Antimicrobial Activity of Daptomycin Tested Against Multidrug-Resistant Gram-Positive Strains Collected in European Hospitals (2003-2007)

HS SADER, TR FRITSCHE, M JANECHECK, RN JONES

JMI Laboratories, North Liberty, IA

JMI Laboratories
North Liberty, IA, USA
www.jmilabs.com
319.665.3370, fax 319.665.3371
helio-sader@jmilabs.com

AMENDED ABSTRACT

Background: Daptomycin is a cyclic lipopeptide approved in the EU for the treatment of complicated skin and soft tissue infections (cSSTI), right sided infective endocarditis (RIE) due to *Staphylococcus aureus* (SA) and for SA bacteraemia when associated with RIE or with cSSTI. We evaluated the activity of daptomycin and comparator agents tested against multidrug-resistant (MDR) Gram-positive organisms isolated in European hospitals.

Methods: 23,269 Gram-positive organisms were collected through the European Daptomycin Surveillance Program in the 2003-2007 period, including SA (11,836), coagulase-negative staphylococci (CoNS; 4,445), enterococci (4,464), viridians group streptococci (VGS; 756) and ß-haemolytic streptococci (BHS; 1,768). Isolates were consecutively collected from patients with documented infections in 32 European hospitals (14 countries) and susceptibility tested by CLSI broth microdilution methods against daptomycin and >20 comparators. Mueller-Hinton broth was supplemented to a 50 mg/L calcium concentration for testing daptomycin. MDR was defined as resistance to drugs in 3 or more antimicrobial classes.

Results: Only 1 of 11,836 (0.01%) SA strains exhibited non-susceptibility to daptomycin (MIC, 2 mg/L), and resistance to oxacillin or other antimicrobials did not adversely influence daptomycin activity (see Table 1). Daptomycin was active against enterococci (100.0% susceptible), including strains resistant to vancomycin. Vancomycin-resistant *E. faecium* increased in Europe from 12.0% in 2004 to 25.8% in 2007 and varied significantly by country. Only 72.1% of *E. faecium* were susceptible to quinupristin/dalfopristin. All VGS strains resistant to penicillin and/or clindamycin and/or levofloxacin were susceptible to daptomycin. CoNS (MIC_{90}, 0.5 mg/L) and BHS (MIC_{90}, 0.25 mg/L) were also highly susceptible to daptomycin.

Conclusions: Daptomycin displayed significant potency and a wide spectrum of activity against problematic clinical Gram-positive cocci causing nosocomial infections in European hospitals, including MDR subsets. Daptomycin activity remained stable over the 5 year period evaluated and resistance to other antimicrobial classes did not affect daptomycin potency.

INTRODUCTION

Staphylococcus aureus remains one of the most frequent causes of a wide variety of hospital- and community-acquired infections, from superficial skin and other soft tissue infections to life threatening endocarditis and septicemia. The remarkable adaptive capacity of this pathogen resulted in the emergence and worldwide spread of lineages that acquired resistance to the majority of available antimicrobial agents. Furthermore, the emergence of multidrug-resistant (MDR) *Streptococcus pneumoniae* and increasing resistances in enterococci have emphasized the need for alternative antimicrobial agents to treat Gram-positive infections.

Daptomycin is a lipopeptide with potent in vitro activity against Gram-positive cocci. This compound has a unique mechanism of action and has demonstrated rapid bactericidal activity against a wide spectrum of Gram-positive organisms, including MDR strains of staphylococci, enterococci and streptococci. Daptomycin was approved by the USA Food and Drug Administration (USA-FDA) and by the European Medicine Agency (EMEA) for the treatment of complicated skin and skin structure infections (cSSSI) using a dose of 4 mg/kg every 24 hours, and more recently, for treatment of *S. aureus* bacteraemia and right-sided endocarditis at a higher dose of 6 mg/kg every 24 hours.

