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Daptomycin Activity and Spectrum when Tested against Contemporary (2009) Gram-positive Strains Collected in European Medical Centers

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ABSTRACT

Objectives: To evaluate the in vitro activity and spectrum of daptomycin (DAP) tested against clinical isolates collected in European (EU) hospitals. Gram-positive antimicrobial resistance (R) continues to pose healthcare concerns worldwide. 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 (cSSSI) and *S. aureus* (SA)-associated bacteremia (BSI) and right-sided endocarditis.

Methods: 2,775 consecutive strains were collected in 2009 from 24 medical centers located in EU countries (Belgium [BE], France [FR], Germany [GE], Ireland [IR], Italy [IT], Spain [SP], Sweden [SD], Switzerland [SL], Turkey [TU], and UK) and Israel [IS]. The collection included: SA (1,398; 22.7% oxacillin-resistant [MRSA]); coagulase-negative staphylococci ([CoNS] 454; 82.8% oxacillin-resistant); *Enterococcus* spp. ([ESP] 613, 15.0% vancomycin [VAN]-R); β-haemolytic (BHS; 212) and viridans group streptococci (VGS; 98). Organisms were isolated mainly from BSI (48.6%) and SSSI (23.3%). The strains were susceptibility tested against DAP and comparators by CLSI broth microdilution methods in cation-adjusted Mueller-Hinton broth supplemented to 50 mg/L of calcium for DAP tests.

Results: DAP was very active against SA and CoNS (100.0% susceptible [S]; $MIC_{50/90}$, 0.25/0.5 mg/L for both). MRSA rates ranged from a low of 0.0% (SD) to a high of 48.1% (IR); seven countries had an MRSA rate >20%. DAP was highly active against MRSA ($MIC_{50/90}$, 0.5/0.5 mg/L) as was linezolid ($MIC_{50/90}$, 2/2 mg/L; 100% S) and vancomycin ($MIC_{50/90}$, 1/1 mg/L, 100% S). All ESP were S to DAP ($MIC_{50/90}$, 1/2 mg/L) and linezolid ($MIC_{50/90}$, 2/2 mg/L). Tigecycline and ampicillin were active against 97.2 and 62.2% of ESP, respectively. The overall prevalence of vancomycin-resistant (VR) ESP was low at 15.0% (16.2% by EUCAST breakpoints), ranging from 0.0% (BE, IS, SP, SD and SL) to 35.9% (IR) and 51.0% (TU). VAN-R did not adversely influence DAP activity against ESP and all VAN-R *E. faecalis* (MIC_{50}, 1 mg/L; 7 strains) and *E. faecium* ($MIC_{50/90}$, 2/2 mg/L; 86 strains) were S to DAP. DAP was also active against BHS (MIC_{90}, 0.25 mg/L) and VGS (MIC_{90}, 0.5 mg/L).

Organism (no. tested)	Cumulative % inhibited at daptomycin MIC (mg/L) of: ≤0.12	0.25	0.5	1	2	4	% S CLSI	EUCAST
S. aureus (1,398)	1.3	56.4	99.2	100.0			100.0	100.0
OXA-S (1,080)	1.4	59.0	99.4	100.0			100.0	100.0
OXA-R (318)	0.9	47.5	98.7	100.0			100.0	100.0
CoNS (454)	9.3	52.9	95.4	100.0			100.0	100.0
Enterococcus spp. (613)	0.2	1.6	11.9	58.1	91.4	100.0	100.0	-
BHS (212)	67.0	98.1	100.0				100.0	100.0
VGS (98)	24.5	54.1	91.8	100			100.0	-

Conclusions: DAP showed significant, sustained potency against recent (2009) clinical Gram-positive organisms isolated in EU medical centers. All organisms presented here were DAP-S based on CLSI and EUCAST breakpoints.

