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Antimicrobial susceptibility of Gram-positive bacteria isolated from European medical centres: results of the Daptomycin Surveillance Programme (2002–2004)

H. S. Sader[1,2], J. M. Streit[1], T. R. Fritsche[1] and R. N. Jones[1,3]

[1]JMI Laboratories, North Liberty, IA, USA, [2]Federal University of Sao Paulo, Sao Paulo, Brazil and [3]Tufts University School of Medicine, Boston, MA, USA

ABSTRACT

The antimicrobial susceptibility patterns of 9322 contemporary (2002–2004) Gram-positive bacterial isolates collected from 31 medical centres in 14 countries in Europe were evaluated by broth microdilution methods according to CLSI guidelines. The isolates collected comprised *Staphylococcus aureus* (4842 isolates), coagulase-negative staphylococci (CoNS; 1942 isolates), *Enterococcus faecalis* (1147 isolates), *Enterococcus faecium* (391 isolates), β-haemolytic streptococci (660 isolates) and viridans group streptococci (340 isolates). The organisms were tested against daptomycin and more than 20 comparator agents in Mueller–Hinton broth, supplemented with calcium to 50 mg/L when testing daptomycin. Overall, methicillin (oxacillin) resistance rates were 26.7% and 77.0% for *S. aureus* (MRSA) and CoNS, respectively, and the vancomycin resistance rate among enterococci was 6.1%. MRSA rates varied from 0.6% in Sweden to 40.2–43.0% in Belgium, Greece, Ireland, the UK and Israel, and VRE rates varied from 0% in Switzerland to 21.2% in Ireland. More than 99.9% of isolates tested were considered susceptible to daptomycin according to breakpoints established by the United States Food and Drug Administration and the CLSI. Daptomycin was active against all Gram-positive species, with the highest MIC being 2, 8, 0.5 and 2 mg/L for staphylococci, enterococci, β-haemolytic streptococci and viridans group streptococci, respectively. Daptomycin activity was not influenced adversely by resistance to other agents among staphylococci or enterococci. This novel lipopeptide (daptomycin) appears to be an excellent alternative therapeutic option for serious infections caused by multidrug-resistant Gram-positive organisms isolated in Europe.

Keywords Antimicrobial susceptibility, daptomycin, Europe, Gram-positive pathogens, resistance, surveillance

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INTRODUCTION

The antimicrobial susceptibility patterns of bacteria isolated from hospitalised patients varies significantly throughout Europe. Several surveillance programmes, including the European Antimicrobial Surveillance System (EARSS) and the SENTRY antimicrobial surveillance programme, routinely collect antimicrobial susceptibility data in Europe [1,2]. These surveillance programmes have revealed remarkable geographical variations in a north–south gradient, with generally lower resistance rates in northern Europe and higher resistance rates in southern and western Europe [1]. This trend is particularly evident for methicillin (oxacillin)-resistant *Staphylococcus aureus* (MRSA) [3]. With the increasing occurrence of vancomycin-resistant enterococci (VRE) and the emergence of *Staph. aureus* strains with decreased susceptibility to vancomycin, antimicrobial agents with activity focused against Gram-positive cocci are required for therapy of infections caused by these multidrug-resistant (MDR) strains [4–6].

Daptomycin is a naturally occurring cyclic lipopeptide produced by *Streptomyces roseosporus*, and has shown activity against most Gram-positive bacterial species [7,8]. This compound joins other newer agents active against Gram-positive

Corresponding author and reprint requests: H. S. Sader, JMI Laboratories, Inc., 345 Beaver Kreek Center, Suite A, North Liberty, IA 52317, USA
E-mail: helio-sader@jmilabs.com

bacteria, including quinupristin–dalfopristin (a streptogramin combination) and linezolid (an oxazolindinone), in their ability to treat contemporary MDR Gram-positive infections. A once-daily dosing regimen, with minimal side-effects, makes daptomycin a promising alternative for the treatment of nosocomial infections caused by Gram-positive organisms [7,9,10]. Daptomycin is active against a wide range of MDR strains for which there are few therapeutic alternatives, including VRE, MRSA, vancomycin-intermediate *Staph. aureus* and penicillin-resistant streptococci [11].

Daptomycin has been approved by the United States Food and Drug Administration (US-FDA) for the treatment of complicated skin and skin-structure infections at a dose of 4 mg/kg every 24 h. Daptomycin has a rapid bactericidal effect, and a supplemental filing has been submitted to the US-FDA for the treatment of *Staph. aureus* bacteraemia and infectious endocarditis at a dose of 6 mg/kg every 24 h [12]. Despite the absence of studies in humans, daptomycin has also been used successfully to treat osteomyelitis, with minimal adverse events and a low potential for the development of drug resistance [13,14]. However, daptomycin is not indicated for treatment of pneumonia, because of its inhibition by pulmonary surfactants [15].

Daptomycin has recently been approved for the treatment of complicated skin and skin-structure infections in Europe. Thus, it is important to review the antimicrobial susceptibility of Gram-positive pathogens isolated in European hospitals during recent years in order to evaluate the necessity for this new compound, as well as the potency and spectrum of daptomycin against isolates from different European countries. The present study evaluated the antimicrobial susceptibility patterns of contemporary (2002–2004) clinical isolates of Gram-positive bacteria collected from Europe and the Middle East.

