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Prevalence and Antimicrobial Susceptibility (S) Profiles of Skin and Skin Structure Infection (SSSI) Pathogens in Europe (EUR): Report from the SENTRY Antimicrobial Surveillance Program (1997-2005)

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AMENDED ABSTRACT*

Objectives: To present a 9-year summary of bacterial pathogens (prevalence and S trends; SENTRY Program) recovered from EUR patients experiencing SSSI. Rising resistance (R) rates are being observed globally in both Gram-positive and -negative SSSI pathogens, challenging accepted approaches to clinical management, especially empiric antimicrobial therapy guidelines.
Methods: Non-duplicate, clinically-significant SSSI isolates (6,828) were collected from >25 medical centers in Europe participating in the SENTRY Program from 1997-2005 (exception, 2001). Identifications were confirmed by the central monitoring laboratory and all isolates were S tested using CLSI methods and interpretive criteria (M100-S17) against antimicrobial agents commonly utilized as empiric or directed therapy.
Results: The ten ranking EUR SSSI pathogens for all years were: *S. aureus* (SA; 38.8%), *P. aeruginosa* (PSA; 11.8%), *E. coli* (EC; 10.4%), *Enterococcus* spp. (ENT; 5.8%), coagulase-negative staphylococci (5.0%), *Enterobacter* spp. (ESP; 4.9%), *Klebsiella* spp. (KSP; 4.3%), beta-haemolytic streptococci (BHS; 3.8%), *P. mirabilis* (3.1%), and *Acinetobacter* spp. (ASP; 2.6%). Analysis of intervals 1997-2000 and 2002-2005 showed that BHS moved from 10th to 4th in prevalence and erythromycin (ERY)-R increased from 12.3 to 22.5%. While prevalence of SA varied widely between countries (highest in the UK [86.1%] and lowest in Turkey [40.5%]), overall EUR methicillin-R (MRSA) rates remained unchanged between intervals (22.8 and 23.0%, respectively) and ERY-R decreased slightly (31.2 to 27.2%). Vancomycin-R rates in ENT increased slightly between intervals (2.9 and 3.7%, respectively). R increases were most notable for imipenem (IPM) with PSA and ASP, and also with levofloxacin (LEV) for KSP and EC. ESBL-phenotypes were detected in 12.7% of EC in 2002-2005; which were increased significantly from the previous monitored interval.

Organism (no.)	R pattern	% Inhibited at CLSI breakpoints 1997-2000	2002-2005
SA (2,652)	MRSA	22.8	23.0
PSA (807)	IPM-R	9.5	12.4
	Ceftazidime (CAZ)-R	17.8	16.8
	LEV-R	28.2	26.2
	Amikacin (AMK)-R	10.4	5.5
EC (711)	CAZ-R	2.2 (8.3)[b]	5.7 (12.7)[b]
	LEV-R	6.5	12.3
ESP (338)	IPM-NS[a]	0.6	1.7
	CAZ-R	22.4	17.5
	LEV-R	7.5	6.2
KSP (283)	CAZ-R	14.9 (20.3)[b]	11.9 (20.0)[b]
	LEV-R	3.4	9.6
	AMK-R	1.4	1.5
ASP (179)	IPM-R	7.9	11.5
	CAZ-R	46.5	41.0
	LEV-R	28.7	30.8
	AMK-R	55.4	28.2

a. NS = non-susceptible.
b. Number in parentheses reflects the ESBL-phenotype rate (MIC values ≥2 mg/L).

Conclusions: With key exceptions (ERY-R in BHS; IPM-R in PSA and ASP; LEV-R in Enterobacteriaceae), R profiles for leading SSSI pathogens did not change significantly during the first decade of SENTRY Program data collection. The continued spread of virulent MRSA into the community setting and increases being detected in ESBL and carbapenem-R rates are, however, cause for concern and require continued monitoring to guide contemporary antimicrobial therapies and searches for new compounds.

*Updated to reflect changes in resistance percentages

INTRODUCTION

Infections of skin and skin structures (SSSI) are among the most common of community- and hospital-acquired infections; in the USA alone, estimates of over 700,000 patients being hospitalized annually for such infections have been projected. Given the prominent role that *Staphylococcus aureus* infections play in SSSI, the recent appearance of virulent, methicillin-resistant (MRSA) clones producing infections in otherwise healthy individuals in the community (CA-MRSA) is of special concern as a looming public health crisis.

