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Antimicrobial Activity of Tigecycline Tested Against Bacterial Pathogens from Intensive Care Units

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AMENDED ABSTRACT

Objectives:

To evaluate the antimicrobial activity of tigecycline (TIG) and selected antimicrobials against bacterial pathogens isolated from patients hospitalized in intensive care units (ICUs) worldwide.

Methods:

A total of 7,129 isolates were consecutively collected in >70 medical centers located in North America (3164), South America (1465), Europe (2428) and the Asia-Australia region (72). The isolates were collected from (no. of isolates/%): bloodstream (5349/75%), respiratory tract (746/10%), skin/soft tissue (323/5%), and urinary tract (182/3%) infections in the 2000-2004 period, and susceptibility tested by CLSI/NCCLS broth microdilution methods.

Results:

The antimicrobial activity of TIG and the frequency of occurrence of bacterial pathogens are summarized in the Table:

	MIC (mg/L)		Cumulative % inhibited at (mg/L):				
Organism (no. tested/% of total)	50%	90%	0.25	0.5	1	2	4
S. aureus (SA; 2,370/33)	0.25	0.5	85	99	100	-	-
Enterococci (1,082/15)	≤0.12	0.25	92	>99	100	-	-
Coag-neg staphylococci (CoNS; 997/14)	0.25	0.5	74	97	100	-	-
P. aeruginosa (PSA; 549/8)	8	16	<1	1	2	6	20
E. coli (533/8)	0.25	0.5	87	99	100	-	-
Klebsiella spp. (388/5)	0.5	1	35	79	93	98	100
Enterobacter spp. (285/4)	0.5	1	21	75	91	96	>99
ß-haemolytic streptococci (143/2)	≤0.12	≤0.12	100	-	-	-	-
Acinetobacter spp. (ASP; 134/2)	1	2	21	37	67	96	99
S. pneumoniae (118/2)	≤0.12	≤0.12	100	-	-	-	-
Total (7,129)	0.25	2	68	84	89	91	94

All Gram-positive pathogens (4,817) were inhibited at ≤ 1 mg/L of TIG. Resistance (R) to oxacillin was detected in 43% of SA and 84% of CoNS, and R to vancomycin was detected in 19% of enterococci. TIG was very active against Enterobacteriaceae (ENT; 1,468) with a MIC_{90} ≤ 1 mg/L, except for *Serratia* spp. 10% of *E. coli* and 30% of *Klebsiella* spp. showed an ESBL phenotype while 28% of *Enterobacter* spp. were R to ceftazidime. 14% of ENT showed R to ciprofloxacin. TIG and trimethoprim/sulfamethoxazole were the most active compounds against *S. maltophilia* (MIC_{90}, 2 and 1 mg/L respectively). TIG was also highly active against ASP (MIC_{90}, 2 mg/L), but PSA showed decreased S to TIG (MIC_{90}, 16 mg/L). Non-S to imipenem (MIC, ≥ 8 mg/L) was observed in 16% of ASP and 31% of PSA isolates.

Conclusions:

Isolates from ICU patients showed high rates of antimicrobial R. The most alarming problems detected were vancomycin R among enterococci, ESBL mediated ß-lactam R and fluoroquinolone R among ENT, and carbapenem R among PSA and ASP. TIG exhibited potent in vitro activity against the vast majority of clinically important pathogenic bacteria (except PSA) isolated from ICU patients and may represent an excellent option for the treatment of infections in this clinical environment.

INTRODUCTION

Tigecycline is a semisynthetic glycylcycline derived from the minocycline molecule. Tigecycline has documented activity against tetracycline-resistant (tet-R) Gram-positive and Gram-negative pathogens refractory by both efflux and ribosomal protection mechanisms.

Patients hospitalized in the intensive care unit (ICU) are at particular risk for acquiring nosocomial infections. Exposure to various antimicrobial agents may further complicate such hospitalization and create conditions that favor resistance selection among host bacterial flora or nosocomially transmitted pathogens. Thus, rates of antimicrobial resistance are generally higher in bacteria isolated from ICUs compared with other hospital wards and outpatient clinics.

