Tigecycline Activity Against Isolates from Medical Centers Located in China, Hong Kong and Taiwan (2006): A SENTRY Antimicrobial Surveillance Program Report

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AMENDED ABSTRACT

Background: Tigecycline is a glycylcycline class agent recently introduced into clinical practice worldwide as an alternative therapy for various evolving multidrug-resistant (MDR) bacterial infections. China, Hong Kong (HK) and Taiwan medical centers (14) were monitored in 2006 by the SENTRY Program for tigecycline spectrum/susceptibility and compared to more than 25 agents.

Methods: CLSI methods were used for testing 2,634 isolates with US-FDA (tigecycline product package insert) and CLSI (M100-S18) breakpoints applied. Resistance phenotypes were screened per CLSI M100-S18 and genotypic-resistances by sequencing when required. Tigecycline was not active against *P. aeruginosa* (MIC_{50}, >4 mg/L), data not shown.

Results: Among 2,634 strains processed, the most frequently tested pathogens and resistance patterns were: *S. aureus* (544, 40% MRSA), *E. coli* (364, 54% ESBL), *K. pneumoniae* (264, 35% ESBL), *E. faecalis* (218, linezolid resistance detected), *A. baumannii* (210, 29% carbapenem-resistant), *S. pneumoniae* (170, 28/80% penicillin/macrolide-resistant), *E. faecium* (168, 2.4% VanA-type glycopeptide resistance). Fluoroquinolone resistance was very high among *E. coli* (64%), *K. pneumoniae* (21%) and *A. baumannii* (62%). MRSA rates varied by nation: Hong Kong and China (38%) and Taiwan (69%), but oxacillin resistance did not affect tigecycline activity. Metallo-ß-lactamases were noted in Enterobacteriaceae (<1%). Tetracycline resistance was frequent (30-86%) in Gram-positive and -negative organisms; but no tigecycline-resistant or non-susceptible strains were detected among indicated species.

	MIC (mg/L)		% by category:[a]	
Organism (no. tested)	50%	90%	Susceptible	Resistant
S. aureus (544)	0.12	0.25	100.0	-
Streptococci (235)[b]	≤0.03	≤0.03	100.0	-
Enterococci (392)[c]	0.12	0.25	97.7	-
E. coli (364)	0.25	0.25	100.0	0.0
Enterobacter spp. (151)	0.5	1	98.7	0.0
K. pneumoniae (264)	0.5	1	98.9	0.0
A. baumannii (210)	0.5	1	99.5	0.0
S. maltophilia (70)	0.5	1	-	-

a. US-FDA and Jones et al. (2007) criteria.
b. Includes ß-haemolytic species and pneumococci.
c. Includes *E. faecalis* (218) and *E. faecium* (168).

Conclusions: Tigecycline retained high activity and treatment potential against MDR pathogens tested from China, Hong Kong and Taiwan. Continued monitoring of the tigecycline class agents in these nations appears prudent as the glycylcyclines become widely used.

INTRODUCTION

Tigecycline is the first glycylcycline for clinical use and possesses a broad range of activity against major Gram-positive and -negative bacterial pathogens. Its major asset is its ability to evade acquired efflux and target-mediated resistances to common tetracyclines. Multidrug resistance (MDR) is very common in the Asia-Pacific (APAC) Region among important pathogens including *Acinetobacter* spp., ESBL-producing Enterobacteriaceae, oxacillin-resistant *Staphylococcus aureus* (MRSA), and vancomycin-resistant enterococci (VRE). We evaluated the activity of tigecycline against recent bacterial isolates from fourteen medical centres in China, Hong Kong and Taiwan during 2006.

MATERIALS AND METHODS

Bacterial isolates: Non-duplicate clinically significant patient isolates were submitted from 14 medical centres from China (n=10), Taiwan (n=3), and Hong Kong (n=1). Species identification of all isolates was confirmed in a central laboratory (Women's and Children's Hospital, Adelaide, Australia) using reference methodologies.

Susceptibility tests: Isolates were tested against tigecycline using validated broth microdilution MIC panels with cation-adjusted Mueller-Hinton broth (TREK Diagnostic Systems; East Grinstead, UK). Testing and incubation were performed using the manufacturer's recommendations and/or reference Clinical and Laboratory Standards Institute (CLSI) methods (2006) and interpretative criteria (2008). MIC tests were performed in cation-adjusted Mueller-Hinton broth (with the addition of 2-5% lysed horse blood for testing of streptococci). Quality control strains utilized included *Escherichia coli* ATCC 25922 and 35218, *Pseudomonas aeruginosa* ATCC 27853, *S. aureus* ATCC 29213 and *Streptococcus pneumoniae* ATCC 49619; all MIC results were within CLSI specified ranges.

