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EVALUATION OF DAPTOMYCIN ACTIVITY TESTED AGAINST 35,058 BACTERIAL STRAINS FROM HOSPITALIZED PATIENTS: SUMMARY OF A 7 YEAR SURVEILLANCE PROGRAM FOR NORTH AMERICA (2002-2008)

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ABSTRACT (REVISED)

Background: Daptomycin (DAP) is increasingly being used for treatment of skin and skin structure infection (SSSI) therapy and *S. aureus* bacteremia in the USA. We report the results for 7 years of the Daptomycin ACTIV™ Surveillance Program.

Methods: Consecutive, non-duplicate bacterial isolates (prevalence format) were collected from 2002 through 2008 from patients with documented infections in 41 medical centers in North America (NA). The isolates were collected by site of infection according to study protocols and susceptibility (S) tested against >30 antimicrobials by broth microdilution methods following CLSI guidelines. Ca^{++} content of the broth was adjusted (50 mg/L) for testing DAP.

Results: A total of 35,058 Gram-positive (GP) isolates were evaluated. They were mainly from bacteremia (53%) and SSSI (21%). During the study period, MRSA rates increased from 45.5 to 57.3%, while resistance (R) to vancomycin (VAN) among *E. faecalis* and *E. faecium* increased from 2.8 and 64.9% to 6.1 and 77.1%, respectively. MRSA and VAN-R enterococci exhibited high R rates to most agents tested. DAP remained very active and no significant year-to-year variation in DAP activity was observed with any tested species. Only 35 DAP-non-S strains (0.1%) were observed, and the vast majority (32; 91.4%) had a DAP MIC only one log_2 dilution above the published S breakpoint.

Organism (no. tested)	Cumulative % inhibited at daptomycin MIC (µg/ml) of ≤0.12	0.25	0.5	1	2	4	8	No. (%) of DAP non-S isolates
MSSA (10,376)	5.6	79.5	99.7	99.97	100.0	-	-	3 (0.03)
MRSA (11,361)	2.2	68.6	99.1	99.91	99.99	100.0	-	10 (0.09)
CoNS (3,091)	10.0	62.5	96.0	99.7	99.94	100.0	-	10 (0.32)
E. faecalis (4,496)	1.2	6.4	49.7	94.3	99.7	99.98	100.0	1 (0.02)
E. faecium (2,875)								
Vancomycin-S (580)	1.0	2.2	6.6	32.6	83.5	99.5	100.0	3 (0.52)
Vancomycin-non-S (2,295)	0.4	1.2	5.2	30.5	84.8	99.7	100.0	6 (0.26)
β-haemolytic strep. (2,006)	76.4	98.1	100.0	-	-	-	-	0 (0.00)
Viridans group strep. (570)	31.9	64.6	92.8	99.7	100.0	-	-	-[a]

a. No breakpoints have been established by CLSI or USA-FDA.

Conclusions: DAP was highly active against an extensive collection of clinically important GP pathogens. Decreased S to DAP remains rare after more than 5 years of clinical use in NA, and non-S isolates (0.1%) usually have only slightly elevated DAP MICs. R to oxacillin or VAN did not adversely affect DAP activity.

INTRODUCTION

Gram-positive bacteria, especially staphylococci and enterococci, are extremely 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 one-half of BSI cases in North American medical centers evaluated by the SENTRY Antimicrobial Surveillance Program. The increasing occurrence of MRSA and vancomycin-resistant enterococci (VRE) prompted the development of antimicrobial agents focused against Gram-positive cocci for therapy of infections caused by these multidrug-resistant (MDR) strains.

Daptomycin is a fermentation product of *Streptomyces roseosporus* and the first lipopeptide developed for clinical use. Daptomycin inserts in the outer leaflet of the bacterial membrane, inducing the leakage of potassium which results in rapid bacterial cell death. Daptomycin is active against a wide-spectrum of Gram-positive organisms, including MDR strains of staphylococci, enterococci and streptococci. United States Food and Drug Administration (USA-FDA) approved daptomycin for the treatment of MRSA or MSSA bacteremia and right sided endocarditis at a dosage of 6mg/kg every 24 hours and for complicated skin and skin structure infections (cSSSI) using a dose of 4 mg/kg every 24.

