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Prevalence of Vancomycin-Resistant *Enterococcus* spp. and Associated Resistance Patterns Among Isolates Collected Over a Decade of SENTRY Program Surveillance in North America

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SENTRY ANTIMICROBIAL SURVEILLANCE

AMENDED ABSTRACT

Objective: To investigate the susceptibility pattern of *E. faecalis* and *E. faecium* in the USA and Canada medical centers over 10 years; secondarily, to analyze trends in vancomycin-resistant *Enterococcus* spp. (VRE) in North America during the same period.

Methods: Isolates from bloodstream infection (BSI; 7,284) and other sources (2,763; mainly urine and wound) recovered as part of a 10-year surveillance program (1997-2006) were analyzed for susceptibility profiles. Isolates were collected from medical centers in the USA (52) and in Canada (8) and were tested at a central laboratory (JMI Laboratories, North Liberty, IA) using CLSI broth microdilution methods and interpretation criteria.

Results: Overall, the VRE rate was higher in BSI (19.1%) compared to other sources (14.5%). In the USA, VR *E. faecalis* rates were stable over ten years (3.3%) with significant year-to-year variation but without trending. In contrast, VR *E. faecium* steadily increased from 50 to 70%. The percentage of VanA phenotype increased in both species over the years, becoming the predominant resistance phenotype in more than 85% of VRE isolates. The table shows the yearly progression of VRE BSI isolates in the USA and Van phenotypes. In Canada, VRE was documented in <1% of BSI isolates and included *E. faecium* only. Higher resistance rates to other agents were noted among VRE compared to susceptible strains. These included ampicillin-resistant *E. faecalis* at 13%, ciprofloxacin-resistance at ≥95% for both species and high-level gentamicin and streptomycin resistance rates were 20-40% higher among VRE compared to vancomycin-susceptible strains. Linezolid-resistance was 1.3% and 2.5% among VR *E. faecium* and *E. faecalis*, respectively, compared to <0.5% among vancomycin-susceptible isolates.

Organism	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006
E. faecalis										
n	371	378	408	348	361	487	431	466	415	436
%R[a]	4.9	2.9	0.7	4.0	1.4	2.9	4.6	2.6	4.3	5.0
%VanA	55.6	45.5	66.7	42.9	40.0	57.1	35.0	50.0	50.0	86.4
E. faecium										
n	130	144	136	133	155	167	190	231	224	281
%R[a]	50.0	50.0	61.0	57.1	60.0	70.7	70.5	68.0	70.5	69.4
%VanA	75.4	88.9	80.7	84.2	88.2	86.4	88.1	94.9	95.6	99.0

a. Represents vancomycin non-susceptible rates (≥8 mg/L, CLSI M100-S18).

Conclusions: At the beginning of this study (1997), VRE were considered to be primarily a USA problem. As expected, VRE has disseminated within other countries, becoming a worldwide concern. The spread of VRE in North America warrants continued susceptibility profiling of large numbers of isolates from multiple medical centers to track changes. The 20% *E. faecium* VR increase in the USA (nearly all caused by the presence of *vanA*) and an associated increase in co-resistance has been alarming. Other countries should take note of the USA VRE experience and initiate infection control measures to limit this important pathogen from becoming widely endemic.

INTRODUCTION

Enterococcus spp. has consistently been the fourth most common pathogen causing bacteremia (10.2%) in North America as monitored by the SENTRY Antimicrobial Surveillance Program. Isolation of vancomycin-resistant enterococci (VRE) has increased in the United States (USA) and an observation from the early years of the SENTRY Program (1997-1999) illustrated that USA isolates were considerably more resistant to vancomycin (17% in 1999) than those enterococci isolated from patients in the rest of the world.

Gastrointestinal colonization with VRE typically precedes infection and occurs most commonly among patients with serious underlying diseases, those in ICUs, on hemodialysis, in nursing homes, the immunocompromised or those being treated with multiple antimicrobial agents. Greater morbidity and mortality related to VRE infections, compared to those by susceptible enterococci, appears secondary to the limited therapeutic options and potentially greater pathogenicity owing to acquisition of virulence genes.