INTRODUCTION

Daptomycin is a lipopeptide with a unique mechanism of action and rapid bactericidal activity against a wide spectrum of Gram-positive organisms, including oxacillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci (VRE). Daptomycin was approved by the European Medicines Agency (EMEA) in 2006 and has shown sustained anti-Gram-positive activity in large European surveillance programs. Daptomycin is currently approved in Europe, USA and many other countries for treatment of complicated skin and skin structure infections at a dose of 4 mg/kg once daily, and for treatment of *S. aureus* bacteremia and right-sided endocarditis at a dose of 6 mg/kg once daily.

With the increasing occurrence of MRSA, VRE and many other resistance phenotypes, surveillance of antimicrobial resistances becomes essential for documenting trends in resistance and for monitoring the effect of interventions. Large multicenter surveillance programs are also critical for monitoring the emergence of resistance to novel antimicrobial agents. In the present study, we evaluated the in vitro activity and spectrum of daptomycin tested against Gram-positive bacteria isolated from European medical centers in 2009.

MATERIALS AND METHODS

Bacterial isolates. A total of 2,775 consecutive strains were collected in 2009 from 24 medical centers located in 10 European countries and Israel. The medical centers are located in Belgium (1), France (5), Germany (3), Ireland (1), Israel (1), Italy (3), Spain (3), Sweden (2), Switzerland (1), Turkey (2) and the United Kingdom (2). The collection included: SA (1,398), coagulase-negative staphylococci (CoNS; 454), *Enterococcus faecalis* (357), *E. faecium* (234), β-haemolytic (212) and viridans group streptococci (98). Organisms were isolated mainly from bloodstream infections (48.6%) and skin and skin structure infections (23.3%).

Susceptibility testing. Daptomycin and comparator agents were tested using the Clinical and Laboratory Standards Institute (CLSI) M07-A8 broth microdilution method. All strains were tested in validated broth microdilution panels manufactured by TREK Diagnostics (Cleveland, Ohio, USA). Mueller-Hinton broth adjusted to contain physiological levels of calcium (50 mg/L) was used when testing daptomycin. Daptomycin susceptible breakpoints of ≤1 mg/L for staphylococci and β-haemolytic *Streptococcus* spp. and ≤4 mg/L for enterococci were used to categorize these Gram-positive organisms as susceptible, as established by CLSI and EUCAST. The following quality control organisms were concurrently tested: *E. faecalis* ATCC 29212, *S. aureus* ATCC 29213 and *Streptococcus pneumoniae* ATCC 49619.

RESULTS

- Overall MRSA rate was only 22.7%, varying from 0.0% in Sweden to as high as 48.1% in Ireland. In all other nations MRSA varied from 13.0 to 30.3% (Table 1).
- VRE (vancomycin MIC, ≥8 mg/L) rates were highest in Turkey (51.9%), followed by Ireland (35.6%) and Germany (15.4%). VRE was not observed in Belgium, Israel, Spain and Sweden (Table 1).
- Daptomycin was very active against MSSA (MIC_{50}, 0.25 μg/ml and MIC_{90}, 0.5 μg/ml) and MRSA (MIC_{50} and MIC_{90}, 0.5 mg/L; Tables 2 and 3). All *S. aureus* isolates were inhibited at a daptomycin MIC of 1 mg/L or less, which is the susceptible breakpoint approved by the CLSI, USA-FDA and EUCAST.
- Linezolid (MIC_{50} and MIC_{90}, 2 mg/L), teicoplanin (MIC_{50} and MIC_{90}, ≤2 mg/L), vancomycin (MIC_{50} and MIC_{90}, 1 mg/L) and tigecycline (MIC_{50} and MIC_{90}, 0.25 mg/L) were also active against all *S. aureus* isolates at the CLSI breakpoint (Table 3).
- Daptomycin activity against CoNS (MIC_{50} of 0.25 mg/L and MIC_{90} of 0.5 mg/L) was similar to that observed against *S. aureus*, and all isolates were inhibited at daptomycin susceptible breakpoint of ≤1 mg/L. Vancomycin (MIC_{50}, 1 mg/L and MIC_{90}, 2 mg/L), linezolid (MIC_{50} and MIC_{90}, 1 mg/L) and tigecycline (MIC_{50} of 0.25 mg/L and MIC_{90} of 0.5 mg/L) were also active against all CoNS strains, while decreased susceptibility for teicoplanin was noted in several countries.
- Daptomycin was highly active against *E. faecalis* strains (MIC_{50}, 1 mg/L and MIC_{90}, 2 mg/L; 100.0% susceptible; Table 3). Daptomycin MIC values ranged from 0.25 to 2 mg/L among vancomycin-non-susceptible strains (Table 2). Ampicillin was very active against *E. faecalis* (MIC_{90}, 2 mg/L; 99.7-100.0% susceptible) but exhibited limited activity against *E. faecium* (MIC_{50}, >16 mg/L; 3.4% susceptible; Table 3).