In the present study, we evaluated the antimicrobial susceptibility patterns of clinical isolates of Gram-positive organisms collected from 41 USA medical centers in the 2002-2008 surveillance period. In addition, we compared the potency of daptomycin tested against *S. aureus, Enterococcus faecalis* and *E. faecium* collected in the 2007-2008 period with those collected in the 2002-2003 interval, i.e. before daptomycin approval by the USA-FDA

MATERIALS AND METHODS

Bacterial Isolates

As part of the Daptomycin ACTIV™ Surveillance Program, 35,058 Gram-positive organisms were collected between January 2002 and December 2008 from 41 USA medical centers. The isolates were consecutively collected from prevalent sources of infection, including BSI, SSSI 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. The collection of organisms tested included: *S. aureus* (21,737 strains), coagulase-negative staphylococci (CoNS; 3,091), *E. faecalis* (4,496), *E. faecium* (2875), *Enterococcus* spp. (236), β-haemolytic streptococci (2,006), viridans group streptococci (570) and other less frequently isolates organisms (47).

Susceptibility test methods

Daptomycin and various comparator agents were tested by Clinical and Laboratory Standards Institute (CLSI) broth microdilution methods in validated, dry-form 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 for staphylococci and streptococci test interpretation, while ≤ 4 µg/ml was used for the enterococcal results, as recommended by the CLSI and the USA-FDA. The following quality control organisms were concurrently tested: *S. aureus* ATCC 29213, *E. faecalis* ATCC 29212 and *Streptococcus pneumoniae* ATCC 49619.

RESULTS

- Daptomycin was very active against 21,737 *S. aureus* isolates tested (MIC_{50}, 0.25 µg/ml and MIC_{90}, 0.5 µg/ml), and 99.9% of isolates tested were inhibited at ≤1 µg/ml. Only 13 strains showed an elevated MIC value, 12 strains with daptomycin MIC of 2 µg/ml and one with daptomycin MIC of 4 µg/ml (Table 1). Oxacillin-susceptible (MSSA) and -resistant (MRSA) *S. aureus* showed very similar daptomycin MIC distributions (Tables 1 and 2).
- During the study period, MRSA rates increased from 45.5 to 57.3% (52.3% overall; Table 2 and Figure 1) and MRSA strains exhibited high rates of resistance to many other antimicrobial agents, including clindamycin (46.1%), erythromycin (94.0%) and levofloxacin (74.6%). MSSA isolates showed higher susceptibility (≥90.0%) to all antimicrobial agents, except erythromycin (MIC_{90}, >4 µg/ml; 68.9% susceptible; Table 2).
- Daptomycin MIC distributions of *S. aureus* collected in 2007-2008 were very similar to those of isolates collected in 2002-2003, i.e. before daptomycin approval for clinical use by the USA-FDA (Table 3).
- Among CoNS (3,091 strains; MIC_{50}, 0.25 µg/ml and MIC_{90}, 0.5 µg/ml), daptomycin MIC values ranged from ≤0.12 to 4 µg/ml (99.9% susceptible; Table 1). Only 10 strains with elevated MIC values were observed, eight strains with daptomycin MIC of 2 µg/ml and two strains with a reproducible daptomycin MIC of 4 µg/ml (Table 1).
- Among the *E. faecalis*, >99.9% of vancomycin-susceptible (MIC_{50} and MIC_{90}, 1 µg/ml) and 100.0% of vancomycin-resistant (MIC_{50}, 0.5 µg/ml and MIC_{90}, 1 µg/ml) isolates were daptomycin-susceptible at ≤4 µg/ml (Table 1). Ampicillin (MIC_{90}, ≤2 mg/L; 97.1-99.7% susceptible) was also very active against *E. faecalis*, while 28.8% of vancomycin-susceptible and 69.0% of vancomycin-resistant strains showed high-level resistance to gentamicin (Table 2).
- *E. faecium* (MIC_{50}, 2 µg/ml and MIC_{90}, 4 µg/ml; 99.5-99.7% susceptible) had daptomycin MIC values slightly higher than *E. faecalis*, which is consistent with premarketing surveillance. The highest daptomycin MIC result observed was 8 µg/ml (only nine strains [0.3%]; Tables 1 and 2).

