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Activity of Daptomycin (DAP) and Comparators Tested Against Gram-positive (GP) Organisms from Bacteremia

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ABSTRACT

Background: We report the antimicrobial susceptibility (S) of the most frequently isolated GP bacteria causing blood stream infections (BSI) in Latin American (LA) hospitals participating in the Global DAP Surveillance Program in the 2007-2008 period.

Methods: Consecutive, non-duplicate bacterial isolates (1,535) were collected from patients in 10 hospitals located in Argentina (ARG; 25% of strains), Brazil (BRA; 38%), Chile (CHI; 23%) and Mexico (MEX; 13%), and tested for susceptibility in a central laboratory by reference broth microdilution methods in cation-adjusted Mueller-Hinton broth (supplemented to 50 mg/L of calcium for DAP tests).

Results: The most frequently isolated pathogens were: *S. aureus* (767, 50%); coagulase-negative staphylococci (CoNS; 417, 27%) and *Enterococcus* spp. (ESP; 199, 13%). Resistance (R) to oxacillin was observed in 43% of *S. aureus* (MRSA) and 78% of CoNS, while 13% of ESP exhibited R to vancomycin (VRE). MRSA/VRE rates were 46/8, 36/21, 46/19 and 51/0% in ARG, BRA, CHI and MEX, respectively. DAP was very active against all strains tested (no R detected), including MRSA ($MIC_{50/90}$, 0.25/0.5 µg/ml) and VRE ($MIC_{50/90}$, 1/2 µg/ml). DAP was four-fold more potent than VAN and linezolid (LZD) against MRSA. MRSA exhibited high R rates to levofloxacin (LEV; 76.1%), clindamycin (73.4%) and TMP/SMX (15.7%), but 100.0% S to DAP, VAN, LZD and teicoplanin. TMP/SMX R among MRSA was higher in BRA (41.5%) compared to other countries (2.1-8.6%). LZD R was observed in 1 ESP from BRA.

Conclusion: DAP showed excellent in vitro activity against contemporary GP organisms (1,535) collected in LA hospitals, including multi-R strains. VRE has emerged and rapidly disseminated in some LA hospitals, mainly in BRA.

INTRODUCTION

Despite advanced diagnostic tests and preventative technologies, morbidity due to bloodstream infections (BSI) remains relatively high. However, mortality can be reduced significantly when appropriate empiric antimicrobial therapy is introduced rapidly. In this context, antimicrobial surveillance studies (global and local) provide important information regarding the prevalence of pathogens responsible for BSI and antimicrobial resistance rate trends.

Daptomycin is a novel lipopeptide that possesses a unique mechanism of action and demonstrates rapid in vitro bactericidal activity against a wide variety of Gram-positive organisms, including multidrug-resistant (MDR) strains of staphylococci, enterococci and streptococci. Daptomycin was approved by the United States Food and Drug Administration (US-FDA) and by the European Medicine Agency (EMEA) for the treatment of complicated skin and skin structure infections (cSSSI) using a dose of 4 mg/kg every 24 hours, and for treatment of *Staphylococcus aureus* bacteremia and right-sided endocarditis at a higher dose of 6 mg/kg every 24 hours.

MATERIALS AND METHODS

Bacterial strains: A total of 1,535 consecutive, non-duplicate bacterial isolates were collected from patients with BSI in 10 hospitals located in Argentina (383; 25%), Brazil (590; 38%), Chile (360; 23%) and Mexico (202; 13%). Each medical center submitted the first 20 unique (one per patient) strains consecutively collected from BSI each month.

Participant centers:

1. C.E.M.I.C., Buenos Aires, Argentina (Jorgelina Smayevsky);
2. Sanatorio Parque y del Niño, Rosario, Santa Fe, Argentina (Jose M. Casellas);
3. Hospital São Paulo / UNIFESP, São Paulo, Brazil (Ana C. Gales and Soraya S. Andrade);
4. Laboratório Médico Santa Luzia, Florianópolis, Brazil (Cassia Zoccoli);
5. Hospital de Clínicas, Porto Alegre, Brazil (Afonso Barth);
6. Hospital de Base do Distrito Federal, Brasília, Brazil (Julival Ribeiro);
7. Pontificia Universidad Católica de Chile, Santiago, Chile (Patricia Garcia);
8. Facultad de Medicina, Universidad de Chile, Santiago (Valeria Prado);
9. Instituto de Patologia Infecciosa, Guadalajara, Mexico (Rayo Morfin and Eduardo Rodriguez-Noriega);
10. Hospital General de Durango, Durango, Mexico (Juan C. Tinoco).

