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Daptomycin In Vitro Activity Tested Against Gram-Positive Strains Collected from European and Latin American Medical Centers (2003)

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AMENDED ABSTRACT

Background: Daptomycin (Cubicin®) is a cyclic lipopeptide recently approved by the US FDA. Activity profiles outside of North America remain limited and are addressed here.

Methods: The strains were consecutively collected in hospitals located in Europe (EU, 5,979 strains) and Latin America (LA, 1,215). The main pathogens evaluated were: *S. aureus* (SA; 3,035, 28% oxacillin [OXA]-resistant [R]); coagulase-negative staphylococci (CoNS; 1,251, 76% OXA-R), *E. faecalis* (EF; 707; 4% vancomycin [VAN]-R), *E. faecium* (EFM; 178, 23% VAN-R), *S. pneumoniae* (SPN; 1,456) and other streptococci (567). The strains were tested by NCCLS broth microdilution methods (broth with 50 mg/L Ca^{++} for DAP). More than 20 comparators were also tested and QC strains utilized.

Results: DAP activity is summarized in the table:

	DAP MIC_{90}/range (µg/ml)	
Organism (no. tested – EU/LA)	EU	LA
OXA-S SA (1,804/393)	0.5/≤0.12-2	0.5/0.12-1
OXA-R SA (695/143)	0.5/≤0.12-1	0.5/0.12-1
OXA-S CoNS (243/58)	0.5/≤0.12-1	0.5/≤0.016-1
OXA-R CoNS (757/193)	0.5/≤0.12-1	0.5/0.12-2
VAN-S EF (548/130)	1/0.06-2	1/≤0.016-1
VAN-R EF (23/6)	1/0.25-2	0.5/0.25-0.5
VAN-S EFM (121/16)	4/0.5-8	4/0.25-4
VAN-R EFM (41/-)	4/0.5-8	-
SPN (1,248/208)	0.25/≤0.06-1	0.25/0.03-1
ß-haemolytic strept. (299/53)	0.25/≤0.12-0.5	0.25/0.03-0.5
viridans gr. strept (200/15)	0.5/≤0.12-2	0.5/≤0.016-1

All isolates, except 2 EFM from EU, were inhibited at DAP MIC of ≤ 4 µg/ml. 99.4 and 97.3% of isolates were inhibited at DAP MIC of ≤ 2 and ≤ 1 µg/ml, respectively. Except for one *S. aureus* and one viridans group streptococci from EU, all staphylococcal and streptococcal isolates were inhibited at ≤ 1 µg DAP/ml.

Conclusions: R to other compounds (VAN, OXA, penicillin) did not influence DAP activity against staphylococci, enterococci or streptococci. The activity of DAP was very similar in both geographic regions evaluated and historically to the US. DAP showed a significant potency and spectrum against all Gram-positive bacteria including multi-drug resistant strains in the EU and LA.

INTRODUCTION

The increasing rate of antimicrobial resistance in Gram-positive pathogens has prompted development of new antimicrobial agents. Daptomycin (Cubicin®) is a cyclic lipopeptide with activity similar to teicoplanin. Daptomycin has a unique mechanism of action, resulting in no cross-resistance with any other drug class. Daptomycin's in vitro activity is dependent upon physiological levels of free calcium Ca^{++} (50 mg/L) for its bactericidal effect.

Daptomycin's spectrum of activity includes many multi-drug-resistant (MDR) Gram-positive organisms. The Food and Drug Administration (FDA) has recently approved breakpoints of ≤ 1 µg/ml for *S. aureus* and ß-haemolytic streptococci and ≤ 4 µg/ml for vancomycin-susceptible *E. faecalis*. Daptomycin activity profiles outside North America have been limited prompting increased worldwide surveillance. Reported in this study, is the daptomycin in vitro activity against 7,194 Gram-positive organisms from Europe and Latin America.

MATERIALS AND METHODS

Bacterial isolates. A total of 7,194 non-duplicate Gram-positive pathogens from Europe (5,979) and Latin America (1,215) were consecutively collected from hospitals in 2003. The main pathogens evaluated were: *S. aureus* (3,035 strains; 28% oxacillin-resistant); coagulase-negative staphylococci (1,251; 76% oxacillin-resistant), *E. faecalis* (707; 4% vancomycin-resistant), *E. faecium* (178; 23% vancomycin-resistant), *S. pneumoniae* (1,456), ß-haemolytic streptococci (352), and viridans group streptococci (215).

