Update on Daptomycin Activity and Spectrum Tested against Gram-positive Organisms Collected in 2011 from European Medical Centers

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HS SADER, RK FLAMM, GJ MOET, RN JONES
JMI Laboratories, North Liberty, Iowa, USA

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

Abstract

Objectives: To evaluate the in vitro activity and spectrum of daptomycin (DAP) by surveillance testing against clinical isolates collected in European (EU) hospitals in 2011 and to compare DAP activity against isolates from two time periods, in 2005 (ie. before approval for clinical use by the European Medicines Agency [EMA]) and 2011. DAP is a cyclic lipopeptide approved in the United States (2003) and EU countries (2006) for the treatment of complicated skin and skin structure infections and *S. aureus* (SA) associated bacteremia and right-sided endocarditis.

Methods: 2,977 and 5,307 consecutive strains were collected in 2011 and 2005, respectively, from 25 medical centers in 11 EU countries and Israel. The strains were susceptibility (S) tested against DAP and comparators by the CLSI broth microdilution method in cation-adjusted Mueller-Hinton broth supplemented to 50 mg/L of calcium for DAP tests. MIC results were interpreted according to EUCAST and CLSI breakpoint criteria.

Results: DAP remains very active against SA (100.0% S) and coagulase-negative staphylococci (CoNS; 99.7% S, only 1 non-S strain from 2011) with $MIC_{50/90}$ of 0.25/0.5 mg/L for both organisms (see Table 1). In 2011, MRSA rates ranged from 1.0% in Sweden to 61.5% in Portugal, and 7 countries had an MRSA rate >25.0%. DAP was highly active against MRSA ($MIC_{50/90}$, 0.25/0.5 mg/L) as was linezolid (LZD; $MIC_{50/90}$, 1/1 mg/L; 100% S), tigecycline (TIG; $MIC_{50/90}$, 0.06/0.12 mg/L) and vancomycin (VAN; $MIC_{50/90}$, 1/1 mg/L). All enterococcal strains were S to DAP ($MIC_{50/90}$, 1/2 mg/L) and TIG ($MIC_{50/90}$, 0.06/0.06 mg/L). LZD and ampicillin were active against 99.3 and 65.0% of enterococci, respectively. The overall VAN resistance (R) among *E. faecalis* and *E. faecium* were 0.7 and 23.7% in 2011. VAN-R did not adversely influence DAP activity against enterococci. DAP was also active against β-haemolytic (BHS; MIC_{90}, 0.25 mg/L) and viridans group streptococci (VGS; MIC_{90}, 1 mg/L) strains from 2011. No significant variation was observed in the overall MRSA rate between time period; in contrast, VAN-R increased from 17.9% in 2005 to 23.7% in 2011 among *E. faecium*.

Conclusions: DAP showed significant, sustained potency against recent (2011) clinical Gram-positive organisms isolated in EU medical centers. Decrease in DAP potency has not been observed since EMA approval for clinical use.

Introduction

Increasing antimicrobial resistance rates have been extensively documented by a large number of local/regional investigations and a few multinational surveillance programs, such as the European Antimicrobial Resistance Surveillance System (EARSS) and the global SENTRY Antimicrobial Surveillance Program. Although local surveillance data is of greatest value to direct clinical therapy management, update treatment guidelines, educate prescribers, and to focus infection control policies, large multicenter surveillance programs are essential for documenting trends in antimicrobial resistance, assessing the effect of interventions, and monitoring the emergence of novel resistance to various agents.

Daptomycin is a natural lipopeptide with rapid in vitro bactericidal activity against a wide spectrum of Gram-positive pathogens, including multidrug-resistant strains of staphylococci and vancomycin-resistant enterococci. Daptomycin was initially approved by the European Medicines Agency (EMA) in January 2006 for the treatment of complicated skin and skin soft tissue infections (cSSTI) caused by susceptible Gram-positive bacteria using a dose of 4 mg/kg every 24 hours. In 2007, daptomycin received approval for the treatment of right-sided infective endocarditis (RIE) due to *Staphylococcus aureus* and *S. aureus* (including oxacillin-resistant strains [MRSA]) bacteremia associated with cSSTI or RIE at a dose of 6 mg/kg every 24 hours.

Daptomycin has been widely used in Europe, the United States (USA) and various other geographic regions for several years with high rates of clinical success. Therefore, it is important to monitor its in vitro potency and for the emergence of resistance among indicated species. In the present study, we evaluated the in vitro activity and spectrum of daptomycin against clinical isolates collected in European (EU) hospitals in 2011 and compared daptomycin activity against isolates from two time periods, in 2005 (ie. before approval for clinical use by the EMA) and 2011.