As part of the Daptomycin Surveillance Program, we evaluated the activity of daptomycin and comparator agents tested by reference methods against MDR Gram-positive organisms isolated in European hospitals.

MATERIALS AND METHODS

Bacterial isolates: A total of 23,269 Gram-positive organisms were collected through the Daptomycin Surveillance Program in the 2003-2007 period. The collection included *S. aureus* (11,836 strains), coagulase-negative staphylococci (CoNS; 4,445), enterococci (4,464), viridians group streptococci (756) and ß-haemolytic streptococci (1,768). Isolates were consecutively collected from patients with documented infections in 32 European hospitals (14 countries).

Susceptibility testing: Antimicrobial susceptibility was evaluated by reference broth microdilution methods performed according to Clinical and Laboratory Standards Institute (CLSI) documents. Daptomycin and many comparator agents were tested in validated broth microdilution panels manufactured by TREK Diagnostics (Cleveland, OH). Mueller-Hinton broth adjusted to contain physiological levels of calcium (50 mg/L) was used when testing daptomycin only.

Daptomycin breakpoints approved by EUCAST / European Medicines Evaluation Agency (EMEA) were applied for *S. aureus* and viridians group streptococci. Since EUCAST/EMEA has not established daptomycin breakpoints for enterococci, daptomycin susceptible breakpoint established by CLSI for this organism was applied for comparison purposes. The following quality control organisms were concurrently tested: *Enterococcus faecalis* ATCC 29212, *S. aureus* ATCC 29213 and *Streptococcus pneumoniae* ATCC 49619.

RESULTS

- A total of 11,836 *S. aureus* strains were tested and only one strain (0.01%) exhibited non-susceptibility to daptomycin with a MIC value of 2 mg/L, which is one doubling dilution above the susceptible breakpoint (Table 1). Daptomycin (MIC_{50}, 0.25 mg/L and MIC_{90}, 0.5 mg/L) was two- to four-fold more potent than vancomycin (MIC_{50} and MIC_{90} of 1 mg/L) and four- to eight-fold more potent than linezolid (MIC_{50} and MIC_{90} of 2 mg/L; Table 2).
- Among *S. aureus*, resistance to oxacillin, levofloxacin, clindamycin, trimethoprim/sulfamethoxazole or quinupristin/dalfopristin did not adversely influence daptomycin activity (Table 1).
- Daptomycin and linezolid (both compounds with MIC_{50} of 1 mg/L, MIC_{90} of 2 mg/L and >99.9% susceptibility) were the most active compounds tested against enterococci (Table 2).
- Vancomycin resistance was observed in 7.7% of enterococci tested and did not affect daptomycin activity (Tables 1 and 2).
- Vancomycin-resistant *E. faecium* increased in Europe from 12.0% in 2004 to 25.8% in 2007 and varied significantly by country, from less than 5% in France (2.1%) and Sweden (3.9%) to more than 40% in Greece (42.9%), United Kingdom (53.0%) and Ireland (65.9%; data not shown). Only 72.1% of *E. faecium* were susceptible to quinupristin/dalfopristin and all quinupristin/dalfopristin-resistant strains were susceptible to daptomycin (Table 1).
- All viridans group streptococci resistant to penicillin and/or clindamycin and/or levofloxacin exhibited daptomycin MIC values of ≤1 mg/L (Table 1).
- Coagulase-negative staphylococci (MIC_{90}, 0.5 mg/L) and ß-haemolytic streptococci (MIC_{90}, 0.25 mg/L) were also very susceptible to daptomycin (data not shown).

Table 1. Antimicrobial activity of daptomycin against *S. aureus*, enterococci and viridans group streptococci with selected resistance patterns.

