Update on Daptomycin Antimicrobial Activity When Tested Against Clinical Strains from North American Medical Centers (2004)

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ABSTRACT

Background: Daptomycin (DAP), Cubicin®, is a cyclic lipopeptide approved by the US-FDA for the treatment of complicated skin and skin structure infections in September 2003. We evaluated the in vitro activity of DAP against bacterial isolates collected in 2004 and compared these surveillance results with those obtained in previous years (2002-3).

Methods: 13,083 clinical strains (7,843 from 2002-3 and 5,240 from 2004) were consecutively collected in 29 hospitals located across the USA (24) and Canada (5). The pathogens evaluated were: *S. aureus* (SA; 7,069, 43% oxacillin [OXA]-resistant [R]); coagulase-negative staphylococci (CoNS; 1,528, 80% OXA-R), *E. faecalis* (EF; 1,954; 5% vancomycin [VAN]-R), *E. faecium* (EFM; 1408, 82% VAN-R), ß-haemolytic streptococci (ßHS; 812) and viridans group streptococci (VGS; 312). The strains were tested for susceptibility (S) by CLSI broth microdilution methods (broth with 50 mg/L Ca^{++} for DAP). More than 20 comparator agents were also tested and QC strains were utilized.

Results: DAP activities for both periods are summarized in the table:

	MIC$_{50}$ (µg/ml)		MIC$_{90}$ (µg/ml)		% S	
Organism (no.: 2002-3/2004)	2002-3	2004	2002-3	2004	2002-3	2004
OXA-S SA (2,347/1,653)	0.25	0.25	0.5	0.5	>99.9	>99.9
OXA-R SA (1,628/1,441)	0.25	0.5	0.5	0.5	100.0	100.0
OXA-S CoNS (207/100)	0.25	0.5	0.5	0.5	99.5	100.0
OXA-R CoNS (807/414)	0.25	0.5	0.5	0.5	99.9	99.8
VAN-S EF (1,074/777)	0.5	1	1	1	100.0	99.9
VAN-R EF (89/14)	0.5	0.5	1	2	100.0	100.0
VAN-S EFM (138/123)	2	2	4	4	98.6	99.2
VAN-R EFM (969/178)	2	2	4	4	99.3	99.4
ßHS (438/374)	≤0.06	≤0.06	0.25	0.25	100.0	100.0
VGS (146/166)	0.25	0.25	0.5	1	100.0	100.0

DAP was highly active against the Gram-positive (GP) isolates tested and the activity remained stable over the 3 year period. Only 17 isolates (0.13%) tested had a decreased susceptibility to DAP, 5 staphylococci (0.06%) with DAP MIC of 2 µg/ml and 12 enterococci (0.85%) with DAP MIC of 8 µg/ml. DAP was the most potent (lowest MIC$_{90}$) among selected antimicrobials commonly used to treat GP infections.

Conclusions: R to OXA or VAN did not influence DAP activity against staphylococci or enterococci. DAP remained very active against the most clinically important GP pathogens after more than one year of clinical use in North America.

INTRODUCTION

Daptomycin is a cyclic lipopeptide approved by the United States Food and Drug Administration (US-FDA) in September 2003 for the treatment of complicated skin and skin structure infections caused by oxacillin-susceptible and -resistant *Staphylococcus aureus*, groups A and B ß-haemolytic streptococci and vancomycin-susceptible *Enterococcus faecalis*.

Previous in vitro studies have shown that daptomycin is active against a wide range of Gram-positive bacteria, including multi-drug-resistant (MDR) strains for which there are very few therapeutic alternatives, such as methicillin-resistant *S. aureus* (MRSA) and vancomycin-resistant enterococci (VRE). Daptomycin has a unique mechanism of action with no cross-resistance with commonly used glycopeptides (teicoplanin and vancomycin). 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 clinical isolates collected in 2004 in North American medicals centers and compared the results with those of isolates collected in the two previous years (2002 and 2003) in the same medical centers.

