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Multicenter Evaluation of Tigecycline Activity in Europe: Report from the SENTRY Antimicrobial Surveillance Program (2009)

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AMENDED ABSTRACT

Objectives: To assess the contemporary potency and spectrum of tigecycline and comparator antimicrobials against recent (2009) Gram-positive (GP) and -negative (GN) pathogens from Europe. Tigecycline, the first glycylcycline, presents a therapy option for emerging multidrug-resistant (MDR) GP and GN pathogens and is approved by the European Medicines Agency (EMEA) for the treatment of complicated skin and skin structure (cSSSI) as well as intra-abdominal infections (IAI).

Methods: A total of 4,284 GP and GN clinically-significant non-duplicate isolates from multiple types of infections were collected from 11 European (EU) countries and Israel that participated in the tigecycline surveillance program during 2009. Susceptibility (S) testing was performed by a central monitoring laboratory (JMI Laboratories) against a large panel of antimicrobials using CLSI methods (M07-A8, 2009). Identifications were confirmed and interpretive/screening criteria were also by CLSI guidelines (M100-S20, 2010). All quality control test results were within published ranges.

Results: Tigecycline inhibited all *S. aureus* isolates at ≤0.5 mg/L (MIC_{90} at 0.25 mg/L) and coagulase-negative staphylococci (CoNS) at ≤1 mg/L (MIC_{90} at 0.5 mg/L) regardless of S to oxacillin. Tigecycline also had potent activity against all enterococci (MIC_{90}, 0.25 mg/L), including vancomycin-resistant (VRE) strains, and beta-haemolytic streptococci (BHS; MIC_{90}, 0.06 mg/L). The MIC_{90} for Enterobacteriaceae was 0.25, 1, 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 Table 1 against nine organism groups.

Table 1. Activity of tigecycline tested against 4,284 isolates of Gram-positive and -negative pathogens from European medical centers (2009).

Organism (no. tested)	Cumulative % inhibited at MIC (mg/L)							
	≤0.03	0.06	0.12	0.25	0.5	1	2	≥4
S. aureus (1,403)	0.0	9.6	41.7	97.6	100.0	-	-	-
CoNS (462)	1.3	12.8	34.4	89.2	99.6	100.0	-	-
Enterococcus spp. (614)	1.5	19.4	48.9	96.4	100.0	-	-	-
BHS (214)	55.6	95.3	99.1	100.0	-	-	-	-
E. coli (795)	0.0	9.8	49.9	94.2	99.9	100.0	-	-
Klebsiella spp. (297)	0.0	0.0	4.0	57.9	87.9	94.6	100.0	-
Enterobacter spp. (147)	0.0	0.0	0.0	39.5	86.4	92.5	96.6	100.0
P. aeruginosa (287)	0.0	0.4	0.4	0.7	0.7	3.1	11.2	100.0
Acinetobacter spp. (65)	0.0	1.5	18.5	36.9	53.9	75.4	96.9	100.0

Conclusions: In 2009, tigecycline continued to demonstrate broad antimicrobial activity against common pathogens associated with cSSSI and IAI occurring in the EU. Tigecycline was active against antimicrobial-resistant as well as MDR strains including MRSA, VRE, and Enterobacteriaceae (including ESBLs). Based on the potency and spectrum shown here, tigecycline has a role in empiric therapy for treating cSSSI and IAI bacterial pathogens in these EU nations. Tigecycline exhibited spectrum/potency generally exceeding currently available agents against sampled isolates from the EU.

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 (cSSSI) 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 generally a bacteriostatic agent which inhibits protein synthesis.

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 4,284 isolates of Gram-positive and -negative aerobic bacterial species collected from patient infections in European (EU) hospitals during 2009. The isolates targeted for this presentation were those indicated for the treatment of cSSSI and IAI, including the following aerobic pathogens: *Staphylococcus aureus* (methicillin-susceptible and -resistant isolates; MSSA and MRSA, respectively), *Enterococcus* spp., β-haemolytic *Streptococcus* spp., *Escherichia coli, Enterobacter* spp., *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 24 medical centers from 11 countries contributed isolates for this EU-based surveillance study. Isolates were forwarded from hospitals in Belgium, France (five sites), Germany (three), Ireland, Israel, Italy (three), Spain (three), Sweden (two), Switzerland, Turkey (two) and the United Kingdom (two). Over 5,500 isolates were collected in a prevalence mode from these countries and included isolates dominantly cultured from blood (51.0%), respiratory tract infections (21.3%) and SSSI (22.6%).

