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ORIGINAL ARTICLE

A Population-Based Investigation of Invasive Vancomycin-Resistant *Enterococcus* Infection in Metropolitan Atlanta, Georgia, and Predictors of Mortality

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Susan M. Ray, MD; James P. Steinberg, MD; Henry M. Blumberg, MD

BACKGROUND. Vancomycin-resistant *Enterococcus* organisms (VRE) have emerged as common nosocomial pathogens, but few population-based data are available on the impact of invasive VRE infections.

METHODS. We assessed the incidence of invasive VRE infections and predictors of mortality among patients identified during prospective, population-based surveillance performed in the metropolitan statistical area (MSA) of Atlanta, Georgia.

RESULTS. From July 1997 through June 2000, a total of 192 patients who resided in the Atlanta MSA developed an invasive VRE infection, for a rate of 1.57 cases per 100,000 person-years. The incidence of invasive VRE disease significantly increased from 0.91 cases per 100,000 person-years during the first year of the study to 1.73 cases per 100,000 person-years during the third year of the study ($P < .001$). Rates of invasive VRE infection were significantly higher among African American patients than white patients (2.59 vs 0.70 cases per 100,000 person-years; $P < .001$). Blood was the most common sterile site from which VRE was recovered (161 [83%] of 193 isolates), followed by deep surgical sites (17 [9%]), peritoneal fluid (10 [5%]), pleural fluid (3 [2%]), and cerebrospinal fluid (1 [0.5%]). In multivariate analysis, a Charlson comorbidity index of 5 or greater, previous receipt of antibiotic therapy, having 2 or more sets of blood cultures positive for VRE, and receipt of central parenteral nutrition were independent predictors of mortality, whereas receipt of an antibiotic with in vitro activity against the VRE isolate was associated with a decreased risk of mortality. Molecular typing revealed 38 different pulsed-field gel electrophoresis patterns, but the 2 most common pulsed-field gel electrophoresis types were found at 3 Emory University-affiliated hospitals.

CONCLUSIONS. The incidence of invasive VRE infection significantly increased in the Atlanta MSA during the 3-year study period, with significant racial disparities detected. Receipt of an antimicrobial agent with in vitro activity against VRE was associated with a lower mortality rate. Molecular typing results demonstrated polyclonal emergence of VRE in Atlanta.

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Enterococcus species have emerged as important nosocomial pathogens, with an increasing prevalence of antibiotic resistance.^{1,2} The Centers for Disease Control and Prevention's National Nosocomial Infections Surveillance System has reported a steady increase in the prevalence of vancomycin resistance among *Enterococcus* isolates during the past decade.³ Infections due to vancomycin-resistant enterococci (VRE) have been reported to be associated with longer hospital stays, increased mortality, and higher costs than infections with vancomycin-susceptible enterococci.⁴⁻⁶ Treatment failures are also more likely among patients with VRE infection.⁷ In the United States, VRE has been reported almost exclusively in patients with a past history of exposure to healthcare settings.⁸⁻¹⁰

VRE can cause invasive infection and colonization. Risk factors for VRE colonization include antecedent treatment

with intravenous or oral vancomycin, cephalosporin antibiotics, fluoroquinolones, and antimicrobials with antianaerobic coverage.¹¹⁻¹⁹ Risk factors for invasive VRE infection, such as bacteremia, have been reported to include receipt of vancomycin and prior receipt of other antibiotics (including those that have antianaerobic activity), hematologic malignancy,²⁰ corticosteroid use,¹⁰ renal failure, neutropenia, hyperalimentation, a history of gastrointestinal procedure, and prolonged hospital stay.^{18,21} Patients with VRE infection often have more comorbidities than do other patients in the hospital.^{10,20} Previous studies have shown that vancomycin resistance,^{17,22,23} hematologic malignancy,¹⁰ more severe illness,^{10,18,23-25} cephalosporin and antianaerobic antimicrobial use,²³ and older age²⁵ are independent predictors of mortality among patients infected with VRE.

