

Evolutionary Trends in Antimicrobial Resistances in *E. faecium* (EFM) Bacteremia: Report from the SENTRY Antimicrobial Surveillance Program (1997-2005)

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AMENDED ABSTRACT

Background: MRSA and VRE rates have escalated over the last 10-15 years, markedly altering antimicrobial therapeutics. Occurrences can markedly vary among geographic areas and between institutions or even nations. An important subgroup of these pathogens, best used as an epidemiologic/R marker, is EFM bloodstream infections (BSI). The 9-year worldwide experience with EFM-BSI in the SENTRY Program were summarized.

Methods: 4,305 EFM infections were analyzed with 2,689 EFM-BSI distributed among Asia-Pacific (APAC; 239), Europe (EU; 852), Latin America (LA; 83) and USA (1,512). The lowest proportion of EFM-BSI among EFM infections was in LA (54.6%) compared to 70.7-79.4% elsewhere. Strains were susceptibility tested and interpreted by CLSI methods.

Results:

		R rates (%) among EFM-BSI isolates:1				
Region (no. tested)	AMP	Van (<i>VanA</i>)	Q-D	GHL	LZD	TIG
APAC (239)	82.0	5.4 (76.9)	7.1	44.8	0.0	0.0
EU (852)	81.2	11.5 (78.6)	10.2	36.1	0.1	0.2
LA (83)	62.7	12.0 (100.0)	12.4	34.9	0.0	0.0
USA (1,512)	89.0	69.4 (80.6)	2.2	32.8	0.9	0.2
1. AMP = ampicillin; VAN = vand	comycin; Q-D = 0	quinupristin/dalfopristin; L	.ZD = linezolid; (GHL = gentamicir	n high-level; TIG =	= tigecycline

Trends included more EFM and EFM-BSI cases/year, most marked in EU (3.1X) and LA (3.5X) compared to USA or APAC (1.6 X 2.0X) with VanA R patterns dominating (≥76.9%). Specific VAN-R trends were: stepwise increase in EU (1.0-17.1%; 1999 to 2005) and a current 70.0% in USA. Q-D R (≥4 µg/ml) has increased in the last 2-4 years (EU [1.2X], LA [4.0X], USA [2.3X]), greater in 2005. GHL-R has remained stable (32.8-44.8%) and R to LZD (≤0.9%) and TIG (≤0.2%) was very rare, but greatest in EU and USA. The majority of EFM-BSI conformed to the characteristics of CC-17.

Conclusions: Multidrug-R EFM-BSI continues to evolve worldwide by longitudinal statistics from the SENTRY Program (9 years). Alarming increases in VAN-R (CC-17 clones) was noted in EU after withdrawal of avoparcin in animal practice. Lowest R rates were for oxazolidinone and glycylcycline class agents; continued surveillance appears warranted.

INTRODUCTION

Low and colleagues have previously summarized the findings of the SENTRY Antimicrobial Surveillance Program for resistance patterns in enterococci (1997-1999). In that report, the following major findings were listed:

- 1. Highest proportion (%) of isolates from a site of infection was urine at 10.7-16.8%, but in Latin America wounds had the highest enterococcal occurrence rate;
- 2. Regional variations existed, with highest occurrences of enterococcal infections in North America (United States [USA] and Canada) at 9.2-9.9% of bloodstream infections (BSI), lowest rate in Latin America (3.0%);
- 3. The most common species were *E. faecalis* (57.2-76.8%) and *E. faecium* (4.6-20.0%);
- 4. Vancomycin resistance (VRE) was highest (14.0-17.0%) in the USA, but cases were detected in all regions and appeared to be increasing;

- 5. Highest VRE isolations were found in the USA northcentral and northeast regions, dominated by the *vanA* type; and
- 6. The best alternative agents for VRE were quinupristin/dalfopristin (Synercid®; 0-82% susceptible, lowest outside of North America), chloramphenicol (33-90%), doxycycline (0-65%) and nitrofurantoin (29-83%), but regional variations were extreme.

