1671

Antimicrobial Susceptibility of Daptomycin and Comparator Agents Tested against Bloodstream Isolates of *Staphylococcus aureus*: Analysis of a Five-year Trend in European Medical Centres (2005-2009)

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ABSTRACT

Objectives: To evaluate daptomycin activity against *S. aureus* collected from patients with bloodstream infections (BSI) in European (EU) hospitals. Daptomycin is a natural lipopeptide derived from *Streptomyces roseosporus* that is rapidly bactericidal against Gram-positive pathogens. Daptomycin is approved by the European Medicine Agency (EMEA) for treating complicated skin and skin structure infections and *S. aureus*-associated bacteremia and right-sided endocarditis, including those caused by methicillin-resistant *S. aureus* (MRSA).

Methods: *S. aureus* BSI isolates (4,886) were consecutively collected from 29 sites in 13 EU countries. Susceptibility (S) was determined by the CLSI broth microdilution method. Cation-adjusted Mueller-Hinton broth was used for testing all agents and was supplemented to 50 mg/L of calcium for testing daptomycin as recommended by the CLSI and EUCAST.

Results: Between 2005 and 2009, the MRSA rate declined nearly 9% in EU, with an overall rate of 27.4% during the five year period. The lowest MRSA rate was observed in Sweden (two sites, 1.1%) and the highest rate was in Greece (two sites, 53.8%). Resistance (R) to erythromycin and clindamycin also declined from 33.6 and 18.1% in 2005 to 26.4 and 10.1% in 2009, respectively. The highest MIC value for daptomycin was 1 mg/L (100.0% S using CLSI and EUCAST breakpoints) with MIC_{50} and MIC_{90} values of 0.25 and 0.5 mg/L, respectively. Vancomycin ($MIC_{50/90}$, 1/1 mg/L; 100.0% S) and linezolid ($MIC_{50/90}$, 1/2 mg/L; >99.9% S) were two- to four-fold less active than daptomycin. Only one linezolid-R was observed and quinupristin/dalfopristin-R isolates were only observed in France. Daptomycin potency was very uniform among the countries evaluated and daptomycin MIC distributions did not vary significantly over time.

Table 1. Distribution of daptomycin MIC values by year.

Year	Organism (no.)	Cumulative % inhibited at daptomycin MIC (mg/L) of: ≤0.06	0.12	0.25	0.5	1
2005	MSSA (701)	0.0	3.7	80.0	99.7	100.0
	MRSA (323)	0.0	1.9	59.1	99.1	100.0
2006	MSSA (826)	0.0	7.1	92.3	99.8	100.0
	MRSA (284)	0.4	2.8	73.6	99.7	100.0
2007	MSSA (823)	0.0	5.0	89.3	99.8	100.0
	MRSA (321)	0.3	3.7	77.9	98.8	100.0
2008	MSSA (814)	0.1	2.7	66.7	99.6	100.0
	MRSA (298)	0.0	2.7	48.3	98.3	100.0
2009	MSSA (384)	0.0	1.0	58.3	100.0	-
	MRSA (112)	0.0	2.7	50.0	97.3	100.0

Conclusions: Daptomycin showed consistent potency against an extensive collection of clinical isolates of *S. aureus*, including MRSA, from numerous EU medical centres over the last five years. All isolates were S to daptomycin, which was more potent compared to vancomycin and linezolid and has excellent activity against *S. aureus* isolates with co-R to other antimicrobial classes.

INTRODUCTION

Staphylococcus aureus is the leading cause of bacteremia worldwide and endocarditis is a serious complication that can occur in 30 to 40% of patients. In 2003, it was estimated that bacteremia caused by *S. aureus* in European countries could be as high as 32 per 100,000 inhabitants and that the rate of methicillin-resistant strains (MRSA), although quite variable, was over 40% in several countries surveyed. MRSA isolates are often resistant to numerous antimicrobial classes posing a significant problem for the treatment of serious infections, including bacteremia and endocarditis. A retrospective cohort study in Europe reported a high rate of patients with MRSA bacteremia that received inadequate empirical (52%) or definitive (49%) antimicrobial therapy. It is therefore extremely important that new generations of existing antimicrobial agents or novel classes of agents continue to be developed and advanced to the clinical setting for adequate patient care.