Materials and Methods

Bacterial isolates: 2,977 and 5,307 consecutive strains were collected in 2011 and 2005, respectively, from 25 medical centers in 11 EU countries and Israel. The isolates were collected primarily from bloodstream infections and cSSTI in hospitalized patients according to a common surveillance design.

Methods-continued

Susceptibility testing: Daptomycin and various comparator agents were tested by Clinical and Laboratory Standards Institute (CLSI) broth microdilution methods in validated, microdilution panels manufactured by ThermoFisher Scientific, Inc. (formerly TREK Diagnostics Systems; Cleveland, Ohio, USA). The test medium was Mueller-Hinton broth adjusted to contain physiological levels of calcium (50 mg/L) when testing daptomycin. CLSI and European Committee on Antimicrobial Susceptibility Testing (EUCAST) interpretive criteria were used to categorize the isolates as susceptible, intermediate and resistant. A daptomycin susceptibility breakpoint of ≤1 mg/L was applied for *S. aureus*, while ≤4 mg/L was used for the enterococcal results, as recommended by the CLSI and the United States Food and Drug Administration (USA-FDA). EUCAST has established daptomycin susceptible and resistant breakpoints for *S. aureus* (≤1 and ≥2 mg/L, respectively), but has not published daptomycin breakpoints for enterococcal strains. The following quality control (QC) organisms were concurrently tested: *S. aureus* ATCC 29213, *E. faecalis* ATCC 29212 and *Streptococcus pneumoniae* ATCC 49619; and all QC results were within published limits.

Results

- Daptomycin remains very active against *S. aureus* ($MIC_{50/90}$, 0.25/0.5 mg/L; 100.0% susceptible [S]) and coagulase-negative staphylococci (CoNS; $MIC_{50/90}$, 0.25/0.5 mg/L; 99.7% S, only 1 non-S strain from 2011 with a daptomycin MIC of 2 mg/L), see Table 1.
- Daptomycin was highly active against MRSA ($MIC_{50/90}$, 0.25/0.5 mg/L) as was linezolid ($MIC_{50/90}$, 1/1 mg/L; 100.0% S), tigecycline ($MIC_{50/90}$, 0.06/0.12 mg/L; 100.0% S), teicoplanin (MIC_{90}, ≤2 mg/L; 100.0% S) and vancomycin ($MIC_{50/90}$, 1/1 mg/L and 100.0% S; Table 2).
- All *E. faecalis* and *E. faecium* strains were susceptible to daptomycin ($MIC_{50/90}$, 1/1 and 2/2 mg/L, respectively) and tigecycline ($MIC_{50/90}$, 0.06/0.06 mg/L for both organisms). Linezolid ($MIC_{50/90}$, 1/1 mg/L for both organisms) was active against 100.0 and 98.1% of *E. faecalis* and *E. faecium*, respectively; while ampicillin exhibited good activity against *E. faecalis* ($MIC_{50/90}$, 1/2 mg/L; 100.0% S) and very limited activity against *E. faecium* (MIC_{50}, >8 mg/L; 5.8/5.1% S by CLSI/EUCAST breakpoint criteria respectively), see Table 2.
- The overall vancomycin resistance rates among *E. faecalis* and *E. faecium* were 0.7 and 23.7% in 2011, and vancomycin resistance did not adversely influence daptomycin activity against enterococci (Table 2).
- Daptomycin was also very active against β-haemolytic streptococci ($MIC_{50/90}$, ≤0.06/0.25 mg/L; 100.0% S) and viridans group streptococci ($MIC_{50/90}$, 0.25/1 mg/L; 99.2% S, only one non-S strain with a MIC of 2 mg/L), see Tables 1 and 2.
- No significant variation was observed in the overall MRSA rate between 2005 (29.1%) and 2011 (27.5%); in contrast, vancomycin resistance increased from 17.9% in 2005 to 23.7% in 2011 (32.4% increase) among *E. faecium* (Table 3).
- In 2011, seven countries had a MRSA rate >25.0%. The highest MRSA rates were observed in Portugal (61.5%), Ireland (45.3%), Greece (44.4%) and Italy (40.0%). Among *E. faecium*, the highest rates of vancomycin resistance were observed in Belgium (42.9%), Germany (41.2%), Ireland (40.0%) and UK (40.0%), see Table 3.

Table 1. Daptomycin activity against Gram-positive organisms collected in European hospitals in two time periods, 2005 and 2011.

