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Update on the Spectrum and Potency of Tigecycline Tested against 7,133 Gram-positive and -negative Pathogens from 13 Nations (2008)

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AMENDED ABSTRACT

Objectives: To assess the contemporary potency and spectrum of tigecycline against Gram-positive (GP) and –negative (GN) pathogens, including strains with various resistant phenotypes. Tigecycline is a glycylcycline antimicrobial recently approved by the European Medicines Agency (EMEA) for the treatment of complicated skin and skin structure as well as intra-abdominal infections.

Methods: A total of 7,133 GN and GP clinically-significant non-duplicate isolates from multiple types of infections were collected from 13 European (EU) countries and Israel that participated in the tigecycline surveillance program during 2008. Susceptibility (S) testing was performed by a central monitoring laboratory (JMI Laboratories) using CLSI methods (M7-A7, 2006). All concurrent quality control tests were within published ranges.

Results: Tigecycline inhibited all *S. aureus* and coagulase-negative staphylococci (CoNS) isolates at ≤0.5 mg/L, regardless of S to oxacillin, with a MIC_{90} at 0.25 mg/L. Tigecycline also had potent activity against all enterococci (MIC_{90}, 0.25 mg/L), including vancomycin-resistant (VRE) strains, and ß-haemolytic streptococci (βHS, MIC_{90}, 0.06 mg/L). The MIC_{90} for Enterobacteriaceae was 0.25, 0.5 and 1 mg/L for *E. coli*, *Klebsiella* spp. and *Enterobacter* spp., respectively. Tigecycline was active against *Acinetobacter* spp. (MIC_{90}, 2 mg/L), but less potent against isolates of *P. aeruginosa* ($MIC_{50/90}$, 4/>4 mg/L). Tigecycline activity is summarized in the Table against nine organism groups.

Table 1. Activity of tigecycline tested against 7,133 isolates of Gram-positive and -negative pathogens from European medical centers (2008).

	Cumulative % inhibited at MIC (mg/L)							
Organism (no. tested)	≤0.03	0.06	0.12	0.25	0.5	1	2	4
S. aureus (2,505)	0.2	22.9	70.0	99.2	100.0	-	-	-
CoNS (648)	2.2	24.9	59.1	94.3	100.0	-	-	-
Enterococcus spp. (898)	9.4	39.0	74.3	100.0	-	-	-	-
βHS (323)	77.1	96.9	99.7	100.0	-	-	-	-
E. coli (1,262)	0.0	16.6	66.6	95.3	99.6	100.0	-	-
Klebsiella spp. (529)	0.0	0.0	11.2	68.6	90.7	96.8	99.8	-
Enterobacter spp. (281)	0.0	0.0	4.6	53.7	87.2	96.4	99.3	100.0
P. aeruginosa (517)	0.0	0.0	0.0	0.0	0.8	2.5	12.0	52.6
Acinetobacter spp. (170)	0.0	2.9	11.2	24.1	38.2	75.5	94.1	98.8

Conclusions: Tigecycline demonstrated broad antimicrobial activity against common pathogens associated with numerous types of clinical infections occurring in EU. Tigecycline was active against antimicrobial-resistant strains including MRSA, VRE, multidrug-resistant isolates of Enterobacteriaceae, including those producing broad-spectrum ß-lactamases such as ESBLs. Based on the potency and spectrum of tigecycline shown here for 2008 isolates, this agent has a role in empiric therapy for treating bacterial pathogens in these EU nations.

INTRODUCTION

Glycylcyclines are semisynthetic derivatives of the tetracycline class agents that have been modified to maintain the antibacterial effect. Tigecycline is a glycylcycline that was first licensed by the United States (USA) Food and Drug Administration (FDA) in 2005 and the European Medicines Agency (EMEA) in 2006 as a parenteral agent for the treatment of complicated skin and skin structure infections (SSSI) and intra-abdominal infections (IAI). This unique agent has stability against mechanisms of tetracycline resistance including increased binding affinity to tetracycline-resistant ribosomes and inhibition of efflux determinants. Tigecycline is a bacteriostatic agent which inhibits protein synthesis without killing the bacterial cell.