Daptomycin, a cyclic lipopeptide, is the first and only member of this novel class of agents approved by the European Medicine Agency (EMEA) and the United States Food and Drug Administration (USA-FDA) for the treatment of complicated skin and skin structure infections (cSSSI) as well as bacteremia and right-sided endocarditis caused by *S. aureus*, including MRSA. Daptomycin is rapidly bactericidal *in vitro* due to a unique mechanism of action that causes rapid depolarization of membrane potential after binding to the cell membrane which causes the inhibition of cellular function and rapid microbial death. Daptomycin shows excellent in vitro activity against Gram-positive isolates resistant to other drug classes including vancomycin, linezolid, MLS_B and multidrug-resistant (MDR) strains such as MRSA.

This study documents the activity of daptomycin against recent *S. aureus* isolates that were collected from patients with bloodstream infections hospitalized in European countries.

MATERIALS AND METHODS

Bacterial isolates. Isolates from patients with documented bloodstream infections (BSI) were collected using a prevalence based surveillance network during 2005-2009 in European countries. One isolate per patient episode was collected for a total of 4,886 *S. aureus* isolates from 29 medical centers in the following 13 countries: Belgium (1 site), France (5), Germany (4), Greece (2), Ireland (2), Israel (1), Italy (3), Poland (1), Spain (3), Sweden (2), Switzerland (1), Turkey (2) and the United Kingdom (UK; 2). Isolates were identified by the local medical center and confirmed by the monitoring reference laboratory (JMI Laboratories, North Liberty, Iowa, USA). Isolates included 1,338 MRSA strains, representing an overall rate of 27.4% in Europe during these five years.

Susceptibility testing. *S. aureus* isolates were tested against 20 antimicrobial agents from 10 drug classes using reference broth microdilution methods recommended by the Clinical and Laboratory Standards Institute (CLSI, M07-A8, 2009). Validated broth microdilution panels were provided by TREK Diagnostics (Cleveland, Ohio, USA) with appropriate supplements including a calcium concentration of 50 mg/L for testing daptomycin. Susceptibility rates were calculated using current criteria by the CLSI (M100-S20, 2010) and current EUCAST recommendations. USA-FDA breakpoints were applied to establish susceptibility for tigecycline.

RESULTS

- The distribution of daptomycin MIC values remained stable over the five year period with all isolates inhibited by ≤1 mg/L for both methicillin-susceptible S. aureus (MSSA) and MRSA isolates (Table 1).
- Table 2 shows a similiar distribution of daptomycin MIC values for each individual country with all MIC_{50} values at 0.25 mg/L, with the exception of Germany ($MIC_{50/90}$, 0.5 mg/L). Among all countries combined, daptomycin was documented to have slightly lower MICs against MSSA (80.1% at 0.25 mg/L) compared to MRSA (63.5%).
- The highest MRSA rates were observed in Greece (53.8%), Israel (48.3%) and Ireland (44.7%) as shown in Table 3. These three countries as well as Italy and the UK also had high rates of macrolide resistance (36.1 – 42.8%) with lower rates of constitutive clindamycin resistance noted in Ireland and the UK.
- Resistance rates to levofloxacin, tetracycline and gentamicin ranged from 2.7 - 46.9% (highest in Israel), 2.5 - 52.1% (highest in Greece) and 0.5 – 30.3% (highest in Italy), respectively.
- Overall, 27.4% of strains collected were MRSA and the MIC_{50} (0.25 mg/L) and MIC_{90} (0.5 mg/L) values for daptomycin were the same for MSSA and MRSA (Table 4). All isolates were susceptible to daptomycin, vancomycin and tigecycline and only rare isolates were resistant to linezolid or teicoplanin (EUCAST breakpoint only).
- Comparable susceptibility rates were observed using either the CLSI or EUCAST breakpoint criteria with higher rates of resistance observed among MRSA isolates for several antimicrobial agents (Table 4).

Table 2. Distribution of daptomycin MIC values for *S. aureus* from 13 European countries (2005-2009).

Nation (no. of strains)	Cumulative % inhibited at daptomycin MIC (mg/L) of: ≤0.12	0.25	0.5	1[a]
Belgium (102)	3.9	83.3	99.0	100.0
France (956)	4.2	75.4	99.6	100.0
Germany (743)	3.5	41.2	99.5	100.0
Greece (119)	0.8	74.6	100.0	100.0
Ireland (414)	3.6	81.2	99.8	100.0
Israel (147)	2.0	66.7	98.6	100.0
Italy (380)	5.8	67.6	98.4	100.0
Poland (249)	3.2	74.3	100.0	-
Spain (351)	5.1	81.8	99.7	100.0
Sweden (366)	3.6	82.0	99.5	100.0
Switzerland (188)	5.3	79.8	98.4	100.0
Turkey (431)	2.3	70.1	99.8	100.0
UK (440)	4.3	80.2	100.0	-
All countries				
MSSA (3,584)	4.3	80.1	99.8	100.0
MRSA (1,338)	2.8	63.5	98.8	100.0

a. Susceptibility breakpoint.