The present study was conducted to evaluate the in vitro activity of tigecycline in comparison to tetracycline and other antimicrobial agents against clinical bacterial isolates collected from patients hospitalized in the ICU.

MATERIALS AND METHODS

To assess the spectrum of activity and potency of tigecycline, recent clinical isolates submitted to a reference laboratory (JMI Laboratories, North Liberty, IA) were examined. A total of 7,129 Gram-positive and –negative bacterial isolates recovered from patients hospitalized in the ICU were processed. Consecutively acquired, non-duplicate patient isolates were submitted from >70 participating medical centers representing 29 countries in the five continents of Asia, Australia, Europe, South America and North America.

MIC values for up to 38 antimicrobials including tigecycline and tetracycline were determined using validated, dry-form broth microdilution panels with cation-adjusted Mueller-Hinton medium (TREK Diagnostics Inc., Cleveland, OH). Antimicrobials tested included those classes and examples of drugs most commonly used for the empiric or directed treatment of the indicated infection. Testing, incubation and MIC interpretation were performed using the manufacturers recommendations and/or recommendations from the Clinical and Laboratory Standards Institute (CLSI, formerly NCCLS). Quality control was performed using American Type Culture Collection (ATCC) strains including *Escherichia coli* ATCC 25922 and 35218, *S. aureus* ATCC 29213, *Enterococcus faecalis* ATCC 29212, *S. pneumoniae* ATCC 49619 and *Pseudomonas aeruginosa* ATCC 27853.

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RESULTS

Table 1. Potency of tigecycline against the main bacterial pathogens isolated from ICU worldwide.

	Cumulative % inhibited at (mg/L):						
Organism (no. tested/% of total)	≤0.12	0.25	0.5	1	2	4	8
1. *Staphylococcus aureus* (2,370/33.2)	49	85	99	100	-	-	-
2. *Enterococcus* spp. (1,082/15.2)	61	92	>99	>99	100	-	-
3. Coagulase-negative staphylococci (997/14.0)	43	74	97	>99	100	-	-
4. *Pseudomonas aeruginosa* (PSA; 549/7.7)	0	<1	1	2	6	20	64
5. *Escherichia coli* (533/7.5)	39	87	99	100	-	-	-
6. *Klebsiella* spp. (388/5.4)	1	35	79	93	98	100	-
7. *Enterobacter* spp. (285/4.0)	2	21	75	91	96	>99	100
8. ß-haemolytic streptococci (143/2.0)	96	100	-	-	-	-	-
9. *Acinetobacter* spp. (134/1.9)	9	21	37	67	96	99	100
10. *Streptococcus pneumoniae* (118/1.7)	96	100	-	-	-	-	-
11. *Serratia* spp. (107/1.5)	0	0	13	81	95	97	100
12. *Stenotrophomonas maltophilia* (94/1.3)	1	4	35	71	93	99	100
Total (7,129)	40	68	84	89	91	94	97

Table 2. Antimicrobial activity and spectrum of tigecycline and selected comparators against Gram-positive bacteria from the ICU.