MATERIALS AND METHODS

Bacterial isolates

The Daptomycin Surveillance Programme was established in 2002 with the objective of monitoring the in-vitro activity of daptomycin and most antimicrobial agents used to treat infections caused by Gram-positive organisms. The programme collected Gram-positive bacterial isolates from documented clinical infections, mainly complicated skin and skin-structure infections and bloodstream infections. The isolates were collected in 31 medical centres located in Europe (14 countries) and 31 centres in North America (these isolates are not reported here), according to a common protocol [2], as commercial susceptibility systems used routinely do not test daptomycin. The European medical centres were located in Belgium (one), France (six), Germany (five), Greece (one), Ireland (one), Israel (one), Italy (three), Poland (one), Russia (one), Spain (three), Sweden (two), Switzerland (one), Turkey (two) and the UK (three). All isolates were identified locally and forwarded to a central monitoring laboratory (JMI Laboratories, North Liberty, IA, USA) for confirmation of species identification, when necessary, and reference susceptibility testing.

Susceptibility testing

The isolates were tested using CLSI broth microdilution methods [16]. Daptomycin and more than 20 comparator agents were tested in validated, dry-form microdilution panels manufactured by TREK Diagnostics Systems (Cleveland, OH, USA). The test medium was Mueller–Hinton broth, adjusted to contain physiological levels of calcium (50 mg/L) when testing daptomycin [16,17]. The isolates were categorised as susceptible, intermediately-resistant or resistant according to CLSI interpretive criteria [17]. A daptomycin susceptibility breakpoint of ≤1 mg/L was used for staphylococci and β-haemolytic streptococci, while ≤4 mg/L was used for interpretation of enterococci, as approved by the US-FDA [11] and CLSI [17]. *Streptococcus pneumoniae* ATCC 49619, *Enterococcus faecalis* ATCC 29212 and *Staph. aureus* ATCC 29213 were tested concurrently as quality control organisms. More recently, the European Committee for Antimicrobial Susceptibility Testing (EUCAST) has recommended daptomycin-susceptible and -resistant breakpoints of ≤1 mg/L and ≥2 mg/L, respectively, for staphylococci and streptococci only [18].

RESULTS

In total, 9322 non-duplicate Gram-positive cocci were evaluated in the present study. The collection comprised *Staph. aureus* (4842 isolates), coagulase-negative staphylococci (CoNS; 1942 isolates), *E. faecalis* (1147 isolates), *Enterococcus faecium* (391 isolates), β-haemolytic streptococci (660 isolates), and viridans group streptococci (340 isolates). The antimicrobial susceptibility patterns of these isolates are summarised in Table 1. Overall, daptomycin and linezolid were the most active compounds tested. The highest daptomycin MICs were 2, 8, 0.5 and 2 mg/L for staphylococci, enterococci, β-haemolytic streptococci and viridans group streptococci, respectively. More than 99.9% of the non-enterococcal isolates tested were inhibited by daptomycin at ≤1 mg/L (0.12% non-susceptible), and all but two enterococcal isolates (also 0.12%) were inhibited at ≤4 mg/L.

Table 1. Antimicrobial susceptibility patterns of Gram-positive bacterial isolates collected from European hospitals during 2002–2004 (9322 isolates)

