

Susceptibility of multi-drug resistant *Staphylococcus aureus*: A global perspective from the TEST program 2006-2010

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Revised Abstract

Objectives: Therapeutic options for multi-drug resistant (MDR) methicillin-resistant *S. aureus* (MRSA) are limited. Linezolid is often used for serious infections by gram-positive bacteria resistant to several antibiotics. This report focuses on *in vitro* susceptibility trends of MDR MRSA to linezolid and comparators using data from the Tigecycline Evaluation and Surveillance Trial (TEST). **Methods:** From 2006-2010, 186 MDR MRSA resistant to agents in ≥ 2 tested drug classes (quinolones, tetracyclines, and/or glycolcyclines) in addition to the β -lactams, were collected in 31 countries from various infection sources. MICs were performed at each site per CLSI guidelines using commercially-prepared microbroth panels. Results were interpreted according to CLSI breakpoints (FDA breakpoints for tigecycline). Susceptibility trends over time were assessed by the Cochran-Armitage test and MIC trends by Spearman's correlation. **Results:** Of 7,258 MRSA, 186 isolates (2.6%) were MDR (0.8% in 2006, 1.1% in 2007, 3.4% in 2008, 4.7% in 2009, and 6.1% in 2010; p for trend $<.0001$). The % susceptible, geometric mean (GM) MIC, and p values for MIC trends for linezolid and selected comparators are shown below for 186 MDR MRSA.

	% Susceptible / GM MIC					MIC trend p
	2006	2007	2008	2009	2010	
Linezolid	100/2.0	100/1.4	100/1.8	100/1.8	100/1.6	0.30
Levofloxacin	0/12.7	0/11.1	0/17.2	0/15.4	0/28.1	0.007
Minocycline	8.3/12.0	0/16.0	0/16.0	3.8/14.2	0/16.0	0.30
Tigecycline	83.3/0.37	100/0.32	100/0.31	96.2/0.35	100/0.26	0.43
Vancomycin	100/1.0	100/1.0	98.2/1.0	98.7/1.1	100/0.96	0.20
n	12	23	56	79	16	

Conclusions: MDR MRSA have been increasing significantly since 2006. Linezolid was the only agent to which 100% of isolates remained susceptible, but tigecycline and vancomycin also maintained excellent *in vitro* activity. Only levofloxacin showed a statistically significant trend of increasing MICs between 2006 and 2010.

Introduction

Methicillin-resistant *S. aureus* (MRSA) account for a large proportion of serious *S. aureus* infections. 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 and MIC "creep" [1]. Even newer agents such as daptomycin have been associated with treatment failures, and (although extremely rare) linezolid resistance has been identified among MRSA. Continued monitoring of existing antimicrobials and development of additional agents is needed to combat this serious pathogen, especially its multi-drug resistant phenotypes.

This study was undertaken to assess *in vitro* activity trends of linezolid and four comparative antimicrobials against multi-drug resistant MRSA from a large diverse population including 31 countries world-wide. This study is part of the larger global Tigecycline Evaluation and Surveillance Trial (TEST) program that has been ongoing since 2004.

Materials & Methods

- ❖ Isolates were derived from blood (28%), respiratory tract (30%), wounds (16%), and various other infection sources. Only one isolate per patient was accepted into the study. Clinical isolates were collected between 2006 and 2010 from 68 medical centers in 31 countries. Isolates were identified to the species level and tested at each site by the participating laboratory. In this report, multi-drug resistance was defined as resistance to agents in two or more tested drug classes (quinolones, tetracyclines, glycolcyclines) in addition to the β -lactams.
- ❖ 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 [2]. Tigecycline was supplied by Pfizer, Inc. (Collegeville, PA, USA). All other agents were supplied by the panel manufacturers MicroScan (Siemens Medical Solutions Diagnostics, West Sacramento, CA, USA) and TREK (TREK Diagnostic Systems, Cleveland, OH).
- ❖ Quality control (QC) of broth microdilution panels followed manufacturers' and CLSI guidelines using *S. aureus* ATCC 29213 and *E. faecalis* ATCC 29212. Results were included in the analysis only when corresponding QC isolates tested within the acceptable range according to CLSI guidelines [3].
- ❖ MIC interpretive criteria followed published breakpoints defined by CLSI [3] and the United States Food and Drug Administration (FDA) package insert for tigecycline [4].
- ❖ MIC trends over time were assessed by Spearman's correlation, while the Cochran-Armitage test for trend was used to assess linear trends in percent MDR MRSA over time. A two-tailed p -value $<.05$ was considered statistically significant. Confidence intervals were calculated using the adjusted Wald method.

