Five-Year Trend of Antimicrobial Susceptibility Rates and Daptomycin Activity among *Staphylococcus aureus* Isolates Collected in Latin American Medical Centers (2005-2009)

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ABSTRACT

Background: Daptomycin is lipopeptide with a unique mechanism of action and rapid bactericidal activity against Gram-positive cocci. Daptomycin is approved for the treatment of Gram-positive pathogen associated complicated skin and skin structure infections (cSSSI) and *S. aureus* (SA)-associated bacteremia and endocarditis in the United States, Europe and some Latin American (LA) countries. The in vitro activity of daptomycin and comparator agents was evaluated against clinical isolates of SA collected in four LA countries over five years.

Methods: 6,031 SA isolates were collected in 10 medical centers located in Argentina (1,075), Brazil (2,637), Chile (1,345) and Mexico (974). Isolates were mainly from bloodstream (42.1%) and cSSSI (28.6%). Susceptibility (S) was determined by the CLSI broth microdilution method in cation-adjusted Mueller-Hinton broth supplemented to 50 mg/L of calcium for daptomycin tests.

Results: The overall oxacillin resistance (MRSA) rate in LA was 41.1% and ranged from 32.1-39.0% in Brazil and Mexico to 51.7-51.9% in Argentina and Chile. MRSA rates increased continuously from 34.7 (2005) to 48.4% (2009). Daptomycin was highly active against SA in all LA countries with MIC_{50} and MIC_{90} values of 0.25 and 0.5 μg/ml, respectively. Overall, daptomycin was highly active against MRSA (100.0% S, see table) as was vancomycin ($MIC_{50/90}$, 1/1 μg/ml; 100% S) and linezolid ($MIC_{50/90}$, 1/2 μg/ml; >99.9% S). Erythromycin resistance was higher in Chile and Mexico (46.5-54.5%) than in Argentina and Brazil (38.2-39.4%). Overall constitutive clindamycin resistance was 81.1% among MRSA. TMP/SMX and tetracycline resistance was much higher in Brazil (20.6-23.6%) compared to other countries (1.5-6.2%). Levofloxacin and gentamicin resistance was highest in Chile at 52.1% and 42.8%, respectively.

Nation (no. of SA strains)	Cumulative % inhibited at daptomycin MIC (μg/ml) of:					
	≤0.06	0.12	0.25	0.5	1	2
Argentina (1,075)	0.0	2.3	62.1	98.5	**100.0**	-
Brazil (2,637)	0.1	2.1	61.1	98.4	**100.0**	-
Chile (1,345)	0.2	2.8	57.3	97.9	**100.0**	-
Mexico (974)	0.5	3.9	74.6	99.2	**99.9**	100.0
All regions						
Methicillin-S (3,552)	0.2	3.3	77.3	99.1	**>99.9**	100.0
MRSA (2,479)	0.1	1.5	41.6	97.5	**100.0**	-

a. Bolded percentages indicate susceptibility rates.

Conclusions: Significant resistance variations among SA and several classes of antimicrobial agents were observed in LA countries. Daptomycin showed consistent potency against recent clinical isolates of SA collected in LA medical centers, including MDR strains. Resistance to other compounds did not adversely influence daptomycin potency and with S rates at over 99.9% during the past five years suggests that daptomycin has maintained in vitro activity in LA countries.

INTRODUCTION

Gram-positive bacteria are very common and important pathogens causing serious infections in the hospital environment. *Staphylococcus aureus*, coagulase-negative staphylococci (CoNS) and enterococci are among the five most frequently isolated organisms from nosocomial bloodstream infections (BSI). These three pathogens are responsible for approximately 40% of BSI cases in Latin American medical centers evaluated by the SENTRY Antimicrobial Surveillance Program.

