

Revised Abstract

Background: There have been increasing reports of *S. aureus* (SA) infections with reduced vancomycin susceptibility (vancomycin MICs ≥ 2 mcg/ml). Tigecycline exhibits good *in vitro* activity against SA, and such activity is not affected by any known resistance mechanism. This study evaluated the activity of tigecycline and comparators against SA with vancomycin MICs ≥ 2 mcg/ml collected from the global Tigecycline Evaluation Surveillance Trial (T.E.S.T.) program. **Methods:** Between January 2004 and March 2009, a cumulative total of 1220 investigational sites in 55 countries collected 17,040 clinically significant SA. 631/17,040 (3.7%) were determined to exhibit vancomycin MICs ≥ 2 mcg/ml. MICs were performed locally using supplied broth microdilution panels according to CLSI and FDA guidelines. **Results:** Percent susceptible and MIC₉₀ for tigecycline and comparators against SA with reduced vancomycin susceptibility are shown below:

	<i>S. aureus</i> (vancomycin MIC ≥ 2 mcg/ml)			
	MSSA* (288)		MRSA* (343)	
	%S	MIC ₉₀	%S	MIC ₉₀
Amox/clav	99.6	2	0	>8
Ceftriaxone	95.8	8	0	>64
Levofloxacin	92.0	1	12.2	>32
Linezolid	100	4	100	4
Meropenem	97.6	1	0	>16
Minocycline	98.6	1	90.1	4
Pip/tazo	99.6	4	0	>16
Tigecycline	100**	0.25	100**	0.5
Vancomycin	98.3	2	98.3	2

*Based upon cefoxitin disc susceptibility; **Using FDA breakpoints.

Conclusions: *S. aureus* with reduced susceptibility to vancomycin (MICs ≥ 2 mcg/ml) are increasingly prevalence worldwide. MRSA exhibiting this phenotype constitute therapeutic challenges. All isolates with reduced susceptibility to vancomycin were susceptible to tigecycline and linezolid *in vitro*.

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 with vancomycin MIC values (1.5 - 2 mcg/ml) heretofore considered susceptible [3, 4]. 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 and comparator antimicrobial agents against isolates of MRSA and MSSA with decreased susceptibility to vancomycin from a large, diverse global population. 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 1,220 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 [5]. MIC interpretive criteria followed published guidelines established by CLSI, where applicable [6]. The CLSI vancomycin susceptibility breakpoint is 2 mcg/ml. Breakpoints for tigecycline are defined by the FDA [7].
- 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 [6].

References

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Acknowledgements

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Results

Figure 1. Regional distribution of *S. aureus* with elevated vancomycin MICs (≥ 2 mcg/ml).