Results from these studies are hard to generalize to all

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patients, because they often focus on a select group of patients, such as those with malignancy or those who have undergone organ transplantation. In addition, nearly all reports on VRE infection have been hospital-based studies from a single center.^{5,6,8,18,20-22,24-31} Similarly, molecular epidemiologic studies of VRE have been usually limited to 1 or 2 institutions as part of outbreak investigations, and in most reports, hospital outbreaks involved oligoclonal spread of VRE.³ Rates of VRE infection in a defined community, such as a metropolitan area, have not, to our knowledge, been previously described.

The purpose of our study was to describe the clinical and molecular epidemiology of invasive VRE infections in the 20-county metropolitan statistical area (MSA) of Atlanta, Georgia. The objectives of our population-based study were as follows: (1) to determine the incidence of invasive VRE infections, (2) to determine the clinical characteristics of patients with VRE infections, (3) to determine the predictors for VRE-related mortality, and (4) to study the molecular epidemiology of VRE infection.

METHODS

Prospective, population-based, laboratory-based surveillance was performed. VRE isolates were collected from 43 hospital and reference laboratories in the Atlanta MSA as part of the Active Bacterial Core Surveillance Program of the Georgia Emerging Infections Program. Initial case reports and data on isolates were obtained from the microbiology laboratories through a review of all VRE-positive cultures of invasive specimens. Laboratory audits at all laboratories occurred every 6 months during the study period to evaluate reporting accuracy and identify cases not originally reported. The method used for prospective collection of isolates has been described elsewhere.³²⁻³⁴ At-risk persons were the entire population of the 20-county Atlanta MSA. The population was 3,746,059 persons in 1998 and increased to 4,112,198 in 2000. Data were collected on VRE isolates recovered from normally sterile body sites between July 1, 1997, and June 30, 2000. Demographic and clinical data were abstracted from the patients' medical records. This study was approved by the Emory University and the Georgia Department of Human Resources institutional review boards and the Grady Memorial Hospital Research Oversight Committee.

Definitions

VRE infection was classified as nosocomial if recovery of the isolate occurred greater than 48 hours after admission. It was classified as a healthcare-associated infection if recovery of the isolate occurred within 48 hours after admission and the patient was admitted to a hospital for at least 2 days within the past 90 days or resided in a nursing home or a long-term care facility before the current admission.³⁶ Invasive VRE infection was defined as recovery of VRE from the blood, cere-

brospinal fluid, pleural fluid, pericardial fluid, synovial fluid, and sterile surgical sites (ie, not from open wounds). Thirty-day in-hospital mortality was defined as death that occurred within 30 days after recovery of an invasive VRE isolate. The site of isolation was defined as the first sterile site from which the VRE isolate was recovered. End-stage renal disease (ESRD) was defined as the need for dialysis before or during the current admission. Chronic renal insufficiency was defined as a creatinine level of 144.4 $\mu\text{mol/L}$ (1.6 mg/dL) or higher, without the need for dialysis, before the admission. Previous antibiotic treatment was defined as receipt of any antimicrobial agent during the period before the date that the culture-positive specimen was collected. Polymicrobial bloodstream infection was defined as the recovery of other pathogens (bacterial or fungal) from the same blood culture that was positive for VRE. Severity of illness was determined using the Charlson comorbidity index.³⁵

Microbiological Analysis and Molecular Typing

Species identification of enterococcal isolates and antimicrobial susceptibility testing to identify vancomycin-resistant isolates were performed at the local laboratories. For the 120 VRE isolates available for analysis, species identification was verified using the API-20 Strep Identification System (bioMérieux) at our own epidemiology laboratory. For the 73 remaining VRE isolates, species identification was based on findings of commercial methods available at the local laboratory. Pulsed-field gel electrophoresis (PFGE) was performed in our laboratory according to the methods described by Bannerman et al.,³⁷ using Chef DR II (Bio-Rad Laboratories) with alternating switch times of 20 seconds and 1 second for 24 hours at 14°C. The DNA plugs were digested with *Sma*I restriction enzymes for 18 hours. Computer-assisted strain analysis was performed with Bionumerics software (Applied Maths). Cluster analysis was performed with unweighted pair group averages. Visual analysis was performed according to the criteria of Tenover et al.³⁸

Statistical Analysis

The χ^2 test for trend was used to compare infection rates (incidence densities) by year. The Student *t* test or the Wilcoxon rank sum test was used to analyze continuous variables, depending on the validity of the normality assumption. The Mantel-Haenszel χ^2 test was used to analyze categorical variables and proportions. A 2-sided *P* value of less than .05 was considered statistically significant. A case-control method was used to assess predictors of 30-day in-hospital mortality. Cases were patients with invasive VRE infection who died within 30 days after the initial recovery of a VRE isolate from a sterile body site, whereas controls were patients with invasive VRE infection who were alive 30 days after the diagnosis of VRE infection. Multivariate analysis was performed with backward stepwise elimination logistic regression analysis.

