Antimicrobial Activity of Daptomycin and Comparator Agents Tested against Methicillin-Resistant *S. aureus* and Vancomycin-Resistant Enterococci: Analysis of Five-year Trends in Europe and USA Hospitals (2009-2013)

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ABSTRACT

Objective: To evaluate daptomycin activity trends among methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci (VRE) in a 5-year period (2009-2013). Daptomycin, the first-in-class cyclic lipopeptide antibiotic, was approved in Europe (EU) for the treatment of complicated skin and soft tissue infections (cSSTIs) in 2006 and for the treatment of right-sided infective endocarditis (RIE) due to *S. aureus* and *S. aureus* bacteraemia when associated with RIE or with cSSTI in 2007; and has increasingly been used for these indications worldwide.

Methods: Consecutive, unique patient isolates of clinical significance were collected in 67 EU (17 nations) and 145 USA medical centres and susceptibility tested in a central reference laboratory against daptomycin and various comparators by CLSI broth microdilution methods. Mueller-Hinton broth was supplemented to 50 mg/L of calcium when testing daptomycin. MIC results were interpreted according to EUCAST and CLSI breakpoint criteria (2013).

Results: A total of (EU/USA) 14,246/22,967 *S. aureus* (26.3/49.8% MRSA), 1,827/1,537 *E. faecium* (EFM; 29.5/77.7% vancomycin-resistant [VR] EFM) and 3,043/2,848 *E. faecalis* (EF; 1.6/3.5% VREF) were evaluated. Isolates were mainly from cSSTI (40%) and bacteraemia (32%). Highest MRSA rates were found in Portugal (66.3%), Russia (52.2%) and USA (49.8%); whereas highest VREFM rates were observed in the USA (77.7%), Poland (63.1%) and Ireland (54.5%). VREFM and VREF were observed in 15 and 8 EU nations, respectively. Daptomycin susceptibility rates were (EU/USA) 99.94/99.97, 100.0/99.7 and 100.0/99.96% for *S. aureus*, EFM and EF, respectively. Daptomycin was very active against MRSA ($MIC_{50/90}$, 0.25/0.5 mg/L in EU and USA), VREFM ($MIC_{50/90}$, 2/2 mg/L in EU and USA) and VREF ($MIC_{50/90}$ of 0.5/1 and 1/2 mg/L in EU and USA, respectively (see **Table 3**). Among MRSA, only 7/6 (0.19/0.05%) daptomycin-nonsusceptible isolates were observed in EU (six cities in four countries)/USA (six states) with no increasing trend over the study period. Only two daptomycin-non-susceptible VRE were identified (both EFM from the USA). Vancomycin ($MIC_{50/90}$, 1/1 mg/L; 100.0% susceptible) and linezolid ($MIC_{50/90}$, 1/2 mg/L; >99.9% susceptible) also remained active against MRSA overall, but were two- to four-fold less potent than daptomycin. Methicillin-susceptible and MRSA, as well as vancomycin-susceptible and VRE exhibited very similar daptomycin MIC distributions.

Conclusion: Daptomycin demonstrated sustained activity against an extensive collection of clinical isolates of MRSA and VRE from numerous European and USA medical centres over the last five years. More than 99.9% of contemporary clinical strains were susceptible to daptomycin in vitro, which was more potent compared to vancomycin and linezolid against MRSA. Daptomycin activity was not adversely influenced by resistance to oxacillin among *S. aureus* or resistance to vancomycin among enterococci.

INTRODUCTION

Methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci (VRE) are extremely important pathogens causing serious infections in the hospital environment. These organisms are usually multidrug-resistant (MDR) which limits the therapeutic options available for patient treatment. Daptomycin is a cyclic lipopeptide with rapid in vitro bactericidal activity against a wide spectrum of gram-positive pathogens, including MDR isolates of staphylococci and enterococci.

Daptomycin was approved in Europe (EU) for the treatment of complicated skin and soft tissue infections (cSSTIs) in 2006. In the United States (USA), daptomycin was initially approved by the Food and Drug Administration (USA-FDA) in 2003 for the treatment complicated skin and skin structure infections (cSSSIs) caused by susceptible gram-positive bacteria. We evaluate daptomycin activity trends among MRSA and VRE from EU and USA hospitals in a 5-year period (2009-2013).

