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Prevalence and Antimicrobial Susceptibility Patterns of Methicillin-resistant *S. aureus* and Vancomycin-resistant *E. faecium* causing Bloodstream Infections in European Hospitals (2005-2008)

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ABSTRACT

Objective: To evaluate the prevalence and antimicrobial susceptibility (S) of methicillin-resistant *S. aureus* (MRSA) and vancomycin-resistant *E. faecium* (VREFM) in European hospitals. These organisms are usually multidrug-resistant (MDR) with very limited therapeutic options.

Methods: Non-duplicate consecutive strains causing blood stream infections (BSI) were collected in the 2005-2008 period from 27 hospitals located in 11 European countries, Turkey and Israel. A total of 22,712 organisms (9,299 Gram-positives [GP]) were collected, including 3,962 *S. aureus* and 1,700 *Enterococcus* spp. (677 *E. faecium*), and tested for S by CLSI broth microdilution methods in cation-adjusted Mueller-Hinton broth.

Results: Overall MRSA rates decreased from 31.5% in 2005 to 23.9% in 2008. Marked decreases occurred in Turkey (from 41.0% in 2005 to 16.2% in 2008), Italy (51.1 to 29.6%), UK (52.3 to 30.9%) and Poland (25.3 to 15.4%). MRSA rates varied widely among the countries evaluated and, in 2008 were highest in Israel (50.0%) and Ireland (44.6%) and lowest in Sweden (1.8%) and Poland (15.4%). Overall, VREFM increased from 6.1% (2005) to 10.0% (2008), but occurred only in 5 countries in 2008, varying from 4.6% in Italy and 5.3% in UK to as high as 26.2% in Germany and 22.2% in Ireland. The only country with a consistent VREFM increase was Germany (from 7.7 to 26.2%). VREFM was not observed in Spain, Sweden and Switzerland during the study interval. Daptomycin (DAP) was the most active compound against these organisms (see Table), followed by linezolid (LZD), and the activity of these compounds was not negatively affected by resistant (R) to oxacillin or vancomycin (VAN). All other compounds exhibited limited activity against VREFM. Among *E. faecalis* (956 strains), only 0.6% were VAN-R, while 77.8% of coagulase-negative staphylococci were oxacillin-R.

Organism/ (no. tested)	MIC_{90} (mg/L) / % susceptible				
	Daptomycin	Vancomycin	Teicoplanin	Q/D[a]	Linezolid
MRSA (1,086)	0.5 / 100.0	1 / 100.0	≤2 / 100.0	1 / 99.8	2 / 99.9
VREFM (134)	2 / 99.3	>16 / 0.0	>16 / 41.8	>2 / 73.1	2 / 98.5

a. Q/D = quinupristin/dalfopristin

Conclusions: *S. aureus* and *Enterococcus* spp. represent important causes of BSI in European hospitals and the prevalence of MRSA and VREFM differs significantly among countries and has varied in many countries in recent years. DAP and LZD were the most active compounds tested against these MDR organisms as well as other GP pathogens isolated from episodes of BSI. Due to broad spectrum, potent bactericidal activity and approved indications, DAP represents a valuable treatment option for BSI caused by GP in European hospitals.

INTRODUCTION

Gram-positive bacteria, especially staphylococci and enterococci, are extremely important pathogens causing serious infections in the hospital environment. *Staphylococcus aureus*, coagulase-negative staphylococci (CoNS) and enterococci are among the five most frequently isolated organisms from nosocomial bloodstream infections (BSI). These three pathogens are responsible for approximately one-half of the cases of BSI in North American medical centers evaluated by the SENTRY Antimicrobial Surveillance Program.

Daptomycin is a lipopeptide with rapid in vitro bactericidal activity against a wide spectrum of Gram-positive organisms, including multidrug-resistant (MDR) strains of staphylococci, enterococci and streptococci. Daptomycin was approved by the United States (USA) Food and Drug Administration (USA-FDA) and by the European Medicine Agency (EMEA) for the treatment of complicated skin and skin structure infections (cSSSI) using a dose of 4 mg/kg every 24 hours and for treatment of *S. aureus* bacteremia and right-sided endocarditis at a dose of 6 mg/kg every 24 hours.

As part of the Daptomycin Surveillance Program, we evaluate the prevalence and antimicrobial susceptibility of MRSA and vancomycin-resistant *Enterococcus faecium* (VREFM) in European hospitals. These organisms are usually MDR with very limited therapeutic options.

MATERIALS AND METHODS

Bacterial isolates: As part of the European Daptomycin Surveillance Program, non-duplicate consecutive strains causing BSI were collected in the 2005-2008 period from 27 hospitals located in 11 European countries, Turkey and Israel. A total of 22,712 organisms (9,299 Gram-positives) were collected from BSI by the program during this period, including 3,962 *S. aureus* and 1,700 *Enterococcus* spp. (677 *E. faecium*).