Table 1. Frequency of occurrence of MRSA and VRE in European countries.

Country	Prevalence in % (no. of isolates tested) MRSA	VRE[a]
Belgium	22.2 (54)	0.0 (17)
France	25.6 (312)	3.6 (138)
Germany	13.0 (207)	15.4 (130)
Ireland	48.1 (106)	35.9 (39)
Israel	25.0 (32)	0.0 (16)
Italy	16.0 (94)	6.7 (30)
Spain	22.1 (208)	0.0 (56)
Sweden	0.0 (96)	0.0 (42)
Switzerland	13.2 (38)	8.7 (23)
Turkey	26.4 (53)	51.9 (104)
UK	30.3 (198)	11.1 (18)
Overall	22.7 (1,398)	16.2 (613)

a. Based on vancomycin resistance breakpoint established by the EUCAST (≥8 mg/L).

- All *E. faecium* isolates were susceptible to daptomycin (MIC_{50}, 2 mg/L and MIC_{90}, 4 mg/L) and vancomycin resistance did not adversely influence daptomycin activity (Table 2). *E. faecium*, especially vancomycin-resistant strains, showed high rates of resistance to most antimicrobial agents tested (Table 3).
- Daptomycin was highly active against β-haemolytic streptococci (MIC_{90}, 0.25 mg/L), as were most comparison agents tested (Tables 2 and 3).
- Viridans group streptococci (MIC_{50}, 0.25 mg/L and MIC_{90}, 0.5 mg/L) showed daptomycin MIC values slightly higher (two-fold) than β-haemolytic streptococci and all isolates were inhibited by daptomycin concentration of 1 mg/L or less (Tables 2 and 3).

Table 2. Frequency of occurrence of daptomycin MIC values for Gram-positive organisms collected from European medical centers in 2009.

Organism (no. of isolates)	No. of isolates (cumulative %) inhibited at daptomycin MIC (mg/L) of: ≤0.06	0.12	0.25	0.5	1	2	4
S. aureus							
oxacillin-susceptible (1,080)	1 (0.1)	14 (1.4)	622 (59.0)	436 (99.4)	7 (100.0)		
oxacillin-resistant (318)		3 (1.0)	148 (47.5)	163 (98.7)	4 (100.0)		
Coagulase-negative staphylococci (454)	9 (2.0)	33 (9.3)	198 (52.9)	193 (95.4)	21 (100.0)		
E. faecalis							
vancomycin-suscpetible (350)		1 (0.3)	3 (1.1)	50 (15.4)	224 (79.4)	65 (98.0)	7 (100.0)
vancomycin-resistant (7)				2 (28.6)	4 (85.7)	1 (100.0)	
E. faecium							
vancomycin-susceptible (148)			3 (2.0)	3 (4.1)	21 (18.2)	84 (75.0)	37 (100.0)
vancomycin-resistant (86)			1 (1.2)	3 (4.7)	26 (34.9)	50 (93.0)	6 (100.0)
β-haemolytic streptococci (212)	93 (43.9)	49 (67.0)	66 (98.1)	4 (100.0)			
viridans group streptococci (98)	4 (4.1)	20 (24.5)	29 (54.1)	37 (91.8)	8 (100.0)		

Table 3. Antimicrobial activity of daptomycin and comparator antimicrobial agents when tested against Gram-positive bacterial isolates (2009 Europe).