Successful treatment of these infections relies upon factors such as severity of disease, patient age, underlying medical condition(s), specific pathogens involved, site of infection, and the pharmacokinetic/pharmacodynamic parameters of the drugs being administered. These factors, combined with the increasing resistance of usual skin pathogens to existing antimicrobials, contributes significantly to rising morbidity, mortality and healthcare costs. While ß-lactams are among the most commonly prescribed agents for SSSI, the increase in CA-MRSA is driving the utilization of other antimicrobials, especially the fluoroquinolones.

The SENTRY Antimicrobial Surveillance Program has been tracking emerging resistance to SSSI pathogens on a global scale since 1997. This report describes changes in SSSI pathogen prevalence and resistance to commonly utilized antimicrobials among isolates collected from European patients during 1997 to 2005.

MATERIALS AND METHODS

Organism Collection: Participating European medical centers (≥25) submitted consecutive, nonduplicate community-acquired or nosocomial SSSI pathogens (a total of 6,828 isolates; see Table 1 for ranking) for the years 1997 to 2005 (exception, 2001). The following participating countries (percent of total isolates) from Europe contributed isolates over the study period: Albania (1.2), Austria (1.4), Belgium (3.3), France (17.5), Germany (12.4), Greece (4.1), Ireland (1.7), Israel (3.1), Italy (9.9), the Netherlands (1.5), Poland (5.1), Portugal (3.5), Russia (1.0), Spain (11.3), Sweden (5.3), Switzerland (3.9), Turkey (8.4), and the United Kingdom (5.4). Species identifications were performed by the submitting laboratories with identification confirmation performed by the central laboratory monitor (JMI Laboratories, Iowa, USA).

Antimicrobial susceptibility testing: Susceptibility testing was performed using validated broth microdilution test panels (TREK Diagnostic Systems, Inc., OH, USA) with cation-adjusted Mueller-Hinton broth (+ 2 to 5% lysed horse blood for testing of fastidious species) according to CLSI methods (M7-A7, 2006). Quality control isolates utilized included *Escherichia coli* ATCC 25922 and 35218, *Pseudomonas aeruginosa* ATCC 27853, *Staphylococcus aureus* ATCC 29213, *S. pneumoniae* ATCC 49619 and *Enterococcus faecalis* ATCC 29212; interpretive criteria used were those recommended by the CLSI (M100-S17; 2007).

Enterobacteriaceae with elevated MIC values (≥2 mg/L) for ceftazidime and/or ceftriaxone and/or aztreonam were considered as extended-spectrum ß-lactamase (ESBL)-producing phenotypes according to CLSI criteria; ESBL confirmation was performed using the disk approximation method.

RESULTS

- *S. aureus* (approximately 23% oxacillin-resistant, stable between intervals) remained the most common SSSI pathogen in European patients across all years followed by *P. aeruginosa* and *E. coli* (Tables 1 and 2).
- Trends toward greater susceptibility among *S. aureus* were apparent for clindamycin, gentamicin and tetracycline over the two study periods (1997-2000 and 2002-2005), with resistance decreasing from 20.3 to 11.6%, 21.1 to 8.0% and 25.0% to 9.9%, respectively (Table 2).
- Resistance rates among MRSA strains have likewise decreased, in some instances considerably, between intervals for erythromycin (-22.9%), clindamycin (-31.1%) and tetracycline (-40.6%; data not shown).
- Linezolid, daptomycin and vancomycin remained effective against all staphylococci; rare quinupristin/dalfopristin resistant strains were found (Table 2).
- Increases in resistance among enterococci were apparent between intervals for erythromycin (+4.9%) and ciprofloxacin (+4.3%) but remained unchanged for vancomycin, ampicillin and tetracycline (Table 2).
- Prevalence of ß-haemolytic streptococci increased from tenth to fourth place between intervals; resistance also increased for erythromycin (+10.2%). The mef(A) phenotype (erythromycin-resistant, clindamycin-susceptible) now predominates (an increase from 49.6 to 69.8%; Table 2).
- *P. aeruginosa* susceptibilities improved between the two study intervals for all agents except imipenem (83.6 to 78.5%, respectively; Table 3) whereas only modest resistance increases were noted for *Acinetobacter* spp. (Table 3)
- Among Enterobacteriaceae, an increase in resistance to levofloxacin was seen among *E. coli* and *Klebsiella* spp. (+9.8% and +6.2%, respectively; Table 3).
- The ESBL phenotype rate in *E. coli* increased from 8.3-12.7% and 6.2-12.9% for ceftazidime and ceftriaxone, respectively, during the study; the ceftazidime ESBL screen rate for *Klebsiella* spp., remained unchanged at 20% but increased markedly for ceftriaxone from 10.9% to 20.7%. Changes in prevailing ESBL enzyme types (e.g., CTX-M variants) would account for these differences.
- Eighteen strains were confirmed as producing MßL enzymes, including 13 *P. aeruginosa* from Italy and one *P. mirabilis* from Greece, all VIM-1. Two *Enterobacter* spp. isolates from Turkey had an IMP-1 enzyme.

