Antimicrobial Activity of Daptomycin Tested Against Gram-Positive Strains Collected from European Medical Centers in 2004

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AMENDED ABSTRACT

Background: Daptomycin (DAP) is a recently FDA approved lipopeptide with activity against relevant Gram-positive pathogens. We evaluated the in vitro activity of DAP tested against recent clinical isolates collected in Europe in 2004.

Methods: A total of 3,986 consecutive strains were collected in 24 medical centers located in 12 European countries. The main pathogens evaluated were: *S. aureus* (SA; 2,166 isolates, 25% oxacillin [OXA]-resistant [R]); coagulase-negative staphylococci (CoNS; 762, 77% OXA-R), *E. faecalis* (EF; 385; 2% vancomycin [VAN]-R), *E. faecium* (EFM; 171, 14% VAN-R), beta-haemolytic *Streptococcus* spp. (BHS; 317), and viridans group *Streptococcus* spp. (VGS; 126). The strains were tested by CLSI/NCCLS broth microdilution methods in Mueller-Hinton broth supplemented to 50 mg/L calcium. Numerous comparators were also tested.

Results: DAP activity is summarized in the table:

Organism (no. tested)		Daptomycin MIC (mg/L)			
		50%	90%	Range	%S
SA	OXA-S (1,631)	0.25	0.5	≤0.06-1	100.0
	OXA-R (535)	0.5	0.5	0.12-2	99.8
CoNS	OXA-S (173)	0.25	0.5	0.12-1	100.0
	OXA-R (589)	0.5	0.5	≤0.06-1	100.0
EF (385)		1	1	≤0.06-4	100.0
EFM	VAN-S (148)	4	4	0.12-4	100.0
	VAN-R (23)	2	4	1-4	100.0
Enterococcus spp. (39)		1	4	0.5-4	100.0
BHS (317)		≤0.06	0.25	≤0.06-0.5	100.0
VGS (73)		0.25	1	≤0.06-2	98.4

All isolates were inhibited at DAP MIC values of ≤ 4 mg/L. DAP and linezolid were the most active agents against VAN-R enterococci. All CoNS and > 99.9% of SA isolates evaluated were inhibited at DAP MIC ≤ 1 mg/L. DAP was highly active against BHS (MIC_{90}, ≤ 0.06 mg/L) and 98.4% of VGS strains were inhibited at DAP MIC ≤ 1 mg/L (susceptible).

Conclusions: R to other compounds did not influence the high DAP activity against staphylococci, enterococci or streptococci. DAP showed high potency and a broad spectrum against recent clinical isolates of facultative Gram-positive cocci isolated in European medical centers, including multi-drug resistant subsets.

INTRODUCTION

Daptomycin is a novel cyclic lipopeptide naturally produced by *Streptomyces rosesporus* (Figure 1). Daptomycin acts at the cytoplasmic membrane of susceptible bacteria and its activity is dependent on physiologic levels of free calcium ions (50 mg/L). Daptomycin inserts into the bacterial cytoplasmic membrane in a calcium-dependent fashion and is followed by oligomerization and disruption of the functional integrity of the cytoplasmic membrane, triggering a release of intracellular ions and rapid cell death. This 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.

Daptomycin has rapid in vitro bactericidal activity against a wide spectrum of Gram-positive organisms. Its spectrum includes multi-drug resistant strains for which there are very few therapeutic alternatives, such as vancomycin-resistant enterococci (VRE) and methicillin-resistant staphylococci.

Daptomycin is approved for use by the United States Food and Drug Administration (FDA) for the treatment of complicated skin and skin structure infections caused by oxacillin-susceptible and -resistant *Staphylococcus aureus* and groups A and B ß-haemolytic streptococci with daptomycin MIC at ≤ 1 mg/L; and vancomycin-susceptible *Enterococcus faecalis* with daptomycin MIC at ≤ 4 mg/L. Daptomycin has been increasingly used in the United States but its activity profile against contemporary isolates in other regions of the world remains limited. We evaluated the in vitro activity of daptomycin tested against recent (2004) clinical isolates collected in Europe.

