Antimicrobial Activity of Tigecycline and Comparator Agents Tested against Clinical Bacterial Strains from the Asia-Pacific Region (2008-2009)

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ABSTRACT

Background: To assess the activity of tigecycline and comparator agents against strains collected in various countries in the Asia-Pacific (APAC) region. Tigecycline is the first glycylcycline approved for clinical use and has demonstrated activity against key Gram-positive and -negative bacterial pathogens worldwide, including multidrug-resistant (MDR) *Acinetobacter* spp., ESBL-producing Enterobacteriaceae (ENT), methicillin-resistant *S. aureus* (MRSA), and vancomycin-resistant enterococci (VRE); pathogens frequently isolated in the APAC region.

Methods: As part of the SENTRY Antimicrobial Surveillance Program, 35 institutions from 8 nations contributed 9,804 strains as follows (no. of medical centres/strains): Australia (7/2,494), China (CH; 17/4,098), Hong Kong China (1/395), South Korea (KOR; 3/960), New Zealand (NZ; 3/634), Singapore (SIN; 1/433), Taiwan (TW; 2/590) and Thailand (1/200). All isolates were forwarded to a central laboratory (USA or Australia) where they were tested against tigecycline and comparators by CLSI broth microdilution methods. CLSI and EUCAST interpretations were applied for comparison agents. Tigecycline breakpoints published by the USA-FDA were applied for indicated species.

Results: MRSA rate was 43.4% overall, ranging from 8.7% in NZ to 70.1% in SIN and 77.3% in KOR. 83.6% of coagulase-negative staphylococci were resistant to oxacillin. VRE rates (10.1% overall) were highest in TW (47.4%) and KOR (32.6%). Prevalences of ESBL phenotype among *E. coli*/*Klebsiella* spp. were 35.4/33.7% overall, highest in TW (41.9/54.2%) and CH (62.0/42.6%). Imipenem (IMI) resistance (R) among *Acinetobacter* spp. was 49.5% overall, highest in KOR (78.7%) and SIN (87.5%). Tigecycline was very active against the most frequently isolated organisms, except *P. aeruginosa* (Table). >99% of staphylococci and enterococci were inhibited at ≤0.5 mg/L of tigecycline. Among ENT (including ESBL-producing strains) and *Acinetobacter* spp. (including IMI-R strains) 97.8-100.0% were inhibited at ≤2 mg/L of tigecycline.

	Cumulative % inhibited at tigecycline MIC (mg/L) of:						
Organism (no. of strains)	≤0.06	0.12	0.25	0.5	1	2	4
S. aureus (3,142)	2.0	29.7	92.1	99.5	100.0	-	-
CoNS (214)	4.7	31.3	86.9	99.1	100.0	-	-
Enterococcus spp. (1,129)	11.6	51.1	97.9	99.8	100.0	-	-
β-haemolytic streptococci (362)	93.4	98.6	100.0	-	-	-	-
Viridans group streptococci (96)	90.6	96.9	99.0	100.0	-	-	-
S. pneumoniae (907)	84.2	93.7	100.0	-	-	-	-
E. coli (1,056)	1.6	29.7	91.1	99.1	99.8	100.0	-
Klebsiella spp. (714)	0.0	1.7	32.1	80.5	95.9	98.3	99.9
Enterobacter spp. (405)	0.0	0.5	21.7	85.2	94.3	97.8	99.0
Acinetobacter spp. (533)	4.7	19.7	32.5	49.2	89.7	99.1	100.0
P. aeruginosa (731)	0.0	0.0	0.3	0.6	1.1	4.2	22.2

Conclusion: Almost 10,000 clinical strains from the APAC region were tested and tigecycline was very active against the organisms most frequently recovered from the hospitals evaluated, except *P. aeruginosa*. Tigecycline spectrum included MRSA, VRE, ENT with ESBL phenotype and IMI-R *Acinetobacter* spp. Tigecycline appears to be a valuable option for the treatment of infections caused by MDR organisms frequently isolated in the APAC region.

INTRODUCTION

Tigecycline is a glycylcycline antimicrobial agent that has demonstrated activity against key Gram-positive and -negative bacterial pathogens worldwide, including multidrug-resistant (MDR) *Acinetobacter* spp., ESBL-producing Enterobacteriaceae (ENT), methicillin-resistant *S. aureus* (MRSA), and vancomycin-resistant enterococci (VRE); pathogens frequently isolated in the APAC region. Tigecycline is a bacteriostatic agent which inhibits protein synthesis. This unique agent has stability against mechanisms of tetracycline resistance including increased binding affinity to tetracycline-resistant ribosomes and inhibition of efflux determinants.