TABLE 1. Demographic Characteristics of Patients With Invasive Vancomycin-Resistant *Enterococcus* (VRE) Infection Who Were Cared for in the Metropolitan Statistical Area (MSA) of Atlanta, Georgia

Characteristic	No. (%) of patients (n = 192)
Sex	
Male	107 (56)
Female	85 (44)
Resident of the Atlanta MSA	156 (81)
Race	
African American	100 (52)
White	76 (40)
Hispanic	7 (4)
Asian	3 (2)
Native American	1 (0.5)
Unknown	5 (2.6)
Age, years, mean $\pm$ SD	54.43 $\pm$ 16.47
Residence before admission	
Home	141 (73)
Nursing home	17 (9)
Personal care home	18 (9)
Unknown	16 (9)
Time of previous hospitalization	
Previous 6 months	100 (52)
Previous year	10 (5)
Previous 2 years	8 (4)
Type of hospital	
Teaching ^a	132 (69)
Nonteaching	60 (31)

NOTE. Data are number (%) of patients, unless otherwise indicated. MSA, metropolitan statistical area.

^a VRE isolates were more likely to be recovered from teaching institutions (relative risk, 1.71 [95% confidence interval, 1.32-2.21]; $P < .001$).

Variables included in the multivariate analysis were those found to be significant predictors of 30-day mortality in univariate analysis and factors that had biologic plausibility, such as receipt of antimicrobial agents; demographic data, such as sex, age, and race/ethnicity, were also included in the logistic regression models.

Two different logistic regression models were created. The first model included all of the individual risk factors except the variables representing the Charlson comorbidity index. The second model was created to determine whether the Charlson comorbidity index is a good predictor of mortality among patients with invasive VRE infection. Any risk factor that was part of the Charlson comorbidity index (ie, acute renal failure, ESRD, malignancy, and receipt of chemotherapy) was excluded from the second logistic regression model. Twenty-three cases were excluded from the multivariate analysis because of insufficient data on outcomes or risk factors. Potential effect modification among race, age, and other risk factors was investigated. No significant interactions were detected between any of the variables. Data analyses were per-

formed with SAS software, version 9.0 (SAS Institute). A P value of .05 or less was considered statistically significant.

RESULTS

During the 3-year study period, 192 patients cared for in the Atlanta MSA had invasive VRE infection. Demographic characteristics of these patients are given in Table 1. A total of 156 patients (81%) were residents of the 20-county Atlanta MSA. The remaining 36 patients (23%) resided outside the 20-county Atlanta MSA but were admitted to hospitals within the MSA. These patients were more likely to be transplant recipients (unadjusted odds ratio [uOR], 4.2 [95% confidence interval {CI}, 1.2-14.8]; $P = .02$) or admitted to a tertiary care academic medical center (uOR, 7.5 [95% CI, 3.2-17.5]; $P < .001$). No other differences were found between the MSA residents and the non-MSA residents in terms of comorbid illnesses or outcomes. The incidence of invasive VRE infection among the 192 patients was 1.29 cases per 100,000 person-years during the 3-year study period. The incidence increased from 0.77 cases per 100,000 person-years in year 1 to 1.60 cases per 100,000 person-years in year 3 of the study (July 1999 through June 2000) ($P = .001$) (Figure 1).

