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Analysis of Resistance and Vancomycin "Reverse Creep" in Latin American *Staphylococcus aureus*: Ten-year Report of the SENTRY Antimicrobial Surveillance Program (1997-2006)

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AMENDED ABSTRACT

Objectives: To evaluate the antimicrobial susceptibility (S) rates of *S. aureus*, including methicillin-resistant (MRSA) strains, collected in Latin American medical centers as part of the SENTRY Antimicrobial Surveillance Program. The MRSA Brazilian clone is highly prevalent in the region and usually shows high rates of antimicrobial resistance.

Methods: 8705 *S. aureus* referred from 7 Latin American countries during a 10-year period (1997-2006) were S tested to 13 antimicrobials by CLSI broth microdilution methods. The frequencies of *S. aureus* with vancomycin MIC values ≥1 mg/L collected by 7 of 10 medical centers that participated in the program since 1999 were analyzed by comparing two time periods, 1999-2002 and 2003-2006.

Results: Overall, 37.4% of strains were MRSA. Brazil contributed with the majority of *S. aureus* (4147/47.6%) and MRSA (1443/44.3%) strains. S rates are shown in the table. MRSA rates increased from 33.8% in 1997 to 40.2% in 2006 (p=0.007). S rates for many non-beta-lactam agents increased among MRSA as follows (1997/2006): clindamycin (13.2/16.3%), erythromycin (3.9/8.6%), gentamicin (7.8/27.3%), tetracycline (29.9/79.5%), co-trimoxazole (30.9/67.0%). Chloramphenicol and rifampin S rates increased from 25.5% and 48.5% in 1997 to 65.6% and 60.7% in 2005, respectively. All increases in S rates among MRSA were statistically significant ($p<0.05$), except for clindamycin. Interestingly, the percentage of *S. aureus*/MRSA with vancomycin MIC ≥1 mg/L decreased from 94.0/96.6% in 1999-2001 to 86.8/92.3% in 2002-2006 ($p=0.00001$).

Conclusions: The increase in the MRSA rates coupled with increased S rates to non-ß-lactam agents and decrease in the frequencies of strains with vancomycin MIC ≥1 mg/L ("reverse creep") may indicate the emergence and dissemination of new MRSA clones, distinct from the Brazilian clone, in the Latin American countries surveyed by the SENTRY Program, especially in Brazil.

INTRODUCTION

Staphylococcus aureus is a common cause of both community-acquired and hospital-acquired infections, and has become progressively more difficult to treat because of the development of antibiotic resistance. Vancomycin has been the cornerstone of therapy for serious methicillin-resistant *S. aureus* (MRSA) infections since the early 1980s, when MRSA emerged as a significant nosocomial pathogen. While studies have shown that patients with MRSA infection have an increased mortality risk compared with patients with MSSA infection, most studies have also shown that MRSA infections occur in sicker patients than do infections due to MSSA, suggesting that differences may be due to underlying illnesses.

Recently, Shurland et al. reported that patients with MRSA infections other than pneumonia have an increased mortality risk, compared with patients with similar MSSA infections, independent of the patients' underlying illnesses. These authors suggested that this difference in mortality risk might be the result of treatment factors, including the use of vancomycin.

Additionally, it has been shown that vancomycin treatment failure in MRSA bacteremia is not uncommon, and mortality associated with MRSA bacteremia is significantly higher when vancomycin MIC is >1 mg/L compared to ≤0.5 mg/L.

The main objective of this study was to evaluate the antimicrobial susceptibility rates of *S. aureus*, including MRSA strains, collected in Latin American medical centers as part of the SENTRY Antimicrobial Surveillance Program (1997-2006). The frequencies of *S. aureus* with vancomycin MIC values ≥1 mg/L were also studied.

MATERIALS AND METHODS

Bacterial strains: *S. aureus* strains isolated from diverse body sites of infections were submitted from Latin American medical center participants of the SENTRY Program between January 2001 and December 2006. All isolates were identified at the participating institution by routine methodologies in use at each laboratory. Upon receipt at the central monitor (JMI Laboratories, North Liberty, IA, USA), isolates were subcultured to ensure viability and purity. Confirmation of species identification was performed with the Vitek system (bioMérieux Vitek, St Louis, MO) or conventional methods, as required.

Medical centers: The participant medical centers included thirteen cities in seven countries: São Paulo (1997-2006), Brasília (1999-2006), Florianópolis (1997-2006) and Porto Alegre (1999-2006) in Brazil; Bueno Aires and San Isidro in Argentina (1997-2006); Santiago in Chile (two sites, 1997-2006); Montevideo in Uruguay (1997); Medelin in Colombia (1997-2006); Mexico City (three sites, 1997-2001), Guadalajara (2004-2006), and Durango (2005-2006) in Mexico; and Caracas in Venezuela (1998-2004).

