Activity of Mupirocin Tested against Staphylococci Isolated in Latin American medical Centers: Report from the SENTRY Antimicrobial Surveillance Program



H.S. SADER, S. ANDRADE-BAIOCCHI, A.C. GALES, R.N. JONES, the SENTRY Participants Group-Latin America Universidade Federal de São Paulo, Brazil; and The Jones Group / JMI Laboratories, North Liberty, IA, USA (www.jmilabs.com)

ABSTRACT

Background: Mupirocin (MUP) has become the topical agent of choice for the elimination of oxacillin-resistant *S. aureus* (ORSA) carriage. The increased use of this product has been followed by emerging resistance (R) at two levels with documented plasmid transmission.

Methods: 1,346 *S. aureus* and 498 coagulase-negative staphylococcal (CNS) strains isolated from patients hospitalized in 11 Latin American medical centers in 2000 and 2001 were tested against MUP by broth microdilution as part of the SENTRY Program. MUP-R breakpoint was established as > 8 g/mL.

Results: Oxacillin R was detected in 38.6% of *S. aureus* and in 78.1% of CNS. The rate of MUP R was low among S. aureus (97.3% susceptibility [S]), but significantly higher among ORSA (5.0%) when compared to oxacillin-susceptible S. aureus (OSSA 1.3%, p < 0.001). MUP-R *S. aureus* strains were detected in 9 of 11 centers (81.8%). MUP-R rate was very high among CNS (27.3%), and again, significantly higher among oxacillin-R strains (33.7% vs. 4.6%, p < 0.0001). The mupirocin resistance rates varied from 10.0% to 48.9% among CNS. The highest rates were detected in Venezuela (48.9%) and Mexico (41.7%).

Conclusions: MUP-R has emerged rapidly among OR-CNS and other staphylococcal populations in Latin American medical centers participating in the SENTRY Program. Epidemiologic investigations at the local level appear warranted to limit further dissemination.

INTRODUCTION

- > Staphylococcus aureus and coagulase-negative staphylococci (CNS) are among the most important pathogens that cause nosocomial infections worldwide. The incidence of oxacillin-resistance among these pathogens varies among different countries, hospitals, and, even, hospital wards within a hospital. Many other resistance genes have readily been acquired by oxacillin-resistant staphylococci, which, alarmingly, limits the choice of therapeutic options for the treatment of infections caused by these microorganisms.
- > Mupirocin is one of the few antimicrobial agents effective against oxacillin-resistant staphylococci. It has successfully been used to treat various staphylococcal skin infections or to eradicate intranasal oxacillin-resistant *S. aureus* colonization. The unique bactericidal action of mupirocin is dependent on its ability to inhibit the isoleucyl-tRNA synthetase.
- > The principal objective of this study was to evaluate the activity of mupirocin against staphylococci isolated from the Latin America region through the SENTRY Antimicrobial Surveillance Program.

MATERIAL AND METHODS

- > **Bacterial strains.** A total of 1,346 *S. aureus* and 498 CNS were collected from the Latin America region through the SENTRY Program between January 2000 to December 2001. All strains were isolated from diverse body sites of hospitalized patients. Only a single isolate per patient was evaluated. The isolates were identified to the species level by the participant medical center and sent to the coordinating laboratory for identification confirmation and reference susceptibility testing.
- > Medical centers. The participant medical centers included eleven cities in six countries: Brasília, Florianópolis, São Paulo, and Porto Alegre in Brazil; Buenos Aires and San Isidro in Argentina; Santiago in Chile; Medelin in Colombia (2000); Mexico City in Mexico; and Caracas in Venezuela.
- > Susceptibility testing. Antimicrobial susceptibility testing was performed using the reference broth microdilution method as described by the National Committee for Clinical Laboratory Standards (NCCLS). Isolates exhibiting mupirocin MICs > 8 g/ml were classified as resistant. Antimicrobial agents were obtained from the respective manufacturers and quality control was performed by testing *Escherichia coli* ATCC 25922, *Staphylococcus aureus* ATCC 29213, and *Enterococcus faecalis* ATCC 29212.