MATERIALS AND METHODS

Bacterial isolates: Consecutive, unique patient isolates of clinical significance were collected in 67 EU (17 nations) and 145 USA medical centres between January 2009 and November 2013. Each participant centre followed a study protocol which indicated the number of consecutive isolates to be collected from specific sites of infection. The number of participant centres as well as the number of isolates per site of infection varied by geographic region as well as overtime. The majority of isolates were collected from complicated skin and soft tissue infections (40%) and bacteraemia (32%). The organism collection includes 37,213 *S. aureus* (14,246 from EU and 22,967 from the USA); 5,891 *Enterococcus faecalis* (3,043 from EU and 2,848 from the USA) and 3,364 *E. faecium* (1,827 from EU and 1,537 from the USA).

Susceptibility testing: Daptomycin and various comparator agents were tested by Clinical and Laboratory Standards Institute (CLSI, 2012) broth microdilution methods in validated, microdilution panels manufactured by ThermoFisher, Inc. (Cleveland, Ohio, USA). The test medium was Mueller-Hinton broth adjusted to contain physiological levels of calcium (50 mg/L) when testing daptomycin. European Committee on Antimicrobial Susceptibility Testing (EUCAST) and CLSI 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 USA-FDA. EUCAST has established daptomycin susceptible and resistant breakpoints for *S. aureus* (≤1 and >1 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 and *E. faecalis* ATCC 29212; all QC results were within published limits.

RESULTS

- The overall MRSA rate in EU was 26.3%, with the highest rates found in Portugal (66.3%), Russia (52.2%) and Ukraine (45.3%), and the lowest rates observed in Sweden (0.3%), Czech Republic (14.0%) and Germany (18.2%). In the USA, the overall MRSA rate was 49.8% (**Table 1**).
- Vancomycin-resistant *E. faecalis* (VR-EF) strains were observed in eight of 17 EU nations surveyed, with rates ranging from 0.2% in France to 12.5% in Poland. VR-EF was NOT identified (0.0%) in Belgium, Czech Republic, Greece, Hungary, Russia, Spain, Sweden, Turkey and Ukraine (**Table 1**).
- Vancomycin-resistant *E. faecium* (VR-EFM) rate was much higher in the USA (77.7%) compared to EU (29.5% overall). The EU countries with highest VR-EFM rates were Poland (63.1%), Ireland (54.5%) and Turkey (45.3%; **Table 1**).
- Daptomycin susceptibility rates were (EU/USA) 99.94/99.97%, 100.0/99.96% and 100.0/99.7% for *S. aureus*, *E. faecalis* and *E. faecium*, respectively (**Table 2**).
- Methicillin-susceptible *S. aureus* (MSSA) and MRSA, as well as vancomycin-susceptible enterococci and VRE exhibited very similar daptomycin MIC distributions (data not shown).
- Daptomycin was very active against MRSA ($MIC_{50/90}$, 0.25/0.5 mg/L in EU and USA), VR-EFM ($MIC_{50/90}$, 2/2 mg/L in EU and USA) and VR-EF ($MIC_{50/90}$ of 0.5/1 and 1/2 mg/L in EU and USA, respectively (**Tables 2** and **3**).
- Vancomycin ($MIC_{50/90}$, 1/1 mg/L; 100.0% susceptible) and linezolid ($MIC_{50/90}$, 1/2 mg/L; >99.9% susceptible) also remained active against MRSA overall, but were two- to four-fold less potent than daptomycin (**Table 3**).
- Among *S. aureus*, only 9 (0.0%; 7 MRSA and 2 MSSA) daptomycin-non-susceptible isolates were observed in EU and 7 in the USA (0.03%; 6 MRSA and 1 MSSA), with no increasing trend over the study period (**Table 4**). Among MRSA, only 7 and 6 (0.19 and 0.05%) daptomycin-non-susceptible isolates were observed in EU (six cities in four countries) and USA (six states) respectively (**Tables 2** and **4**).
- Only two daptomycin-non-susceptible VRE were identified, both EFM from the USA (**Table 4**).