Tigecycline was first approved by the United States Food and Drug Administration (USA-FDA) and later by the European Medicines Agency (EMEA) as a parenteral agent for the treatment of complicated skin and skin structure infections and intra-abdominal infections. Tigecylcine has also been approved for the treatment of community-acquired pneumonia in the USA. In the present study, we assessed the activity of tigecycline and comparator agents against a large collection of contemporary (2008-2009) bacterial strains from various nations in the Asia-Pacific (APAC) region.

MATERIALS AND METHODS

Bacterial isolates: As part of the SENTRY Antimicrobial Surveillance Program, 35 institutions from eight nations contributed 9,804 patient unique clinical strains as shown in Table 1. The isolates were collected from bloodstream infections (26.0%), skin and skin structure infections (23.4%), lower respiratory tract infections (22.7%), community-acquired respiratory infections (5.0%) and other infection types (22.7%). Species identification was confirmed by standard biochemical tests and the Vitek Systems (bioMerieux, Hazelwood, Missouri, USA), when necessary.

Susceptibility testing: All isolates were forwarded to a central laboratory (JMI Laboratories, Iowa, USA or SA Pathology at Women's and Children's Hospital, North Adelaide, Australia) where they were tested against tigecycline and comparators by CLSI broth microdilution methods using commercially prepared and validated panels (TREK Diagnostic Systems, Ohio, USA) in fresh cation-adjusted Mueller-Hinton broth (CLSI M07-A8). CLSI and EUCAST interpretations were applied for comparison agents. Tigecycline breakpoints published by the USA-FDA and EUCAST were applied for the indicated species.

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RESULTS

- MRSA rates were generally high (43.4% overall), ranging from only 8.7% in New Zealand to 70.1% in Singapore and 77.3% in Korea. VRE rates (10.1% overall) were highest in Taiwan (47.4%) and Korea (32.6%), and very low or nil in Hong Kong (0.0%), Singapore (0.0%), Thailand (0.0%), New Zealand (1.8%) and China (2.6%; Table 2).
- Prevalences of ESBL phenotype also varied significantly among the nations surveyed. Among *E. coli*, the ESBL phenotype rate was 35.4% overall, highest in China (62.0%) and Taiwan (41.9%), and lowest in New Zealand (3.4%) and Australia (6.7%; Table 2).
- *Klebsiella* spp. exhibited ESBL phenotype rates similar to *E. coli* (33.7% overall). The highest rates were observed in Taiwan (54.2%), China (42.6%) and Korea (41.0%; Table 2).
- Imipenem resistance (MIC, ≥16 mg/L) among *Acinetobacter* spp. was 49.5% overall, and >60% in four of eight nations surveyed: Singapore (87.5%), Korea (78.7%), Thailand (69.2%) and Taiwan (62.4%; Table 2).
- Against the *S. aureus* and CoNS tested in this study, 99.5 and 99.1% of isolates, respectively, were inhibited by ≤0.5 mg/L of tigecycline, which is the susceptibility breakpoint criteria for these pathogens (Table 3). Tigecycline activity was similar against MRSA and MSSA (MIC_{50}, 0.25 mg/L; data not shown).
- Among *Enterococcus* spp., 97.9% of strains, including 98.4% of VRE, were susceptible to tigecycline (MIC, ≤0.25 mg/L). Tigecycline had equivalent activity (MIC_{50}, 0.12 mg/L and MIC_{90}, 0.25 mg/L) against both vancomycin-susceptible and non-susceptible *Enterococcus* spp. (Table 3).
- Linezolid (98.4-100.0% susceptible) and daptomycin (98.4% susceptible) were very active against VRE. In contrast, approximately one-third (29.1-33.9%) of strains were susceptible to teicoplanin, indicating a high prevalence of VanA phenotype among VRE in this geographic region (Table 3).

Table 1. Number of sites and isolates per nation.

