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Potency and Spectrum of Tigecycline Tested Against Bacterial Pathogens Producing Skin and Skin Structure Infections in European Medical Centers, Including Community-acquired Methicillin-resistant *S. aureus*

HS SADER, RN JONES, GJ MOET, TR FRITSCHE
JMI Laboratories, North Liberty, IA, USA

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JMI Laboratories
North Liberty, IA, USA
www.jmilabs.com
319.665.3370, fax 319.665.3371
helio-sader@jmilabs.com

ABSTRACT

Objective:
To evaluate the activity and potency of tigecycline when tested against a large collection of bacterial pathogens causing skin and skin structure infections (SSSI). Tigecycline is the sentinel representative of the glycylcycline class and was recently approved by the European Medicines Agency for the treatment of complicated SSSI and intra-abdominal infections.

Methods:
Consecutive, non-duplicate bacterial isolates (4,567 strains) were collected from 2000 to 2007 from patients with documented SSSI in >30 medical centers (14 countries) participating in the Tigecycline Surveillance Program in Europe. All isolates were tested using CLSI broth microdilution methods against tigecycline and key comparator agents commonly used for therapy of SSSI. Tigecycline-susceptible (S) breakpoints (USA-FDA/EUCAST) were defined as ≤2/≤1 mg/L for Enterobacteriaceae (ENT); ≤0.5/≤0.5 mg/L for staphylococci, and ≤0.25/≤0.25 mg/L for streptococci and enterococci. *S. aureus* infections diagnosed within the first 48 hours of hospitalization were considered to be of community origin.

Results:
SSSI pathogen rank order (top 8), potency (MIC_{90}) and S rates for tigecycline are shown in the Table. *S. aureus* (22.7% MRSA) was isolated from 45.7% of SSSI cases and tigecycline inhibited 99.8% of strains, including all community-acquired (CA)-MRSA, at the S breakpoint. CA-MRSA showed low S to erythromycin (37.5%), clindamycin (63.5%) and levofloxacin (17.5%). Tigecycline was also very active against enterococci (93.2% S), including vancomycin-non-S strains (100.0% S), BHS (99.6% S) and CoNS (97.9% S). Linezolid was also active against Gram-positive organisms, but generally 8-fold less potent than tigecycline. Tigecycline (98.4-100.0% S) and imipenem (98.4-100.0% S) were the most active compounds tested against *E. coli*, *Klebsiella* spp. and *Enterobacter* spp., while high rates of R to levofloxacin (5.5-16.4%) and gentamicin (7.1-12.7%) were observed among these pathogens.

Organism (no. of isolates/% of total)	MIC_{90} / % S[a]				
	TIG	LEV	CLI	T/S	LZD
S. aureus (2,089 / 45.7)	0.25 / 99.8	>4 / 76.4	>2 / 88.5	≤0.5 / 97.6	2 / 100.0
Methicillin-resistant *S. aureus* (MRSA; 474/10.4)	0.25 / 99.6	>4 / 11.0	>2 / 59.1	2 / 91.7	2 / 100.0
Community-acquired (CA)-MRSA (137 / 6.6)	0.25 / 100.0	>4 / 17.5	>2 / 63.5	1 / 94.9	2 / 100.0
E. coli (426 / 9.3)	0.25 / 99.5	>4 / 80.3	- / -	>2 / 70.1	- / -
P. aeruginosa (PSA; 399 / 8.7)	>4 / -	>4 / 71.4	- / -	>2 / 6.3	- / -
Enterococci (293 / 6.4)	0.25 / 93.2	>4 / 59.0	- / -	- / -	2 / 100.0
Beta-haemolytic streptococci (BHS; 256 / 5.6)	≤0.12 / 100.0	1 / 100.0	≤0.25 / 92.6	≤0.5 / 99.6	1 / 100.0
Coagulase-neg. staphylococci (CoNS; 234 / 5.1)	0.5 / 97.9	>4 / 49.6	>2 / 74.4	>2 / 69.3	1 / 100.0
Enterobacter spp. (ESP; 182 / 4.0)	1 / 98.4	1 / 92.3	- / -	>2 / 89.6	- / -
Klebsiella spp. (KSP; 142 / 3.1)	1 / 100.0	4 / 88.0	- / -	>2 / 81.0	- / -

a. According to USA-FDA breakpoints. TIG = tigecycline, LEV = levofloxacin, CLI = clindamycin, T/S = trimethoprim/ sulfamethoxazole and LZD = linezolid.

