Vancomycin-resistant enterococci colonization in patients at seven hemodialysis centers

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Background. Vancomycin-resistant enterococci (VRE) are increasing in prevalence at many institutions, and are often reported in dialysis patients. We studied the prevalence of and risk factors for VRE at seven outpatient hemodialysis centers (three in Baltimore, MD, USA, and four in Richmond, VA, USA).

Methods. Rectal or stool cultures were performed on consenting hemodialysis patients during December 1997 to April 1998. Consenting patients were recultured during May to July 1998 (median 120 days later). Clinical and laboratory data and functional status (1 to 10 scale: 1, normal function; 9, home attendant, not totally disabled; 10, disabled, living at home) were recorded.

Results. Of 478 cultures performed, 20 (4.2%) were positive for VRE. Among the seven centers, the prevalence of VREpositive cultures varied from 1.0 to 7.9%. Independently significant risk factors for a VRE-positive culture were a functional score of 9 to 10 (odds ratio 6.9, P < 0.001), antimicrobial receipt within 90 days before culture (odds ratio 6.1, P < 0.001), and a history of injection drug use (odds ratio 5.4, P = 0.004).

Conclusions. VRE-colonized patients were present at all seven participating centers, suggesting that careful infectioncontrol precautions should be used at all centers to limit transmission. In agreement with previous studies, VRE colonization was more frequent in patients who had received antimicrobial agents recently, underscoring the importance of judicious antimicrobial use in limiting selection for this potential pathogen.

Vancomycin-resistant enterococci (VRE) were first reported in the late 1980s and in the interim have spread rapidly in the United States and many other countries.

Key words: pathogen, bacterial infection, infection control, transmission of VRE, ESRD, epidemic, chronic hemodialysis.

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Among intensive care unit patients with nosocomial infections that have been reported to the Centers for Disease Control and Prevention's (CDC) National Nosocomial Infections Surveillance (NNIS) system, the percentage of enterococcal isolates resistant to vancomycin increased from 0.5% in 1989 to 25.2% in 1999 [1, 2]. Because spontaneous mutations that would result in vancomycin resistance have not been described in enterococci, this increase is attributable to patient-to-patient transmission in healthcare settings and transmission of resistance genes among previously susceptible enterococci. The rapid spread of VRE is of concern because infections due to this organism remain difficult to treat, despite the recent availability of two new drugs, quinupristindalfopristin and linezolid, that are active against vancomycin-resistant strains. The primary risk factors for VRE are increasing severity of illness and receipt of antimicrobial agents, particularly vancomycin [3–5].

Vancomycin resistance has been common in patients with end-stage renal disease (ESRD). One of the first reports of VRE was among renal failure patients in a hospital in London (UK) [6]. ESRD patients comprised 17 to 29% of VRE case-patients in three hospital-based studies [5, 7, 8]. The percentage of U.S. hemodialysis centers reporting \geq 1 patients infected or colonized with VRE increased from 11% in 1995 to 34% in 1999 [9, 10]. Additionally, strains of *Staphylococcus aureus* with reduced susceptibility to vancomycin have recently been reported [11, 12]; of six U.S. patients from whom these strains were isolated, four had received chronic and one acute dialysis [13].

Because of the prominent role that ESRD patients have played in the epidemic of vancomycin resistance, it is important to understand the epidemiology of VRE in this patient population so that preventive measures can be taken. We report the results of a study of the prevalence of, and risk factors for, VRE colonization among chronic hemodialysis patients at seven U.S. dialysis centers.

METHODS

Study centers and patients

Seven dialysis centers—three in Baltimore (MD, USA) and four in Richmond (VA, USA)—participated in this study. Centers were selected to represent both urban and suburban outpatient dialysis facilities. All chronic dialysis patients ≥ 18 years of age at the participating centers were eligible for enrollment in the study. The study protocol was approved by the Institutional Review Board (IRB) at the Centers for Disease Control and Prevention (CDC) and at all study sites.

