1829

Activity of Daptomycin and Selected Antimicrobial Agents Tested against Gram-positive Organisms Isolated from European Patients with Complicated Skin and Skin Structure Infections (cSSSI)

HS SADER, TR FRITSCHE, P STRABALA, RN JONES
JMI Laboratories, North Liberty, IA, USA

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

ABSTRACT

Objective: To evaluate the activity of daptomycin tested against Gram-positive organisms isolated from patients with cSSSI hospitalized in European hospitals in the last 4 years (2003-2006). Daptomycin has been used for the treatment of cSSSI in the United States since October 2003 and was recently approved for clinical use in European countries by the European Medicines Agency (EMEA).

Methods: A total of 2,725 bacterial strains causing cSSSI were collected from 24 medical centers located in 12 European countries, Turkey and Israel. The strains were susceptibility (S) tested against daptomycin and numerous comparator agents by reference broth microdilution methods performed according to CLSI documents (M7-A7; M100-S17). Test medium was supplemented with calcium (50 mg/L) for testing daptomycin only. All quality control results were within published CLSI ranges.

Results: Daptomycin and selected comparator activities (vancomycin [VAN], quinupristin/dalfopristin [Q/D], linezolid [LZD] and levofloxacin [LEVO]) are summarized in the table. Rates of oxacillin-resistant *S. aureus* (MRSA) varied widely from 0.7% in Sweden to more than 40% in Greece (41.0%) and Ireland (47.8%). Vancomycin-resistant *Enterococcus* (VRE) was observed in Germany, Greece, Ireland, Italy, Turkey and the United Kingdom, and prevalence remained low in most European countries relative to the USA. Daptomycin was active against all strains at the S breakpoint and its activity remained stable over the 4 years evaluated. Daptomycin and LZD showed the broadest spectrum of activity (100.0% S) among the antimicrobials tested, but daptomycin was generally more potent (lower MIC_{50} and MIC_{90}) than LZD. Non-S to Q/D has increased significantly among *E. faecium* (42.2%; 27.5% at 2 mg/L) and also emerged among staphylococci (0.4-0.5%). LEVO showed limited activity against staphylococci and enterococci. Resistance (R) to other antimicrobial classes did not adversely affect daptomycin activity against staphylococci, enterococci or streptococci. Daptomycin was very active against ORSA (MIC_{50}, 0.25 mg/L) and VAN-R *E. faecium* (MIC_{50}, 2 mg/L).

Organism (no.)	MIC_{90} (mg/L) / % S				
	Daptomycin	VAN	Q/D	LZD	LEVO
S. aureus (1,878)	0.5/100.0	1/100	0.5/99.5	2/100.0	>4/75.5
Coagulase-negative staphylococci (235)	0.5/100.0	2/100	0.5/99.6	1/100.0	>4/56.2
E. faecalis (198)	1/100.0	2/98.0	>2/0.0	2/100.0	>4/61.1
E. faecium (51)	4/100.0	1/90.2	>2/58.8	2/100.0	>4/27.5
ß-haemolytic streptococci (306)	0.25/100.0	0.5/100.0	0.5/100.0	1/100.0	1/100.0
Viridans group streptococci (38)	0.5/100.0	1/100.0	1/100.0	2/100.0	1/97.4

Conclusions: Daptomycin was highly active (100.0% S) against the most clinically important Gram-positive pathogens causing cSSSI in European medical centers, including multi-drug resistant organisms. Continued wide geographic monitoring would be preferred to detect emerging daptomycin-R strains, especially among strains with compromised VAN activity.

INTRODUCTION

Daptomycin is a novel lipopeptide antimicrobial agent designed specifically for the treatment of drug-resistant Gram-positive bacterial infections. Daptomycin has been shown to be active against *Staphylococcus aureus* resistant to methicillin (oxacillin), linezolid, and quinupristin/dalfopristin, vancomycin-resistant enterococci (VRE), and macrolide-resistant streptococci. This compound has been used for the treatment of patients with complicated skin and skin structure infections (cSSSI) in the United States since October 2003.