References

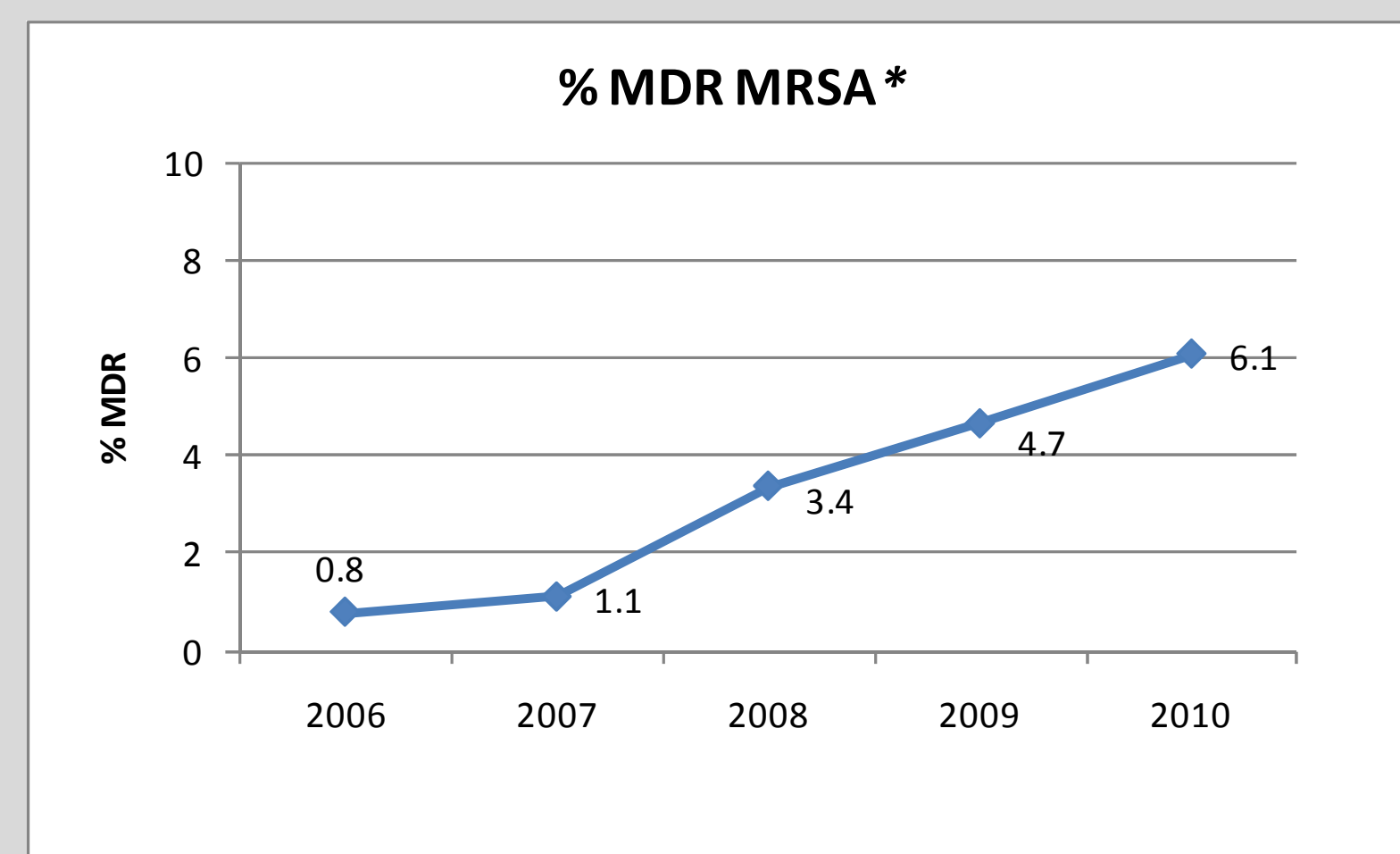
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Acknowledgements

