

Vancomycin-Resistant Enterococci among Chronic Hemodialysis Patients: A Prospective Study of Acquisition

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To determine the prevalence and rate of acquisition of vancomycin-resistant enterococci (VRE) among patients undergoing chronic (i.e., long-term) hemodialysis who were admitted to a tertiary care center, serial rectal cultures for VRE were performed at hospital admission and every 5 days until hospital discharge. A total of 7 (6%) of the 119 patients were colonized with VRE at admission. Six (19%) of the 32 patients who remained in the hospital ≥ 4 days acquired VRE. A nonambulatory status was significantly associated with colonization at admission (OR, 9.7; 95% CI, 1.8–53; $P = .01$), and vancomycin exposure was significantly associated with VRE acquisition (relative risk, 1.8; 95% CI, 1.1–2.9; $P = .02$). All patients acquired VRE from epidemiologically linked dialysis patients colonized with similar VRE genotypes. Hospital acquisition of VRE contributes substantially to the increasing prevalence of VRE in the chronic hemodialysis patient population.

The percentage of hemodialysis centers in the United States reporting ≥ 1 patient colonized or infected with vancomycin-resistant enterococci (VRE) rose from 11% in 1995 to 21% in 1996 [1]. Several factors unique to the dialysis population may contribute substantially to these rapidly rising rates. The proximity of patients in a hemodialysis unit during extended periods provides an optimal setting for cross-transmission of pathogens between them. Furthermore, dialysis patients are predisposed to colonization with VRE as a result of comorbid conditions, frequent antibiotic exposure, and numerous hospitalizations [2–5]. The role of each of these factors in the acquisition and dissemination of VRE

among the chronic (i.e., long-term) hemodialysis population has not been fully investigated.

In 1997, 38% of all VRE isolates at our institution were recovered from patients requiring hemodialysis, compared with only 1% during the previous year. To understand the factors contributing to these rapidly rising rates, we performed a prospective epidemiological investigation of chronic hemodialysis patients. Pulsed-field gel electrophoresis (PFGE) was used to compare the genotypic profile of VRE isolates.

METHODS

Patients and study design. Vanderbilt University Medical Center is a 663-bed tertiary-care facility with an average of 28,000 admissions per year. Chronic hemodialysis patients are predominantly housed on the same floor and receive inpatient hemodialysis in a single 7-bed unit with 1 isolation room. Patients admitted to intensive care units (ICUs) receive hemodialysis treatments in their rooms.

From 1 August through 1 November 1998, all patients who were undergoing maintenance hemodialysis

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before admission to the hospital were enrolled in the study. Baseline rectal surveillance cultures for VRE were performed within 72 h of admission. Patients were excluded from enrollment if they declined to participate in the study. Rectal culture specimens were obtained with cotton swabs (Culturette II; Becton Dickinson). Follow-up cultures were obtained from patients who remained in the hospital ≥ 4 days; these were performed at 5-day intervals (± 2 days [SD]) until hospital discharge. Surveillance cultures were performed during a 5-day work week.

Demographic and clinical data on all patients were recorded from medical charts. The Charlson score was used as a measure of comorbidity [6]. This scoring system generates a composite value of preexisting medical conditions and has been validated in a patient population with end-stage renal disease [7]. Information on in-hospital antibiotic exposure was obtained through a computerized pharmacy database. Antibiotic exposure was assessed according to the number of days of exposure to any antibiotic, in addition to the number of different antibiotics received. Antibiotic exposure was also analyzed by individual antibiotic classes: simple penicillins (oxacillin, penicillin, and ampicillin); vancomycin; first-, second-, and third-generation cephalosporins; antibiotics with predominantly anaerobic activity (metronidazole and clindamycin); aminoglycosides (tobramycin and gentamicin); and fluoroquinolones. Data regarding antibiotic exposure before hospitalization and

previous VRE colonization/infection could not be accurately collected because of patients' recollection bias.

Contact precautions were instituted when VRE were isolated from a patient's surveillance cultures, as per the guidelines of the Centers for Disease Control and Prevention (CDC) [8]. The study was approved by the Institutional Review Board and the Infection Control Committee of Vanderbilt University School of Medicine (Nashville).