Table 1. Oxacillin resistance among *S. aureus* (MRSA) and vancomycin resistance among *E. faecalis* (VREF) and *E. faecium* (VREFM) strains from European countries and the USA (2009-2013).

Country	% Resistant (no. tested)		
	MRSA	VR-EF	VR-EFM
Belgium	22.9 (389)	0.0 (111)	15.3 (59)
Czech Republic	14.0 (321)	0.0 (40)	21.7 (23)
France	22.7 (2,433)	0.2 (546)	3.1 (159)
Germany	18.2 (1,662)	1.6 (380)	32.9 (313)
Greece	37.0 (308)	0.0 (108)	42.9 (70)
Hungary	32.3 (192)	0.0 (25.0)	12.5 (8)
Ireland	38.0 (953)	0.8 (128)	54.5 (176)
Israel	37.6 (378)	3.4 (119)	9.1 (22)
Italy	33.4 (1,243)	2.8 (354)	12.5 (96)
Poland	37.0 (521)	12.5 (128)	63.1 (168)
Portugal	66.3 (522)	2.9 (136)	10.0 (80)
Russia	52.2 (502)	0.0 (54)	4.0 (50)
Spain	19.2 (1,346)	0.0 (279)	0.7 (135)
Sweden	0.3 (875)	0.0 (209)	0.0 (82)
Turkey	22.4 (871)	0.0 (237)	45.3 (296)
UK	21.7 (1,602)	3.4 (176)	32.8 (74)
Ukraine	45.3 (128)	0.0 (13)	0.0 (16)
All Europe	**26.3 (14,246)**	**1.6 (3,043)**	**29.5 (1,827)**
USA	**49.8 (22,967)**	**3.5 (2,848)**	**77.7 (1,537)**

Table 2. Summary of daptomycin activity when tested against *S. aureus* and enterococci from Eurpean and USA hospitals (2009-2013).

Organism/continent (no.)	No. of isolates (cumulative %) inhibited at daptomycin MIC (mg/L) of:							
	≤0.12	0.25	0.5	1	2	4	8	>8
S. aureus								
All isolates								
Europe (14,246)	480 (3.4)	10,917 (80.0)	2,740 (99.2)	100 (>99.9)[a]	9 (100.0)			
USA (22,967)	676 (2.9)	16,754 (75.9)	5,354 (99.2)	176 (>99.9)	7 (100.0)			
MRSA[b]								
Europe (3,748)	70 (1.9)	2,637 (72.2)	996 (98.8)	38 (99.8)	7 (100.0)	-	-	
USA (11,440)	232 (2.0)	7,925 (71.3)	3,170 (99.0)	107 (>99.9)	6 (100.0)	-	-	
E. faecalis								
All isolates								
Europe (3,043)	27 (0.9)	50 (2.5)	940 (33.4)	1,747 (90.8)	262 (99.4)	17 (100.0)		
USA (2,848)	25 (0.9)	51 (2.7)	857 (32.8)	1,570 (87.9)	320 (99.1)	24 (>99.9)	1 (100.0)	
Vancomycin-R[c]								
Europe (48)	-	-	25 (52.1)	22 (97.9)	1 (100.0)	-	-	
USA (99)	1 (1.0)	0 (1.0)	38 (39.4)	50 (89.9)	10 (100.0)	-	-	
E. faecium								
All isolates								
Europe (1,827)	6 (0.3)	22 (1.5)	75 (5.6)	437 (29.6)	1,101 (89.8)	186 (100.0)		
USA (1,537)	9 (0.6)	7 (1.0)	72 (5.7)	453 (35.2)	865 (91.5)	126 (99.7)	4 (>99.9)	1 (100.0)
Vancomycin-R[c]								
Europe (539)	1 (0.2)	4 (0.9)	26 (5.8)	151 (33.8)	311 (91.5)	46 (100.0)	-	
USA (1,194)	5 (0.4)	3 (0.7)	55 (5.3)	376 (36.8)	671 (93.0)	82 (99.8)	2 (100.0)	

a. Underline values indicate susceptibility rate according to CLSI [2014] and EUCAST (*S. aureus* only)[2014].
b. MRSA = methicillin-resistant *S. aureus*.
c. Vancomycin-R = vancomycin-resistant (MIC, >4 mg/L; EUCAST, 2013).