	MIC (mg/L)			% category:[a]	
Organism (no. tested/antimicrobial agent	50%	90%	Range	Susceptible	Resistant
Staphylococcus aureus (2,370)					
Tigecycline	0.25	0.5	≤0.016-1	-[b]	-
Tetracycline	≤4	>8	≤4->8	87.9	11.5
Oxacillin	1	>2	≤0.06->8	56.9	43.1
Clindamycin	0.12	>8	≤0.06->8	65.8	34.1
Levofloxacin	0.25	>4	≤0.03->4	57.0	41.2
Trimethoprim/Sulfamethoxazole	≤0.5	≤0.5	≤0.5->2	94.4	5.6
Quinupristin/Dalfopristin	0.5	0.5	≤0.06->8	99.7	0.1
Teicoplanin	≤2	≤2	≤2-8	100.0	0.0
Vancomycin	1	1	0.25-4	100.0	0.0
Linezolid	2	2	0.12-4	100.0	-
Coagulase-negative staphylococci (997)					
Tigecycline	0.25	0.5	0.03-2	-	-
Tetracycline	≤4	>8	≤4->8	83.0	16.4
Oxacillin	>2	>2	≤0.06->2	15.6	84.4
Clindamycin	0.12	>8	≤0.06->8	53.1	46.2
Levofloxacin	2	>4	≤0.03->4	48.5	44.8
Trimethoprim/Sulfamethoxazole	1	>2	≤0.5->2	63.9	36.1
Quinupristin/Dalfopristin	≤0.25	0.5	≤0.25->8	99.0	0.6
Teicoplanin	≤2	8	≤2->16	95.4	1.1
Vancomycin	1	2	0.25-4	100.0	0.0
Linezolid	1	1	0.12-2	100.0	-
Enterococcus spp. (1,082)					
Tigecycline	0.12	0.25	≤0.016-2	-	-
Tetracycline	>8	>8	≤0.25->8	38.8	60.8
Ampicillin	2	>16	0.25->16	71.7	28.3
Gentamicin HL	≤500	>1000	≤500->1000	65.5	34.5
Streptomycin	≤1000	>2000	≤1000->2000	58.3	41.7
Levofloxacin	>4	>4	0.06->4	46.2	52.3
Quinupristin/Dalfopristin	>2	8	≤0.25->8	27.8	65.7
Teicoplanin	≤2	>16	≤2->16	83.3	14.3
Vancomycin	1	>16	0.25->16	81.1	18.6
Linezolid	2	2	0.25->8	99.4	0.3
Streptococcus pneumoniae (118)					
Tigecycline	≤0.12	≤0.12	0.03-0.25	-	-
Tetracycline	≤4	>8	≤4->8	43.2	14.4
Penicillin	≤0.016	2	≤0.016-8	77.1	13.6
Ceftriaxone	≤0.25	1	≤0.25-8	97.5	0.8
Erythromycin	≤0.06	8	≤0.06->8	83.9	16.1
Clindamycin	≤0.06	≤0.06	≤0.06->8	90.7	8.5
Levofloxacin	1	1	0.06-2	100.0	0.0
Vancomycin	0.25	0.5	≤0.12-1	100.0	-
Linezolid	1	1	0.12-2	100.0	-
ß-haemolytic streptococci (143)					
Tigecycline	≤0.06	≤0.12	≤0.016-0.25	-	-
Tetracycline	>8	>8	≤0.25->8	37.8	52.4
Penicillin	0.03	0.06	≤0.016-0.12	100.0	-
Ceftriaxone	≤0.25	≤0.25	≤0.25-0.5	100.0	-
Erythromycin	≤0.06	2	≤0.06->8	83.9	16.1
Clindamycin	≤0.06	≤0.06	≤0.06->8	94.4	5.6
Levofloxacin	0.5	1	0.06->4	98.6	0.7
Vancomycin	0.25	0.5	0.25-1	100.0	-
Linezolid	1	1	≤0.06-2	100.0	-

a. Criteria as published by the CLSI.
b. - = no breakpoint has been established by the CLSI.

Table 3. Antimicrobial activity and spectrum of tigecycline and selected comparators against Enterobacteriaceae from the ICU.