	MIC (mg/L)			% by category	
Organism/antimicrobial agent (no. tested)	**50%**	**90%**	**Range**	**Susceptible[a]**	**Resistant[a]**
Staphylococcus aureus					
Oxacillin-susceptible (3550)					
Daptomycin	0.25	0.5	≤0.06–2	>99.9	–
Erythromycin	0.25	>8	≤0.06 to >8	84.8	14.1
Clindamycin	0.12	0.12	≤0.06 to >8	96.9	2.8
Ciprofloxacin	0.25	0.5	≤0.03 to >4	92.8	6.1
Levofloxacin	0.12	0.25	≤0.03 to >4	94.1	5.5
Tetracycline	≤4	≤4	≤4 to >8	93.7	5.8
Trimethoprim–sulphamethoxazole	≤0.5	≤0.5	≤0.5 to >2	99.1	0.9
Quinupristin–dalfopristin	≤0.25	0.5	≤0.25 to >2	99.9	0.1
Teicoplanin	≤2	≤2	≤2–4	100.0	0.0
Vancomycin	1	1	≤0.12–4	>99.9	0.0
Linezolid	2	2	0.12–8	>99.9	–
Oxacillin-resistant (1292)					
Daptomycin	0.25	0.5	≤0.12–2	99.9	–
Erythromycin	>8	>8	0.12 to >8	24.9	74.1
Clindamycin	0.25	>8	≤0.06 to >8	50.9	49.0
Ciprofloxacin	>4	>4	0.06 to >4	9.2	90.4
Levofloxacin	>4	>4	0.06 to >4	9.4	86.8
Tetracycline	≤2	>8	≤2 to >8	74.9	23.4
Trimethoprim–sulphamethoxazole	≤0.5	1	≤0.5 to >2	93.2	6.8
Quinupristin–dalfopristin	0.5	1	0.12 to >8	98.8	0.9
Teicoplanin	≤2	≤2	≤2–16	99.8	0.0
Vancomycin	1	1	0.25–2	100.0	0.0
Linezolid	2	2	0.25–2	100.0	–
Coagulase-negative staphylococci					
Oxacillin-susceptible (447)[b]					
Daptomycin	0.25	0.5	0.06–1	100.0	–
Erythromycin	0.25	>8	≤0.06 to >8	71.8	28.0
Clindamycin	≤0.06	0.12	≤0.06 to >8	95.5	3.8
Ciprofloxacin	0.25	1	≤0.03 to >4	90.4	8.7
Levofloxacin	0.25	0.5	≤0.03 to >4	90.8	7.8
Tetracycline	≤2	>8	≤2 to >8	83.4	16.2
Trimethoprim–sulphamethoxazole	≤0.5	>2	≤0.5 to >2	89.0	11.0
Quinupristin–dalfopristin	≤0.25	≤0.25	≤0.25–1	100.0	0.0
Teicoplanin	≤2	4	≤2–16	97.3	0.0
Vancomycin	1	2	0.25–4	100.0	0.0
Linezolid	1	1	≤0.25–2	100.0	–
Oxacillin-resistant (1495)[c]					
Daptomycin	0.25	0.5	≤0.06–1	100.0	–
Erythromycin	>8	>8	≤0.06 to >8	29.0	70.5
Clindamycin	0.12	>8	≤0.06 to >8	62.9	36.6
Ciprofloxacin	>4	>4	0.06 to >4	30.8	63.9
Levofloxacin	4	>4	0.06 to >4	32.2	58.7
Tetracycline	≤2	>8	≤2 to >8	82.0	17.4
Trimethoprim–sulphamethoxazole	2	>2	≤0.5 to >2	50.9	49.1
Quinupristin–dalfopristin	≤0.25	0.5	≤0.25 to >8	99.2	0.5
Teicoplanin	≤2	8	≤2 to >16	97.0	0.6
Vancomycin	1	2	≤0.12–4	100.0	0.0
Linezolid	1	1	0.25–2	100.0	–
Enterococcus faecalis					
Vancomycin-susceptible (1113)					
Daptomycin	0.5	1	≤0.06–4	100.0	–
Ampicillin	2	4	≤1 to >16	99.1	0.9
Gentamicin (high-level)	≤500	>1000	≤500 to >1000	72.3	27.7
Streptomycin (high-level)	≤1000	>2000	≤1000 to >2000	65.5	34.5
Levofloxacin	1	>4	0.06 to >4	71.4	27.6
Chloramphenicol	8	>16	≤2 to >16	73.8	25.7
Quinupristin–dalfopristin	>2	>2	≤0.25 to >2	1.9	91.3
Teicoplanin	≤2	≤2	≤2–4	100.0	0.0
Linezolid	2	2	0.5–4	99.9	0.0
Vancomycin-resistant (34)					
Daptomycin	0.5	1	0.25–2	100.0	–
Ampicillin	2	4	≤1–8	100.0	0.0
Gentamicin (high-level)	>1000	>1000	≤500 to >1000	27.6	72.4
Streptomycin (high-level)	>2000	>2000	≤1000 to >2000	27.6	72.4
Levofloxacin	>4	>4	0.5 to >4	23.5	76.5
Chloramphenicol	8	>16	4 to >16	85.3	14.7
Quinupristin–dalfopristin	>2	>2	>2	0	100.0
Teicoplanin	>16	>16	≤0.12 to >16	17.6	79.4
Linezolid	1	2	0.5–2	100.0	0.0
Enterococcus faecium					
Vancomycin-susceptible (322)					
Daptomycin	2	4	≤0.06–8	99.7	–
Ampicillin	>16	>16	≤1 to >16	17.8	82.2
Gentamicin (high-level)	≤500	>1000	≤500 to >1000	71.8	28.2

Table 1. Continued

Organism/antimicrobial agent (no. tested)	MIC (mg/L)			% by category	
	50%	90%	Range	Susceptible[a]	Resistant[a]
Streptomycin (high-level)	≤1000	>2000	≤1000 to >2000	52.6	47.4
Levofloxacin	>4	>4	0.5 to >4	26.1	63.4
Chloramphenicol	8	16	≤2 to >16	75.7	8.4
Quinupristin–dalfopristin	1	2	≤0.25 to >2	70.8	8.4
Teicoplanin	≤2	≤2	≤2	100.0	0.0
Linezolid	2	2	≤0.25–2	100.0	0.0
Vancomycin-resistant (69)					
Daptomycin	2	4	0.5–8	98.6	–
Ampicillin	>16	>16	≤1 to >16	4.6	95.4
Gentamicin (high-level)	≤500	>1000	≤500 to >1000	54.5	45.5
Streptomycin (high-level)	≤1000	>2000	≤1000 to >2000	52.7	47.3
Levofloxacin	>4	>4	1 to >4	15.9	81.2
Chloramphenicol	8	16	4 to >16	72.5	7.2
Quinupristin–dalfopristin	0.5	2	≤0.25 to >2	84.1	8.7
Teicoplanin	>16	>16	0.25 to >16	17.4	71.0
Linezolid	2	2	1–2	100.0	0.0
β-Haemolytic streptococci (660)[d]					
Daptomycin	≤0.06	0.25	≤0.06–0.5	100.0	–
Penicillin	≤0.016	0.06	≤0.016–0.12	100.0	–
Erythromycin	≤0.06	4	≤0.06 to >32	84.1	15.6
Clindamycin	≤0.06	≤0.06	≤0.06 to >8	94.2	5.2
Tetracycline	≤2	>8	≤2 to >8	51.5	41.1
Levofloxacin	0.5	1	0.06 to >4	99.5	0.3
Vancomycin	0.25	0.5	≤0.12–1	100.0	–
Linezolid	1	1	0.06–2	100.0	0.3
Viridans group streptococci (340)[e]					
Daptomycin	0.25	0.5	0.03–2	99.1	–
Penicillin	0.06	2	≤0.016 to >32	72.9	7.9
Erythromycin	≤0.06	>8	≤0.06 to >8	58.5	36.5
Clindamycin	≤0.06	>8	≤0.06 to >8	84.1	14.1
Levofloxacin	1	1	≤0.03 to >4	98.2	1.8
Vancomycin	0.5	1	≤0.12–1	100.0	–
Linezolid	1	1	0.06–2	100.0	–