Of patients cared for in the Atlanta MSA, the mean annual incidence rates among African American patients were significantly higher than those among white patients (2.59 vs 0.70 cases per 100,000 person-years; $P < .001$). During the 3-year study period, the incidence of invasive VRE infections increased significantly among African American patients, from 1.85 per 100,000 person-years in year 1 of the study to 3.61 per 100,000 person-years in year 3 ($P < .001$), but not among white patients (Table 2 and Figure 1). African Amer-

FIGURE 1. Incidence rate of invasive vancomycin-resistant *Enterococcus* infection during the 3-year period. Year 1: July 1, 1997, through June 30, 1998; year 2: July 1, 1998, through June 30, 1999; and year 3: July 1, 1999, through June 30, 2000.

TABLE 2. Rates of Invasive Vancomycin-Resistant *Enterococcus* (VRE) Infection Among Residents of the Metropolitan Statistical Area of Atlanta, Georgia

Period	No. of VRE infections per 100,000 person-years, by ethnicity			P
	Overall	African American	White	
Year 1 ^a	0.77	1.85	0.53	<.01
Year 2 ^b	1.01	2.10	0.77	<.01
Year 3 ^c	1.60	3.61	0.81	<.01
Overall	1.29	2.59	0.70	<.01
P	.001	<.001	.21	

^a July 1, 1997, through June 30, 1998.^b July 1, 1998, through June 30, 1999.^c July 1, 1999, through June 30, 2000.

ican patients were more likely than white patients to be female (uOR, 2.4 [95% CI, 1.3-4.4]; $P = .006$), have a diagnosis of acquired immunodeficiency syndrome (uOR, 7.0 [95% CI, 1.6-31.7]; $P = .004$), and be admitted to a teaching hospital (uOR, 8.4 [95% CI, 1.9-7.0]; $P < .001$). No race-based differences in mortality rates were found.

Two distinct VRE species (*Enterococcus faecium* and *Enterococcus faecalis*) were recovered from 1 patient. Of the 193 isolates recovered from the 192 patients, *E. faecium* was the most common VRE species recovered (161 isolates [83%]), followed by *E. faecalis* (12 isolates [6%]) (Figure 2). Thirteen isolates (7%) were not speciated by the participating laboratory, and these isolates were not available for further testing in our laboratory. Blood was the most common sterile site from which VRE was isolated (161 isolates [83%]), followed by deep surgical sites (17 [9%]), peritoneal fluid (10 [5%]), pleural fluid (3 [2%]), and cerebrospinal fluid (1 [0.5%]).

One hundred forty-three (74%) of 192 patients with an invasive infection had VRE isolated more than 48 hours after admission (ie, representing nosocomial infection). Of the remaining 49 patients, all of whom had VRE isolated from culture within 48 hours after admission, 35 (71%) were considered to have healthcare-associated infections; 9 of these 35 patients were transferred from other hospitals, 10 resided in a nursing home or long-term care facility, and 16 were hospitalized within 90 days before the current admission. Therefore, at least 93% of the infections could be considered healthcare associated, and we suspect that the remaining 7% would also have been classified as healthcare associated if complete medical records were available for the affected patients. Data on demographic and clinical characteristics, diseases and conditions, and treatments and procedures are presented in Table 3.

The crude mortality rate for patients with invasive VRE infection was 43% (82 of 192) and was not significantly different from that for individuals with bacteremia alone (47% [75 of 161]; $P = .45$). The crude mortality rate for patients who did not receive an antimicrobial that had in vitro activity

against VRE was 46% (39 of 85). The risk factors for 30-day in-hospital mortality in univariate analysis were as follows: ESRD, acute renal failure without the need for dialysis, receipt of chemotherapy, receipt of antimicrobial treatment before recovery of the VRE isolate, presence of a central venous catheter, Charlson comorbidity index of 4 or greater, receipt of central parenteral nutrition, diagnosis of candidemia independent of the VRE infection, VRE infection in the bloodstream instead of another invasive site, and, for persons with a bloodstream infection, and presence of 2 or more sets of blood cultures positive for VRE (Tables 3 and 4).