Susceptibility testing. Daptomycin and more than 20 comparator agents were tested using the National Committee for Clinical Laboratory Standards (NCCLS) M7-A6 broth microdilution method [NCCLS, 2003]. All strains were tested in validated, dry-form broth microdilution panels manufactured by TREK Diagnostics (Cleveland, OH). Mueller-Hinton Broth (MHB) adjusted to contain physiological levels of calcium (50 mg/L) was used when testing daptomycin. FDA and NCCLS approved daptomycin susceptibility breakpoints of ≤ 1 µg/ml for staphylococci and ß-haemolytic 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: *S. pneumoniae* ATCC 49619, *E. faecalis* ATCC 29212 and *S. aureus* ATCC 29213.

RESULTS

- The activity of daptomycin and comparators against 5,979 and 1,215 pathogenic Gram-positive strains from Europe and Latin America, respectively, are summarized in Table 1 and 2. Overall, > 99.9% of non-enterococcal strains (6,309) were inhibited at ≤ 1 µg/ml of daptomycin and 99.8% of enterococcal strains (885) were inhibited at ≤ 4 µg/ml of daptomycin.
- Among species that have been approved by the FDA for treatment with daptomycin, all but five isolates (0.1%) were susceptible to daptomycin (4,066 isolates tested) when using FDA approved breakpoints or breakpoints established by the NCCLS (publication pending in 2005).
- Daptomycin was highly potent against *S. aureus* (MIC_{50}, 0.25 µg/ml and MIC_{90}, 0.5 µg/ml) with the highest MIC result being 2 µg/ml, which was observed in only one isolate (0.03%).
- Oxacillin-susceptible *S. aureus* showed susceptibility rates of > 90% for most antimicrobials tested, except erythromycin (83.2 - 88.3% susceptible) and tetracycline (88.3% susceptible in Latin America).
- Daptomycin, linezolid and vancomycin were active against all oxacillin-resistant *S. aureus* while teicoplanin and quinupristin/dalfopristin were active against > 98% of these strains at the susceptible breakpoints.
- All CoNS strains showed a daptomycin result of ≤ 1 µg/ml. Decreased susceptibility to teicoplanin (90.7 - 98.3% susceptibility) and quinupristin/dalfopristin (99.2 - 100.0% susceptibility) among CoNS was detected in both regions, whereas vancomycin and linezolid remained active against all isolates at the susceptible breakpoints.
- Daptomycin was highly active against *E. faecalis* (MIC_{50}, 0.5 µg/ml and MIC_{90}, 1 µg/ml). All *E. faecium* isolates, except two from Europe, were inhibited at a daptomycin MIC of ≤ 4 µg/ml.
- All ß-haemolytic streptococcal strains were inhibited by ≤ 0.5 µg/ml of daptomycin. Only tetracycline showed high resistance rates among the comparators evaluated (41.5 - 46.1%).
- Daptomycin showed excellent activity against viridans group streptococci (MIC_{50}, 0.25 µg/ml and MIC_{90}, 0.5 µg/ml).

Table 1. In vitro activity of daptomycin and selected comparators tested against 4,371 Gram-positive strains from European hospitals.