Daptomycin was approved by the United States Food and Drug Administration (US-FDA) and by the European Medicine Agency (EMEA) for the treatment of cSSSI caused by oxacillin-susceptible and –resistant *S. aureus*, and groups A and B ß-haemolytic streptococci with a daptomycin MIC breakpoint of ≤1 mg/L, and for vancomycin-susceptible *Enterococcus faecalis* with a susceptible breakpoint of ≤4 mg/L. Furthermore, this compound has also been recently approved by the US-FDA for the treatment of *S. aureus* bacteremia, including right-sided endocarditis.

The Daptomycin Surveillance Program was implemented in Europe in 2003 with the objective of monitoring the in vitro activity of daptomycin and comparator agents. In the present study, we evaluated the activity of daptomycin tested against Gram-positive organisms isolated from patients with cSSSI hospitalized in European hospitals in the last 4 years (2003-2006).

MATERIALS AND METHODS

Bacterial strains: A total of 2,725 bacterial strains were evaluated. The strains were collected from patients hospitalized with cSSSI in 24 medical centers located in 12 European countries, Turkey and Israel. Only one bacterial strain per patient was included in the study.

Susceptibility testing: Daptomycin and comparator agents were tested in validated microdilution panels manufactured by TREK Diagnostics (Cleveland, USA) according to the Clinical and Laboratory Standards Institute (CLSI) guidelines. The test medium was Mueller-Hinton broth adjusted to contain physiologic levels of calcium (50 mg/L) when testing daptomycin. US-FDA and CLSI approved daptomycin susceptible breakpoints of ≤1 mg/L for staphylococci and 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: *Enterococcus faecalis* ATCC 29212, *S. aureus* ATCC 29213 and *Streptococcus pneumoniae* ATCC 49619.

RESULTS

- Daptomycin MIC values ranged from ≤0.12 to 1 mg/L among 1,878 *S. aureus* strains causing cSSSI (MIC_{50}, 0.25 mg/L and MIC_{90}, 0.5 mg/L). Thus, all isolates tested were inhibited at the susceptible breakpoint approved by CLSI, US-FDA and EUCAST (≤1 mg/L; Tables 1 and 2).
- Daptomycin was also active against all CoNS strains at the susceptible breakpoint (MIC_{50}, 0.25 mg/L and MIC_{90}, 0.5 mg/L).
- Oxacillin-susceptible and -resistant staphylococci showed very similar daptomycin MIC distributions.
- Among the *E. faecalis*, daptomycin MIC values ranged from ≤0.12 to 4 mg/L with an MIC_{50} of 0.5 mg/L and an MIC_{90} of 2 mg/L; while *E. faecium* exhibited daptomycin MIC values slightly higher (MIC_{50}, 2 mg/L and MIC_{90}, 4 mg/L).
- All enterococcal strains were susceptible to daptomycin and resistance to vancomycin did not adversely affect daptomycin activity.
- Decreased susceptibility to quinupristin/dalfopristin has increased significantly among *E. faecium* (only 58.8% susceptible), especially in Germany and Italy. Quinupristin/dalfopristin-resistance has also emerged among staphylococci (0.4-0.5%), but only in France.
- ß-haemolytic streptococci (306 strains tested) showed very low daptomycin MIC values (MIC_{50}, ≤0.12 mg/L; MIC_{90}, 0.25 mg/L; 100.0% susceptible); while 97.4% of viridans group streptococci were inhibited at ≤0.5 mg/L (100.0% susceptible; Tables 1 and 2).
- Overall, 23.5% of *S. aureus* were resistant to oxacillin. The highest oxacillin resistance rates were shown in Ireland (47.8%), Greece (41.0%), Israel (36.0%) and the United Kingdom (32.6%; Table 3).
- Vancomycin-resistant *Enterococcus* (VRE) was observed in Germany, Greece, Ireland, Italy, Turkey and the United Kingdom, but the overall VRE rate was low (3.5%) relative to the USA. (Table 3).
- Daptomycin and linezolid showed the broadest spectrum of activity (100.0% susceptible) among the antimicrobials tested, but daptomycin was generally more potent (lower MIC_{50} and MIC_{90}) than linezolid.

