ORIGINAL INVESTIGATION

Role of Environmental Contamination as a Risk Factor for Acquisition of Vancomycin-Resistant Enterococci in Patients Treated in a Medical Intensive Care Unit

José A. Martínez, MD; Robin Ruthazer, MPH; Karen Hansjosten, RN; Laurie Barefoot, RN; David R. Snydman, MD

Background: Colonization pressure, proximity to another case, exposure to a nurse who cares for another case, enteral feeding, and the use of sucralfate, vancomycin hydrochloride, cephalosporins, or antibiotics are among the defined risk factors for acquisition of vancomycin-resistant enterococci (VRE) in the intensive care unit (ICU) setting. However, the role of rooms with contaminated environmental surfaces has not been well delineated.

Methods: Retrospective case-control study conducted on patients admitted to the medical ICU (MICU) of a tertiary-care, university-affiliated medical center during a 9-month period. Patients who acquired VRE (cases) were matched with 2 randomly selected control subjects who did not acquire VRE and had been in the MICU for at least the same number of days.

Results: Thirty cases were matched with 60 appropriate controls. Cases were more likely to have been in the hospital for longer than 7 days before MICU admission ($P=.009$); to have occupied a specific room with persisting contaminated surfaces ($P=.06$); to have had a central venous catheter ($P=.05$); to have received vancomycin ($P=.02$), cephalosporins ($P=.03$), and quinolones ($P=.006$) before MICU admission; and to have received vancomycin ($P=.02$) and metronidazole sodium phosphate ($P=.03$) after MICU admission. Multivariate analysis showed that a hospital stay of longer than 1 week before MICU admission ($P=.04$), use of vancomycin before or after MICU admission ($P=.03$), use of quinolones before MICU admission ($P=.03$), and placement in a contaminated room ($P=.02$) were the best predictors of VRE acquisition.

Conclusions: Among all other factors associated with VRE transmission, VRE acquisition may depend on room contamination, even after extensive cleaning. This study underscores the need for better cleaning and the role of the environment in transmission of VRE.

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From the Division of Geographic Medicine and Infectious Disease and Clinical Care Research, Department of Medicine, Tufts New England Medical Center and Tufts University School of Medicine, Boston, Mass. Dr Martinez is now with the Division of Infectious Diseases, Department of Medicine, University of Barcelona, Barcelona, Spain. *The authors have no relevant financial interest in this article.*

SINCE THEIR FIRST appearance in 1988, vancomycin-resistant enterococci (VRE) have become endemic in many hospitals throughout the United States. According to data from the National Nosocomial Infections Surveillance System, by the end of 1999 about 25% of all enterococci involved in nosocomial infections were resistant to vancomycin hydrochloride.[1] For patients admitted to the intensive care unit (ICU), the prevalence of resistance in the first 5 months of 1999 was 47% higher than during the period from 1994 to 1998.[2] Patients with hematologic malignancies, transplant recipients, and the critically ill are at particular risk for colonization and subsequent infection with VRE.[3] Because in the United States there are no reservoirs of vancomycin-resistant *Enterococcus faecium* or *Enterococcus faecalis* other than colonized patients,[4-7] and because resistance to glycopeptides cannot be selected by antibiotics from a previously susceptible bacterial population,[8] each instance of colonization or infection with these organisms represents an episode of horizontal transmission, many of which occur in the hospital setting. Once colonized, patients become long-term carriers,[9] so in a given facility or unit the endemic prevalence of VRE is related to the admission rate of previously colonized patients.[10] This basal rate will eventually be increased by new cases resulting from cross-transmission through the hands of health care workers and, possibly, other items.

During the past decade, at least 28 studies investigating the factors related to VRE acquisition have been published.[11-38] Most of them were designed as case-control studies, but they have been het-

erogeneous in terms of sample size, definition of the outcome variable (ie, colonization, infection, or both), the type and number of explicative variables, criteria for the selection of control subjects, study population, and statistical analysis. Nine studies* focused on critically ill patients, but 2 of these[23,32] explored the same database using a different set of independent variables, and two others[31,35] investigated the risk factors for the presence of VRE at ICU admission. Colonization pressure, proximity to another case, exposure to a nurse in charge of another case, enteral feeding, and the use of sucralfate, vancomycin, cephalosporins, or antibiotics are among the defined risk factors for acquisition of VRE in the ICU setting. Despite this abundant information, some questions remain unanswered or controversial. Although it is well known that VRE can contaminate the surfaces and equipment of the patient's room and remain viable for several days,[39-42] no clear evidence links this kind of environmental contamination with VRE acquisition. On the other hand, a recent meta-analysis[43] has suggested that the association between antecedent vancomycin treatment and acquisition of VRE tends to be magnified when patients with cultures that are positive for vancomycin-susceptible enterococci (VSE) are selected as controls.*

