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ANTIMICROBIAL SUSCEPTIBILITY OF GRAM-POSITIVE ORGANISMS ISOLATED FROM NORTH AMERICAN HOSPITALS: RESULTS FROM THE DAPTOMYCIN SURVEILLANCE PROGRAM, 2004 – 2006

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ABSTRACT

BACKGROUND: Gram-positive bacteria represent an important cause of nosocomial infection and exhibit great ability to acquire antimicrobial resistance (R). Daptomycin was approved by the US-FDA for the treatment of cutaneous infections (CI) in Sept/03 and later for *S. aureus* bacteremia/right-sided endocarditis. We evaluated DAP activity tested against GP organisms collected in North American hospitals for the 3-year period following DAP approval.

METHODS: Consecutive, non-duplicate bacterial isolates (prevalence format) were collected in 2004–2006 from patients with documented infections in 30 hospitals. The isolates were collected by site of infection according to the study protocol and susceptibility (S) tested by CLSI broth microdilution method with appropriate broth Ca^{++} content (50 mg/L) for testing DAP.

ESULTS: A total of 18,427 GP isolates, mainly from bacteremia (>60%) and CI, were evaluated. The most common pathogens were *S. aureus* (11,231 strains; 61%), *E. faecalis* (2,524; 14%), coag.-neg. staphylococci (1,707; 9%) and *E. faecium* (1,098; 6%). DAP, linezolid (LNZ) and vancomycin (VAN) were the most active compounds. DAP was generally two- to four-fold more potent than either LNZ or VAN. Only 11 DAP-non-S strains (0.06%) were observed, and all had a DAP MIC one log2 dilution above the S breakpoint. Non-S to LNZ was observed in 29 (0.16%) strains with MICs ranging from 8->256 µg/mL. No significant year-to-year variation in DAP activity was observed. *S. aureus* S to oxacillin varied from 53% in 2004 to 48% in 2006. *E. faecium* exhibited high rates of R to VAN (59-72%) and gentamicin (high-level; 18-26%).

	No / % of non-S strains (no. tested):			
Organism	2004	2005	2006	Total
S. aureus	(3,094)	(3,848)	(4,289)	(11,231)
Daptomycin	1/<0.1	3/<0.1	2/<0.1	6/<0.1
Linezolid	0/0.0	0/0.0	1/<0.1	1/<0.1
Vancomycin	1/<0.1	0/0.0	1/<0.1	2/0.1
E. faecalis	(791)	(951)	(782)	(2,524)
Daptomycin	1/0.1	0/0.0	0/0.0	1/<0.1
Linezolid	3/0.4	1/0.1	1/1.0	5/0.2
Vancomycin	14/1.8	34/3.6	32/4.1	80/3.2
E. faecium	(301)	(398)	(399)	(1,098)
Daptomycin	1/0.3	0/0.0	0/0.0	1/0.1
Linezolid	1/0.3	8/2.0	8/2.0	17/1.5
Vancomycin	177/58.9	247/62.1	288/72.2	712/64.8

CONCLUSIONS: DAP showed excellent spectrum and sustained activity against GP isolated in NA during the 3 years following FDA approval. Decreased S to DAP remains extremely rare and low level.

INTRODUCTION

Daptomycin is a novel lipopeptide antimicrobial agent designed specifically for the treatment of drug-resistant Gram-positive bacterial infections. Its spectrum includes multidrug-resistant strains for which there are very few therapeutic alternatives, such as vancomycin-resistant enterococci (VRE) and methicillin-resistant staphylococci. Daptomycin acts at the cytoplasmic membrane of susceptible bacteria and its activity is dependent on physiologic levels of free calcium ions (50 mg/L). Its mechanism of action is novel compared to classes of antimicrobial agents currently marketed and no cross-resistance with any other drug class has been demonstrated. It is important to note that the in vitro activity of daptomycin is dependent upon the calcium content of the culture medium, making accurate testing of this agent challenging for clinical microbiology laboratories.

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 caused by oxacillin-susceptible and -resistant *S. aureus*, and groups A and B β-haemolytic streptococci with a daptomycin MIC breakpoint of ≤1 µg/ml, and for vancomycin-susceptible *Enterococcus faecalis* with a susceptible breakpoint of ≤4 µg/ml. Furthermore, this compound has also been recently approved by the US-FDA for the treatment of *S. aureus* bacteremia, including right-sided endocarditis.