MATERIALS AND METHODS

Bacterial isolates. A total of 13,083 clinical strains (7,843 in 2002-2003 and 5,240 in 2004) were consecutively collected from 29 medical centers located in the United States and Canada. The collection included *S. aureus* (7,069 strains; 43.4% MRSA), coagulase-negative staphylococci (CoNS; 1,528 strains; 79.9% oxacillin-resistant), *E. faecalis* (1,954 strains; 5.3% vancomycin-resistant), *E. faecium* (1,408 strains; 81.5% vancomycin-resistant), ß-haemolytic streptococci (812 strains), and viridans group streptococci (312 strains).

Susceptibility testing. The strains were tested by Clinical and Laboratory Standards Institute (CLSI, formerly NCCLS) M7-A6 broth microdilution methods. 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 CLSI guidelines [2005]. A daptomycin susceptible breakpoint of ≤ 1 µg/ml was used for staphylococci and streptococci, while ≤ 4 µg/ml was used for enterococci. The following quality control organisms were concurrently tested: *Streptococcus pneumoniae* ATCC 49619, *E. faecalis* ATCC 29212, and *S. aureus* ATCC 29213.

RESULTS

- Overall, more than 99.9% of non-enterococcal strains (9,721) were inhibited at ≤ 1 µg/ml of daptomycin and 99.7% of enterococcal strains (3,362) were inhibited at ≤ 4 µg/ml of daptomycin. Twelve daptomycin-non-susceptible strains (0.2%) were detected in 2002-2003 period (seven of them [58.3%] among the vancomycin-resistant *E. faecium*), while only five (0.1%) were detected in 2004.
- Daptomycin was highly potent against *S. aureus* in both periods evaluated (MIC$_{90}$, 0.5 µg/ml). Only two daptomycin-non-susceptible strains were observed (0.03%), one in each time period evaluated. Both strains had daptomycin MIC values of 2 µg/ml.
- Daptomycin activity against CoNS (MIC$_{90}$, 0.5 µg/ml) was similar to that against *S. aureus.* Three daptomycin-non-susceptible strains were detected (0.2%; two in 2002-2003 and one in 2004), all with daptomycin MIC values of 2 µg/ml.
- Daptomycin was highly active against *E. faecalis* (MIC$_{90}$, 1-2 µg/ml), with only one daptomycin-non-susceptible (MIC, 8 µg/ml) isolate detected. The strain was isolated in 2004 and it was susceptible to vancomycin.
- Most of the daptomycin-non-susceptible strains (11 of 17) were observed among *E. faecium*. The majority of these strains (7 of 11) were among vancomycin-resistant strains collected in the 2002-2003 period. However, the number of vancomycin-resistant *E. faecium* collected in this period (969 strains) was much higher than that collected in 2004 (178 strains) due to program emphasis on these VRE.
- Daptomycin was the most active antimicrobial agent tested against enterococci (99.7% susceptibility overall), followed by linezolid (99.6%).
- All ß-haemolytic streptococcal strains were inhibited by ≤ 0.5 µg/ml of daptomycin. All strains were also susceptible to penicillin, ceftriaxone and linezolid, while susceptibility rates varied from 90.9 to 93.6% for clindamycin and from 98.1 to 98.9% for levofloxacin.
- Daptomycin showed excellent activity against viridans group streptococcal strains collected in both monitored periods evaluated (MIC$_{90}$, 0.5-1 µg/ml; 100% susceptible).
- The in vitro activities of daptomycin and the other antimicrobial agents tested were very similar in the time periods evaluated.

Table 2. Antimicrobial activity of daptomycin and selected comparators in two periods.