[a]According to CLSI criteria [17]; β-lactam susceptibility should be directed by the oxacillin test results.
[b]Includes: *Staphylococcus auricularis* (4), *Staphylococcus capitis* (24), coagulase-negative staphylococci (CoNS) (110), *Staphylococcus epidermidis* (228), *Staphylococcus haemolyticus* (13), *Staphylococcus hominis* (29), *Staphylococcus intermedius* (2), *Staphylococcus lugdunensis* (3), *Staphylococcus saprophyticus* (2), *Staphylococcus schleiferi* (2), *Staphylococcus simulans* (3), *Staphylococcus* spp. (4), *Staphylococcus warnerii* (15) and *Staphylococcus xylosis* (8).
[c]Includes: *Staph. auricularis* (4), *Staph. capitis* (18), *Staphylococcus chromogenes* (1), CoNS (328), *Staphylococcus cohnii* (3), *Staph. epidermidis* (858), *Staph. haemolyticus* (107), *Staph. hominis* (54), *Staph. intermedius* (5), *Staph. lugdunensis* (18), *Staph. saprophyticus* (27), *Staphylococcus sciuri* (1), *Staph. simulans* (16), *Staphylococcus* spp. (8), *Staph. warnerii* (23) and *Staph. xylosis* (24).
[d]Includes: β-haemolytic streptococci (14), *Streptococcus dysgalactiae* (13), *Streptococcus equi* (2), *Streptococcus equisimilis* (5), group A streptococci (334), group B streptococci (190), group C streptococci (21), group F streptococci (2) and group G streptococci (79).
[e]Includes: *Streptococcus acidominimus* (2), α-haemolytic streptococci (9), *Streptococcus anginosus* (39), *Streptococcus bovis* (21), *Streptococcus constellatus* (26), *Streptococcus equinus* (1), *Streptococcus gallolyticus* (2), *Streptococcus gordonii* (6), *Streptococcus intermedius* (11), *Streptococcus milleri* (11), *Streptococcus mitis* (65), *Streptococcus mutans* (8), *Streptococcus oralis* (40), *Streptococcus parasanguis* (5), *Streptococcus salivarius* (19), *Streptococcus sanguis* (24), *Streptococcus* spp. (23), *Streptococcus vestibularis* (1) and *Streptococcus viridans* (27).

Staphylococci

Overall oxacillin resistance rates for Europe were 26.7% and 77.0% for *Staph. aureus* and CoNS, respectively (Table 1). However, some countries had resistance rates >40% for *Staph. aureus* (Belgium, Greece, Ireland, Israel and the UK) and >85% for CoNS (Ireland, Israel, Poland, Russia and Turkey). The highest oxacillin susceptibility rates for *Staph. aureus* were observed in Sweden (99.4%), where the lowest susceptibility rate for any of the study agents was 94.5% (ciprofloxacin and erythromycin; Table 2). Only one *Staph. aureus* and one CoNS isolate with decreased susceptibility to teicoplanin were detected, both from Poland. MRSA isolates demonstrated high rates of co-resistance to erythromycin (24.9% susceptible), ciprofloxacin (9.2% susceptible) and levofloxacin (9.4% susceptible); however, resistance to oxacillin did not influence daptomycin activity adversely.

All *Staph. aureus* isolates were susceptible to daptomycin (MIC_{90} 0.5 mg/L), except two isolates with daptomycin MICs of 2 mg/L, isolated in France and Switzerland. All CoNS isolates were susceptible to daptomycin. Vancomycin (MIC_{90} 1 mg/L) was active against all but one of the 6784 staphylococcal isolates at the current CLSI susceptible breakpoint of ≤2 mg/L. Linezolid, teicoplanin and quinupristin–dalfopristin were also highly active against staphylococci, with susceptibility rates of ≥99.8%.

Daptomycin was the most potent compound against MRSA (lowest MIC_{50} and MIC_{90} values; Table 1). There were no significant variations in the daptomycin potency against staphylococci

Table 2. Antimicrobial spectrum of antimicrobial agents used to treat Gram-positive infections, grouped by country