Country	No. of Sites	No. of Strains
Australia	7	2,494
China	17	4,098
Hong Kong	1	395
Korea	3	960
New Zealand	3	634
Singapore	1	433
Taiwan	2	590
Thailand	1	200
TOTAL	35	9,804

- β-haemolytic and viridans group streptococci were highly susceptible to tigecycline (MIC_{50}, ≤0.03 mg/L and MIC_{90}, 0.06 mg/L for both). *S. pneumoniae* exhibited slightly higher tigecycline MIC results (MIC_{50}, 0.06 mg/L and MIC_{90}, 0.12 mg/L), but all strains were inhibited at tigecycline MIC of 0.25 mg/L or less (Table 3).
- *E. coli* (MIC_{90}, 0.25 mg/L) was more susceptible to tigecycline compared to *Klebsiella* spp. and *Enterobacter* spp. (MIC_{90}, 0.5 mg/L for both). Tigecycline was active against Enterobacteriaceae isolates producing ESBL and AmpC derepressed β-lactamases found within this collection of isolates (data not shown).

Table 2. Frequency of occurrence various resistance phenotypes by nation.

			ESBL phenotype[c]		Ceftazidime-resistant	Imipenem-resistant[e]	
Country	MRSA[a]	VRE[b]	*E. coli*	*Klebsiella* spp.	*Enterobacter* spp.[d]	*Acinetobacter* spp.	*P. aeruginosa*
Australia	30.3	12.3	6.7	6.6	28.6	0.0	11.7
China	52.1	2.6	62.0	42.6	38.6	38.9	22.8
Hong Kong	31.4	0.0	32.0	23.7	7.1	26.3	16.3
Korea	77.3	32.6	20.2	41.0	29.6	78.7	29.4
New Zealand	8.7	1.8	3.4	30.0	7.7	-	9.5
Singapore	70.1	0.0	24.6	36.4	40.0	87.5	20.0
Taiwan	60.5	47.4	41.9	54.2	64.3	62.4	16.7
Thailand	23.0	0.0	27.8	28.6	20.0	69.2	26.1
OVERALL	43.4	10.1	35.4	33.7	34.8	49.5	19.6

a. Methicillin-resistant *S. aureus*.
b. Vancomycin-resistant enterococci.
c. ESBL phenotype, defined as MIC ≥2 mg/L for ceftazidime and/or ceftriaxone
d. Isolates with ceftazidime MIC ≥32 mg/L.
e. Isolates with imipenem MIC ≥16 mg/L.

- Tigecycline ($MIC_{50/90}$, 1/2 mg/L and 99.1% inhibited at ≤2 mg/L) and polymyxin B ($MIC_{50/90}$, ≤0.5/≤0.5 mg/L and 99.8% inhibited at ≤2 mg/L) were the most active compounds tested against *Acinetobacter* spp. Only 39.0 - 45.8% and 33.4 - 35.5% of *Acinetobacter* spp. strains were susceptible to imipenem and amikacin, respectively. In contrast, tigecycline showed very limited activity against *P. aeruginosa* isolates (Table 3).

CONCLUSIONS

- Almost 10,000 clinical strains from the APAC region were tested and tigecycline continues to be very active against the organisms most frequently recovered from the hospitals evaluated, except *P. aeruginosa*.
- Tigecycline spectrum included MRSA, VRE, Enterobacteriaceae with an ESBL phenotype and imipenem-resistant *Acinetobacter* spp.
- Tigecycline appears to be a treatment option for infections caused by bacterial organisms frequently isolated in the APAC region, including many multidrug-resistant phenotypes.

Table 3. Antimicrobial activity of tigecycline and comparator antimicrobial agents when tested against clinical isolates from medical centers located in the APC regions (2008-2009).