RESULTS

Table 1. Distribution of mupirocin-resistant isolates according to the oxacillin category of susceptibility among 1,843 staphylococcal isolates collected from Latin America (SENTRY Antimicrobial Surveillance Program, 2000/2001).

	S. au	ireus	SCN ^a		
	Oxacilin-S ^b (827)	Oxacilin-R° (519)	Oxacilin-S ^b (109)	Oxacilin-R° (389)	
Mupirocin-R ^d	11	26	5	131	
isolates (%)	(1.3)	(5.0)	(4.6)	(33.7)	

- a. CNS, coagulase-negative staphylococci; b. Susceptibility to oxacillin defined according to the NCCLS breakpoints: 2 g/ml for *S. aureus*, and 0.25 g/ml for CNS; c. Resistance to oxacillin defined according to the NCCLS breakpoints: 4 g/ml for *S. aureus*, and 0.5 g/ml for CNS; d. Isolates exhibiting mupirocin MICs > 8 g/ml were classified as resistant.
- Table 3. Antimicrobial activity of 14 antimicrobial agents against 1,346 *S. aureus* isolates categorized by oxacillin susceptibility pattern (SENTRY Antimicrobial Surveillance Program, 2000/2001).

Antimicrobial	Oxacillin-Susceptible (827) μg/ml				Oxacillin-Resistent (519) μg/ml		
Agent	MIC 50	MIC 90	% Susc. ^a	MIC 50	MIC 90	% Susc. ^a	
Mupirocin	≤ 8	< 8	98.7	4	8	95.0	
Chloramphenicol	8	8	94.6	> 16	> 16	39.5	
Ciprofloxacin	0.25	0.5	96.7	> 2	> 2	8.9	
Gatifloxacin	0.06	0.12	99.9	2	4	74.2	
Clindamycin	0.12	0.12	98.5	> 8	> 8	10.4	
Erythromycin	0.25	> 8	84.8	> 8	> 8	7.7	
Gentamicin	≤ 1	≤ 1	95.8	> 8	> 8	4.6	
Rifampin	≤ 0.25	≤ 0.25	96.9	> 2	> 2	40.8	
Tetracycline	4	4	90.6	> 8	> 8	43.5	
TMP/SMX ^b	≤ 0.5	≤ 0.5	96.6	> 1	> 8	38.7	
Linezolid	2	2	100.0	2	2	100.0	
Q/D ^c	0.25	0.5	100.0	0.5	0.5	100.0	
Teicoplanin	0.5	1	99.8	1	2	99.6	
Vancomycin	1	1	100.0	1	1	100.0	

a. Percentage of susceptibility interpreted using NCCLS breakpoints, except for TMP/SMX. Isolates exhibiting MICs > 0.5 g/ml for TMP/SMX were considered resistant to this association; b. TMP/SMX, trimethoprim/sulfamethoxazole; c. Q/D, quinupristin/dalfopristin.

Table 5. Antimicrobial activity of 13 antimicrobial agents against 37 mupirocin-resistant *S. aureus* isolates (SENTRY Antimicrobial Surveillance Program, 2000/2001).

Program, 2000	/2001).		
Antimicrobial	μ g /		
Agent	MIC 50	MIC 90	% Susc. ^a
Chloramphenicol	> 16	> 16	13.5
Ciprofloxacin	> 2	> 2	32.4
Gatifloxacin	2	4	81.1
Clindamycin	> 8	> 8	37.8
Erythromycin	> 8	> 8	27.0
Gentamicin	> 8	> 8	32.4
Rifampin	2	> 2	43.2
Tetracycline	> 8	> 8	48.6
TMP/SMX ^b	> 1	> 1	35.1
Linezolid	2	2	100.0
Q/D°	0.25	1	100.0
Teicoplanin	1	2	100.0
Vancomycin	1	1	100.0

a. Percentage of susceptibility interpreted using NCCLS breakpoints, except for TMP/SMX. Isolates exhibiting MICs > 0.5 g/ml for TMP/SMX were considered resistant to this association; b. TMP/SMX, trimethoprim/sulfamethoxazole; c. Q/D,

Table 6. Antimicrobial activity of 13 antimicrobial agents against 136 mupirocin-resistant coagulase-negative staphylococci isolates (SENTRY Antimicrobial Surveillance Program, 2000/2001).

