Susceptibility of Gram-negative Pathogens from China to Tigecycline and Comparators (TEST 2009 - 2010)

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Revised Abstract

Background: Tigecycline has demonstrated significant broad-spectrum activity against aerobic and anaerobic gram-positive and gram-negative microorganisms. The Tigecycline Evaluation and Surveillance Trial (TEST) has been monitoring the activity of tigecycline and comparators against multiple pathogens collected worldwide since 2004. The current report describes the activity of these agents against gram-negative pathogens isolated in China during 2009 – 2010. **Methods:** A total of 1,090 gram-negative clinical isolates were collected from multiple infection sources in China. Susceptibility testing was performed at each site following CLSI guidelines and interpreted using CLSI and FDA (tigecycline) clinical breakpoints. **Results:** Susceptibility of 1,090 isolates to tigecycline is shown below:

Species	N	MIC $_{50}$	MIC $_{90}$	%S	%I	%R
Acinetobacter baumannii	130	1	2	na	na	na
Enterobacteriaceae	718	0.5	2	95.1	4.2	0.7
ESBL-positive EcKpKo	155	0.5	2	93.6	6.4	0
Haemophilus influenzae	65	0.12	0.25	100	0	0
Pseudomonas aeruginosa	177	8	16	na	na	na

na - no clinical breakpoints exist for this drug/organism combination; EcKpKo: *E. coli, Klebsiella pneumoniae, K. oxytoca*

Conclusions: Tigecycline exhibited an MIC$_{90}$ of 2 mcg/ml against *Acinetobacter baumannii* and *Enterobacteriaceae*, including ESBL positive isolates. The ESBL rate in China for 2009-2010 was 35.6%. 100% of *H. influenzae* were susceptible to tigecycline, with an MIC$_{90}$ of 0.25 mcg/ml. Tigecycline continues to exhibit good activity against the majority of gram-negative TEST isolates from China.

Introduction

Tigecycline is a broad-spectrum antimicrobial which 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 multidrug resistant 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 of less than 10^{-9} observed [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, 7-11]. The MIC$_{90}$ values for pseudomonal isolates are generally elevated, in the range of 8-16 mcg/ml due to synergism between outer membrane impermeability and efflux mechanisms [10]. However, tigecycline has been shown to be highly effective against multi-drug resistant *Acinetobacter* spp., particularly *A. baumannii* that are commonly associated with serious nosocomial infections [5].

This study compared the activity of tigecycline to that of several other antimicrobial agents against gram-negative clinical isolates from demographically diverse populations across China.

Materials & Methods

- ❖ All isolates were derived from blood, respiratory tract, urine (no more than 25% of all isolates), skin, wound, fluids and few other defined sources. Isolates were identified to genus and species at each site by the local laboratory. Isolates were tested by the local laboratory. Only one isolate per patient was accepted.
- ❖ Clinical isolates were collected and tested between January 2009 and December 2010 from 9 study centers in China.
- ❖ Custom broth microdilution panels were supplied by Trek (TREK Diagnostic Systems, Cleveland, OH) with the following antimicrobial agents and concentrations (expressed in mcg/ml): amoxicillin/clavulanic acid (0.12/0.06-32/16); 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); and meropenem (0.12-16).
- ❖ MIC testing and interpretive criteria followed published guidelines established by the Clinical and Laboratory Standards Institute (CLSI) where available [12, 13]. Tigecycline breakpoints were defined by the FDA [14].
- ❖ Quality control of broth microdilution panels followed manufacturer's and CLSI guidelines using the following ATCC strains: *P. aeruginosa* ATCC 27853, *E. coli* ATCC 25922, *H. influenzae* ATCC 49247 and *H. influenzae* ATCC 49766.
- ❖ 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).

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Results

Table 1. *In vitro* activity of tigecycline and comparative agents against 436 ESBL positive and -negative isolates from China, 2009-2010.

		MIC (mcg/ml)				
		MIC$_{50}$	MIC$_{90}$	%S[a]	%I	%R
ESBL-positive EcKpKo* (n=155)	Tigecycline	0.5	2	93.6	6.5	0
	Amikacin	2	64	88.4	1.3	10.3
	Amox-clav	16	32	44.5	35.5	20.0
	Ampicillin	> 32	> 32	0	0.7	99.4
	Cefepime	16	> 32	47.7	17.4	34.8
	Ceftriaxone	> 64	> 64	1.3	0	98.7
	Levofloxacin	> 8	> 8	21.9	7.7	70.3
	Meropenem	≤0.06	≤0.06	99.4	0.7	0
	Minocycline	8	> 16	44.5	14.2	41.3
	Pip-tazo	4	128	80.0	9.0	11.0
ESBL-negative EcKpKo* (n=281)	Tigecycline	0.25	1	97.5	1.8	0.7
	Amikacin	1	4	98.2	0.7	1.1
	Amox-clav	4	32	74.0	13.2	12.8
	Ampicillin	> 32	> 32	13.5	5.7	80.8
	Cefepime	≤0.5	4	95.7	1.8	2.5
	Ceftriaxone	≤0.06	32	80.1	2.1	17.8
	Levofloxacin	0.5	> 8	72.6	5.0	22.4
	Meropenem	≤0.06	≤0.06	99.3	0.4	0.4
	Minocycline	4	> 16	66.6	15.0	18.5
	Pip-tazo	4	16	94.0	1.1	5.0

*Species include: *E. coli* (217), *K. pneumoniae* (205) and *K. oxytoca* (14); total % ESBL positive = 35.6%.
[a]Interpretive criteria as defined by CLSI, document M100-S21 (2011), where available; tigecycline breakpoints defined by FDA (Tygacil®, 2010).