Table 1. Prevalence of ranking SSSI pathogens from among 6,828 isolates collected as part of the SENTRY Program in Europe (1997-2000 and 2002-2005).

Organism (no. tested)	Rank (no. tested) 1997-2000	2002-2005
S. aureus (2,652)	1 (1,097)	1 (1,555)
P. aeruginosa (807)	2 (444)	3 (363)
E. coli (711)	3 (324)	2 (387)
Enterococcus spp. (397)	4 (209)	5 (188)
Coagulase-negative staphylococci (344)	5 (163)	6 (181)
Enterobacter spp. (338)	6 (161)	7 (177)
Klebsiella spp. (283)	7 (148)	8 (135)
Proteus mirabilis (212)	8 (101)	9 (111)
Acinetobacter spp. (179)	9 (101)	10 (78)
ß-haemolytic streptococci (331)	10 (81)	4 (250)

Table 2. Antimicrobial activity of selected agents tested against the top four ranked Gram-positive pathogens causing SSSI in the European SENTRY Program (1997 - 2005).

Organism (no. tested)	1997-2000 MIC (mg/L) 50%	90%	% by category[a] Susceptible	Resistant	2002-2005 MIC (mg/L) 50%	90%	% by category[a] Susceptible	Resistant
S. aureus (2,652)								
Oxacillin	0.5	>8	77.2	22.8	0.5	>2	77.0	23.0
Erythromycin	0.5	>8	61.8	31.2	0.25	>8	71.7	27.2
Clindamycin	0.12	>8	79.4	20.3	0.12	>2	88.3	11.6
Levofloxacin	0.12	>4	77.8	21.3	0.25	>4	76.9	22.0
Gentamicin	0.5	>16	78.2	21.1	≤2	<2	91.1	8.0
Daptomycin	-	-	-	-	0.25	0.5	100.0	-
Linezolid	2	2	100.0	-	2	2	100.0	-
Quin/dalfo[b]	0.25	0.5	99.4	0.3	≤0.25	0.5	99.4	0.5
Tetracycline	≤4	>8	74.5	25.0	≤2	8	89.2	9.9
Trim/sulfa[b]	-	-	-	-	≤0.5	≤0.5	97.4	2.6
Vancomycin	1	1	100.0	0.0	1	1	100.0	0.0
Enterococcus spp.(397)								
Ampicillin	1	>16	85.6	14.4	2	>16	85.1	14.9
Erythromycin	4	>8	15.3	47.8	8	>8	5.3	52.7
Levofloxacin	2	>4	60.8	37.3	1	>4	63.8	33.0
Gentamicin HL	≤500	>1000	69.4	30.6	≤500	>1000	71.3	28.7
Daptomycin	-	-	-	-	1	2	100.0	-
Linezolid	2	2	99.3	0.0	2	2	100.0	0.0
Quin/dalfo[b]	4	>8	16.7	66.5	>2	>2	13.3	75.0
Tetracycline	>8	>8	34.4	65.1	>8	>8	35.1	64.4
Vancomycin	1	2	96.7	2.9	1	2	96.3	3.7
Coagulase-negative staphylococci[c] (344)								
Oxacillin	2	>8	30.1	69.9	2	>2	28.2	71.8
Erythromycin	>8	>8	44.2	52.8	>2	>2	43.1	43.1
Clindamycin	0.12	>8	69.9	27.6	0.12	>8	74.0	26.0
Levofloxacin	4	>4	41.2	58.8	≤0.5	>4	55.2	38.7
Gentamicin	≤1	>16	58.3	33.7	≤2	>8	69.6	22.7
Daptomycin	-	-	-	-	0.25	0.5	100.0	-
Linezolid	1	2	100.0	-	1	1	100.0	-
Quin/dalfo[b]	0.25	0.5	98.8	0.6	≤0.25	0.5	100.0	0.0
Tetracycline	≤4	>8	72.4	26.4	≤2	>8	76.1	23.3
Trim/sulfa[b]	-	-	-	-	≤0.5	>2	76.2	23.8
Vancomycin	2	2	100.0	0.0	1	2	100.0	0.0
ß-haemolytic streptococci[d] (331)								
Penicillin	≤0.03	0.06	98.8[e]	-	≤0.015	0.03	100.0	-
Erythromycin	≤0.25	1	87.7	12.3	≤0.06	>2	77.5	22.5
Clindamycin	≤0.06	0.12	92.6	6.2	≤0.25	≤0.25	93.2	6.8
Levofloxacin	1	1	100.0	0.0	0.5	1	100.0	0.0
Linezolid	1	1	100.0	-	1	1	100.0	-
Quin/dalfo[b]	0.25	1	100.0	0.0	≤0.25	0.5	100.0	0.0
Tetracycline	≤4	>16	45.7	46.9	≤2	>8	55.6	39.6
Vancomycin	0.5	0.5	100.0	-	0.25	0.5	100.0	-

