Antimicrobial activity of daptomycin tested against Gram-positive strains collected from European medical centers in 2005: Results of the Daptomycin Surveillance Program

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Amended abstract

Objective: To evaluate the in vitro activity of daptomycin (DAP) tested against recent clinical isolates collected in Europe in 2005. DAP is a cyclic lipopeptide with activity against Gram-positive cocci (GPC) that displays no cross-resistance to other agents, making it ideal for treatment of multi-drug resistant (MDR) strains.

Methods: A total of 4,806 consecutive strains were collected in 23 medical centers located in 12 European countries. The main pathogens evaluated were: *S. aureus* (SA; 30% oxacillin [OXA]-resistant [R]); coagulase-negative staphylococci (CoNS; 72% OXA-R), *E. faecalis* (EF; 1% vancomycin [VAN]-R), *E. faecium* (EFM; 19% VAN-R), beta-haemolytic *Streptococcus* spp. (βHS), and viridans group *Streptococcus* spp. (VGS). The strains were susceptibility (S) tested by broth microdilution methods in Mueller-Hinton broth supplemented to 50 mg/L of calcium. Numerous comparators were also tested.

Results: DAP activity is summarized in the table:

	DAP MIC (mg/L)			
Organism (no.tested)	**50%**	**90%**	**Range**	**%S**
SA OXA-S (1,780)	0.25	0.5	≤0.06–1	100.0
OXA-R (746)	0.25	0.5	≤0.06–1	100.0
CoNS OXA-S (243)	0.25	0.5	≤0.06–4	99.6
OXA-R (614)	0.25	0.5	≤0.06–1	100.0
EF (595)	1	1	≤0.06–2	100.0
EFM VAN-S (229)	2	4	0.5–4	100.0
VAN-R (53)	2	4	0.5–4	100.0
βHS (370)	≤0.06	0.25	≤0.06–1	100.0
VGS (159)	0.25	1	≤0.06–1	100.0

All enterococci and staphylococci were inhibited at DAP S breakpoint (BKP) established by the Clinical and Laboratory Standards Institute (formerly NCCLS; ≤4 and ≤1 mg/L, respectively). DAP and linezolid were the only compounds active against all enterococci at the S BKP, and R to VAN did not adversely affect DAP activity. DAP was highly active against SA and CoNS (MIC_{90}, 0.5 mg/L) and independent of their S to OXA. βHS was highly S to DAP (MIC_{90}, 0.25 mg/L) and most comparison agents tested. DAP was also active against all VGS strains at the S breakpoint.

Conclusions: All GPC tested were S to DAP except one CoNS strain. R to other compounds did not influence the high DAP activity against staphylococci, enterococci or streptococci. DAP showed significant potency and broad spectrum activity against recent clinical isolates of GPC isolated in European medical centers, including MDR subsets.

Introduction

Daptomycin is a novel cyclic lipopeptide that has rapid in vitro bactericidal activity against a wide spectrum of Gram-postitive 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 acts at the cytoplasmic membrane of susceptible bacteria and its activity is dependent on physiologic levels of free calcium ions (50 mg/L). Its 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 been approved for the treatment of complicated skin and skin structure infections (cSSTI) in the United States since October 2003 and has been evaluated for treatment of bacteremia with or without endocarditis. More recently, daptomycin was approved for treatment of cSSTI in Europe. In this study, we evaluated the in vitro activity of daptomycin tested against clinical isolates collected in Europe in 2005.

Materials and methods

Bacterial isolates

A total of 4,806 non-duplicate Gram-positive pathogens were consecutively collected from patients hospitalized in 23 European medical centers in 2005. The medical centers are located in France (5), Germany (3), Greece (1), Ireland (1), Israel (1), Italy (3), Poland (1), Spain (2), Sweden (2), Switzerland (1) and Turkey (2). The main pathogens evaluated were: *Staphylococcus aureus* (2,526 strains; 30% oxacillin-resistant), coagulase-negative staphylococci (CoNS; 857; 72% oxacillin-resistant), *Enterococcus faecalis* (595; 1% vancomycin-resistant), *E. faecium* (282; 19% vancomycin-resistant), β-haemolytic streptococci (370), viridans group streptococci (159) and S*treptococcus bovis* (17 strains).

Susceptibility testing

Daptomycin and more than 20 comparator agents were tested using the Clinical Laboratory Standards Institute (CLSI) M7-A7 broth microdilution method. 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. US FDA- and CLSI-approved daptomycin-susceptible breakpoints of ≤1 mg/L for staphylococci and β-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: *E. faecalis* ATCC 29212, *S. aureus* ATCC 29213 and *Streptococcus pneumoniae* ATCC 49619.

