Multi-Drug Resistant (MDR) Methicillin-Resistant *Staphylococcus aureus* Isolates in the U.S.

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Revised Abstract

Background: Worldwide *S. aureus* are increasingly displaying resistance to multiple drug classes (MDR). Therapeutic options to MDR, methicillin-resistant *S. aureus* (MRSA) phenotypes are limited. Tigecycline offers the potential of enhanced activity against MDR *S. aureus*. The Tigecycline Evaluation Surveillance Trial (T.E.S.T.) evaluated the activity of tigecycline and comparators against MDR *S. aureus* isolated in the United States. **Methods:** 508 cumulative hospital sites in the United States collected 4,220 clinically significant MRSA between 2004 and 2009. MICs were performed as specified by CLSI at each site. **Results**: MIC_{90} of tigecycline and comparators to MDR MRSA resistant groups 1-3 are shown in the following table.

	MIC_{90} - mcg/ml (%Sus)		
Drug	*Group 1 n=1274	*Group 2 n=2940	*Group 3 n=6
Tigecycline	0.25(100)	0.25(100)	0.5(100)
AmoxClav	8(0)	>8(0)	>8(0)
Ampicillin	>16(0)	>16(0)	>16(0)
Ceftriaxone	32(0)	>64(0)	>64(0)
Imipenem	1(100)	16(0)	16(0)
Levofloxacin	1(90.3)	>32(0)	>32(0)
Linezolid	2(100)	4(100)	4(100)
Meropenem	2(0)	16(0)	16(0)
Minocycline	≤0.25(99.7)	0.5(99.1)	>8(0)
PipTazo	>16(0)	>16(0)	>16(0)
Vancomycin	1(100)	1(100)	2(100)

*MDR MRSA groups are defined as resistant to cefoxitin (30 µg disk) and all beta-lactams (Group 1), beta-lactams plus 1 additional CLSI drug class (Group 2) and beta-lactams plus 2 additional CLSI drug classes (Group 3).

Conclusions: Tigecycline demonstrated *in vitro* activity comparable to that of linezolid and vancomycin against all MDR groups of MRSA. Tigecycline *in vitro* activity is unaffected by MDR MRSA and should be considered in the treatment of infections due to *S. aureus* where approved indications apply.

Introduction

Methicillin-resistant *S. aureus* (MRSA) now account for approximately 60% of all serious *S. aureus* infections in the United States [1, 2]. Vancomycin has been the mainstay of treatment for MRSA for over 50 years and has remained remarkably effective. However, the fact that vancomycin is beginning to lose efficacy is showing up clinically as treatment failures and microbiologically as vancomycin heteroresistance [3]. Even newer agents such as linezolid and daptomycin have had resistant isolates identified within a year or two of their introduction. It is clear that additional antimicrobial agents are needed to combat this serious pathogen.

This study was undertaken to document the *in vitro* activity of tigecycline against a significant number of multi-drug resistant MRSA from a large diverse population within the United States. This study is part of the larger ongoing global Tigecycline Evaluation Surveillance Trial (T.E.S.T.) program.

Materials & Methods

- Clinical isolates were collected and tested between January 2004 and March 2009 from 508 cumulative total investigative sites (68% participated more than one year) from the United States. Isolates were identified to the species level and tested at each site by the participating laboratory.
- Organism collection, transport, confirmation of organism identification, and development and management of a centralized database were coordinated by Laboratories International for Microbiology Studies (LIMS), a division of International Health Management Associates, Inc. located in Schaumburg, IL, USA.
- Minimum inhibitory concentrations (MICs) were determined by the Clinical and Laboratory Standards Institute (CLSI) recommended broth microdilution testing method [4]. MIC interpretive criteria followed published guidelines established by CLSI, where applicable [5]. Breakpoints for tigecycline are defined by the FDA [6].
- Quality controls (QC) were performed by each testing site on each day of testing using *S. aureus* ATCC 29213 and *Enterococcus faecalis* ATCC 29212 according to CLSI guidelines [5].

References

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Results

Group 1. *In vitro* activity of tigecycline and comparators against 1,274 isolates of methicillin-resistant *S. aureus* resistant only to the beta-lactams.

				MIC (mcg/ml)			
Drug	%Sus[a]	%Int	%Res	MIC_{50}	MIC_{90}	Min	Max
Tigecycline	100	na	na	0.12	0.25	≤0.008	0.5
AmoxClav	0	0	100	8	8	0.25	>8
Ampicillin	0	0	100	>16	>16	0.5	>16
Ceftriaxone	0	0	100	16	32	≤0.03	>64
Imipenem	0	0	100	0.25	1	≤0.12	>16
Levofloxacin	90.3	9.7	0	0.12	1	≤0.06	2
Linezolid	100	na	na	2	2	≤0.5	4
Meropenem	0	0	100	1	2	≤0.12	>16
Minocycline	99.7	0.3	0	≤0.25	≤0.25	≤0.25	8
Penicillin	0	0	100	>8	>8	0.25	>8
PipTazo	0	0	100	16	>16	≤0.25	>16
Vancomycin	100	0	0	0.5	1	≤0.12	2

[a] Interpretive criteria are defined in CLSI document M100-S19 (2009), where available. Tigecycline breakpoints defined by FDA (Tygacil®, 2005); na = not applicable; breakpoints not defined for intermediate and resistant.