a. Criteria as published by the CLSI; - = agent not tested, or CLSI interpretive criteria not available.
b. Abbreviations: Quin/dalfo = Quinupristin/dalfopristin; Trim/sulfa = Trimethoprim/sulfamethoxazole.
c. Includes: *S. capitis* (8 strains), *S. chromogenes* (1 strain), *S. cohnii* (1 strain), *S. epidermidis* (161 strains), *S. haemolyticus* (19 strains), *S. hominis* (7 strains), *S. intermedius* (2 strains), *S. lugdunensis* (22 strains), *S. saprophyticus* (1 strain), *S. schleiferi* (1 strain), *S. sciuri* (1 strain), *S. simulans* (3 strains), *S. warneri* (10 strains), *S. xylosis* (1 strain), and unspeciated coagulase-negative staphylococci (106 strains).
d. Includes: *S. dysgalactiae* (2 strains), *S. equi* (1 strain), *S. equisimilis* (2 strains), Group A (188 strains), Group B (73 strains), Group C (12 strains), Group G (50 strains) and unidentified beta-haemolytic streptococci (2 strains).
e. One strain with an MIC of 0.25 mg/L.

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Table 3. Antimicrobial activity of selected antimicrobial agents tested against Gram-negative pathogens causing SSSI in the European SENTRY Program (1997 - 2005).