Antimicrobial agent (No. of strains)	MIC (mg/L)		% Susceptible / Resistant	
	50%	90%	CLSI[a]	EUCAST[a]
S. aureus (3,142)				
Tigecycline[b]	0.25	0.25	99.5 / -	99.5 / 0.0
Oxacillin	1	>2	56.6 / 43.4	56.6 / 43.4
Erythromycin	0.5	>2	51.1 / 48.1	51.1 / 48.1
Clindamycin	≤0.25	>2	67.2 / 32.7	66.7 / 32.8
Levofloxacin	≤0.5	>4	61.9 / 37.9	61.9 / 37.9
Linezolid	2	2	100.0 / 0.0	100.0 / 0.0
Trimethoprim/sulfamethoxazole	≤0.5	>2	85.1 / 14.9	85.1 / 14.9
Daptomycin	0.5	0.5	99.9 / -	99.9 / 0.1
Vancomycin	1	1	99.9 / 0.0	99.9 / 0.0
CoNS (214)				
Tigecycline[b]	0.25	0.5	- / -	99.1 / 0.9
Oxacillin	>2	>2	16.4 / 83.6	16.4 / 83.6
Erythromycin	>2	>2	41.6 / 58.4	41.6 / 58.4
Clindamycin	≤0.25	>2	66.4 / 32.2	65.9 / 33.6
Levofloxacin	1	>4	51.9 / 47.7	51.9 / 47.7
Linezolid	1	1	100.0 / -	100.0 / 0.0
Trimethoprim/sulfamethoxazole	≤0.5	>2	57.9 / 42.1	57.9 / 42.1
Daptomycin	0.5	1	99.1 / -	99.1 / 0.9
Vancomycin	2	2	100.0 / 0.0	100.0 / 0.0
Enterococcus spp.				
All strains (1,129)				
Tigecycline[b]	0.12	0.25	97.9 / -	97.9 / 0.2
Ampicillin	2	>16	60.8 / 39.2	57.8 / 39.2
Linezolid	2	2	99.0 / 0.3	99.7 / 0.3
Quinupristin/dalfopristin	>2	>2	26.7 / 62.6	26.7 / 62.6
Teicoplanin	≤2	≤2	92.5 / 7.1	91.9 / 7.5
Vancomycin	1	>16	88.8 / 10.1	88.8 / 10.5
Daptomycin	2	4	99.4 / -	- / -
Vancomycin-resistant[c] (127)				
Tigecycline[b]	0.12	0.25	98.4 / -	98.4 / 1.6
Ampicillin	>16	>16	11.8 / 88.2	11.8 / 88.2
Linezolid	2	2	98.4 / 0.0	100.0 / 0.0
Quinupristin/dalfopristin	1	>2	76.4 / 21.3	76.4 / 21.3
Teicoplanin	>16	>16	33.9 / 62.2	29.1 / 66.1
Vancomycin	>16	>16	0.0 / 89.8	0.0 / 93.7
Daptomycin	2	4	99.2 / -	- / -

Antimicrobial agent (No. of strains)	MIC (mg/L)		% Susceptible / Resistant	
	50%	90%	CLSI[a]	EUCAST[a]
β-haemolytic streptococci (362)				
Tigecycline[b]	≤0.03	0.06	100.0 / -	100.0 / 0.0
Penicillin	≤0.015	0.06	100.0 / -	100.0 / 0.0
Clindamycin	≤0.25	≤0.25	91.2 / 8.3	91.7 / 8.3
Erythromycin	≤0.25	>2	87.3 / 12.7	87.3 / 12.7
Tetracycline	≤2	>8	53.9 / 42.5	53.9 / 46.1
Levofloxacin	1	1	98.9 / 1.1	93.9 / 1.1
Linezolid	1	1	100.0 / -	100.0 / 0.0
Vancomycin	0.5	0.5	100.0 / -	100.0 / 0.0
Daptomycin	≤0.06	0.25	100.0 / -	100.0 / 0.0
Viridans group streptococci (96)				
Tigecycline[b]	≤0.03	0.06	99.0 / -	- / -
Penicillin	0.06	1	70.8 / 6.3	80.2 / 6.3
Ceftriaxone	≤0.25	1	92.7 / 3.1	88.5 / 11.5
Clindamycin	≤0.25	>2	82.3 / 16.7	83.3 / 16.7
Levofloxacin	1	2	93.8 / 5.2	- / -
Linezolid	1	1	100.0 / -	- / -
Vancomycin	1	1	100.0 / -	100.0 / 0.0
Daptomycin	0.5	1	99.0 / -	- / -
S. pneumoniae (701)				
Tigecycline[b]	0.06	0.12	84.2 / -	- / -
Penicillin[d]	0.5	4	66.5 / 3.7	- / -
Penicillin[e]	0.5	4	43.7 / 47.4	43.7 / 33.5
Amoxicillin/clavulanate	≤1	8	67.2 / 27.1	- / -
Ceftriaxone	0.5	4	65.8 / 15.0	51.9 / 15.0
Cefuroxime	4	>8	43.9 / 54.6	43.9 / 56.1
Erythromycin	>2	>2	26.0 / 73.9	26.0 / 73.9
Clindamycin	>2	>2	32.7 / 66.8	33.2 / 66.8
Levofloxacin	1	2	97.7 / 2.1	97.7 / 2.3
Linezolid	1	1	100.0 / -	100.0 / 0.0
Vancomycin	≤1	≤1	100.0 / -	100.0 / 0.0
E. coli (1,056)				
Tigecycline[b]	0.25	0.25	100.0 / 0.0	99.8 / 0.0
Ceftriaxone	≤0.25	>32	65.8 / 31.7	64.6 / 35.2
Levofloxacin	≤0.5	>4	57.9 / 39.8	57.6 / 42.1
Gentamicin	≤2	>8	66.4 / 32.9	65.3 / 33.6
Imipenem	0.25	0.5	99.6 / 0.1	99.4 / 0.1
Polymyxin B[f]	≤0.5	≤0.5	99.8 / 0.1	- / -

