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ECCMID 2005
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In Vitro Activity of New Compounds Tested Against Multi-Drug Resistant *S. aureus* Isolated in Latin American Medical Centers

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SENTRY ANTIMICROBIAL SURVEILLANCE

AMENDED ABSTRACT

Background: Oxacillin-resistant *S. aureus* (ORSA) isolated in Latin American medical centers (LMAC) show high rates of co-resistance (R) with most antimicrobial classes used in the clinical setting. We evaluated the MDR patterns of ORSA strains collected in LAMC by the SENTRY Antimicrobial Surveillance Program in 2003. We also evaluated the susceptibilities (S) of new, investigational compounds against these important endemic pathogens.

Methods: Among 1,437 *S. aureus* collected, 507 (35.3%) were R to oxacillin. These strains were isolated from 10 LAMCs (5 countries) and tested against > 30 antimicrobials by NCCLS broth microdilution methods. ORSA strains were grouped by the multidrug-resistant (MDR) patterns for the 8 primary drugs (47).

Results: The MIC_{90} in mg/L/% S for the primary drugs were: erythromycin (ERY) > 8/8; clindamycin (CC) > 8/13; ciprofloxacin (CIP) > 8/8; tetracycline (TC) ≤ 4/61, co-trimoxazole (T/S) > 2/49, chloramphenicol (CHL) 16/47, rifampin 2/48, gentamicin (GM) > 8/14; and newer agents were: daptomycin (DAP) 0.5/100, dalbavancin (DAL) 0.06/-, linezolid (LZD) 2/100, quinupristin/dalfopristin (Q/D) 0.5/100, teicoplanin (TEI) ≤ 2/100 and vancomycin (VAN) 1/100. The table shows 6 MDR-ORSA patterns (77.5% of all ORSA):

Pattern (no.)	R antibiogram	Geographic distribution (%)
1 (126)	All primary drugs	Brazil (82%)
2 (6)	CHL, CIP, CC, ER, GM	Chile (66%)
3 (65)	CIP, CC, ER, GM	Argentina (51%), Brazil (48%)
4 (51)	All, except CHL	Brazil (75%)
5 (48)	All, except TC	Brazil (100%; 75% one site)
6 (37)	CIP, CC, ER	Mexico (86%)

Conclusions: All newer compounds (LZD, Q/D, DAP and DAL), TEI and VAN were very active against endemic and epidemic ORSA in LAMCs. These *S. aureus* having MDR patterns (ave. R to 6 agents) will require greater use of newer compounds particularly in Brazil.

INTRODUCTION

Oxacillin-resistant *Staphylococcus aureus* (ORSA) is a remarkable bacterial pathogen responsible for a variety of infections commonly observed in patients of all ages. Acquisition of this organism is typically associated with health care institutions, such as hospitals and long-term care facilities (nursing homes), and risk factors including prolonged hospitalization, past antimicrobial use and the presence of indwelling catheter(s), among others. Infections due to ORSA present a considerable dilemma to clinicians, since therapeutic options are often limited and suboptimal dosing contributes to heightened mortality and compromised outcomes.

Although alteration of target penicillin-binding protein is the primary mechanism of resistance to ß-lactams, over the years ORSA strains have acquired multiple mechanisms of resistance to several classes of antimicrobials, including aminoglycosides, chloramphenicol, fluoroquinolones, lincosamides, macrolides, tetracyclines, and more recently, glycopeptides.

Resistance rates to oxacillin among *S. aureus*, as well as rates of co-resistance to other antimicrobial classes among ORSA strains, may vary significantly from geographic region to region or even among institutions within a region. In the present study we evaluated the antimicrobial resistance patterns among ORSA strains collected from Latin American medical centers throughout the SENTRY Antimicrobial Surveillance Program.

MATERIALS AND METHODS

The SENTRY Antimicrobial Surveillance Program has monitored the predominant pathogens and antimicrobial resistance patterns of nosocomial and community-acquired infections via a broad network of sentinel hospitals in four major geographic regions: Asia-Pacific, Europe, Latin America, and North America. We report here the evaluation of the antimicrobial susceptibility patterns of ORSA strains collected in Latin American medical centers during the 2002-2003 period. Individual, non-duplicate strains were collected consecutively from patients hospitalized in 10 participant medical centers located in Argentina (2), Brazil (4), Chile (2), Mexico (1) and Venezuela (1).

A total of 507 ORSA isolates were analyzed. The isolates were identified by the participant laboratories and confirmed by the monitoring facility (JMI Laboratories, North Liberty, IA, USA). All strains were tested against >20 antimicrobial agents using validated, dry-form broth microdilution panels manufactured by TREK Diagnostics (Cleveland, OH, USA) according to the Clinical and Laboratory Standards Institute (CLSI, formerly National Committee for Clinical Laboratory Standards [NCCLS]) M7-A6 document. The antimicrobial agents (eight classes) used to characterize the antibiogram phenotypes were: chloramphenicol, ciprofloxacin, clindamycin, erythromycin, gentamicin, rifampin, tetracycline and trimethoprim/sulfamethoxazole. Interpretation of quantitative MIC results was in accordance with the most recent CLSI/NCCLS document (M100-S15, 2005).

