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Antimicrobial Activity of Daptomycin Tested Against Clinical Strains of Indicated Species Isolated in North American Medical Centers (2003)

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AMENDED ABSTRACT

Background: Daptomycin (DAP, Cubicin®), is a cyclic lipopeptide recently approved for use by the US-FDA for the treatment of complicated skin and skin structure infections caused by oxacillin (OXA)-susceptible (S) and -resistant (R) *S. aureus* (SA) and groups A and B ß-haemolytic streptococci (ßHS) with DAP MIC at ≤ 1 µg/ml; and vancomycin [VAN]-S *E. faecalis* with DAP MIC at ≤ 4 µg/ml.

Methods: Over 2,000 clinical strains consecutively collected in hospitals located across the US and Canada (> 30) were susceptibility tested against DAP and >20 comparators by the reference broth microdilution method. Mueller-Hinton broth was supplemented to a 50 µg/ml Ca^{++} concentration for testing DAP. The pathogens evaluated included SA (1,863, 41.5% OXA-R); VAN-S *E. faecalis* (674), group A ßHS (84) and group B ßHS (138).

Results: DAP and selected comparator activities are summarized in the table:

	MIC_{90} (µg/ml)/% S					
Organism (no.)	DAP	Linezolid	Synercid	Teicoplanin	VAN	Levofloxacin
OXA-S *S. aureus* (1,090)	0.25/100	2/100	0.5/>99	≤2/100	1/100	1/91
OXA-R *S. aureus* (773)	0.5/100	2/100	1/100	≤2/100	1/100	>4/11
VAN-S EF (674)	1/100	2/99.9	>2/<1	≤2/100	2/100	>4/57
Group A ßHS (84)	≤0.06/100	1/100	≤0.25/100	≤2/100	0.5/100	1/100
Group B ßHS (138)	0.25/100	1/100	0.5/100	≤2/100	0.5/100	1/100

DAP was very active against indicated species with the highest MIC results being 1, 2 and 0.5 µg/ml for SA, *E. faecalis* and ßHS respectively. All 2,759 isolates tested were considered S to DAP. DAP was the most potent (lowest MIC_{90}) among selected antimicrobials commonly used to treat Gram-positive infections. DAP also showed excellent activity against OXA-S and -R coagulase-negative staphylococci (395 isolates; MIC range 0.12-0.5 µg/ml) and VAN-R *E. faecalis* (79 strains; MIC range, 0.06-2 µg/ml).

Conclusions: DAP showed excellent activity against clinical strains for which this compound has been approved in the baseline year of introduction. R to OXA or VAN did not influence DAP activity against staphylococci or *E. faecalis*.

INTRODUCTION

Daptomycin is a cyclic lipopeptide recently approved by the US-FDA for the treatment of complicated skin and skin structure infections caused by oxacillin-susceptible and -resistant *S. aureus* and groups A and B ß-haemolytic streptococci with a daptomycin MIC breakpoint at ≤ 1 µg/ml; and a vancomycin-susceptible *E. faecalis* breakpoint at ≤ 4 µg/ml.

Daptomycin is also active against a wide range of multi-drug-resistant (MDR) strains for which there are very few therapeutic alternatives, such as methicillin-resistant *S. aureus* and vancomycin-resistant enterococci. Daptomycin has a unique mechanism of action with no cross-resistance to glycopeptide (teicoplanin and vancomycin) resistant strains. Daptomycin acts on the cytoplasmic membrane in the presence of physiological levels of calcium ions. In vitro susceptibility testing requires appropriate supplementation of calcium to the test media.

In the present study, we evaluated the in vitro activity of daptomycin tested against recent clinical isolates of FDA-indicated species collected in North American medical centers (2003).

MATERIALS AND METHODS

Bacterial isolates. A total of 2,759 strains were evaluated from more than 30 medical centers located in the United States and Canada; all isolates were collected in 2003. The collection included oxacillin-susceptible *S. aureus* (1,090 strains), oxacillin-resistant *S. aureus* (773 strains), vancomycin-susceptible *E. faecalis* (674 strains), group A ß-haemolytic streptococci (84 strains), and group B ß-haemolytic streptococci (138 strains).

Susceptibility Testing. The strains were tested by National Committee for Clinical Laboratory Standards (NCCLS) M7-A6 broth microdilution methods [NCCLS, 2003]. Daptomycin and more than 20 comparator agents were tested in validated, dry-form microdilution panels manufactured by TREK Diagnostics Systems (Cleveland, OH). The test medium was Mueller-Hinton broth adjusted to contain physiological levels of calcium (50 mg/L) when testing daptomycin. The isolates were categorized as susceptible, intermediate and resistant according to NCCLS guidelines [2004]. A daptomycin susceptible breakpoint of ≤ 1 µg/ml was used for staphylococci and ß-haemolytic streptococci, while ≤ 4 µg/ml was used for enterococci, as recently approved by the FDA and NCCLS [2005]. The following quality control organisms were concurrently tested: *S. pneumoniae* ATCC 49619, *E. faecalis* ATCC 29212, and *S. aureus* ATCC 29213.