Design and data collection

This study was conducted during December 1997 to June 1998 at the centers in Richmond and January to July 1998 at the centers in Baltimore (that is, study period). Study personnel used standardized forms to abstract data from clinical and administrative records. A baseline form was completed on all patients at initiation of the study. An incident form was completed at each outpatient initiation of a course of intravenous antimicrobials or at hospital admission. Data from the incident form were used to tabulate intravenous antimicrobial uses and hospitalizations that occurred during 90 days before culture for VRE; however, since these events were recorded only during the study period, their ascertainment was incomplete for cultures performed during the first 90 days of the study.

The baseline form contained data on demographics; the presence of diabetes, human immunodeficiency virus (HIV) infection, or injection drug use known to dialysis center staff; smoking; vascular access type (catheter, graft, or fistula; patients having both a catheter and graft or fistula were categorized as having a catheter); albumin level (the mean of two determinations); urea reduction ratio (the mean of two determinations); whether skin/ clothing was clean versus visibly soiled; and functional status. At baseline, functional status, similar to the Karnofsky performance scale [14], was scored as follows: 1, normal function; 2, minor signs and symptoms, full activity; 3, usual activities with effort; 4, independent, most out-of-home activities; 5, independent, limited to home; 6, needs assistance with errands; 7, needs assistance with meal preparation; 8, needs assistance with bathing/dressing; 9, home attendant, not totally disabled; and 10, disabled, living at home.

Cultures

Stool or rectal cultures, according to patient preference, were performed on consenting patients. Initial cultures were performed during December 1997 to April 1998. Repeat cultures were performed during May to July 1998 among patients who consented to a second culture. Specimens were inoculated onto selective agar plates containing 10 µg/mL of vancomycin; isolates growing on these plates were tested for vancomycin resistance using National Committee for Clinical Laboratory Standards methods (disk diffusion or the E-test) [15]. Isolates showing vancomycin resistance by these methods were transported to the CDC, where the genus and species were determined by standard biochemical tests, and those found to be Enterococcus faecium or E. faecalis were tested by the broth microdilution technique. Isolates with a vancomycin minimum inhibitory concentration of \geq 32 μ g/mL were considered to be VRE [15]. The isolates were typed by pulsed-field gel electrophoresis. Isolates were considered to be indistinguishable or closely related (that is, to have a common pattern) if they were isolated from patients at the same dialysis center and there were \leq 3 band fragment differences when compared with the common (modal) type for that dialysis center [16].

Statistical analysis

Since some patients were cultured twice, the number of cultures performed was higher than the number of patients cultured. Thus, VRE prevalence was determined both for patients (that is, the percentage of patients that were VRE positive on either the first or second culture) and cultures (that is, the percentage of all cultures that were positive).

To study the influence of potential risk factors at the time of VRE culture more precisely, the VRE prevalence among cultures was used for risk factor analyses, that is, the unit of analysis was the culture rather than the patient. For univariate analyses, P values were calculated by the chi-squared or Fisher exact test for dichotomous variables or the likelihood ratio test for heterogeneity (determined by logistic regression) for categorical variables with \geq 3 levels. For continuous variables, univariate P values were calculated with the nonparametric Wilcoxon test.

A multivariate model was constructed using generalized estimating equations [17]. This technique produces odds ratios similar to those produced by logistic regression, but accounts for the lack of independence of observations (that is, that some patients were cultured twice). Using a forward stepwise algorithm, all potential risk factors were considered for inclusion in the model; however, only factors that were independently statistically significant (P < 0.05) were retained in the final model. All P values are two-tailed. All data analyses were performed using SAS for Personal Computers (SAS Institute, Cary, NC, USA).

Table 1. Comparison of hemodialysis patients cultured vs. not cultured for vancomycin-resistant enterococci (VRE) colonization	on in
Baltimore and Richmond. December 1997–July 1998	

Factor	Cultured $(N = 346)$	Not cultured $(N=454)$	P value
Age median	62.0	57.0	0.006
Race % white	23.5	23.8	0.92
Functional status median	3.0	3.0	0.33
Diabetes %	43.7	41.2	0.48
HIV infection %	3.2	6.6	0.029
Injection drug use %	6.6	11.4	0.027
Albumin median	3.8	3.8	0.99
Urea reduction ratio median	71.0	70.5	0.14
Received any intravenous antimicrobial during the study period %	27.8	37.7	0.0032
Received intravenous vancomycin during the study period %	17.6	26.2	0.0047

RESULTS

Characteristics of dialysis centers and patients

Of the seven centers, five were freestanding and two were hospital-affiliated; three were located in an inner city and four were suburban. These units treated a total of 800 patients (range 73 to 169 patients per center).

