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Susceptibility of *S. aureus* from Inpatient vs. Outpatient Settings - a Global Analysis 2009/2010

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Revised Abstract

Objective: *Staphylococcus aureus* is a common cause of nosocomial and community–acquired infections. Strains isolated from inpatients usually exhibit higher resistance than community-acquired strains. In this study, data from the Tigecycline Evaluation and Surveillance Trial (TEST) were used to compare the *in vitro* activity of several antimicrobial agents against methicillin-susceptible *S. aureus* (MSSA) and methicillin-resistant *S. aureus* (MRSA) from inpatient and outpatient settings. **Methods:** In 2009 and 2010, 5,220 *S. aureus* isolates from multiple specimen sources were collected in 47 countries. MICs were performed at each site following CLSI guidelines using commercially-prepared broth microdilution panels. Results were interpreted according to CLSI breakpoints (FDA breakpoints for tigecycline). % susceptible differences between inpatients and outpatients were tested using the Fisher exact test, while geometric mean MICs were compared by the non-parametric Wilcoxon rank sum test. **Results**: 2,805 and 674 MSSA and 1,435 and 306 MRSA from inpatients and outpatients, respectively, were collected. The following table shows the MIC_{50}, geometric mean (GM) MIC, and % susceptible for several antimicrobials, as well as p-values comparing isolates from inpatient and outpatient settings.

Drug	MIC_{50}		GM MIC			%Susceptible		
	Inpatient	Outpatient	Inpatient	Outpatient	p-value*	Inpatient	Outpatient	p-value[1]
MSSA								
Amox-Clav	0.5	0.5	0.60	0.61	0.37	99.9	100	1
Levofloxacin	0.25	0.25	0.28	0.26	**0.009**	92.5	92.9	0.81
Linezolid	2	2	1.90	1.96	0.31	100	100	1
Meropenem	≤ 0.12	≤ 0.12	0.15	0.15	0.82	99.9	100	1
Minocycline	≤ 0.25	≤ 0.25	0.33	0.34	0.25	98.3	98.2	0.87
Tigecycline	0.12	0.12	0.16	0.16	0.08	100	100	1
Vancomycin	1	1	0.86	0.81	**<0.0001**	99.8	99.7	0.69
MRSA								
Amox-Clav	> 8	8	11.1	9.37	**<0.0001**	0[2]	0[2]	1
Levofloxacin	16	8	9.88	5.05	**<0.0001**	13.0	24.8	**< 0.0001**
Linezolid	2	2	1.74	1.85	**0.048**	100	100	1
Meropenem	16	4	7.41	3.71	**<0.0001**	0[2]	0[2]	1
Minocycline	≤ 0.25	≤ 0.25	0.60	0.46	**0.012**	84.9	91.5	**0.002**
Tigecycline	0.25	0.12	0.19	0.18	0.08	99.9	99.7	0.32
Vancomycin	1	1	0.88	0.86	0.48	99.7	100	1

[1] Boldface indicates statistical significance (p<0.05).
[2] Based on susceptibility to oxacillin.

Conclusions: In 2009/2010, amoxicillin-clavulanic acid, levofloxacin, meropenem, and minocycline exhibited significantly higher MICs (p<0.05) in inpatient isolates than in outpatient specimens, while linezolid demonstrated marginally higher MICs in outpatients. Examining the GM MIC and testing for significant differences is often more sensitive for detecting changes in *in vitro* activity than examining the $MIC_{50/90}$ or than testing differences in % susceptible (e.g., levofloxacin vs MSSA). Linezolid, tigecycline, and vancomycin remained almost universally active against both MSSA and MRSA. Tigecycline was the only agent that demonstrated no significant differences in GM MIC or % susceptible between inpatient and outpatient isolates.

Introduction

Staphylococcus aureus is a common cause of nosocomial and community–acquired infections. Strains isolated from inpatients usually exhibit higher resistance than community-acquired strains. In this study, data from the Tigecycline Evaluation and Surveillance Trial (TEST) were used to compare the *in vitro* activity of several antimicrobial agents against methicillin-susceptible *S. aureus* (MSSA) and methicillin-resistant *S. aureus* (MRSA) from global inpatient and outpatient settings.

