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Geographic Variations and Trends in Key Bacteremic Pathogen Resistance: Report from the SENTRY Antimicrobial Surveillance Program (1997 - 2001)

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ABSTRACT

Background: R in enterococci, staphylococci, *Klebsiella* (KSP) and *P. aeruginosa* (PSA) continue to be prevalent despite various infection control interventions and appropriate contemporary therapy. Regional R variations do occur depending on local drug-use practices, pathogen prevalence and co-R transmission. The SENTRY Program has consistently monitored these key R patterns in blood cultures over 5-years.
Methods: A total of 28,692 isolates of *S. aureus* (SA), PSA, *Enterococcus* spp. (ESP) and KSP from Europe (EU), Latin (LA) and North America (NA) were tested against more than 30 antimicrobials. 4 R subgroups were examined: MRSA, vancomycin (VAN)-R ESP, KSP-ESBL phenotypes and multidrug-R (MDR) PSA. NCCLS susceptibility methods and interpretative criteria were applied, including ESBL-screening criteria. MDR in PSA was defined as R to ceftazidime, piperacillin, gentamicin and ciprofloxacin.
Results: 5-year occurrence rates for MDR-PSA by region were: LA (15.0%), EU (9.3) and NA (2.1), for which only LA rates appear to be steadily increasing. The most active agent against MDR-PSA was polymyxin B (> 95% S in EU and LA). The rank order of KSP-ESBL phenotypes was: LA (45.5%) > EU (24.4) > NA (6.9). These regional endemic rates of ESBL phenotypes have remained constant over 5 years. VAN-R ESP comprise 1.6 - 6.5% of isolates in both EU and LA (emerging in 1999), however, in NA there was a consistent upward trend from 1997 (13.0%) to 2001 (15.8). The MRSA rate in EU was stable at 30% for the past 3 years as was the rate in LA (26.9 - 36.6%). In contrast, the MRSA rate in NA increased from 22.4% in 1997 to 38.7% in 2001 with a greater co-R.
Conclusions: Incidence of MRSA in NA has continued to increase annually at a rate over 4% per year. NA has a 4-fold greater incidence of VAN-R ESP compared to EU or LA. ESBL phenotypes in KSP vary greatly by region with NA under 7% and LA approaching 50%. MDR-PSA incidence varied widely (2.1 - 15%) across regions and the most active agents were polymyxins, amikacin and isepamicin.

INTRODUCTION

Antimicrobial resistance continues to require longitudinal surveillance systems to assure the ability to communicate necessary information to clinical practitioners. The resultant effect will be the ability to maximize therapeutic outcomes in patient care. Previous concerns regarding the influence of methicillin-resistant staphylococcus and vancomycin-resistant enterococcus strains are now compounded by contemporary resistance mechanisms including extended-spectrum and metallo ß-lactamases, efflux pumps and altered targets.

In recent years, several international surveillance studies have been initiated to evaluate various objectives ranging from individual groups of organisms (European Antimicrobial Resistance Surveillance System [EARSS], and National Antimicrobial Resistance Monitoring System [NARMS]) to systems that test a wide range of organisms (The Surveillance Network [TSN], SENTRY Antimicrobial Surveillance Program, Meropenem Yearly Susceptibility Test Information Collection [MYSTIC]), systems which target specific disease states (The Alexander Project), or studies which evaluate the in vitro activity of a specific antimicrobial (Zyvox® Antimicrobial Potency Study [ZAPS]).

The SENTRY Antimicrobial Surveillance Program was established in 1997 to monitor the predominant pathogens and antimicrobial resistance patterns of nosocomial and community-acquired infections via national and international networks of sentinel hospitals. The purpose of this report is to compare the resistance rates for oxacillin-resistant *S. aureus*, vancomycin-resistant enterococcus, ESBL-phenotypes in *Klebsiella pneumoniae*, and multidrug-resistant *P. aeruginosa* in three different geographic areas during the first 5 years of the SENTRY Program using only isolates from bloodstream infections.

MATERIALS AND METHODS

Bacterial isolates. A total of over 28,962 bacterial bloodstream isolates were obtained from participant laboratories in North America (31 sites), Latin America (10 sites), and Europe (17 sites) during the years of 1997 – 2001 as part of the SENTRY program. The study protocol directed each medical center to collect the first 20 consecutive clinically-significant BSI isolates (one per patient episode) per month and forward them to the central laboratory (JMI Laboratories, North Liberty, Iowa, USA) for susceptibility testing. Isolates were identified using conventional tests, as needed, supplemented with the Vitek System (bioMerieux Inc., Hazelwood, MO, USA). Stock cultures of all isolates were kept at –80∞C.