	MIC (µg/ml)			Category	
Antimicrobial agent (no. of strains)	50%	90%	Range	% susceptible[a]	% resistant[a]
Oxacillin-susceptible *S. aureus* (1,804)					
Daptomycin	0.25	0.5	≤0.12-2	>99.9[b]	-[c]
Clindamycin	0.12	0.12	≤0.06->8	96.9	2.9
Levofloxacin	0.12	0.5	≤0.03->4	94.4	3.9
Quinupristin/dalfopristin	≤0.25	0.5	≤0.25->2	99.9	0.1
Trimethoprim/sulfamethoxazole	≤0.5	≤0.5	≤0.5->2	98.9	1.1
Teicoplanin	≤2	≤2	≤2-4	100.0	0.0
Vancomycin	1	1	≤0.12-4	100.0	0.0
Linezolid	2	2	0.12-8	99.9	-
Oxacillin-resistant *S. aureus* (695)					
Daptomycin	0.25	0.5	≤0.12-1	100.0[b]	-
Clindamycin	>8	>8	≤0.06->8	48.9	50.9
Levofloxacin	>4	>4	0.06->4	13.5	55.7
Quinupristin/dalfopristin	0.5	1	≤0.25->2	98.7	0.9
Trimethoprim/sulfamethoxazole	≤0.5	2	≤0.5->2	93.8	6.2
Teicoplanin	≤2	≤2	≤2-16	99.7	0.0
Vancomycin	1	1	0.5-2	100.0	0.0
Linezolid	2	2	0.5-2	100.0	-
Oxacillin-susceptible CoNS (243)					
Daptomycin	0.25	0.5	≤0.12-1	100.0[b]	-
Clindamycin	≤0.06	0.12	≤0.06->8	94.7	4.1
Levofloxacin	0.25	1	≤0.03->4	93.0	4.5
Quinupristin/dalfopristin	≤0.25	≤0.25	≤0.25-0.5	100.0	0.0
Trimethoprim/sulfamethoxazole	≤0.5	>2	≤0.5->2	88.1	11.9
Teicoplanin	≤2	4	≤2-16	96.7	0.0
Vancomycin	1	2	0.5-4	100.0	0.0
Linezolid	1	1	≤0.25-2	100.0	-
Oxacillin-resistant CoNS (757)					
Daptomycin	0.25	0.5	≤0.12-1	100.0[b]	-
Clindamycin	0.12	>8	≤0.06->8	63.0	36.5
Levofloxacin	4	>4	0.06->4	42.4	37.6
Quinupristin/dalfopristin	≤0.25	0.5	≤0.25->2	99.2	0.7
Trimethoprim/sulfamethoxazole	2	>2	≤0.5->2	51.1	48.9
Teicoplanin	≤2	4	≤2->16	97.0	0.8
Vancomycin	1	2	0.5-4	100.0	0.0
Linezolid	1	1	0.25-2	100.0	-
Vancomycin-susceptible *E. faecalis* (548)					
Daptomycin	0.5	1	0.06-2	100.0[b]	-
Ampicillin	2	4	≤1->16	99.1	0.9
Quinupristin/dalfopristin	>2	>2	≤0.25->2	2.6	90.1
Teicoplanin	≤2	≤2	≤2-4	100.0	0.0
Vancomycin	1	2	0.5-4	100.0	0.0
Linezolid	2	2	0.5-4	99.8	0.0
Vancomycin-resistant *E. faecalis* (23)					
Daptomycin	0.5	1	0.25-2	100.0[b]	-
Ampicillin	2	4	≤1-8	100.0	0.0
Quinupristin/dalfopristin	>2	>2	>2	0.0	100.0
Teicoplanin	>16	>16	≤2->16	21.7	73.9
Vancomycin	>16	>16	8->16	0.0	87.0
Linezolid	1	2	1-2	100.0	0.0
Vancomycin-susceptible *E. faecium* (121)					
Daptomycin	2	4	0.5-8	99.2[b]	-
Ampicillin	>16	>16	≤1->16	19.8	80.2
Quinupristin/dalfopristin	1	>2	≤0.25->2	73.6	10.7
Teicoplanin	≤2	≤2	≤2	100.0	0.0
Vancomycin	1	2	0.25-2	100.0	0.0
Linezolid	2	2	1-2	100.0	0.0
Vancomycin-resistant *E. faecium* (41)					
Daptomycin	2	4	0.5-8	97.6	-
Ampicillin	>16	>16	2->16	2.4	97.6
Quinupristin/dalfopristin	0.5	2	≤0.25->2	82.9	9.8
Teicoplanin	>16	>16	≤2->16	14.6	75.6
Vancomycin	>16	>16	8->16	0.0	95.1
Linezolid	2	2	1-2	100.0	0.0
ß-haemolytic streptococci (299)[e]					
Daptomycin	≤0.12	0.25	≤0.12-0.5	100.0[b]	-
Penicillin	≤0.016	0.06	≤0.016-0.12	100.0	-
Erythromycin	≤0.06	4	≤0.06->8	85.3	14.7
Levofloxacin	0.5	1	0.25->4	100.0	0.0
Quinupristin/dalfopristin	≤0.25	0.5	≤0.25-1	100.0	0.0
Tetracycline	≤4	>8	≤4->8	53.8[e]	46.1
Trimethoprim/sulfamethoxazole	≤0.5	≤0.5	≤0.5->2	-	-
Vancomycin	0.25	0.5	≤0.12-1	100.0	-
Linezolid	1	1	≤0.06-1	100.0	-
viridans group streptococci (200)					
Daptomycin	0.25	0.5	≤0.12-2	-	-
Penicillin	0.06	0.5	≤0.016-32	78.0	4.5
Erythromycin	≤0.06	>8	≤0.06->8	60.5	35.0
Levofloxacin	1	1	≤0.03->4	98.0	2.0
Quinupristin/dalfopristin	0.5	1	≤0.25-2	99.5	0.0
Tetracycline	≤4	>8	≤4->8	67.3[f]	32.7
Trimethoprim/sulfamethoxazole	≤0.5	>2	≤0.5->2	-	-
Vancomycin	0.5	1	≤0.12-1	100.0	-
Linezolid	1	1	≤0.25-2	100.0	-