	MIC$_{50}$ (µg/ml)		% susceptible	
Antimicrobial agent (no. in 2002-2003/2004)	2002-2003	2004	2002-2003	2004
S. aureus				
Oxacillin-susceptible (2,317/1,653)				
Daptomycin	0.5	0.5	>99.9	>99.9
Clindamycin	0.25	0.12	93.4	95.0
Levofloxacin	0.5	0.5	91.1	93.2
Linezolid	2	2	100.0	100.0
Trimethoprim/Sulfamethoxazole	≤0.5	≤0.5	97.7	98.5
Vancomycin	1	1	100.0	100.0
Oxacillin-resistant (1,628/1,441)				
Daptomycin	0.5	0.5	100.0	100.0
Clindamycin	>8	>8	28.3	46.1
Levofloxacin	>4	>4	9.8	22.0
Linezolid	2	2	99.9	100.0
Trimethoprim/Sulfamethoxazole	≤0.5	≤0.5	95.1	97.4
Vancomycin	1	1	100.0	100.0
CoNS				
Oxacillin-susceptible (207/100)				
Daptomycin	0.5	0.5	99.5	100.0
Clindamycin	0.12	>8	92.8	82.0
Levofloxacin	4	>4	83.6	80.0
Linezolid	1	1	100.0	100.0
Trimethoprim/Sulfamethoxazole	>2	>2	82.1	82.0
Vancomycin	2	2	100.0	100.0
Oxacillin-resistant (807/414)				
Daptomycin	0.5	0.5	99.9	99.8
Clindamycin	>8	>8	52.4	48.6
Levofloxacin	>4	>4	33.0	44.0
Linezolid	1	1	100.0	100.0
Trimethoprim/Sulfamethoxazole	>2	>2	53.2	56.3
Vancomycin	2	2	100.0	100.0
E. faecalis				
Vancomycin-susceptible (1,074/777)				
Daptomycin	1	1	100.0	99.9
Ampicillin	2	2	99.3	99.7
Levofloxacin	>4	>4	56.0	61.6
Linezolid	2	2	99.9	99.7
Gentamicin (HL)	>1000	>1000	71.7	64.6
Vancomycin-resistant (89/14)				
Daptomycin	1	2	100.0	100.0
Ampicillin	2	2	94.9	100.0
Levofloxacin	>4	>4	0.0	7.1
Linezolid	2	2	98.9	92.9
Gentamicin (HL)	>1000	>1000	38.0	21.4
E. faecium				
Vancomycin-susceptible (138/123)				
Daptomycin	4	4	98.6	99.2
Ampicillin	>16	>16	24.2	21.1
Levofloxacin	>4	>4	23.2	19.5
Linezolid	2	2	99.3	100.0
Quinupristin/dalfopristin	2	2	72.5	80.5
Gentamicin (HL)	>1000	≤500	87.9	91.9
Vancomycin-resistant (969/178)				
Daptomycin	4	4	99.3	99.4
Ampicillin	>16	>16	0.9	1.1
Levofloxacin	>4	>4	0.3	0.0
Linezolid	2	2	99.6	99.4
Quinupristin/dalfopristin	1	1	96.3	96.6
Gentamicin (HL)	>1000	>1000	56.9	61.8
ß-haemolytic streptococci (438/374)				
Daptomycin	0.25	0.25	100.0	100.0
Penicillin	0.06	0.06	100.0	100.0
Ceftriaxone	≤0.25	≤0.25	100.0	100.0
Clindamycin	≤0.06	0.12	93.6	90.9
Levofloxacin	1	1	98.9	98.1
Linezolid	1	1	100.0	100.0
viridans group streptococci (146/166)				
Daptomycin	0.5	1	100.0	100.0
Penicillin	0.5	1	80.1	70.8
Ceftriaxone	0.5	0.5	95.9	97.3
Clindamycin	≤0.06	0.12	93.8	90.3
Levofloxacin	2	2	96.6	96.5
Linezolid	1	1	100.0	100.0

CONCLUSIONS

- Daptomycin demonstrated excellent in vitro activity against clinically significant Gram-positive bacteria recently (2004) isolated from North American hospitals; more than one year following US-FDA release.
- 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 remained very stable in 2004 compared to 2002-2003. Increasing resistance was not observed.
- Based on the results of this study and breakpoints approved by the US-FDA and CLSI, daptomycin remains an excellent therapeutic alternative for Gram-positive infections, especially those caused by MDR strains.

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