RESULTS

- From 2004 to 2008, vancomycin resistance increased from 2.0 to 6.1% among *E. faecalis* and from 69.6 to 77.1% among *E. faecium* (Figure 1). Daptomycin and linezolid were the only compounds remaining highly active (>98% susceptible) against both vancomycin-susceptible and -resistant enterococci (Table 2).
- Daptomycin MIC distributions for *E. faecalis* and *E. faecium* (vancomycin-susceptible and -resistant strains) did not vary significantly between the 2002-2003 and 2007-2008 periods, and vancomycin resistance did not adversely affect daptomycin activity against these organisms (Tables 1 to 3).
- *E. faecium*, especially vancomycin-resistant strains, showed elevated rates of resistance to most comparator antimicrobial agents tested. Furthermore, 1.3% of *E. faecium* strains were resistant to linezolid and 7.7% showed reduced susceptibility (≥2 µg/ml) to quinupristin/dalfopristin (Table 2).
- β-haemolytic streptococci had very low daptomycin MIC values (MIC_{50}, ≤0.12 µg/ml; MIC_{90}, 0.25 µg/ml; 100.0% susceptible) and decreased susceptibility to levofloxacin was observed in 20 (1.0%) strains. Viridans group streptococci (MIC_{50}, 0.25 µg/ml and MIC_{90}, 0.5 µg/ml) generally exhibited daptomycin MIC values slightly higher (two-fold) than β-haemolytic streptococci (Tables 1 and 2).

Figure 1. Yearly rates of methicillin-resistant *S. aureus* (MRSA) and vancomycin-resistant *E. faecalis* (VREF) and *E. faecium* (VREFM).

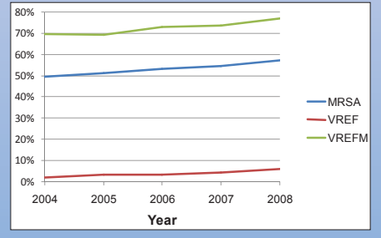

Table 1. Daptomycin MIC distributions of Gram-positive organisms collected in USA medical centers (2002-2008).

Organism (no. tested)	No. of isolates (%) inhibited at daptomycin MIC (µg/ml) of: ≤0.12	0.25	0.5	1	2	4	8
S. aureus (21,737)							
MSSA (10,376)	583(5.6)	7,667(73.9)	2,090(20.1)	33(0.3)	3(<0.1)	-	-
MRSA (11,361)	244(2.2)	7,549(66.5)	3,469(30.5)	89(0.8)	9(<0.1)	1(<0.1)	-
CoNS (3,091)	310(10.0)	1,621(52.4)	1,036(33.5)	114(3.7)	8(0.3)	2(<0.1)	-
E. faecalis							
Vancomycin-susc. (4,254)	50(1.2)	215(5.1)	1,836(43.2)	1,912(45.0)	229(5.4)	11(0.3)	1(<0.1)
Vancomycin-resistant (242)	3(1.2)	20(8.3)	111(45.9)	92(38.0)	16(6.6)	-	-
E. faecium (2,875)							
Vancomycin-susc. (580)	6(1.0)	7(1.2)	25(4.3)	151(26.0)	295(50.9)	93(16.0)	3(0.5)
Vancomycin-resistant (2,295)	8(0.4)	20(0.9)	91(4.0)	581(25.3)	1,247(54.3)	342(14.9)	6(0.3)
β-haemolytic streptococci (2,006)	1,533(76.4)	435(21.7)	38(1.9)	-	-	-	-
Viridans group streptococci (570)	182(31.9)	186(32.6)	161(28.3)	39(6.8)	2(0.4)	-	-

Table 2. Antimicrobial activity of daptomycin and comparator agents tested against Gram-positive organisms from USA medical centers.