Microbiological methods. Samples from rectal swabs were plated onto media containing colistin and nalidixic acid. Plates were incubated at 35°C with 5% carbon dioxide and examined for bacterial growth at 24 and 48 h. Identification of enterococci was based on colony morphology and results of gram stains and standard biochemical tests [9]. The enterococcal species was determined with use of API-Rapid Strep Strips (bioMérieux Vitek). Screening for vancomycin resistance was performed by plating isolates on brain-heart infusion agar with vancomycin (6 $\mu\text{g}/\text{mL}$). Resistance was confirmed by means of MIC testing with the broth microdilution method [10]. Isolates for which the MIC of vancomycin was ≥ 32 $\mu\text{g}/\text{mL}$ were classified as resistant.

Molecular typing. PFGE was performed by means of the GenePath Group 1 Reagent Kit (catalog no. 310-0111; Bio-Rad Laboratories). Genomic DNA was extracted from logarithmic-phase VRE cultures grown in brain-heart infusion broth (BBL; Becton Dickinson Microbiology Systems), prepared in low-

Table 1. Characteristics of chronic hemodialysis patients, as related to detection of colonization with vancomycin-resistant enterococci (VRE) at the time of hospital admission.

Characteristic	VRE status on admission		Unadjusted OR (95% CI)	P
	Positive (n = 7)	Negative (n = 112)		
Age, mean $\bar{y} \pm \text{SD}$	52 \pm 5	58 \pm 16	—	.3
Sex, men : women	6:1	59:53	5.4 (0.6–46)	.09
Race, whites : African Americans	1:6	61:51	7.2 (1.1–61)	.04
Underlying kidney disease				
Diabetes mellitus	3	51	1.1 (0–2.5)	.8
Hypertension	3	20	4 (0.9–19)	.07
Other	1	41	0.3 (0–2.3)	.3
Duration of hemodialysis, mean $\bar{y} \pm \text{SD}$	10 \pm 10	4 \pm 4	—	<.001
Charlson, mean score $\pm \text{SD}$	5 \pm 2	4 \pm 1	—	.3
Serum albumin concentration, mean mg/dL $\pm \text{SD}$	3 \pm 0.5	3.5 \pm 0.7	—	.09
Nursing home residence	1	12	1.3 (0.2–12)	.8
Nonambulatory (wheelchair or bed bound)	5	23	9.6 (2–53)	.002
Previous hospitalizations in the past year, mean $\pm \text{SD}$	4 \pm 3	3 \pm 3	—	.2
Duration of current hospitalization, median d $\pm \text{SD}$	8 \pm 18	5 \pm 9	—	.06

NOTE. Data are no. of patients, unless otherwise indicated.

Table 2. Characteristics of chronic hemodialysis patients who remained in the hospital ≥ 4 days, as related to acquisition of vancomycin-resistant enterococci (VRE).

Characteristic	VRE status		Unadjusted RR (95% CI)	P
	Acquisition (n = 6)	No acquisition (n = 26)		
Age, mean $\bar{y} \pm$ SD	60 \pm 25	54 \pm 18	—	.5
Sex, men : women	4:2	14:12	0.8 (0.4–1.6)	.6
Race, whites : African Americans	4:2	15:11	0.9 (0.4–1.7)	.7
Underlying kidney disease patients				
Diabetes mellitus	2	16	0.4 (0.1–1.8)	.2
Hypertension	1	3	1.4 (0.2–9)	.7
Other	3	7	2.2 (0.5–9)	.3
Duration of hemodialysis, mean $\bar{y} \pm$ SD	3 \pm 2	4 \pm 5	—	.7
Charlson score, mean \pm SD	4 \pm 1	5 \pm 1	—	.5
Serum albumin concentration, mean mg/dL \pm SD	3.3 \pm 0.5	3.4 \pm 0.6	—	.7
Nonambulatory (wheelchair or bed bound)	2	10	0.8 (0.1–5.2)	.8
Duration of current hospital stay, mean d \pm SD	14 \pm 8	12 \pm 8	—	.6
Admission to intensive care unit during current hospital stay	3	8	1.9 (0.5–7.9)	.4
Different antibiotics received, mean \pm SD	4 \pm 1	3 \pm 1	—	.03
Antimicrobial d/doses ^a , mean \pm SD	36 \pm 12	14 \pm 16	—	.02
Patients who died in hospital	0	1	—	.6

NOTE. Data are no. of patients, unless otherwise indicated.