In the first logistic regression model, independent predictors of 30-day in-hospital mortality included receipt of chemotherapy, previous receipt of antibiotic therapy, ESRD or acute renal failure at the time of infection, and having 2 or more sets of blood cultures positive for VRE. Receipt of an antimicrobial with in vitro activity against the VRE isolate was protective against 30-day in-hospital mortality (Table 5). In the second logistic regression model, in which comorbidities already included in the Charlson comorbidity index were removed from analysis, a Charlson comorbidity index of 5 or greater, previous receipt of antibiotic therapy, having 2 or more sets of blood cultures positive for VRE, and receipt of central parenteral nutrition were independent predictors of 30-day in-hospital mortality (Table 5). As in the first model, receipt of an antimicrobial with in vitro activity against the VRE isolate was protective against 30-day in-hospital mortality.

Molecular Analysis

A total of 66 distinct PFGE patterns were noted among the 109 vancomycin-resistant *E. faecium* isolates available for molecular typing. Eleven vancomycin-resistant *E. faecium* isolates that had an identical PFGE pattern (type A) were recovered from patients receiving care at 5 different hospitals, and vancomycin-resistant *E. faecium* isolates with another PFGE pat-

FIGURE 2. Species identification of 193 vancomycin-resistant *Enterococcus* isolates recovered from 192 patients. Vancomycin-resistant *Enterococcus faecium* and vancomycin-resistant *Enterococcus faecalis* were both isolated from a single patient.

TABLE 3. Baseline Characteristics of Patients With Invasive Vancomycin-Resistant *Enterococcus* (VRE) Infection and Univariate Analysis Determining the Comorbid Illnesses Associated With 30-Day In-Hospital Mortality

Risk factor	Overall (<i>n</i> = 192)	In-hospital mortality		uOR (95% CI)	<i>P</i>
		With risk factor	Without risk factor		
Demographic or clinical characteristic					
Male sex	107 (56)	41/107 (38)	36/85 (42)	0.85 (0.47-1.51)	.57
Charlson comorbidity index ≥4	68 (35)	35/68 (51)	42/124 (34)	2.07 (1.13-3.79)	.02
≥2 sets of VRE-positive blood cultures	47 (24)	27/47 (57)	50/145 (34)	2.56 (1.31-5.02)	.005
Disease or condition					
Diabetes mellitus	42 (22)	15/42 (36)	62/141 (44)	0.71 (0.35-1.44)	.34
COPD	25 (13)	9/25 (36)	68/157 (43)	0.74 (0.31-1.77)	.49
ESRD	54 (28)	31/54 (57)	46/129 (36)	2.43 (1.27-4.65)	.004
ARF	39 (20)	27/39 (69)	50/142 (35)	4.14 (1.93-8.87)	<.001
CRI	24 (13)	11/24 (46)	66/158 (42)	1.18 (0.50-2.80)	.71
Liver disease	24 (13)	13/24 (54)	64/158 (41)	1.74 (0.73-4.12)	.21
Malignancy	44 (23)	24/44 (55)	53/137 (39)	1.91 (0.96-3.78)	.06
Neutropenia	48 (25)	26/48 (54)	47/111 (42)	1.61 (0.82-3.18)	.17
HIV infection	23 (12)	12/23 (52)	65/169 (38)	1.75 (0.73-4.19)	.39
AIDS	19 (10)	9/19 (48)	68/173 (39)	1.39 (0.54-3.60)	.50
Trauma	10 (5)	3/10 (30)	73/170 (43)	0.57 (0.14-2.28)	.42
Bacteremia					
Monomicrobial	51 (27)	25/51 (49)	52/130 (40)	1.44 (0.75-2.77)	.27
Polymicrobial	69 (36)	32/69 (46)	45/123 (37)	1.50 (0.82-2.73)	.19
Candidemia	26 (14)	16/26 (62)	61/155 (39)	2.47 (1.05-5.79)	.03
Bloodstream infection	161 (84)	70/161 (43)	7/31 (23)	1.44 (1.07-6.47)	.03
Treatment or procedure					
Chemotherapy	28 (15)	19/28 (68)	58/153 (38)	3.46 (1.47-8.15)	.003
Transplantation	11 (6)	6/11 (55)	71/170 (42)	1.67 (0.49-5.70)	.41
Surgery	77 (40)	31/77 (40)	45/103 (44)	0.87 (0.48-1.58)	.65
Central venous access	139 (72)	65/139 (47)	11/39 (28)	2.24 (1.03-4.84)	.04
Total parenteral nutrition	79 (41)	43/79 (54)	34/102 (33)	2.39 (1.31-4.37)	.005
Previous antibiotic treatment	151 (79)	72/151 (48)	3/20 (15)	5.16 (1.45-18.36)	.006