Table 3. Comparative resistance rates among *S. aureus* for five antimicrobial agents in 13 European countries during 2005-2009.

Nation (no. of strains)	Antimicrobial agent/% resistance[b]: Oxacillin	Ery[b]	Clinda	Levo	Tetra	Genta
Belgium (102)	14.7	23.5	5.9	17.6	4.9	0.9
France (956)	26.8	30.8	16.4	29.0	4.6	2.0
Germany (743)	18.7	25.0	16.7	30.7	4.4	5.8
Greece (119)	53.8	41.2	33.6	36.1	52.1	28.6
Ireland (414)	44.7	42.8	3.1	44.9	2.2	4.3
Israel (147)	48.3	36.1	25.2	46.9	3.4	25.9
Italy (380)	39.5	39.7	20.5	40.0	5.5	30.3
Poland (249)	24.5	24.9	15.3	17.7	23.7	10.8
Spain (351)	23.1	23.6	5.1	25.9	2.6	5.4
Sweden (366)	1.1	4.6	1.4	2.7	4.6	0.5
Switzerland (188)	14.4	20.7	8.5	19.7	2.7	4.8
Turkey (431)	28.8	28.3	11.1	27.1	37.8	26.7
UK (440)	37.8	37.0	8.0	40.9	2.5	2.5

a. Criteria as published by the CLSI [2010] and EUCAST [2009].
b. Abbreviations: Ery = Erythromycin, Clinda = Clindamycin, Levo = Levofloxacin, Tetra = Tetracycline, Genta = Gentamicin.

Table 4. Antimicrobial activity of daptomycin and comparator agents when tested against 4,886 isolates of *S. aureus* from Europe.

Antimicrobial agent	MIC_{50}	MIC_{90}	Range	CLSI[a] %S / %R	EUCAST[a] %S / %R
All isolates					
Daptomycin	0.25	0.5	≤0.06 – 1	100.0 / -	100.0 / 0.0
Oxacillin	0.5	>2	≤0.25 – >2	72.6 / 27.4	72.6 / 27.4
Amoxicillin/clavulanate	≤1	>16	≤1 – >16	72.6 / 27.4	72.6 / 27.4
Cefepime	2	>16	≤0.12 – >16	72.6 / 27.4	72.6 / 27.4
Ceftriaxone	4	>32	≤0.25 – >32	72.6 / 27.4	72.6 / 27.4
Ciprofloxacin	≤0.5	>4	≤0.5 – >4	69.3 / 29.6	69.3 / 30.7
Clindamycin	≤0.25	>2	≤0.25 – >2	87.4 / 12.4	87.0 / 12.6
Erythromycin	≤0.25	>2	≤0.25 – >2	70.9 / 28.4	71.4 / 28.4
Gentamicin	≤2	≤2	≤2 – >8	90.8 / 8.7	90.4 / 9.6
Imipenem	≤0.12	>8	≤0.12 – >8	72.6 / 27.4	72.6 / 27.4
Levofloxacin	≤0.5	>4	≤0.5 – >4	70.3 / 29.1	70.3 / 29.1
Linezolid	1	2	0.25 – 8	>99.9 / <0.1	>99.9 / <0.1
Moxifloxacin	≤0.5	4	≤0.5 – >4	70.8 / 23.3	70.8 / 23.3
Quinupristin/dalfopristin	≤0.25	0.5	≤0.25 – >2	99.5 / 0.3	99.5 / 0.3
Teicoplanin	≤2	≤2	≤2 – 8	100.0 / 0.0	>99.9 / 0.0
Tetracycline	≤2	≤2	≤2 – >8	91.0 / 8.5	90.6 / 9.4
Tigecycline[b]	0.12	0.25	≤0.03 – 0.5	100.0 / -	100.0 / 0.0
TMP/SMX[c]	≤0.5	≤0.5	≤0.5 – >2	99.0 / 1.0	99.0 / 1.0
Vancomycin	1	1	≤0.12 – 2	100.0 / 0.0	100.0 / 0.0
MRSA (1,338)					
Daptomycin	0.25	0.5	≤0.06 – 1	100.0 / -	100.0 / 0.0
Ciprofloxacin	>4	>4	≤0.5 – >4	7.4 / 91.9	7.4 / 92.6
Clindamycin	≤0.25	>2	≤0.25 – >2	59.2 / 40.4	58.7 / 40.8
Erythromycin	>2	>2	≤0.25 – >2	27.7 / 71.2	28.6 / 71.2
Gentamicin	≤2	>8	≤2 – >8	70.2 / 28.3	69.9 / 30.1
Levofloxacin	>4	>4	≤0.5 – >4	7.8 / 90.6	7.8 / 90.6
Linezolid	1	2	0.25 – 8	99.9 / 0.1	99.9 / 0.1
Moxifloxacin	2	4	≤0.5 – >4	9.3 / 72.6	9.3 / 72.6
Quinupristin/dalfopristin	0.5	1	≤0.25 – >2	98.7 / 0.8	98.7 / 0.8
Teicoplanin	≤2	≤2	≤2 – 8	100.0 / 0.0	99.9 / 0.0
Tetracycline	≤2	>8	≤2 – >8	82.1 / 17.0	81.8 / 18.2
Tigecycline[b]	0.12	0.25	≤0.03 – 0.5	100.0 / -	100.0 / 0.0
TMP/SMX	≤0.5	≤0.5	≤0.5 – >2	97.4 / 2.6	97.4 / 2.6
Vancomycin	1	1	0.25 – 2	100.0 / 0.0	100.0 / 0.0

