1325

In Vitro Efficacy of Tigecycline Tested Against Community-Associated Methicillin-Resistant *S. aureus* (CA-MRSA) Including Analyses of 72 Co-Resistance Patterns

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ABSTRACT

Objective:
To determine if the activity of tigecycline (TIG) varies among prevalent susceptibility (S) patterns of CA-MRSA (1,989 strains) isolated in North America between 2000-2004. The S patterns were defined by S and resistant (R; includes intermediate) criteria recommended by the CLSI (2005) for 10 drugs: chloramphenicol (CH), ciprofloxacin (CI), clindamycin (CL), erythromycin (ER), gentamicin (GT) rifampin (RF), tetracycline (TC), TMP/SMX, Synercid®, and vancomycin (VA).

Methods:
CA-MRSA isolates were defined as *S. aureus* infections acquired in the non-healthcare setting or appearing in hospitalized patients during the initial 48 hours as determined by the demographic records of the laboratory and hospital infection control services. A total of 1,989 MRSA met inclusion criteria and were categorized by S patterns and the S testing used the CLSI both microdilution method with fresh Mueller-Hinton medium for TIG. Patterns ranged from 1 to 8 drugs being R; the 7 most common patterns accounting for 81.6% of CA-MRSA isolates (72 total patterns). ER-R (94.2%) was highest followed by fluoroquinolones (CI-R, 84.4%)

Results:
TIG-S rates varied from 89.7-100.0% among the most frequently isolated S patterns (see table). Across all CA-MRSA, TIG inhibited 98.2 and 100.0% of strains at <= 1 and <=2 mg/L, respectively. All non-S TIG MIC results were at 1mg/L only 2-fold greater than the US-FDA breakpoint for staphylococci. However, 1 mg/L was 2-fold lower than the TIG breakpoint applied to Enterobacteriaceae. The overall comparison agent S rates (%) were: CH (82.6), GT (86.6), linezolid (>99.9), Synercid® (>99.9), RF (93.7), TC (90.4), TMP/SMX (91.1), and VA (100.0).

	Tigecycline MIC (mg/L)		Cum %	
Strain origin/antibiogram (no. / %)	MIC_{50}	MIC_{90}	<=0.5 mg/L	1 mg/L
CA-MRSA (1,989)	<=0.12	0.5	98.2	100.0
None (58/2.9)	<=0.12	0.5	100.0	100.0
ER (162/8.1)	<=0.12	0.25	99.1	100.0
ER, CI (287/14.4)	<=0.12	0.5	99.3	100.0
ER, CI, CL (707/35.5)	<=0.12	0.5	98.3	100.0
ER, CI, CL, CH (259/13.0)	0.25	0.5	100.0	100.0
ER, CI, CL, GT (111/5.6)	0.25	1	89.7	100.0
ER, CI, CL, RF (42/2.1)	0.25	0.5	100.0	100.0
Nosocomial (1907)	<=0.12	0.5	98.7	100.0

TIG activity versus nosocomial MRSA isolates (98.7% S) was comparable to that observed for CA-MRSA.

Conclusions:
TIG demonstrates high potency (MIC_{90}, 0.25-0.5 mg/L) and breadth of coverage (98.2-98.7%) against CA-MRSA as well as nosocomial isolates (1,907 strains). MDR patterns (72) did not adversely influence TIG activity and high-level R was not observed among nearly 4,000 *S. aureus* isolates (all non-S MICs to tigecycline were at 1 mg/L).

INTRODUCTION

Community-associated (CA) methicillin (oxacillin)-resistant *Staphylococcus aureus* (MRSA) infections have emerged in the last decade at an alarming rate, particularly among youthful patients or those without healthcare-associated (HCA) risk factors. Specific molecular characteristics have been identified in the dominant clones which includes the staphylococcal cassette chromosome *mec*IVa and the Panton-Valentine leucocidin genes. These organisms have become ubiquitous in the United States (USA) and PFGE clonal patterns designated USA300 or 400 with variants are very common and widely disseminated geographically. The number of cutaneous infections caused by these staphylococci is very high and generally benign with treatment by orally administered antimicrobials and local wound care that includes drainage procedures. However, some cases have presented with advanced sepsis and/or necrotizing pneumonia progressing to rapidly fatal outcomes. Clearly, a limited number of agents are available for ambulatory-care use versus CA-MRSA.

Tigecycline, a glycylcycline derived from the minocycline molecule has recently been approved by the USA-Food and Drug Administration. Its broad-spectrum includes documented activity against many Gram-negative and Gram-positive pathogens including Enterobacteriaceae, *Acinetobacter* spp., MRSA, vancomycin-resistant enterococci, penicillin-resistant *Streptococcus pneumoniae*, anaerobic wound infection pathogens, *Neisseria gonorrhoeae*, and commonly occurring respiratory pathogens. Tigecycline has documented activity against tigecycline-resistant (tet-R) pathogens refractory to therapy by both efflux and ribosomal protection mechanisms. In addition, tigecycline does not show cross-resistance to other antimicrobial classes.