In November 1998, a surveillance program to detect VRE colonization was started in patients admitted to the medical ICU (MICU) of our center. The information gathered from this screening survey allowed us to undertake a case-control study aimed to determine the risk factors for acquisition of VRE in critically ill patients during an apparently endemic situation. Matching was used to control for the potential confounding effect of length of stay. Among other putative risk factors, we were able to explore the influence of a particular room that was contaminated during the study period.

METHODS

SETTING AND STUDY DESIGN

The study was conducted in the MICU of the New England Medical Center, a 350-bed tertiary-care, university-affiliated hospital in Boston, Mass. The MICU contains 10 private rooms. At the study center, VRE was first detected in 1994, and from 1996 to the end of 1998 the number of patients with VRE isolated from clinical specimens remained stable at approximately 100 per year; about 80% of the cases were considered hospital acquired from the standpoint of infection control surveillance. From 1994 to 1998, the mean±SD number of annual hospital discharges was 16 734±1850. Since VRE was first detected in the hospital, specific isolation precautions were issued. These included the placement of infected patients in private rooms and the requirement that personnel wear gloves and gowns for all room entries and wash their hands with antiseptic soap (containing chlorhexidine gluconate) before leaving the room.

In November 1998, an active surveillance monitoring for VRE colonization of patients admitted to the MICU was implemented. In accordance with monitoring, a rectal swab had to be obtained from all patients within 48 hours after admission to the MICU and then weekly as long as findings of previous cultures remained negative and the patient stayed in the unit. Patients who had a positive finding of VRE surveillance or a clinical sample within the first 48 hours after admission were considered to be colonized on admission. Acquisition of VRE was defined by the absence of clinical samples that were positive for VRE on ICU admission, negative findings of a first rectal culture, and any positive findings at follow-up (after 48 hours) surveillance or from a clinical specimen culture. Nonacquisition of VRE was defined by only negative findings of surveillance and clinical cultures during the active MICU stay. Patients admitted to the MICU from November 15, 1998, through August 6, 1999, who underwent screening for VRE colonization were the source population from which cases and controls were selected. Patients who acquired VRE (cases) were matched with 2 randomly selected controls who had not acquired VRE and had been in the MICU for at least the same number of days from the admission to the MICU to the isolation of VRE from the corresponding case.

MEASUREMENTS

The medical records of cases and controls were reviewed and the following information was collected in a specific questionnaire: age, sex, hospital days before MICU admission, number of previous admissions to the hospital and MICU during the past year, admission diagnosis, reason for MICU admission, underlying diseases (≤5), prognosis of the underlying disease according to a modification of the McCabe criteria,[44] APACHE II (Acute Physiology and Chronic Health Evaluation II) score on admission to the MICU, the room where the patient was placed, presence of shock on MICU admission, presence of neutropenia (<500 neutrophils/μL) on admission to the MICU, antibiotics administered within the month before MICU admission and during MICU stay until acquisition of VRE or discharge, surgical procedures performed during the current admission before VRE acquisition or discharge from the MICU, and other therapeutic interventions during MICU stay until VRE acquisition or discharge (intubation and mechanical ventilation; nasogastric tube; rectal tube; enteral feeding; total parenteral nutrition; central venous catheterization; hemodialysis; administration of antacids; antihistamine (anti-H_2) receptor blockers, proton pump inhibitors and sucralfate, corticosteroids [≥20 mg/d], cyclosporins, or tacrolimus; and antineoplastic therapy). For all procedures and therapies, we recorded starting and ending dates. As previously described,[32] a colonization pressure score was calculated for each patient using the MICU's daily prevalence of VRE defined as the average proportion of patients on each study day who were known to have VRE among those under active surveillance. Prognosis of underlying disease was classified according to a modification of the McCabe criteria[44] as rapidly fatal (when death was expected in <3 months), ultimately fatal (when death was expected from >3 months but <5 years), and nonfatal (when life expectancy was >5 years). Shock was defined as systolic pressure of lower than 90 mm Hg unresponsive to fluids or requiring vasoactive drugs.[45]