The Daptomycin Surveillance Program was implemented in 2002 with the objective of accurately monitoring the in vitro activity of daptomycin and comparator agents. The program has been performed in North America and Europe and recently expanded to the Asia-Pacific region. In the present study, we evaluated daptomycin activity tested against Gram-positive organisms collected in North American hospitals for the 3-year period following daptomycin approval.

MATERIALS AND METHODS

Bacterial isolates: Consecutive, non-duplicate bacterial isolates (prevalence format) were collected in 2004-2006 from patients with documented infections in 30 North American hospitals. The isolates were collected by site of infection according to the study protocols. The strains were isolated mainly from bloodstream and skin and soft tissue infections from hospitalized patients.

Susceptibility testing: Daptomycin and comparator agents were tested in validated microdilution panels manufactured by TREK Diagnostics (Cleveland, OH) according to the Clinical and Laboratory Standards Institute (CLSI) guidelines. The test medium was Mueller-Hinton broth adjusted to contain physiologic levels of calcium (50 mg/L) when testing daptomycin. US-FDA and CLSI approved daptomycin susceptible breakpoints of ≤1 µg/ml for staphylococci and streptococci, and ≤4 µg/ml for enterococci were used to categorize these Gram-positive organisms as susceptible. The following quality control organisms were concurrently tested: *E. faecalis* ATCC 29212, *S. aureus* ATCC 29213 and *Streptococcus pneumoniae* ATCC 49619.

RESULTS

- Daptomycin MIC values ranged from ≤0.06 to 2 µg/ml among 11,231 *S. aureus* strains tested (MIC_{50}, 0.25 µg/ml; MIC_{90}, 0.5 µg/ml), and 99.96% of isolates tested were inhibited at ≤1 µg/ml (Tables 1). Only six strains showed an elevated MIC value of only 2 µg/ml.
- Oxacillin-susceptible and -resistant staphylococci showed very similar daptomycin MIC distributions (**Table 1** and **Table 2**).
- Daptomycin was also very active against coagulase-negative staphylococci (1,707 strains tested; MIC_{50}, 0.25 µg/ml and MIC_{90}, 0.5 µg/ml). Only two strains with elevated MIC values were observed (99.88% susceptible), both with daptomycin MIC of 2 µg/ml (**Table 1**).

RESULTS

- Among the enterococci tested (3,081 strains), 99.94% of strains were susceptible to daptomycin (MIC_{50}, 1 µg/ml; MIC_{90}, 2 µg/ml). Only one *E. faecalis* and one *E. faecium* strains exhibit elevated daptomycin MIC values, both strains with daptomycin MIC of 8 µg/ml, which is one doubling dilution above the susceptible breakpoint (**Table 1**).
- Vancomycin-susceptible and -resistant enterococci showed very similar daptomycin MIC distributions (**Table 1**).
- β-haemolytic streptococci (1,223 strains tested) showed very low daptomycin MIC values (MIC_{50}, ≤0.06 µg/ml; MIC_{90}, 0.25 µg/ml; 100.0% susceptible); while 99.8% of viridans group streptococci were inhibited at ≤0.5 µg/ml (100.0% susceptible; **Table 1** and **Table 2**).
- Approximately half (49.6%) of *S. aureus* strains tested were resistant to oxacillin (MRSA) and exhibited high rates of co-resistance to many antimicrobials evaluated. Isolates with reduced susceptibility linezolid, quinupristin/dalfopristin or vancomycin were observed but at a very low frequency (<0.1%; **Table 2**).
- Daptomycin was highly active against *E. faecalis*, including vancomycin-resistant strains (MIC_{50}, 0.5 µg/ml and MIC90, 1 µg/ml; 100.0% susceptible at ≤4 µg/ml; *see* **Table 2**).
- Daptomycin (99.7-99.9% susceptible), linezolid (97.9-99.5% susceptible) and quinupristin/dalfopristin (80.3-96.1% susceptible) were the most active and the only compounds with acceptable activity against *E. faecium* (**Table 2**).
- Vancomycin resistance rates were highest among *E. faecium* (64.4%), and daptomycin and linezolid were the only compounds remaining highly active (>98% susceptible) against both vancomycin-susceptible and -resistant *E. faecium* isolates (**Table 2**).