RESULTS

- The ORSA isolates originated from Brazil (242 isolates; 47.7%), Argentina (114 isolates; 22.5%), Chile (107 isolates; 21.1%), Mexico (40 isolates; 7.9%), and Venezuela (4 isolates; 0.8%).
- Table 1 shows the antimicrobial susceptibility of ORSA strains isolated in Latin American medical centers in the 2002-2003 period. Resistance rates were very high (>50%) for fluoroquinolones (7.7-7.9% susceptible), macrolides (8.1% susceptible to erythromycin), lincosamides (13.0% susceptible to clindamycin), aminoglycosides (14.4% susceptible to gentamicin), rifampin (47.7% susceptible), and trimethoprim/sulfamethoxazole (48.9% susceptible).
- Daptomycin (MIC_{90}, 0.5 mg/L), linezolid (MIC_{90}, 2 mg/L), quinupristin/dalfopristin (MIC_{90}, 0.5 mg/L), teicoplanin (MIC_{90}, ≤ 2 mg/L) and vancomycin (MIC_{90}, 1 mg/L) were active against all ORSA isolates tested at the respective CLSI/NCCLS susceptible breakpoints (100% susceptible). Dalbavancin (MIC_{90}, 0.06 mg/L) was the most potent antimicrobial agent tested, and mupirocin (MIC_{90}, 0.5 mg/L; 91.7% susceptible) and doxycycline (MIC_{90}, >4 mg/L; 79.3% susceptible, greater than tetracycline) showed reasonable in vitro activity against ORSA strains tested (Table 1).
- The in vitro activity of the eight antimicrobial agents selected to characterize the antibiogram phenotypes showed significant variations among the Latin American countries (Table 2). Isolates from Brazil demonstrated decreased susceptibility to all antimicrobials (6-32% susceptibility rates); while tetracycline and trimethoprim/sulfamethoxazole remained very active (≥ 93% susceptibility rates) against ORSA strains from Chile and Mexico.

Table 1. Antimicrobial susceptibility of 507 MRSA strains isolated in Latin American medical centers by the SENTRY Program (2002 - 2003).

	MIC (mg/L)				
Antimicrobial agent	50%	90%	Range	% susceptible	% resistant
Chloramphenicol	16	>16	≤2->16	47.1	49.3
Ciprofloxacin	>4	>4	0.06->4	7.7	90.5
Clindamycin	>8	>8	≤0.06->8	13.0	87.0
Dalbavancin	0.06	0.06	≤0.016-0.06	-	-
Daptomycin	0.5	0.5	≤0.12-1	100.0	-
Doxycycline	≤0.5	>4	≤0.5->4	79.3	20.7
Erythromycin	>8	>8	0.12->8	8.1	91.9
Gentamicin	>8	>8	≤2->8	14.4	84.0
Levofloxacin	4	>4	≤0.03->4	7.9	88.4
Linezolid	2	2	0.25-2	100.0	-
Mupirocin	≤2	≤2	≤2->8	91.7[a]	-
Quinupristin/Dalfopristin	0.5	0.5	≤0.25-1	100.0	0.0
Rifampin	2	2	≤0.25->2	47.7	17.9
Teicoplanin	≤2	≤2	≤2-8	100.0	0.0
Tetracycline	≤4	>8	≤4->8	61.3	38.3
Trimethoprim/Sulfamethoxazole	>2	>2	≤0.5->2	48.9	51.1
Vancomycin	1	1	0.5-2	100.0	0.0

a. Percentage of isolates with mupirocin MIC at ≤ 4 mg/L.

Table 2. Antimicrobial susceptibility of ORSA strains by country.

	% susceptible/resistant (no. tested)			
Antimicrobial agent	Argentina (114)	Brazil (242)	Chile (107)	Mexico (40)
Chloramphenicol	61/33	32/66	48/48	95/2
Ciprofloxacin	14/86	8/91	1/99	3/97
Clindamycin	18/82	11/89	14/86	3/97
Erythromycin	10/90	6/94	12/88	3/97
Gentamicin	13/87	6/91	4/96	95/5
Rifampin	63/26	15/20	87/10	95/5
Tetracycline	72/28	36/63	93/7	100/0
Trimethoprim/Sulfamethoxazole	73/27	10/90	94/6	95/5