a. According to NCCLS (2004) breakpoints.
b. According to breakpoints approved by the FDA (Package insert, 2004) and NCCLS (2005).
c. - = no breakpoints have been established by the NCCLS or FDA.
d. Includes intermediate and susceptible.
e. Includes group A (149 strains), group B (89 strains), group C (13 strains), group G (35 strains), ß-haemolytic *Streptococcus* spp. (two strains), *S. dysgalactiae* (seven strains) and *S. equisimilis* (four strains).

Table 2. In vitro activity of daptomycin and selected comparators tested against 1,007 Gram-positive strains from Latin American hospitals.

	MIC (µg/ml)			Category	
Antimicrobial agent (no. of strains)	50%	90%	Range	% susceptible[a]	% resistant[a]
Oxacillin-susceptible S. aureus (393)					
Daptomycin	0.25	0.5	0.12-1	100.0[b]	-[c]
Clindamycin	0.12	0.12	≤0.06->8	98.0	2.0
Levofloxacin	0.12	0.25	0.06->4	96.7	1.8
Quin/Dalfo	≤0.25	0.5	≤0.25-1	100.0	0.0
Trim/Sulfa	≤0.5	≤0.5	≤0.5->2	95.7	4.3
Teicoplanin	≤2	≤2	≤2-8	100.0	0.0
Vancomycin	1	1	0.5-2	100.0	0.0
Linezolid	2	2	0.25-2	100.0	-
Oxacillin-resistant *S. aureus* (143)					
Daptomycin	0.5	0.5	0.12-1	100.0[b]	-
Clindamycin	>8	>8	≤0.06->8	8.4	91.6
Levofloxacin	4	>4	0.06->4	8.4	27.3
Quin/Dalfo	0.5	1	≤0.25-1	100.0	0.0
Trim/Sulfa	≤0.5	>2	≤0.5->2	53.1	46.9
Teicoplanin	≤2	≤2	≤2-4	100.0	0.0
Vancomycin	1	1	0.5-2	100.0	0.0
Linezolid	2	2	0.25-2	100.0	-
Oxacillin-susceptible CoNS (58)[d]					
Daptomycin	0.25	0.5	0.06-1	100.0[b]	-[c]
Clindamycin	≤0.06	0.12	≤0.06->8	93.1	6.9
Levofloxacin	0.25	0.5	0.06-4	96.6	0.0
Quin/Dalfo	≤0.25	≤0.25	≤0.25-0.5	100.0	0.0
Trim/Sulfa	≤0.5	>2	≤0.5->2	89.7	10.3
Teicoplanin	≤2	4	≤2-16	98.3	0.0
Vancomycin	1	2	0.25-2	100.0	0.0
Linezolid	1	1	0.5-2	100.0	-
Oxacillin-resistant CoNS (193)[d]					
Daptomycin	0.25	0.5	0.12-1	99.5[b]	-
Clindamycin	>8	>8	≤0.06->8	48.2	51.3
Levofloxacin	2	>4	0.06->4	59.1	22.8
Quin/Dalfo	≤0.25	0.5	≤0.25-2	99.5	0.0
Trim/Sulfa	>2	>2	≤0.5->2	45.1	54.9
Teicoplanin	≤2	8	≤2->16	90.7	2.6
Vancomycin	1	2	0.5-4	100.0	0.0
Linezolid	1	1	0.5-2	100.0	-
Vancomycin-susceptible *E. faecalis* (130)					
Daptomycin	0.5	1	0.12-1	100.0[b]	-
Ampicillin	2	4	≤1-16	98.5	1.5
Quin/Dalfo	>2	>2	0.5->2	0.8	90.8
Teicoplanin	≤2	≤2	≤2-8	100.0	0.0
Vancomycin	2	2	0.5-4	100.0	0.0
Linezolid	2	2	1-2	100.0	0.0
Vancomycin-resistant *E. faecalis* (6)					
Daptomycin	0.5	-	0.25-0.5	100.0[b]	-
Ampicillin	4	-	2-8	100.0	0.0
Quin/Dalfo	>2	-	>2	0.0	100.0
Teicoplanin	>16	-	16->16	0.0	83.3
Vancomycin	>16	-	>16	0.0	0.0
Linezolid	2	-	1-2	100.0	0.0
Vancomycin-susceptible *E. faecium* (16)					
Daptomycin	2	4	0.25-4	100.0[b]	-
Ampicillin	>16	>16	≤1->16	25.0	75.0
Quin/Dalfo	1	>2	≤0.25->2	75.0	12.5
Teicoplanin	≤2	≤2	≤2-8	100.0	0.0
Vancomycin	1	2	0.5-4	100.0	0.0
Linezolid	1	2	1-2	100.0	0.0
ß-haemolytic streptococci (53)[f]					
Daptomycin	0.06	0.25	0.03-0.5	100.0[b]	-
Penicillin	≤0.016	0.06	≤0.016-0.12	100.0	-
Erythromycin	≤0.06	≤0.06	≤0.06-2	98.1	1.9
Levofloxacin	0.5	0.5	0.12-1	100.0	0.0
Quin/Dalfo	≤0.25	0.5	≤0.25-0.5	100.0	0.0
Tetracycline	≤4	>8	≤4->8	58.5	41.5
Trim/Sulfa	≤0.5	≤0.5	≤0.5-2	-	-
Vancomycin	0.25	0.5	0.25-1	100.0	-
Linezolid	1	1	0.25-1	100.0	-
viridans group streptococci (15)[g]					
Daptomycin	0.25	0.5	≤0.12-1	-	-
Penicillin	0.06	4	≤0.016-8	53.3	20.0
Erythromycin	≤0.06	1	≤0.06-2	73.3	20.0
Levofloxacin	1	4	0.5-4	86.7	0.0
Quin/Dalfo	0.5	1	≤0.25-1	100.0	0.0
Tetracycline	≤4	>8	≤4->8	73.3	26.7
Trim/Sulfa	≤0.5	>2	≤0.5->2	-	-
Vancomycin	0.5	1	0.25-1	100.0	-
Linezolid	1	1	0.5-1	100.0	-