Table 1. Daptomycin MIC population distributions for Gram-positive organisms isolated from cSSSI in Europe, 2003-2006.

Organism (no. tested)	Occurrences at MIC in mg/L (cumulative %):					
	≤0.12	0.25	0.5	1	2	4
S. aureus (1,878)	68 (3.6)	1,268 (71.1)	531 (99.4)	11 (100.0)	-	-
CoNS (235)	24 (11.5)	127 (64.3)	75 (96.2)	9 (100.0)	-	-
E. faecalis (198)	1 (0.5)	6 (3.5)	89 (48.5)	97 (97.5)	4 (99.5)	1 (100.0)
E. faecium (51)	0 (0.0)	0 (0.0)	1 (2.0)	9 (19.6)	30 (78.4)	11 (100.0)
ß-haemolytic streptococci (306)	273 (89.2)	30 (99.0)	3 (100.0)	-	-	-
Viridans group streptococci (38)	12 (31.6)	17 (76.3)	8 (97.4)	1 (100.0)	-	-

Table 2. In vitro activity of daptomycin and selected comparators tested against 2,725 Gram-positive organisms causing cSSSI in European Medical Centers.

Organism (no. tested)	MIC (mg/L)		% Susceptible	% Resistant
	50	90		
S. aureus (1,878)				
Daptomycin	0.25	0.5	100.0	-[a]
Oxacillin	0.5	>2	76.5	23.5
Levofloxacin	≤0.5	>4	75.5	23.4
Trimethoprim/sulfamethoxazole	≤0.5	≤0.5	97.4	2.6
Clindamycin	≤0.25	>2	88.6	11.2
Quinupristin/dalfopristin	≤0.25	0.5	99.5	0.4
Linezolid	2	2	100.0	-
Teicoplanin	≤2	≤2	100.0	0.0
Vancomycin	1	1	100.0	0.0
CoNS (235)				
Daptomycin	0.25	0.5	100.0	-
Oxacillin	2	>2	29.1	71.9
Levofloxacin	≤0.5	>4	56.2	38.7
Trimethoprim/sulfamethoxazole	≤0.5	>2	76.6	23.4
Clindamycin	≤0.25	>2	75.3	24.3
Quinupristin/dalfopristin	≤0.25	0.5	99.6	0.0
Linezolid	1	1	100.0	-
Teicoplanin	≤2	4	97.0	0.4
Vancomycin	1	2	100.0	0.0
E. faecalis (198)				
Daptomycin	1	1	100.0	-
Ampicillin	≤1	2	98.0	2.0
Gentamicin (HL)[b]	≤500	>1000	66.2	33.8
Quinupristin/dalfopristin	>2	>2	0.0	94.9
Linezolid	1	2	100.0	0.0
Teicoplanin	≤2	≤2	98.0	2.0
Vancomycin	1	2	98.0	2.0
E. faecium (51)				
Daptomycin	2	4	100.0	-
Ampicillin	>16	>16	21.6	78.4
Gentamicin (HL)[b]	≤500	>1000	66.7	33.3
Quinupristin/dalfopristin	1	>2	58.8	13.7
Linezolid	2	2	100.0	0.0
Teicoplanin	≤2	8	90.2	7.8
Vancomycin	1	2	90.2	9.8
ß-haemolytic streptococci (306)				
Daptomycin	≤0.12	0.25	100.0	-
Penicillin	≤0.016	0.03	100.0	0.0
Erythromycin	<0.25	>2	78.8	18.3
Clindamycin	≤0.25	≤0.25	93.5	6.2
Levofloxacin	0.5	1	100.0	0.0
Linezolid	1	1	100.0	-
Viridans group streptococci (38)				
Daptomycin	0.25	0.5	100.0	-
Penicillin	0.0	0.25	89.5	0.0
Ceftriaxone	≤0.25	0.5	97.4	0.0
Erythromycin	≤0.25	>2	71.1	23.7
Clindamycin	≤0.25	>2	86.8	13.2
Levofloxacin	≤0.5	1	97.4	2.6
Linezolid	1	1	100.0	-