In the last 6 years, multiple interventions have occurred that have attempted to address the VRE problem including withdrawal of avoparcin as a growth promoter in animal husbandry, application of strict infection control practices and local colonization screens, and lastly, the release of several VRE-active novel antimicrobial agents (daptomycin, linezolid, and tigecycline). Indifferent to these events, VRE continues to be a global resistance problem as documented by the SENTRY Program.

This report focuses on the most problematic enterococci, *E. faecium* strains from all infection types; but we particularly address the *E. faecium* BSI statistics across geographic regions. Also, the trends in resistance were calculated to chronicle the changes since the report by Low et al (*Clin Inf Dis* 2001; 32 [Suppl 2]: S133-S145). USA data will be compared to Europe (EU), the Asia-Pacific region (APAC) and countries in Latin America (LA) using results from 4,305 *E. faecium* infections (2,689 BSI cases). All SENTRY Program results from 1997-2005 (9 years) are presented.

MATERIALS AND METHODS

Study Design: The SENTRY Program was initiated in 1997 to investigate the longitudinal trends in antimicrobial resistance and the frequency of pathogen occurrence. The 5 major objectives have addressed the most common types of infection, in a prevalence-style format: BSI, community-acquired respiratory tract infections caused by *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis*, pneumonias in hospitalized patients, skin and soft tissue or wound infections and urinary tract infections. Consecutive isolates (≥500 strains/year for all objectives per laboratory) were forwarded to the regional monitors for reference-quality antimicrobial susceptibility testing and confirmation of organism identification. Nearly 350,000 bacteria have been processed, the vast majority within the cited objectives. A total of 4,305 strains of *E. faecium* were processed through 2005, each accompanied by key demographic parameters. Of those isolates, BSI strains predominated with 2,689 processed since 1997.

Participants and monitors: Four reference laboratories acted as monitoring sites during the 1997-2005 interval: the University of Iowa College of Medicine (Iowa City, IA) for North America and LA regions in 1997-2000 and EU in 1999-2000; Utrecht University (Utrecht, The Netherlands) for EU region in 1997-1998; Women's and Children's Hospital (Adelaide, Australia) for APAC region in 1998-2005; and JMI Laboratories (North Liberty, IA) for North America, LA, and EU regions in 2001-2005.

The participating sites varied slightly in number by year and included the following: 5-8 sites in Canada (North American region); 26-30 sites in the USA (North American region); 10 sites in Latin American region; 12-30 sites in Europe, Israel and Turkey (EU region); and 17 sites in the Asia-Pacific (APAC) region.

Antimicrobial agents: Representatives from all clinically important antimicrobial classes have been tested, as well as investigational compounds such as linezolid, daptomycin, dalbavancin, doripenem, tigecycline, evernimicin, quinupristin/dalfopristin, gatifloxacin, garenoxacin and others. Antimicrobials were obtained from their USA manufacturer or representative, and were dispensed into validated broth microdilution trays (MicroScan/Dade Behring, Deerfield, IL; TREK/Sensitre, Cleveland, OH). Each lot of trays was shared among all monitoring sites, and quality control (QC) results were satisfactory in all cases using QC strains recommended by the Clinical and Laboratory Standards Institute (CLSI; formerly the NCCLS).

Antimicrobial susceptibility testing: All susceptibility testing was performed with the above cited reagents in cation-adjusted Mueller-Hinton broth and according to the CLSI methods. Identifications of the species were initially determined at the participating sites and were confirmed by means of the Vitek system (bioMerieux, Hazelwood, MO) or conventional test procedures.

The determination of various *van* genotypes was also accomplished by PCR with use of methods and primers described elsewhere.