MATERIALS AND METHODS

Bacterial isolates. A total of 3,986 non-duplicate Gram-positive pathogens were consecutively collected from patients hospitalized in 24 European hospitals in 2004. All organisms were isolated from human infections and only one strain per patient was included in the study. The pathogens evaluated were: *S. aureus* (2,166 strains; 24.7% oxacillin-resistant), coagulase-negative staphylococci (CoNS; 762; 77.3% oxacillin-resistant), *E. faecalis* (385; 1.6% vancomycin-resistant), *E. faecium* (171; 13.5% vancomycin-resistant) , ß-haemolytic streptococci (317), viridans group streptococci (126; 63.5 penicillin-non-susceptible), *Streptococcus bovis* (20 strains).

Susceptibility testing. Daptomycin and more than 20 comparator agents were tested using the Clinical and Laboratory Standards Institute (CLSI, formerly NCCLS) M7-A6 broth microdilution methods. 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 CLSI/NCCLS approved daptomycin susceptibility breakpoints of ≤ 1 mg/L for staphylococci and ß-haemolytic streptococci and ≤ 4 mg/L 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 3,986 pathogenic Gram-positive strains from Europe are summarized in Tables 1 - 3. Overall, > 99.9% of non-enterococcal strains (3,411) were inhibited at ≤ 1 mg/L of daptomycin and all enterococcal strains (585) were inhibited at ≤ 4 mg/L of daptomycin.
- Among species that have been approved by the FDA for treatment with daptomycin, all but one isolate (0.04%) were susceptible to daptomycin (2,744 isolates tested) when using FDA approved breakpoints or breakpoints established by the CLSI/NCCLS.
- Daptomycin was highly potent against *S. aureus* (MIC_{50}, 0.25 – 0.5 mg/L and MIC_{90}, 0.5 mg/L). Only one isolate (0.05%; daptomycin MIC of 2 mg/L) showed daptomycin MIC values of >1 mg/L, which is the susceptible breakpoint approved by the FDA and CLSI/NCCLS. Resistance to oxacillin did not significantly influence daptomycin activity and daptomycin was the most potent compound against oxacillin-resistant *S. aureus* (Table 1).
- All CoNS showed a daptomycin result of ≤ 1 mg/L. Decreased susceptibility to teicoplanin (96.6 - 98.3% susceptibility) and quinupristin/dalfopristin (99.3 - 100.0% susceptibility) among CoNS was observed, especially among oxacillin-resistant strains, whereas vancomycin and linezolid remained active against all isolates at the susceptible breakpoints.

Table 1. In vitro activity of daptomycin and selected comparators tested against staphylococcal strains from European hospitals.

Antimicrobial agent	MIC (mg/L)			Category	
	50%	90%	Range	% susceptible[a]	% resistant[a]
S. aureus					
Oxacillin-susceptible (1,631)					
Daptomycin	0.25	0.5	≤0.06-1	100.0	-[b]
Clindamycin	0.12	0.12	≤0.06->8	96.9	2.8
Levofloxacin	0.12	0.25	≤0.03->4	94.4	5.4
Trimethoprim/sulfamethoxazole	≤0.5	≤0.5	≤0.5->2	99.3	0.7
Quinupristin/dalfopristin	≤0.25	0.5	≤0.25->2	99.8	0.2
Teicoplanin	0.5	1	≤0.12-4	100.0	0.0
Vancomycin	1	1	≤0.12-2	100.0	0.0
Linezolid	2	2	0.25-2	100.0	-
Oxacillin-resistant (535)					
Daptomycin	0.5	0.5	0.12-2	99.8	-
Clindamycin	0.12	>8	≤0.06->8	54.8	45.2
Levofloxacin	>4	>4	0.06->4	9.7	86.9
Trimethoprim/sulfamethoxazole	≤0.5	1	≤0.5->2	92.3	7.7
Quinupristin/dalfopristin	0.5	1	≤0.25->2	98.9	1.1
Teicoplanin	0.5	2	≤0.12-8	100.0	0.0
Vancomycin	1	1	0.25-2	100.0	0.0
Linezolid	2	2	0.25-2	100.0	-
Coag.-negative staphylococci					
Oxacillin-susceptible (173)					
Daptomycin	0.25	0.5	0.12-1	100.0	-
Clindamycin	≤0.06	0.12	≤0.06->8	97.1	2.9
Levofloxacin	0.12	0.25	0.06->4	92.5	7.5
Trimethoprim/sulfamethoxazole	≤0.5	2	≤0.5->2	91.9	8.1
Quinupristin/dalfopristin	≤0.25	≤0.25	≤0.25-0.5	100.0	0.0
Teicoplanin	1	4	≤0.12-16	98.3	0.0
Vancomycin	1	2	0.25-2	100.0	0.0
Linezolid	1	1	0.25-2	100.0	-
Oxacillin-resistant (589)					
Daptomycin	0.5	0.5	≤0.06-1	100.0	-
Clindamycin	0.12	>8	≤0.06->8	62.5	37.0
Levofloxacin	4	>4	0.06->4	32.3	57.6
Trimethoprim/sulfamethoxazole	2	>2	≤0.5->2	52.7	47.3
Quinupristin/dalfopristin	≤0.25	0.5	≤0.25->2	99.3	0.3
Teicoplanin	2	8	≤0.12->16	96.6	0.3
Vancomycin	1	2	≤0.12-4	100.0	0.0
Linezolid	1	1	0.25-2	100.0	-