Table 2. *In vitro* activity of tigecycline and comparative agents against 307 selected gram-negative non-fermenting bacilli from China, 2009-2010.

		MIC (mcg/ml)				
		MIC$_{50}$	MIC$_{90}$	%S[a]	%I	%R
Acinetobacter baumannii (n=130)	Tigecycline	1	2	na	na	na
	Amikacin	> 64	> 64	46.2	0	53.9
	Cefepime	32	> 32	31.5	8.5	60.0
	Ceftazidime	> 32	> 32	30.0	5.4	64.6
	Ceftriaxone	> 64	> 64	13.9	23.9	62.3
	Levofloxacin	8	> 8	33.1	15.4	51.5
	Meropenem	16	> 16	44.6	2.3	53.1
	Minocycline	4	16	61.5	23.9	14.6
	Pip-tazo	> 128	> 128	31.5	4.6	63.9
Pseudomonas aeruginosa (n=177)	Tigecycline	8	16	na	na	na
	Amikacin	4	16	91.5	0.6	7.9
	Cefepime	8	32	68.4	11.3	20.3
	Ceftazidime	≤8	> 32	63.8	9.0	27.1
	Ceftriaxone	> 64	> 64	7.9	9.6	82.5
	Levofloxacin	1	> 8	66.1	7.9	26.0
	Meropenem	1	16	72.9	10.7	16.4
	Pip-tazo	16	> 128	71.2	0	28.8

[a]Interpretive criteria as defined by CLSI, document M100-S21 (2011), where available.
na- no interpretive breakpoints available

Table 3. *In vitro* activity of tigecycline and comparative agents against 718 *Enterobacteriaceae* from China, 2009-2010.

		MIC (mcg/ml)				
		MIC$_{50}$	MIC$_{90}$	%S[a]	%I	%R
*Enterobacteriaceae** (n=718)	Tigecycline	0.5	2	95.1	4.2	0.7
	Amikacin	2	8	96.2	0.6	3.2
	Amox-clav	16	> 32	40.4	13.1	46.5
	Ampicillin	> 32	> 32	5.7	5.0	89.3
	Cefepime	≤0.5	16	85.0	5.2	9.9
	Ceftriaxone	0.5	> 64	55.4	2.4	42.2
	Levofloxacin	0.5	> 8	66.9	5.7	27.4
	Meropenem	≤0.06	0.12	99.3	0.4	0.3
	Minocycline	4	> 16	57.8	18.7	23.5
	Pip-tazo	4	32	86.4	5.9	7.8

*Species include: *Enterobacter aerogenes* (42), *Enterobacter asburiae* (2), *Enterobacter cloacae* (158), *E. coli* (217), *K. oxytoca* (14), *K. pneumoniae* (205), *Serratia liquefaciens* (1), *Serratia marcescens* (78) and *Serratia odorífera* (1).
[a]Interpretive criteria as defined by CLSI, document M100-S21 (2011), where available; tigecycline breakpoints defined by FDA (Tygacil®, 2010).

Table 4. *In vitro* activity of tigecycline and comparative agents against 65 beta-lactamase negative and beta-lactamase positive *H. influenzae* isolates from China, 2009-2010.

		MIC (mcg/ml)				
		MIC$_{50}$	MIC$_{90}$	%S[a]	%I	%R
Beta-lactamase negative - *Haemophilus influenzae* (n=50)	Amox-clav	0.5	1	100	0	0
	Ampicillin	≤0.5	≤0.5	100	0	0
	Cefepime	≤0.5	≤0.5	100	0	0
	Ceftriaxone	≤0.06	≤0.06	100	0	0
	Levofloxacin	0.015	0.06	100	0	0
	Meropenem	≤0.06	0.12	100	0	0
	Pip-tazo	≤0.06	≤0.06	98	0	2
	Tigecycline	0.12	0.25	100	0	0
Beta-lactamase positive - *Haemophilus influenzae* (n=15)	Amox-clav	1	2	93.3	0	6.7
	Ampicillin	32	> 32	0	6.7	93.3
	Cefepime	≤0.5	≤0.5	100	0	0
	Ceftriaxone	≤0.06	≤0.06	100	0	0
	Levofloxacin	0.015	0.5	100	0	0
	Meropenem	0.12	0.25	100	0	0
	Pip-tazo	≤0.06	≤0.06	100	0	0
	Tigecycline	0.12	0.25	100	0	0

[a]Interpretive criteria as defined by CLSI, document M100-S21 (2011), where available; tigecycline breakpoints defined by FDA (Tygacil®, 2010).

Conclusions

- ❖ Tigecycline and meropenem had the lowest MIC$_{90}$ of all the antimicrobials tested for ESBL-positive EcKpKo isolates, at 2 mcg/ml and ≤0.06 mcg/ml, respectively.
- ❖ Tigecycline’s MIC$_{90}$ of 2 mcg/ml was the lowest of all the comparator agents against *Acinetobacter baumannii*.
- ❖ Amikacin exhibited the highest percent susceptible against *Pseudomonas aeruginosa* at 91.5%.
- ❖ All antimicrobials compared in this study showed good *in vitro* activity against *H. influenzae* isolates, with most exhibiting percent susceptible of ≥98%, with the exception of amoxicillin-clavulanic acid and ampicillin against beta–lactamase positive strains, with percent susceptible at 93.3% and 0%, respectively.
- ❖ Tigecycline's *in vitro* activity in this study suggests that it is a promising compound for the treatment of gram-negative isolates in China.