Results

- The activity of daptomycin and comparators against 4,806 pathogenic Gram-positive strains from Europe are summarized in Table 1. All isolates, except one CoNS strain, were considered susceptible to daptomycin when applying breakpoints approved by the CLSI and US FDA.
- Daptomycin was highly active against *S. aureus* (MIC_{50}, 0.25 mg/L and MIC_{90}, 0.5 mg/L). All 2,526 strains were inhibited at the daptomycin susceptible breakpoint of ≤1 mg/L and 99.3% were inhibited at ≤0.5 mg/L. Resistance to oxacillin or other antimicrobial agents did not adversely influence daptomycin activity.
- CoNS strains were also very susceptible to daptomycin (MIC_{50}, 0.25 mg/L and MIC_{90}, 0.5 mg/L), but one strain (0.1%) showed an elevated daptomycin MIC value (4 mg/L). Decreased susceptibility to teicoplanin (98.1% susceptible) and quinupristin/dalfopristin (99.6% susceptible) was also observed among CoNS strains.
- All *E. faecalis* (MIC_{90}, 1 mg/L) and *E. faecium* (MIC_{90}, 4 mg/L) strains were inhibited at 4 mg/L of daptomycin (CLSI and US FDA susceptible breakpoint for these organisms). Vancomycin resistance rate was relatively high among *E. faecium* (MIC_{90}, >16 mg/L; 81.2% susceptible), but this resistance phenotype did not affect daptomycin activity.
- β-haemolytic streptococcal and *S. bovis* strains were very susceptible to daptomycin (MIC_{90}, 0.25 and 0.12 mg/L, respectively). Viridans group streptococcal strains showed daptomycin MIC values slightly higher (MIC_{50}, 0.25 mg/L and MIC_{90}, 0.5 mg/L), but all isolates were inhibited at 1 mg/L.

Table 1. *In vitro* activity of daptomycin and selected comparators tested against 4,806 Gram-positive organisms from European hospitals.

	MIC (mg/L)		Category	
Antimicrobial agent (no. tested)	**50%**	**90%**	**% Susceptible[a]**	**% resistant[a]**
S. aureus				
Oxacillin-susceptible (1,780)				
Daptomycin	0.25	0.5	100.0	-[b]
Clindamycin	≤0.25	≤0.25	97.2	2.6
Levofloxacin	0.12	0.25	93.8	6.0
Trimethoprim/sulfamethoxazole	≤0.5	≤0.5	99.7	0.3
Quinupristin/dalfopristin	≤0.25	0.5	99.9	0.1
Teicoplanin	0.5	1	99.9	0.1
Vancomycin	1	1	100.0	0.0
Linezolid	1	2	100.0	-
Oxacillin-resistant (746)				
Daptomycin	0.5	0.5	100.0	-
Clindamycin	≤0.25	2	50.8	48.9
Levofloxacin	>4	>4	7.1	90.9
Trimethoprim/sulfamethoxazole	≤0.5	1	94.2	5.8
Quinupristin/dalfopristin	0.5	1	98.7	1.2
Teicoplanin	0.5	2	100.0	0.0
Vancomycin	1	1	100.0	0.0
Linezolid	1	2	100.0	-
Coagulase-negative staphylococci				
Oxacillin-susceptible (243)				
Daptomycin	0.25	0.5	99.6[c]	-
Clindamycin	≤0.25	0.12	94.7	2.5
Levofloxacin	0.12	0.25	86.8	10.7
Trimethoprim/sulfamethoxazole	≤0.5	2	91.4	8.6
Quinupristin/dalfopristin	≤0.25	≤0.25	100.0	0.0
Teicoplanin	1	4	88.1	11.1
Vancomycin	1	2	100.0	0.0
Linezolid	1	1	100.0	-
Oxacillin-resistant (614)				
Daptomycin	0.25	0.5	100.0	-
Clindamycin	≤0.25	>2	66.6	32.9
Levofloxacin	4	>4	28.2	63.3
Trimethoprim/sulfamethoxazole	2	>2	52.3	47.7
Quinupristin/dalfopristin	≤0.25	0.5	99.5	0.3
Teicoplanin	2	8	97.4	0.7
Vancomycin	1	2	100.0	0.0
Linezolid	1	1	100.0	-
E. faecalis				
Vancomycin-susceptible (589)				
Daptomycin	0.5	1	100.0	-
Ampicillin	≤1	2	99.3	0.7
Quinupristin/dalfopristin	>2	>2	1.0	93.4
Teicoplanin	0.25	0.25	100.0	0.0
Linezolid	1	2	100.0	0.0
Vancomycin-non-susceptible (6)				
Daptomycin	0.5	NA[d]	100.0	-
Ampicillin	≤1	NA	100.0	0.0
Quinupristin/dalfopristin	>2	NA	0.0	100.0
Teicoplanin	>16	NA	0.0	100.0
Linezolid	1	NA	100.0	0.0
E. faecium				
Vancomycin-susceptible (229)				
Daptomycin	2	4	100.0	-
Ampicillin	>16	>16	12.2	87.8
Quinupristin/dalfopristin	1	>2	69.4	18.8
Teicoplanin	≤2	≤2	100.0	0.0
Linezolid	1	2	100.0	0.0
Vancomycin-non-susceptible (53)				
Daptomycin	2	4	100.0	-
Ampicillin	>16	>16	0.0	100.0
Quinupristin/dalfopristin	1	>2	71.7	18.9
Teicoplanin	16	>16	41.5	41.5
Linezolid	1	2	100.0	0.0
β-haemolytic streptococci[b] (370)				
Daptomycin	≤0.06	0.25	100.0	-[c]
Penicillin	≤0.016	0.03	100.0	-
Clindamycin	≤0.06	≤0.06	92.2	7.6
Erythromycin	≤0.06	4	75.4	24.1
Tetracycline	≤2	>8	58.6	38.4
Vancomycin	0.25	0.5	100.0	-
Linezolid	1	1	100.0	-
Viridans group streptococci (159)				
Daptomycin	0.25	0.5	100.0	-
Penicillin	0.03	2	79.2	8.8
Clindamycin	≤0.25	0.5	89.9	9.4
Erythromycin	≤0.25	>2	64.8	31.4
Vancomycin	0.5	0.5	100.0	-
Linezolid	0.5	1	100.0	-
Streptococcus bovis (17)				
Daptomycin	≤0.06	0.12	100.0	-
Penicillin	0.03	0.06	100.0	0.0
Clindamycin	≤0.25	>2	58.8	41.2
Erythromycin	≤0.25	>2	52.9	47.2
Vancomycin	0.25	0.5	100.0	-
Linezolid	1	2	100.0	-