MICROBIOLOGIC PROCEDURES

Rectal swabs were directly plated on Campy CVA agar containing 10-mg/L vancomycin (Becton Dickinson, Cockeysville, Md). Identification of the species level and antibiotic susceptibility was performed by means of the Vitek system (bioMerieux, Inc, St Louis, Mo). An agar plate containing 6-mg/L vancomycin[46] was used to confirm resistance to vancomycin on enterococci isolated from clinical samples. Environmental samples were obtained by swabbing surfaces with culturettes (Baltimore Biological Laboratories, Sparks, Md) that had been premoistened with thioglycolate broth and placed directly on the agar plates. Surface samples included those of bed rails, side

*References 13, 14, 18, 23, 26, 28, 31, 32, 35.

tables, drawers, switches, telephone handles, sink handles, soap dispensers, doorknobs, monitors, curtains, intravenous (IV) pumps, bathroom faucets, and toilet rinsers. Blood pressure cuffs and stethoscopes were not cultured. We performed pulsed-field gel electrophoresis (PFGE) on all available patient and environmental strains.[47]

STATISTICAL ANALYSIS

Since the length of MICU stay of controls could be longer than that of the corresponding cases, all exposures in controls were censored at the same number of days elapsed between admission to the MICU and VRE acquisition of the corresponding case. Exposures were considered as occurring before or after MICU admission. Antibiotics were grouped as follows: cephalosporins, a combination of penicillin and β-lactamase inhibitors, antianaerobic β-lactams, other β-lactams, IV vancomycin, quinolones, metronidazole, clindamycin hydrochloride, and other antibiotics. Administration of antibiotics before MICU admission was analyzed only as a dichotomous variable (present or absent), since information about duration of therapy could not be retrieved from the medical records of all patients. In addition, pre- or post-MICU exposure to the different antibiotics (present or absent) was considered. Admission diagnoses to the hospital were recoded as infectious processes vs others, and reasons for MICU admission as acute respiratory failure, sepsis, or multiple organ failure vs others. Only the 5 most frequent underlying diseases (liver cirrhosis, diabetes mellitus, chronic obstructive pulmonary disease, chronic renal failure, and congestive and ischemic heart disease) were considered as putative risk factors. A room that proved to be contaminated after post–patient discharge cleaning (ie, terminal cleaning) during the study period was considered a high-risk room and compared with the others.

Comparison of selected continuous variables between more than 2 groups was performed by means of analysis of variance with the Bonferroni correction or the Kruskal-Wallis test. We used the χ^2 test to compare sex distribution between different patient cohorts. Conditional logistic regression analysis was used for the estimation of the odds ratio for acquiring VRE, given the presence of each one of the putative exposures (univariate analysis). Variables with univariate *P* values of no greater than .20 were entered in a multivariable conditional logistic regression model with further selection by a stepwise process; adjusted *P* values of no greater than .15 allowed variables to step into the model, and adjusted *P* values of no greater than .10, to stay in it. We performed all statistical analysis by using the SAS system for Windows, version 6.12 (SAS Institute, Inc, Cary, NC).

RESULTS

During the study period, there were 365 admissions to the MICU. One hundred sixty-nine patients (46%) underwent screening for VRE colonization; 32 (19%) of them proved to be colonized on admission, and of 137 patients who were not colonized on admission, 31 (23%) acquired VRE during their MICU stay. Two appropriate controls could only be found for 30 of the 31 cases, and these 90 patients constituted the base for the case-control study.

In patients who acquired VRE, colonization occurred a mean ± SD of 9 ± 6 days (median, 7 days) after admission to the MICU. Common reasons alleged by the MICU staff for noncompliance with the screening program were an expected very short length of stay and refusal of patients to provide a rectal swab; this information, however, was not specifically recorded. Length of MICU stay was significantly less for patients not undergoing screening (mean ± SD, 3.2 ± 3 days; median, 2 days) than for patients colonized on admission (mean ± SD, 11.3 ± 14 days; median, 6 days), patients who acquired VRE during the MICU stay (mean ± SD, 17.6 ± 13 days; median, 4 days), and patients undergoing screening who did not acquire VRE (mean ± SD, 8.1 ± 7 days; median, 6 days) ($P<.05$ for all comparisons). Age and sex were not significantly different among these groups (data not shown).

Sixty-two of 63 VRE isolates acquired or cultured at admission were *E faecium* with high-level resistance to vancomycin and ampicillin sodium; 1 *E faecalis* strain had high-level resistance to vancomycin but was sensitive to ampicillin.

