determine Antibacterial Activity of Tigecycline and Comparators Against *H. influenzae* and *S. pneumoniae* from 2004-2006

S. Bouchillon¹, M. Hackel¹, J. Johnson¹, R. Badal¹, D. Hoban¹, B. Johnson¹, M. Dowzicky²

¹International Health Management Associates, Schaumburg, IL, USA
²Wyeth Pharmaceuticals, Collegeville, PA, USA

IHMA, Inc.
2122 Palmer Dr.
Schaumburg, IL 60173
Tel: (847) 303-5003
Fax: (847) 303-5601
www.ihmainc.com

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 respective gram positive/negative species. Isolates 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*:

	<i>H. influenzae</i> (2,433)			<i>S. pneumoniae</i> (2,651)				
	%S	%I	%R	MIC ₉₀	%S	%I	%R	MIC ₉₀
Tigecycline	n/a	-	-	0.5	n/a	-	-	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
Amox/Clav	99.9	0.1	-	1	95	3.1	1.9	2
Penicillin	-	-	-	-	61.9	26.8	11.3	2
PipTazo	99.8	0	0.2	≤0.06	n/a	-	-	2
Linezolid	-	-	-	-	-	-	-	1
Vancomycin	-	-	-	-	100	-	-	0.5

*n/a = breakpoints not available

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 demonstrated potent inhibitory activity with MIC₉₀ 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 novel antimicrobial with expanded broad-spectrum activity from a new class of compounds, the glycylicyclines. 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 10⁻⁸ [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 MIC₉₀ values of ≤0.5 mcg/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 MIC₉₀s of 0.5 mcg/mL regardless of beta-lactamase activity.

This study was designed to better define the in vitro activity of tigecycline in a limited number of fastidious clinical isolates collected worldwide.

MATERIALS & METHODS

- A total of 5,084 clinically significant respiratory isolates collected worldwide were analyzed in this survey. Only one isolate per patient was accepted.
- Clinical isolates were collected and tested between 2004 and 2006 from 205 study centers in 30 countries.
- Minimum inhibitory concentrations (MICs) were determined by the CLSI recommended broth microdilution testing method [11]. 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): 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); 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 CLSI where applicable [11]. MIC interpretive criteria for tigecycline followed published guidelines established by the FDA where applicable [12].
- 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 manufacturer'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

The results are listed in the following tables.

Table 1. In vitro activity of tigecycline and 10 comparators against 2,433 strains of *Haemophilus influenzae* - Worldwide Results.

Organism (n)	Drug ^a	%Sus	%Int	%Res	MIC (mcg/mL)			
					MIC ₅₀	MIC ₉₀	Range	
<i>H. influenzae</i> (n=2,433)	Tigecycline	na	na	na	0.12	0.5	≤0.008 - 2	
	Amox-Clav	99.8	0	0.2	0.5	1	≤0.12 - >32	
	Ampicillin	75.6	2.1	22.3	≤0.5	>32	≤0.5 - >32	
	Cefepime	98.9	0	1.1	≤0.5	≤0.5	≤0.5 - >32	
	Ceftazidime	0	0	100	≤8	≤8	≤8 - >32	
	Ceftriaxone	99.8	0	0.2	≤0.06	≤0.06	≤0.06 - >64	
	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 Negative	Tigecycline	na	na	na	0.12	0.5	≤0.008 - 2
	Amox-Clav	100	0	0	0.25	1	≤0.12 - 4	
<i>H. influenzae</i> (n=1,867)	Ampicillin	98.5	1.4	0.1	≤0.5	≤0.5	≤0.5 - 16	
	Cefepime	99	0	1	≤0.5	≤0.5	≤0.5 - 32	
	Ceftazidime	0	0	100	≤8	≤8	≤8 - >32	
	Ceftriaxone	99.8	0	0.2	≤0.06	≤0.06	≤0.06 - 16	
	Imipenem	100	0	0	0.5	1	≤0.06 - 4	
	Levofloxacin	100	0	0	0.015	0.03	≤0.008 - 2	
	PipTazo	99.9	0	0.1	≤0.06	≤0.06	≤0.06 - 2	
	Beta-lactamase Positive	Tigecycline	na	na	na	0.12	0.5	≤0.008 - 2
		Amox-Clav	99.1	0	0.9	1	2	≤0.12 - >32
	<i>H. influenzae</i> (n=566)	Ampicillin	0	4.4	95.6	32	>32	2 - >32
Cefepime		98.6	0	1.4	≤0.5	≤0.5	≤0.5 - >32	
Ceftazidime		0	0	100	≤8	≤8	≤8 - >32	
Ceftriaxone		99.6	0	0.4	≤0.06	≤0.06	≤0.06 - >64	
Imipenem		100	0	0	0.5	1	≤0.06 - 4	
Levofloxacin		100	0	0	0.015	0.03	≤0.008 - 2	
PipTazo		99.3	0	0.7	≤0.06	≤0.06	≤0.06 - 16	

^a Breakpoints as defined by CLSI where available (M100-S16), 2006. na = CLSI breakpoints not available.

Table 2. Frequency distribution and cumulative percents inhibited for tigecycline and comparative agents against 2,433 strains of *Haemophilus influenzae*.

n/Cum%	MIC (mcg/mL)													
	≤0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	>32
Tigecycline	15	11	57	407	1023	630	207	62	21					
	0.6	1.1	3.4	20.1	62.2	88.1	96.6	99.1	100					
Amikacin							96	37	161	961	1051	110	2	
							3.9	5.5	12.1	51.6	94.8	99.3	100	
Amox-Clav				205	843	818	395	138	29	1	1	1	2	
				8.4	43.1	76.7	92.9	98.6	99.8	99.8	99.9	99.9	100	
Ampicillin				1687	152	52	58	58	79	100	247			
				69.3	75.6	77.7	80.1	82.5	85.7	89.8	100			
Cefepime				2353	35	18	11	9	4	1	2			
				96.7	98.2	98.9	99.3	99.7	99.9	99.9	100			
Ceftazidime										2413	14	2	4	
										99.2	99.8	99.8	100	
Ceftriaxone				2321	54	20	14	10	9	2				1
				95.4	97.6	98.4	99	99.4	99.8	99.9				100
Imipenem				76	73	451	1179	449	91	24				
				3.2	6.4	25.6	75.9	95.1	99	100				
Levofloxacin	604	1547	186	45	21	11	7	10	2					
	24.8	88.4	96.1	97.9	98.8	99.2	99.5	99.9	100					
Minocycline							1826	432	126	32	11	5	1	
							75.1	92.8	98	99.3	99.8	100	100	
PipTazo				2296	78	24	18	11	5					1
				94.4	97.6	98.6	99.3	99.8	100					100

CONCLUSIONS

- Tigecycline presented an MIC₉₀ of 0.5 mcg/ml against all strains of *H. influenzae* without regard to beta-lactamase production.
- Tigecycline inhibited 99.9% all strains of *S. pneumoniae* at MICs ≤0.5 mcg/ml without regard to penicillin sensitivity.
- Tigecycline exhibited excellent activity against sensitive penicillin non-susceptible *S. pneumoniae*, with an MIC₉₀ of 0.25 mcg/ml.
- Tigecycline demonstrates in vitro activity comparable to or greater than commonly prescribed antimicrobial agents such as linezolid, ceftriaxone, levofloxacin and amoxicillin-clavulanic acid currently used for the treatment of serious infections caused by fastidious gram-negative and gram-positive pathogens including penicillin-resistant *S. pneumoniae* and beta-lactamase producing strains of *H. influenzae*.