Daptomycin is a lipopeptide with a unique mechanism of action and rapid bactericidal activity against Gram-positive cocci. United States Food and Drug Administration (USA-FDA) approved daptomycin for the treatment of oxacillin-resistant (MRSA) and –susceptible *S. aureus* (MSSA) bacteremia and right sided endocarditis at a dosage of 6 mg/kg every 24 hours, and for complicated skin and skin structure infections (cSSSI) using a dose of 4 mg/kg every 24. Daptomycin is also approved for the same indications in various European and Latin American countries. In the present study, we evaluated the antimicrobial activity of daptomycin and comparator agents tested against clinical isolates of *S. aureus* collected in four Latin American countries over five years.

MATERIALS AND METHODS

Bacterial isolates: As part of a worldwide Daptomycin Surveillance Program, 6,031 *S. aureus* isolates were collected in 10 medical centers located in Argentina (1,075 isolates from two medical centers), Brazil (2,637 isolates from four medical centers), Chile (1,345 isolates from two medical centers) and Mexico (974 isolates from two medical centers). Isolates were consecutively collected from prevalent sources of infection, including BSI (42.1%), SSSI (28.6%) and others, according to a common surveillance design. All organisms were isolated from documented human infections and only one isolate per patient infection episode was included in the study. The isolates were identified locally and forwarded to a central monitoring laboratory (JMI Laboratories, North Liberty, Iowa, USA) for confirmation of species identification, when necessary, and reference susceptibility testing.

Susceptibility test methods: Daptomycin and various comparator agents were tested by the Clinical and Laboratory Standards Institute (CLSI) broth microdilution methods in validated microdilution panels manufactured by TREK Diagnostics Systems (Cleveland, Ohio). The test medium was Mueller-Hinton broth adjusted to contain physiological levels of calcium (50 mg/L) when testing daptomycin. CLSI interpretive criteria were used to categorize the isolates as susceptible, intermediate and resistant. A daptomycin susceptibility breakpoint of ≤1 μg/ml was applied as recommended by the CLSI and the USA-FDA. The following quality control (QC) organisms were concurrently tested: *S. aureus* ATCC 29213, *Enterococcus faecalis* ATCC 29212 and *Streptococcus pneumoniae* ATCC 49619. All QC results were within published ranges.

RESULTS

- Daptomycin was very active against 6,031 *S. aureus* isolates tested ($MIC_{50/90}$, 0.25/0.5 μg/ml; >99.9% susceptible; Tables 1 and 2). Only one strain showed a non-susceptible daptomycin MIC value; an oxacillin-susceptible *S. aureus* with a daptomycin MIC of 2 μg/ml (only one doubling dilution above the susceptible breakpoint) isolated from a patient with SSSI in Mexico in 2008.
- The overall oxacillin resistance (MRSA) rate in Latin America was 41.1% and varied from 32.1% in Brazil, 39.0% in Mexico, 51.7% in Chile and 51.9% in Argentina.
- During the study period, overall MRSA rates increased from 34.7 to 48.4%. Major increases were observed in Chile (from 36.2 to 57.6%) and Mexico (from 29.7 to 52.6%; Figure 1).
- Overall, daptomycin was highly active against MRSA ($MIC_{50/90}$, 0.5/0.5 μg/ml; 100.0% susceptible), as was vancomycin ($MIC_{50/90}$, 1/1 μg/ml; 100.0% susceptible) and linezolid ($MIC_{50/90}$, 1/2 μg/ml; >99.9% susceptible).
- MRSA strains exhibited high rates of resistance to many other antimicrobial agents, including clindamycin (81.1% resistance), erythromycin (87.4%) and levofloxacin (84.0%).
- MSSA isolates exhibited higher susceptibility (≥90.0%) to all antimicrobial agents, except erythromycin ($MIC_{90,}$ >2 μg/ml; 86.2% susceptible) and tetracycline ($MIC_{90,}$ 8 μg/ml; 89.1% susceptible; Table 1).
- Erythromycin resistance was higher in Chile (54.5%) and Mexico (46.5%) when compared to Argentina (38.2%) and Brazil (39.4%). Resistance to levofloxacin (52.1%) and gentamicin (42.8%) were also highest in Chile (Table 2). In contrast, trimethoprim/ sulfamethoxazole (TMP/SMX) and tetracycline resistance was much higher in Brazil (20.6 and 23.6%, respectively) compared to other Latin American countries (1.5-6.2%; Table 2).
- Resistance to clindamycin and levofloxacin showed substantial increases in Chile and Mexico, a decrease in Argentina, and remained stable in Brazil during the study interval (Figures 2 and 3).
- Interestingly, in Argentina resistance rates to clindamycin and levofloxacin decreased from approximately 40% to 16.0-16.4% while oxacillin resistance increased from 49.2 to 58.9% over the study period.
- Resistance to TMP/SMX decreased in all four countries and the reduction was more remarkable in Brazil. In this country, TMP/SMX resistance declined from 25.3 to only 10.2% overall (Figure 4) and from 75.0 to 30.0% among MRSA.