a. According to CLSI/NCCLS (2005) breakpoints.
b. - = no breakpoints have been established by the CLSI/NCCLS or FDA.

- Daptomycin was highly active against *E. faecalis* (MIC_{90}, 1 mg/L) and *E. faecium* (MIC_{90}, 4 mg/L) isolates. All enterococcal isolates were considered susceptible to daptomycin and resistance to vancomycin did not significantly influence daptomycin activity.
- ß-haemolytic streptococcal strains were very susceptible to daptomycin (MIC_{90}, 0.25 mg/L) with 98.1% of isolates being inhibited at ≤ 0.25 mg/L. The highest daptomycin MIC value was 0.5 mg/L. Group A ß-haemolytic streptococci was slightly more susceptible to daptomycin (MIC_{50} and MIC_{90}, ≤ 0.06 mg/L) than group B ß-haemolytic streptococci (MIC_{50} and MIC_{90} at 0.25 mg/L). Tetracycline (63.1% susceptible) and erythromycin (83.0% susceptible) showed high resistance rates among the comparators evaluated.

Table 2. In vitro activity of daptomycin and selected comparators tested against enterococcal strains from European hospitals.

Antimicrobial agent	MIC (mg/L)			Category	
	50%	90%	Range	% susceptible[a]	% resistant[a]
E. faecalis					
Vancomycin-susceptible (379)					
Daptomycin	1	1	≤0.06-4	100.0	-[b]
Ampicillin	≤1	2	≤1->16	98.9	1.1
Quinupristin/dalfopristin	>2	>2	0.5->2	1.8	92.1
Teicoplanin	0.25	0.25	≤0.12-2	100.0	0.0
Linezolid	2	2	0.5-2	100.0	0.0
Vancomycin-resistant (6)					
Daptomycin	0.5	NA[c]	0.5-1	100.0	-
Ampicillin	2	NA	≤1-4	100.0	0.0
Quinupristin/dalfopristin	>2	NA	>2	0.0	100.0
Teicoplanin	>16	NA	≤0.12->16	16.7	83.3
Linezolid	1	NA	1-2	100.0	0.0
E. faecium					
Vancomycin-susceptible (148)					
Daptomycin	4	4	0.12-4	100.0	-
Ampicillin	>16	>16	≤1->16	16.2	83.8
Quinupristin/dalfopristin	1	2	≤0.25->2	70.9	8.1
Teicoplanin	0.5	0.5	≤0.12-2	100.0	0.0
Linezolid	2	2	0.5-2	100.0	0.0
Vancomycin-resistant (23)					
Daptomycin	2	4	1-4	100.0	-
Ampicillin	>16	>16	≤1->16	4.3	95.7
Quinupristin/dalfopristin	0.5	2	≤0.25->2	87.0	8.7
Teicoplanin	>16	>16	0.25->16	21.7	60.9
Linezolid	2	2	1-2	100.0	0.0
Enterococcus spp.[d] (39)					
Daptomycin	1	4	0.5-4	100.0	-
Ampicillin	2	>16	≤1->16	71.8	28.2
Quinupristin/dalfopristin	2	>2	≤0.25->2	25.6	23.1
Teicoplanin	0.25	1	≤0.12->16	97.4	2.6
Vancomycin	1	4	0.5->16	92.3	2.6
Linezolid	2	2	0.5-2	100.0	0.0