	% susceptible													
Organism/antimicrobial agent	**Belgium**	**France**	**Germany**	**Greece**	**Ireland**	**Israel**	**Italy**	**Poland**	**Russia**	**Spain**	**Sweden**	**Switzerland**	**Turkey**	**UK**
Staphylococcus aureus (no. tested)	(100)	(1100)	(715)	(128)	(328)	(121)	(386)	(242)	(69)	(317)	(325)	(189)	(291)	(531)
Daptomycin	100.0	99.9	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	99.5	100.0	100.0
Oxacillin	59.0	71.5	90.2	59.4	59.8	57.0	64.8	67.8	66.7	82.0	99.4	81.5	73.2	58.0
Erythromycin	48.0	69.3	75.8	75.0	57.0	64.5	57.3	69.0	53.6	75.7	94.5	78.8	69.1	56.5
Clindamycin	73.0	81.9	89.7	79.7	92.1	78.5	72.3	77.3	68.1	96.5	97.2	87.8	85.2	81.9
Ciprofloxacin	58.0	70.2	77.6	68.8	57.6	56.2	62.7	71.7	75.4	78.5	94.5	76.2	73.9	56.7
Levofloxacin	62.0	71.5	78.3	71.1	58.2	56.2	63.0	72.7	75.4	79.8	96.9	77.2	74.2	56.9
Tetracycline	79.0	93.5	94.4	62.5	98.2	94.2	94.0	54.5	72.7	98.4	96.3	94.7	61.9	88.3
Trimethoprim–sulphamethoxazole	97.0	99.1	98.7	96.9	99.7	93.3	95.9	90.9	100.0	99.1	100.0	98.9	99.0	92.7
Quinupristin–dalfopristin	100.0	98.5	99.9	100.0	100.0	100.0	99.7	100.0	100.0	100.0	100.0	100.0	100.0	99.8
Linezolid	100.0	100.0	100.0	99.2	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
Teicoplanin	100.0	100.0	100.0	100.0	100.0	100.0	100.0	99.2	100.0	100.0	100.0	100.0	100.0	100.0
Vancomycin	100.0	100.0	100.0	100.0	100.0	100.0	100.0	99.6	100.0	100.0	100.0	100.0	100.0	100.0
Coagulase-negative staphylococci (no. tested)	(29)	(379)	(517)	(57)	(18)	(76)	(299)	(29)	(7)	(129)	(67)	(107)	(171)	(62)
Daptomycin	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
Oxacillin	17.2	22.9	31.5	19.3	11.1	5.3	15.4	13.8	14.3	26.4	36.9	24.3	14.0	25.8
Erythromycin	41.4	46.8	38.9	35.1	22.2	36.8	33.8	27.6	28.6	40.3	64.6	29.9	32.2	35.5
Clindamycin	65.5	79.0	66.0	50.9	77.8	68.4	66.6	55.2	71.4	81.4	67.7	72.0	68.4	85.5
Ciprofloxacin	44.8	46.0	44.1	56.1	50.0	46.1	37.5	55.2	42.9	49.6	56.9	37.4	39.2	58.1
Levofloxacin	44.8	47.1	44.7	59.6	50.0	46.1	39.5	55.2	42.9	49.6	60.0	36.4	40.9	64.5
Tetracycline	75.9	85.4	84.9	87.7	72.2	78.9	81.9	48.3	85.7	89.1	87.7	89.7	62.9	87.1
Trimethoprim–sulphamethoxazole	50.0	60.3	59.7	61.4	55.6	38.2	66.6	58.6	28.6	70.5	61.5	46.7	55.9	64.5
Quinupristin–dalfopristin	100.0	98.1	99.8	96.5	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	98.8	100.0
Linezolid	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
Teicoplanin	96.6	97.6	96.9	98.2	94.4	97.4	100.0	96.6	100.0	97.7	96.9	99.1	98.8	98.4
Vancomycin	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
Enterococcus spp. (no. tested)	(48)	(247)	(353)	(62)	(80)	(39)	(166)	(32)	(23)	(144)	(131)	(58)	(134)	(99)
Daptomycin	100.0	100.0	99.7	100.0	100.0	97.4	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
Ampicillin	87.9	91.3	73.5	68.5	52.2	78.4	69.3	73.7	76.2	100.0	100.0	81.3	61.2	78.8
Gentamicin (high-level)	89.6	85.0	67.8	51.0	44.4	61.5	62.7	46.4	60.9	89.4	80.8	90.2	71.6	62.0
Levofloxacin	75.0	78.5	56.1	27.4	22.5	59.0	48.8	59.4	78.3	64.6	89.7	84.5	65.7	35.4
Chloramphenicol	85.4	70.0	79.3	93.5	61.3	63.2	70.5	62.5	47.8	73.6	61.8	77.6	68.7	76.8
Quinupristin–dalfopristin	18.8	10.5	19.5	32.3	41.3	17.9	23.5	21.9	26.1	6.9	89.3	15.5	40.3	21.2
Linezolid	100.0	99.6	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
Teicoplanin	100.0	99.2	96.9	80.6	81.3	87.2	86.7	96.9	100.0	99.3	99.2	100.0	96.3	86.7
Vancomycin	95.8	98.4	95.8	80.6	78.8	84.6	84.3	96.9	91.3	98.6	96.9	100.0	96.3	84.8
β-Haemolytic streptococci (no. tested)	(12)	(169)	(80)	(3)	(18)	(18)	(16)	(9)	(34)	(60)	(85)	(31)	(7)	(118)
Daptomycin	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
Penicillin	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
Clindamycin	100.0	86.4	97.5	100.0	100.0	100.0	100.0	100.0	97.1	95.0	92.9	100.0	100.0	97.5
Erythromycin	100.0	76.8	91.3	100.0	94.4	88.9	50.0	88.9	85.3	65.0	90.6	100.0	85.7	89.8
Tetracycline	25.0	49.7	37.5	66.7	50.0	50.0	68.8	55.6	61.8	76.7	45.0	67.7	57.1	47.9
Linezolid	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
Vancomycin	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
Viridans group streptococci (no. tested)	(22)	(85)	(45)	(1)	(4)	(13)	(6)	(2)	(0)	(22)	(48)	(35)	(26)	(31)
Daptomycin	100.0	98.8	97.8	100.0	100.0	100.0	100.0	100.0	–	100.0	100.0	100.0	100.0	96.8
Penicillin	68.2	72.9	84.4	100.0	50.0	53.8	50.0	0.0	–	72.7	83.3	82.9	30.8	87.1
Clindamycin	72.7	78.8	93.3	100.0	100.0	92.3	50.0	100.0	–	63.6	93.8	91.4	73.1	93.5
Erythromycin	59.1	54.1	57.8	–	50.0	30.8	16.7	0.0	–	45.5	79.2	65.7	42.3	80.6
Linezolid	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	–	100.0	100.0	100.0	100.0	100.0
Vancomycin	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	–	100.0	100.0	100.0	100.0	100.0

among the countries evaluated, with 98.2–100% of isolates being inhibited by daptomycin ≤0.5 mg/L (Table 3), or over time (data not shown).