RESULTS

- A total of 4,305 *E. faecium* isolates were tested, of which 2,689 (62.5%) were from BSI. The proportion of BSI: total tested cases was APAC (71%), EU (72%), USA (79%) and LA (only 55%).
- The absolute numbers (Table 1) and proportions of *E. faecium* BSI have increased across all regions of the SENTRY Program from 1997 through 2005. Highest numbers of cases occurred in the USA (average, 215/year for 2003-2005), but the largest increase was observed in LA (3.5%).
- Table 2 lists the antibiogram highlights by region for *E. faecium* BSI cases.
- Ampicillin was minimally active (62.7-89.0% resistant)
- Vancomycin resistance (usually *vanA*) was found in all regions and varied from 5.4% in APAC to 69.4% in the USA
- Quinupristin/dalfopristin resistance was greatest in EU and LA, least in the USA (2.2% over all years)
- Linezolid and tigecycline resistances were rare (≤0.9%) and the only documented cases were in EU and the USA
- High-level aminoglycoside resistance was very geographically uniform (32.8%-44.8%)

Table 1. Trends in absolute numbers of *E. faecium* bacteremias comparing rates in 1997-1999 to 2003-2005.^a

	Average no./year of b	ar of bacteremias recorded:			
Region	1997-1999	2003-2005	Increase		
Asia-Pacific ^b	24	49	+2.0X		
Europe	48	147	+3.1X		
Latin America	4	14	+3.5X°		
USA	137	215	+1.6X		

- a. Number of monitored medical centers in each region did not significantly vary, or total number of monitored positive blood cultured.
- b. For the Asia-Pacific region, the early audit period was 1998-2000.
- c. Very small sample size.

• Trends in *E. faecium* VRE strains (Figure 1) since the last SENTRY Program publication (through 1999), shows consistent increases in the USA (50 to 71%) and EU (1 to 17%). The EU rise appeared post-avoparcin withdrawal as a growth promoter and isolates resemble clonal complex-17 (CC-17). Sample sizes in APAC and LA were too small for analysis and were heavily effected by epidemic outbreaks.

Trends toward higher quinupristin/dalfopristin-resistant (MIC, ≥4 μg/ml) strain rates were noted among VREF isolates in all regions (Table 3). Highest initial endemic resistance was noted in EU (1997-1999) with a modest increase to 13.9% by 2003-2005. Large increases in the intermediate MIC results (2 μg/ml) were noted, ranging from 8.1% (USA) to 21.7% (LA). Total non-susceptible rates (resistant and intermediate) for quinupristin/dalfopristin among BSI *E. faecium* strains were: USA (10.3%), APAC (18.0%), EU (27.2%), and LA (34.1%).