During the study period, 3 patients had an infection due to VRE. One of them was transferred to our MICU from another center with severe sepsis, and a similar strain of *E faecium* was isolated from blood and a rectal swab on admission. Another patient was admitted to the MICU with a urinary tract infection caused by *E faecium*. In the third patient, an asymptomatic catheter-related urinary tract infection due to vancomycin-resistant *E faecium* developed shortly after acquisition of rectal colonization with a similar strain.

ENVIRONMENTAL CULTURES AND PFGE TYPES

From March 23 to March 26, 1999, an environmental survey was conducted in our MICU. After the discharge of patients and a routine terminal room cleaning, 6 to 12 samples were taken from each room (**Table 1**). The routine cleaning procedure included the use of a phenolic disinfectant on all surfaces in the room and took about 20 to 30 minutes to be completed. Two of the 10 rooms proved to have contaminated items (a light switch, a toilet flusher, a telephone handle, and a bathroom faucet in one room, and 2 IV pumps in the other).

Seventeen of the 31 strains isolated from patients who acquired VRE during MICU admission and 7 of the 32 strains isolated from patients colonized on admission plus all the environmental isolates were available for PFGE typing. Six different PFGE types were found. The isolates from 11 patients who acquired VRE during their MICU stay and 5 from patients colonized on admission were identical or differed from each other in no more than 1 band (type 1). Three patients acquired another PFGE type (type 2), and 3 additional patients acquired unique strains during their stay in the unit. A strain of a totally different type was isolated from another patient on admission. Eleven patients acquired a VRE strain that was the same as other strains present in the unit. The environmental isolates pertained to type 1 or 2. Type 1 was isolated from a light switch and a toilet flusher in 1 room where a patient colonized by the same strain had been staying for a month. In this room, a type 2 strain was also found at the same time on a bath faucet and a telephone handle. Three days later, a type 2 strain was isolated from 2 IV pumps in another room where a patient with an identical PFGE type had been staying until 4 days earlier.

Table 1. 1999 Environmental Surveys Performed at Several Intervals After Terminal Room Cleaning

Cleaning Procedure	Date	Room No.	No. of Positive Samples/ No. of Samples Taken	Soiled Items	PFGE Type
Conventional	March 23	10	4/9	Light switch, toilet rinser, bathroom faucets, telephone handle	1, 1, 2, 2
Conventional	March 24	6	0/9	NA	NA
Conventional	March 26	7	2/6	2 IV pumps	2
Intensive	May 25	7	0/12	NA	NA
Intensive	June 21	9	0/10	NA	NA

Abbreviations: IV, intravenous; NA, not applicable; PFGE, pulsed-field gel electrophoresis.

In an attempt to eliminate the environmental VRE from the MICU, the decision was made to clean the rooms by following a more thorough cleaning protocol that took approximately 4 hours to complete. After this procedure, no environmental samples (10 per room) were positive for VRE.

RISK FACTORS FOR VRE ACQUISITION

Univariate analysis of putative risk factors present on admission and during the MICU stay is shown in **Table 2** and **Table 3**, respectively. On admission, cases and controls did not differ in terms of age, sex, number of admissions to the hospital or to the MICU in the past year, number or type of underlying diseases, APACHE II score, the McCabe prognosis score, or the presence of shock or neutropenia. However, patients who acquired VRE were significantly more likely to stay longer than 1 week in the hospital before admission to the MICU ($P=.009$); to have acute respiratory failure, sepsis, or multiple organ failure on admission ($P=.048$); and to receive vancomycin ($P=.02$), cephalosporins ($P=.03$), quinolones ($P=.006$), and other antibiotics ($P=.006$) within the month before MICU admission. As a whole, 24 cases (80%) had received some antibiotic compared with only 23 controls (38%) ($P=.001$). A tendency to be hospitalized due to an infectious disease was also noted ($P=.09$).

During MICU stay, more cases than controls were placed in the high-risk room ($P=.06$), had a central venous line ($P=.05$), and received vancomycin ($P=.02$), metronidazole ($P=.03$), other antibiotics ($P=.003$), and more than 1 antibiotic ($P=.002$). However, when exposure to antibiotics was measured as duration of therapy, only vancomycin ($P=.045$) and other antibiotics ($P=.06$) were administered for a longer period to cases than controls. In addition, patients who acquired VRE were more likely to receive vancomycin ($P=.003$), cephalosporins ($P=.06$), metronidazole ($P=.009$), other antibiotics ($P=.002$), and more than 1 antibiotic ($P=.002$) before or after MICU admission. No other exposures during the MICU stay were associated with VRE acquisition.