This study reports the antimicrobial activity against 4,284 isolates of the most common Gram-positive and -negative pathogens collected during 2009. Gram-positive isolates included *S. aureus* (1,403; 22.8% MRSA), CoNS (462; 67.8% oxacillin-resistant), *Enterococcus* spp. (614; 16.4% vancomycin non-susceptible) and β-haemolytic *Streptococcus* spp. (214; 29.4% group A and 50.0% group B). Enteric Gram-negative pathogens included *E. coli* (795; 11.2% ESBL phenotype), *Klebsiella* spp. (297; 17.5% ESBL phenotype) and *Enterobacter* spp. (147). Non-enteric Gram-negative pathogens included *P. aeruginosa* (287; 18.5% carbapenem-resistant) and *Acinetobacter* spp. (65; 33.8% carbapenem-resistant).

Susceptibility testing. All isolates were tested by reference broth microdilution methods using the Clinical Laboratory Standards Institute recommendations (CLSI, M07-A8). All isolates 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-S20). The following American Type Culture Collection (ATCC) quality control organisms were concurrently tested confirming test quality assurance: *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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RESULTS

- Against the *S. aureus* and CoNS tested in this study, 97.6 and 89.2% of isolates were inhibited by ≤0.25 mg/L of tigecycline, respectively (Table 1). All *S. aureus* were inhibited by ≤0.5 mg/L, the susceptibility breakpoint criteria for tigecycline. However, 0.4% of CoNS were inhibited by 1 mg/L and hence were one doubling dilution above the susceptibility breakpoint.
- Table 2 shows that tigecycline activity was similar against MRSA and MSSA as well as CoNS, with MIC_{50} and MIC_{90} values of 0.25 for MSSA and MRSA, and 0.25 and 0.5 mg/L for CoNS.
- Good activity was observed for several comparator agents (82.6 – 100.0% susceptibility rates, Table 2) tested against MSSA. Higher resistance rates were seen among MRSA strains and CoNS. Approximately two-thirds (63.6 – 65.6%) were resistant to erythromycin and approximately one-third were resistant to clindamycin (29.4 - 30.3%).
- The vast majority of *Enterococcus* spp. (96.4%) and all β-haemolytic streptococci were inhibited by ≤0.25 mg/L of tigecycline (Table 1).
- Tigecycline had slightly greater activity (MIC_{90}, 0.25 versus 0.5 mg/L) against vancomycin-susceptible compared to non-susceptible *Enterococcus* spp. (Table 2), with high rates of resistance noted among the comparator agents. Linezolid (99.0 - 100.0% susceptible) was also very active.
- Tetracycline resistance was high among the β-haemolytic streptococci (highest for Group B, 73.8%). Tigecycline maintained excellent activity (MIC_{90}, 0.06 mg/L) against these β-haemolytic 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}, 1 mg/L) and *Enterobacter* spp. (MIC_{90}, 1 mg/L). However, 100.0 and 96.6%, respectively, of isolates 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 96.9% of isolates having MIC values ≤2 mg/L; a potency comparable to polymyxin B (MIC_{90}, ≤0.5 mg/L, 98.5% susceptible), the most potent agent tested against this species group.

Table 2. Antimicrobial activity of tigecycline and comparator agents tested against Gram-positive isolates collected from patients hospitalized in European hospitals (2009).