^a For vancomycin and aminoglycosides, no. of doses was calculated instead of no. of days.

melting-point agarose plugs, and digested with *Sma*I enzyme (New England Biolabs) according to the manufacturer's instructions. Bacteriophage lambda ladder consisting of concatemers starting at 48.5 kbp and increasing to \sim 1000 kbp (Bio-Rad) were used as DNA size standards. Electrophoresis was performed with a GenePath system using a dedicated program 6. Gels were stained with ethidium bromide, rinsed, and photographed under ultraviolet light by use of the Gel Doc 2000 computerized documentation system (Bio-Rad).

Isolates were considered genetically indistinguishable and were assigned to the same strain type (e.g., type A) if their restriction patterns had the same number and size of bands. Isolates with 1–6 band differences in their restriction patterns were considered closely or possibly related and were assigned to a subtype (e.g., A1). Isolates whose restriction patterns differed by >6 bands were considered unrelated and were assigned to a different strain type [11].

Definitions. Infections were classified according to the criteria established by the CDC [12]. Colonization was defined as isolation of VRE from a rectal culture without evidence of an infection. Acquisition of VRE was defined as a negative baseline culture with ≥ 1 positive follow-up culture.

Statistical analysis. Categorical variables were analyzed by use of the χ^2 test or Fisher's exact test. Continuous variables

were analyzed by means of Student's *t* test or the Wilcoxon rank sum test for nonparametric distributions. Independent risk factors for colonization and acquisition were evaluated by means of a stepwise logistic regression model using variables that were statistically significant on crude analysis ($P \leq .05$). Potentially significant interaction terms were considered in the regression models (release 6.0; Stata Statistical Software).

RESULTS

The prevalence of vancomycin resistance among isolates of *Enterococcus faecium* recovered by the hospital microbiology laboratory from all hospitalized patients was 57% from January through June 1998; it increased to 81% during the following 6 months.

Study population. During the 3-month study period, 130 chronic hemodialysis patients were admitted; 11 declined study participation. The mean age of study patients was 58 years (range, 23–89 years); 45% were men, and 52% were white. The most common underlying kidney diseases were hypertension and diabetes mellitus, which were present in 110 (92%) patients. The mean number of years for which patients had been undergoing hemodialysis was 4 (range, <1 –25 years). Study patients were affiliated with 30 different outpatient hemodi-

alysis units. Patients had been admitted to the medical center an average of 3 times during the previous year (range, 0–15 admissions). A total of 13 (11%) patients were colonized with vancomycin-resistant *E. faecium* isolates.

VRE colonization at admission. A total of 119 baseline rectal culture specimens from 119 patients were collected; 106 (89%) were collected within 72 h of admission to the hospital, and the remaining 13 (11%) were obtained on day 4 following admission.

VRE were isolated from the baseline cultures of 7 (6%) patients. All of the positive culture specimens were collected during the first 72 h after admission to the hospital. Demographic and clinical data for patients colonized at admission versus those not colonized are presented in table 1.

Univariate analysis revealed that African American race, number of years on hemodialysis, and nonambulatory status were significantly associated with VRE colonization at admission (table 1). In stepwise logistic regression, only a nonambulatory status was independently associated with VRE colonization (OR, 9.7; 95% CI, 1.8–53; $P = .01$). Total duration of current hospitalization did not differ significantly between the 2 groups.