Susceptibility Testing: The strains were susceptibility tested against daptomycin and numerous comparator agents by reference broth microdilution methods performed according to Clinical and Laboratory Standards Institute (CLSI) documents. All strains were tested in validated broth microdilution panels manufactured by TREK Diagnostics (Cleveland, Ohio, USA). Mueller-Hinton broth adjusted to contain physiological levels of calcium (50 mg/L) was used when testing daptomycin. Daptomycin susceptible breakpoints approved by the USA-FDA, CLSI and EUCAST for staphylococci and ß-haemolytic streptococci (≤1 µg/ml) and for enterococci (≤4 µg/ml) were applied. The following quality control organisms were concurrently tested: *Enterococcus faecalis* ATCC 29212, *S. aureus* ATCC 29213 and *Streptococcus pneumoniae* ATCC 49619.

RESULTS

- Daptomycin MIC distributions for 1,535 Gram-positive isolates (2007-2008) from Latin America are summarized in Table 1. All isolates were considered susceptible to daptomycin when applying breakpoints approved by the CLSI and USA-FDA.
- Daptomycin was very active against oxacillin-susceptible (MSSA) and -resistant (MRSA) *S. aureus* (MIC_{50} of 0.25 µg/ml and MIC_{90} of 0.5 µg/ml for both pathogen groups; Table 1). Linezolid (MIC_{50}, 1 µg/ml and MIC_{90}, 2 µg/ml) and vancomycin (MIC_{50} and MIC_{90}, 1 µg/ml) also inhibited all *S. aureus* isolates at published breakpoints, but these compounds were four-fold less active (higher MICs) than daptomycin (Table 2).
- MRSA rates varied from 35.9% in Brazil to as high as 51.1% in Mexico (Table 3).
- MRSA strains exhibited high rates of resistance to erythromycin (80.1%), clindamycin (73.4%) and fluoroquinolones (76.6% for ciprofloxacin and 76.1% for levofloxacin). Trimethoprim/sulfamethoxazole (TMP/SMX) resistance varied from 2.1% in Argentina, 6.3% in Mexico, 8.6% in Chile to as high as 41.5% in Brazil (data not shown).
- Daptomycin was the most active compound tested against *Enterococcus* spp. strains (MIC_{50}, 1 µg/ml and MIC_{90}, 2 µg/ml; 100.0% susceptible at ≤4 µg/ml).
- Vancomycin-resistant *Enterococcus* spp. (VRE) rates were high in Brazil (20.5%) and Chile (19.2%), relatively low in Argentina (7.5%) and 0.0% in Mexico (Table 3). All vancomycin-non-susceptible strains (25 strains) were susceptible to daptomycin with MIC values ranging from 0.25 to 2 µg/ml (Table 2).
- Viridans group streptococci (MIC_{50}, 0.25 µg/ml and MIC_{90}, 0.5 µg/ml) were also very susceptible to daptomycin. Only 71.4% of strains were susceptible to penicillin and 92.9% were susceptible to ceftriaxone (Table 2).
- Daptomycin was very potent against ß-haemolytic streptococcal isolates with a MIC range of ≤0.06 to 0.25 µg/ml (MIC_{90}, 0.25 µg/ml). This organism group was also very susceptible to other tested antimicrobial agents.

Table 1. Daptomycin MIC population distributions for Gram-positive organisms isolated from BSI in Latin America (2007-2008).

Organism (no. of isolates)	Cumulative % inhibited at daptomycin MIC (µg/ml) of: ≤0.12	0.25	0.5	1	2	4
S. aureus (767)						
Oxacillin-susceptible (436)	3.0	81.0	99.1	100.0	-	-
Oxacillin-resistant (331)	1.2	57.1	98.2	100.0	-	-
Coagulase-negative staphylococci (417)	11.5	59.7	95.4	100.0	-	-
Enterococcus spp. (199)						
Vancomycin-susceptible (174)	0.0	2.3	32.8	79.9	98.3	100.0
Vancomycin-non-susceptible (25)	0.0	8.0	12.0	56.0	100.0	-
ß-haemolytic streptococci (41)	70.7	100.0	-	-	-	-
Viridans group streptococci (14)	42.9	85.7	92.9	100.0	-	-

Table 2. Antimicrobial activity of daptomycin and comparator agents tested against Gram-positive organisms isolated from bloodstream infections in Latin American medical centers (2007-2008).