Clonal spread of VRE has been documented, but non-clonal outbreaks associated with antimicrobial use are also described. The relationship between antimicrobial use and VRE colonization is complex and related to the level of anti-enterococcal activity, biliary excretion, and anti-anaerobic activity of the utilized agent. In addition, the recently demonstrated in-vivo transmission of vancomycin resistance from VRE to methicillin-resistant *Staphylococcus aureus* (MRSA) highlights the potential danger of a coexisting reservoir and shared resistance mechanisms.

In this study, we evaluated susceptibility profiles of *E. faecalis* and *E. faecium* in North American medical centers over 10 years and the VRE trends in USA and Canada hospitals during the same period.

MATERIALS AND METHODS

Study Design. The SENTRY Program was initiated in 1997 to investigate longitudinal trends in antimicrobial resistance and the frequency of pathogen occurrence. Isolates originated from bloodstream infections (BSI), community-acquired respiratory tract infections, pneumonia in hospitalized patients, skin and soft tissue or wound infections and urinary tract infections. Consecutive isolates are forwarded to the regional monitors for reference-quality antimicrobial susceptibility testing and confirmation of organism identification.

Bacterial isolates. A total of 10,047 non-duplicate *E. faecalis* and *E. faecium* isolates from North America were processed during the 10 year period (1997-2006). The participating sites varied slightly in number by year and included up to 8 sites in Canada and 52 sites in the USA. Identifications were determined at the participating site and confirmed as needed by the Vitek system (bioMerieux, Hazelwood, MO) or conventional tests at the central laboratory.

Susceptibility testing. Isolates were susceptibility tested against >20 antimicrobial agents using the Clinical Laboratory Standards Institute (CLSI) M7-A7 broth microdilution method. All strains were tested in validated, broth microdilution panels manufactured by TREK Diagnostics (Cleveland, OH). Mueller-Hinton Broth (MHB) adjusted to contain physiological levels of calcium (50 mg/L) was used when testing daptomycin. The following quality control (QC) organisms were concurrently tested: *E. faecalis* ATCC 29212 and *S. aureus* ATCC 29213; all QC results were within ranges specified by the CLSI (2008).

RESULTS

- Among 10,047 *E. faecium* (24.5%) and *E. faecalis* (75.5%) isolates, 7,284 were recovered from BSI (72.5%). The remaining strains were isolated from other sources including respiratory tract (rare), skin and soft tissue or wound and urinary tract infections.

Figure 1. Trends in vancomycin resistance in *E. faecium* (EFM) and *E. faecalis* (EF) in USA for 1997 to 2006.

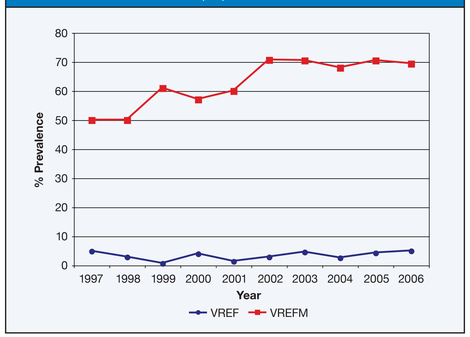
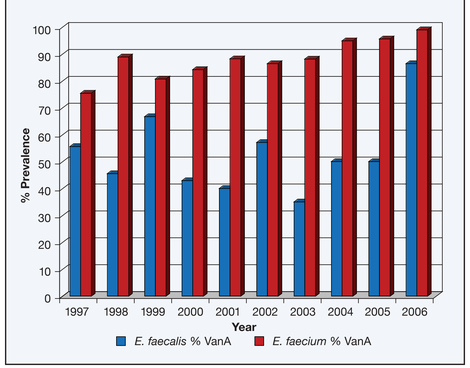


Figure 2. Prevalence of VanA phenotype among *E. faecium* (EFM) and *E. faecalis* (EF) in the USA for 1997 to 2006.



- Overall, daptomycin (99.8 to 100.0% susceptible), tigecycline (94.8 to 98.3%) and linezolid (96.6 to 99.2%) were the most active compounds tested against *E. faecium* and *E. faecalis* (Table 1).
- The proportion of VRE continues to rise in USA medical centers (Figure 1), with the majority of infections due to *E. faecium*.
- VRE rates were higher in BSI (19.1%) when compared to other infection sources (14.5%).

Table 1. Antimicrobial susceptibility profiles of *E. faecium* and *E. faecalis* isolates from North America evaluated during the SENTRY Antimicrobial Surveillance Program from 1997 to 2006 (overall and according to infection type).