NOTE. Data are no. (%) or proportion (%) of patients. The total for each risk factor may not equal 192 patients because of incomplete information. AIDS, acquired immunodeficiency syndrome; ARF, acute renal failure; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CRI, chronic renal insufficiency; ESRD, end-stage renal disease; HIV, human immunodeficiency virus; uOR, unadjusted odds ratio.

tern (type B) were recovered from patients at 4 different hospitals. Type A and type B isolates were recovered from patients at 3 of the Emory University-affiliated teaching hospitals (house staff rotate among the hospitals).

Ten of 12 vancomycin-resistant *E. faecalis* isolates were also available for molecular typing. A total of 6 distinct PFGE patterns were noted among *E. faecalis* isolates; 5 isolates had an identical PFGE type and were recovered from a single institution. The other 5 *E. faecalis* isolates had distinct PFGE types.

DISCUSSION

VRE is a multidrug-resistant pathogen, and infection and colonization with VRE is generally associated with healthcare contact. Previous studies have been institution based, and few data on the incidence of infection in a community are available.^{5,6,18,20-22,24,25,28-30,39-41} No prior molecular epidemiologic analysis has been performed in a population-based

study. Our population-based study demonstrated a significant increase in the incidence of invasive VRE infection in the Atlanta MSA (from 0.77 to 1.60 per 100,000 person-years) during the 3-year study period. VRE isolates were more likely to be associated with teaching hospitals than with nonteaching hospitals, a finding that was only reported in 1 other study.⁴²

Our study found significantly higher rates of invasive VRE infection among African American patients, compared with white patients (2.59 vs. 0.70 infections per 100,000 person-years; relative risk, 3.70). This racial disparity has not been previously reported for invasive VRE infections but has been described in a population-based study on invasive pneumococcal disease.⁴³ The reasons for the higher rates of invasive VRE infection among African American patients treated in the Atlanta MSA are not entirely clear, but we speculate that this is related to higher rates of chronic diseases, such as ESRD, among African American patients. Higher rates of

TABLE 4. Continuous Variables and Their Association With 30-Day In-Hospital Mortality Among Patients With Invasive Vancomycin-Resistant *Enterococcus* (VRE) Infection

Variable	Overall	Patients who died <30 days after VRE isolation	Patients who were alive 30 days after VRE isolation	P
Age, years, mean $\pm$ SD	54.43 $\pm$ 16.47	52.34	49.77	.28
Charlson comorbidity index, mean $\pm$ SD	3.29 $\pm$ 2.41	3.97	2.79	.002
Defined daily dose of antibiotic, median	20 (0-246)	99.32	81.23	.02
Length of stay, days, median	33 (1-228)	88.69	100.14	.16
Time to infection, days, median	14 (0-131)	110.73	84.18	.001

ESRD among African American patients have been reported elsewhere.^{44,45} Having ESRD would necessitate more frequent contact with healthcare institutions, including inpatient facilities.

Blood was the most common sterile site from which VRE was recovered. This finding is not surprising, because *Enterococcus* organisms have been reported to be the second⁴⁶ and third⁴⁷ most common pathogens isolated from patients with bloodstream infections. In our study, *E. faecium* was the most common species of VRE isolated, followed by *E. faecalis*. Vancomycin-resistant *Enterococcus gallinarum* and *Enterococcus durans* were also recovered from a few patients but accounted for less than 5% of VRE isolates. Only 1 multicenter study on enterococcal bacteremia provided data on the species of

the VRE isolates recovered and found a distribution similar to that observed in our study.¹⁰ Two other multicenter studies did not provide any data on speciation.^{7,42}

The 30-day in-hospital mortality rate for all patients with an invasive VRE infection was 40%. This crude mortality rate is 37%-76% among patients with VRE bacteremia^{5,6,17,18,20,22,23,25,28,30,48} reported from single-institution studies and similar to that reported for *Candida* bloodstream infections.⁴⁹ The Charlson comorbidity index was found to be predictive of 30-day in-hospital mortality on both univariate and multivariate analyses. The Charlson comorbidity index may be a good measure of severity of illness, because it was found to have the highest adjusted OR (aOR; 5.2) for 30-day in-hospital mortality. The following risk factors included in the

