Activity of Tigecycline Against Clinical Pathogens Collected in Indonesia (2006)

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ABSTRACT

Background: There are no published information on tigecycline potency and spectrum from isolates from Indonesia. As a component of the SENTRY Antimicrobial Surveillance Program (Asia-Pacific Region), we evaluated the activity of tigecycline tested against recent (2006) isolates from Indonesia by reference MIC methods.

Methods: Non-duplicate strains were consecutively collected from three medical centres in Indonesia. All isolates were tested against tigecycline using validated commercial broth microdilution panels (TREK Diagnostics), with concurrent acceptable quality control and CLSI interpretations (M100-S18) for comparison agents. Tigecycline breakpoints published by the United States - Food and Drug Administration were applied for each indicated species or genus, and the proposed/provisional *Acinetobacter* spp. breakpoint (≤2 mg/L) per Jones et al. (2007) was applied.

Results: A total of 383 (307 Gram-negative and 76 Gram-positive) isolates were evaluated. Tigecycline was highly active against the top 10 most frequently isolated non-pseudomonal pathogens which comprised 82% of all strains. The highest tigecycline MIC_{90} results (2 mg/L were recorded for non-indicated species, *Proteus-Providencia*. *P. aeruginosa* was also not significantly inhibited by tigecycline (MIC_{90}, >8 mg/L; data not shown).

Organism (n)	Cumulative % inhibited at (mg/L) 0.12	0.25	0.5	1	2	4	%S[a]
Klebsiella spp. (96)	3	35	81	96	100		100
Acinetobacter spp. (50)	40	74	90	98	100		100
Enterobacter spp. (34)	0	23	97	100			100
S. aureus (29)	24	86	100				100
Proteus spp. (28)	0	0	7	18	96	100	96.4
E. coli (25)	28	92	100				100
viridans streptococci (18)	94	100					100
Citrobacter spp. (15)	7	60	93	100			100
Providencia spp. (9)	0	0	0	44	100		100
CoNS (9)[b]	67	89	100				100

a. US-FDA package insert criteria.
b. CoNS = coagulase-negative staphylococci.

Conclusions: Tigecycline demonstrated excellent activity against all the commonly isolated pathogens from Indonesia, including those being multidrug-resistant to other antimicrobial classes. Tigecycline shows promise for therapy of indicated, antimicrobial-resistant species in this nation and indeed, the entire Asia-Pacific region.

INTRODUCTION

Tigecycline, a novel glycylcycline, represents an important advance in the treatment for a range of infections where mixed and/or resistant organisms occur. It is able to bypass the standard mechanisms of tetracycline resistance, and hence has a very broad spectrum that includes virtually all Gram-positive bacteria, most Gram-negative bacteria including anaerobes, and many strains harbouring resistance to other antimicrobials. Information on the prevalence of resistance in pathogens isolated in Indonesia has been limited, although there has been a suspicion that resistance rates could be elevated. The study provided an opportunity to examine the prevalence of resistance in key human pathogens isolated from clinical sources in Indonesia, and to examine the in vitro activity of tigecycline against those pathogens.

MATERIALS AND METHODS

Bacterial isolates: Non-duplicate clinically significant patient isolates were submitted from four medical centres from Indonesia. 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, *Staphylococcus aureus* ATCC 29213 and *Streptococcus pneumoniae* ATCC 49619; all MIC results were within CLSI specified ranges.

Analysis: Data were analysed 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 MIC ≥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.

ACKNOWLEDGEMENT

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SELECTED REFERENCES

1. Clinical and Laboratory Standards Institute. (2006). *M7-A7, Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically; approved standard - seventh edition.* Wayne, PA: CLSI.
2. Clinical and Laboratory Standards Institute. (2008). *M100-S18, Performance standards for antimicrobial susceptibility testing, 18th informational supplement.* Wayne, PA: CLSI.
3. Jones RN, Ferraro MJ, Reller LB, Schreckenberger PC, Swenson JM, Sader HS (2007). Multicenter studies of tigecycline disk diffusion susceptibility results for *Acinetobacter* spp. *J Clin Microbiol* 45: 227-230.

RESULTS

- A total of 572 (493 Gram-negative and 79 Gram-positive) isolates were processed. The rank order of pathogens is shown in Table 1.
- The prevalence of screen-positive ESBL strains was high among *E. coli* (37%) and *K. pneumoniae* (43%).
- Tigecycline MIC distributions and MIC_{50}/MIC_{90} against the most common species are found in Table 2. Apart from the Proteae, 100% of Enterobacteriaceae, including screen-positive ESBL *E. coli* and *K. pneumoniae* strains, had tigecycline MIC values at ≤2 mg/L (Table 2).
- For *A. baumannii* MIC values ranged from 0.06 to >4 mg/L, but 98.5% were inhibited at ≤2 mg/L. One *A. baumannii* strain had a tigecycline MIC of >4 mg/L.
- The presence of tetracycline resistance determinants resulted in minimal elevations of tigecycline MIC values, but were most noticeable in *K. pneumoniae* and oxacillin-resistant *S. aureus* (Figure 1).
- The potency and susceptibility of tigecycline and comparator agents tested against the most common pathogens collected from Indonesian patients are shown in Table 3.

Figure 1. Tigecycline MIC distribution vs tetracycline resistance in *Staphylococcus aureus* (n=32).