Susceptibility methods. All isolates were susceptibility tested, utilizing NCCLS reference broth microdilution methods, against a panel of greater than 30 antimicrobial agents. A bacterial suspension equal to a 0.5 McFarland standard was made for all organisms and a volume of 50 µL (100 µL for *S. pneumoniae*) of this suspension was pipetted into 10 mL of appropriate testing media (Mueller Hinton broth, MHB + 3-5% LHB or Haemophilus Test Medium). Using an autoinoculator, 100 µL of the diluted inoculum suspension was dispensed into the wells of a commercial dry form panel (TREK Diagnostics, Westlake, OH, USA). Colony counts were performed regularly to ensure a starting inoculum of 5 x 10^5 cfu per mL. The panels were incubated in an ambient air environment at 35ºC for 16 – 20 hours for all Gram-negative organisms and 20 – 24 hours for all Gram-positive and fastidious organisms. Trays were then read manually and an endpoint of no organism growth was established as the MIC. NCCLS 2002 interpretive criteria were used for classification of the following resistant strains: 1) Oxacillin-resistant *S. aureus*, 2) Vancomycin-resistant enterococci, 3) ESBL-phenotype *Klebsiella* spp. and 4) Multidrug-resistant *P. aeruginosa*, based on resistance to gentamicin (aminoglycoside representative), piperacillin (extended-spectrum penicillin), ciprofloxacin (fluoroquinolone), and ceftazidime (third-generation cephalosporin).

Quality control was performed using the following strains recommended by NCCLS: *S. aureus* ATCC 29213, *E. faecalis* ATCC 29212. *S. pneumoniae* ATCC 49619, *Haemophilus influenzae* ATCC 49247 and 49766, *E. coli* ATCC 25922 and 35218, and *P. aeruginosa* ATCC 27853.

RESULTS

- LA sites had the highest incidence of multi-drug resistant *P. aeruginosa* (15%) > EU (9.3%) > NA (2.1%); oxacillin-resistant *S. aureus* (31.7%) > NA (30.8%) > EU (27.5%); and ESBL-phenotype *Klebsiella* spp. (45.5%) > EU (24.4%) > NA (6.9%). NA sites had the highest incidence of vancomycin-resistant *Enterococcus* spp. (14.4%) > EU (3.6%) > LA (2.7%).

- A significant trend identified during the five-year period was the increased incidence of oxacillin-resistant *S. aureus* by an average of 4.1% in N.A. A similar increase was noted in EU from 1997-1999, but stabilized at about 30%, thereafter.

- Vancomycin and linezolid demonstrated complete activity against oxacillin-resistant *S. aureus* strains from each geographic region (MIC_{90},2µg/ml; 100% susceptible [S]) while teicoplanin (MIC_{90} 2-4 µg/ml; 98.6-99.8% S) and quinupristin/dalfopristin (MIC_{90}1 µg/ml; 94.6-99.2% S) provided a near complete spectrum coverage.

Table 1. SENTRY isolates tested in Europe, Latin America, and North America for four resistant phenotypes; oxacillin-resistant *S. aureus*, vancomycin-resistant enterococci, ESBL-phenotype *Klebsiella* spp. and multi-drug-resistant *P. aeruginosa* from 1997 to 2001.

	Total no. isolates (% resistant)					
Organisms/nation	1997	1998	1999	2000	2001	Total
Oxacillin-resistant *S. aureus*						
Europe	931(22.1)	759(25.7)	334(30.2)	695(30.8)	1,081(30.4)	3,800(27.5)
Latin America	339(29.2)	388(36.6)	420(26.9)	482(30.1)	431(36.0)	2,060(31.7)
North America	1,802(22.4)	1,683(27.8)	1,945(30.7)	1,917(34.4)	1,742(38.7)	9,089(30.8)
Vancomycin-resistant enterococci						
Europe	338(4.1)	280(4.3)	12.9(1.6)	281(5.3)	367(1.9)	1,395(3.6)
Latin America	49(0.0)	67(0.0)	49(4.1)	62(6.5)	66(3.6)	293(2.7)
North America	745(13.0)	724(13.5)	775(14.3)	709(15.7)	660(15.8)	3,613(14.4)
ESBL-phenotype *Klebsiella* spp.						
Europe	281(14.6)	311(26.4)	150(28.7)	337(32.3)	378(21.4)	1,457(24.4)
Latin America	175(48.0)	192(48.4)	186(45.7)	232(48.3)	201(37.3)	986(45.5)
North America	592(6.9)	518(9.7)	597(5.7)	494(6.3)	488(6.1)	2,689(6.9)
Multi-drug-resistant *P. aeruginosa*						
Europe	257(5.1)	248(10.1)	106(14.2)	232(9.5)	309(10.4)	1,152(9.3)
Latin America	92(12.0)	154(14.3)	119(16.0)	124(14.5)	119(17.6)	608(15.0)
North America	359(2.5)	306(1.6)	335(2.1)	306(2.0)	244(2.0)	1,550(2.1)

- Linezolid provided excellent activity against vancomycin-resistant enterococci strains in all geographical regions (MIC_{90},2 µg/ml; 94.4-100% S) and chloramphenicol provided very good coverage in NA isolates (MIC_{90},8 µg/ml; 90.2% S). However, quinupristin/dalfopristin and doxycycline demonstrated little or varied activity in all geographic regions.