Table 1. Antimicrobial activity of daptomycin and comparator antimicrobial agents when tested against isolates of *Staphylococcus aureus* from Latin American medical centers.

Antimicrobial agent	MIC in μg/ml			%S / %R [a]
	50%	90%	Range	
S. aureus				
All (6,031)				
Daptomycin	0.25	0.5	≤0.06 – 2	>99.9 / -
Oxacillin	0.5	>2	≤0.25 – >2	58.9 / 41.1
Levofloxacin	≤0.5	>4	≤0.5 – >4	63.4 / 36.1
Ciprofloxacin	≤0.5	>4	≤0.5 – >4	61.7 / 36.5
Erythromycin	0.5	>2	≤0.25 – >2	55.9 / 43.7
Clindamycin	≤0.25	>2	≤0.25 – >2	65.2 / 34.5
Gentamicin	≤2	>8	≤2 – >8	71.6 / 27.2
Linezolid	1	2	0.25 – 8	>99.9 / <0.1
Tetracycline	≤2	>8	≤2 – >8	86.7 / 12.7
Trimethoprim/sulfamethoxazole	≤0.5	>2	≤0.5 – >2	89.8 / 10.2
Teicoplanin	≤2	≤2	≤2 – >16	>99.9 / <0.1
Vancomycin	1	1	≤0.12 – 2	100.0 / 0.0
Oxacillin-susceptible (3,552)				
Daptomycin	0.25	0.5	≤0.06 – 2	>99.9 / -
Levofloxacin	≤0.5	≤0.5	≤0.5 – >4	97.0 / 2.6
Ciprofloxacin	≤0.5	≤0.5	≤0.5 – >4	95.0 / 3.0
Erythromycin	≤0.25	>2	≤0.25 – >2	86.2 / 13.2
Clindamycin	≤0.25	≤0.25	≤0.25 – >2	97.8 / 2.0
Gentamicin	≤2	≤2	≤2 – >8	96.4 / 3.1
Linezolid	2	2	0.25 – 2	100.0 / 0.0
Tetracycline	≤2	8	≤2 – >8	89.1 / 9.9
Trimethoprim/sulfamethoxazole	≤0.5	≤0.5	≤0.5 – >2	99.2 / 0.8
Teicoplanin	≤2	≤2	≤2 – 8	100.0 / 0.0
Vancomycin	1	1	≤0.12 – 2	100.0 / 0.0
Oxacillin-resistant (2,479)				
Daptomycin	0.5	0.5	≤0.06 – 1	100.0 / -
Levofloxacin	>4	>4	≤0.5 – >4	15.4 / 84.0
Ciprofloxacin	>4	>4	≤0.5 – >4	14.0 / 84.6
Erythromycin	>2	>2	≤0.25 – >2	12.4 / 87.4
Clindamycin	>2	>2	≤0.25 – >2	18.6 / 81.1
Gentamicin	>8	>8	≤2 – >8	36.0 / 61.7
Linezolid	1	2	0.25 – 8	>99.9 / <0.1
Tetracycline	≤2	>8	≤2 – >8	83.2 / 16.7
Trimethoprim/sulfamethoxazole	≤0.5	>2	≤0.5 – >2	76.4 / 23.6
Teicoplanin	≤2	≤2	≤2 – >16	99.9 / 0.1
Vancomycin	1	1	0.25 – 2	100.0 / 0.0

a. % susceptible/resistant according to the interpretive criteria published by the CLSI [2010].