Multivariable conditional logistic regression analysis identified the following 4 variables as being the best independent risk factors associated with VRE acquisition: the administration of vancomycin before or after MICU admission ($P=.03$), having received quinolones before admission to the MICU ($P=.03$), a stay of longer than 1 week in the hospital before transfer to the MICU ($P=.04$), and location in a high-risk room ($P=.02$) (**Table 4**).

COMMENT

In our study sample of critically ill patients, length of hospitalization before MICU admission, use of quinolones before MICU admission, administration of vancomycin before or during MICU admission, and placement in a particular room were the most important predictors for VRE acquisition.

Despite the outstanding role that the hands of personnel have in VRE cross-transmission, some outbreaks of VRE have been linked to fomites such as thermometers[48,49] or fluidized beds,[50] and it is well known that many surfaces in the rooms of colonized or infected patients may become contaminated, particularly if patients have diarrhea.[14] However, it has been difficult to prove that this kind of surface contamination is an important factor in VRE transmission. Usually, the same strain found in the environment is also present in the gastrointestinal tract of other patients staying at the same time in the ward, which makes it almost impossible to rule out the transmission through the hands of personnel.[26] In the present study, location of patients in a specific room was an independent risk factor for VRE acquisition. The room in question had not any particular characteristic that could make it more likely to be occupied by a specific type of patient. We selected this room on the basis that it contained contaminated items (2 IV pumps) after terminal cleaning as shown by an environmental survey conducted during the study period. The epidemiological link between placement of patients in a particular room and VRE acquisition constitutes new evidence supporting the putative role of environmental contamination on VRE transmission.

Antibiotic administration has been one of the most frequently reported risk factors for VRE colonization or infection. In clinical studies, the drugs more commonly associated with VRE acquisition have been parenteral vancomycin† and cephalosporins,[15,17,22,25,26,32,35] although antibiotics with potent antianaerobic activity,[16,27] aminoglycosides,[20,22,30] and ciprofloxacin hydrochloride[18] have also

†*References 11-13, 15, 17-20, 22, 25, 26, 28, 30, 38.*

Table 2. Univariate Analysis of the Association of Variables Available at MICU Admission With VRE Acquisition*

Variable	Cases (n = 30)	Control Subjects (n = 60)	OR† (95% CI)	*P* Value
Age, mean ± SD, y	61 ± 17	62 ± 18	1.0 (0.97-1.02)	.95
Male	14 (47)	32 (53)	0.8 (0.3-1.9)	.55
Previous hospital days				
None	13 (43)	42 (70)	1.0	
1-7	8 (27)	13 (22)	2.1 (0.7-6.4)	.009
>7	9 (30)	5 (8)	8.7 (1.7-44.3)	
Hospitalizations in the past year	15 (50)	22 (37)	1.7 (0.7-4.0)	.25
Hospital admission for infection	12 (40)	14 (23)	2.6 (0.8-8.0)	.09
MICU admission in past year	3 (10)	5 (8)	1.2 (0.3-5.0)	.81
MICU admission for ARF/sepsis/MOF	20 (67)	26 (43)	2.5 (1.0-6.4)	.048
No. of underlying diseases, mean ± SD	2.1 ± 1.3	1.7 ± 1.1	1.3 (0.9-1.8)	.19
Underlying disease				
Liver cirrhosis	2 (7)	5 (8)	0.9 (0.1-4.1)	.79
Diabetes mellitus	11 (37)	12 (20)	2.4 (0.8-6.1)	.11
COPD	6 (20)	12 (20)	1.0 (0.3-2.9)	>.99
Congestive heart failure	5 (17)	9 (15)	1.2 (0.3-4.0)	.84
Ischemic heart disease	4 (13)	11 (18)	0.6 (0.2-2.5)	.53
Chronic renal failure	4 (13)	7 (12)	1.2 (0.2-6.1)	.80
Prognosis of underlying disease				
Nonfatal	9 (30)	18 (30)	1.0	
Ultimately fatal	16 (53)	38 (63)	0.9 (0.3-2.3)	.38
Rapidly fatal	5 (17)	4 (7)	2.2 (0.5-9.6)	
Shock	7 (23)	7 (12)	2.1 (0.7-6.4)	.18
Neutropenia	3 (10)	2 (3)	3.0 (0.5-18.0)	.23
APACHE II score, mean ± SD	18.1 ± 7.4	17.2 ± 8.0	1.0 (0.9-1.1)	.62
Pre-MICU antibiotics				
Vancomycin hydrochloride	9 (30)	5 (8)	5.1 (1.3-19.2)	.02
Cephalosporins	7 (23)	4 (7)	6.0 (1.2-29.8)	.03
Clindamycin	1 (3)	2 (3)	1.0 (0.1-11.1)	>.99
Metronidazole	3 (10)	3 (5)	2.0 (0.4-9.9)	.40
Combination of penicillins and β-lactamase inhibitors	9 (30)	11 (18)	1.8 (0.6-4.9)	.24
Antianaerobic β-lactams‡	3 (10)	1 (2)	6.0 (0.6-57.7)	.13
Other β-lactams§	1 (3)	2 (3)	1.0 (0.1-11.1)	>.99
Quinolones	10 (33)	4 (7)	8.6 (1.8-39.8)	.006
Other antibiotics‖	12 (40)	6 (10)	4.0 (1.5-10.7)	.006

Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; ARF, acute respiratory failure; CI, confidence interval; COPD, chronic obstructive pulmonary disease; MICU, medical intensive care unit; MOF, multiple organ failure; OR, odds ratio; VRE, vancomycin-resistant enterococci.

*Unless otherwise indicated, data are expressed as number (percentage) of subjects.

†Estimated from conditional regression analysis.

‡Includes cefoxitin sodium and carbapenems.

§Includes penicillin, ampicillin sodium, and oxacillin sodium.

‖Includes macrolides, a combination of trimethoprim and sulfamethoxazole, and aminoglycosides.

been occasionally involved. However, concerning the ICU setting, only two[18,32] of the 4 previous studies[14,18,23,32] in which multivariate analysis was used showed a link between exposure to antibiotics and VRE colonization or infection, and in the most recent study,[32] this association did not reach statistical significance at the 95% confidence level. In these 2 studies, vancomycin, ciprofloxacin, and cephalosporins were the antibiotics involved. The role of vancomycin has been further questioned in a recent meta-analysis,[43] which suggests that the association between previous vancomycin treatment and VRE acquisition may have been magnified in studies that included patients with cultures that were positive for VSE as controls.

The only common characteristic of the antibiotics associated with VRE acquisition is that they lack intrinsic activity against these microorganisms. In experimental[51] and clinical[52] studies, administration of vancomycin and drugs with potent antianaerobic activity (ie, clindamycin, metronidazole, a combination of ticarcillin disodium and clavulanate potassium, a combination of piperacillin sodium and tazobactam sodium, a combination of ampicillin sodium and sulbactam sodium, cefotetan disodium, and meropenem) promotes persisting high-density intestinal colonization, whereas antibiotics with less or negligible antianaerobic activity (ie, dicloxacillin sodium, cephalexin hydrochloride, ceftriaxone sodium, cefepime hydrochloride, aztreonam, quinolones, and a combination of trimethoprim and sulfamethoxazole) do not. However, in the clinical setting and with respect to some antibiotics, there is not a good correlation between their influence on the intestinal anaerobic flora and the association with VRE acquisition. In fact, our data and those of others have demonstrated an independent association of quinolone administration with VRE colonization. On the other hand, clinical evidence suggests that combined piperacillin-tazobactam, a potent antianaerobic antibiotic, may protect against VRE

Table 3. Univariate Analysis of the Association of Variables Available During MICU Admission With VRE Acquisition*