Tigecycline has a proven broad-spectrum of activity against numerous bacterial pathogens, including aerobic and anaerobic species. In this study, we evaluated the activity of tigecycline against over 7,100 isolates of Gram-positive and -negative aerobic bacterial species collected from patient infections in European (EU) hospitals during 2008. The isolates targeted for this presentation were those indicated for the treatment of complicated SSSI and IAI, including the following aerobic pathogens *Staphylococcus aureus* (methicillin-susceptible and -resistant isolates; MRSA and MSSA, respectively), *Enterococcus* spp., ß-haemolytic *Streptococcus* spp., *Escherichia coli*, *Enterobacter* spp. and *Klebsiella* spp. In addition, two common non-fermentative Gram-negative pathogens, *Pseudomonas aeruginosa* and *Acinetobacter* spp. were included in this investigation.

MATERIALS AND METHODS

Bacterial isolates. A total of 27 medical centers from 13 countries contributed isolates for this EU based surveillance study. Strains were forwarded from hospitals in Belgium, France (five sites), Germany (three), Greece (two), Ireland (two), Israel, Italy (three), Poland, Spain (two), Sweden (two), Switzerland, Turkey (two) and the United Kingdom (two). Isolates were collected in a prevalence mode from these countries and included strains dominantly cultured from blood (48.3%), respiratory tract infections (24.3%) and SSSI (20.3%). This study reports the antimicrobial activity against 7,133 strains of the most common Gram-positive and -negative pathogens collected during 2008. Gram-positive isolates included *S. aureus* (2,505; 26.0% MRSA), CoNS (648; 78.4% oxacillin-resistant), *Enterococcus* spp. (898; 11.7% vancomycin non-susceptible) and ß-haemolytic *Streptococcus* spp. (323; 44.3% group A and 38.4% group B). Enteric Gram-negative pathogens included *E. coli* (1,262; 10.5% ESBL phenotype), *Klebsiella* spp. (529; 22.1% ESBL phenotype) and *Enterobacter* spp. (281). Non-enteric Gram-negative pathogens included *P. aeruginosa* (517; 20.3% carbapenem-resistant) and *Acinetobacter* spp. (170; 45.9% carbapenem-resistant).

Susceptibility testing. All isolates were tested by reference broth microdilution methods using the Clinical Laboratory Standards Institute recommendations (CLSI, M7-A7). All strains were tested using validated broth microdilution panels manufactured by TREK Diagnostics (Cleveland, OH) and freshly prepared Mueller-Hinton broth (MHB) which is necessary for testing tigecycline. MHB was adjusted with 3-5% lysed-horse blood when testing streptococci. CLSI approved susceptible breakpoints were used to categorize susceptibility (M100-S18). The following American Type Culture Collection (ATCC) quality control organisms were concurrently tested: *Enterococcus faecalis* ATCC 29212, *S. aureus* ATCC 29213, *E. coli* ATCC 25922, *P. aeruginosa* ATCC 27853 and *Streptococcus pneumoniae* ATCC 49619.