Susceptibility testing: Antimicrobial susceptibility testing was performed by the broth microdilution method, following the recommendations of the Clinical and Laboratory Standards Institute (CLSI, 2007). Antimicrobial powders were obtained from the respective manufacturers and microdilution plates were prepared by TREK Diagnostics (Cleveland, OH, USA). Susceptibility results were interpreted according to CLSI document M100-S18 (2008) for all comparison agents. Quality control was performed by testing *Escherichia coli* ATCC 25922 and *Staphylococcus aureus* ATCC 29213.

Statistical analysis: Statistical analysis was carried out with Epi-Info version 6.04b software package (Centers for Disease Control and Prevention, Atlanta, GA, US). Antimicrobial resistance trends were determined by χ^2 test; p values < 0.05 were considered to be statistically significant.

RESULTS

- A total of 8,705 *S. aureus* were collected in Latin American medical centers as part of the SENTRY Program between January 2001 and December 2006. The largest number of *S. aureus* isolates were collected in Brazil (47.6%), followed by Chile (22.1%) and Argentina (17.7%), as shown in Table 1.
- Bloodstream (45.7%) was the most common body site of infection, followed by skin and soft tissue (20.9%) and the lower respiratory tract (17.8%).
- Overall, the oxacillin resistance rate was 37.4% and was higher among *S. aureus* isolates collected from the respiratory tract (54.4%) compared to those isolated from other body sites of infection.
- The highest oxacillin resistance rates were observed among *S. aureus* isolates collected from Chilean (44.2%) and Argentinean (44.1%) medical centers, followed by Mexican (35.0%) and Brazilian (34.8%) sites.

Table 1. Distribution of *Staphylococcus aureus* isolates collected in the Latin American region according to body site of infection and nation of isolation (SENTRY Program, 1997-2006).

Nation	No. of *S. aureus* (% of MRSA) by site of infection					
	Bloodstream	Respiratory tract	Skin/soft tissues	Urine	Others	Total
Argentina	983 (43.6)	282 (54.6)	228 (38.6)	12 (8.3)	36 (19.4)	1541 (44.1)
Brazil	2409 (34.4)	767 (46.5)	800 (26.5)	28 (35.7)	143 (25.2)	4147 (34.8)
Chile	1071 (32.8)	405 (76.3)	399 (41.4)	13 (53.8)	40 (50.0)	1928 (44.2)
Colombia	136 (6.6)	15 (0.0)	58 (8.6)	4 (25.0)	0 (0.0)	213 (7.0)
Mexico	294 (35.4)	43 (39.5)	272 (33.5)	9 (88.9)	83 (30.1)	701 (35.0)
Uruguay	18 (5.6)	15 (40.0)	14 (21.4)	0 (0.0)	0 (0.0)	47 (21.3)
Venezuela	47 (12.8)	25 (8.0)	49 (0.0)	4 (0.0)	3 (33.3)	128 (7.0)
Total	3975 (32.7)	1552 (54.4)	1820 (31.0)	70 (38.6)	305 (29.2)	8705 (37.4)

Table 2. Activity of 13 antimicrobial agents against *Staphylococcus aureus* collected from the Latin American region (SENTRY Program, 1997-2006).

Antimicrobial Agents	*S. aureus* (705)			MRSA (253)			MSSA (452)		
	MIC_{50}[a]	MIC_{90}[a]	% Susc[b]	MIC_{50}[a]	MIC_{90}[a]	% Susc[b]	MIC_{50}[a]	MIC_{90}[a]	% Susc[b]
Ciprofloxacin	0.5	>4	63.4	>4	>4	8.3	0.25	0.5	96.2
Clindamycin	≤0.25	>8	66.0	>8	>8	12.4	0.12	0.25	98.0
Chloramphenicol	8	>16	72.6	16	>16	42.6	8	8	90.0
Erythromycin	0.5	>8	54.0	>8	>8	6.9	0.25	8	82.0
Gentamicin	≤2	>8	65.9	>8	>8	15.6	≤2	≤2	95.9
Linezolid	2	2	100.0	2	2	100.0	2	2	100.0
Mupirocin	≤4	≤4	85.3	≤4	≤4	94.3	≤4	≤8	98.0
Quinupristin/dalfopristin	0.25	0.5	99.9	0.5	1	99.8	0.25	0.5	99.9
Rifampin	≤0.25	2	79.0	2	>2	48.0	≤0.5	≤0.5	97.6
Teicoplanin	1	2	100.0	≤2	2	100.0	1	≤2	100.0
Tetracycline	≤4	>8	77.2	≤4	>8	57.4	≤4	>8	88.9
Trimethoprim/sulfamethoxazole	≤0.5	>2	86.2	>1	>2	65.1	≤0.5	≤0.5	98.8
Vancomycin	1	1	100.0	1	1	100.0	1	1	100.0