Organism/Resistance pattern[a] (no. of strains)	Cumulative % inhibited at daptomycin MIC (mg/L) of: ≤0.06	0.12	0.25	0.05	1	2	4	8
S. aureus (11,836)	0.1	4.7	77.1	99.3	>99.9[b]	100.0	-	-
OXA (3,277)	0.1	2.9	66.4	98.7	100.0	-	-	-
OXA, LEV, CLI (1,342)	0.2	1.4	52.4	97.3	100.0	-	-	-
OXA, LEV, CLI, T/S (111)	1.8	5.4	40.5	95.5	100.0	-	-	-
Q/D (45)	0.0	0.0	62.2	100.0	-	-	-	-
Enterococci (4,464)	0.3	0.9	4.7	36.9	77.2	94.9	>99.9	100.0
VAN (386)	0.0	0.3	3.1	14.5	53.1	92.2	100.0	-
GEN (1,297)	0.1	0.2	4.2	36.5	74.9	94.5	100.0	-
VAN, TEI, AMP, GEN (102)	0.0	0.0	0.0	3.9	36.3	89.2	100.0	-
Q/D (*E. faecium*; 380)	0.0	0.3	1.3	5.8	33.9	86.8	100.0	-
Viridans group streptococci (756)	15.2	34.1	66.8	93.7	99.1	100.0	-	-
PEN (60)	1.7	23.3	56.7	86.7	100.0	-	-	-
CLI (86)	9.3	26.7	55.8	87.2	100.0	-	-	-
LEV (11)	27.3	36.4	45.5	100.0	-	-	-	-

a. OXA = oxacillin, LEV = levofloxacin, CLI = clindamycin, T/S = trimethoprim/sulfamethoxazole, Q/D = quinupristin/ dalfopristin, VAN = vancomycin, GEN = gentamicin (high-level; >500 mg/L), TEI = teicoplanin, AMP = ampicillin and PEN = penicillin.
b. Underline values indicated percentage suseptible according to EUCAST and/or CLSI breakpoints.

Table 2. Antimicrobial activity of daptomycin and comparator agents tested against Gram-positive organisms isolated in European medical centers (2003-2007).

Organism/antimicrobial agent (no. tested)	MIC (mg/L) 50%	90%	% susceptible	% resistant
S. aureus (11,836)				
Daptomycin	0.25	0.5	>99.9	<0.1
Vancomycin	1	1	>99.9	0.0
Linezolid	2	2	100.0	0.0
Clindamycin	≤0.25	>2	86.3	13.4
Levofloxacin	≤0.5	>4	70.3	28.8
Quinupristin/dalfopristin	≤0.25	0.5	99.6	0.3
Trimethoprim/sulfamethoxazole	≤0.5	≤0.5	98.2	1.8
Oxacillin	0.5	>2	72.3	27.7
Enterococcus spp. (4,464)				
Daptomycin	1	2	>99.9	-[a]
Vancomycin	1	2	91.4	7.7
Teicoplanin	≤2	≤2	93.6	5.5
Linezolid	1	2	99.9	<0.1
Ampicillin	2	>16	71.7	28.3
Gentamicin (HL)	1000	>1000	65.4	34.6
Streptomycin (HL)	≤1000	>2000	67.3	32.7
Viridans group streptococci (756)				
Daptomycin	0.25	0.5	99.1	0.9
Vancomycin	0.5	1	100.0	0.0
Linezolid	0.5	1	100.0	0.0
Penicillin	0.06	2	74.7	7.9
Ceftriaxone	≤0.25	1	90.3	6.7
Clindamycin	≤0.25	>2	88.0	11.4
Levofloxacin	1	1	98.0	1.5

a. - = No breakpoint has been established by EUCAST or CLSI.

CONCLUSIONS

- Daptomycin displayed significant potency and a wide spectrum of activity against problematic clinical isolates of Gram-positive cocci causing nosocomial infections in European hospitals, including MDR organism subsets.
- Daptomycin activity remained stable over the 5 year period evaluated and resistance to other antimicrobial classes did not affect the high daptomycin activity.

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