Antimicrobial agent/ Organism (no. tested)	MIC_{50}	MIC_{90}	Range	% susceptible/resistant[a]
S. aureus				
MSSA (10,376)				
Daptomycin	0.25	0.5	≤0.12 – 2	>99.9 / -
Clindamycin	≤0.25	≤0.25	≤0.25 – >2	94.4 / 5.4
Erythromycin	≤0.25	>2	≤0.25 – >2	68.9 / 30.3
Levofloxacin	≤0.5	≤0.5	≤0.5 – >4	91.4 / 8.0
Linezolid	2	2	0.25 – 4	100.0 / -
Tetracycline	≤4	≤4	≤4 – >8	96.2 / 3.2
TMP/SMX[b]	≤0.5	≤0.5	≤0.5 – >2	98.3 / 1.7
Vancomycin	1	1	≤0.12 – 2	100.0 / 0.0
MRSA (11,361)				
Daptomycin	0.25	0.5	≤0.12 – 4	99.9 / -
Clindamycin	≤0.25	>2	≤0.25 – >2	53.7 / 46.1
Erythromycin	>2	>2	≤0.25 – >2	5.7 / 94.0
Levofloxacin	>4	>4	≤0.5 – >4	24.0 / 74.6
Linezolid	2	2	≤0.25 – >8	99.9 / -
Tetracycline	≤4	≤4	≤4 – >8	93.9 / 5.7
TMP/SMX[b]	≤0.5	≤0.5	≤0.5 – >2	97.5 / 2.5
Vancomycin	1	1	0.25 – 4	>99.9 / 0.0
CoNS (3,091)				
Daptomycin	0.25	0.5	≤0.12 – 4	99.7 / -
Oxacillin	>2	>2	≤0.25 – >2	21.5 / 78.5
Clindamycin	≤0.25	>2	≤0.25 – >2	59.7 / 39.0
Erythromycin	>2	>2	≤0.25 – >2	28.4 / 70.9
Levofloxacin	4	>4	≤0.5 – >4	41.5 / 55.3
Linezolid	1	1	≤0.25 – >8	99.2 / -
Tetracycline	≤4	>8	≤4 – >8	87.1 / 12.2
TMP/SMX	≤0.5	>2	≤0.5 – >2	61.5 / 38.5
Vancomycin	1	2	≤0.12 – 8	>99.9 / 0.0
E. faecalis				
Vancomycin-susceptible (4,254)				
Daptomycin	1	1	≤0.12 – 8	>99.9 / -
Ampicillin	≤2	≤2	≤2 – >16	99.7 / 0.3
Erythromycin	>2	>2	≤0.25 – >2	9.1 / 91.7
Gentamicin (HL)[c]	≤500	>1000	≤500 – >1000	71.2 / 28.8
Levofloxacin	1	>4	≤0.5 – >4	65.0 / 34.8
Linezolid	1	2	≤0.25 – >8	99.9 / 0.1
Streptomycin (HL)[c]	≤1000	>2000	≤1000 – >2000	75.0 / 25.0
Teicoplanin	≤2	≤2	≤2 – 4	100.0 / 0.0
Vancomycin-resistant (242)				
Daptomycin	0.5	1	≤0.06 – 2	100.0 / -
Ampicillin	≤2	≤2	≤2 – >16	97.1 / 2.9
Erythromycin	>2	>2	≤0.25 – >2	0.8 / 98.5
Gentamicin (HL)[c]	>1000	>1000	≤500 – >1000	31.0 / 69.0
Levofloxacin	>4	>4	1 – >4	1.7 / 97.1
Linezolid	1	2	0.5 – >8	98.8 / 1.2
Quinupristin/dalfopristin	>2	>2	≤0.25 – >2	1.7 / 97.9
Streptomycin (HL)[c]	>2000	>2000	≤1000 – >2000	35.5 / 64.5
Teicoplanin	>16	>16	≤2 – >16	43.0 / 55.0
E. faecium				
Vancomycin-susceptible (580)				
Daptomycin	2	4	≤0.12 – 8	99.5 / -
Ampicillin	>16	>16	≤2 – >16	23.1 / 76.9
Erythromycin	>2	>2	≤0.25 – >2	9.3 / 75.3
Gentamicin (HL)[c]	≤500	>1000	≤500 – >1000	86.9 / 13.1
Levofloxacin	>4	>4	≤0.5 – >4	21.9 / 72.8
Linezolid	1	2	0.5 – >8	99.1 / 0.9
Quinupristin/dalfopristin	1	>2	≤0.25 – >2	76.4 / 10.3
Streptomycin (HL)[c]	≤1000	>2000	≤1000 – >2000	66.8 / 33.2
Teicoplanin	≤2	≤2	≤2 – 4	100.0 / 0.0
Vancomycin-resistant (2,295)				
Daptomycin	2	4	≤0.06 – 8	99.7 / -
Ampicillin	>16	>16	≤1 – >16	0.7 / 99.3
Erythromycin	>2	>2	≤0.25 – >2	1.8 / 94.6
Gentamicin (HL)[c]	≤500	>1000	≤500 – >1000	67.8 / 32.2
Levofloxacin	>4	>4	≤0.5 – >4	0.3 / 99.6
Linezolid	1	2	≤0.06 – >8	98.4 / 1.4
Quinupristin/dalfopristin	0.5	1	≤0.25 – >2	96.3 / 1.3
Streptomycin (HL)[c]	>2000	>2000	≤1000 – >2000	38.2 / 61.8
Teicoplanin	>16	>16	≤2 – >16	6.6 / 82.5
β-haemolytic streptococci (2,006)				
Daptomycin	≤0.12	0.25	≤0.12 – 0.5	100.0 / -
Ceftriaxone	≤0.25	≤0.25	≤0.25 – 2	99.9 / -
Clindamycin	≤0.25	1	≤0.25 – >2	89.6 / 10.1
Erythromycin	≤0.25	>2	≤0.25 – >2	74.8 / 24.9
Levofloxacin	≤0.5	1	≤0.5 – >4	99.0 / 0.8
Linezolid	1	1	≤0.06 – 2	100.0 / -
Penicillin	≤0.015	0.06	≤0.015 – 0.12	100.0 / -
Tetracycline	≤4	>8	≤4 – >8	46.3 / 49.5
Viridans group streptococci (570)				
Daptomycin	0.25	0.5	≤0.12 – 2	99.7 / -
Ceftriaxone	≤0.25	1	≤0.25 – 32	93.9 / 2.8
Clindamycin	≤0.25	≤0.25	≤0.25 – >2	91.4 / 7.9
Erythromycin	0.5	>2	≤0.25 – >2	48.9 / 48.9
Levofloxacin	1	2	≤0.5 – >4	91.6 / 7.2
Linezolid	1	1	≤0.25 – 2	100.0 / -
Penicillin	0.06	1	≤0.015 – 32	72.6 / 4.9
Tetracycline	≤4	>8	≤4 – >8	63.2 / 28.8
Vancomycin	0.5	1	≤0.12 – 2	99.8 / -