Of the 800 patients eligible for culture, 346 (43.2%) consented and were cultured one to two times (216 were cultured once and 130 were cultured twice). Compared with patients who were not cultured, the cultured patients were significantly older and less likely to be HIV-infected, to have known injection drug use, to have received any antimicrobial agents, and to have received vancomycin (Table 1). Cultured versus noncultured patients were similar in race, functional status, presence of diabetes, albumin level, and urea reduction ratio.

Prevalence of VRE by patient

Among the 346 patients cultured, 20 (5.8%) were VRE positive on either the first or second culture. Among patients cultured twice, 121 were VRE negative both times, one was negative then positive, eight were positive then negative, and none were positive on both cultures. The median duration between cultures was 120 days.

Prevalence of VRE by culture and risk factor analysis

Of 478 cultures performed, 20 (4.2%) were positive for VRE. VRE prevalence was not related to city (Richmond vs. Baltimore), urban versus suburban center, or hospital versus freestanding location (data not shown). VRE prevalence varied from 1.0 to 7.9% among the seven dialysis centers, but the differences were not statistically significant (P = 0.32; Table 2). VRE prevalence was higher (14%) among patients with functional status scores of 9 to 10 than among those with lower scores. Other variables significantly related to VRE prevalence included known injection drug use, hospitalization, and antimicrobial receipt.

Among 59 patients who had received an antimicrobial \leq 90 days before culture, 37 had received vancomycin, 27 an aminoglycoside, 9 a first-generation cephalosporin,

7 a third-generation cephalosporin, 5 a quinolone, 3 a penicillin, and 3 another antimicrobial (total >59 since some patients received >1 antimicrobial). VRE prevalence was 2.9% among patients who had received no antimicrobials, 14.3% among those who had received only vancomycin, 9.1% among those who had received only antimicrobials other than vancomycin, and 17.4% among patients who had received both vancomycin and other antimicrobials (Table 2).

The urea reduction ratio was significantly lower for patients with VRE positive versus negative cultures (median 66.5% vs. 71.0%, P = 0.019). However, VRE colonization was not related to age (median 58.4 years for VRE positive vs. 62.6 years for VRE negative, P = 0.48) or albumin level (median 3.6 g/dL for VRE positive vs. 3.8 g/dL for VRE negative, P = 0.13).

The multivariate model included three independent predictors of VRE colonization: (1) functional status score 9 to 10 (odds ratio = 6.9), (2) antimicrobial receipt during the previous 90 days (odds ratio = 6.1), and (3) injection drug use (odds ratio = 5.4; Table 3). Hospitalization during 90 days prior to culture had an odds ratio of 2.3 and a *P* value of 0.12 if inserted into the model.

Genetic typing of VRE isolates

Two of the facilities (Centers B and E) had only one isolate, so an evaluation for clustering of genetic types was not possible. There was no intrafacility clustering of genetic types among the isolates from centers A (2 isolates), C (3 isolates), D (2 isolates), or G (3 isolates). Among isolates from center F (8 isolates), three shared a common type, while two shared a second common type, and the remaining three isolates were unrelated.

DISCUSSION

We report VRE prevalence and risk factors among hemodialysis patients at seven U.S. dialysis centers. Overall, 5.8% of the patients were VRE positive on either the first or second culture, and 4.2% of all cultures were positive. When analyzed by culture, VRE prevalence

Table 2. Potential risk factors for vancomycin-resistant enterococci (VRE) colonization among hemodialysis outpatient	s in
Baltimore and Richmond, December 1997–July 1998	

