

Tigecycline Evaluation Surveillance Trial (T.E.S.T.) - In vitro Antibacterial Activity Against Fastidious Isolates

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REVISED ABSTRACT

Background: Tigecycline is a new glycycline, 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 TEST determined the activity of tigecycline as compared to those of comparative agents against *Streptococcus pneumoniae*, *Streptococcus agalactiae* and *Haemophilus influenzae* from hospitals-based investigative centers worldwide. **Methods:** A total of 1,336 clinical isolates were identified to the species level at each participating site and confirmed by the central laboratory. Isolates were collected between January 2004 – September 2004. MIC's were determined by the local laboratory using broth microdilution panels from Dade Microscan according to NCCLS guidelines and manufacturer's instructions. **Results:** Tigecycline had a MIC₅₀ of ≤ 0.25 mcg/mL against all the fastidious organisms tested with a MIC₉₀ of 0.5 mcg/mL against penicillin susceptible *S. pneumoniae* (PSSP), 1 mcg/mL against penicillin resistant *S. pneumoniae* (PRSP), 0.5 mcg/mL against *S. agalactiae*, 0.25 mcg/mL against both beta-lactamase negative and positive *H. influenzae*. Results are compared and contrasted with the comparative agents, amoxicillin-clavulanic acid, ampicillin, ceftriaxone, levofloxacin, minocycline, linezolid, minocycline and penicillin. **Conclusion:** Tigecycline had potent *in vitro* activity against all fastidious strains tested including penicillin-resistant *S. pneumoniae* and beta-lactamase producing strains of *H. influenzae*.

Drug	In vitro activity – MIC ₅₀ /MIC ₉₀ (mcg/mL)				
	<i>S. pneumoniae</i> n=482	PRSP n=84	<i>S. agalactiae</i> n=358	<i>H. influenzae</i> n=496	Beta-Lac Positive n=134
Tigecycline	0.06/0.5	0.06/1	0.06/0.5	0.12/0.25	0.12/0.25
Amox/Clav	$\leq 0.03/2$	4/8	0.06/0.12	0.5/1	1/2
Ampicillin	$\leq 0.06/4$	4/8	0.12/0.12	$\leq 0.5/32$	32/32
Ceftriaxone	$\leq 0.03/1$	1/1	0.06/0.12	$\leq 0.06/0.06$	$\leq 0.06/0.06$
Levofloxacin	0.5/1	1/1	0.5/1	0.015/0.03	0.015/0.015
Linezolid	0.5/1	$\leq 0.5/1$	3/987	–	–
Minocycline	$\leq 0.25/4$	2/8	8/8	$\leq 0.5/1$	$\leq 0.5/1$
Penicillin	$\leq 0.06/2$	2/4	$\leq 0.06/0.12$	–	–

INTRODUCTION

In recent years there has been a dramatic rise in resistance to commonly used antimicrobial agents in the treatment of both community acquired and nosocomial infections. Many of these strains have developed resistance to two or more antibiotics agent curtailing the use of entire genres of antimicrobials. Some countries are reporting more than 50% resistance of *S. pneumoniae* to penicillin and macrolides [1].

Tigecycline is a novel antimicrobial with an expanded broad-spectrum of activity from a new class of compounds, glycyclines. 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 MIC₉₀ values of ≤ 0.5 mcg/ml have been demonstrated against methicillin-resistant and multi-drug resistant *Staphylococcus aureus* and *Streptococcus pneumoniae* [3-5].

Tigecycline resistance is very infrequent and difficult to induce in the laboratory with a selection frequency observed at less than 10^{-6} [6, 7]. Most tetracycline-resistant bacteria with either tetracycline efflux pumps or ribosomal protective features are sensitive to tigecycline.

This study compared the activity of tigecycline with other agents against clinical isolates of three fastidious species, *S. pneumoniae*, with penicillin non-susceptible phenotypes, *S. agalactiae*, and *H. influenzae*, with beta-lactamase producing strains from geographically diverse institutions in North America and Europe.

MATERIALS & METHODS

- All isolates were derived from blood and respiratory tract sources. Only one isolate per patient was accepted.
- Clinical isolates were collected tested between January 2004 – September 2004 from 20 study centers in 6 countries.
- Antimicrobial agents tested with concentrations (expressed in mcg/ml) were for Gram-positive isolates amoxicillin/clavulanic acid (0.03-8); piperacillin/tazobactam (0.25-16); levofloxacin (0.06-32); ceftriaxone (0.03-64); linezolid (0.5-8); minocycline (0.25-8); vancomycin (0.12-32); ampicillin (0.06-16); penicillin (0.06-8); tigecycline (0.008-16); imipenem (0.12-16) and Gram-negative isolates 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); imipenem (0.06-16). MIC interpretive criteria followed published guidelines established by the NCCLS where applicable [8]. Tigecycline tentative breakpoints (in units of mcg/mL) are defined as susceptible ≤ 2 ; intermediate = 4; and resistant ≥ 8 .
- Isolates were identified to genus and species at each site by the local laboratory. Isolates were tested by the local laboratory.
- Organism collection, transport, confirmation of organism identification, as well as, construction and management of a centralized database was coordinated by Laboratories International for Microbiology Studies (LIMS).