- Chloramphenicol, gentamicin and rifampin showed good in vitro activity (95.0% susceptibility rates) against isolates from Mexico. Conversely, resistance rates to ciprofloxacin, clindamycin and erythromycin were very high (≥ 82%) among isolates from the four countries evaluated (Table 2).
- More than 40 distinct antibiogram phenotypes were detected among the strains evaluated. Table 3 shows the susceptibility profile and occurrence of the six most common antibiogram patterns. Resistance to all antimicrobial agents was the most common phenotype (phenotype 1; 25.1% of the isolates). Phenotypes with susceptibility to only one antimicrobial were also common. Susceptibility only to chloramphenicol (phenotype 4) was observed in 10% of isolates, while susceptibility only to tetracycline (phenotype 5) was observed in 9.0% of isolates.
- Table 4 shows the distribution of the resistance phenotypes among the countries. Phenotype 1 (resistance to all antimicrobials) was isolated mainly in Brazil (82% of the isolates), while phenotypes 2 and 3 were mainly from Chile and Argentina. Phenotype 5 was observed only in Brazil while 86% of isolates with phenotype 6 came from Mexico.
- Approximately 80% of isolates from Brazil showed resistance to at least 7 of the 8 antimicrobial classes, other than oxacillin, used to characterize the phenotypes. On the other hand, 80% of isolates from Mexico (32 of 40) showed phenotype 6, which indicates resistance only to ciprofloxacin, erythromycin and clindamycin.

Table 3. Antimicrobial susceptibility and prevalence of the most frequent multidrug-resistant phenotypes.

	Phenotypes[a]					
Antimicrobial agents	1	2	3	4	5	6
Chloramphenicol	R	R	S	S	R	S
Ciprofloxacin	R	R	R	R	R	R
Clindamycin	R	R	R	R	R	R
Erythromycin	R	R	R	R	R	R
Gentamicin	R	R	R	R	R	S
Rifampin	R	S	S	R	R	S
Tetracycline	R	S	S	R	S	S
Trimethoprim/Sulfamethoxazole	R	S	S	R	R	S
No. of isolates (% of total)	126 (25.1)	66 (13.0)	65 (13.0)	51 (10.0)	48 (9.0)	37 (7.0)

a. R = intermediate or resistant and S = susceptible (CLSI, 2005).

Table 4. Distribution of the most frequent multidrug-resistant phenotypes in four Latin American countries.

	No. of isolates (% of isolates with the phenotype)			
Phenotype	Argentina	Brazil	Chile	Mexico
1	20 (16)	103 (82)	2 (2)	0 (0)
2	23 (35)	0 (0)	43 (65)	0 (0)
3	33 (51)	0 (0)	31 (48)	1 (1)
4	9 (18)	37 (73)	4 (8)	0 (0)
5	0 (0)	48 (100)	0 (0)	0 (0)
6	2 (5)	0 (0)	2 (5)	32 (86)
Other	27	54	25	7
Total	114	242	107	40

CONCLUSIONS

- All newer compounds (daptomycin, dalbavancin, linezolid and quinupristin/dalfopristin), as well as vancomycin and teicoplanin, were very active against ORSA isolates from Latin American medical centers (2002 - 2003).
- The antimicrobial susceptibility profiles of ORSA strains varied widely among the countries evaluated with the most resistant phenotypes being isolated in Brazil and the least resistant phenotypes being isolated in Mexico.
- The majority of ORSA strains from Latin American medical centers, especially those located in Brazil, showed co-resistance to multiple antimicrobial agents (≥ five classes).
- The newer antimicrobials with higher potency and broader spectrum against Gram-positive bacteria may have an increasingly important role in the treatment of ORSA infections in medical centers located in the Latin American region.

SELECTED REFERENCES

Charlebois ED Perdreau-Remington F, Kreiswirth B, Bangsberg DR, Ciccarone D, Diep BA, Ng VL, Chansky K, Edlin B, Chambers HF. (2004). Origins of communitys trains of methicillin-resistant *Staphylococcus aureus*. *Clinical Infectious Disease* 39:47-54.

Clinical and Laboratory Standards Institute. (2005). *Performance standards for antimicrobial susceptibility testing, 15th informational supplement M100-S15*. Wayne, PA:CLSI.

Deresinski S. (2005). Methicillin-resistant *Staphylococcus aureus*: An evolutionary, epidemiologic, and therapeutic odyssey. *Clinical Infectious Disease* 40:562-573.

National Committee for Clinical Laboratory Standards. (2003) *Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically. Document M7-A6*. Wayne, PA:NCCLS.

Oliveira DC, Tomasz A, de Lencastre H. (2002). Secrets of success of a human pathogen: Molecular evolution of pandemic clones of methicillin-resistant *Staphylococcus aureus*. *Lancet Infectious Diseases* 2:180-189.

Rybak MJ, LaPlante KL. (2005). Community associated methicillin-resistant *Staphylococcus aureus*: A review. *Pharmacotherapy* 25:74-85.