Factor	No. of cultures	No. (%)	Relative risk	P value
	cultures	VRE positive	11SK	<i>r</i> value
Center	54	2 (2 0)	2.0	
A	71	2 (2.8)	2.8	
B	47	1 (2.1)	2.1	
C^{a}	59	3 (5.1)	5.0	
D	41	2(4.9)	4.8	
E	98	1(1.0)	Ref	
F ^a	101	8 (7.9)	7.8	0.2 0 h
G	59	3 (5.1)	5.0	0.32 ^b
Gender	200		Def	
Female	209	8 (3.8)	Ref	0.72
Male	267	12 (4.5)	1.2	0.72
Race	270	14 (2.9)	Def	
Black, other White	370	14(3.8)	Ref	0.41
Functional status	105	6 (5.7)	1.5	0.41
	207	7(24)	Ref	
1–2 3–4		7 (3.4)	Ref	
5–4 5–6	144 30	5 (3.5) 1 (3.3)	Ref	
5–6 7–8	43	1(5.3) 1(2.3)	Ref	
9–10	43		4.2	0.0061
Diabetes	45	6 (14.0)	4.2	0.0001
No	259	11 (4.2)	Ref	
Yes	209	9 (4.3)	1.0	1.0
Known injection drug use	209	9 (4.3)	1.0	1.0
No	448	16 (3.6)	Ref	
Yes	28	4 (14.3)	4.0	0.024
Known HIV infection	28	4 (14.3)	4.0	0.024
No	463	19 (4.1)	Ref	
Yes	13	1 (7.7)	1.9	0.43
Access	15	1 (7.7)	1.7	0.45
Catheter	79	5 (6.3)	2.4	
Fistula	79 77	2 (2.6)	Ref	
Graft	314	12 (3.8)	1.5	0.59 ^b
Hospitalizations in previous 90 days	514	12 (3.8)	1.5	0.59
	418	14 (3.3)	Ref	
≥1	58	6 (10.3)	3.1	0.025
Receipt of intravenous antimicrobials in previous 90 days	50	0 (10.5)	5.1	0.025
None	417	12 (2.9)	Ref	
Any	59	8 (13.6)	4.7	0.0001
Receipt of intravenous antimicrobials in previous 90 days	57	0 (15.0)	-1.7	0.0001
None	417	12 (2.9)	Ref	
Vancomycin only	14	2(14.3)	5.0	0.07
Other antimicrobials only	22	2 (9.1)	3.2	0.15
Both vancomycin and other antimicrobials	23	4 (17.4)	6.0	0.0068
Culture specimen	20	(+,,+)	0.0	0.0000
Rectal swab	92	2 (2.2)	Ref	
Stool	374	18 (4.8)	2.2	0.39

Ref denotes reference group (relative risk = 1.0).

^aHospital-affiliated unit (other units are freestanding)

 ${}^{\mathrm{b}}P$ value for heterogeneity among the groups calculated by logistic regression

ranged from 1.0% to 7.9% among the centers, and all centers had at least one patient with a VRE positive culture. Independent risk factors for VRE colonization included functional status score, antimicrobial receipt, and injection drug use.

These results are similar to those found in a number of previous studies that have examined VRE colonization among dialysis patients. VRE prevalence was 9.5% at the center affiliated with the University of Maryland Hospital [18] (this center also was included in the currently reported study), 9% among 111 dialysis patients

near New York City [19], 6.0% at the Vanderbilt University Medical Center [20], and 8.1% at Johns Hopkins University Hospital [21]. Using a highly sensitive broth enrichment technique, VRE were found in 13.8% of patients hospitalized on the renal service of the University Hospital in Belgium [22] and 14% of dialysis outpatients at 29 dialysis centers in Belgium [23]. In a study in which selective media were not used, possibly reducing the probability of isolating VRE, VRE was found in 2.4% of dialysis outpatients at the Veterans Administration Hospital in Indianapolis [24].

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Variable	Adjusted odds risk	95% Confidence interval		
Functional status score				
1-8	Ref			
9–10	6.9	2.3-20.9	0.0006	
Receipt of any intravenous anti- microbial in previous 90 days				
No	Ref	_	_	
Yes	6.1	2.3-16.4	0.0003	
Injection drug use				
No	Ref	_	_	
Yes	5.4	1.7 - 17.0	0.004	

 Table 3. Multivariate model, risk factors for vancomycin-resistant enterococci (VRE) colonization among hemodialysis outpatients in Baltimore and Richmond, December 1997–July 1998

The functional status score previously has not been linked to VRE prevalence. However, functional status is a plausible risk factor since various manifestations of severity of illness are known to be associated with VRE [4, 5, 7, 8]. An association between injection drug use and VRE may have occurred because patients who abuse drugs may require more antimicrobials and hospitalizations.