[a] According to CLSI (2006) and/or US FDA breakpoints.
[b] - = no breakpoint has been established by the CLSI or US FDA.
[c] One isolate with a daptomycin MIC of 4 mg/L.
[d] NA: Not applicable.

CONCLUSIONS

Daptomycin showed excellent in vitro activity against a wide spectrum of Gram-positive pathogens isolated from European hospitals in 2005.

Resistance to oxacillin, vancomycin or quinupristin/dalfopristin did not adversely influence daptomycin activity against the indicated organisms, staphylococci or enterococci.

Based on the results of this surveillance program performed in 23 European medical centers, daptomycin represents a valuable alternative for the treatment of serious infections caused by Gram-positive cocci, including multi-drug resistant strains.

Selected references

1. Carpenter CF, Chambers HF. (2004). Daptomycin: another novel agent for treating infections due to drug-resistant gram-positive pathogens. *Clin Infect Dis* 38: 994–1000.
2. Clinical and Laboratory Standards Institute. (2006). Approved Standard M7-A7: *Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically, 7th ed.* Wayne, PA: CLSI.
3. Clinical and Laboratory Standards Institute. (2006). *Performance standards for antimicrobial susceptibility testing, 16th informational supplement M100-S16.* Wayne, PA: CLSI.
4. Dvorchik BH, Brazier D, DeBruin MF, Arbeit RD. (2003). Daptomycin pharmacokinetics and safety following administration of escalating doses once daily to healthy subjects. *Antimicrob Agents Chemother* 47: 1318–23.
5. Garcia C, Marco F, Armero Y, Amat E, Soy D, Del Rio A, Moreno A, Almela M, Manzardo C, Claramonte X, Mestres C, Perez N, Gatell J, Jimenez de Anta M, Miro J, Hospital Endocarditis Study Group. (2005). Efficacy of daptomycin in the treatment of experimental endocarditis due to methicillin-resistant (MRSA) and reduced susceptibility to glycopeptides (GISA) *Staphylococcus aureus.* 45th ICAAC, Washington, D.C.
6. Package insert. Cubicin (daptomycin for injection). Lexington MA. (Cubist Pharmaceuticals, Inc) 2003. Available at http://www.cubist.com/shared/cubicin_label.pdf. Accessed on September 22, 2003.