We gratefully acknowledge the contributions of the investigators, laboratory personnel, and all members of the Tigecycline Evaluation Surveillance Trial program group. This study was sponsored by Pfizer Inc.

Results

Figure 1. Proportion of 7,258 methicillin-resistant *S. aureus* isolates that were multi-drug resistant¹ by year, 2006-2010.



¹ Multi-drug resistance in MRSA was defined in this report as resistance to agents in two or more tested drug classes (quinolones, tetracyclines, glycolcyclines) in addition to the β -lactams.

* p for trend $<.0001$. Note that the maximum on the y-axis is 10%.

Table 1. Proportion of 7,258 MRSA isolates that were multi-drug resistant¹ by region, 2006-2010.

	MRSA n	MDR MRSA n	MDR MRSA % (95% CI)
Africa	73	4	5.5 (1.7-13.7)
Asia	606	102	16.8 (14.1-20.0)
Europe	1974	41	2.1 (1.5-2.8)
Latin America	1268	10	0.8 (0.4-1.5)
Middle East	219	13	5.9 (3.4-10.0)
North America	2995	15	0.5 (0.3-0.8)
South Pacific	123	1	0.8 (0-4.9)

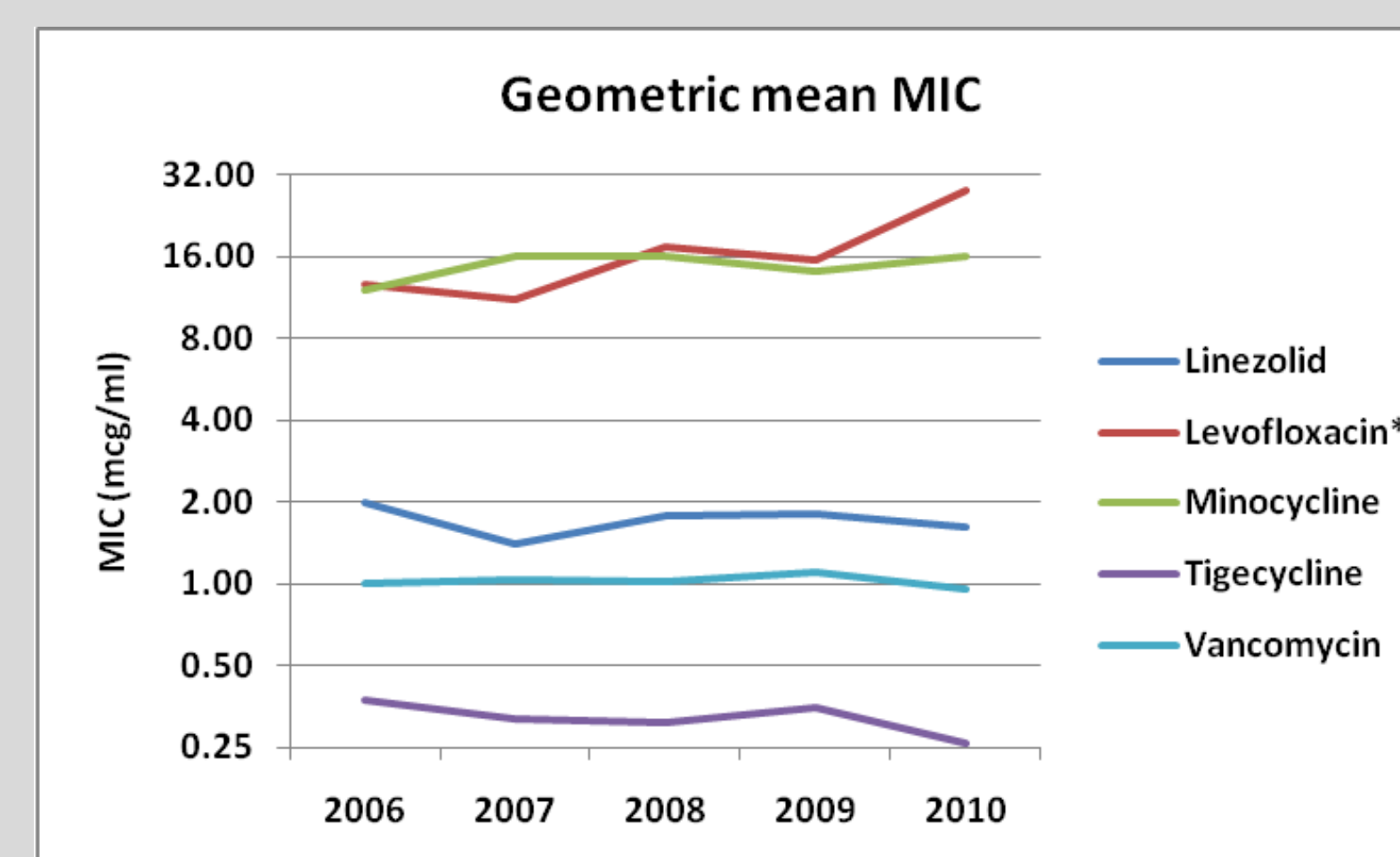
¹ Multi-drug resistance in MRSA was defined in this report as resistance to agents in two or more tested drug classes (quinolones, tetracyclines, glycolcyclines) in addition to the β -lactams.
CI: confidence interval