	MIC mg/L (no. tested)								
	Total (10,047)			Bloodstream infection (7,284)			Others (2,763)		
Organism/antimicrobial agent	MIC_{50}	MIC_{90}	% susceptible[a]	MIC_{50}	MIC_{90}	% susceptible[a]	MIC_{50}	MIC_{90}	% susceptible[a]
E. faecium									
Total		(2,459)			(1,996)			(463)	
Ampicillin	>16	>16	10.7	>16	>16	11.3	>16	>16	8.2
Teicoplanin	16	>16	45.7	16	>16	47.9	>16	>16	36.5
Vancomycin	>16	>16	40.1	>16	>16	42.1	>16	>16	31.5
Gentamicin (HL)	≤500	>1000	69.9	≤500	>1000	69.9	≤500	>1000	70.2
Streptomycin (HL)	>2000	>2000	40.1	>2000	>2000	41.1	≤1000	>2000	35.6
Quinupristin/dalfopristin	0.5	2	89.3	0.5	2	89.2	0.5	2	89.4
Ciprofloxacin	>2	>2	5.4	>2	>2	5.7	>2	>2	4.1
Tetracycline	≤4	>8	51.7	≤4	>8	52.0	≤4	>8	50.1
Tigecycline[b]	≤0.12	0.25	98.3	≤0.12	0.25	97.8	≤0.12	≤0.12	100.0
Daptomycin	2	4	99.9	2	4	99.8	2	4	100.0
Linezolid	2	2	97.9	2	2	98.1	1	2	96.6
Vancomycin-susceptible		(985)			(840)			(145)	
Ampicillin	>16	>16	24.8	>16	>16	25.2	>16	>16	22.8
Teicoplanin	≤2	≤2	100.0	≤2	≤2	100.0	≤2	≤2	100.0
Vancomycin	1	1	100.0	1	1	100.0	1	1	100.0
Gentamicin (HL)	≤500	>1000	83.7	≤500	>1000	83.2	≤500	>1000	86.9
Streptomycin (HL)	≤1000	>2000	53.6	≤1000	>2000	54.5	2000	>2000	48.3
Quinupristin/dalfopristin	0.5	2	80.3	0.5	2	79.9	0.5	2	82.8
Ciprofloxacin	>2	>2	12.6	>2	>2	12.8	>2	>2	11.7
Tetracycline	≤4	>8	56.5	≤4	>8	56.2	≤4	>8	57.9
Tigecycline[b]	≤0.12	0.25	95.6	≤0.12	0.25	94.5	≤0.12	≤0.12	100.0
Daptomycin	2	4	99.8	2	4	99.7	2	4	100.0
Linezolid	2	2	97.9	2	2	98.5	2	2	94.3
Vancomycin non-susceptible		(1,474)			(1,156)			(318)	
Ampicillin	>16	>16	1.3	>16	>16	1.2	>16	>16	1.6
Teicoplanin	>16	>16	9.5	>16	>16	10.0	>16	>16	7.5
Vancomycin	>16	>16	0.0	>16	>16	0.0	>16	>16	0.0
Gentamicin (HL)	≤500	>1000	60.7	≤500	>1000	60.2	≤500	>1000	62.6
Streptomycin (HL)	>2000	>2000	31.1	>2000	>2000	31.4	>2000	>2000	29.9
Quinupristin/dalfopristin	0.5	1	95.3	0.5	1	96.0	0.5	1	92.5
Ciprofloxacin	>2	>2	0.6	>2	>2	0.6	>2	>2	0.6
Tetracycline	>8	>8	48.5	8	>8	49.0	>8	>8	46.5
Tigecycline[b]	≤0.12	0.25	99.7	≤0.12	0.25	99.5	≤0.12	≤0.12	100.0
Daptomycin	2	4	99.9	2	4	99.9	2	2	100.0
Linezolid	1	2	97.8	2	2	97.9	1	2	97.6
E. faecalis									
Total		(6,262)			(4,600)			(1,662)	
Ampicillin	≤2	≤2	99.1	≤2	≤2	99.0	≤2	≤2	99.1
Teicoplanin	≤2	≤2	98.3	≤2	≤2	98.3	≤2	≤2	98.3
Vancomycin	1	2	96.9	1	2	97.0	1	2	96.7
Gentamicin (HL)	≤500	>1000	69.3	≤500	>1000	68.3	≤500	>1000	72.0
Streptomycin (HL)	≤1000	>2000	70.6	≤1000	>2000	70.2	≤1000	>2000	71.7
Ciprofloxacin	1	>2	52.9	1	>2	52.6	1	>2	53.9
Tetracycline	>8	>8	31.9	>8	>8	32.8	>8	>8	29.4
Tigecycline[b]	≤0.12	0.25	95.3	≤0.12	0.25	94.8	≤0.12	0.25	96.5
Daptomycin	0.5	1	>99.9	0.5	1	>99.9	0.5	1	100.0
Linezolid	2	2	98.9	2	2	98.9	1	2	99.2
Vancomycin-susceptible		(6,067)			(4,460)			(1,607)	
Ampicillin	≤2	≤2	99.5	≤2	≤2	99.5	≤2	≤2	99.4
Teicoplanin	≤2	≤2	100.0	≤2	≤2	100.0	≤2	≤2	100.0
Vancomycin	1	2	100.0	1	2	100.0	1	2	100.0
Gentamicin (HL)	≤500	>1000	70.4	≤500	>1000	69.4	≤500	>1000	73.0
Streptomycin (HL)	≤1000	>2000	71.6	≤1000	>2000	71.2	≤1000	>2000	72.9
Ciprofloxacin	1	>2	54.5	1	>2	54.1	1	>2	55.7
Tetracycline	>8	>8	31.5	>8	>8	32.5	>8	>8	28.8
Tigecycline[b]	≤0.12	0.25	95.3	≤0.12	0.25	94.7	≤0.12	0.25	96.4
Daptomycin	0.5	1	>99.9	0.5	1	>99.9	0.5	1	100.0
Linezolid	2	2	99.0	2	2	98.9	1	2	99.2
Vancomycin non-susceptible		(195)			(140)			(55)	
Ampicillin	≤2	>16	86.2	≤2	>16	84.3	≤2	4	90.9
Teicoplanin	16	>16	46.2	16	>16	45.7	16	>16	47.3
Vancomycin	>16	>16	0.0	>16	>16	0.0	>16	>16	0.0
Gentamicin (HL)	>1000	>1000	34.9	>1000	>1000	32.1	1000	>1000	41.8
Streptomycin (HL)	>2000	>2000	38.5	>2000	>2000	39.3	>2000	>2000	36.4
Ciprofloxacin	>2	>2	3.1	>2	>2	3.6	>2	>2	1.8
Tetracycline	>8	>8	45.1	>8	>8	45.0	>8	>8	45.5
Tigecycline[b]	≤0.12	0.25	96.8	≤0.12	0.25	96.5	≤0.12	0.25	97.5
Daptomycin	0.5	1	100.0	0.5	1	100.0	1	1	100.0
Linezolid	1	2	98.2	1	2	97.5	1	2	100.0