Antimicrobial	μ g .		
Agent	MIC 50	MIC 90	% Susc.
Chloramphenicol	16	> 16	49.3
Ciprofloxacin	> 2	> 2	33.8
Gatifloxacin	1	2	95.6
Clindamycin	> 8	> 8	27.9
Erythromycin	> 8	> 8	8.8
Gentamicin	> 8	> 8	28.7
Rifampin	≤ 0.25	> 2	56.6
Tetracycline	≤ 4	> 8	83.1
TMP/SMX ^b	> 1	> 1	32.6
Linezolid	1	2	100.0
Q/D°	0.25	0.5	97.0
Teicoplanin	2	8	91.9
Vancomycin	2	2	100.0

a. Percentage of susceptibility interpreted using NCCLS breakpoints, except for TMP/SMX. Isolates exhibiting MICs > 0.5 g/ml for TMP/SMX were considered resistant to this association; b. TMP/SMX, trimethoprim/sulfamethoxazole; c. Q/D,

Table 2. Distribution of staphylococci collected according to the body site of infection (SENTRY Antimicrobial Surveillance Program, 2000/2001).

	S. a	ureus	Coagulase-negative staphylococci		
Sites of	No. of isolates tested (%)	No. of Mup-R ^a isolates (%)	No. of isolates tested (%)	No. of Mup-R ^a isolates (%)	
Infection	1346	37	498	136	
Blood	790 (58.7)	25 (3.2)	444 (89.2)	125 (28.2)	
Respiratory tract	376 (28.0)	11 (2.9)	23 (4.6)	2 (8.7)	
Skin and soft tissue	168 (12.5)	1 (0.6)	25 (5.0)	9 (36.0)	
Urine	12 (0.8)	0 (0.0)	6 (1.2)	0 (0.0)	

- a. Mup-R, mupirocin-resistant isolates (MICs > 8 g/ml). The percentage of mupirocin-resistant isolates was calculated using the total number of isolates collected by body site of infection as the denominator, respectively.
- Table 4. Antimicrobial activity of 14 antimicrobial agents against 498 Coagulase-negative staphylococci isolates categorized by oxacillin susceptibility pattern (SENTRY Antimicrobial Surveillance Program, 2000/2001).

Antimicrobial Agent	Oxacillin-Susceptible (109) μg/ml				Oxacillin-Resistent (389) μg/ml		
	MIC 50	MIC 90	% Susc. ^a	MIC 50	MIC 90	% Susc. ^a	
Mupirocin	≤ 8	≤ 8	95.4	≤ 8	8	66.3	
Chloramphenicol	4	8	95.4	8	> 16	59.9	
Ciprofloxacin	0.25	0.2	97.2	> 2	> 2	44.	
Gatifloxacin	0.12	0.12	99.1	1	4	92.8	
Clindamycin	0.06	0.12	92.7	> 8	> 8	43.2	
Erythromycin	0.25	> 8	67.2	> 8	> 8	20.	
Gentamicin	≤ 1	4	93.5	> 8	> 8	31.	
Rifampin	\leq 0.25	0.25	97.2	≤ 0.25	> 2	65.3	
Tetracycline	4	> 8	78.0	4	> 8	75.8	
TMP/SMX ^b	≤ 0.25	> 1	82.4	> 1	> 1	38.6	
Linezolid	2	2	100.0	1	2	100.0	
Q/D°	0.25	0.2	100.0	0.2	0.5	97.7	
Teicoplanin	2	8	95.4	2	2	90.0	
Vancomycin	1	2	100.0	2	2	100.0	

a. Percentage of susceptibility interpreted using NCCLS breakpoints, except for TMP/SMX. Isolates exhibiting MICs > 0.5 g/ml for TMP/SMX were considered resistant to this association; b. TMP/SMX, trimethoprim/sulfamethoxazole; c. Q/D, quinupristin/dalfopristin.