	MIC (mg/L)			% category:[a]	
Organism (no. tested/antimicrobial agent	50%	90%	Range	Susceptible	Resistant
Escherichia coli (533)					
Tigecycline	0.25	0.5	0.03-1	-[b]	-
Tetracycline	≤2	>8	0.5->8	61.4	37.9
Ceftriaxone	≤0.25	0.5	≤0.25->32	92.3	6.8
Ceftazidime	≤1	≤1	≤1->16	94.9	3.8
Cefepime	≤0.12	0.5	≤0.12->16	94.6	3.8
Piperacillin/Tazobactam	2	8	≤0.12->256	93.4	3.9
Imipenem	≤0.5	≤0.5	≤0.5-8	99.8	0.0
Ciprofloxacin	≤0.03	>4	≤0.03->4	82.9	17.1
Gentamicin	≤2	8	≤2->8	89.5	9.8
Amikacin	2	4	0.5->32	97.9	0.8
Klebsiella spp. (388)					
Tigecycline	0.5	1	0.12-4	-	-
Tetracycline	≤2	>8	0.5->8	79.1	16.0
Ceftriaxone	≤0.25	>32	≤0.25->32	74.2	19.1
Ceftazidime	≤1	>16	≤1->16	78.4	18.3
Cefepime	≤0.12	>16	≤0.12->16	84.8	12.9
Piperacillin/Tazobactam	2	>64	≤0.5->256	80.7	17.0
Imipenem	≤0.5	≤0.5	≤0.5->8	99.0	1.0
Ciprofloxacin	≤0.03	>4	≤0.03->4	84.0	12.1
Gentamicin	≤2	>8	≤2->8	74.7	23.5
Amikacin	1	32	0.5->32	88.7	5.4
Enterobacter spp. (285)					
Tigecycline	0.5	1	0.06-8	-	-
Tetracycline	2	>8	1->8	80.7	14.0
Ceftriaxone	≤0.25	>32	≤0.25->32	68.4	18.2
Ceftazidime	≤1	>16	≤1->16	66.3	28.4
Cefepime	≤0.12	8	≤0.12->16	94.0	4.2
Piperacillin/Tazobactam	4	>64	≤0.12->256	70.9	13.0
Imipenem	≤0.5	1	≤0.5-8	99.6	0.0
Ciprofloxacin	≤0.03	4	≤0.03->4	87.0	11.9
Gentamicin	≤2	>8	≤2->8	86.2	11.7
Amikacin	2	8	1->32	94.0	3.9

a. Criteria as published by the CLSI.
b. - = no breakpoint has been established by the CLSI.

Table 4. Antimicrobial activity and spectrum of tigecycline and selected comparators against non-fermentative Gram-negative bacteria from the ICU.

	MIC (mg/L)			% category:[a]	
Organism (no. tested/antimicrobial agent	50%	90%	Range	Susceptible	Resistant
Pseudomonas aeruginosa (549)					
Tigecycline	8	16	0.25->32	-[b]	-
Tetracycline	>8	>8	≤2->8	1.5	84.9
Ceftazidime	4	>16	≤1->16	65.9	27.7
Cefepime	8	>16	≤0.12->16	66.1	18.8
Piperacillin/Tazobactam	16	>64	≤0.12->64	72.1	27.9
Imipenem	1	>8	≤0.12->8	68.9	19.1
Meropenem	1	>8	0.03->8	73.2	18.9
Ciprofloxacin	0.5	>4	≤0.03->4	61.7	34.1
Gentamicin	≤2	>8	≤2->8	68.9	28.6
Amikacin	4	>32	≤0.25->32	83.4	12.9
Polymyxin B	≤1	≤1	≤1->8	99.6	0.4
Acinetobacter spp. (134)					
Tigecycline	1	2	0.06-8	-	-
Tetracycline	8	>8	0.5->8	40.3	35.1
Ceftazidime	>16	>16	2->16	27.6	67.9
Cefepime	16	>16	0.5->16	30.6	50.0
Piperacillin/Tazobactam	>64	>64	≤0.12->64	24.6	66.4
Imipenem	1	>8	≤0.12->8	83.6	14.2
Meropenem	2	>8	0.12->16	75.4	16.4
Ciprofloxacin	>4	>4	0.06->4	27.6	72.4
Amikacin	32	>32	≤0.25->32	47.0	49.3
Polymyxin B	≤1	≤1	≤1	100.0	0.0

a. Criteria as published by the CLSI.
b. - = no breakpoint has been established by the CLSI.