Some studies have found that vancomycin receipt, but not receipt of other antimicrobials, is associated with VRE [3, 20]. However, in agreement with our findings, many studies have found that receipt of a variety of antimicrobials is associated with VRE [4, 5, 8, 19, 25]. Broad-spectrum antimicrobials, especially those with activity against anaerobes, are most likely to be associated with VRE [26]. Our study did not have sufficient power to determine the independent effect of various antimicrobials, but our results are most consistent with higher VRE prevalence in patients who received either vancomycin or other intravenously administered antimicrobials. It has been hypothesized that antimicrobial agents themselves do not cause vancomycin resistance; however, once resistant organisms have spread to a given patient, antimicrobials select for vancomycin-resistant strains, allowing them to increase in number [26].

Hospitalization has been associated previously with VRE in ESRD patients [18]. Our analysis showed that hospitalization was significantly associated with VRE in univariate analysis, but after controlling for antimicrobial use in a multivariate model, hospitalization was of only borderline statistical significance (P = 0.12).

Transmission of VRE within a healthcare facility may be inferred if a single genetic pattern is found among VRE isolates from the facility [27]. Evaluation of possible clustering of genetic types within the dialysis centers in our study was hampered by the small numbers of isolates available for testing. At four of five centers having ≥ 2 VRE isolates, no clusters were found. At one center (center F), there were two clusters of three and two isolates each, and three additional isolates that were unrelated; these clusters may have resulted from transmission in center F or in a local hospital or other healthcare facility. Overall, these results shed little light on the risk of VRE transmission from patient-to-patient in outpatient hemodialysis centers.

This study has a number of limitations. Patients at only seven centers were studied. Only 42% of eligible patients consented to be cultured. Comparing cultured versus noncultured patients, cultured patients were less likely to have injection drug use and to have received intravenous antimicrobials; therefore, VRE may have been even more common in noncultured than cultured patients. The small number (N = 20) of VRE isolates limited our ability to evaluate risk factors and identify clusters by genetic typing. Hospitalization and antimicrobial receipt during 90 days before culture were examined as risk factors; since these events were recorded only once the study started, their ascertainment was incomplete for cultures performed during the first 90 days of the study. However, this limitation would be expected to make it less likely to find a statistically significant result, and therefore hospitalization and antimicrobial receipt would be expected to show a stronger association with VRE colonization had more complete data been available.

We found that VRE-colonized patients were present in all seven outpatient units studied. Since stool or rectal cultures are rarely performed routinely at outpatient dialysis centers, VRE colonization in patients often will be unknown to staff members. Therefore, careful infection control precautions should be practiced during care of all patients to prevent transmission. CDC recommends private rooms, disposable gloves, and gowns for care of hospitalized patients with VRE [28]. However, similar recommendations have not been made for outpatient dialysis units [29, 30]. This is based partially on the assumption that, in the dialysis unit, infection control precautions will be followed for all patients (that is, gloves will be worn for all touching of patients, gloves will be removed and hands washed between patients, and surfaces at the dialysis station will be wiped with a disinfectant between patients). Such precautions were originally recommended for hemodialysis units in 1977 to prevent spread of the hepatitis B virus [31], but, with the increasing prevalence of antimicrobial-resistant organisms, careful adherence to these precautions remains critical. In addition to the use of general infection control measures, practices designed to prevent infections arising from hemodialysis catheters and implanted accesses should be followed [32, 33].

Judicious antimicrobial use, especially of vancomycin, is recommended to limit selection for vancomycin-resistant strains [34]. Two recent studies suggest that cefazolin, a first-generation cephalosporin, could be substituted for vancomycin where a β -lactam susceptible organism is identified, or where infection with a β -lactam-resistant organism is unlikely [35, 36]. Antimicrobial use and control policies have been useful in limiting inappropriate use of antimicrobials in hospitals [37, 38] and may be useful in outpatient dialysis centers as well. Because of the important role of ESRD patients in the epidemic of vancomycin resistance, physicians providing care for dialysis patients have an important responsibility to use antimicrobials judiciously and to carefully follow other practice guidelines that could limit the further spread of vancomycin resistance.

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