RESULTS

- Table 1 summarizes the activity of daptomycin and comparators against the 2,759 pathogenic Gram-positive strains tested. The highest daptomycin MIC results were 1, 2, and 0.5 µg/ml for *S. aureus, E. faecalis* and ß-haemolytic streptococci, respectively.
- All strains were considered daptomycin-susceptible using the FDA approved breakpoints or the breakpoints established by the NCCLS (M100-S15) pending for publication in 2005. Only daptomycin and vancomycin were active against all isolates at the susceptible breakpoints. Only one isolate (*E. faecalis*) was resistant to linezolid (MIC, > 8 µg/ml), and displayed a G2576U mutation.
- All *S. aureus* strains (oxacillin-susceptible and -resistant) were susceptible to daptomycin (MIC_{90}, 0.25 - 0.5 µg/ml), teicoplanin (MIC_{90}, 2 µg/ml), vancomycin (MIC_{90}, 1 µg/ml) and linezolid (MIC_{90}, 2 µg/ml). Oxacillin-susceptible *S. aureus* showed susceptibility rates > 90% for most antimicrobials tested, except erythromycin (71% susceptible) and ciprofloxacin (88.5% susceptible).
- Daptomycin activity against oxacillin-resistant *S. aureus* (MIC_{50}, 0.25 µg/ml and MIC_{90}, 0.5 µg/ml) was very similar to that against oxacillin-susceptible *S. aureus* (MIC_{50} and MIC_{90}, 0.25 µg/ml). Oxacillin-resistant *S. aureus* showed high rates of cross-resistance to erythromycin (4.4% susceptible), ciprofloxacin (9.6% susceptible) and levofloxacin (11.3% susceptible).
- Daptomycin was highly active against vancomycin-susceptible *E. faecalis* (MIC_{50}, 0.5 µg/ml and MIC_{90}, 1 µg/ml; range 0.06 - 2 µg/ml). Ampicillin (MIC_{90}, 2 µg/ml; 99.3% susceptibility) and linezolid (MIC_{90}, 2 µg/ml; 99.9% susceptibility) were also very active against vancomycin-susceptible *E. faecalis*.
- Daptomycin was uniformly active against oxacillin-susceptible and -resistant coagulase-negative staphylococci (624 isolates, 80% oxacillin-resistant; MIC range ≤ 0.06 - 1 µg/ml) and vancomycin-resistant *E. faecalis* (79 strains; MIC range, 0.06 - 2 µg/ml; data not shown).
- Daptomycin showed higher potency against group A ß-haemolytic streptococci (MIC_{50} and MIC_{90}, ≤ 0.06 µg/ml) when compared to group B ß-haemolytic streptococci (MIC_{50} and MIC_{90}, 0.25 µg/ml). All ß-haemolytic streptococcal isolates were inhibited at 0.5 µg/ml of daptomycin. Group A ß-haemolytic streptococci showed high rates of susceptibility to most antimicrobial agents tested, except tetracycline (90.5% susceptibility) and erythromycin (92.9% susceptibility). Group B ß-haemolytic streptococci showed low susceptibility rates to tetracycline (16.7%), erythromycin (68.6%) and clindamycin (86.9%). In addition, one isolate (0.7%) showed resistance to levofloxacin (MIC, > 4 µg/ml).

Table 1. In vitro activity of daptomycin and selected comparators tested against five organism groups (2,759 strains) from North American hospitals.