a. According to NCCLS (2004) breakpoints.
b. According to breakpoints approved by the FDA (Package insert, 2004) and NCCLS (2005).
c. - = no breakpoints have been established by the NCCLS or FDA.
d. Includes: *Staphylococcus capitis* (one strain), *Staphylococcus* coagulase negative (39 strains), *S. epidermidis* (14 strains), *S. haemolyticus* (one strain), *S. hominis* (one strain), *Staphylococcus* spp. (one strain) and *S. warneri* (one strain).
e. Includes: *S. auricularis* (one strain), *Staphylococcus* coagulase negative (125 strains), *S. epidermidis* (32 strains), *S. haemolyticus* (15 strains), *S. hominis* (five strains), *S. lugdunensis* (one strain), *S. saprophyticus* (six strains), *S. simulans* (two strains), *Staphylococcus* spp. (two strains) and *S. warneri* (four strains).
f. Includes: *Streptococcus* ß-haemolytic (one strain), *Streptococcus* group A (33 strains), *Streptococcus* group B (15 strains), *Streptococcus* group C (three strains) and *Streptococcus* group G (one strain).
g. Includes *Streptococcus anginosus* (one strain), *S. bovis* (two strains), *S. mitis* (five strains), *S. oralis* (one strain), *S. salivarius* (one strain), *S. sanguis* (two strains) and *S. viridans* (three strains).

CONCLUSIONS

- Daptomycin demonstrated excellent in vitro activity against clinically significant Gram-positive bacteria isolated from patients in Europe and Latin America.
- Oxacillin resistance in *Staphylococcus* spp., vancomycin resistance in *Enterococcus* spp. and penicillin resistance in *Streptococcus* spp. did not adversely influence the activity of daptomycin.
- The activity of daptomycin was very similar in both geographic regions evaluated and historically to the U.S.
- Based on the results of this study and breakpoints recently approved by the FDA and NCCLS, daptomycin appears to be an excellent therapeutic alternative for Gram-positive infections, especially those caused by multi-drug-resistant strains.

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