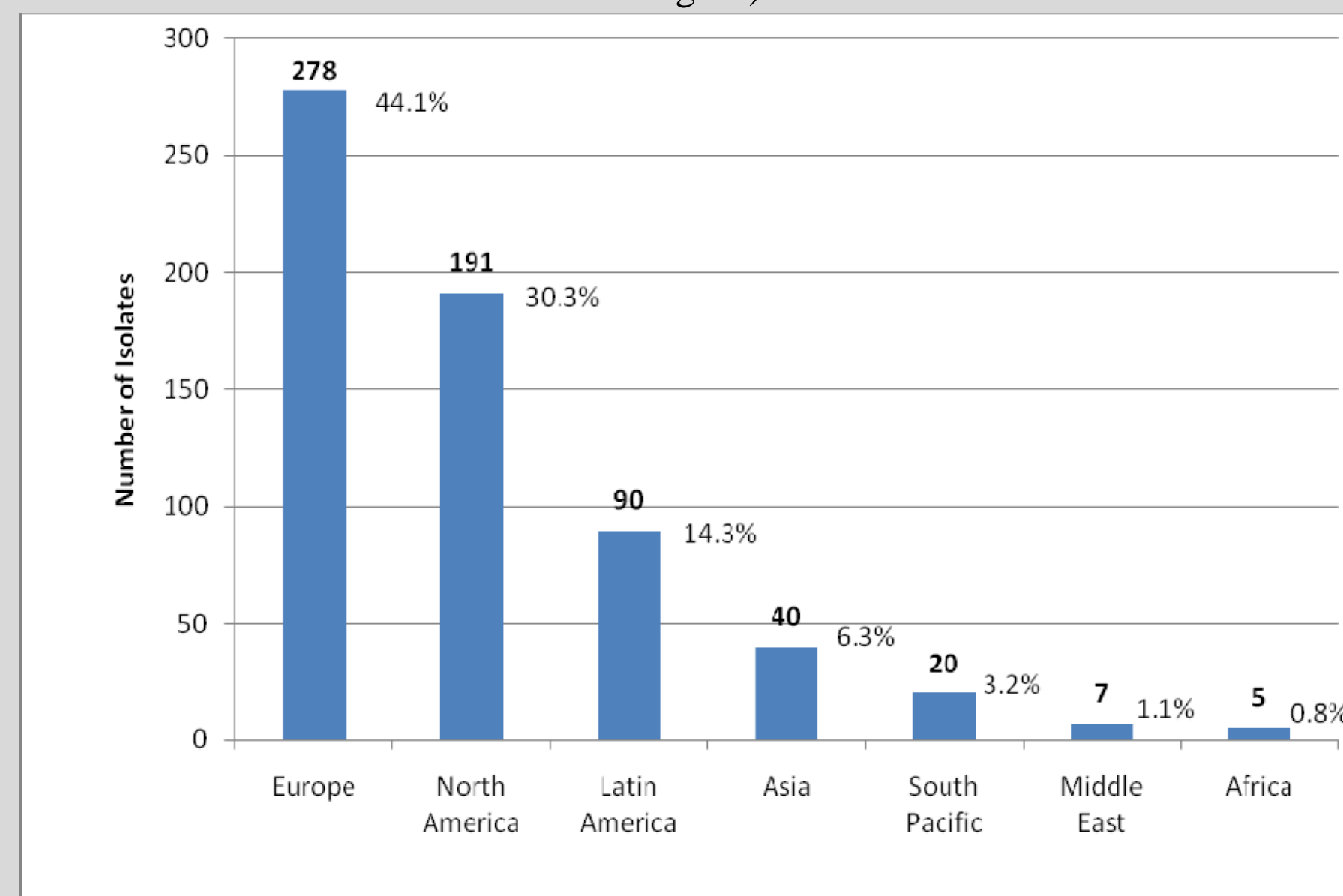


Figure 2. Distribution of *S. aureus* with elevated vancomycin MICs (≥ 2 mcg/ml).