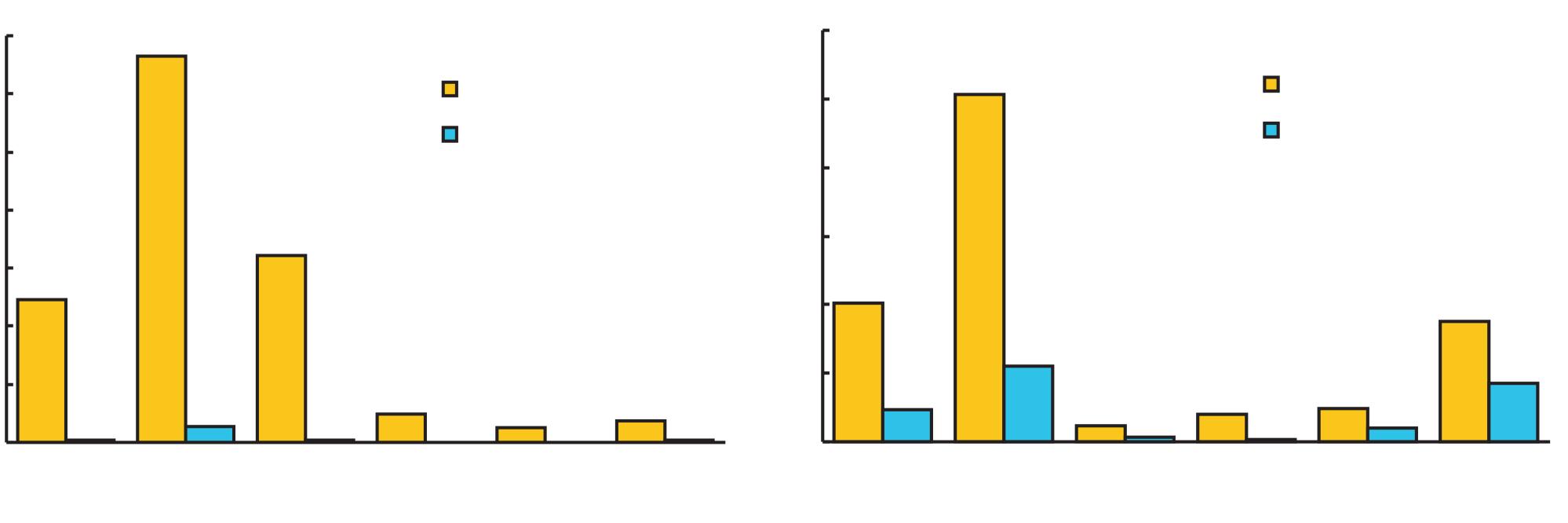


Figure 1. Distribution of mupirocin-resistant *S. Aureus* isolated according to the Latin American Nation (SENTRY Antimicrobial Surveillance Program, 2000/2001).

Figure 2. Distribution of mupirocin-resistant coagulase-negative staphylococci (CNS) isolated according to the Latin American Nation (SENTRY Antimicrobial Surveillance Program, 2000/2001).