Organisms (no. tested: 2005/2011)	Cumulative % (2005/2011) inhibited at daptomycin MIC (mg/L) of:					
	≤0.12	0.25	0.5	1	2	4
S. aureus (2,746/1,572)	3.4/2.6	68.9/83.9	99.3/99.8	100/100[a]	-	-
MSSA (1,946/1,140)	4.0/2.9	74.7/86.8	99.6/99.9	100/100[a]	-	-
MRSA (800/432)	2.0/1.9	54.8/76.4	98.5/99.5	100/100[a]	-	-
CoNS (941/344)	9.1/13.1	56.6/52.9	97.1/96.5	100/99.7	100/100	-
E. faecalis (646/271)	0.6/2.2	5.9/4.4	52.8/30.3	97.8/92.3	100/100	-
E. faecium (307/156)	0.3/0.6	1.3/1.9	7.5/10.9	31.0/40.4	80.1/93.0	100/100
VAN-S (252/119)	0.4/0.8	1.6/2.5	8.7/11.8	32.5/41.2	80.2/92.4	100/100
VAN-non-S (55/37)	-	-	1.8/8.1	23.6/37.8	80.0/94.6	100/100
βHS (439/245)	83.8/76.3	100/97.6	100/100	-	-	-
VGS (195/132)	34.4/22.0	72.3/54.6	93.3/84.9	100/99.2	100/100	-

a. Susceptible breakpoint (EUCAST and CLSI).
Abbreviations: MSSA = methicillin-susceptible *S. aureus*; MRSA = methicillin-resistant *S. aureus*; CoNS = coagulase-negative staphylococci; VAN-S = vancomycin-susceptible (MIC, ≤4 mg/L); VAN-non-S = vancomycin-non-susceptible (MIC, ≥8 mg/L); βHS = β-haemolytic streptococci; VGS = viridans group streptococci.

Table 3. Frequency of methicillin-resistant *S. aureus* (MRSA) and vancomycin-resistant *E. faecium* (VR-EFM; MIC ≥8 mg/L) by country sampled (2005 and 2011).

	% resistant (no. tested)			
	MRSA		VR-EFM	
Country	2005	2011	2005	2011
Belgium	-[a]	26.0 (50)	-	42.9 (7)
France	31.5 (594)	23.0 (404)	0.0 (18)	3.9 (26)
Germany	17.2 (471)	15.6 (128)	19.7 (73)	41.2 (34)
Greece	36.6 (41)	44.4 (18)	16.7 (6)	20.0 (5)
Ireland	54.7 (203)	45.3 (148)	71.4 (14)	40.0 (20)
Israel	46.0 (113)	37.0 (27)	40.0 (10)	0.0 (1)
Italy	38.3 (240)	40.0 (135)	19.4 (36)	0.0 (4)
Poland	27.2 (213)	-	4.3 (23)	-
Portugal	-	61.5 (104)	-	33.3 (9)
Spain	25.3 (241)	21.4 (140)	14.3 (14)	0.0 (17)
Sweden	2.1 (187)	1.0 (101)	0.0 (21)	6.7 (15)
Switzerland	15.7 (102)	-	0.0 (4)	-
Turkey	30.9 (188)	29.4 (92)	8.6 (70)	30.8 (13)
UK	42.5 (153)	20.0 (225)	66.7 (18)	40.0 (5)
Overall	29.1 (2746)	27.5 (1572)	17.9 (307)	23.7 (156)

a. "-" indicates that the country was not surveyed at that year.

Conclusions

- Daptomycin showed significant, sustained potency against recent (2011) clinical Gram-positive organisms isolated in EU medical centers.
- Decrease in daptomycin potency has not been observed since EMA approval and widespread clinical use in the region.
- Emerging resistance to other compounds, including vancomycin resistance among enterococci, did not adversely influence the daptomycin potency against Gram-positive species.

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Table 2. Activity of daptomycin and comparator antimicrobial agents when tested against isolates from European Medical centers in 2011.