a. - = No breakpoint has been established by CLSI or US-FDA.
b. HL: high level.

Table 3. Rates of methicillin (oxacillin)-resistant *S. aureus* (MRSA) and vancomycin-resistant enterococci (VRE) among isolates causing complicated skin and skin structure infections in European medical centers (2003-2006).

Country	Prevalence (no. of isolates tested)	
	MRSA	VRE
Belgium	20.0 (15)	0.0 (7)
France	27.4 (369)	0.0 (38)
Germany	6.0 (253)	1.7 (60)
Greece	41.0 (61)	22.2 (9)
Ireland	47.8 (134)	11.1 (18)
Israel	36.0 (75)	0.0 (20)
Italy	28.2 (157)	2.3 (43)
Poland	29.5 (44)	0.0 (1)
Russia	2.9 (34)	-
Spain	19.9 (228)	0.0 (19)
Sweden	0.7 (143)	0.0 (21)
Switzerland	21.3 (47)	0.0 (2)
Turkey	17.6 (102)	7.7 (13)
UK	32.6 (216)	33.3 (6)
Overall	23.5 (1,878)	3.5 (257)

CONCLUSIONS

- Daptomycin was highly active in vitro (100% susceptible) against *S. aureus* and a wide spectrum of Gram-positive pathogens isolated from patients with skin and skin structure infections in European hospitals, including multi-drug resistant organisms.
- Daptomycin activity against enterococci, staphylococci and streptococci was not affected by resistance to vancomycin, quinupristin/dalfopristin, oxacillin or penicillin.
- Wide geographic monitoring should be continued to determine if emerging daptomycin-resistant strains occur, especially among strains with compromised vancomycin activity.

SELECTED REFERENCES

1. Clinical and Laboratory Standards Institute. (2006). *M7-A7, Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically; approved standard - seventh edition.* Wayne, PA: CLSI.
2. Clinical and Laboratory Standards Institute. (2007). *M100-S17, Performance standards for antimicrobial susceptibility testing, 17th informational supplement.* Wayne, PA: CLSI.
3. Fluit AC, Schmitz FJ, Verhoef J, Milatovic D (2004). In vitro activity of daptomycin against Gram-positive European clinical isolates with defined resistance determinants. *Antimicrob Agents Chemother* 48: 1007-1011.
4. Fuchs PC, Barry AL, Brown SD (2000). Daptomycin susceptibility tests: Interpretive criteria, quality control, and effect of calcium on in vitro tests. *Diagn Microbiol Infect Dis* 38: 51-58.
5. Package insert. Cubicin (daptomycin for injection). Lexington MA. (Cubist Pharmaceuticals, Inc) 2003. Available at http://www.cubist.com/prescribe.htm Accessed on March 9, 2006.
6. Sader HS, Jones RN (2006). The activity of daptomycin against wild-type *Staphylococcus aureus* and strains with reduced susceptibility to vancomycin. *Clin Infect Dis* 43: 798-799.
7. Sader HS, Streit JM, Fritsche TR, Jones RN (2006). Antimicrobial susceptibility of Gram-positive bacteria isolated from European medical centres: Results of the Daptomycin Surveillance Programme (2002-2004). *Clin Microbiol Infect* 12: 844-852.

This study was funded by Novartis Pharmaceuticals