a. Criteria as published by the CLSI [2008].
b. US-FDA breakpoints were applied.

- The prevalence of vancomycin resistance (VR) among *E. faecalis* in the USA was stable over ten years (average 3.3%), showing no trending pattern but with significant year-to-year variation. In contrast, VR *E. faecium* steadily increased from 50.0 to 70.0% (Figure 1).
- The VanA phenotype increased in both species over the years, becoming the predominant resistance phenotype in more than 85.0% of VRE isolates (Figure 2).
- In Canada, VR was detected only in *E. faecium* at very low rates (<1% of BSI isolates).
- VR *E. faecium* and VR *E. faecalis* isolates were more resistant to ciprofloxacin, high-level gentamicin and streptomycin, and tetracycline when compared to susceptible isolates (Table 1). Additionally, VR *E. faecalis* displayed higher MIC values against ampicillin when compared to vancomycin-susceptible *E. faecalis*.

CONCLUSIONS

- In general, VRE (both common enterococcal species) showed higher resistance rates to other antimicrobial agents when compared to vancomycin-susceptible isolates of the same species.
- Daptomycin, tigecycline and linezolid retained potent activity against vancomycin-resistant and -susceptible strains of both species, regardless of the infection site.
- As the prevalence of VRE in hospitalized patients continues to increase, implementation of appropriate infection control measures would benefit from routine surveillance of VRE transmission patterns.

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