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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. Fraise AP (2006). Tigecycline: The answer to ß-lactam and fluoroquinolone resistance? *J Infect* 53: 293-300.
4. Frampton JE, Curran MP (2005). Tigecycline. *Drugs* 65: 2623-2635; Discussion 2636-2627.
5. Fritsche TR, Sader HS, Stilwell MG, Dowzicky MJ, Jones RN (2005). Potency and spectrum of tigecycline tested against an international collection of bacterial pathogens associated with skin and soft tissue infections (2000-2004). *Diagn Microbiol Infect Dis* 52: 195-201.
6. Popovich KJ, Weinstein RA, Hota B (2008). Are community-associated methicillin-resistant *Staphylococcus aureus* (MRSA) strains replacing traditional nosocomial MRSA strains? *Clin Infect Dis* 46: 787-794.
7. Sader HS, Mallick R, Kuznik A, Fritsche TR, Jones RN (2007). Use of in vitro susceptibility and pathogen prevalence data to model the expected clinical success rates of tigecycline and other commonly used antimicrobials for empirical treatment of complicated skin and skin-structure infections. *Int J Antimicrob Agents* 30: 514-520.
8. Stein GE, Craig WA (2006). Tigecycline: A critical analysis. *Clin Infect Dis* 43: 518-524.
9. Tygacil Package Insert (2005). Philadelphia (PA): Wyeth Pharmaceuticals Inc. (June, 2005).

RESULTS

- Against the *S. aureus* and CoNS tested in this study, 99.2 and 94.3% of isolates were inhibited by ≤0.25 mg/L of tigecycline, respectively (Table 1). All *Staphylococcus* spp. were inhibited by ≤0.5 mg/L, the susceptibility breakpoint criteria for tigecycline and these pathogens.
- Table 2 shows that tigecycline activity was similar against MRSA and MSSA as well as CoNS, with MIC_{50} and MIC_{90} values of 0.12 and 0.25 mg/L, respectively.
- Good activity was noted for several comparator agents (84.0 - 100% susceptibility rates, Table 2) tested against MSSA. Higher resistance rates were observed among MRSA strains and CoNS. Approximately two-thirds (66.2 - 66.4%) were resistant to erythromycin and over one-third were resistant to clindamycin (34.7 - 35.3%). Tigecycline was more active than tetracycline (MIC_{90}, >8 mg/L) against these isolates.
- All *Enterococcus* spp. and ß-haemolytic streptococci were inhibited by ≤0.25 mg/L of tigecycline, indicating 100% susceptibility among these species groups (Table 1).
- Tigecycline had equivalent activity (MIC_{90}, 0.25 mg/L) against both vancomycin-susceptible and non-susceptible *Enterococcus* spp. (Table 2), with high rates of resistance noted among the comparator agents. Linezolid (100% susceptible) was very active.
- Tetracycline-resistance was high among the ß-haemolytic streptococci (highest for Group B, 83.1%). Tigecycline maintained excellent activity (MIC_{90}, 0.06 mg/L) against these species (Table 2).
- As shown in Tables 1 and 3, *E. coli* (MIC_{90}, 0.25 mg/L) were more susceptible to tigecycline compared to *Klebsiella* spp. (MIC_{90}, 0.5 mg/L) and *Enterobacter* spp. (MIC_{90}, 1 mg/L). However, >99% of strains among these latter two enteric pathogens were susceptible to tigecycline.
- Tigecycline was active against Enterobacteriaceae isolates with ESBL phenotypes and those harboring carbapenemase enzymes found within this collection of isolates.
- Tigecycline was not active against *P. aeruginosa* isolates (Table 1). In contrast, greater tigecycline activity was observed against *Acinetobacter* spp. with 94.1% of isolates having MIC values ≤2 mg/L; a potency (MIC_{90}, 2 mg/L) comparable to polymyxin B, the most potent agent tested against this species group (Table 3).

Table 2. Antimicrobial activity of tigecycline and comparator agents tested against Gram-positive isolates collected from patients hospitalized in European hospitals (2008).