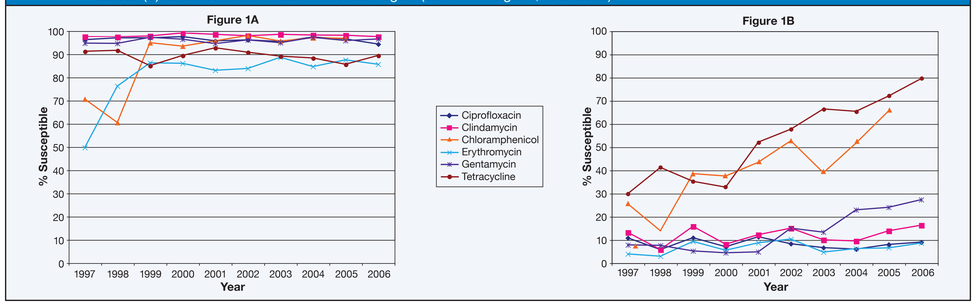
a. MIC values in mg/L determined by broth microdilution according CLSI guidelines (2006).
b. Interpretative CLSI breakpoint criteria (2008) were applied.

Table 3. Percentage of *S. aureus* isolates with vancomycin MIC values, ≥1 mg/L, according to body site of infection and nation of isolation, during the periods 1999-2002 and 2003-2006 (SENTRY Program, 1999-2006).

Nation / site of infection	Period	Percentage (no. of isolates) with vancomycin MIC values of ≥1 mg/L		
		S. aureus	MRSA[a]	MSSA[a]
Argentina	1999-2002	94.5% (584)	98.0% (247)	92.0% (337)
	2003-2006	88.8% (668)	93.1% (317)	84.9% (351)
Brazil	1999-2002	94.1% (1331)	95.0% (498)	93.6% (833)
	2003-2006	86.1% (1536)	88.7% (476)	85.0% (1060)
Chile	1999-2002	93.4% (667)	98.5% (264)	90.1% (403)
	2003-2006	86.4% (950)	96.0% (421)	78.8% (529)
Bloodstream	1999-2002	94.1% (1556)	96.9% (524)	92.6% (1032)
	2003-2006	85.7% (1851)	92.9% (662)	81.7% (1189)
Respiratory tract	1999-2002	95.1% (599)	96.4% (366)	93.6% (233)
	2003-2006	89.1% (485)	90.8% (273)	86.8% (212)
Skin/soft tissue	1999-2002	91.8% (403)	95.6% (113)	90.3% (290)
	2003-3006	87.6% (615)	92.7% (218)	84.9% (397)
Overall	1999-2002	94.0% (2582)	96.6% (1009)	92.4% (1573)
	2003-3006	86.8% (2154)	92.3 % (1214)	83.3% (1940)

a. MRSA, methicillin-resistant *S. aureus*; MSSA, methicillin-susceptible *S. aureus*.

Figure 1. Temporal evolution of susceptibility rates for non ß-lactam agents among methicillin-susceptible *S. aureus* (A) and methicillin-resistant *S. aureus* (B) collected from the Latin American region (SENTRY Program, 1997-2006).



- As expected, vancomycin (MIC_{90}, 1 mg/L), teicoplanin (MIC_{90}, 2 mg/L) and linezolid (MIC_{90}, 2 mg/L) exhibited complete activity (100.0% susceptible) against *S. aureus* regardless of the oxacillin resistance phenotype (Table 2).
- A significant increase in chloramphenicol susceptibility rates was noticed among both MSSA and MRSA during the study period. Susceptibility rates to erythromycin and tetracycline also increased among MSSA and MRSA, respectively (Figure 1).
- The percentage of *S. aureus* with vancomycin MIC values ≥1 mg/L decreased from 94.0% to 86.8% between the periods 1999-2002 and 2003-2006 ($p < 0.05$) as shown in Table 3, and was more pronounced among MSSA (92.4/83.3%; $p < 0.0005$) than among MRSA (96.6/92.3%; $p < 0.0005$) isolates. This was observed among *S. aureus* isolates collected from Argentinean, Brazilian and Chilean medical centers.

CONCLUSIONS

- The results of this study clearly showed a decrease in the frequencies of strains with vancomycin MIC values ≥1 mg/L ("reverse creep") in the Latin American medical centers surveyed by the SENTRY Program, especially those located in Brazil.
- The results of the study also showed a continued increase in the MRSA rates coupled with increased susceptibility rates to non-ß-lactam agents during the study period.
- These findings may indicate the emergence and dissemination of new MRSA clones, distinct from the Brazilian clone, in Latin American medical centers.

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