Enterococci

The overall rate of vancomycin resistance was 6.7%, and VRE isolates also showed increased rates of high-level resistance to gentamicin (45.5–72.4%; Table 1). Daptomycin was the most potent agent (MIC_{90} 1 mg/L) and was the only compound active against all *E. faecalis* isolates at the current susceptible breakpoint (Table 1). Ampicillin (MIC_{90} 4 mg/L) and linezolid (MIC_{90} 2 mg/L) were active against all vancomycin-resistant *E. faecalis* isolates. Two *E. faecium* isolates were non-susceptible to daptomycin, both with MICs of 8 mg/L (susceptible at ≤4 mg/L [17]). Linezolid and daptomycin were the only agents with significant activity (>99% susceptibility) against *E. faecium*.

Table 3. Distribution of daptomycin MICs, grouped by country

Organism/country (no. tested)	No. of isolates (cumulative %) inhibited at MIC (mg/L):							
	≤0.06	0.12	0.25	0.5	1	2	4	8
Staphylococcus aureus								
Belgium (100)		5 (5.0)	69 (74.0)	26 (100.0)				
France (1100)		47 (4.3)	750 (72.5)	297 (99.5)	5 (99.9)	1 (100.0)		
Germany (715)		25 (3.5)	488 (71.7)	194 (98.9)	8 (100.0)			
Greece (128)		6 (4.7)	88 (73.4)	33 (99.2)	1 (100.0)			
Ireland (328)		11 (3.4)	227 (72.6)	89 (99.7)	1 (100.0)			
Israel (121)		1 (0.8)	76 (63.6)	43 (99.2)	1 (100.0)			
Italy (386)		22 (5.7)	200 (57.5)	151 (96.6)	13 (100.0)			
Poland (242)		8 (3.3)	159 (69.0)	71 (98.3)	4 (100.0)			
Russia (69)		3 (4.3)	56 (85.5)	10 (100.0)				
Spain (317)		13 (4.1)	227 (75.7)	76 (99.7)	1 (100.0)			
Sweden (325)	1 (0.3)	12 (4.0)	228 (74.2)	78 (98.2)	6 (100.0)			
Switzerland (189)		9 (4.8)	119 (67.7)	54 (96.3)	6 (99.5)	1 (100.0)		
Turkey (291)	1 (0.3)	10 (3.8)	180 (65.6)	99 (99.7)	1 (100.0)			
UK (531)		13 (2.3)	361 (70.2)	154 (99.2)	4 (100.0)			
Total (4842)	2 (0.0)	184 (3.8)	3228 (70.5)	1375 (98.9)	51 (>99.9)	2 (100.0)		
Coagulase-negative staphylococci								
Belgium (29)		3 (10.3)	22 (86.2)	4 (100.0)				
France (376)	2 (0.5)	35 (9.8)	213 (66.5)	116 (97.3)	10 (100.0)			
Germany (517)	4 (0.8)	39 (8.3)	262 (59.0)	190 (95.7)	22 (100.0)			
Greece (57)	1 (1.8)	4 (8.8)	29 (59.6)	23 (100.0)				
Ireland (18)		2 (11.1)	13 (83.3)	3 (100.0)				
Israel (76)	2 (2.6)	7 (11.8)	39 (63.2)	27 (98.7)	1 (100.0)			
Italy (299)		22 (7.4)	134 (52.2)	123 (93.3)	20 (100.0)			
Poland (29)			16 (55.2)	13 (100.0)				
Russia (7)		1 (14.3)	5 (85.7)	1 (100.0)				
Spain (129)	1 (0.8)	9 (7.8)	83 (72.1)	35 (99.2)	1 (100.0)			
Sweden (65)		6 (9.2)	35 (63.1)	20 (93.8)	4 (100.0)			
Switzerland (107)		5 (4.7)	66 (66.4)	34 (98.1)	2 (100.0)			
Turkey (171)		10 (5.8)	97 (62.6)	59 (97.1)	5 (100.0)			
UK (62)		6 (9.7)	38 (71.0)	12 (90.3)	6 (100.0)			
Total (1942)	39 (2.0)	120 (8.2)	1052 (62.4)	659 (96.3)	72 (100.0)			
Enterococcus spp.								
Belgium (48)			1 (2.1)	21 (45.8)	9 (64.6)	14 (93.8)	3 (100.0)	
France (247)		2 (0.8)	11 (5.3)	104 (47.9)	87 (82.6)	25 (92.7)	18 (100.0)	
Germany (353)	1 (0.3)		5 (1.7)	93 (28.0)	153 (71.4)	61 (88.7)	39 (99.7)	1 (100.0)
Greece (62)			2 (3.2)	23 (40.3)	17 (67.7)	16 (93.5)	4 (100.0)	
Ireland (80)				17 (21.3)	29 (57.5)	30 (95.0)	4 (100.0)	
Israel (39)			2 (5.1)	17 (48.7)	13 (82.1)	4 (92.3)	2 (97.4)	1 (100.0)
Italy (166)	1 (0.6)	4 (3.0)	7 (7.2)	39 (30.7)	63 (68.7)	37 (91.0)	15 (100.0)	
Poland (32)			3 (9.4)	10 (40.6)	10 (71.9)	8 (96.9)	1 (100.0)	
Russia (23)			1 (4.3)	7 (34.8)	8 (69.6)	5 (91.3)	2 (100.0)	
Spain (144)		1 (0.7)	1 (1.4)	48 (34.7)	69 (82.6)	17 (94.4)	8 (100.0)	
Sweden (131)		1 (0.8)	13 (10.7)	51 (49.6)	39 (79.4)	22 (96.2)	5 (100.0)	
Switzerland (58)			2 (3.4)	24 (44.8)	17 (74.1)	13 (96.6)	2 (100.0)	
Turkey (134)	1 (0.7)	2 (1.5)	6 (6.0)	46 (40.3)	25 (59.0)	21 (74.6)	34 (100.0)	
UK (99)	1 (1.0)		5 (6.1)	46 (52.5)	28 (80.8)	10 (90.9)	9 (100.0)	
Total (1616)	4 (0.2)	9 (0.8)	59 (4.5)	546 (38.2)	567 (73.3)	283 (90.8)	146 (99.9)	2 (100.0)
β-Haemolytic streptococci								
Belgium (12)	4 (33.3)	4 (66.7)	4 (100.0)					
France (169)	87 (51.5)	49 (80.5)	28 (97.0)	5 (100.0)				
Germany (80)	34 (42.5)	27 (76.3)	19 (100.0)					
Greece (3)	3 (100.0)							
Ireland (18)	16 (88.9)		2 (100.0)					
Israel (18)	10 (55.6)	5 (83.3)	2 (94.4)	1 (100.0)				
Italy (16)	10 (62.5)	4 (87.5)	2 (100.0)					
Poland (9)	7 (77.8)	1 (88.9)	1 (100.0)					
Russia (34)	34 (100.0)							
Spain (60)	44 (73.3)	7 (85.0)	8 (98.3)	1 (100.0)				
Sweden (85)	41 (48.2)	18 (69.4)	21 (94.1)	5 (100.0)				
Switzerland (31)	20 (64.5)	9 (93.5)	2 (100.0)					
Turkey (7)	3 (42.9)	4 (100.0)						
UK (118)	68 (57.6)	26 (79.7)	20 (96.6)	4 (100.0)				
Total (660)	437 (66.2)	98 (81.1)	109 (97.6)	16 (100.0)				
Viridans group streptococci								
Belgium (22)		7 (31.8)	9 (72.7)	4 (90.9)	2 (100.0)			
France (85)	12 (14.1)	26 (44.7)	19 (67.1)	20 (90.6)	7 (98.8)	1 (100.0)		
Germany (45)	11 (24.4)	6 (37.8)	10 (60.0)	12 (86.7)	5 (97.8)	1 (100.0)		
Greece (1)				1 (100.0)				
Ireland (4)			2 (50.0)	1 (100.0)				
Israel (13)	3 (23.1)	4 (53.8)	2 (69.2)	1 (100.0)				
Italy (6)	1 (16.7)		3 (66.7)	2 (100.0)				
Poland (2)		1 (50.0)	1 (100.0)					
Russia (46)		1 (2.2)	38 (84.8)	7 (100.0)				
Spain (22)	3 (13.6)	4 (31.8)	9 (72.7)	6 (100.0)				
Sweden (48)	7 (14.6)	8 (31.3)	15 (62.5)	16 (95.8)	2 (100.0)			