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RESULTS

The results are published in the following tables.

Table 1. *In vitro* Activity (MIC mcg/mL) of Tigecycline and Comparative Agents against 496 *Haemophilus influenzae* and Beta-lactamase Positive and Negative Phenotypes.

Organism Name	Drug	MIC (mcg/mL)			%SUS*
		MIC ₅₀	MIC ₉₀	Range	
<i>Haemophilus influenzae</i> (n=496)	Tigecycline	0.12	0.25	$\leq 0.008/16$	99.2
	Amox/Clav	0.5	1	$\leq 0.12/4$	100
	Ampicillin	≤ 0.5	>32	$\leq 0.5/32$	73
	Cefepime	≤ 0.5	≤ 0.5	$\leq 0.5/8$	98.8
	Ceftazidime	≤ 8	≤ 8	$\leq 8/16$	0.4
	Ceftriaxone	≤ 0.06	≤ 0.06	$\leq 0.06/32$	99.6
	Imipenem	0.5	1	$\leq 0.06/16$	99.6
	Levofloxacin	0.015	0.03	$\leq 0.008/8$	99.6
	Pip/Tazo	≤ 0.06	≤ 0.06	$\leq 0.06/1$	100
	Minocycline	≤ 0.5	1	$\leq 0.5/16$	98.4
Beta-lactamase Positive <i>Haemophilus influenzae</i> (n=134)	Tigecycline	0.12	0.25	$\leq 0.008/16$	98.5
	Amox/Clav	1	2	$\leq 0.12/4$	100
	Ampicillin	32	>32	$\leq 0.5/32$	7.5
	Ceftazidime	≤ 8	≤ 8	$\leq 8/8$	0.0
	Ceftriaxone	≤ 0.06	≤ 0.06	$\leq 0.06/32$	98.5
	Levofloxacin	0.015	0.015	$\leq 0.008/8$	98.5
	Minocycline	≤ 0.5	1	$\leq 0.5/16$	98.2
	Pip/Tazo	≤ 0.06	≤ 0.06	$\leq 0.06/0.5$	100
	Cefepime	≤ 0.5	≤ 0.5	$\leq 0.5/8$	98.5
	Imipenem	0.5	1	0.12/4	100
Beta-lactamase Negative <i>Haemophilus influenzae</i> (n=362)	Tigecycline	0.12	0.25	$\leq 0.008/4$	99.4
	Amox/Clav	0.5	1	$\leq 0.12/4$	100
	Ampicillin	≤ 0.5	≤ 0.5	$\leq 0.5/32$	97.2
	Ceftazidime	≤ 8	≤ 8	$\leq 8/16$	0.6
	Ceftriaxone	≤ 0.06	≤ 0.06	$\leq 0.06/0.5$	100
	Levofloxacin	0.015	0.03	$\leq 0.008/0.06$	100
	Minocycline	≤ 0.5	1	$\leq 0.5/4$	98.3
	Pip/Tazo	≤ 0.06	≤ 0.06	$\leq 0.06/1$	100
	Cefepime	≤ 0.5	≤ 0.5	$\leq 0.5/8$	98.9
	Imipenem	0.5	2	$\leq 0.06/16$	99.4

* Breakpoints defined by the NCCLS 2004, document M100-S14; Tigecycline and minocycline breakpoints (in mcg/mL) defined as susceptible ≤ 2 ; intermediate = 4; resistant ≥ 8 .

Table 2. *In vitro* Activity (MIC mcg/mL) of Tigecycline and Comparative Agents against 482 *Streptococcus pneumoniae* and Penicillin-Susceptible, -Intermediate and -Resistant Phenotypes.