Conclusions:
Tigecycline was highly active against the top 8-ranked pathogens producing SSSI, except for *P. aeruginosa*, and showed the broadest spectrum of activity among the antimicrobials tested. Tigecycline, linezolid and vancomycin were the most active compounds tested against Gram-positive species while tigecycline, amikacin and imipenem were the most active against Gram-negatives. Tigecycline represents a welcome choice for use in treating common Gram-positive and negative pathogens producing serious SSSI.

INTRODUCTION

Infections of skin and skin structures (SSSI) are among the most common of community- and hospital-acquired infections; in the United States (USA) alone, estimates of over 700,000 patients being hospitalized annually for such infections have been projected. Furthermore, the management of complicated SSSI (cSSSI) is often compromised by the potential microbiological diversity of prevalent pathogens. In particular, cSSSIs are characterized by a fairly high prevalence of *Staphylococcus aureus*, including the emergence of methicillin-(oxacillin) resistant *S. aureus* (MRSA) in both the hospital and community settings.

The emergence and rapid dissemination of community-acquired MRSA (CA-MRSA) necessitates reconsideration of current empirical treatment with ß-lactam antimicrobials for community-acquired *S. aureus* infections and current control strategies for MRSA in hospitals. Although CA-MRSA infections are commonly mild, they may also be severe or invasive, and require prompt initiation of effective parenteral antimicrobial therapy.

In the present study, we evaluated the antimicrobial potency of tigecycline and other commonly used antimicrobial agents for treatment of cSSSI against clinical bacterial isolates recovered in European medical centers.

MATERIALS AND METHODS

Organism Collection: Thirty-three European medical centers submitted consecutive, nonduplicate community-acquired or nosocomial SSSI pathogens for the years 2000 to 2007. The participating centers were located in (no. of medical centers): Belgium (2), France (6), Germany (5), Greece (1), Ireland (2), Israel (1), Italy (3), Poland (1), Russia (1), Spain (3), Sweden (2), Switzerland (1), Turkey (2), and the United Kingdom (3). Species identifications were performed by the submitting laboratories with identification confirmation performed by the central laboratory monitor (JMI Laboratories, Iowa, USA). *S. aureus* isolated from outpatients or from inpatients within the first 48 hours of hospitalization was considered to be of community origin or onset.

Antimicrobial susceptibility testing: Susceptibility testing was performed using validated broth microdilution test panels (TREK Diagnostic Systems, Inc., OH, USA) with cation-adjusted Mueller-Hinton broth (added 2 to 5% lysed horse blood for testing of fastidious species) according to Clinical and Laboratory Standards Institute (CLSI) methods (M7-A7, 2006). Tigecycline was tested on fresh Mueller-Hinton broth and the breakpoints utilized were those recommended by the USA-Food and Drug Administration (FDA), which are ≤2 mg/L (susceptible) and ≥8 mg/L (resistant) for Enterobacteriaceae; ≤0.5 mg/L for staphylococci (susceptible only) and ≤0.25 mg/L for streptococci and enterococci (susceptible only).

Enterobacteriaceae with elevated MIC values (≥2 mg/L) for ceftazidime and/or ceftriaxone were considered as extended-spectrum ß-lactamase (ESBL)-producing phenotypes according to CLSI criteria; ESBL confirmation was performed using the disk approximation method or Etest ESBL strips (AB BIODISK, Solna, Sweden). Quality control isolates utilized included *Escherichia coli* ATCC 25922 and 35218, *Pseudomonas aeruginosa* ATCC 27853, *S. aureus* ATCC 29213, *S. pneumoniae* ATCC 49619 and *Enterococcus faecalis* ATCC 29212; interpretive criteria used were those recommended by the CLSI (M100-S18; 2008).