Table 2. Antimicrobial susceptibility of *S. aureus* according to the country of origin.

Antimicrobial agent	% susceptible / resistant (no. of isolates)			
	Argentina	Brazil	Chile	Mexico
	(1,075)	(2,637)	(1,345)	(974)
Daptomycin	100.0 / -	100.0 / -	100.0 / -	99.9 / -
Oxacillin	48.1 / 51.9	67.9 / 32.1	48.3 / 51.7	61.0 / 39.0
Levofloxacin	71.1 / 28.4	69.3 / 30.2	47.4 / 52.1	61.3 / 38.5
Ciprofloxacin	67.2 / 28.9	67.2 / 30.8	47.2 / 52.4	61.0 / 38.7
Erythromycin	61.6 / 38.2	60.0 / 39.7	45.2 / 54.5	53.0 / 46.5
Clindamycin	74.0 / 25.9	70.2 / 29.5	50.9 / 48.8	61.2 / 38.0
Gentamicin	64.0 / 34.3	73.6 / 25.3	55.5 / 428	96.5 / 3.0
Linezolid	100.0 / 0.0	>99.9 / <0.1	100.0 / 0.0	100.0 / 0.0
Tetracycline	95.8 / 4.2	75.2 / 23.6	97.0 / 2.9	93.5 / 6.2
TMP/SMX	98.0 / 2.0	79.4 / 20.6	97.5 / 2.5	98.5 / 1.5
Teicoplanin	100.0 / 0.0	100.0 / 0.0	100.0 / 0.0	100.0 / 0.0
Vancomycin	100.0 / 0.0	100.0 / 0.0	100.0 / 0.0	100.0 / 0.0

Figure 1. Five-year trend of oxacillin resistance rates among *S. aureus* from Latin American countries.

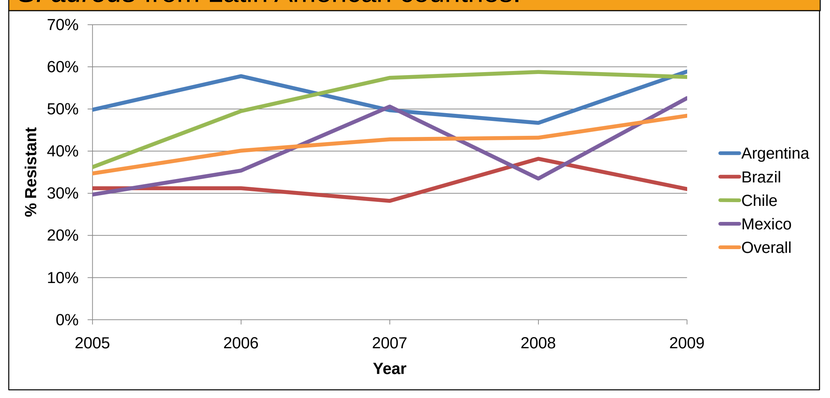


Figure 2. Five-year trend of levofloxacin resistance rates among *S. aureus* from Latin American countries.