Antimicrobial agent	MIC_{50}	MIC_{90}	Range	CLSI[a] %S / %R	EUCAST[a] %S / %R
S. aureus (1,398)					
Daptomycin	0.25	0.5	≤0.06 – 1	100.0 / -	100.0 / 0.0
Oxacillin	0.5	>2	≤0.25 – >2	77.3 / 22.7	77.3 / 22.7
Clindamycin	≤0.25	≤0.25	≤0.25 – >2	91.0 / 8.7	90.3 / 9.0
Erythromycin	0.5	>2	≤0.25 – >2	71.4 / 27.5	72.4 / 27.5
Levofloxacin	≤0.5	>4	≤0.5 – >4	75.1 / 24.7	75.1 / 24.7
Linezolid	2	2	0.5 – 2	100.0 / 0.0	100.0 / 0.0
Quinupristin/dalfopristin	0.5	0.5	≤0.25 – >2	99.7 / 0.1	99.7 / 0.1
Teicoplanin	≤2	≤2	≤2 – 8	100.0 / 0.0	99.9 / 0.0
Tetracycline	≤2	≤2	≤2 – >8	94.8 / 4.3	94.4 / 5.6
Tigecycline[b]	0.25	0.25	0.06 – 0.5	100.0 / -	100.0 / 0.0
TMP/SMX[c]	≤0.5	≤0.5	≤0.5 – >2	98.9 / 1.1	98.9 / 1.1
Vancomycin	1	1	≤0.12 – 2	100.0 / 0.0	100.0 / 0.0
CoNS (454)					
Daptomycin	0.25	0.5	≤0.06 – 1	100.0 / -	100.0 / 0.0
Oxacillin	>2	>2	≤0.25 – >2	17.2 / 82.8	17.2 / 82.8
Clindamycin	≤0.25	>2	≤0.25 – >2	69.2 / 30.0	66.7 / 30.8
Erythromycin	>2	>2	≤0.25 – >2	35.7 / 63.7	35.7 / 63.7
Levofloxacin	4	>4	≤0.5 – >4	43.0 / 54.0	43.0 / 54.0
Linezolid	1	1	0.25 – 4	100.0 / 0.0	100.0 / 0.0
Quinupristin/dalfopristin	≤0.25	0.5	≤0.25 – >2	97.6 / 1.8	97.6 / 1.8
Teicoplanin	≤2	8	≤2 – >16	98.0 / 0.4	89.9 / 10.1
Tetracycline	≤2	>8	≤2 – >8	85.9 / 12.3	77.8 / 22.2
Tigecycline[b]	0.25	0.5	≤0.03 – 0.5	- / -	100.0 / 0.0
TMP/SMX	≤0.5	>2	≤0.5 – >2	59.4 / 40.6	59.4 / 40.6
Vancomycin	1	2	≤0.12 – 4	100.0 / 0.0	100.0 / 0.0
E. faecalis (357)					
Daptomycin	1	2	0.12 – 4	100.0 / -	- / -
Ampicillin	≤1	2	≤1 – 8	100.0 / 0.0	99.7 / 0.0
Levofloxacin	2	>4	≤0.5 – >4	64.1 / 35.0	- / -
Linezolid	2	2	0.25 – 2	100.0 / 0.0	100.0 / 0.0
Teicoplanin	≤2	≤2	≤2 – >16	99.2 / 0.8	99.2 / 0.8
Tetracycline	>8	>8	≤2 – >8	23.0 / 76.8	- / -
Tigecycline[b]	0.25	0.25	≤0.03 – 0.5	95.8 / -	95.8 / 0.0
Vancomycin	1	2	0.5 – >16	98.0 / 1.7	98.0 / 2.0
E. faecium (234)					
Daptomycin	2	4	0.25 – 4	100.0 / -	- / -
Ampicillin	>16	>16	≤1 – >16	3.4 / 96.6	3.4 / 96.6
Linezolid	1	2	1 – 2	100.0 / 0.0	100.0 / 0.0
Quinupristin/dalfopristin	1	>2	≤0.25 – >2	73.1 / 18.8	73.1 / 18.8
Teicoplanin	≤2	>16	≤2 – >16	68.8 / 28.6	66.2 / 31.2
Tetracycline	≤2	>8	≤2 – >8	71.8 / 26.9	- / -
Tigecycline[b]	0.12	0.25	≤0.03 – 0.5	99.1 / -	99.1 / 0.0