- The most frequently isolated pathogen from ICU patients in the 2000-2004 period was *S. aureus* (33.2%), followed by *Enterococcus* spp. (15.2%), coagulase-negative staphylococci (CoNS, 14.0%), and *P. aeruginosa* (7.7%). These four pathogens showed high rates of resistance to commonly used antimicrobial agents and accounted for 70.1% of the isolates collected during the study period (Table 1).

- Tigecycline was highly active against *S. aureus* isolates (MIC_{50}, 0.25 mg/L and MIC_{90}, 0.5 mg/L) independently of their susceptibility to oxacillin (Table 2). The highest tigecycline MIC value was 1 mg/L and 99% of isolates were inhibited at 0.5 mg/L of tigecycline.

- Similar to *S. aureus*, both oxacillin-resistant and -susceptible coagulase-negative staphylococci were highly susceptible to tigecycline (MIC_{50}, 0.25 mg/L and MIC_{90}, 0.5 mg/L). The highest tigecycline MIC value was 2 mg/L (one strain) and >99% of isolates were inhibited at 0.5 mg/L of tigecycline (Tables 1 and 2).

- Tigecycline was the most active compound against *Enterococcus* spp. strains (MIC_{50}, 0.12 mg/L and MIC_{90}, 0.25 mg/L). Tigecycline was eight-fold more potent than vancomycin (MIC_{50}, 1 mg/L and MIC_{90}, >16 mg/L) and 16-fold more potent than linezolid (MIC_{50} and MIC_{90} at 2 mg/L) against this pathogen. Vancomycin was active against 81.1% of isolates at the susceptible breakpoint and seven isolates showed elevated MIC values (≥ 4 mg/L) to linezolid (Table 2).

- All streptococcal species tested were highly susceptible to tigecycline. The highest tigecycline MIC value was 0.25 mg/L and the vast majority of strains (96%) were inhibited at ≤ 0.12 mg/L of tigecycline (Table 2).

- Tigecycline was highly active against *S. pneumoniae* (MIC_{50} and MIC_{90} of ≤ 0.12 mg/L), including isolates resistant to penicillin and/or tetracycline and/or erythromycin (Table 2).

- Among the most frequent Enterobacteriaceae species isolated from ICU patients, e.g. *E. coli*, *Klebsiella* spp. and *Enterobacter* spp., tigecycline MIC_{50} values ranged from 0.25 to 0.5 mg/L, while MIC_{90} values ranged from 0.5 to 1 mg/L (Table 3). An ESBL phenotype was detected in 10% of *E. coli* and 30% of *Klebsiella* spp., while 28% of *Enterobacter* spp. were resistant to ceftazidime. In addition, resistance to ciprofloxacin was detected in 14% of Enterobacteriaceae strains.

- Tigecycline was the most active compound tested against *Acinetobacter* spp. (MIC_{50}, 1 mg/L and MIC_{90}, 2 mg/L) after polymyxin B (MIC_{50} and MIC_{90}, ≤ 1 mg/L; Table 4). Tigecycline was also highly active against *S. maltophilia* strains (MIC_{50}, 1 mg/L and MIC_{90}, 2 mg/L; Table 1).

- *P. aeruginosa* strains showed high rates of resistance to most antimicrobial agents tested. Polymyxin B was the most active compound (MIC_{50} and MIC_{90}, ≤ 1 mg/L; 99.6% susceptible) against this pathogen and tigecycline MIC values were generally elevated (Table 4).

CONCLUSIONS

- Resistance rates were extremely high among isolates from ICU patients evaluated in the present study.

- Tigecycline was highly active against the most frequently isolated pathogens from ICU patients, except for *P. aeruginosa*. This compound may play an important role in the treatment of serious infectious diseases in patients hospitalized in the ICU.

- Continued surveillance through longitudinal programs remains necessary to guide both empiric antimicrobial therapy and infection control strategies for patients hospitalized in the ICU.