Organism (no. tested)	MIC (mg/L)		% Susceptible[a]	% Resistant[a]
	50%	90%		
S. aureus				
Oxacillin-susceptible (1,083)				
Tigecycline	0.25	0.25	100.0	-[b]
Erythromycin	0.5	>2	82.6	16.2
Clindamycin	≤0.25	≤0.25	97.1	2.6
Levofloxacin	≤0.5	≤0.5	94.5	5.4
Gentamicin	≤2	≤2	98.0	1.8
Quinupristin/dalfopristin	0.5	0.5	99.8	0.1
Tetracycline	≤2	≤2	94.7	4.2
Trimethoprim/sulfamethoxazole	≤0.5	≤0.5	99.1	0.9
Linezolid	2	2	100.0	0.0
Vancomycin	1	1	100.0	0.0
Oxacillin-resistant (320)				
Tigecycline	0.25	0.25	100.0	-
Erythromycin	>2	>2	33.4	65.6
Clindamycin	≤0.25	>2	70.0	29.4
Levofloxacin	>4	>4	9.4	90.3
Gentamicin	≤2	>8	87.2	12.5
Quinupristin/dalfopristin	0.5	1	99.1	0.6
Tetracycline	≤2	≤2	94.1	5.3
Trimethoprim/sulfamethoxazole	≤0.5	≤0.5	98.9	1.9
Linezolid	2	2	100.0	0.0
Vancomycin	1	1	100.0	0.0
CoNS (462)[c]				
Tigecycline	0.25	0.5	-	-
Erythromycin	>2	>2	35.5	63.6
Clindamycin	≤0.25	>2	68.6	30.3
Levofloxacin	4	>4	42.6	54.3
Gentamicin	4	>8	52.4	40.5
Quinupristin/dalfopristin	≤0.25	0.5	97.2	2.2
Tetracycline	≤2	>8	85.5	12.8
Trimethoprim/sulfamethoxazole	≤0.5	>2	59.4	40.6
Linezolid	1	1	100.0	0.0
Vancomycin	1	2	100.0	0.0
Enterococcus spp.[d]				
Vancomycin-susceptible (513)				
Tigecycline	0.25	0.25	96.1	-
Ampicillin	2	>16	71.3	28.7
Tetracycline	>8	>8	36.1	63.0
Quinupristin/dalfopristin	>2	>2	20.1	72.7
Linezolid	2	2	100.0	0.0
Vancomycin-non-susceptible (101)				
Tigecycline	0.06	0.5	98.0	-
Ampicillin	>16	>16	11.9	88.1
Tetracycline	≤2	>8	74.3	25.7
Quinupristin/dalfopristin	1	>2	75.2	17.8
Linezolid	1	2	99.0	1.0
β-haemolytic streptococci (214)[e]				
Tigecycline	≤0.03	0.06	100.0	-
Penicillin	0.03	0.06	99.5	-
Erythromycin	≤0.25	>2	81.8	16.8
Clindamycin	≤0.25	≤0.25	90.1	8.9
Tetracycline	≤2	>8	52.3	45.3
Levofloxacin	≤0.5	1	100.0	0.0
Linezolid	1	1	100.0	-

a. According to CLSI (2010) criteria or the USA-FDA (tigecycline only).
b. - = no breakpoints have been established by the CLSI or the USA-FDA.
c. *Staphylococcus auricularis* (2 isolates), *Staphylococcus capitis* (17 isolates), *Staphylococcus caprae* (1 strain), *Staphylococcus cohnii* (1 strain), *Staphylococcus epidermidis* (251 isolates), *Staphylococcus haemolyticus* (23 isolates), *Staphylococcus hominis* (47 isolates), *Staphylococcus lugdunensis* (8 isolates), *Staphylococcus saprophyticus* (3 isolates), *Staphylococcus schleiferi* (2 isolates), *Staphylococcus sciuri* (1 strain), *Staphylococcus simulans* (4 isolates), *Staphylococcus warneri* (9 isolates), *Staphylococcus xylosus* (15 isolates), and unspecified coagulase-negative staphylococci (78 isolates).
d. *Enterococcus avium* (6 isolates), *Enterococcus casseliflavus* (3 isolates), *Enterococcus durans* (2 isolates), *Enterococcus faecalis* (356 isolates), *Enterococcus faecium* (236 isolates), *Enterococcus gallinarum* (7 isolates), *Enterococcus hirae* (1 strain), *Enterococcus raffinosus* (1 strain), and unspecified *Enterococcus* (2 isolates).
e. *Streptococcus dysgalactiae* (15 isolates), Group A *Streptococcus* (63 isolates), Group B *Streptococcus* (107 isolates), Group C *Streptococcus* (10 isolates), Group F *Streptococcus* (3 isolates), and Group G *Streptococcus* (16 isolates).

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.

Table 3. Antimicrobial activity of tigecycline and comparator agents tested against Gram-negative isolates collected from patients hospitalized in European hospitals (2009).