a According to CLSI/NCCLS (2005) breakpoints.
b. - = no breakpoints have been established by the CLSI/NCCLS or FDA.
c. NA = not applicable.
d. Includes *Enterococcus avium* (nine strains), *E. casseliflavus* (four strains), *E. gallinarum* (three strains), *E. durans* (two strains), *E. gallinarum* (11 strains), *E. hirae* (three strains) and *Enterococcus* spp. (10 strains).

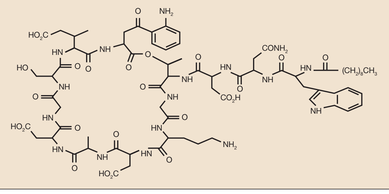
- Daptomycin showed excellent activity against viridans group streptococci (MIC_{50}, 0.25 mg/L and MIC_{90}, 1 mg/L). All isolates except two (1.6%; penicillin-susceptible strains with a daptomycin MIC of 2 mg/L) were inhibited by a daptomycin concentration of 1 mg/L.
- *Streptococcus bovis* was highly susceptible to daptomycin with MIC values ranging from ≤ 0.06 to 0.12 mg/L (MIC_{50} and MIC_{90} at ≤ 0.06 mg/L). The vast majority of isolates (95%) were inhibited at ≤ 0.06 mg/L.

Table 3. In vitro activity of daptomycin and selected comparators against streptococcal strains from European hospitals.

Antimicrobial agent	MIC (mg/L)			Category	
	50%	90%	Range	% susceptible[a]	% resistant[a]
ß-haemolytic streptococci[b] (317)					
Daptomycin	≤0.06	0.25	≤0.06-0.5	100.0	-[c]
Penicillin	≤0.016	0.06	≤0.016-0.25	100.0	-
Clindamycin	≤0.06	≤0.06	≤0.06->8	95.6	3.5
Erythromycin	≤0.06	4	≤0.06->32	83.0	26.1
Tetracycline	≤2	>8	≤2->8	63.1	35.3
Vancomycin	0.25	0.5	≤0.12-1	100.0	-
Linezolid	1	1	≤0.25-2	100.0	-
viridans group streptococci (126)					
Daptomycin	0.25	1	≤0.06-2	98.4	-
Penicillin	0.06	4	≤0.016->32	63.5	13.5
Clindamycin	≤0.06	4	≤0.06->8	88.1	11.1
Erythromycin	≤0.06	8	≤0.06->8	57.1	38.9
Vancomycin	0.5	1	≤0.12-1	100.0	-
Linezolid	1	1	0.12-1	100.0	-
Streptococcus bovis (20)					
Daptomycin	≤0.06	≤0.06	≤0.06-0.12	100.0	-
Penicillin	0.03	0.06	≤0.016-0.06	100.0	-
Clindamycin	≤0.25	>8	≤0.25->8	95.0	0.0
Erythromycin	2	>8	≤0.06->8	45.0	55.0
Vancomycin	0.25	0.5	0.25-0.5	100.0	-
Linezolid	1	1	0.5-1	100.0	-

a. According to CLSI/NCCLS (2005) breakpoints.
b. Includes; group A ß-haemolytic streptococci (166 strains), group B ß-haemolytic streptococci (83 strains) and other ß-haemolytic streptococci (68 strains).
c. - = no breakpoint has been established by the CLSI/NCCLS or FDA.

Figure 1. Structure of daptomycin.



CONCLUSIONS

- Daptomycin showed excellent in vitro activity against a wide spectrum of Gram-positive pathogens isolated from European hospitals in 2004.
- Resistance to vancomycin, quinupristin/dalfopristin, oxacillin or penicillin did not adversely influence daptomycin activity against enterococci, staphylococci or streptococci.
- Based on the results of this study and breakpoints recently approved by the FDA and CLSI/NCCLS, daptomycin appears to be an excellent therapeutic alternative for Gram-positive infections, especially those caused by multidrug-resistant strains.

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