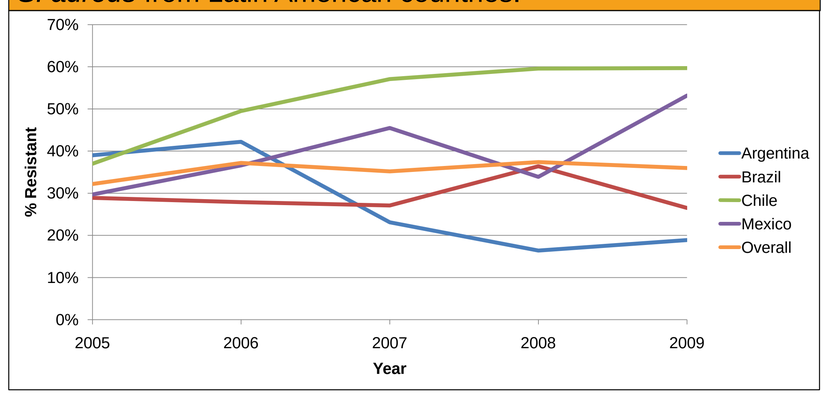


Figure 3. Five-year trend of clindamycin resistance rates among *S. aureus* from Latin American countries.

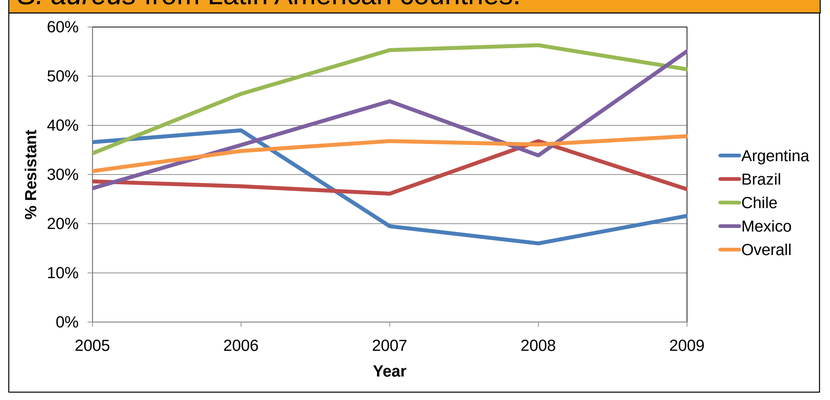
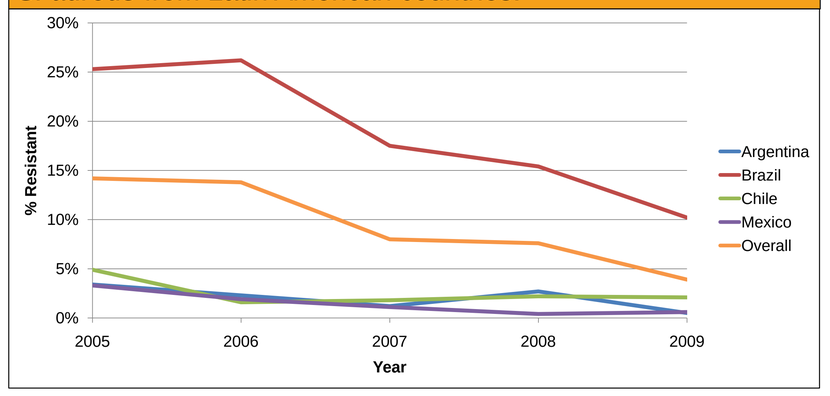


Figure 4. Five-year trend of TMP/SMX resistance rates among *S. aureus* from Latin American countries.



CONCLUSIONS

- Considerable geographical and temporal variations in resistance between *S. aureus* and several classes of antimicrobial agents were observed in Latin American countries (2005-2009).
- Daptomycin showed consistent potency against recent clinical isolates of *S. aureus* collected in Latin American medical centers, including MDR strains. Non-susceptibility to daptomycin was extremely rare and observed in only one of 6,031 (0.02%) *S. aureus* strains tested.
- Daptomycin exhibited sustained in vitro activity in Latin American countries over the last five years and represents a valuable option for treatment of serious *S. aureus* infections, including those caused by endemic MDR strains.

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