Table 1. Frequency of occurrence of daptomycin MIC values for all organisms tested.

	No. (cumulative %) of isolates inhibited at daptomycin MIC (µg/ml) of:							
Organisms (no. tested)	**≤0.06**	**0.12**	**0.25**	**0.5**	**1**	**2**	**4**	**8**
S. aureus (11,231)	17 (0.2)	370 (3.5)	7,566 (70.8)	3,209 (99.4)	63 (>99.9)[a]	6 (100.0)	-	-
Oxacillin-susceptible (5,659)	12 (0.2)	263 (4.9)	4,010 (75.7)	1,353 (99.6)	19 (>99.9)	2 (100.0)	-	-
Oxacillin-resistant (5,572)	5 (0.1)	107 (2.0)	3,556 (65.8)	1,856 (99.1)	44 (>99.9)	4 (100.0)	-	-
Coagulase-negative staphylococci (1,707)	16 (0.9)	107 (7.2)	822 (55.4)	695 (96.1)	95 (99.9)	2 (100.0)	-	-
Enterococcus spp. (3,081)	17 (0.5)	24 (1.1)	137 (4.7)	1,312 (39.2)	1,473 (78.0)	640 (94.8)	195 (99.9)	3 (100.0)
E. faecalis (2,524)	10 (0.4)	21 (1.2)	116 (5.8)	1,194 (53.1)	1,074 (95.7)	98 (99.6)	10 (>99.9)	1 (100.0)
Vancomycin-susceptible (2,444)	10 (0.4)	21 (1.3)	112 (5.9)	1,153 (53.0)	1,047 (95.9)	90 (99.6)	10 (>99.9)	1 (100.0)
Vancomycin-non-susceptible (80)	0 (0.0)	0 (0.0)	4 (5.0)	41 (56.3)	27 (90.0)	8 (100.0)	-	-
E. faecium (1,098)	3 (0.3)	2 (0.5)	8 (1.2)	68 (7.4)	334 (37.8)	513 (84.5)	168 (99.8)	2 (100.0)
Vancomycin-susceptible (385)	3 (0.8)	2 (1.3)	3 (2.1)	21 (7.5)	106 (35.1)	174 (80.3)	75 (99.7)	1 (100.0)
Vancomycin-non-susceptible (713)	0 (0.0)	0 (0.0)	5 (0.7)	47 (7.3)	228 (39.3)	339 (86.8)	93 (99.9)	1 (100.0)
β-haemolytic streptococci (1,223)	665 (54.4)	292 (78.3)	236 (97.6)	30 (100.0)	-	-	-	-
Viridans group streptococci (448)	67 (15.0)	88 (34.6)	135 (64.7)	123 (99.8)	1 (100.0)	-	-	-

a. Shaded values indicate percentage of susceptible isolates.

Table 2. Antimicrobial activity of daptomycin and comparator agents tested against bacterial isoaltes collected in North American hospitals (2004-2006).