	MIC (mg/L)			
Organism (no. tested)	50%	90%	% Susceptible[a]	% Resistant[a]
S. aureus				
Oxacillin-susceptible (1,854)				
Tigecycline	0.12	0.25	100.0	-[b]
Erythromycin	≤0.25	>2	84.0	14.9
Clindamycin	≤0.25	≤0.25	98.0	1.9
Levofloxacin	≤0.5	≤0.5	94.3	5.3
Gentamicin	≤2	≤2	98.5	1.4
Quinupristin/dalfopristin	≤0.25	0.5	99.8	0.0
Tetracycline	≤2	≤2	94.2	5.6
Trim/sulfa[c]	≤0.5	≤0.5	99.6	0.4
Linezolid	2	2	100.0	-
Vancomycin	1	1	100.0	0.0
Oxacillin-resistant (651)				
Tigecycline	0.12	0.25	100.0	-
Erythromycin	>2	>2	32.1	66.4
Clindamycin	≤0.25	>2	64.2	35.3
Levofloxacin	>4	>4	12.9	86.2
Gentamicin	≤2	>8	82.0	14.4
Quinupristin/dalfopristin	0.5	1	98.9	0.6
Tetracycline	≤2	>8	80.8	18.4
Trim/sulfa[c]	≤0.5	≤0.5	98.9	1.1
Linezolid	2	2	100.0	-
Vancomycin	1	1	100.0	0.0
CoNS (648)[d]				
Tigecycline	0.12	0.25	-	-
Erythromycin	>2	>2	33.5	66.2
Clindamycin	≤0.25	>2	63.6	34.7
Levofloxacin	4	>4	42.1	55.6
Gentamicin	≤2	>8	55.9	36.7
Quinupristin/dalfopristin	≤0.25	0.5	97.7	1.4
Tetracycline	≤2	>8	84.9	13.6
Trim/sulfa[c]	≤0.5	>2	59.7	40.3
Linezolid	1	1	99.5	-
Vancomycin	2	2	100.0	0.0
Enterococcus spp.[e]				
Vancomycin-susceptible (793)				
Tigecycline	0.12	0.25	100.0	-
Ampicillin	≤1	>16	73.8	26.2
Gentamicin (HL)	≤500	>1000	67.9	32.1
Streptomycin (HL)	≤1000	>2000	57.6	42.4
Tetracycline	>8	>8	40.0	59.9
Quinupristin/dalfopristin	>2	>2	20.1	74.9
Linezolid	1	2	100.0	0.0
Vancomycin-non-susceptible (105)				
Tigecycline	0.06	0.25	-	-
Ampicillin	>16	>16	9.5	90.5
Gentamicin (HL)	≤500	>1000	60.6	39.4
Streptomycin (HL)	2000	>2000	41.9	58.1
Tetracycline	≤2	>8	61.9	38.1
Quinupristin/dalfopristin	1	>2	76.2	17.1
Linezolid	1	2	100.0	0.0
ß-haemolytic streptococci (323)[f]				
Tigecycline	≤0.03	0.06	100.0	-
Penicillin	≤0.015	0.06	100.0	-
Erythromycin	≤0.25	>2	82.4	16.7
Clindamycin	≤0.25	≤0.25	91.3	8.1
Tetracycline	≤2	>8	53.6	44.0
Levofloxacin	≤0.5	1	99.7	0.3
Linezolid	1	1	100.0	-

a. According to CLSI criteria or the USA-FDA.
b. - = no breakpoints have been established by the CLSI or the USA-FDA.
c. Trimethoprim/sulfamethoxazole.
d. 80.7% of isolates included *S. epidermidis* (360 strains), *S. hominus* (62), *S. haemolyticus* (39), *S. capitis* (26), *S. saprophyticus* (13), *S. warneri* (13) and *S. lugdunensis* (10). Nine other species (15 strains) and 108 unspeciated isolates were also tested.
e. Included *E. faecalis* (554 strains), *E. faecium* (316), *E. avium* (nine), *E. gallinarum* (seven), *E. durans* (six), *E. casseliflavus* (four), *E. raffinosus* (one) and one unspeciated isolate.
f. Included Group A (143 strains), Group B (124), Group C (23) and Group G (33) *Streptococcus* spp.