Table 3. Activity of daptomycin and comparator agents when tested against methicillin-resistant *S. aureus* (MRSA) and vancomycin-resistant (MIC, ≥8 mg/L) enterococci from Europe and USA.

Antimicrobial agent	MIC_{50}	MIC_{90}	%S / %I / %R	
			CLSI[a]	EUCAST[a]
MRSA				
Europe (3,748)				
Daptomycin	0.25	0.5	99.8 / - / -	99.8 / 0.0 / 0.2
Clindamycin	≤0.25	>2	65.8 / 0.2 / 34.0	65.4 / 0.4 / 34.2
Erythromycin	>2	>2	30.4 / 2.6 / 67.0	30.8 / 1.1 / 68.1
Levofloxacin	>4	>4	11.6 / 1.5 / 86.9	11.6 / 1.5 / 86.9
Linezolid	1	2	99.9 / 0.0 / 0.1	99.9 / 0.0 / 0.1
Tigecycline[b]	0.06	0.25	99.9 / - / -	99.9 / 0.0 / 0.1
TMP/SMX[c]	≤0.5	≤0.5	97.7 / 0.0 / 2.3	97.7 / 0.2 / 2.1
Teicoplanin	≤2	≤2	>99.9 / <0.1 / 0.0	99.0 / 0.0 / 1.0
Vancomycin	1	1	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
USA (11,440)				
Daptomycin	0.25	0.5	>99.9 / - / -	>99.9 / 0.0 / <0.1
Clindamycin	≤0.25	>2	70.7 / 0.2 / 29.1	70.4 / 0.3 / 29.3
Erythromycin	>2	>2	9.8 / 1.4 / 88.8	9.9 / 0.4 / 89.7
Levofloxacin	4	>4	30.6 / 2.3 / 67.1	30.6 / 2.3 / 67.1
Linezolid	1	2	99.9 / 0.0 / 0.1	99.9 / 0.0 / 0.1
Tigecycline[b]	0.06	0.25	>99.9 / - / -	>99.9 / 0.0 / <0.1
TMP/SMX	≤0.5	≤0.5	97.9 / 0.0 / 2.1	97.9 / 0.2 / 1.9
Teicoplanin	≤2	≤2	100.0 / 0.0 / 0.0	99.9 / 0.0 / 0.1
Vancomycin	1	1	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
Vancomycin-R[d] *E. faecalis*				
Europe (48)				
Daptomycin	0.5	1	100.0 / - / -	- / - / -
Ampicillin	2	4	97.9 / 0.0 / 2.1	97.9 / 0.0 / 2.1
Levofloxacin	>4	>4	14.6 / 0.0 / 85.4	- / - / -
Linezolid	1	1	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
Tigecycline[b]	0.06	0.25	100.0 / - / -	100.0 / 0.0 / 0.0
Teicoplanin	>8	>8	29.2 / 0.0 / 70.8	22.9 / 0.0 / 77.1
Vancomycin	>16	>16	0.0 / 12.5 / 87.5	0.0 / 0.0 / 100.0
USA (99)				
Daptomycin	1	2	100.0 / - / -	- / - / -
Ampicillin	≤1	2	99.0 / 0.0 / 1.0	99.0 / 0.0 / 1.0
Levofloxacin	>4	>4	5.1 / 0.0 / 94.9	- / - / -
Linezolid	1	1	98.0 / 0.0 / 2.0	98.0 / 0.0 / 2.0
Tigecycline[b]	0.06	0.25	99.0 / - / -	99.0 / 1.0 / 0.0
Teicoplanin	>8	>8	20.2 / 1.0 / 78.8	17.2 / 0.0 / 82.8
Vancomycin	>16	>16	0.0 / 3.0 / 97.0	0.0 / 0.0 / 100.0
Vancomycin-R[d] *E. faecium*				
Europe (539)				
Daptomycin	2	2	100.0 / - / -	- / - / -
Ampicillin	>8	>8	0.0 / 0.0 / 100.0	0.0 / 0.0 / 100.0
Levofloxacin	>4	>4	3.3 / 0.8 / 95.9	- / - / -
Linezolid	1	2	98.9 / 0.2 / 0.9	99.1 / 0.0 / 0.9
Tigecycline[b]	≤0.03	0.12	100.0 / - / -	100.0 / 0.0 / 0.0
Teicoplanin	>8	>8	14.5 / 7.4 / 78.1	12.1 / 0.0 / 87.9
Vancomycin	>16	>16	0.0 / 3.2 / 96.8	0.0 / 0.0 / 100.0
USA (1,194)				
Daptomycin	2	2	99.8 / - / -	- / - / -
Ampicillin	>8	>8	0.4 / 0.0 / 99.6	0.3 / 0.1 / 99.6
Levofloxacin	>4	>4	0.2 / 0.0 / 99.8	- / - / -
Linezolid	1	2	98.3 / 0.6 / 1.1	98.9 / 0.0 / 1.1
Tigecycline[b]	0.06	0.25	99.0 / - / -	99.0 / 0.7 / 0.3
Teicoplanin	>8	>8	3.8 / 3.3 / 92.9	2.8 / 0.0 / 97.2
Vancomycin	>16	>16	0.0 / 0.7 / 99.3	0.0 / 0.0 / 100.0