a According to CLSI breakpoint criteria.
b TMP/SMX = trimethoprim/sulfamethoxazole
c HL = high level resistance.

Table 3. Frequency of occurrence of daptomycin MIC values for the organisms tested.

Organism (no. total)	No. of isolates (%) inhibited at MIC (µg/ml) of: ≤0.06	0.12	0.25	0.5	1	2	4	8
S. aureus								
Oxacillin-susceptible								
2007-2008 (3,563)	5 (0.1)	207 (5.8)	2,769 (77.7)	572 (16.1)	10 (0.3)	-	-	-
2002-2003 (1,879)	2 (0.1)	123 (6.5)	1,440 (76.6)	305 (16.3)	6 (0.3)	1 (<0.1)	-	-
Oxacillin-resistant								
2007-2008 (4,514)	2 (<0.1)	106 (2.4)	3,171 (70.3)	1,189 (26.3)	38 (0.8)	7 (0.2)	1 (<0.1)	-
2002-2003 (1,598)	1 (0.1)	32 (2.0)	1,043 (65.3)	512 (32.0)	10 (0.6)	-	-	-
Enterococcus faecalis								
2007-2008 (1,401)	5 (0.4)	9 (0.6)	48 (3.4)	484 (34.6)	726 (51.8)	125 (8.9)	4 (0.3)	-
2002-2003 (981)	2 (0.2)	10 (1.0)	87 (8.9)	478 (48.7)	367 (37.1)	38 (3.9)	2 (0.2)	-
Enterococcus faecium								
vancomycin-susceptible								
2007-2008 (203)	0 (0.0)	2 (1.0)	4 (2.0)	7 (3.5)	57 (28.1)	117 (57.6)	14 (6.9)	2 (1.0)
2002-2003 (93)	0 (0.0)	2 (2.2)	1 (1.1)	1 (1.1)	12 (12.9)	52 (55.9)	24 (25.8)	1 (1.1)
vancomycin-resistant								
2007-2008 (640)	2 (0.3)	2 (0.3)	10 (1.6)	14 (2.2)	204 (31.9)	376 (58.8)	30 (4.7)	2 (0.3)
2002-2003 (949)	1 (0.1)	3 (0.3)	5 (0.5)	29 (3.1)	153 (16.2)	535 (56.4)	219 (23.1)	4 (0.4)

- = No isolate with this MIC value.

CONCLUSIONS

- Daptomycin was highly active against *S. aureus*. Only 13 of 21,737 (0.06%) isolates tested were found to have daptomycin MIC values greater than 1 µg/ml (non-susceptible), with no significant trend towards higher MIC results over time.
- Resistance to vancomycin or quinupristin/dalfopristin or linezolid or oxacillin did not compromise daptomycin potency against staphylococci or enterococci.
- Daptomycin non-susceptibility remains extremely rare after many years of clinical use, indicating that the emergence of non-susceptibility is very low in USA medical centers.

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