Vancomycin	1	>16	0.5 – >16	63.2 / 36.3	63.2 / 36.7
β-haemolytic streptococci (212)					
Daptomycin	0.12	0.25	≤0.06 – 0.5	100.0 / -	100.0 / 0.0
Penicillin	0.03	0.06	≤0.015 – 0.12	100.0 / -	100.0 / 0.0
Ceftriaxone	≤0.25	≤0.25	≤0.25 – 0.5	100.0 / -	100.0 / 0.0
Clindamycin	≤0.25	≤0.25	≤0.25 – >2	90.0 / 9.0	91.0 / 9.0
Erythromycin	≤0.25	>2	≤0.25 – >2	82.5 / 16.0	82.5 / 16.0
Levofloxacin	≤0.5	1	≤0.5 – 2	100.0 / 0.0	92.9 / 0.0
Linezolid	1	1	0.5 – 2	100.0 / -	100.0 / 0.0
Tetracycline	≤2	>8	≤2 – >8	52.4 / 45.3	52.4 / 47.6
Tigecycline[b]	≤0.03	0.06	≤0.03 – 0.25	100.0 / -	100.0 / 0.0
TMP/SMX	≤0.5	≤0.5	≤0.5 – >2	- / -	99.1 / 0.5
Vancomycin	0.5	0.5	0.25 – 1	100.0 / -	100.0 / 0.0
Viridans group streptococci (98)					
Daptomycin	0.25	0.5	≤0.06 – 1	100.0 / -	- / -
Penicillin	0.06	1	≤0.015 – 32	74.5 / 4.1	83.7 / 4.1
Ceftriaxone	≤0.25	1	≤0.25 – >32	92.9 / 3.1	87.8 / 12.2
Clindamycin	≤0.25	≤0.25	≤0.25 – >2	90.8 / 8.2	91.8 / 8.2
Erythromycin	≤0.25	>2	≤0.25 – >2	65.3 / 34.7	- / -
Levofloxacin	1	2	≤0.5 – >4	99.0 / 1.0	- / -
Linezolid	1	1	0.12 – 2	100.0 / -	- / -
Tetracycline	≤2	>8	≤2 – >8	56.1 / 39.8	- / -
Tigecycline[b]	≤0.03	0.12	≤0.03 – 0.25	100.0 / -	- / -
Vancomycin	0.5	1	0.25 – 1	100.0 / -	100.0 / 0.0

a. Criteria as published by the CLSI (2010) and EUCAST (2009). β-lactam susceptibility should be directed by the oxacillin test results.
b. US-FDA breakpoints were applied (Tygacil Product Insert, 2005).
c. Trimethoprim/sulfamethoxazole.

CONCLUSIONS

- Daptomycin showed sustained potency and broad-spectrum activity against recent (2009) clinical isolates of Gram-positive organisms isolated from European medical centers, including resistant subsets.
- All organisms tested were susceptible to daptomycin based on CLSI and EUCAST breakpoints, and resistance to other compounds did not adversely influence the daptomycin potency against staphylococci, enterococci or streptococci.
- The results of the present study indicate that daptomycin continue to provide excellent empiric coverage against Gram-positive organisms isolated in European medical centers, including MDR strains.

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