Materials & Methods

- Isolates were derived from blood, respiratory tract, skin and skin structures, bodily fluids, and various other infection sources. Only one isolate per patient was accepted into the study. 2,805 and 674 MSSA as well as 1,435 and 306 MRSA from inpatients and outpatients, respectively, were collected in 2009 and 2010 from 217 medical centers in 47 countries. 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 [1]. 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 [2].
- MIC interpretive criteria followed published breakpoints defined by CLSI [2] and the United States Food and Drug Administration (FDA) package insert for tigecycline [3].
- Confidence intervals were calculated using the adjusted Wald method. Differences in percent susceptible between inpatients and outpatients were tested using the Fisher exact test, while geometric mean MICs were compared by the non-parametric Wilcoxon rank sum test. A two-tailed p-value <0.05 was considered statistically significant.

References

1. Clinical Laboratory Standards Institute. 2009. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standards -- Eighth Edition. CLSI document M07-A8. Wayne, PA.
2. Clinical and Laboratory Standards Institute. 2011. Performance Standards for Antimicrobial Susceptibility Testing; Twenty-First Informational Supplement. CLSI Document M100-S21. Wayne, PA.
3. Tygacil®, 2010. Tigecycline FDA prescribing information. Pfizer, Inc., Collegeville, PA.

Acknowledgements

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

Results

Figure 1. Distribution of 4,240 inpatient *S. aureus* isolates across infection sources, 2009-2010.

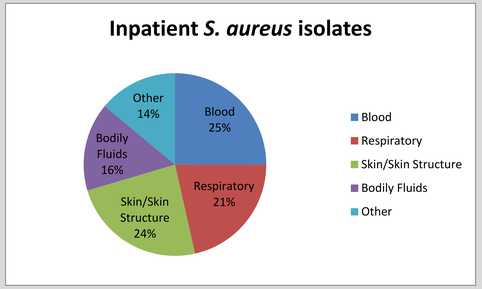


Figure 2. Distribution of 980 outpatient *S. aureus* isolates across infection sources, 2009-2010.

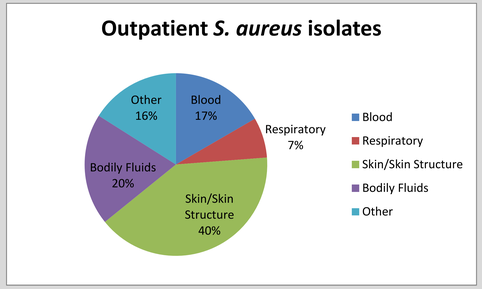
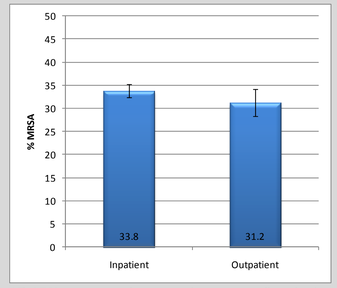


Figure 3. Percentage (with 95% confidence interval) of inpatient and outpatient *S. aureus* isolates that were MRSA, 2009-2010.[1]



[1] The MRSA rate in inpatient and outpatient samples was not statistically significantly different (p=0.13).

Table 1. *In vitro* activity of several agents against 5,220 *S. aureus* isolates from inpatient and outpatient settings, 2009-2010.