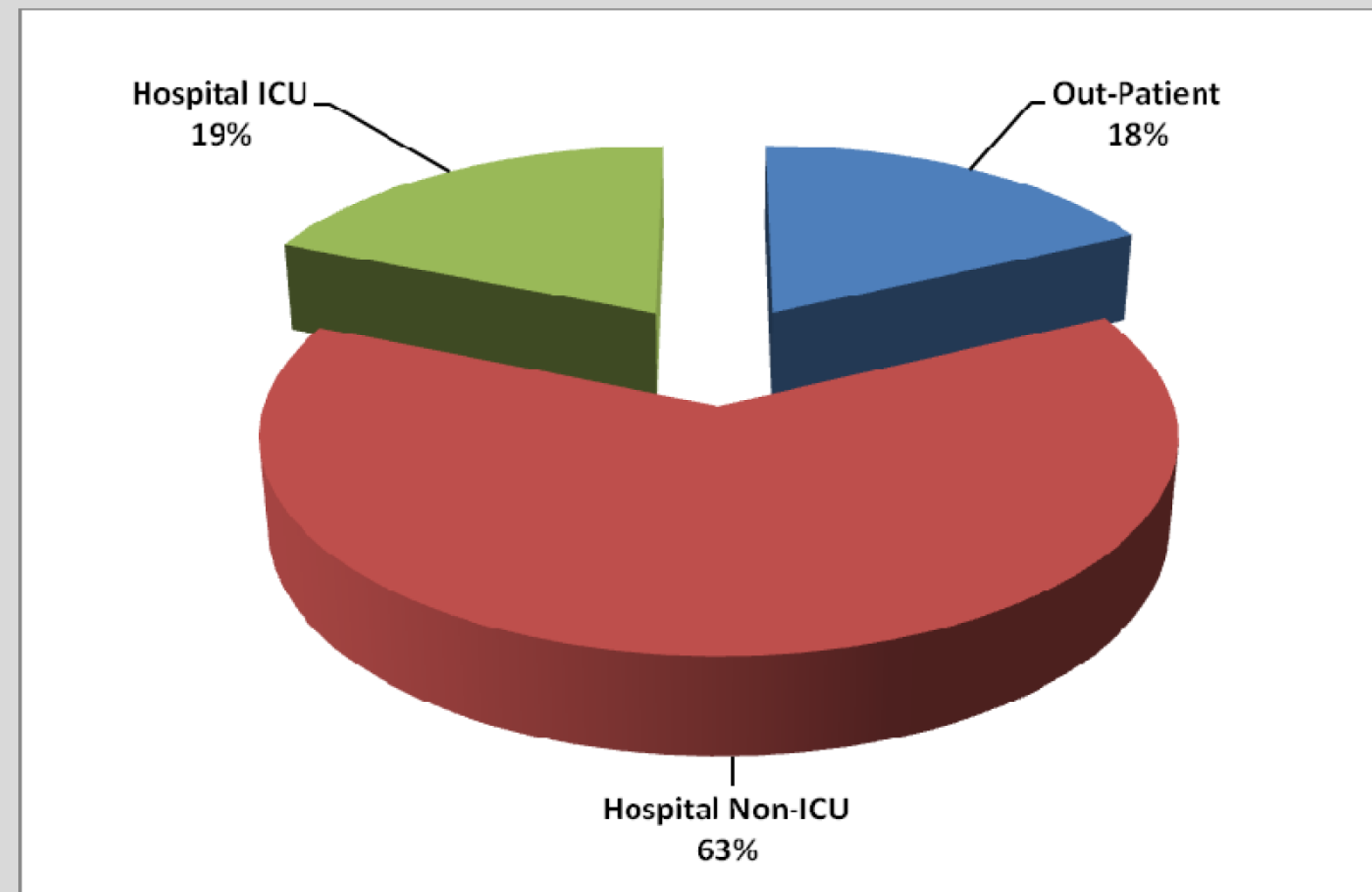


Table 1. *In vitro* activity of tigecycline and comparative agents against *S. aureus* with elevated vancomycin MICs (≥ 2 mcg/ml).

Drug	N	%Sus ^a	%Int	%Res	MIC (mcg/mL)	
					MIC ₅₀	MIC ₉₀
<i>S. aureus</i> MRSA						
Amox-Clav	343	0	0	100	>8	>8
Ceftriaxone	343	0	0	100	>64	>64
Imipenem ^b	122	0	0	100	16	>16
Levofloxacin	343	12.2	0.9	87	16	>32
Linezolid	343	100	0	0	2	4
Meropenem ^b	221	0	0	100	8	>16
Minocycline	343	90.1	7.3	2.6	≤ 0.25	4
Pip-Tazo	343	0	0	100	>16	>16
Tigecycline	343	100	0	0	0.25	0.5
Vancomycin	343	98.3	1.7	0	2	2
<i>S. aureus</i> MSSA						
Amox-Clav	288	99.6	0	0.4	1	2
Ceftriaxone	288	95.8	3.2	1	4	8
Imipenem ^b	81	100	0	0	0.25	0.5
Levofloxacin	288	92.0	4.2	3.8	0.25	1
Linezolid	288	100	0	0	2	4
Meropenem ^b	207	97.6	2.4	0	≤ 0.12	1
Minocycline	288	98.6	1	0.4	≤ 0.25	1
Pip-Tazo	288	99.6	0	0.4	1	4
Tigecycline	288	100	0	0	0.12	0.25
Vancomycin	288	98.3	1.7	0	2	2

^a Breakpoints defined in CLSI document M100-S19, where available. Tigecycline breakpoints defined by FDA (Tygacil®). 2005).
^b Meropenem was substituted for imipenem in 2006.

Conclusions

- 3.7% of over 17,000 *S. aureus* isolates in this study were seen to have MICs to vancomycin that were ≥ 2 mcg/ml. Tigecycline and linezolid retained 100% *in vitro* susceptibility at their respective breakpoints against all *S. aureus* with elevated MICs against vancomycin. All other comparator susceptibilities followed in accordance with the methicillin phenotype presented.
- Regional heteroresistance to vancomycin was seen more frequently in Europe (44%) and North America (30%) followed to lesser degrees in Latin America (14%), Asia (6%), South Pacific (3%), the Middle East (1%) and Africa (0.8%).
- The largest percentage (63%) of isolates with elevated MICs to vancomycin was seen in hospital-associated, non-intensive care areas such as general medical, pediatric and surgery wards.
- Tigecycline, linezolid and vancomycin remain potent antimicrobial agents against *S. aureus* but surveillance of vancomycin MIC “creep” should be further monitored through ongoing surveillance programs.