	MIC (µg/ml)			Category	
Antimicrobial agent (no. strains)	50%	90%	Range	% susceptible[a]	% resistant[a]
Oxacillin-susceptible *S. aureus* (1,090)					
Daptomycin	0.25	0.25	0.06-1	100.0[b]	-[c]
Oxacillin	0.5	1	≤0.25-2	100.0	0.0
Chloramphenicol	8	8	≤2->16	98.3	0.1
Clindamycin	0.12	0.25	≤0.06->8	92.1	7.3
Erythromycin	0.5	>8	≤0.06->8	71.0	27.8
Ciprofloxacin	0.25	4	0.06->4	88.5	10.1
Levofloxacin	0.12	1	≤0.03->4	90.9	7.1
Quinupristin/dalfopristin	≤0.25	0.5	≤0.25-2	99.9	0.0
Tetracycline	≤2	≤2	≤2->8	96.9	2.8
Trimethoprim/sulfamethoxazole	≤0.5	≤0.5	≤0.5->2	98.0	2.0
Teicoplanin	≤2	≤2	≤2-4	100.0	0.0
Vancomycin	1	1	0.25-2	100.0	0.0
Linezolid	2	2	0.12-4	100.0	-
Oxacillin-resistant *S. aureus* (773)					
Daptomycin	0.25	0.5	≤0.016-1	100.0[b]	-[c]
Oxacillin	>2	>2	>2	0.0	100.0
Chloramphenicol	8	16	4->16	89.4	0.1
Clindamycin	>8	>8	≤0.06->8	29.2	70.4
Erythromycin	>8	>8	≤0.06->8	4.4	94.7
Ciprofloxacin	>4	>4	0.12->4	9.6	90.0
Levofloxacin	>4	>4	0.12->4	11.3	74.4
Quinupristin/dalfopristin	0.5	1	≤0.25-1	100.0	0.0
Tetracycline	≤2	≤2	≤2->8	92.6	7.1
Trimethoprim/sulfamethoxazole	≤0.5	≤0.5	≤0.5->2	94.8	5.2
Teicoplanin	≤2	≤2	≤2-8	100.0	0.0
Vancomycin	1	1	0.25-4	100.0	0.0
Linezolid	2	2	0.5-4	100.0	-[c]
Vancomycin-susceptible *E. faecalis* (674)					
Daptomycin	0.5	1	0.06-2	100.0[b]	-[c]
Ampicillin	≤1	2	≤1->16	99.3	0.7
Chloramphenicol	8	>16	≤2->16	83.1	15.0
Levofloxacin	1	>4	0.25->4	57.4	41.8
Gentamicin (High level)	≤500	>1000	≤500->1000	71.1	28.9
Streptomycin (High level)	≤1000	>2000	≤1000->2000	70.5	29.5
Quinupristin/dalfopristin	>2	>2	0.5->2	0.7	95.8
Tetracycline	>8	>8	≤2->8	30.1	69.1
Teicoplanin	≤2	≤2	≤2-4	100.0	0.0
Vancomycin	1	2	0.25-4	100.0	0.0
Linezolid	2	2	0.25->8	99.9	0.1
group A ß-haemolytic streptococci (84)					
Daptomycin	≤0.06	≤0.06	≤0.06-0.25	100.0[b]	-[c]
Penicillin	≤0.016	≤0.016	≤0.016-0.03	100.0	0.0
Chloramphenicol	≤2	4	≤2-4	100.0	0.0
Clindamycin	≤0.06	≤0.06	≤0.06	100.0	0.0
Erythromycin	≤0.06	≤0.06	≤0.06->8	92.9	7.1
Levofloxacin	0.5	1	0.25-2	100.0	0.0
Quinupristin/dalfopristin	≤0.25	≤0.25	≤0.25-0.5	100.0	0.0
Tetracycline	≤2	≤2	≤2->8	90.5	9.5
Trimethoprim/sulfamethoxazole	≤0.5	1	≤0.5->2	-	-
Vancomycin	0.25	0.5	0.25-1	100.0	-
Linezolid	1	1	0.5-2	100.0	-
group B ß-haemolytic streptococci (138)					
Daptomycin	0.25	0.25	0.06-0.5	100.0[b]	-[c]
Penicillin	0.06	0.06	≤0.016-0.12	100.0	0.0
Chloramphenicol	≤2	4	≤2-4	100.0	0.0
Clindamycin	≤0.06	>8	≤0.06->8	86.9	12.4
Erythromycin	≤0.06	>8	≤0.06->8	68.6	31.4
Levofloxacin	0.5	1	0.25->4	99.3	0.7
Quinupristin/dalfopristin	≤0.25	0.5	≤0.25-0.5	100.0	0.0
Tetracycline	>8	>8	≤2->8	16.7	83.3
Trimethoprim/sulfamethoxazole	≤0.5	≤0.5	≤0.5	-	-
Vancomycin	0.5	0.5	0.25-1	100.0	-
Linezolid	1	1	≤0.06-1	100.0	-

a. According to NCCLS (2004) breakpoints.
b. According to breakpoints approved by the FDA (Package insert, 2003) or NCCLS (2005).
c. - = no breakpoints have been established by the NCCLS or FDA.

CONCLUSIONS

- Daptomycin demonstrated excellent in vitro activity against recent clinical isolates of Gram-positive species (2,759 isolates) for which this compound has been approved for clinical use by the FDA.
- Daptomycin activity was not influenced by oxacillin resistance in staphylococci or vancomycin resistance in *E. faecalis*.
- Based on these surveillance results, daptomycin appears to be an excellent therapeutic option for infections caused by these Gram-positive organisms, regardless of their resistance profiles to other antimicrobial classes.

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