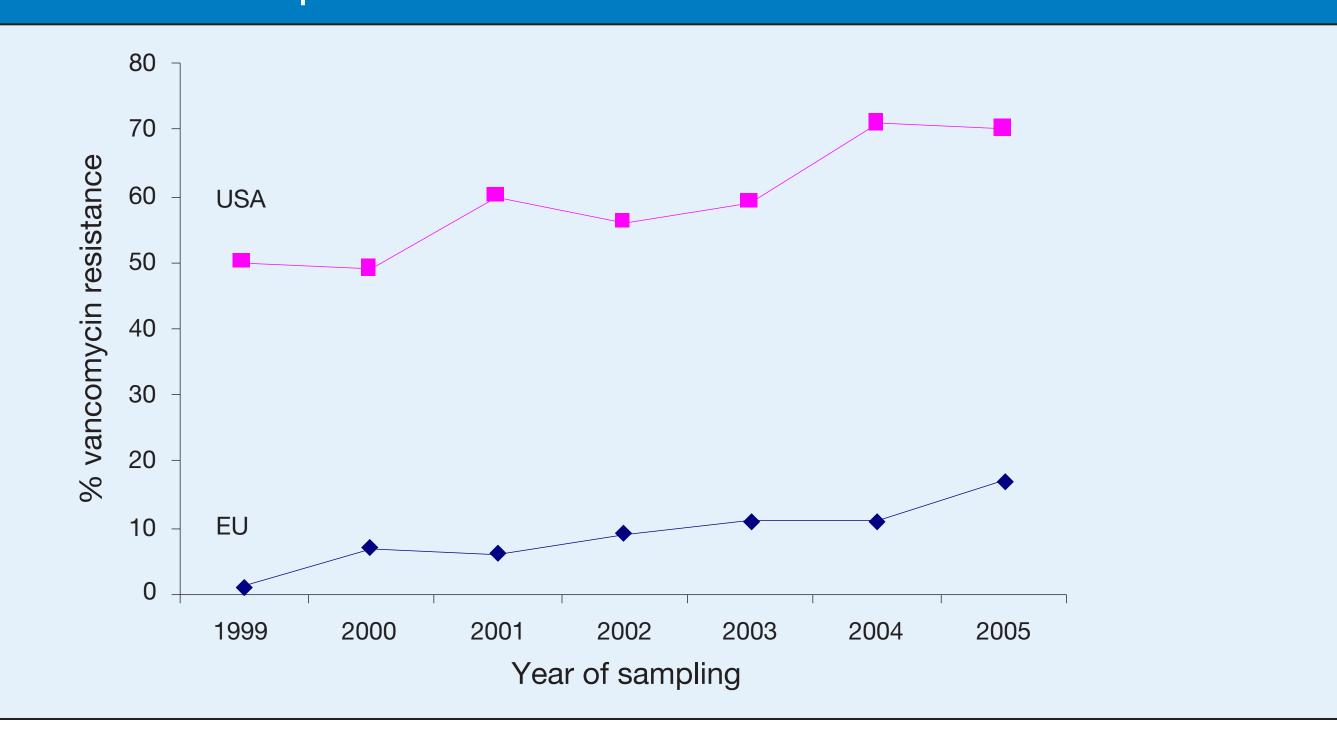
Table 2. Key antibiogram differences between geographic sampling areas of the SENTRY Program (1997-2005) for *E. faecium* isolates from bacteremias; 2,689 strains.

	Resistance rates (%):					
Region (no. tested)	Ampicillin	Vancomycin (vanA) ^a	Synercid®	Linezolid	Tigecycline	Gentamicin ^b
Asia-Pacific (239)	82.0	5.4 (76.9)	7.1	0.0	0.0	44.8
Europe (852)	81.2	11.5 (78.6)	10.2	0.1	0.2	36.1
Latin America (83)	62.7	12.0 (100.0)	12.4	0.0	0.0	34.9
USA (1,512)	89.0	69.4 (80.6)	2.2	0.9	0.2	32.8
a. % of all strains w b. High-level resista		cin resistance that werg/ml.	re the <i>vanA</i> p	oattern.		

Table 3. Trends in the occurrence of quinupristin/dalfopristin-resistant (MIC, >2 μg/ml) bacteremic *E. faecium* from monitored SENTRY Program regions.

	Average %		
Region	1997-1999	2003-2005	Increase
Asia-Pacific ^a	5.6	11.0	+2.0X
Europe	10.8	13.9	+1.3X
Latin America	3.7	14.9	+4.0X
USA	1.2	2.8	+2.3X

Figure 1. Trends in vancomycin resistance in *E. faecium* bacteremias in the USA and Europe for 1999-2005.



CONCLUSIONS

- *E. faecium* infections, many of them being BSI, continue to be a serious and increasing clinical problem.
- Vancomycin resistance among E. faecium BSI continues to escalate in all regions, most recently in the EU region (CC-17 dissemination).
- Resistance to other antimicrobial agents, new and old, are generally increasing among vancomycin-resistant *E. faecium* isolates.
- Oxazolidinone- and tigecycline-resistant isolates are very rare and have emerged in geographic areas of greatest (usually long-term) drug exposure e.g. USA and EU.
- Continued monitoring of *E. faecium* as an important drug resistance marker species appears justified.

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