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RESULTS

- *S. aureus* was the most frequently isolated pathogen from SSSI in the European medical centers surveyed (2,089 strains; 45.7%), followed by *E. coli* (426 strains; 9.3%), *P. aeruginosa* (399 strains; 8.7%), *Enterococcus* spp. (293 strains; 6.4%) and ß-haemolytic streptococci (256 strains; 5.6%; see Table 1).
- Tigecycline was highly active against *S. aureus* (MIC_{90}, 0.25 mg/L; 99.8% susceptible). Vancomycin and linezolid were also very active against this pathogen (100.0% susceptible), while 22.7% of strains were resistant to oxacillin (MRSA; Table 1).
- Tigecycline also exhibited good activity against other frequently isolated Gram-positive pathogens, including *Enterococcus* spp. (MIC_{90}, 0.25 mg/L; 93.2% susceptible), ß-haemolytic streptococci (MIC_{90}, 0.06 mg/L; 100.0% susceptible) and coagulase-negative staphylococci (MIC_{90}, 0.5 mg/L; 97.9% susceptible).
- Linezolid and vancomycin were also very active against Gram-positive organisms, but generally eight- to 16-fold less potent than tigecycline (Table 1).
- Tigecycline was active against the most frequently isolated Gram-negative pathogens, except *P. aeruginosa* (only 8.7% of cSSSI pathogens).
- Tigecycline and imipenem were the most active compounds tested against *E. coli* (MIC_{90}, 0.25 mg/L and ≤0.5 mg/L, respectively), *Enterobacter* spp. (MIC_{90}, 1 mg/L for both compounds) and *Klebsiella* spp. (MIC_{90}, 1 mg/L and ≤0.5 mg/L, respectively) with 98.4-100.0% susceptibility rates (Table 1). Amikacin was also very active against Enterobacteriaceae with susceptibility rates of 96.5-99.5% (Table 1).
- ESBL phenotypes were observed in 11.7-12.0% of *E. coli*, 20.4-21.1% of *Klebsiella* spp. and 9.3% of *Enterobacter* spp. (Table 1). Tigecycline was active against all ESBL-like isolates (MIC, ≤2 mg/L).
- Tigecycline was also active against all CA-MRSA strains at the susceptible breakpoint of ≤0.5 mg/L. In contrast, CA-MRSA showed elevated rates of resistance to ciprofloxacin (82.5%), levofloxacin (78.8%), erythromycin (61.3%) and clindamycin (36.5%; Table 2).

Table 1. Antimicrobial activity of tigecycline and selected comparator agents tested against bacterial isolates causing SSSI in European medical centers.