Variable	Cases (n = 30)	Control Subjects (n = 60)	OR† (95% CI)	*P* Value
High-risk MICU room	4 (13)	1 (2)	8.0 (0.9-71.2)	.06
Diarrhea	14 (47)	27 (45)	1.1 (0.4-2.5)	.89
Antacids	1 (3)	3 (5)	0.7 (0.1-6.4)	.73
Antihistamine/omeprazole sodium	28 (93)	54 (90)	1.6 (0.3-8.6)	.60
Sucralfate	1 (3)	9 (15)	0.2 (0-1.6)	.14
Corticosteroids	12 (40)	23 (38)	1.1 (0.4-2.6)	.89
Chemotherapy	4 (13)	2 (3)	4.0 (0.7-21.8)	.11
Cyclosporine	3 (10)	3 (5)	2.0 (0.4-9.9)	.40
Surgery	3 (10)	12 (20)	0.5 (0.1-1.7)	.25
Endoscopy	6 (20)	13 (22)	0.9 (0.3-2.5)	.87
GI contrast procedures	8 (27)	18 (30)	0.9 (0.3-2.2)	.75
Blood products	22 (73)	38 (63)	1.6 (0.6-4.4)	.34
Mechanical ventilation	24 (80)	43 (72)	1.6 (0.5-5.0)	.39
Urinary catheter	29 (97)	52 (87)	4.5 (0.5-38.7)	.17
Nasogastric tube	25 (83)	47 (78)	1.4 (0.4-4.9)	.56
Rectal tube	6 (20)	19 (32)	0.5 (0.2-1.5)	.21
Hemodialysis	5 (17)	5 (8)	2.0 (0.5-6.9)	.28
Enteral feeding	18 (60)	28 (47)	1.8 (0.7-4.4)	.23
Parenteral nutrition	12 (40)	16 (27)	2.1 (0.7-5.9)	.18
Central line	28 (93)	45 (75)	7.9 (1.0-63.6)	.052
Colonization pressure, mean ± SD	35.3 ± 14.0	31.3 ± 15.2	1.0 (0.9-1.1)	.27
Antibiotics in MICU, mean ± SD‡				
Vancomycin hydrochloride	3.7 ± 5.1	2.0 ± 4	1.2 (1.0-1.4)	.045
Cephalosporins	2.3 ± 4	1.4 ± 3.6	1.1 (0.9-1.2)	.29
Metronidazole	2.5 ± 3.9	1.7 ± 4.6	1.0 (0.9-1.2)	.41
Clindamycin	0.0 ± 0.2	0.2 ± 1.1	0.7 (0.2-2.2)	.57
Combination of penicillin and β-lactamase inhibitors	2.1 ± 4.7	2.5 ± 3.6	1.0 (0.8-1.1)	.64
Antianaerobic β-lactams§	0.4 ± 1.4	0.3 ± 1.7	1.1 (0.7-1.5)	.67
Other β-lactams‖	1.0 ± 3	0.8 ± 3.1	1.0 (0.8-1.2)	.72
Quinolones	2.8 ± 4.8	2.2 ± 3.4	1.0 (0.9-1.2)	.44
Other antibiotics¶	2.0 ± 3	0.8 ± 2.7	1.2 (0.9-1.5)	.06
Antibiotics in MICU				
Vancomycin	17 (57)	19 (32)	3.4 (1.2-9.7)	.02
Cephalosporins	10 (33)	12 (20)	1.9 (0.7-5.0)	.19
Metronidazole	12 (40)	11 (18)	3.0 (1.0-8.4)	.03
Clindamycin	1 (3)	2 (3)	1.0 (0.1-11.1)	>.99
Combined penicillin and β-lactamase inhibitors	11 (37)	26 (43)	0.8 (0.3-1.9)	.58
Antianaerobic β-lactams§	3 (10)	2 (3)	4.6 (0.4-46.9)	.20
Other β-lactams‖	4 (13)	7 (12)	1.2 (0.3-4.3)	.83
Quinolones	11 (37)	27 (45)	0.7 (0.3-1.7)	.48
Other antibiotics¶	14 (47)	9 (15)	6.8 (1.9-24.4)	.003
No. of different antibiotics in MICU				
0-1	4 (13)	29 (48)	1.0	
2-3	17 (57)	19 (32)	7.7 (1.7-34.9)	.002
4-6	9 (30)	12 (20)	8.9 (1.6-49.7)	
Antibiotics given in or before MICU				
Vancomycin	20 (67)	19 (32)	6.7 (1.9-23.5)	.003
Cephalosporins	13 (43)	14 (23)	2.4 (0.9-6.0)	.06
Metronidazole	14 (47)	11 (18)	3.7 (1.3-9.8)	.009
Clindamycin	1 (3)	3 (5)	0.7 (0.6-6.4)	.73
Combined penicillin and β-lactamase inhibitors	14 (47)	29 (48)	0.9 (0.4-2.2)	.89
Antianaerobic β-lactams§	4 (13)	2 (3)	6.6 (0.7-61.0)	.10
Other β-lactams‖	4 (13)	9 (15)	0.9 (0.2-3.0)	.84
Quinolones	15 (50)	27 (45)	1.2 (0.5-2.9)	.66
Other antibiotics¶	18 (60)	11 (18)	8.8 (2.5-30.5)	.001

Abbreviations: CI, confidence interval; GI, gastrointestinal; MICU, medical intensive care unit; OR, odds ratio; VRE, vancomycin-resistant enterococci.
*Unless otherwise specified, data are expressed as number (percentage) of subjects.
†Estimated from conditional regression analysis.
‡Includes from MICU day 1 through case censor day.
§Includes cefoxitin sodium and carbapenems.
‖Includes penicillin, ampicillin sodium, and oxacillin sodium.
¶Includes macrolides, a combination of trimethoprim and sulfamethoxazole, and aminoglycosides.