Organism (n inpat./outpat.)	Drug	MIC_{50} (mg/L)		MIC_{90} (mg/L)		GM MIC (mg/L)		
		Inpatient	Outpatient	Inpatient	Outpatient	Inpatient	Outpatient	p-value[1]
S. aureus (4,240/980)	Amox-Clav	1	1	> 8	> 8	1.61	1.44	**<0.0001**
	Levofloxacin	0.25	0.25	32	16	0.93	0.66	**<0.0001**
	Linezolid	2	2	4	4	1.85	1.92	**0.002**
	Meropenem	≤ 0.12	≤ 0.12	> 16	8	0.55	0.40	**<0.0001**
	Minocycline	≤ 0.25	≤ 0.25	1	1	0.40	0.37	0.27
	Tigecycline	0.12	0.12	0.5	0.5	0.17	0.17	0.74
	Vancomycin	1	1	1	1	0.86	0.83	**<0.0001**
MSSA (2,805/674)	Amox-Clav	0.5	0.5	1	1	0.60	0.61	0.37
	Levofloxacin	0.25	0.25	1	1	0.28	0.26	**0.009**
	Linezolid	2	2	4	4	1.90	1.96	0.31
	Meropenem	≤ 0.12	≤ 0.12	0.25	0.25	0.15	0.15	0.82
	Minocycline	≤ 0.25	≤ 0.25	0.5	0.5	0.33	0.34	0.25
	Tigecycline	0.12	0.12	0.25	0.5	0.16	0.16	0.08
	Vancomycin	1	1	1	1	0.86	0.81	**<0.0001**
MRSA (1,435/306)	Amox-Clav	> 8	8	> 8	> 8	11.1	9.37	**<0.0001**
	Levofloxacin	16	8	> 32	> 32	9.88	5.05	**<0.0001**
	Linezolid	2	2	2	2	1.74	1.85	**0.048**
	Meropenem	16	4	> 16	> 16	7.41	3.71	**<0.0001**
	Minocycline	≤ 0.25	≤ 0.25	8	4	0.60	0.46	**0.012**
	Tigecycline	0.25	0.12	0.5	0.5	0.19	0.18	0.08
	Vancomycin	1	1	1	1	0.88	0.86	0.48

[1] p-value comparing GM MIC between inpatient and outpatient isolates. Boldface indicates a statistically significant difference (p<0.05).

Table 2. Susceptibility of 5,220 *S. aureus* isolates from inpatient and outpatient settings, 2009-2010.

Organism (n inpat./outpat.)	Drug	%Susceptible		
		Inpatient	Outpatient	p-value[1]
S. aureus (4,240/980)	Amox-Clav	66.1	68.8	0.11
	Levofloxacin	65.6	71.6	**0.0003**
	Linezolid	100	100	1
	Meropenem	66.1	68.8	0.11
	Minocycline	93.8	96.1	**0.004**
	Tigecycline	100	99.9	0.34
	Vancomycin	99.7	99.8	1
MSSA (2,805/674)	Amox-Clav	99.9	100	1
	Levofloxacin	92.5	92.9	0.81
	Linezolid	100	100	1
	Meropenem	99.9	100	1
	Minocycline	98.3	98.2	0.87
	Tigecycline	100	100	1
	Vancomycin	99.8	99.7	0.69
MRSA (1,435/306)	Amox-Clav	0[2]	0[2]	1
	Levofloxacin	13.0	24.8	**< 0.0001**
	Linezolid	100	100	1
	Meropenem	0[2]	0[2]	1
	Minocycline	84.9	91.5	**0.002**
	Tigecycline	99.9	99.7	0.32
	Vancomycin	99.7	100	1

[1] p-value comparing % susceptible between inpatient and outpatient isolates. Boldface indicates statistically significant difference (p<0.05).
[2] Based on susceptibility to oxacillin.

Conclusions

- In 2009/2010, the MRSA rate of 33.8% and 31.2% in inpatients and outpatients, respectively, was not statistically significantly different between the two samples (p<0.05).
- However, there were differences in *in vitro* activity for isolates from inpatient and outpatient settings: As expected, amoxicillin-clavulanic acid, levofloxacin, meropenem, and minocycline exhibited significantly higher MICs (p<0.05) in inpatient than in outpatient isolates, mostly for *S. aureus* overall and MRSA. Linezolid, on the other hand, showed slightly higher MICs in outpatients for *S. aureus* overall and MRSA (p<0.05).
- Examining the GM MIC and testing for significant differences in the distribution of MICs is often more sensitive for detecting differences in *in vitro* activity than examining the $MIC_{50/90}$ value or testing for significant differences in the % susceptible (e.g., levofloxacin vs MSSA). However, especially if the sample sizes are large, statistically significant changes in MICs may not equate to clinically significant differences.
- Linezolid, tigecycline, and vancomycin remained almost universally active against both MSSA and MRSA.
- Tigecycline was the only agent that demonstrated no significant differences in GM MIC or % susceptible between isolates from inpatient and outpatient settings.