a. Criteria as published by the CLSI [2014] and EUCAST [2014].
b. USA-FDA breakpoints were applied when available [Tygacil Product Insert, 2012].
c. TMP/SMX = trimethoprim/sulfamethoxazole.
d. Vancomycin-R = vancomycin-resistant (MIC, >4 mg/L) [EUCAST, 2014].

Table 4. Occurrence of MRSA, VRE and daptomycin-non-susceptible strains stratified by year.

Region (Europe)/organism	Year					Region (USA)/organism	Year				
	2009	2010	2011	2012	2013		2009	2010	2011	2012	2013
S. aureus						*S. aureus*					
MRSA rate	25.9	26.1	29.1	26.7	23.1	MRSA rate	51.0	51.7	49.2	47.3	49.8
No. of DAP-NS[a] isolates (%)	0	1(0.03)	3(0.11)	2(0.07)	3(0.13)	No. of DAP-NS isolates (%)	1(0.03)	2(0.05)	2(0.05)	1(0.03)	1 (0.01)
No. of VAN ≥2 mg/L (%)[b]	60 (2.4)	35 (0.9)	47 (1.7)	52 (1.9)	20 (0.9)	No. of VAN ≥2 mg/L (%)[b]	123 (3.5)	51 (1.3)	59 (1.5)	81 (2.2)	80 (1.0)
No. tested	2,541	3,763	2,837	2,804	2,301	No. tested	3,521	3,919	4,044	3,747	7,736
E. faecalis						*E. faecalis*					
Vancomycin-resistance rate	2.3	1.2	1.7	1.7	0.8	Vancomycin-resistance rate	2.9	4.8	4.5	4.5	1.4
No. of DAP-NS isolates (%)	0	0	0	0	0	No. of DAP-NS isolates (%)	1(0.14)	0	0	0	0
No. tested	724	943	543	459	374	No. tested	696	705	463	336	648
E. faecium						*E. faecium*					
Vancomycin-resistance rate	27.8	19.8	23.6	50.3	30.0	Vancomycin-resistance rate	78.6	79.5	77.3	75.3	74.5
No. of DAP-NS isolates (%)	0	0	0	0	0	No. of DAP-NS isolates (%)	2(0.52)	2(0.40)	1(0.37)	0	0
No. tested	417	474	326	340	270	No. tested	385	494	268	170	220

a. DAP-NS = daptomycin-non-susceptible; MIC ≥2 mg/L for *S. aureus* and ≥8 mg/L for enterococci [CLSI, 2014].
b. VAN ≥2 mg/L = *S. aureus* isolates with vancomycin MIC of ≥2 mg/L. All of them had vancomycin MIC at 2 mg/L.

CONCLUSIONS

- Daptomycin demonstrated sustained activity against an extensive collection of clinical isolates of MRSA and VRE from numerous European and USA medical centres over the last five years.
- More than 99.9% of contemporary clinical strains were susceptible to daptomycin in vitro, which was more potent compared to vancomycin and linezolid against MRSA.
- Daptomycin activity was not adversely influenced by resistance to oxacillin among *S. aureus* or resistance to vancomycin among enterococci.

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