colonization if used instead of third-generation cephalosporins.[53,54] Some experimental data support that the piperacillin-tazobactam combination does not promote persisting high-density intestinal colonization after gas-

tric inoculation of small numbers of VRE.[55] This has been attributed to the possibility that the minimum inhibitory concentration of combined piperacillin-tazobactam for VRE may be below the concentration reached by this drug in the intestinal lumen after regular parenteral dosage. In our study, no difference was found in pre- or post-MICU exposure to combinations of penicillins with β-lactamase inhibitors between cases and controls.

The present study provides additional evidence that exposure to antibiotics has a role on the acquisition of VRE in the ICU setting that cannot be attributed to the selection of patients with VSE as controls. In our study, exposure to different antibiotics was explored as occurring before, after, or at any time during MICU admission, and the most significant associations included the use of quinolones before MICU admission and the administration of IV vancomycin at any given time before or after MICU admission. An interesting derivation from our data is that the conditioning effect of antibiotics on patients, which predisposes them to VRE acquisition, may occur before the admission to the clinical setting where VRE is endemic. This finding raises the question that in units where a high proportion of admitted patients have previously received antibiotics, the impact of a restrictive antibiotic policy on the VRE endemic prevalence may be less than expected.

Another variable of importance that we found to explain VRE acquisition was a pre-MICU hospitalization of longer than 1 week, but this variable may be a surrogate marker of a confounding factor that remained unidentified. Longer hospitalization is usually associated with a poor clinical condition, hospital complications, and as occurred in our study population, more frequent administration of antibiotics. In our logistic model, we did not include the intake of any antibiotic before MICU admission as an explanatory variable to explore the relative influence of different antibiotics. However, cases were exposed more frequently than controls to any kind of antibiotics, with the exception of clindamycin and other β-lactams. Therefore, we believe that antibiotics are still the most probable factor explaining the conditioning effect of a prolonged hospitalization on VRE acquisition after MICU admission.

Inherent drawbacks of this study are its moderate sample size and the retrospective retrieval of clinical and epidemiological data. In addition, the relative low rate of compliance with the surveillance protocol and the weekly interval of follow-up surveillance cultures may have added some decreased rates in the estimate of colonization pressure. The range of colonization pressure values observed in this study was similar to that of the investigation in which this variable was first described,[32] but we did not find it to be a useful predictor for VRE acquisition. Another potential shortcoming of our study may relate to the information bias derived from the limited sensitivity of our screening procedure to detect low-density VRE gastrointestinal tract colonization. In this regard, it has been pointed out recently[56] that rectal swab cultures may have only a 58% sensitivity, ranging from 100% at VRE densities of at least 7.5 logarithm_{10} colony-forming units per gram of stool to 0% at densities of no greater than 4.5 logarithm_{10} colony-forming units per gram. Therefore, we cannot rule out that a small proportion of patients included in our study were already colonized on admission to the MICU. We do not believe that the lack of sensitivity of the screening procedure had any significant influence on the association of VRE acquisition with a particular room, because the likelihood of being a carrier with false-negative VRE findings was probably the same for all the patients occupying that room.

Table 4. Multivariable Conditional Logistic Regression Model Explaining the Acquisition of VRE

Variable	OR (95% CI)	*P* Value
Hospitalization longer than 1 week before MICU admission	18.5 (1.1-301.0)	.04
Administration of vancomycin before or during MICU admission	6.3 (1.2-34.0)	.03
Administration of quinolones before or during MICU admission	14.8 (1.2-180.0)	.04
Location in a high-risk MICU room	81.7 (2.2-3092.0)	.02

Abbreviations: CI, confidence interval; MICU, medical intensive care unit; OR, odds ratio; VRE, vancomycin-resistant enterococci.

CONCLUSIONS

A prolonged hospitalization and the administration of quinolones before MICU admission are important conditioning factors for the later acquisition of VRE; parenteral vancomycin has a substantial influence on VRE acquisition, and the epidemiological link between placement of patients in a particular room and acquisition of VRE supports the putative role of environmental contamination on VRE transmission.

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Corresponding author and reprints: David R. Snydman, MD, Department of Medicine, New England Medical Center, 750 Washington St, Box 238, Boston, MA 02111 (e-mail: dsnydman@Tufts-nemc.org).

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