Table 3. Continued

Organism/country (no. tested)	No. of isolates (cumulative %) inhibited at MIC (mg/L): ≤0.06	0.12	0.25	0.5	1	2	4	8
Switzerland (35)	6 (17.1)	7 (37.1)	9 (62.9)	8 (85.7)	5 (100.0)			
Turkey (26)	1 (3.8)	3 (15.4)	5 (34.6)	12 (80.8)	5 (100.0)			
UK (31)	3 (9.7)	6 (29.0)	10 (61.3)	10 (93.5)	1 (96.8)	1 (100.0)		
Total (340)	47 (13.8)	72 (35.0)	94 (62.6)	96 (90.9)	28 (99.1)	3 (100.0)		

The lowest antimicrobial susceptibility rates were observed in Ireland, with 52.2% of enterococcal isolates being susceptible to ampicillin, 44.4% to gentamicin, 81.3% to teicoplanin, and 78.8% to vancomycin. Belgium, France, Germany, Poland, Spain, Sweden, Switzerland (the only country without a VRE isolate) and Turkey had vancomycin susceptibility rates of >95% (Table 2). Vancomycin resistance did not appear to affect daptomycin activity adversely.

The potency of daptomycin against enterococci did not vary significantly among the studied countries. MIC_{90} values were 2 mg/L in all countries except Germany and Turkey, where the daptomycin MIC_{90} was 4 mg/L (Table 3). In Turkey, only 74.6% of enterococcal isolates were inhibited at daptomycin 2 mg/L, compared with 88.7–96.6% in the other countries evaluated. One linezolid-non-susceptible isolate of *E. faecalis* (MIC 4 mg/L) was isolated in France (Table 2), while daptomycin-non-susceptible *E. faecium* isolates were recovered in Germany (one isolate) and Israel (one isolate) (Table 3).