Antimicrobial agent (No. of strains)	MIC (mg/L)		% Susceptible / Resistant	
	50%	90%	CLSI[a]	EUCAST[a]
Klebsiella spp. (714)				
Tigecycline[b]	0.5	1	98.3 / 0.1	95.9 / 1.7
Ceftriaxone	≤0.25	>32	69.9 / 26.5	66.2 / 32.8
Levofloxacin	≤0.5	>4	78.3 / 19.9	76.3 / 21.7
Gentamicin	≤2	>8	77.3 / 21.4	77.2 / 22.7
Imipenem	0.25	1	98.2 / 1.1	98.0 / 1.1
Polymyxin B[f]	≤0.5	≤0.5	99.0 / 1.0	- / -
Enterobacter spp. (405)				
Tigecycline[b]	0.5	1	97.8 / 1.0	94.3 / 2.2
Ceftriaxone	1	>32	60.5 / 28.1	52.3 / 46.2
Levofloxacin	≤0.5	>4	81.0 / 16.5	78.8 / 19.0
Gentamicin	≤2	>8	77.3 / 19.3	74.6 / 22.7
Imipenem	0.5	1	98.8 / 0.0	98.0 / 0.0
Polymyxin B[f]	≤0.5	>4	82.2 / 16.8	- / -
Acinetobacter spp. (533)				
Tigecycline[b]	1	2	- / -	- / -
Ceftazidime	>16	>16	27.8 / 67.0	- / -
Ampicillin/sulbactam	>16	>16	27.2 / 67.5	- / -
Imipenem	8	>8	45.8 / 49.5	39.0 / 49.5
Levofloxacin	>4	>4	29.6 / 67.2	29.3 / 70.4
Amikacin	>32	>32	35.5 / 63.0	33.4 / 64.5
Gentamicin	>8	>8	26.5 / 71.9	26.5 / 73.5
Tobramycin	>16	>16	31.7 / 67.7	31.7 / 68.3
Polymyxin B	≤0.5	≤0.5	99.8 / 0.2	99.8 / 0.2
P. aeruginosa (731)				
Tigecycline[b]	>4	>4	- / -	- / -
Ceftazidime	4	>16	71.1 / 23.1	71.1 / 28.9
Piperacillin/tazobactam	>2	>2	6.4 / 93.6	100.0 / 0.0
Imipenem	2	>8	75.1 / 19.4	75.1 / 19.4
Levofloxacin	1	>4	73.6 / 21.1	64.6 / 26.4
Amikacin	2	8	93.6 / 5.3	90.0 / 6.4
Gentamicin	≤2	>8	84.0 / 14.0	84.0 / 16.0
Tobramycin	0.5	>16	85.9 / 13.5	85.9 / 14.1
Polymyxin B	1	1	99.7 / 0.0	99.7 / 0.0

a. Criteria as published by the CLSI [2009] and EUCAST [2009].
b. US-FDA breakpoints were applied [Tygacil Product Insert, 2005].
c. Vancomycin MIC ≥ 8 mg/L.
d. Criteria as published by the CLSI [2009] for parenteral penicillin (non-meningitis).
e. Criteria as published by the CLSI [2009] for oral penicillin V or for isolates from meningitis cases.
f. Criteria established by the CLSI [2009] for *P. aeruginosa* were applied for comparison purposes only.