Organism (no. tested)	1997-2000 MIC (mg/L) 50%	90%	% by category[a] Susceptible	Resistant	2002-2005 MIC (mg/L) 50%	90%	% by category[a] Susceptible	Resistant
P. aeruginosa (807)								
Cefepime	4	>16	76.4	15.8	4	>16	79.6	10.2
Ceftazidime	2	>16	76.6	17.8	4	>16	79.1	16.8
Levofloxacin	1	>4	66.4	28.2	0.5	>4	70.2	26.2
Gentamicin	2	>16	67.3	28.8	≤2	>8	76.3	21.5
Imipenem	1	8	83.6	9.5	1	>8	78.5	12.4
Polymyxin B	-	-	-	-	≤1	≤1	99.7	0.3
Pip/tazo[b]	8	>64	84.5	15.5	8	>64	84.0	16.0
E. coli (711)								
Ampicillin	>16	>16	45.1	54.6	>16	>16	42.6	56.3
Amox/clav[b]	8	>16	69.8	14.5	8	16	72.1	9.3
Cefepime	≤0.12	0.25	98.1	1.5	≤0.12	1	93.8	4.4
Ceftazidime	0.25	0.5	96.9	2.2 (8.3)[c]	≤1	8	91.2	5.7 (12.7)[c]
Ceftriaxone	≤0.25	≤0.25	96.0	2.8 (6.2)[c]	≤0.25	16	89.9	8.5 (12.9)[c]
Levofloxacin	≤0.5	2	89.8	6.5	≤0.5	>4	79.8	16.3
Gentamicin	≤1	4	90.1	8.6	≤2	4	90.2	8.5
Imipenem	0.12	0.5	100.0	0.0	≤0.5	≤0.5	100.0	0.0
Pip/tazo[b]	1	16	90.4	5.2	2	16	91.7	2.8
Tetracycline	≤4	>8	50.6	49.1	≤2	>8	57.1	42.1
Trim/sulfa[b]	-	-	-	-	≤0.5	>2	68.1	31.9
Enterobacter spp. (332)								
Cefepime	≤0.12	4	96.3	2.5	≤0.12	2	97.7	1.1
Ceftazidime	0.25	>16	75.2	22.4	≤1	>16	79.1	17.5
Ceftriaxone	≤0.25	>32	77.0	14.3	≤0.25	>32	80.8	11.3
Levofloxacin	≤0.5	1	90.7	7.5	≤0.5	2	90.4	6.2
Gentamicin	≤1	4	92.5	6.8	≤2	≤2	91.0	6.2
Imipenem	0.5	2	99.4	0.0	≤0.5	≤0.5	98.3	0.0
Pip/tazo[b]	2	64	75.2	7.5	2	64	83.1	6.2
Tetracycline	≤4	8	83.9	9.3	≤2	8	88.1	9.0
Trim/sulfa[b]	-	-	-	-	≤0.5	>2	87.6	12.4
K. pneumoniae (283)								
Amox/clav[b]	4	>16	74.3	16.9	4	>16	71.9	10.4
Cefepime	≤0.12	8	91.2	6.1	≤0.12	>16	87.4	11.9
Ceftazidime	≤0.12	>16	83.1	14.9 (20.3)[c]	≤1	>16	83.7	11.9 (20.0)[c]
Ceftriaxone	≤0.25	32	84.5	8.8 (10.9)[c]	≤0.25	>32	81.5	14.1 (20.7)[c]
Levofloxacin	≤0.5	≤0.5	95.9	3.4	≤0.5	4	89.6	9.6
Gentamicin	≤1	16	83.1	16.2	≤2	>8	84.4	14.8
Imipenem	0.25	1	100.0	0.0	≤0.5	≤0.5	100.0	0.0
Pip/tazo[b]	2	>64	81.8	12.2	2	>64	79.3	15.6
Tetracycline	≤4	>8	73.6	25.7	≤2	>8	83.7	11.9
Trim/sulfa[b]	-	-	-	-	≤0.5	>2	79.3	20.7
P. mirabilis (212)								
Ampicillin	1	>16	57.4	40.6	2	>16	51.4	47.7
Cefepime	≤0.12	0.25	98.0	2.0	≤0.12	0.25	98.2	1.8
Ceftazidime	≤0.12	<0.12	100.0	0.0 (5.9)[c]	≤1	≤1	96.4	1.8 (8.1)[c]
Ceftriaxone	≤0.25	8	93.1	4.0 (10.9)[c]	≤0.25	≤0.25	96.4	1.8 (5.4)[c]
Levofloxacin	≤0.5	1	96.0	3.0	≤0.5	2	90.1	7.2
Gentamicin	1	16	81.2	15.8	≤2	>8	88.3	10.8
Imipenem	1	2	100.0	0.0	1	2	98.2	0.9
Pip/tazo[b]	≤0.5	1	100.0	0.0	≤0.5	1	98.2	0.0
Trim/sulfa[b]	-	-	-	-	≤0.5	>2	64.0	36.0
Acinetobacter spp. (179)								
Amp/sulba[b]	-	-	-	-	8	>16	61.8	30.3
Cefepime	16	>16	42.6	22.8	8	>16	52.6	28.2
Ceftazidime	16	>16	34.7	46.5	16	>16	48.7	41.0
Levofloxacin	1	>4	55.4	28.7	1	>4	59.0	30.8
Gentamicin	>8	>8	27.7	67.3	≤2	>8	57.7	39.7
Imipenem	1	8	87.1	7.9	≤0.5	>8	82.1	11.5
Polymyxin B	-	-	-	-	≤1	≤1	100.0	0.0
Pip/tazo[b]	32	>64	38.6	38.6	32	256	47.4	41.0
Tetracycline	>8	>8	45.5	53.5	4	>8	53.8	43.6
Trim/sulfa[b]	-	-	-	-	>2	>2	47.4	52.6

a. Criteria as published by the CLSI; - = agent not tested, or CLSI interpretive criteria not available.
b. Abbreviations: Amox/clav = Amoxacillin/clavulanate; Trim/sulfa = Trimethoprim/sulfamethoxazole; Pip/tazo = Piperacillin/tazobactam; Amp/sulba = Ampicillin/sulbactam.
c. Percentage screen-positive as ESBL-producers (MIC values ≥2 mg/L).

CONCLUSIONS

- *S. aureus, P. aeruginosa, E. coli* and *Enterococcus* spp. prevail as the most common SSSI pathogens in Europe, not changing between 1997 and 2005; an increase in prevalence of ß-haemolytic streptococci was detected, however.
- Worrisome resistance increases were detected in recent years (2002 – 2005), primarily among ß-haemolytic streptococci (erythromycin), non-fermentative bacilli (imipenem), and Enterobacteriaceae (fluoroquinolones).
- The continued spread of virulent MRSA into the community setting and increases being detected in ESBL and carbapenem-resistance rates are, however, cause for concern and require continued monitoring to guide contemporary antimicrobial therapies.