Susceptibility testing: Daptomycin and selected comparator agents were tested by Clinical and Laboratory Standards Institute (CLSI, formerly the NCCLS) criteria. All strains were tested for antimicrobial susceptibility by the broth microdilution method. Dry-form, validated microdilution panels and broth reagents were 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. Comparator agents included those representing the most common classes and examples of drugs used for the empiric or directed treatment of the indicated pathogen. The isolates were categorized as susceptible and resistant according to CLSI guidelines. A daptomycin susceptible breakpoint of ≤1 mg/L was used for staphylococci, while ≤4 mg/L was used for enterococci, as approved by the USA-FDA, CLSI and EUCAST. The following quality control organisms were concurrently tested: *E. faecalis* ATCC 29212, and *S. aureus* ATCC 29213.

RESULTS

- Overall MRSA rates decreased from 31.5% in 2005 to 23.9% in 2008. Greatest decreases occurred in Turkey (from 41.0% in 2005 to 16.2% in 2008), Italy (from 51.1% to 29.6%), UK (from 52.3% to 30.9%) and Poland (from 25.3% to 15.4%; Table 1).
- MRSA rates varied widely among the countries evaluated. In 2008, the highest rates were observed in Israel (50.0%) and Ireland (44.6%) and the lowest rates in Sweden (1.8%) and Poland (15.4%; Table 1).
- Overall VREFM rates increased from 6.1% in 2005 to 10.0% in 2008, but occurred only in 5 countries in 2008: Germany (26.2%), Ireland (22.2%), Italy (4.6%), Turkey (10.9%) and UK (5.3%; Table 2).
- Germany was the only country with a consistent VREFM increase: from 7.7% in 2005 to 26.2% in 2008. VREFM was not observed in Spain, Sweden and Switzerland during the study interval (Table 2).
- Daptomycin was the most active compound tested against MRSA (MIC_{50}, 0.25 mg/L and MIC_{90}, 0.5 mg/L; 100.0% susceptible), and VREFM (MIC_{50} and MIC_{90}, 2 mg/L; 99.3% susceptible), followed by linezolid (99.9 and 98.5% susceptibility for MRSA and VREFM, respectively, see Table 3.
- Teicoplanin (MIC_{50} and MIC_{90}, ≤2 mg/L) and vancomycin (MIC_{50} and MIC_{90}, 1 mg/L) also showed complete activity (100.0% susceptibility) against MRSA. Furthermore, quinupristin/ dalfopristin (98.8% susceptible) and trimethoprim/ sulfamethoxazole (97.1% susceptible) were generally very active against this organism (Table 3).
- All compounds, except daptomycin and linezolid, exhibited limited activity against VREFM. Only 73.1% of VREFM strains were susceptible to quinupristin/dalfopristin (Table 3).Daptomycin activity against *S. aureus* and *E. faecium* was not negatively influenced by resistance to oxacillin or vancomycin (Table 4).
- Daptomycin was also very active against *E. faecalis* (956 strains tested, only 0.6% vancomycin-resistant) with a MIC_{90} at 2 mg/L and 100.0% susceptibility (Table 4).

Table 1. Yearly MRSA rates in European countries (2005-2008).

Country	% of MRSA (no. of isolates tested)			
	2005	2006	2007	2008
Belgium	-[a]	19.4 (32)	7.7 (26)	19.1 (21)
France	26.7 (206)	23.4 (265)	32.2 (230)	24.7 (142)
Germany	22.4 (183)	13.6 (147)	17.5 (154)	19.1 (115)
Greece	58.3 (12)	-	-	-
Ireland	46.6 (73)	47.8 (115)	47.3 (91)	44.6 (65)
Israel	48.7 (39)	54.3 (35)	44.8 (29)	50.0 (22)
Italy	51.1 (90)	36.9 (84)	44.0 (91)	29.6 (44)
Poland	25.3 (99)	29.6 (44)	25.7 (70)	15.4 (26)
Spain	30.0 (60)	18.2 (77)	15.8 (76)	24.2 (62)
Sweden	1.3 (77)	1.2 (88)	4.1 (73)	1.8 (55)
Switzerland	22.2 (36)	6.5 (46)	11.1 (36)	17.1 (35)
Turkey	41.0 (83)	29.3 (106)	27.0 (100)	16.2 (74)
UK	52.3 (65)	35.3 (102)	38.7 (111)	30.9 (81)
Overall	31.5 (1,023)	25.6 (1,110)	27.9 (1,087)	23.9 (742)

a. - = no one medical center participated in the program in that year.