VRE acquisition. Thirty-eight (32%) patients remained in the hospital ≥ 4 days, from whom follow-up culture specimens were obtained every 5 days (± 2 days) until hospital discharge. Of the 32 patients (61 follow-up cultures) who were not colonized at admission, 6 (19%) had ≥ 1 positive follow-up culture. The average time to the first positive follow-up culture was 12 days (median, 11 days; range, 5–25 days). The number of patients who acquired VRE, stratified by duration of hospitalization, is shown in figure 1. Patients were more likely to acquire VRE in the hospital than to be colonized with VRE at the time of admission (OR, 2.5; 95% CI, 1.2–4.9; $P = .02$).

On univariate analysis, both the total number of antibiotics received and the total number of antimicrobial days were significantly associated with acquisition of VRE (table 2). When antibiotic exposure was analyzed according to type of antibiotic, only vancomycin and third-generation cephalosporin exposures were significantly associated with acquisition of VRE (table 3). When these 2 antibiotics were entered into a stepwise logistic-regression model along with duration of hospitalization to adjust for varying lengths of hospital stays, only vancomycin exposure was independently associated with acquisition of VRE (RR, 1.8; 95% CI, 1.1–2.9; $P = .02$).

Comparison of PFGE profiles. Among the isolates recovered from the 7 patients colonized at admission, 4 different strain types were identified (types A, B, O, and F). The most common strain types were O and F, isolated from 5 (71%) patients. These patients had been hospitalized at the medical center during the previous year (table 4). Of the 6 isolates acquired during hospitalization, 5 were available for typing.

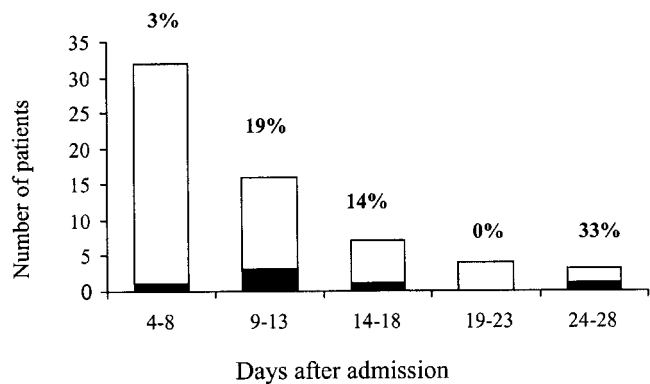


Figure 1. Proportion of chronic hemodialysis patients who acquired vancomycin-resistant enterococci (VRE), stratified by duration of hospital admission. Percentages are based on the total number of patients who acquired VRE (black bars), divided by the total number of patients per interval.

Three distinct strain types were identified (type B, F, and O). All 5 patients were epidemiologically linked to a chronic hemodialysis patient who was colonized at admission with an indistinguishable or closely related strain (figure 2). These linked patients had overlapping hospital stays and were housed on the same hospital ward. Patients who acquired VRE were affiliated with 5 different outpatient hemodialysis units (units IV–VIII).

Duration of VRE carriage. Among patients colonized at admission, VRE continued to be isolated from 3 patients throughout their hospital stay (mean, 13 days; range, 10–20 days). VRE were detected intermittently in 1 patient who remained in the hospital for 48 days, with 4 of 11 serial follow-up cultures positive for VRE. The remaining 3 patients were discharged before a follow-up culture was obtained.

Among the 6 patients who acquired VRE during hospitalization, 2 continued to have VRE isolated in all follow-up cultures throughout the duration of their hospitalization (at 9 and 14 days). One of the 6 patients had 2 VRE-negative follow-up cultures over a 10-day period after the initial positive follow-up culture. The remaining 3 patients were discharged before a second follow-up culture was performed. Thus, among 7 patients who were colonized at admission or acquired VRE and who had ≥ 1 follow-up culture after VRE was initially isolated, 6 (86%) remained colonized throughout their hospitalization. Serial VRE isolates from individual patients had identical PFGE DNA band patterns.

Nosocomial infections with VRE. Two patients developed an infection due to VRE. One patient had 3 positive rectal cultures over a 16-day period before to the diagnosis of a line-related bloodstream infection due to VRE. The second patient developed a urinary tract infection; the urine culture was positive for VRE 1 day before the rectal culture was positive. Thus,

Table 3. Antibiotic exposure and acquisition of vancomycin-resistant enterococci (VRE) among chronic hemodialysis patients during hospitalization.