- Imipenem and meropenem provided near complete activity against ESBL-phenotype *Klebsiella* spp. isolates from each geographical region (MIC_{90},0.5 µg/ml; 99.7-100.0% S) and (MIC_{90},0.12-0.25 µg/ml; 99.4 – 100.0% S), respectively. Cefepime provided very good activity against NA isolates (MIC_{90},16 µg/ml; 88% S), but piperacillin/tazobactam provided little benefit in all geographic regions (MIC_{90},> 64 µg/ml; 36.6-53.6% S).

- None of the antimicrobials tested provided acceptable levels of activity throughout all regions against multi-drug resistant *P. aeruginosa* . However, amikacin did demonstrate good activity against multi-drug resistant *P. aeruginosa* isolates from NA (MIC_{90},>32 µg/ml; 68.6% S and 15.5% resistance).

Table 2. Most active antimicrobial agents tested against isolates from 1997-2001 for each region for the three resistant phenotypes.

	MIC_{90}/% susceptible		
Organsims/antimicrobial agent	Europe (n=1,045)	Latin America (n=654)	North America (n=2,803)
Oxacillin-resistant *S. aureus*			
Vancomycin	2/100.0	2/100.0	2/100.0
Teicoplanin	4/99.8	4/98.6	2/99.8
Linezolid	2/100.0	2/100.0	2/100.0
Quinupristin/dalfopristin	1/94.6	1/99.2	1/99.2
Vancomycin-resistant enterococci			
Linezolid	2/94.4	-/100.0	2/97.4
Quinupristin/dalfopristin	8/46.0	-/0.0	4/82.7
Doxycycline	>4/66.0	-/50.0	>4/55.9
Chloramphenicol	>16/70.0	-/37.5	8/90.2
ESBL phenotype *Klebsiella* spp.			
Meropenem	0.12/99.4	0.25/99.5	0.12/100.0
Imipenem	0.5/99.7	0.5/99.8	0.5/100.0
Piperacillin/tazobactam	>64/40.6	>64/36.6	>64/53.6
Cefepime	>16/69.0	>16/50.0	16/88.0

Table 3. Most active antimicrobial agents tested against multi-drug resistant *P. aeruginosa* isolates from 1997-2001 for each region.

	Europe (n=107)		Latin America (n=91)		North America (n=32)	
Antimicrobial agent	$MIC_{50/90}$[a]	% S/R[b]	$MIC_{50/90}$[a]	% S/R[b]	$MIC_{50/90}$[a]	% S/R[b]
Amikacin	32/>32	41.1/40.2	>32/>32	19.8/78.0	16/>32	68.8/15.6
Tobramycin	>16/>16	6.5/91.6	>16/>16	1.1/97.8	>16/>16	28.1/71.9
Cefepime	>16/>16	5.6/69.2	16/>16	4.4/44.0	>16/>16	3.1/56.2
Imipenem	8/>8	28.0/49.5	>8/>8	41.8/50.5	>8/>8	37.5/53.1
Meropenem	>8/>8	27.1/59.8	>8/>8	35.2/53.8	8/>8	40.6/43.7
Piperacillin/tazobactam	>64/>64	16.8/83.2	>64/>64	13.2/86.8	>64/>64	9.4/90.6

a. MIC_{50} and MIC_{90} in µg/ml at which 50 and 90% of the isolates were inhibited, respectively.
b. Susceptibility (S)/resistance (R) rates based on interpretive criteria of the NCCLS [2002].

CONCLUSIONS

- Regional differences continue to exist in the prevalence rates of VRE, ESBL-phenotype *K. pneumoniae*, and multidrug-resistant *P. aeruginosa* within the SENTRY Antimicrobial Surveillance Program. However, all regions demonstrated resistance rates of concern for oxacillin-resistant *S. aureus*.
- VRE (14.4%) is of major concern within the NA region, versus EU where multidrug-resistant *P. aeruginosa* (9.3%) prevails, versus LA where ESBL-phenotype *K. pneumoniae* (45.5%) and multidrug-resistant *P. aeruginosa* (15%) dominate resistance problems.
- Each region needs to address its specific resistance issues by developing and implementing strategies to reduce their occurrence rate, followed closely by continued resistance monitoring (SENTRY Program) to evaluate the outcomes associated with the strategies.

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