Analysis: Data were analyzed for MIC_{50}, MIC_{90} and percentage susceptible and resistant according to US-FDA tigecycline package insert interpretive criteria (2005). Enterobacteriaceae with elevated MIC values (≥2 mg/L) for ceftazidime and/or ceftriaxone and/or aztreonam were considered as extended-spectrum ß-lactamase (ESBL)-producing phenotypes. *Acinetobacter* spp., with imipenem or meropenem MICs ≥8 mg/L; and Enterobacteriaceae with imipenem or meropenem MICs at ≥2 mg/L, were screened for metallo-ß-lactamase (MBL) enzymes and OXA-23, -24, and -58 enzymes by PCR. Enterobacteriaceae with an ertapenem MIC at ≥1 mg/L were screened for KPC-type serine carbapenemases.

SELECTED REFERENCES

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RESULTS

- A total of 2,634 (1,412 Gram-negative and 1,222 Gram-positive) isolates were processed and the top 10 pathogens for each country are shown in Table 1.
- The prevalence of screen-positive ESBL strains was extremely high among *E. coli* (54%; range 15% [Taiwan] to 61% [China]) and *K. pneumoniae* (35%; range 22% [Taiwan] to 39% [China]).
- Tigecycline MIC distributions and MIC_{50}/MIC_{90} against the most common Gram-negative species are found in Table 2. Apart from the Proteae, 99.4% of Enterobacteriaceae, including screen-positive ESBL *E. coli* and *Klebsiella pneumoniae* strains, had tigecycline MICs at ≤2 mg/L (Table 2).
- Observed shifts in modal tigecycline MIC values in both *E. coli* and *Klebsiella* spp. (Figure 1) were linked to higher rates of reduced susceptibility to minocycline, most notably in ESBL producers.
- For *A. baumannii* MIC values ranged from ≤0.06 to 4 mg/L, but 99.5% were inhibited at ≤2 mg/L including the 98.8% of strains with presumptive carbapenemases. One *A. baumannii* from China had a tigecycline MIC of 4 mg/L; this strain had an OXA-23-like enzyme.
- Modal tigecycline MIC values for enterococci and staphylococci were only 0.12 mg/L (Table 3) and all strains were inhibited at tigecycline MICs of ≤0.5 mg/L. Four *E. faecium* (2.4%) contained a *vanA* gene. Two stains were from China and 2 from Taiwan. Tigecycline remained effective against these strains.
- Despite very high rates of penicillin-non-susceptibility (36.5%) in *S. pneumoniae* from these countries, all strains were inhibited by tigecycline at ≤0.12 mg/L.

Table 1. Frequency of occurrence of pathogens from China, Taiwan and Hong Kong (2006).

China (n=2,135)	No. tested	Taiwan (n=299)	No. tested	Hong Kong (n=200)	No. tested
Staphylococcus aureus	419	*Staphylococcus aureus*	53	*Staphylococcus aureus*	72
Enterococcus spp.	371	ß-haemolytic streptococci	48	*Escherichia coli*	25
Escherichia coli	300	*Klebsiella* spp.	45	*Klebsiella* spp.	22
Klebsiella spp.	210	*Escherichia coli*	39	*Pseudomonas* spp.	19
Acinetobacter spp.	182	*Acinetobacter* spp.	24	ß-haemolytic streptococci	12
Streptococcus pneumoniae	163	*Pseudomonas* spp.	23	*Enterococcus* spp.	11
Pseudomonas spp.	133	*Enterobacter* spp.	14	*Acinetobacter* spp.	8
Enterobacter spp.	130	*Enterococcus* spp.	10	*Enterobacter* spp.	7
Stenotrophomonas maltophilia	62	*Serratia* spp.	7	*Stenotrophomonas maltophilia*	7
Proteus mirabilis	39	*Streptococcus pneumoniae*	6	Viridans group streptococci	5

Table 2. Activity of tigecycline against Gram-negative pathogens from China, Taiwan, and Hong Kong (2006).