In this report, we summarize the potential application of tigecycline in the parenteral treatment of CA-MRSA by in vitro tests of 1,989 strains said to be *S. aureus* emerging in non-HCA environments. Tigecycline and numerous comparison agents were tested by reference MIC methods with rigorous concurrent quality assurance procedures.

MATERIALS AND METHODS

Bacterial Strains: To assess the spectrum of activity and potency of tigecycline against CA-MRSA, recent clinical isolates submitted to a reference laboratory (JMI Laboratories, North Liberty, IA, USA) were examined. A total of 1,989 isolates were tested, each noted by the referring institution to be of community origin (CA-MRSA). The *S. aureus* identification was confirmed by the monitoring laboratory using routine methods (coagulase, colony morphology, etc.) and automated procedures when needed (Vitek System, bioMerieux, Hazelwood, MO, USA). A sample of 1,907 *S. aureus* of nosocomial origin were also tabulated for comparison (Table 3).

Susceptibility Testing: MIC values were determined for tigecycline, and comparator agents using "validated", dry-form broth microdilution panels with cation-adjusted Mueller-Hinton medium. Testing, incubation and MIC interpretations were performed using the recommendations of the Clinical and Laboratory Standards Institute (CLSI; formerly NCCLS) and the manufacturer. Quality control (QC) strains utilized included *Escherichia coli* ATCC 25922 and 35218, *S. aureus* ATCC 29213, *Enterococcus faecalis* ATCC 29212, *Streptococcus pneumoniae* ATCC 49619 and *Pseudomonas aeruginosa* ATCC 27853; all QC results were within CLSI specified ranges. The interpretation applied to tigecycline was found in the USA-FDA-approved product package insert for *S. aureus* (including methicillin-resistant isolates) e.g. ≤ 0.5 mg/L, with a correlate zone diameter of ≥ 19 mm. The interpretations of 12 antimicrobial agents were analyzed by patterns of susceptibility/resistance with intermediate (I) and resistant (R) interpretations grouped as resistant. Only eight of the agents demonstrated significant resistance rates (see footnotes of Table 1). Rare (linezolid and quinupristin/dalfopristin) or no (teicoplanin and vancomycin) non-susceptible isolates were encountered for some agents in the 2000-2004 surveillance (North American) samples.

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RESULTS

- A total of 72 antimicrobial resistance patterns were recognized with seven (7) patterns having an occurrence of ≥ 2.0%. These seven patterns comprised 81.6% of all North American CA-MRSA (Table1).
- The most common non-ß-lactam resistance was erythromycin (MIC, ≥ 1 mg/L; 94.2% resistant) followed by fluoroquinolones and clindamycin (Tables 1 and 2).
- Among 14 agents listed in Table 2, the antimicrobials with the least "resistance" were: glycopeptides (teicoplanin and vancomycin) = quinupristin/dalfopristin (0.0% resistant) < linezolid (<0.1%) < chloramphenicol (0.7%) < rifampicin (4.4%) < trimethoprim/sulfamethoxazole (7.2%) < tetracycline (9.1%) < gentamicin (12.8%).

Table 1. Occurrence of antimicrobial resistant patterns (72) among 1,989 CA-MRSA isolated in North America[a].

Antimicrobial resistance patterns (Drugs with resistance)[b]	Occurrences (%)
None	58 (2.9)
One antimicrobial	
ER	162 (8.1)
CP	27 (1.4)
TC	9 (0.5)
Others[c]	2 (0.1)
Two antimicrobials	
ER, CI	287 (14.4)
ER, TC	34 (1.7)
ER, CL	17 (0.9)
CI, TC	6 (0.3)
Others[c]	5 (0.3)
Three antimicrobials	
ER,CI, CL	707 (35.5)
ER, CI, TC	27 (1.4)
ER, CI, CH	14 (0.7)
ER, CI, GT	9 (0.5)
ER, CI, RF	8 (0.4)
ER, CI, T/S	4 (0.2)
CI, GT, TC	4 (0.2)
ER, CL, TC	3 (0.2)
ER, CL, RF	2 (0.1)
Others[c]	7 (0.4)
Four antimicrobials	
ER, CL, CI, CH	259 (13.0)
ER, CL, CI, GT	111 (5.6)
ER, CL, CI, RF	42 (2.1)
ER, CL, CI, TC	12 (0.6)
ER, CL, CI, T/S	3 (0.2)
ER, CI, GT, TC	3 (0.2)
CI, GT, TC, T/S	3 (0.2)
ER, CI, CH, TC	2 (0.1)
ER, CI, GT, T/S	2 (0.1)
Others[c]	6 (0.3)
Five antimicrobials	
ER, CL, CI, CH, GT	32 (1.6)
ER, CL, CI, GT, RF	13 (0.7)
ER, CL, CI, GT, TC	13 (0.7)
ER, CL, CI, GT, T/S	10 (0.5)
ER, CL, CI, CH, RF	9 (0.5)
ER, CL, CI, RF, TC	5 (0.3)
ER, CL, CI, CH, TC	3 (0.2)
ER, CL, CI, TC, T/S	3 (0.2)
ER, CI, GT, TC, T/S	3 (0.2)
ER, CL, CI, CH, T/S	2 (0.1)
ER, CI, CH, RF, TC	2 (0.1)
Others[c]	2 (0.1)
Six antimicrobials	
ER, CL, CI, GT, RF, TC	17 (0.9)
ER, CL, CI, CH, GT, TC	10 (0.5)
ER, CL, CI, GT, TC, T/S	7 (0.4)
ER, CL, CI, GT, RF, T/S	4 (0.2)
ER, CL, CI, CH, GT, T/S	2 (0.1)
Others[c]	5 (0.3)
Seven antimicrobials	
ER, CL, CI, GT, RF, TC, T/S	8 (0.4)
Others[c]	3 (0.2)
Eight antimicrobials	
ER, CL, CI, CH, GT, RF, TC, T/S	1 (<0.1)