Antibiotic	No. (%) of patients		Antibiotic exposure, ^a mean d ± SD		P ^b
	VRE acquisition (n = 6)	No VRE acquisition (n = 26)	VRE acquisition (n = 6)	No VRE acquisition (n = 26)	
Vancomycin	6 (100)	18 (69)	5 ± 3	2 ± 2	.002
Simple penicillins ^c	2 (33)	7 (27)	7 ± 12	2 ± 3	.06
First-generation cephalosporin	1 (17)	13 (50)	<1	<1	.1
Second-generation cephalosporin	0 (0)	2 (8)	0	<1	.5
Third-generation cephalosporin	4 (67)	5 (19)	5 ± 2	1 ± 0.4	.01
Metronidazole/clindamycin	3 (50)	7 (27)	6 ± 8	3 ± 7	.5
Aminoglycosides	5 (83)	15 (58)	7 ± 7	3 ± 5	.08
Fluoroquinolones	4 (67)	3 (12)	6 ± 7	2 ± 6	.2

^a For vancomycin and aminoglycosides, no. of doses was calculated instead of no. of days.

^b P value for mean no. of antibiotic doses/d.

^c Oxacillin, penicillin, or ampicillin.

among the 13 patients colonized with VRE, the colonization of only 2 (15%) would have been detected by clinically directed cultures alone. The genotypes of isolates recovered from rectal cultures were similar to those of isolates recovered from clinical cultures.

DISCUSSION

Chronic hemodialysis patients were infrequently colonized with VRE at the time of admission to the hospital. However, during hospitalization, acquisition of VRE was substantial: 19% of patients who remained in the hospital ≥ 4 days became colonized de novo with VRE. Acquisition of VRE was through horizontal transmission from other hemodialysis patients, since each acquired strain could be paired to an indistinguishable or closely related VRE strain colonizing an epidemiologically

linked hemodialysis patient. The high rates of VRE acquisition among chronic hemodialysis patients are similar to those in other high-risk populations, such as patients in ICUs, where acquisition rates range from 13% to 34% [2, 13]. These comparable rates may reflect similarities between the ICU and the dialysis unit: both settings are associated with an increased risk of cross-transmission due to the frequent contact between patients and health care workers. In addition, acquisition of VRE among chronic hemodialysis patients may have occurred in the inpatient dialysis unit or during an ICU stay.

The majority of VRE isolates recovered from patients at admission belonged to strain type O or F. These 2 strain types are endemic at the study institution, accounting for over two-thirds of VRE isolates collected from 1996 through 1998 [14]. Since these study patients had numerous prior hospitalizations and were affiliated with different outpatient hemodialysis units, acquisition of these VRE strain types likely occurred during a previous hospital admission. Prior hospitalization has also been associated with VRE colonization in the outpatient setting [15]. These results provide further evidence that exposure to the hospital setting contributes substantially to the rising rates of VRE among chronic hemodialysis patients. Although the frequency of cross-transmission in the outpatient setting is not known, the risk of acquiring VRE in the hospital is probably greater since hospitalized patients are usually sicker and are exposed to numerous antibiotics [2–5]. In addition, contacts between health care workers and patients are more frequent in the hospital setting, further increasing the risk of VRE acquisition through contaminated hands. The increase in contact with health care workers may also partially explain the association between a nonambulatory status and colonization with

Table 4. Vancomycin-resistant enterococci (VRE) strain types, prior hospitalizations, and outpatient hemodialysis unit affiliations of chronic hemodialysis patients colonized with VRE at the time of admission to the hospital.