Organism Name	Drug	MIC (mcg/mL)			%SUS*	
		MIC ₅₀	MIC ₉₀	Range		
<i>Streptococcus pneumoniae</i> (n=482)	Tigecycline	0.06	0.5	$\leq 0.03/8$	97.5	
	Amox/Clav	≤ 0.03	2	$\leq 0.008/8$	90.5	
	Ampicillin	≤ 0.06	4	$\leq 0.06/8$	61	
	Ceftriaxone	≤ 0.03	1	$\leq 0.03/4$	98.8	
	Levofloxacin	0.5	1	$\leq 0.06/32$	99.2	
	Linezolid	≤ 0.5	1	$\leq 0.5/2$	100	
	Minocycline	≤ 0.25	4	$\leq 0.25/8$	85.1	
	Penicillin	≤ 0.06	2	$\leq 0.06/4$	61	
	Penicillin-Susceptible <i>Streptococcus pneumoniae</i> (n=294)	Tigecycline	0.06	0.5	$\leq 0.008/4$	98.6
		Amox/Clav	≤ 0.03	≤ 0.03	$\leq 0.03/0.25$	100
Ampicillin		≤ 0.06	≤ 0.06	$\leq 0.06/0.12$	100	
Ceftriaxone		≤ 0.03	≤ 0.03	$\leq 0.03/0.12$	100	
Levofloxacin		0.5	1	$\leq 0.06/2$	100	
Linezolid		≤ 0.5	1	$\leq 0.5/2$	100	
Minocycline		≤ 0.25	1	$\leq 0.25/8$	93.2	
Penicillin		≤ 0.06	≤ 0.06	$\leq 0.06/0.06$	100	
Penicillin-Intermediate <i>Streptococcus pneumoniae</i> (n=104)		Tigecycline	0.06	1	$\leq 0.008/4$	96.2
		Amox/Clav	0.25	2	$\leq 0.03/4$	98.1
	Ampicillin	0.5	2	$\leq 0.06/4$	100	
	Ceftriaxone	0.25	0.5	$\leq 0.03/1$	100	
	Levofloxacin	1	1	$\leq 0.06/32$	96.2	
	Linezolid	≤ 0.5	1	$\leq 0.5/2$	100	
	Minocycline	≤ 0.25	8	$\leq 0.25/8$	84.6	
	Penicillin	0.5	1	0.12/1	0.0	
	Penicillin-Resistant <i>Streptococcus pneumoniae</i> (n=84)	Tigecycline	0.06	1	0.015/8	95.2
		Amox/Clav	4	8	4-8	47.6
Ampicillin		4	8	4-8	0.0	
Ceftriaxone		1	1	0.5/4	92.9	
Levofloxacin		1	1	0.25/1	100	
Linezolid		≤ 0.5	1	$\leq 0.5/1$	100	
Minocycline		2	8	$\leq 0.25/8$	57.1	
Penicillin		2	4	2-4	0.0	

* Breakpoints defined by the NCCLS 2004, document M100-S14; Tigecycline and minocycline breakpoints (in mcg/mL) defined as susceptible ≤ 2 ; intermediate = 4; resistant ≥ 8 ; ampicillin susceptibility defined according to the susceptibility of penicillin.

Table 3. *In vitro* Activity (MIC mcg/mL) of Tigecycline and Comparative Agents against 358 *Streptococcus agalactiae*.

Organism Name	Drug	MIC (mcg/mL)			%SUS*
		MIC ₅₀	MIC ₉₀	Range	
<i>Streptococcus agalactiae</i> (n=358)	Tigecycline	0.06	0.5	0.015/1	100
	Amox/Clav	0.06	0.12	$\leq 0.03/8$	93.3
	Ampicillin	0.12	0.12	$\leq 0.06/16$	93.3
	Ceftriaxone	0.06	0.12	$\leq 0.03/64$	92.7
	Levofloxacin	0.5	1	0.25/32	97.2
	Linezolid	1	1	$\leq 0.5/2$	100
	Minocycline	8	>8	$\leq 0.25/8$	13.4
	Penicillin	≤ 0.06	0.12	$\leq 0.06/8$	93.3

* Breakpoints defined by the NCCLS 2004, document M100-S14; Tigecycline and minocycline breakpoints (in mcg/mL) defined as susceptible ≤ 2 ; intermediate = 4; resistant ≥ 8 ; Amoxicillin-clavulanic acid susceptibility defined according to the susceptibility of penicillin.

CONCLUSIONS

- Tigecycline had a MIC₅₀ and MIC₉₀ of 0.12 and 0.25 mcg/mL, respectively, against all strains of *Haemophilus influenzae* that was not affected by the production of beta-lactamase.
- Tigecycline's MIC₉₀ of 1 mcg/mL against penicillin-resistant *Streptococcus pneumoniae* was equal to ceftriaxone, levofloxacin, and linezolid and 8 fold lower than amoxicillin-clavulanic acid.
- Tigecycline's MIC₉₀ of 0.5 mcg/mL was the lowest of all comparative agents against all strains of *Streptococcus pneumoniae*.
- Tigecycline inhibited 100% of all *Streptococcus agalactiae* at a MIC of 1 mcg/mL.
- Tigecycline is a promising potent antimicrobial agent against fastidious organisms.