a. Antibiogram using 12 antimicrobials with intermediate and resistant results grouped as resistant. Criteria for susceptibility were those published by the CLSI (2006).
b. ER = erythromycin, CL = clindamycin, CH = chloramphenicol, CP = ciprofloxacin, GT = gentamicin, TC = tetracycline, T/S = trimethoprim/sulfamethoxazole and RF = rifampin. Single occurrences of quinupristin/dalfopristin (Q/D) and linezolid non-susceptibility were deleted from analysis and no non-susceptible isolates were noted for teicoplanin or vancomycin.
c. Single antibiogram pattern events.

- Table 3 illustrates the excellent activity of tigecycline against the strains having the most common CA-MRSA resistance patterns. The overall tigecycline-susceptible rate for CA-MRSA was 98.2%; compared to 98.7% for HCA isolates.
- Only one prevalent pattern (ER, CI, CL, and GT resistance) had a significantly reduced rate of tigecycline susceptibility (89.7%; Table 3).

Table 2. Antibiogram profiles of all CA-MRSA strains recorded in the SENTRY Antimicrobial Surveillance Program (North America, 2000-2004) as determined by laboratory/epidemiology-based demographics (1,989 isolates)[a].

	MIC (mg/L)			% by category[b]	
Antimicrobial agents	Range	50%	90%	Susceptible	Resistant
Chloramphenicol	≤2->6	8	16	82.6	0.7
Ciprofloxacin	≤0.03->4	>4	>4	15.1	84.4
Clindamycin	≤0.06->8	>8	>8	34.2	65.3
Erythromycin	≤0.06->8	>8	>8	5.7	94.2
Gatifloxacin	≤0.03->4	4	>4	15.9	82.8
Gentamicin	≤2->8	≤2	>8	86.6	12.8
Levofloxacin	0.06->4	>4	>4	15.5	82.9
Linezolid	≤0.06-16	2	2	>99.9	<0.1[c]
Quinupristin/dalfopristin	≤0.25-2[d]	0.5	1	>99.9	0.0
Rifampicin	≤0.5->2	≤0.5	≤0.5	93.7	4.4
Teicoplanin	≤2-8	≤2	≤2	100.0	0.0
Tetracycline	≤2->8	≤2	4	90.7	9.1
Trimethoprim/sulfamethoxazole	≤0.5->2	≤0.5	≤0.5	91.1	7.2
Vancomycin	0.25-4	1	1	100.0	0.0

a. Infection acquired in the community or appearing during the first 48 hours of hospitalization.
b. CLSI breakpoint criteria, not US-FDA.
c. One isolate with a linezolid MIC of 16 mg/L (resistant).
d. One isolate with an intermediate MIC of 2 mg/L.

Table 3. Activity of tigecycline tested against the most frequently occurring antimicrobial resistance patterns of CA-MRSA and a sample of nosocomial MRSA (North America, 2000-2004).

	Tigecycline MIC (mg/L)		Cum. % inhibited	
Strain origin/antibiogram (no / %)	MIC_{50}	MIC_{90}	≤0.5 mg/L	1 mg/L
CA-MRSA (1,989)	≤0.12	0.5	98.2	100.0
None (58/2.9)	≤0.12	0.5	100.0	100.0
ER (162/8.1)	≤0.12	0.25	99.1	100.0
ER, CI (287/14.4)	≤0.12	0.5	99.3	100.0
ER, CI, CL (707/35.5)	≤0.12	0.5	98.3	100.0
ER, CI, CL, CH (259/13.0)	0.25	0.5	100.0	100.0
ER, CI, CL, GT (111/5.6)	0.25	1	89.7	100.0
ER, CI, CL, RF (42/2.1)	0.25	0.5	100.0	100.0
Nosocomial	≤0.12	0.5	98.7	100.0

CONCLUSIONS

- A wide variety of resistance patterns were documented among CA-MRSA strains isolated in North America with macrolide and fluoroquinolone resistance predominating.
- Tigecycline was very active (98.2% susceptible; MIC_{90}, 0.5 mg/L) versus CA-MRSA, as well as HCA-MRSA (98.7% susceptible; MIC_{90}, 0.5 mg/L).
- Tigecycline coverage of MRSA in North America, regardless of clinical site of origin, was comparable to other highly active parenteral agents such as the glycopeptides, streptogramin combinations and oxazolidinones.