Table 3. Antimicrobial activity of tigecycline and comparator agents tested against Gram-negative isolates collected from patients hospitalized in European hospitals (2008).

	MIC (mg/L)			
Organism (no. tested)	50%	90%	% Susceptible[a]	% Resistant[a]
E. coli (1,262)				
Tigecycline	0.12	0.25	100.0	0.0
Piperacillin/tazobactam	2	16	92.0	4.5
Ceftazidime	≤1	2	93.7	3.9
Cefepime	≤0.12	1	94.4	4.1
Imipenem	≤0.12	0.25	100.0	0.0
Gentamicin	≤2	8	89.8	9.8
Ciprofloxacin	≤0.03	>4	76.8	22.8
Tetracycline	≤2	>8	60.2	39.4
Trim/sulfa[b]	≤0.5	>2	64.0	36.1
Klebsiella spp. (529)				
Tigecycline	0.25	0.5	99.8	0.0
Piperacillin/tazobactam	2	>64	82.2	11.9
Ceftazidime	≤1	>16	84.1	12.5
Cefepime	≤0.12	>16	85.1	11.7
Imipenem	0.25	0.5	96.8	2.1
Gentamicin	≤2	>8	86.4	12.5
Ciprofloxacin	≤0.03	>4	83.4	14.9
Tetracycline	≤2	>8	78.1	18.9
Trim/sulfa[b]	≤0.5	>2	76.6	23.3
Enterobacter spp. (281)				
Tigecycline	0.25	1	99.3	0.0
Piperacillin/tazobactam	4	>64	76.5	11.0
Ceftazidime	≤1	>16	68.7	26.3
Cefepime	≤0.12	2	97.5	2.5
Imipenem	0.5	1	98.9	0.4
Gentamicin	≤2	4	91.5	7.5
Ciprofloxacin	≤0.03	4	86.1	12.1
Tetracycline	≤2	>8	82.6	10.3
Trim/sulfa[b]	≤0.5	>2	85.1	14.9
P. aeruginosa (517)				
Tigecycline	4	>4	-[c]	-
Piperacillin/tazobactam	8	>64	86.3	13.7
Ceftazidime	2	>16	79.5	16.1
Cefepime	4	16	83.0	9.9
Imipenem	1	>8	79.7	13.9
Gentamicin	≤2	>8	82.2	13.5
Ciprofloxacin	0.12	>4	76.0	19.3
Tetracycline	>8	>8	-	-
Trim/sulfa[b]	>2	>2	-	-
Polymyxin B	1	2	99.8	0.0
Acinetobacter spp. (170)				
Tigecycline	1	2	-	-
Piperacillin/tazobactam	>64	>64	20.6	77.1
Ceftazidime	>16	>16	21.9	68.6
Cefepime	>16	>16	26.5	62.4
Imipenem	2	>8	54.7	40.6
Gentamicin	>8	>8	27.1	70.6
Ciprofloxacin	>4	>4	21.2	78.2
Tetracycline	>8	>8	31.8	62.4
Trim/sulfa[b]	>2	>2	29.4	70.6
Polymyxin B	≤0.5	1	100.0	0.0

a. According to CLSI criteria or the USA-FDA.
b. Trimethoprim/sulfamethoxazole.
c. - = no breakpoints have been established by the CLSI or the USA-FDA.

CONCLUSIONS

- Tigecycline was documented to have excellent and sustained potency against the species that are included in the product indications approved by the USA-FDA and EMEA.
- All isolates (5,636 strains) of staphylococci, enterococci, streptococci and *E. coli* were susceptible to tigecycline using the current breakpoint criteria established by the USA-FDA. Tigecycline was active against >99% of *Klebsiella* spp. and *Enterobacter* spp. and was shown to have measurable potency against *Acinetobacter* spp.
- Continued monitoring of tigecycline activity on a global scale is needed to determine the overall role of this novel, broad-spectrum antimicrobial agent.