TABLE 5. Multivariate Analyses of Risk Factors for Invasive Vancomycin-Resistant *Enterococcus* (VRE) Infection, According to the Exclusion (Model 1) and Inclusion (Model 2) of the Charlson Comorbidity Index

Independent predictor	aOR (95% CI)	P
Model 1 ^a		
Chemotherapy	5.6 (1.9-16.4)	.002
Previous antibiotic use	5.5 (1.3-23.6)	.02
End-stage renal disease	4.1 (1.7-9.3)	.001
≥ 2 sets of VRE-positive blood cultures	3.95 (1.6-9.8)	.003
Acute renal failure	3.4 (1.45-8.0)	.005
Treatment with antimicrobial active against VRE ^b	0.33 (0.14-0.77)	.01
Model 2 ^c		
Charlson comorbidity index ≥ 5	5.2 (2.2-12.4)	<.001
Previous antibiotic use	4.1 (1.0-16.9)	.047
≥ 2 sets of VRE-positive blood cultures	3.5 (1.4-8.3)	.006
Receipt of central parenteral nutrition	3.1 (1.5-6.7)	.003
Age ≥ 65 years	2.1 (0.97-4.7)	.06
Treatment with antimicrobial active against VRE ^b	0.45 (0.20-0.996)	.045

NOTE. aOR, adjusted odds ratio; CI, confidence interval.

^a The following variables were also included in the backward stepwise logistic regression model but were eliminated from the final model: age, race, sex, receipt of central parenteral nutrition, presence of candidemia, site of infection, and presence of a central venous catheter.

^b Receipt of any antimicrobial agent with in vitro activity against the VRE isolate (eg, ampicillin, chloramphenicol, linezolid, and quinupristin-dalfopristin).

^c Any risk factor that was part of the Charlson comorbidity index (ie, acute renal failure, ESRD, malignancy, and receipt of chemotherapy) was excluded from model 2. The following variables were also included in the backward stepwise logistic regression model but were eliminated from the final model: race, sex, presence of candidemia, primary site of infection, and presence of a central venous catheter.

Charlson comorbidity index were also found to be independent predictors for mortality: receipt of chemotherapy, a surrogate marker for malignancy (aOR, 5.6); ESRD (aOR, 4.1); and acute renal failure at the time of diagnosis (aOR, 3.4). Other independent predictors of mortality found in both logistic regression models were history of antibiotic therapy (aOR, 5.5) and having multiple sets of blood cultures positive for VRE (aOR, 4.0). Receipt of central parenteral nutrition (aOR, 3.1) was also an independent predictor of mortality in the second logistic regression model.

Our study was not designed to assess attributable mortality associated with invasive VRE infection. However, the finding that multiple positive blood cultures (compared with recovery of VRE from a single culture) were an independent predictor of mortality may be a surrogate for differentiating between skin or catheter colonization versus a true VRE bloodstream infection and suggests that VRE infection may have been the cause of mortality in many cases. Previous antibiotic therapy may have also been a surrogate for severity of illness in this study, and this finding suggests that the Charlson comorbidity index is not a complete measure of severity of illness. We investigated several risk factors that are not accounted for in the Charlson comorbidity index. Receipt of chemotherapy, as opposed to just having an active malignancy, was found to be an independent risk factor for mortality after an invasive VRE infection. Patients with malignancies who receive chemotherapy are likely to be more immunocompromised than patients with malignancies who are not receiving chemotherapy. Although acute renal failure and receipt of hemodialysis have been previously reported as risk factors for VRE colonization⁵⁰ and infection,²¹ they have not been previously reported as independent predictors of VRE-related mortality.