Table 2. *In vitro* activity of linezolid and comparators against 186 MDR MRSA¹, 2006-2010.

	MIC _{50/90} (mcg/ml)					%Susceptible				
	2006	2007	2008	2009	2010	2006	2007	2008	2009	2010
Linezolid	2/4	1/2	2/2	2/4	2/2	100	100	100	100	100
Levofloxacin	8/32	8/>32	16/>32	16/>32	32/>32	0	0	0	0	0
Minocycline	>8/>8	>8/>8	>8/>8	>8/>8	>8/>8	8.3	0	0	3.8	0
Tigecycline	0.25/1	0.5/0.5	0.25/0.5	0.5/0.5	0.25/0.5	83.3	100	100	96.2	100
Vancomycin	1/1	1/2	1/1	1/2	1/2	100	100	98.2	98.7	100
n	12	23	56	79	16	12	23	56	79	16

¹ MDR MRSA were defined in this report as resistant to agents in two or more tested drug classes (quinolones, tetracyclines, glycolcyclines) in addition to the β -lactams.

Figure 2: Geometric mean MIC (mcg/ml) for linezolid and comparators against 186 MDR MRSA¹, 2006-2010.



¹ MDR MRSA were defined in this report as resistant to agents in two or more tested drug classes (quinolones, tetracyclines, glycolcyclines) in addition to the β -lactams.
* p for trend $<.05$

Conclusions

- ❖ Although the proportion of MRSA that are multi-drug resistant is still low (6.1% in 2010), MDR MRSA have been increasing significantly since 2006 ($p<.0001$).
- ❖ Region-specific proportions of MDR MRSA ranged between 0.5% of all MRSA in North America and 16.8% in Asia.
- ❖ Linezolid was the only agent to which 100% of MDR MRSA isolates remained susceptible over the entire study period, but tigecycline and vancomycin also maintained excellent *in vitro* activity with more than 96% and 98% of strains, respectively, susceptible in 2009 and 100% susceptible in 2010. The two isolates non-susceptible to vancomycin were vancomycin intermediate *S. aureus* (VISA) strains.
- ❖ For linezolid, tigecycline, and vancomycin, no evidence of MIC "creep" was found in this study sample ($p>.05$). Only levofloxacin showed a statistically significant trend of increasing MICs between 2006 and 2010.