Table 2. Yearly rates of vancomycin resistance among *E. faecium* collected in European medical centers (2005-2008).

Country	% vancomycin-resistant (no. of isolates tested)			
	2005	2006	2007	2008
Belgium	-[a]	0 (4)	5.6 (17)	0 (8)
France	1.8 (55)	0 (59)	1.7 (58)	0 (44)
Germany	7.7 (104)	10.6 (104)	11.9 (134)	26.2 (65)
Greece	10.0 (10)	-	-	-
Ireland	21.9 (32)	23.5 (34)	11.6 (43)	22.2 (45)
Israel	8.3 (12)	9.5 (21)	18.2 (11)	0 (19)
Italy	11.1 (54)	2.6 (39)	13.8 (29)	4.6 (22)
Poland	0 (43)	0 (10)	14.3 (14)	0 (19)
Spain	0 (20)	0 (18)	0 (17)	0 (16)
Sweden	0 (31)	0 (44)	0 (42)	0 (22)
Switzerland	0 (15)	0 (17)	0 (13)	0 (15)
Turkey	4.6 (66)	1.7 (59)	5.0 (40)	10.9 (46)
UK	10.0 (20)	22.9 (35)	11.1 (36)	5.3 (19)
Overall	6.1 (462)	7.0 (444)	8.2 (454)	10.0 (340)

a. - = no one medical center participated in the program in that year.

Table 3. Antimicrobial susceptibility of methicillin-resistant *S. aureus* (MRSA) and vancomycin-resistant *E. faecium* (VREFM) isolated in European hospitals (2005-2008).

Organism/antimicrobial (no. tested)	MIC (mg/L)		% susceptible[a]	% resistant[a]
	MIC_{50}	MIC_{90}		
MRSA (1,086)				
Daptomycin	0.25	0.5	100.0	-[b]
Erythromycin	>4	>4	27.3	71.5
Clindamycin	≤0.25	>2	58.7	41.0
Gentamycin	≤2	>8	69.4	29.8
Levofloxacin	>4	>4	6.5	91.9
Linezolid	1	2	99.9	-[b]
Quinupristin/dalfopristin	0.5	1	98.8	1.0
Tetracycline	≤2	>8	84.3	14.9
Trim/sulfa[c]	≤0.5	≤0.5	97.1	2.9
Teicoplanin	≤2	≤2	100.0	0.0
Vancomycin	1	1	100.0	0.0
VREFM (134)				
Daptomycin	2	2	99.3	-[b]
Ampicillin	>16	>16	0.0	100.0
Levofloxacin	>4	>4	3.0	95.5
Erythromycin	>4	>4	0.7	97.0
Gentamicin (HL)[d]	≤500	>1000	63.4	36.6
Streptomycin (HL)	≤1000	>2000	59.7	40.3
Tetracycline	≤2	>8	71.6	28.4
Quinupristin/dalfopristin	1	>2	73.1	18.7
Linezolid	1	2	98.5	0.0
Teicoplanin	16	>16	41.8	50.0

a. According to CLSI criteria.
b. - = no breakpoints have been established by the CLSI.
c. Trimethoprim/sulfamethoxazole.
d. HL = high-level aminoglycoside resistance

Table 4. Daptomycin MIC distributions of *S. aureus* and enterococci collected in Europe (2005-2008).

Organism (no. tested)	No. of isolates (cumulative %) inhibited at daptomycin MIC (mg/L) of:						
	≤0.12	0.25	0.5	1	2	4	8
S. aureus							
Oxacillin-susceptible (2,876)	143 (5.0)	2,345 (86.5)	381 (99.8)	7 (100.0)	-	-	-
Oxacillin-resistant (1,086)	34 (3.1)	714 (68.9)	328 (99.1)	10 (100.0)	-	-	-
E. faecalis (956)	5 (0.5)	36 (4.3)	401 (46.2)	468 (95.2)	46 (100.0)		
E. faecium							
Vancomycin-susceptible (543)	5 (0.9)	6 (2.0)	31 (7.7)	163 (37.8)	284 (90.1)	54 (100.0)	-
Vancomycin-non-susceptible (134)	0 (0.0)	2 (1.5)	9 (8.2)	50 (45.5)	62 (91.8)	10 (99.3)	1 (100.0)

CONCLUSIONS

- The prevalence of MRSA appears to be decreasing while VREFM showed a continuous increase in the 2005-2008 period in the European medical centers evaluated in this study. However, the VREFM increase appears to be driven by epidemic events.
- Daptomycin and linezolid were the most active compounds tested against these MDR organisms as well as other Gram-positive organisms isolated from episodes of a BSI.
- Due to broad-spectrum, potent bactericidal activity and approved indications, daptomycin represent a valuable treatment option for BSI caused by Gram-positive pathogens in European hospitals.

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