Antimicrobial agent (no. tested)	MIC (mg/L)		% susceptible / % resistant	
	MIC_{50}	MIC_{90}	CLSI[a]	EUCAST[a]
Staphylococcus aureus (1,572)				
MSSA (1,140)				
Daptomycin	0.25	0.5	100.0 / -	100.0 / 0.0
Erythromycin	0.25	>16	84.6 / 13.7	84.6 / 14.9
Clindamycin	≤0.25	≤0.25	97.9 / 2.0	97.5 / 2.1
Levofloxacin	≤0.12	0.25	94.8 / 4.7	94.8 / 4.7
Linezolid	1	2	100.0 / 0.0	100.0 / 0.0
TMP/SMX[b]	≤0.5	≤0.5	99.6 / 0.4	99.6 / 0.4
Tigecycline	0.06	0.06	100.0 / -	100.0 / 0.0
Teicoplanin	≤2	≤2	100.0 / 0.0	100.0 / 0.0
Vancomycin	1	1	100.0 / 0.0	100.0 / 0.0
MRSA (432)				
Daptomycin	0.25	0.5	100.0 / -	100.0 / 0.0
Erythromycin	>16	>16	33.6 / 62.7	34.0 / 64.4
Clindamycin	≤0.25	>2	75.7 / 24.3	75.0 / 24.3
Levofloxacin	>4	>4	11.6 / 86.8	11.6 / 86.8
Linezolid	1	1	100.0 / 0.0	100.0 / 0.0
TMP/SMX[b]	≤0.5	≤0.5	97.9 / 2.1	97.9 / 1.9
Tigecycline	0.06	0.12	100.0 / -	100.0 / 0.0
Teicoplanin	≤2	≤2	100.0 / 0.0	99.8 / 0.2
Vancomycin	1	1	100.0 / 0.0	100.0 / 0.0
CoNS (344)				
Daptomycin	0.25	0.5	99.7 / -	99.7 / 0.3
Oxacillin	>2	>2	28.5 / 71.5	28.5 / 71.5
Erythromycin	>16	>16	37.5 / 62.2	37.5 / 62.2
Clindamycin	≤0.25	>2	77.6 / 22.4	75.3 / 22.4
Levofloxacin	2	>4	45.1 / 49.7	45.1 / 49.7
Linezolid	0.5	1	99.1 / 0.9	99.1 / 0.9
TMP/SMX[b]	≤0.5	>4	62.5 / 37.5	62.5 / 21.5
Tigecycline	0.06	0.06	100.0 / -	100.0 / 0.0
Teicoplanin	≤2	8	97.1 / 0.0	87.2 / 12.8
Vancomycin	1	2	100.0 / 0.0	98.5 / 1.5
Enterococcus faecalis (271)				
Daptomycin	1	1	100.0 / -	- / -
Ampicillin	1	2	100.0 / 0.0	100.0 / 0.0
Levofloxacin	1	>4	76.0 / 23.6	- / -
Linezolid	1	2	100.0 / 0.0	100.0 / 0.0
Tigecycline	0.06	0.06	100.0 / -	100.0 / 0.0
Teicoplanin	≤2	≤2	99.3 / 0.7	98.9 / 1.1
Vancomycin	1	2	99.3 / 0.7	99.3 / 0.7

Antimicrobial agent (no. tested)	MIC (mg/L)		% susceptible / % resistant	
	MIC_{50}	MIC_{90}	CLSI[a]	EUCAST[a]
Vancomycin-susc. *E. faecium* (119)				
Daptomycin	2	2	100.0 / -	- / -
Ampicillin	>8	>8	7.6 / 92.4	6.7 / 92.4
Levofloxacin	>4	>4	9.2 / 87.4	- / -
Linezolid	1	1	99.2 / 0.8	99.2 / 0.8
Tigecycline	0.06	0.06	100.0 / -	100.0 / 0.0
Teicoplanin	≤2	≤2	100.0 / 0.0	100.0 / 0.0
Vancomycin	1	1	100.0 / 0.0	100.0 / 0.0
Vancomycin-non-susc. *E. faecium* (37)				
Daptomycin	2	2	100.0 / -	- / -
Ampicillin	>8	>8	0.0 / 100.0	0.0 / 100.0
Levofloxacin	>4	>4	0.0 / 100.0	- / -
Linezolid	1	2	94.6 / 5.4	94.6 / 5.4
Tigecycline	0.06	0.06	100.0 / -	100.0 / 0.0
Teicoplanin	>16	>16	8.1 / 86.5	8.1 / 91.9
Vancomycin	>16	>16	0.0 / 100.0	0.0 / 100.0
β-haemolytic streptococci (245)				
Daptomycin	≤0.06	0.25	100.0 / -	100.0 / 0.0
Penicillin	≤0.06	≤0.06	100.0 / -	100.0 / 0.0
Ceftriaxone	≤0.06	0.12	100.0 / -	100.0 / 0.0
Erythromycin	≤0.12	8	78.4 / 21.6	78.4 / 21.6
Clindamycin	≤0.25	≤0.25	90.6 / 9.4	90.6 / 9.4
Levofloxacin	0.5	1	99.2 / 0.8	95.1 / 0.8
Linezolid	1	1	100.0 / -	100.0 / 0.0
Tetracycline	0.5	>8	54.3 / 42.9	51.8 / 45.7
Vancomycin	0.5	0.5	100.0 / -	100.0 / 0.0
Viridans group streptococci (132)				
Daptomycin	0.25	1	99.2 / -	- / -
Penicillin	≤0.06	2	64.4 / 9.8	73.5 / 9.8
Ceftriaxone	0.25	2	87.9 / 9.1	82.6 / 17.4
Clindamycin	≤0.25	>2	80.3 / 19.7	80.3 / 19.7
Levofloxacin	1	2	94.7 / 5.3	- / -
Linezolid	1	1	100.0 / -	- / -
Vancomycin	0.5	1	100.0 / -	100.0 / 0.0

a. Criteria as published by the CLSI [2012] and EUCAST [2012].
b. Trimethoprim/sulfamethoxazole.