	MIC (mg/L)		No. of isolates inhibited at MIC (mg/L):									% by category:[a]	
Organism (no. tested)	50%	90%	≤0.03	0.06	0.12	0.25	0.5	1	2	4	>4	Susceptible	Resistant
Enterobacteriaceae (868)	0.25	1	1	5	125	335	281	93	23	5		99.4	0.0
Escherichia coli (364)	0.25	0.25	1	5	124	201	33					100.0	0.0
ESBL screen-negative (167)	0.25	0.25	1	2	63	87	14					100.0	0.0
ESBL screen-positive (197)	0.25	0.25		3	61	114	19					100.0	0.0
Klebsiella pneumoniae (264)	0.5	1			1	83	121	46	10	3		98.9	0.0
ESBL screen-negative (171)	0.5	1				63	79	22	6	1		99.4	0.0
ESBL screen-positive (93)	0.5	1			1	20	42	24	4	2		97.8	0.0
Enterobacter spp. (151)	0.5	1				22	100	19	8	2		98.7	0.0
Acinetobacter spp.(214)	0.5	1	1	19	35	27	59	64	8	1		99.5[b]	0.0
carbapenem-susceptible (134)	0.25	1	1	19	30	27	31	22	4			100.0[b]	0.0
carbapenem-non-susceptible (80)	1	1			5		28	42	4	1		98.8[b]	0.0
Class D-positive[c] (36)	1	1			4		13	16	2	1		97.2[b]	0.0

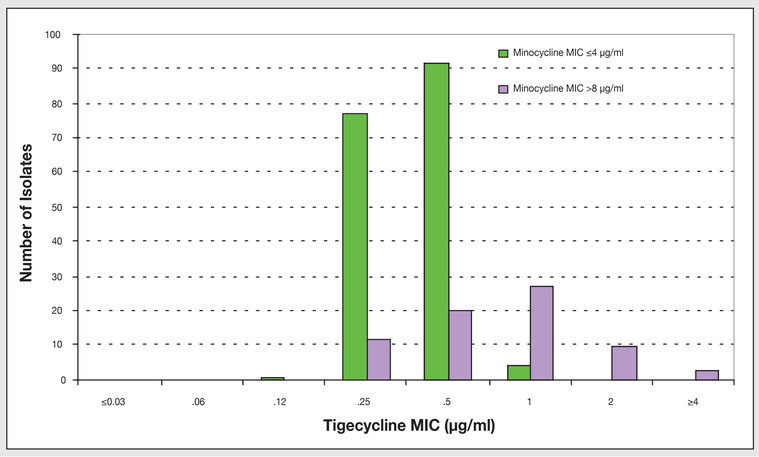
a. US-FDA package insert breakpoints (2005) applied; *Acinetobacter* breakpoints were ≤2/≥8 mg/L per Jones et al. (2007).
b. No criteria for this category have been proposed. The Enterobacteriaceae breakpoint found in the US-FDA product package insert was applied.
c. OXA-23, -24, or -58-types (n=36).

Table 3. Activity of tigecycline against Gram-positive pathogens from China, Taiwan, and Hong Kong (2006).

	MIC (mg/L)		No. of isolates inhibited at MIC (mg/L)					% by category:[a]	
Organism (no. tested)	50%	90%	≤0.03	0.06	0.12	0.25	0.5	Susceptible	Resistant
Staphylococcus aureus (544)	0.12	0.25		45	275	208	16	100.0	-[b]
oxacillin-susceptible (329)	0.12	0.25		40	176	110	3	100.0	-
oxacillin-resistant (215)	0.25	0.25		5	99	98	13	100.0	-
Enterococcus spp. (392)	0.12	0.25	15	91	188	98		100.0	-
vancomycin-susceptible (388)	0.12	0.25	15	91	184	98		100.0	-
vancomycin-resistant[c] (4)	0.12	0.12			4			100.0	-
ß-haemolytic *Streptococcus* spp. (60)	≤0.03	0.06	49	9	2			100.0	-
Streptococcus pneumoniae (170)	≤0.03	≤0.03	167	2	1			100.0	-
Coagulase-negative staphylococci (24)	0.12	0.5		4	8	9	3	100.0	-

a. US-FDA package insert breakpoints (2005) applied.
b. No criteria for this category have been proposed.
c. *vanA E. faecium* (n=4).

Figure 1 Tigecycline MIC distribution vs minocycline resistance in *Klebsiella* spp. (n=162)



CONCLUSIONS

- Tigecycline appears to be effective in vitro against recent (2006) clinical isolates from China, Taiwan, and Hong Kong, including prevalent MDR strains and those harbouring resistances to important classes, such as third-generation cephalosporins, carbapenems, glycopeptides and anti-staphylococcal penicillins.