Patient no.	Strain type	No. of prior admissions to study hospital	Outpatient hemodialysis unit
1	F	6	I
2	O	1	I
3	F	6	II
4	F1	7	II
5	A	6	I
6	B	2	II
7	O	4	III

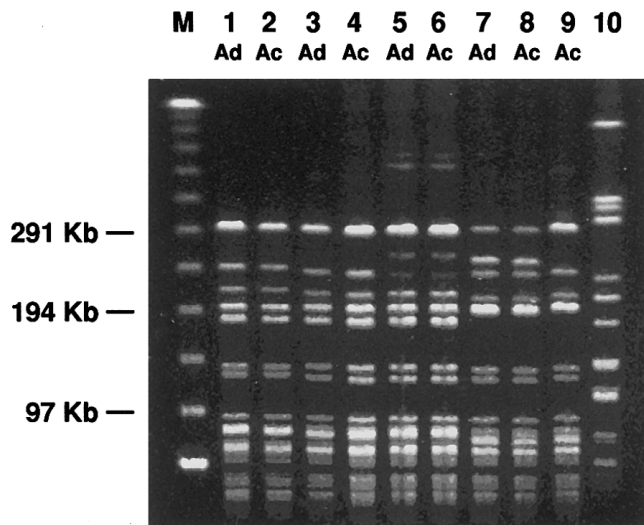


Figure 2. PFGE types of vancomycin-resistant enterococci isolated from epidemiologically linked chronic hemodialysis patients, demonstrating similar strain types among isolates recovered at the time of admission to the hospital (*Ad*) and isolates acquired during hospitalization (*Ac*). Lane *M*, bacteriophage lambda ladder; lanes 1 and 2, strain B; lanes 3 and 4, strain F; lanes 5 and 6, strain F2; lanes 7 and 8, strain O; lane 9, strain O1; lane 10, isolate from a nonhemodialysis patient, recovered during the 3-month study period, illustrating a differing strain type.

VRE at the time of admission to the hospital, since these patients require a substantial amount of assistance from health care workers. Prior antibiotic exposure could not be accurately assessed in this study, but it probably contributed to a higher risk of VRE colonization among nonambulatory patients.

The association between antibiotic exposure, especially exposure to vancomycin, and acquisition of VRE was confirmed for the population of chronic hemodialysis patients. Judicious use of vancomycin is particularly relevant among chronic hemodialysis patients, since these patients receive vancomycin substantially more often than other hospitalized patients [16]. A recent study addressing the indications for administration of vancomycin to hospitalized chronic hemodialysis patients demonstrated that although >80% of vancomycin dosings were warranted, the most common inappropriate indication for vancomycin administration was for treatment of infections due to β -lactam-susceptible pathogens in patients without β -lactam allergies [16].

Rectal surveillance culture techniques may be suboptimal for detecting VRE at low concentrations in the stool. Thus, colonization may go unrecognized until fecal levels of VRE carriage become detectable, for example, after antibiotic exposure. Furthermore, variations in sampling technique and sampling error may contribute to false-negative results for rectal cultures. Patients may therefore be misclassified as having acquired VRE, when in fact colonization was present at admission to the hospital. In this study, the majority of patients who acquired VRE

had ≥ 2 negative rectal cultures before isolation of VRE. Thus, patients were likely to have actually acquired VRE during their hospitalization. Furthermore, patients who acquired strain O or F were affiliated with outpatient hemodialysis units that differed from those of patients who were colonized with strains O and F at the time of admission to the hospital, mitigating against a common source in the outpatient setting.

There are several limitations to this study. First, selective plates and enrichment broth for VRE were not used, and thus the prevalence of VRE at admission and the rate of acquisition may have been underestimated [2, 17]. Second, VRE could have been acquired before the first baseline culture was performed. However, this is unlikely, since VRE acquisition was documented, on average, after 12 days of hospitalization.

This study underscores the importance of the hospital setting in the acquisition of VRE in the chronic hemodialysis population. As in other hospitalized populations, continued enforcement of infection-control measures and judicious use of antibiotics, in particular vancomycin, are necessary. In addition, in view of the high rate of VRE acquisition in the hospital, it may be prudent for outpatient dialysis units to perform screening rectal cultures for all patients recently hospitalized at institutions with high rates of enterococcal resistance to vancomycin, in an attempt to identify newly colonized patients. These interventions should have a beneficial impact on the rapidly rising rates of VRE among chronic hemodialysis patients.

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