Organism (no. tested)	MIC (mg/L)		% Susceptible[a]	% Resistant[a]
	50%	90%		
E. coli (795)				
Tigecycline	0.25	0.25	100.0	0.0
Piperacillin/tazobactam	2	16	92.1	7.9
Ceftazidime	≤1	2	92.9	5.1
Cefepime	≤0.12	1	95.0	3.4
Imipenem	0.25	0.25	99.7	0.0
Gentamicin	≤2	≤2	92.7	7.2
Ciprofloxacin	≤0.5	>4	75.5	24.2
Tetracycline	≤2	>8	60.8	39.0
Trimethoprim/sulfamethoxazole	≤0.5	>2	65.7	34.3
Klebsiella spp. (297)[b]				
Tigecycline	0.25	1	100.0	0.0
Piperacillin/tazobactam	2	>64	82.2	11.8
Ceftazidime	≤1	>16	83.7	15.3
Cefepime	≤0.12	>16	87.5	10.1
Imipenem	0.25	0.5	96.3	3.0
Gentamicin	≤2	>8	88.6	10.1
Ciprofloxacin	≤0.5	>4	85.9	13.1
Tetracycline	≤2	>8	77.8	19.5
Trimethoprim/sulfamethoxazole	≤0.5	>2	81.8	18.2
Enterobacter spp. (147)[c]				
Tigecycline	0.5	1	96.6	0.0
Piperacillin/tazobactam	4	>64	72.1	10.2
Ceftazidime	≤1	>16	69.0	30.3
Cefepime	≤0.12	2	95.2	3.4
Imipenem	0.5	1	92.5	2.0
Gentamicin	≤2	≤2	93.2	6.1
Ciprofloxacin	≤0.5	4	88.4	10.9
Tetracycline	≤2	>8	85.7	11.6
Trimethoprim/sulfamethoxazole	≤0.5	>2	89.8	10.2
P. aeruginosa (287)				
Tigecycline	>4	>4	-[d]	-
Piperacillin/tazobactam	8	>64	82.2	17.8
Ceftazidime	4	>16	68.9	24.1
Cefepime	4	>16	72.8	13.6
Imipenem	2	>8	73.5	18.5
Gentamicin	≤2	>8	78.0	18.8
Ciprofloxacin	≤0.5	>4	71.4	22.6
Tetracycline	>8	>8	-	-
Trimethoprim/sulfamethoxazole	>2	>2	-	-
Polymyxin B	1	1	98.3	1.0
Acinetobacter spp. (65)[e]				
Tigecycline	0.5	2	-	-
Piperacillin/tazobactam	>64	>64	33.8	66.2
Ceftazidime	>16	>16	36.9	55.4
Cefepime	16	>16	41.5	44.6
Imipenem	2	>8	63.1	33.8
Gentamicin	>8	>8	44.6	50.8
Ciprofloxacin	>4	>4	32.3	66.2
Polymyxin B	≤0.5	≤0.5	98.5	1.5

a. According to CLSI (2010) criteria or the USA-FDA (tigecycline only).
b. Includes: *Klebsiella oxytoca* (78 isolates), *Klebsiella ozaenae* (1 strain), and *Klebsiella pneumoniae* (218 isolates).
c. Includes: *Enterobacter aerogenes* (34 isolates), *Enterobacter amnigenus* (1 strain), *Enterobacter cloacae* (107 isolates), *Enterobacter sakazakii* (1 strain), and unspecified *Enterobacter* (4 isolates).
d. - = no breakpoints have been established by the CLSI or the USA-FDA.
e. Includes: *Acinetobacter baumannii* (51 isolates), *Acinetobacter lwoffii* (5 isolates), and unspecified *Acinetobacter* (9 isolates).

- All isolates of *S. aureus* (including MRSA), streptococci, *E. coli* and *Klebsiella* spp. were susceptible to tigecycline using the current breakpoint criteria established by the USA-FDA. Tigecycline was active against >99% of CoNS, >96% of enterococci and *Enterobacter* spp., and was shown to have measurable potency against *Acinetobacter* spp. (>96% at ≤2 mg/L; the breakpoint criteria for Enterobactaeriaceae).
- Continued monitoring of tigecycline activity on a global scale is needed to determine the overall role of this novel, broad-spectrum antimicrobial agent.