Group 2. *In vitro* activity of tigecycline and comparators against 2,940 isolates of methicillin-resistant *S. aureus* resistant to beta-lactams and one additional CLSI drug class (quinolone).

				MIC (mcg/ml)			
Drug	%Sus[a]	%Int	%Res	MIC_{50}	MIC_{90}	Min	Max
Tigecycline	100	na	na	0.12	0.25	≤0.008	0.5
AmoxClav	0	0	100	8	>8	0.25	>8
Ampicillin	0	0	100	>16	>16	0.5	>16
Ceftriaxone	0	0	100	32	>64	≤0.03	>64
Imipenem	0	0	100	0.5	16	≤0.12	>16
Levofloxacin	0	0	100	16	>32	0.12	>32
Linezolid	100	na	na	2	4	≤0.5	4
Meropenem	0	0	100	2	16	≤0.12	>16
Minocycline	99.1	0.8	0.1	≤0.25	0.5	≤0.25	>8
Penicillin	0	0	100	>8	>8	0.25	>8
PipTazo	0	0	100	16	>16	≤0.25	>16
Vancomycin	100	0	0	1	1	0.25	2

[a] Interpretive criteria are defined in CLSI document M100-S19 (2009), where available. Tigecycline breakpoints defined by FDA (Tygacil®, 2005); na = not applicable; breakpoints not defined for intermediate and resistant.

Group 3. *In vitro* activity of tigecycline and comparators against 6 isolates [a] of methicillin-resistant *S. aureus* resistant to beta-lactams and two additional CLSI drug classes (quinolone and tetracycline).

				MIC (mcg/ml)			
Drug	%Sus[b]	%Int	%Res	MIC_{50}	MIC_{90}	Min	Max
Tigecycline	100	na	na	0.25	0.5	0.12	0.5
AmoxClav	0	0	100	4	>8	0.5	>8
Ampicillin	0	0	100	16	>16	1	>16
Ceftriaxone	0	0	100	>64	>64	2	>64
Imipenem	0	0	100	16	16	16	16
Levofloxacin	0	0	100	8	>32	8	>32
Linezolid	100	na	na	2	4	2	4
Meropenem	0	0	100	1	16	0.25	16
Minocycline	0	0	100	>8	>8	>8	>8
Penicillin	0	0	100	8	>8	4	>8
PipTazo	0	0	100	4	>16	0.5	>16
Vancomycin	100	0	0	1	2	0.5	2

[a] %Susceptible, %Intermediate, %Resistant, MIC_{50} and MIC_{90} may not be statistically reliable for n's <20. The reader is referred to the Minimum and Maximum evaluations for more reliable information in this case.
[b] Interpretive criteria are defined in CLSI document M100-S19 (2009), where available. Tigecycline breakpoints defined by FDA (Tygacil®, 2005); na = not applicable; breakpoints not defined for intermediate and resistant.

Table 1. *In vitro* activity of all 4,220 methicillin-resistant *S. aureus* (MRSA) combined.

				MIC (mcg/ml)			
Drug	%Sus[a]	%Int	%Res	MIC_{50}	MIC_{90}	Min	Max
Tigecycline	100	na	na	0.12	0.25	≤0.008	0.5
Amox-Clav	0	0	100	8	>8	0.25	>8
Ampicillin	0	0	100	>16	>16	0.5	>16
Ceftriaxone	0	0	100	16	>64	≤0.03	>64
Imipenem	0	0	100	0.5	16	≤0.12	>16
Meropenem	0	0	100	1	16	≤0.12	>16
Levofloxacin	27.3	2.9	69.8	8	>32	≤0.06	>32
Linezolid	100	na	na	2	4	≤0.5	4
Minocycline	99.1	0.7	0.2	≤0.25	0.5	≤0.25	>8
Penicillin	0	0	100	>8	>8	0.25	>8
Pip-Tazo	0	0	100	16	>16	≤0.25	>16
Vancomycin	100	0	0	1	1	≤0.12	2

[a] Interpretive criteria are defined in CLSI document M100-S19 (2009), where available. Tigecycline breakpoints defined by FDA (Tygacil®, 2005); na = not applicable; breakpoints not defined for intermediate and resistant.

Conclusions

- Tigecycline, linezolid, and vancomycin retained 100% *in vitro* susceptibility at their respective breakpoints against MRSA regardless of multidrug resistance.
- Heteroresistance to glycopeptides and MIC "creep" are proving problematic for both the clinician and microbiologist, and this study demonstrates a 1 doubling dilution MIC_{90} increase for vancomycin against multidrug resistant MRSA isolates. Whether this represents MIC "creep" remains to be proven but similar increases are also seen for tigecycline and linezolid against the 6 MRSA isolates resistant to 2 CLSI drug classes.
- Tigecycline, linezolid and vancomycin remain potent antimicrobial agents against multidrug resistant MRSA but continued surveillance is warranted against this adaptable and challenging species.