β-Haemolytic streptococci

β-Haemolytic streptococci exhibited high rates of susceptibility to most antimicrobial agents tested. Decreased susceptibility was detected only to tetracycline (51.5%), erythromycin (84.1%) and clindamycin (94.2%) (Table 1). All β-haemolytic streptococcal isolates were inhibited at daptomycin ≤0.5 mg/L, with 97.6% inhibited at ≤0.25 mg/L (the CLSI and US-FDA susceptible breakpoint is ≤1 mg/L).

There were no significant inter-country variations in the antimicrobial resistance patterns of β-haemolytic streptococci, except for tetracycline and erythromycin (Table 2). The lowest rates of susceptibility to tetracycline were observed in Belgium (25.0%, only 12 isolates) and Greece (37.5%), while the highest rates were observed in Spain (76.7%). Erythromycin susceptibility rates varied from 50.0% in Italy to 100.0% in Belgium, Greece and Switzerland (Table 2). This group of organisms showed the narrowest daptomycin MIC range (≤0.06–0.5 mg/L). Isolates from all countries had a daptomycin MIC_{50} of ≤0.06 mg/L or 0.12 mg/L, and an MIC_{90} of 0.12 mg/L or 0.25 mg/L (Table 3).

Viridans group streptococci

Vancomycin and linezolid were the compounds most active against viridans group streptococci (MIC_{90} 1 mg/L; 100% susceptible), followed by daptomycin (MIC_{90} 0.5 mg/L; 99.1% susceptible), clindamycin (MIC_{90} >8 mg/L; 84.1% susceptible) and levofloxacin (MIC_{90} 1 mg/L; 98.2% susceptible). Overall, 72.9% of isolates were fully susceptible to penicillin (7.9% resistant), with susceptibility rates varying from only 30.8% in Turkey to 87.1% in the UK among countries from which >20 isolates were tested (Table 2). Only three isolates had an elevated, reproducible daptomycin MIC of 2 mg/L (one each from France, Germany and the UK). The susceptibility patterns by country of viridans group streptococci, as well as country-to-country variation of daptomycin potency, could not be evaluated adequately because of limited numbers of isolates submitted from invasive infections by some countries.

DISCUSSION

The emergence and dissemination of MRSA in Europe is a concern because these isolates are often resistant to multiple antimicrobial agents. The overall MRSA rate in the present study was 26.7%, which is comparable to or slightly higher than that reported in previous studies [1–3,19]. However, MRSA rates varied greatly among countries, with Belgium, Greece, Ireland, Israel and the UK displaying >40% resistance, while Sweden showed only 0.6% resistance. Similar geographical variations have been reported in

previous studies, and may reflect differences in infection control policies and other factors [4,20,21]. The emergence of MRSA is caused largely by dissemination of clonal strains, and hospital outbreaks are typically the result of cross-transmission of these strains among patients. However, a direct correlation between antimicrobial usage and resistance rates has been difficult to establish because of the high number of variables involved [21,22].

Vancomycin-resistant *Staph. aureus* is a serious concern, but very few isolates have been reported to date, all of which have been in the USA. In addition, there are many reports of vancomycin-intermediate *Staph. aureus*, and following the reduction in the CLSI vancomycin-susceptible breakpoint from 4 to 2 mg/L [17], such reports may become more frequent. In the present study, only one *Staph. aureus* isolate with a vancomycin-intermediate MIC value (4 mg/L) was detected. This isolate was oxacillin- and daptomycin-susceptible (MIC 0.5 mg/L for both agents), and was isolated from a patient with bloodstream infection in Poland.

A further interesting finding of this study was the detection of 20 *Staph. aureus* isolates with quinupristin–dalfopristin MICs ≥2 mg/L. Germany, Italy and the UK each submitted one quinupristin–dalfopristin-resistant isolate, while France submitted 17 such isolates. Quinupristin–dalfopristin-resistant *Staph. aureus* isolates have been reported previously from France, and the emergence and dissemination of this resistance phenotype may be related to the clinical use of natural streptogramin mixtures, e.g., pristiniamycin and synergistin, orally and topically since the 1960s [23].

Although vancomycin resistance rates in Europe are relatively low compared with those reported in the USA [19], VRE appear to have become more prevalent in Europe in recent years, with 21.0% of *E. faecium* isolates displaying resistance in 2005 [24]. In the present study, overall vancomycin resistance rates were relatively high (>15.0%), with levels of 19.7% in Greece, 21.2% in Ireland, 15.7% in Italy, 15.4% in Israel and 15.2% in the UK. Interestingly, the highest MRSA rates (>40.0%) were also observed in these five countries plus Belgium (Table 2), indicating that these two resistance phenotypes may be related epidemiologically [21,22]. Furthermore, the results of the present study confirmed previous reports by showing that daptomycin is active against many MDR Gram-positive strains, and that vancomycin resistance does not significantly affect the in-vitro activity of daptomycin [11].

In conclusion, daptomycin demonstrated excellent in-vitro activity against recent clinical isolates of Gram-positive bacteria (9322 isolates) collected from 14 countries in Europe. As daptomycin possesses a unique mechanism of action (i.e., it targets the bacterial membrane in the presence of calcium), it demonstrates no cross-resistance with other classes of antimicrobial agent, making it an excellent option for the treatment of infections caused by MDR organisms [8,11,24–27]. Although the in-vitro activities of daptomycin were very consistent among the participating countries, variations were apparent for other antimicrobial agents.

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