Organism (no. tested)/Antimicrobial agent	MIC_{50}	MIC_{90}	% susceptible[a]	% resistant[a]
S. aureus (767)				
Daptomycin	0.25	0.5	100.0	-[b]
Oxacillin	0.5	>2	56.8	43.2
Erythromycin	≤0.25	>4	57.4	42.2
Clindamycin	≤0.25	>2	66.8	33.1
Levofloxacin	≤0.5	>4	64.5	35.2
Tetracycline	≤2	≤2	91.7	8.0
TMP/SMX	≤0.5	≤0.5	93.0	7.0
Linezolid	1	2	100.0	-
Vancomycin	1	1	100.0	0.0
CoNS (417)				
Daptomycin	0.25	0.5	100.0	-
Oxacillin	>2	>2	21.8	78.2
Erythromycin	>2	>2	34.5	65.5
Clindamycin	≤0.25	>2	56.1	43.6
Levofloxacin	4	>4	43.4	51.3
Tetracycline	≤2	>8	86.8	12.5
TMP/SMX	≤0.5	>2	56.8	43.2
Linezolid	1	1	100.0	-
Vancomycin	1	2	99.8	0.0
Enterococcus spp (199)				
Daptomycin	1	2	100.0	-
Ampicillin	≤1	>16	76.9	23.1
Levofloxacin	2	>4	51.3	45.2
Gentamicin (HL)	≤500	>1000	66.8	33.2
Streptomycin (HL)	≤1000	>2000	59.3	40.7
Linezolid	1	2	99.5	0.5
Teicoplanin	≤2	>16	88.4	11.6
Vancomycin	1	>16	87.4	12.6
Viridans group streptococci (14)				
Daptomycin	0.25	0.5	-	-
Penicillin	0.03	1	71.4	7.1
Ceftriaxone	≤0.25	0.5	92.9	7.1
Erythromycin	≤0.25	>2	64.3	35.7
Clindamycin	≤0.25	≤0.25	100.0	0.0
Levofloxacin	1	2	100.0	0.0
Linezolid	1	1	100.0	0.0
Vancomycin	0.5	0.5	100.0	0.0
ß-haemolytic streptococci (41)				
Daptomycin	0.12	0.25	100.0	-
Penicillin	0.03	0.06	100.0	0.0
Erythromycin	≤0.25	>2	82.9	14.6
Clindamycin	≤0.25	≤0.25	95.1	2.4
Levofloxacin	≤0.5	1	100.0	0.0
Linezolid	1	1	100.0	-
Vancomycin	0.5	0.5	100.0	-

a. According to breakpoints established by the CLSI.
b. - = No breakpoint has been established by the CLSI or USA-FDA.
Abbreviations: TMP/SMX: trimethoprim/sulfamethoxazole; HL = high-level.

Table 3. Prevalence of methicillin-resistant *S. aureus* (MRSA) and vancomycin-resistant *Enterococcus* spp. (VRE) by country among isolates from bloodstream infections.

Country	No. of *S. aureus*/*Enterococus* spp. tested	MRSA %	VRE %
Argentina	209/53	45.9	7.5
Brazil	262/78	35.9	20.5
Chile	202/26	46.0	19.2
Mexico	94/42	51.1	0.0

CONCLUSIONS

- Daptomycin demonstrated excellent in vitro activity against recently isolated Gram-positive organisms (1,535) collected in Latin American hospitals, including MDR subsets.
- VRE has emerged and rapidly disseminated in some Latin American hospitals, mainly in Brazil and Chile.
- Resistance to other compounds did not adversely influence daptomycin potency against staphylococci, enterococci or streptococci.
- Daptomycin represents a valuable alternative for the treatment of serious infections caused by contemporary Gram-positive cocci.

SELECTED REFERENCES

1. Appelbaum PC (2007). Reduced glycopeptide susceptibility in methicillin-resistant *Staphylococcus aureus* (MRSA). *Int J Antimicrob Agents* 30: 398-408.
2. Centers for Disease Control and Prevention (2007). Invasive methicillin-resistant *Staphylococcus aureus* infections among dialysis patients--United States, 2005. *MMWR Morb Mortal Wkly Rep* 56: 197-199.
3. Clinical and Laboratory Standards Institute. (2006). *M7-A7, Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically; approved standard - seventh edition.* Wayne, PA: CLSI.
4. Clinical and Laboratory Standards Institute. (2008). *M100-S18, Performance standards for antimicrobial susceptibility testing, 18th informational supplement*. Wayne, PA: CLSI.
5. Fowler VG, Jr., Boucher HW, Corey GR, et al. (2006). Daptomycin versus standard therapy for bacteremia and endocarditis caused by *Staphylococcus aureus*. *N Engl J Med* 355: 653-665.
6. Gales AC, Sader HS, Ribeiro J, Zoccoli C, Barth A, Pignatari AC. (2009) Antimicrobial susceptibility of Gram-Positive bacteria isolated in Brazilian hospitals participating in the SENTRY Program (2005-2008). *Braz J Infect Dis* 13 [In press].
7. Hair PI, Keam SJ (2007). Daptomycin: A review of its use in the management of complicated skin and soft-tissue infections and *Staphylococcus aureus* bacteraemia. *Drugs* 67: 1483-1512.
8. Sader HS, Fritsche TR, Jones RN. (2008) Frequency of occurrence and daptomycin susceptibility rates of Gram-positive organisms causing bloodstream infections in cancer patients. *J Chemother*; 20:570-576.
9. Sakoulas G, Moise-Broder PA, Schentag J, Forrest A, Moellering RC, Jr., Eliopoulos GM (2004). Relationship of MIC and bactericidal activity to efficacy of vancomycin for treatment of methicillin-resistant *Staphylococcus aureus* bacteremia. *J Clin Microbiol* 42: 2398-2402.
10. Sauermann R, Rothenburger M, Graninger W, Joukhadar C (2008). Daptomycin: A review 4 years after first approval. *Pharmacology* 81: 79-91.