Organism (no. tested)/ antimicrobial agent	MIC (mg/L)			
	MIC_{50}	MIC_{90}	% Susceptible[a]	% Resistant[a]
S. aureus (2,089)				
Tigecycline	0.12	0.25	99.8	-[b]
Oxacillin	0.5	>2	77.3	22.7
Erythromycin	0.25	>8	71.3	27.8
Clindamycin	≤0.25	>2	88.4	11.5
Levofloxacin	≤0.5	>4	76.4	22.6
Trimethoprim/sulfamethoxazole	≤0.5	≤0.5	98.0	2.0
Linezolid	2	2	100.0	-
Vancomycin	1	1	100.0	0.0
E. coli (426)				
Tigecycline	0.12	0.25	100.0	0.0
Piperacillin/tazobactam	2	8	92.7	2.8
Ceftriaxone	≤0.25	8	90.8	8.2 (12.0)[c]
Ceftazidime	≤1	2	92.7	4.7 (11.7)[c]
Cefepime	≤0.12	1	94.1	4.2
Imipenem	≤0.5	≤0.5	100.0	0.0
Levofloxacin	≤0.5	>4	80.3	16.4
Gentamicin	≤2	≤2	91.5	7.5
Amikacin	2	4	99.3	0.2
P. aeruginosa (399)				
Tigecycline	>4	>4	-	-
Piperacillin/tazobactam	8	>64	86.2	13.8
Ceftazidime	2	>16	80.5	15.8
Imipenem	1	>8	80.2	12.5
Levofloxacin	0.5	>4	71.4	24.6
Gentamicin	≤2	>8	78.4	19.3
Amikacin	2	16	90.5	5.3
Polymyxin B	≤1	≤1	99.7	0.3
Enterococcus spp. (293)				
Tigecycline	0.12	0.25	93.2	-
Ampicillin	2	>16	80.5	19.5
Levofloxacin	2	>4	59.0	38.6
Gentamicin (HL)[d]	≤500	>1000	63.1	36.9
Quinupristin/dalfopristin	>2	>2	16.7	73.4
Linezolid	1	2	100.0	0.0
Vancomycin	1	2	95.6	3.4
ß-haemolytic streptococci (256)				
Tigecycline	0.03	0.06	100.0	-
Penicillin	≤0.015	0.03	100.0	-
Erythromycin	≤0.06	>2	79.3	20.7
Clindamycin	≤0.25	≤0.25	92.6	7.4
Levofloxacin	0.5	1	100.0	0.0
Tetracycline	≤2	>8	55.9	39.5
Linezolid	1	1	100.0	-
Coagulase-negative staphylococci (234)				
Tigecycline	0.12	0.5	97.9	-
Oxacillin	2	>2	26.9	73.1
Erythromycin	>2	>2	44.4	55.6
Clindamycin	≤0.25	>8	73.9	25.6
Levofloxacin	2	>4	49.6	44.9
Trimethoprim/sulfamethoxazole	≤0.5	>2	77.4	22.6
Linezolid	1	1	100.0	-
Vancomycin	1	2	100.0	0.0
Enterobacter spp. (182)				
Tigecycline	0.5	1	98.4	0.0
Piperacillin/tazobactam	2	64	81.9	7.1
Ceftriaxone	≤0.25	>32	80.2	12.6
Ceftazidime	≤1	>16	76.4	19.2
Cefepime	≤0.12	2	97.8	1.6 (9.3)[e]
Imipenem	≤0.5	1	98.4	0.0
Levofloxacin	≤0.5	1	92.3	5.5
Gentamicin	≤2	4	90.1	7.1
Amikacin	1	4	99.5	0.5
Klebsiella spp. (142)				
Tigecycline	0.25	1	100.0	0.0
Piperacillin/tazobactam	2	>64	79.6	15.5
Ceftriaxone	≤0.25	>32	81.0	15.5 (20.4)[c]
Ceftazidime	≤1	>16	84.5	10.6 (21.1)[c]
Cefepime	≤0.12	>16	88.0	11.3
Imipenem	≤0.5	≤0.5	100.0	0.0
Levofloxacin	≤0.5	4	88.0	9.9
Gentamicin	≤2	>8	85.9	12.7
Amikacin	1	8	96.5	1.4

a. According to CLSI (M100-S18) breakpoints except tigecycline, for which USA-FDA breakpoints were applied.
b. - = no breakpoint has been established by CLSI or USA-FDA.
c. Percentage of strains with ESBL phenotype in parentheses per CLSI (2008) criteria.
d. HL = high-level resistance (MIC > 500 mg/L).
e. Percentage of isolates with cefepime MIC ≥4 mg/L, indicating possible ESBL production.

Table 2. Antimicrobial susceptibility of 137 strains of CA-MRSA[a] isolated in European medical centers.

Antimicrobial agent	MIC (mg/L)			% Susceptible	% Resistant
	50%	90%	Range		
Tigecycline	0.12	0.25	0.06-0.5	100.0	-
Erythromycin	>2	>2	≤0.25->2	37.2	61.3
Clindamycin	≤0.25	>8	≤0.25->8	63.5	36.5
Ciprofloxacin	>4	>4	0.12->4	17.5	82.5
Levofloxacin	>4	>4	0.12->4	17.5	78.8
Gentamicin	≤2	>8	≤2->8	77.4	21.2
Tetracycline	≤2	>8	≤2->8	74.5	21.9
Trimethoprim/sulfamethoxazole	≤0.5	1	≤0.5->2	94.9	5.1
Vancomycin	1	1	0.25-2	100.0	0.0

a. *S. aureus* collected from an outpatient or from an inpatient within the first 48 hours of hospitalization was considered to be of community origin.

CONCLUSIONS

- Tigecycline was highly active against the eight most common pathogens producing SSSI in the European medical centers surveyed (except for *P. aeruginosa*), and showed the broadest spectrum of activity among the antimicrobials tested.
- Tigecycline, linezolid and vancomycin were the most active compounds tested against Gram-positive species, while tigecycline, amikacin and imipenem were the most active against Gram-negative organisms.
- Tigecycline represents a welcome alternative for use in treating common Gram-positive and -negative pathogens producing serious SSSI in Europe.