Antimicrobial agent	MIC_{50}	MIC_{90}	Range	CLSI[a] %S / %R	EUCAST[a] %S / %R
MSSA (3,548)					
Daptomycin	0.25	0.5	≤0.06 – 1	100.0 / -	100.0 / 0.0
Amoxicillin/clavulanate	≤1	≤1	≤1 – 4	100.0 / 0.0	100.0 / 0.0
Cefepime	2	4	≤0.12 – 8	100.0 / 0.0	100.0 / 0.0
Ceftriaxone	4	4	≤0.25 – 16	>99.9 / 0.0	100.0 / 0.0
Ciprofloxacin	≤0.5	1	≤0.5 – >4	92.7 / 6.1	92.7 / 7.3
Clindamycin	≤0.25	≤0.25	≤0.25 – >2	98.1 / 1.9	97.7 / 1.9
Erythromycin	≤0.25	>2	≤0.25 – >2	87.2 / 12.3	87.5 / 12.3
Gentamicin	≤2	≤2	≤2 – >8	98.5 / 1.4	98.2 / 1.8
Imipenem	≤0.12	≤0.12	≤0.12 – 0.5	100.0 / 0.0	100.0 / 0.0
Levofloxacin	≤0.5	≤0.5	≤0.5 – >4	93.8 / 5.9	93.8 / 5.9
Linezolid	2	2	0.25 – 2	100.0 / 0.0	100.0 / 0.0
Moxifloxacin	≤0.5	≤0.5	≤0.5 – >4	94.0 / 4.7	94.0 / 4.7
Quinupristin/dalfopristin	≤0.25	0.5	≤0.25 – >2	99.9 / 0.1	99.9 / 0.1
Teicoplanin	≤2	≤2	≤2 – 4	100.0 / 0.0	100.0 / 0.0
Tetracycline	≤2	≤2	≤2 – >8	94.3 / 5.3	94.0 / 6.0
Tigecycline[b]	0.12	0.25	≤0.03 – 0.5	100.0 / -	100.0 / 0.0
TMP/SMX	≤0.5	≤0.5	≤0.5 – >2	99.6 / 0.4	99.6 / 0.4
Vancomycin	1	1	≤0.12 – 2	100.0 / 0.0	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. USA-FDA breakpoints were applied [Tygacil Product Insert, 2005].
c. TMP/SMX = Trimethoprim/sulfamethoxazole

CONCLUSIONS

- This large collection of contemporary *S. aureus* isolates demonstrates that daptomycin has retained excellent activity against this very significant pathogen over the last five years in Europe (2005-2009).
- Significant variability in the MRSA rates and resistance to other commonly prescribed antimicrobial agents was observed among contributing nations during these five years of *S. aureus* analysis.
- Daptomycin was two- to four-fold more active than vancomycin against these isolates and demonstrated similar activity in all countries sampled in this ongoing investigation.

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