A Charlson comorbidity index of 4 or greater, which is indicative of severe illness, was predictive of mortality after invasive VRE infection. The association between more-severe illness and mortality among patients with VRE infection is consistent with findings from previously published studies.^{7,10,18,20,23-25} Although Acute Physiology and Chronic Health Evaluation II scores have been used to control for severity of illness in some studies, we opted to use the Charlson comorbidity index,³⁵ since we were unable to collect all the information required to accurately assign Acute Physiology and Chronic Health Evaluation II scores to all patients. The use of the Charlson index as a measurement of illness severity has been validated in a cohort of patients with *Staphylococcus aureus* bacteremia⁵¹ but has not been previously used in a study that involved a cohort of patients with invasive VRE infection.

Multivariate analysis revealed that receipt of an antimicrobial agent with in vitro activity against VRE was associated with a reduced risk of mortality. This finding suggests that treatment of invasive VRE infections is an important factor in preventing mortality. Our study is one of the few studies that has accounted for treatment modalities in the multivariate analyses.^{10,52} Because our study was performed during

1997-2000, most of the patients with VRE bacteremia or invasive infection were treated with chloramphenicol or quinupristin-dalfopristin. Antimicrobials active against resistant gram-positive bacteria, including VRE, such as linezolid, daptomycin, and tigecycline, were not approved by the Food and Drug Administration at the time of the study and therefore were not commonly used. Linezolid was only available through compassionate use during the study period, and only 1 patient included in our study received it. The clinical efficacy of chloramphenicol in treating VRE infection has been debated.²⁸ However, our study shows that, after adjusting for other risk factors, treatment with any active agent against VRE was protective against 30-day in-hospital mortality. Patients who were treated with any agent with in vitro activity against the VRE isolate were pooled into 1 group, because there would have been too few patients receiving each specific treatment to arrive at a meaningful conclusion.

Molecular typing studies revealed a large number of distinct clones of VRE. A total of 66 different PFGE types were found among the *E. faecium* isolates, indicating the emergence of a great deal of genetic heterogeneity among VRE in the Atlanta MSA. The 2 most common PFGE patterns (types A and B) were recovered from patients from at least 4 different hospitals, 3 of which were Emory University-affiliated teaching hospitals. Introduction of these strains into these institutions could have occurred because of transfer of patients among institutions or, potentially, because of carriage by personnel (eg, house staff or faculty physicians) who rotate among the Emory University-affiliated hospitals. This polyclonal spread of VRE in the Atlanta MSA is consistent with other reports that have shown that the polyclonal proliferation of VRE is common within single institutions.^{12,48,53,54}

Our study has a few limitations. The isolation of VRE from a single set of blood cultures may in some cases have represented colonization rather than infection. This approach may account for the finding that isolation of VRE from 2 or more sets of blood cultures was an independent predictor for in-hospital mortality, although persistent or longer courses of bacteremia could also reflect enhanced immunosuppression among some patients. This study also underscores the importance of appropriate treatment with an agent active against VRE, because the mortality rate for the 85 patients who did not receive an active agent was still high at 46%. We were also unable to perform our own analysis on every isolate, so vancomycin resistance and species identification were not verified in 38% of the cases. Finally, the study period occurred before the introduction of newer agents (eg, linezolid and daptomycin) for the treatment of VRE infection. Further studies are needed to assess the impact of these newer agents on outcome and mortality.

In summary, to our knowledge, this is the first population-based study of invasive VRE infection that included molecular analysis. Our study showed an increase in the incidence rate of invasive VRE infections (from 0.77 to 1.60 per 100,000 person-years) during the 3-year study period and significantly

higher rates of infection among African American patients compared with white patients, which may reflect higher incidence of some chronic diseases (eg, ESRD) in the former group. Although African American persons constituted only 27% of the population in the Atlanta MSA during the study period, most cases of invasive VRE infection occurred in this group. VRE infection was overwhelmingly healthcare associated and was also associated with a high crude mortality rate. Risk factors for mortality after VRE infection included receipt of chemotherapy, ESRD, previous receipt of antibiotic therapy, multiple VRE-positive blood cultures, and acute renal failure. Treatment with an antimicrobial agent active against VRE was associated with reduced mortality and emphasizes the need for prompt treatment of patients with invasive VRE infection. Molecular typing results demonstrated polyclonal emergence of VRE in the Atlanta MSA, although interhospital spread was noted among several university-affiliated teaching hospitals.

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