Organism/Antimicrobial agent	MIC_{50}	MIC_{90}	% susceptible/resistant[a]
S. aureus			
Oxacillin-susceptible (5,659)			
Daptomycin	0.25	0.5	>99.9 / -[b]
Clindamycin	≤0.25	≤0.25	94.7 / 5.1
Levofloxacin	≤0.5	≤0.5	91.9 / 7.2
Quinupristin-dalfopristin	≤0.25	0.5	99.9 / 0.0
Linezolid	2	2	100.0 / -
Vancomycin	1	1	100.0 / 0.0
Oxacillin-resistant (5,572)			
Daptomycin	0.25	0.5	>99.9 / -
Clindamycin	≤0.25	>8	52.0 / 47.9
Levofloxacin	>4	>4	23.1 / 74.6
Quinupristin-dalfopristin	0.5	0.5	99.9 / 0.0
Linezolid	2	2	>99.9 / -
Vancomycin	1	1	>99.9 / 0.0
Coagulase-negative staphylococci			
Oxacillin-susceptible (383)			
Daptomycin	0.25	0.5	100.0 / -
Clindamycin	≤0.25	>2	89.0 / 10.4
Levofloxacin	≤0.5	>4	83.6 / 15.4
Quinupristin-dalfopristin	≤0.25	≤0.25	99.7 / 0.0
Linezolid	1	1	100.0 / -
Vancomycin	1	2	100.0 / 0.0
Oxacillin-resistant (1,324)			
Daptomycin	0.25	0.5	99.8 / -
Clindamycin	>2	>2	48.9 / 50.1
Levofloxacin	>4	>4	34.8 / 62.1
Quinupristin-dalfopristin	≤0.25	0.5	99.8 / 0.1
Linezolid	1	1	99.5 / -
Vancomycin	1	2	100.0 / 0.0
E. faecalis			
Vancomycin-susceptible (2,444)			
Daptomycin	0.5	1	>99.9 / -
Ampicillin	≤1	2	99.4 / 0.6
Levofloxacin	1	>4	62.4 / 37.1
Gentamicin (HL)[c]	≤500	>1000	69.1 / 30.9
Streptomycin (HL)	≤1000	>2000	74.7 / 25.3
Linezolid	1	2	99.8 / 0.2
Vancomycin	1	2	96.8 / 2.7
Vancomycin-resistant (80)			
Daptomycin	0.5	1	100.0 / -
Ampicillin	≤1	2	92.5 / 7.5
Levofloxacin	>4	>4	2.5 / 93.8
Gentamicin (HL)	>1000	>1000	35.0 / 65.0
Streptomycin (HL)	>2000	>2000	33.8 / 66.3
Linezolid	1	2	97.5 / 2.5
Vancomycin	>16	>16	0.0 / 83.8
E. faecium			
Vancomycin-susceptible (385)			
Daptomycin	2	4	99.7 / -
Ampicillin	>16	>16	19.5 / 80.5
Levofloxacin	>4	>4	18.7 / 76.9
Gentamicin (HL)	≤500	≤500	91.2 / 8.8
Streptomycin (HL)	≤1000	>2000	64.2 / 35.8
Quinupristin-dalfopristin	0.5	2	80.3 / 8.1
Linezolid	1	2	99.5 / 0.5
Vancomycin	1	1	100.0 / 0.0
Vancomycin-resistant (713)			
Daptomycin	2	4	99.9 / -
Ampicillin	>16	>16	0.8 / 99.2
Levofloxacin	>4	>4	0.4 / 99.6
Gentamicin (HL)	≤500	>1000	72.2 / 27.8
Streptomycin (HL)	2000	>2000	39.3 / 60.7
Quinupristin-dalfopristin	0.5	1	96.1 / 1.5
Linezolid	1	2	97.9 / 1.8
Vancomycin	>16	>16	0.0 / 99.2
β-haemolytic streptococci (1,223)			
Daptomycin	≤0.06	0.25	100.0 / -
Penicillin	≤0.015	0.06	100.0 / -
Ceftriaxone	≤0.25	≤0.25	99.8 / -
Clindamycin	≤0.25	≤0.25	90.7 / 8.8
Levofloxacin	≤0.5	1	98.9 / 0.9
Quinupristin-dalfopristin	≤0.25	0.5	100.0 / 0.0
Linezolid	1	1	100.0 / -
Vancomycin	0.5	0.5	100.0 / -
Viridans group streptococci (448)			
Daptomycin	0.25	0.5	99.8 / -
Penicillin	0.06	1	73.4 / 3.6
Ceftriaxone	≤0.25	0.5	96.9 / 1.8
Clindamycin	≤0.25	≤0.25	94.2 / 5.8
Levofloxacin	1	2	94.0 / 5.1
Quinupristin-dalfopristin	0.5	1	98.9 / 0.0
Linezolid	0.5	1	100.0 / -
Vancomycin	0.5	0.5	100.0 / -

a. According to CLSI breakpoint criteria.
b. - = no breakpoint has been established by the CLSI.
c. HL = high-level.

CONCLUSIONS

- Daptomycin demonstrated an excellent spectrum and sustained activity against Gram-positive organisms isolated in North America during the three years following USA-FDA approval (2004-2006).
- Decreased susceptibility to daptomycin remains extremely rare (11 of 17,690 isolates; 0.06%) and low level (one log_2 dilution step above current CLSI susceptible breakpoints).
- The prevalences of MRSA (49.6%) and vancomycin-resistant *E. faecium* (64.4%) remain extremely high among isolates found in the North American medical centers participating in the Daptomycin Surveillance Program.

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