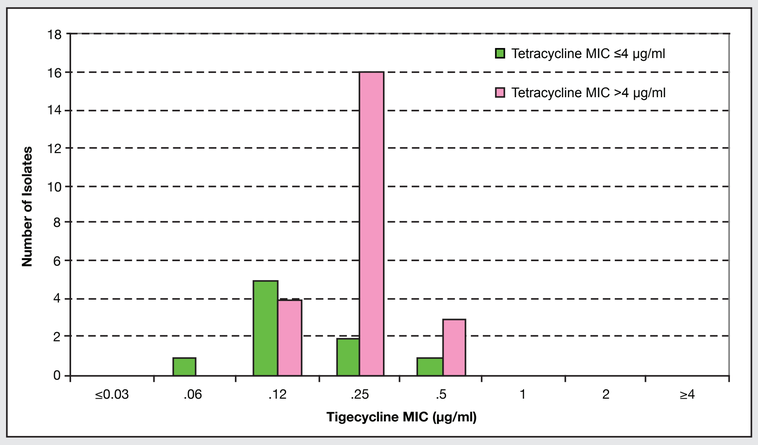

Table 1. Frequency of occurrence of pathogens (top 10) isolated from Indonesia (2006).

Organism	No. of isolates	% of total
Klebsiella spp.	132	23.1
Acinetobacter spp.	68	11.9
Proteus mirabilis	63	11.0
Enterobacter spp.	57	10.0
Pseudomonas spp.	56	9.8
Escherichia coli	54	9.4
Staphylococcus aureus	32	5.6
Citrobacter spp.	29	5.1
Viridans group streptococci	19	3.3
Indole-positive *Proteus* spp.	15	2.6
Other	46	8.2

Table 3. Potency and susceptibility rates of tigecycline and comparator agents tested against the most common pathogens collected from patients in Indonesia.

	MIC (mg/L) MIC_{50}	MIC_{90}	Range	%susceptible
Klebsiella spp. (132)				
Tigecycline	0.5	1	0.12 - 2	100.0
Tetracycline	4	>8	≤2 - >8	50.0
Minocycline	4	>8	≤1 - >8	67.4
Ceftriaxone	≤0.25	>32	≤0.25 - >32	54.5
Ceftazidime	≤1	>16	≤1 - >16	66.7
Levofloxacin	≤0.5	>4	≤0.5 - >4	72.0
Gentamicin	≤2	>8	≤2 - >8	65.2
Imipenem	0.25	0.5	≤0.12 - 2	100.0
E. coli (54)				
Tigecycline	0.25	0.25	0.12 - 0.5	100.0
Tetracycline	>8	>8	≤2 - >8	20.4
Minocycline	4	>8	≤1 - >8	50.0
Ceftriaxone	≤0.25	>32	≤0.25 - >32	63.0
Ceftazidime	≤1	>16	≤1 - >16	70.4
Levofloxacin	≤0.5	>4	≤0.5 - >4	51.9
Gentamicin	≤2	>8	≤2 - >8	72.2
Imipenem	0.25	0.5	≤0.12 - 1	100.0
Enterobacter spp. (57)				
Tigecycline	0.5	0.5	0.12 - 1	100.0
Tetracycline	≤2	>8	≤2 - >8	75.4
Minocycline	2	8	≤1 - >8	87.7
Ceftriaxone	≤0.25	>32	≤0.25 - >32	78.9
Ceftazidime	≤1	16	≤1 - >16	87.7
Levofloxacin	≤0.5	≤0.5	≤0.5 - 4	98.2
Gentamicin	≤2	>8	≤2 - >8	86.0
Imipenem	0.5	1	0.25 - 2	100.0
S. aureus (32)				
Tigecycline	0.25	0.5	0.06 - 0.5	100.0
Oxacillin	>2	>2	≤0.25 - >2	34.4
Erythromycin	>2	>2	≤0.25 - >2	34.4
Ciprofloxacin	>4	>4	0.06 - >4	31.3
Tetracycline	>8	>8	≤2 - >8	28.1
Trimethoprim/sulfa	>2	>2	≤0.5 - >2	40.6
Vancomycin	1	1	0.5 - 2	100.0

Table 2. Activity of tigecycline against key pathogens from Indonesia (2006).

Organism (number tested)	MIC (mg/L) 50%	90%	Number of isolates inhibited at MIC (mg/L): ≤0.03	0.06	0.12	0.25	0.5	1	2	4	>4	% by category:[a] Susceptible	Resistant
Enterobacteriaceae (358)	0.5	2		1	23	131	103	36	59	5		98.6	0.0
Escherichia coli (54)	0.25	0.25		17	34	3						100.0	0.0
ESBL screen-negative (34)	0.25	0.25		14	18	2						100.0	0.0
ESBL screen-positive (20)	0.25	0.25		3	16	1						100.0	0.0
Klebsiella pneumoniae (118)	0.5	1				45	53	16	4			100.0	0.0
ESBL screen-negative (67)	0.25	0.5				38	23	5	1			100.0	0.0
ESBL screen-positive (51)	0.5	1				7	30	11	3			100.0	0.0
Enterobacter spp. (57)	0.5	0.5			1	24	31	1				100.0	0.0
Acinetobacter spp.(68)	0.25	1		7	20	19	10	7	4		1	98.5[b]	0.0
Staphylococcus aureus (32)	0.25	0.5		1	9	18	4	32				100.0	-
oxacillin-susceptible (11)	0.12	0.25		1	6	3	1	11				100.0	-
oxacillin-resistant (21)	0.25	0.5			3	15	3	21				100.0	-
Viridans group streptococci (19)	≤0.03	0.06	17	1		1						100.0	-

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.

CONCLUSIONS

- Tigecycline demonstrated excellent activity against all commonly isolated pathogens from Indonesia, including those multidrug-resistant to other antimicrobial classes.
- Tigecycline shows promise for therapy of indicated, antimicrobial-resistant species in this nation and indeed, across the entire Asia-Pacific region