COMMENTS

- ? Oxacillin resistance was detected in 38.6% of *S. aureus* and in 78.1% of CNS.
- ? Linezolid and vancomycin inhibited 100.0% of staphylococci tested.
- As expected, most of the antimicrobial agents were active against OSSA, while decreased susceptibility rates were observed among ORSA.
- High resistance rates to erythromycin, tetracycline, TMP/SMX and teicoplanin were observed even among oxacillin-susceptible SCN. Among oxacillin-resistant SCN, gatifloxacin (MIC₅₀, 1 g/ml; 92.8% susceptible) was more active than teicoplanin (MIC₅₀, 2 g/ml; 90.0% susceptible).
- The rate of mupirocin resistance was low among S. aureus (97.3% susceptibility), but significantly higher among ORSA (5.0%) when compared to OSSA (1.3%, p < 0.001).
- ? Mupirocin-resistant *S. aureus* strains were detected in 9 of 11 centers (81.8%).
- S. aureus was more frequently isolated from blood stream (58.7%) followed by respiratory tract (28.0%). However, mupirocin-resistant S. aureus strains were equally isolated from blood stream and respiratory tract (3.2% vs. 2.7%; p > 0.5).
- The mupirocin resistance rates varied from 0.0% to 7.9% among *S. aureus*. The highest rates were detected in Venezuela (7.9%) > Brazil (4.1%) > Chile (1.2%) and Argentina (1.2). No mupirocin-resistant isolates were detected among *S. aureus* collected from the Colombian and Mexican medical centers.
- ? Against mupirocin-resistant *S. Aureus*, gatifloxacin (81.1%) showed the highest susceptibility rate followed by the glycopeptides (100.0%), Q/D (100.0%), and linezolid (100.0%).
- The mupirocin resistance rate was very high among CNS (27.3%), and again, significantly higher among oxacillin-R strains (33.7% vs. 4.6%; p < 0.0001).
- The blood stream was also the most frequent body site of isolation of CNS. Although mupirocin-resistant CNS isolates were more often isolated from skin and soft tissue (36.0%) than from blood stream (28.2%), this difference was not statistically significant.
- ? The mupirocin resistance rates varied from 10.0% to 48.9% among CNS. The highest rates were detected in Venezuela (48.9%) and Mexico (41.7%) followed by Chile (25.0%) > Argentina (22.8%), and Brazil (21.7%).
- ? Interestingly, 95.6% and 83.1% of mupirocin-resistant CNS were susceptible to gatifloxacin and tetracycline.

SELECTED REFERENCES

- 1. Santos KR, Teixeira LM, Bravo Neto GP, Fonseca LS, Gontijo Filho PP. (1998) Mupirocin- and methicillin-resistant

 Staphylococcus aureus spreading in an intermediate-care unit in a Brazilian hospital. Infect Control Hosp Epidemiol.

 19:622-623.
- 2. Leski TA, Gniadkowski M, Skoczynska A, Stefaniuk E, Trzcinski K, Hryniewicz W. (1999). Outbreak of mupirocinresistant staphylococci in a hospital in Warsaw, Poland, due to plasmid transmission and clonal spread of several strains. *J Clin Microbiol*. 37:2781-2788.

3. Deshpande LM, Fix AM, Pfaller MA, Jones RN. (2002). Emerging elevated mupirocin resistance rates among

- staphylococcal isolates in the SENTRY Antimicrobial Surveillance Program (2000): correlations of results from disk diffusion, Etest and reference dilution methods. *Diagn Microbiol Infect Dis.* 42:283-290.

 4. Perl TM, Cullen JJ, Wenzel RP, Zimmerman MB, Pfaller MA, Sheppard D, Twombley J, French PP, Herwaldt LA. (2002).
- 4. Peri TM, Cullen JJ, Wenzel RP, Zimmerman MB, Pfaller MA, Sheppard D, Twombley J, French PP, Herwaldt LA. (2002). Intranasal mupirocin to prevent postoperative *Staphylococcus aureus* infections. *N Engl J Med.* 346:1871-1877.
- 5. Delgado-Hachmeister JE, Graviss EA. (2002). Intranasal mupirocin to prevent postoperative infections. *N Engl J Med.* 347:1207-1208.

SENTRY PARTICIPANT GROUP LATIN AMERICA

! Argentii

Jose M. Casellas - Centro de Estudos en Antimicrobianos, San Isidro Jorgelina Smayevsky - Microbiology Laboratory C.E.M.I.C.; Buenos Aires

Brasil

Helio S. Sader / Ana C. Gales (Latin America Coordinator) - Universidade Federal de São Paulo Cassia Zoccoli - Laboratório Médico Santa Luzia, Florianópolis Afonso Barth (1998 - 2001) - Hospital de Clínicas, Porto Alegre

Julival Ribeiro (2001) - Hospital de Base, Brasília Chile

Valeria Prado - Faculdad de Medicina de Chile, Santiago Patricia Garcia (2000 - 2001) - Universidad Catolica del Chile, Santiago

! Mexic

Jose Sifuentes-Osomio - Instituto Nacional de la Nutricion, Ciudad del Mexico

Venezuela

Manuel Guzman Bianco (1998 - 2001) - Centro Medico de Caracas