MAJOR ARTICLE

Effect of Gastrointestinal Bleeding and Oral Medications on Acquisition of Vancomycin-Resistant *Enterococcus faecium* in Hospitalized Patients

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There has been minimal investigation of medications that affect gastrointestinal function as potential risk factors for the acquisition of vancomycin-resistant enterococci (VRE). We performed a retrospective case-control study, with control subjects matched to case patients by time and location of hospitalization. Strict exclusion criteria were applied to ensure that only case patients with a known time of acquisition of VRE were included. Control patients were patients with ⩾1 culture negative for VRE. The risk factors identified were use of vancomycin (odds ratio [OR], 3.2; 95% confidence interval [CI], 1.7–6.0; $P = .0003$), presence of central venous lines (OR, 2.2; 95% CI, 1.04–4.6; $P = .04$), and use of antacids (OR, 2.9; 95% CI, 1.5–5.6; $P = .002$). Two protective factors included gastrointestinal bleeding (OR, 0.26; 95% CI, 0.08–0.79; $P = .02$) and use of Vicodin (Knoll Labs; hydrocodone and acetaminophen; OR, 0.93; 95% CI, 0.90–0.97; $P = .0003$). Changes in gastrointestinal function, whether due to bleeding or to the effects of oral medications, may affect whether patients become colonized with VRE.

Shortly after the first isolates of vancomycin-resistant enterococci (VRE) were reported by investigators in the United Kingdom [1], similar strains were detected in a hospital in France and in New York City [2, 3]. Subsequently, VRE have spread with unanticipated rapidity and are now encountered by hospitals located in most states [4, 5].

Given the very limited therapeutic options for the treatment of infections due to VRE, the prevention of colonization and infection with VRE assumes great importance. The implementation of effective prevention programs requires a detailed understanding of the epidemiology of VRE in hospitalized patients. A large amount of the published data on risk factors for the acquisition of VRE are from studies in which the data were subjected only to univariate analysis [6–15]. Ten case-control studies that had been designed to identify risk factors for the acquisition of VRE made use of multivariable analytical techniques [16–25]. In some of these studies, the exact time of onset of the outcome (colonization/infection) was not determined [16–18, 21, 23], patients with cultures positive for vancomycin-sensitive enterococci (VSE) were used as control subjects [17, 23], or control subjects were not well defined [18]. Only 2 of the case-control studies published elsewhere that were analyzed by means of multivariable techniques included use of any medications that affect gastrointestinal function as variables [19, 20].

From February 1994 through December 1998, 313 patients with VRE colonization or infection were iden-

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tified at the University of Texas Medical Branch Hospitals (Galveston). A retrospective case-control study was designed to identify risk factors for the acquisition of vancomycin-resistant *Enterococcus faecium* (VREF), with precise timing of the outcome, the use of control patients who had negative cultures for VREF, and the study of many medications that have some effect on gastrointestinal function.

MATERIALS AND METHODS

The present study was approved by the Institutional Review Board at the University of Texas Medical Branch at Galveston. The study hospital is an 800-bed tertiary care referral hospital. VRE were first isolated at this hospital in February 1994. A surveillance program was implemented by the Department of Healthcare Epidemiology. All patients in high-risk areas (i.e., medical intensive care unit, surgical intensive care unit, neurological intensive care unit, burn intensive care unit, coronary care unit, HIV unit, and units for hospitalized inmates of the Texas Department of Criminal Justice) were screened weekly for VRE colonization by culture of perianal swabs. All clinical VRE isolates were reported to the Department of Healthcare Epidemiology by the clinical microbiology laboratory. Surveillance cultures were processed in the laboratory of the Department of Healthcare Epidemiology.

Patients with VRE colonization/infection were identified from the records of the Department of Healthcare Epidemiology. A case patient was defined as any patient in one of the study units who had $\geqslant$1 VREF-positive culture of a sample from a colonized and/or infected site during the study period. Study units included the units listed above, which were routinely screened for VRE. Cases of infection were defined according to criteria by the Centers for Disease Control and Prevention (CDC) published elsewhere [26]. To control for differences in exposures and patient care practices among the study units, case patients and control patients were matched according to location and time of hospitalization. Control patients were defined as patients who were hospitalized in the same unit and found to have VRE-negative cultures (all clinical and surveillance cultures) 1 month before through 1 month after the date of the first positive culture for VRE in the case patient. By use of this definition, a pool of possible control patients for each case patient was created, and 2 control patients were chosen from this pool for each case patient by use of a randomization table created by Microsoft Excel 1997.

Because the objective of the study was to identify risk factors that affected the outcome (i.e., acquisition of VRE in hospitalized patients), exclusion criteria were defined carefully, and all patients for whom the exact time of VRE acquisition could not be determined were excluded from the study. The following patients were excluded from the study: patients with VRE isolates other than *E. faecium* on clinical or surveillance cultures; patients who provided samples for culture during the first 48 h after admission, the results of which were found to be VRE positive; patients with cultures positive for VRE from units where VRE may have been present but where no surveillance cultures for VRE had been performed; patients with multiple admissions to one of the units where VRE were known to be present but who did not provide samples for culture at every admission, thus making it impossible to determine the precise time of VRE acquisition; outpatients; patients admitted from long-term care facilities or nursing homes; patients undergoing chronic hemodialysis; and patients who had enterostomy or gastrostomy at the time of admission (because of concern that patients with a chronic enterostomy may have an inherently different and undefined risk for colonization with VRE). Patients undergoing chronic hemodialysis and those with gastrostomy or enterostomy at admission were also not chosen as control patients.

By use of standardized forms for data collection, the charts of case and control patients were reviewed to obtain information regarding the following variables: age; sex; race; date of admission to the hospital; date of discharge or death; unit where the patient was located when cultures were performed; whether the patient had infection or only colonization; comorbidities; nasogastric tube (NGT), Dobhoff tube (DHT), and rectal tube placements (total number of tube days and number of insertions); enteric feedings (type and duration); diarrhea (defined as $\geqslant$2 unformed stools in a 24-h period); arterial and central venous lines (number of insertions); endoscopies (type); operations (elective and emergent intra-abdominal operations, laparoscopic intra-abdominal operations, and other major operations); endotracheal intubations (number of intubations); use of steroids, histamine type 2 (H_2) blockers, antacids, sucralfate and proton-pump inhibitors (including duration of treatment), stool softeners (docusate), laxatives (lactulose and bisacodyl), antidiarrheals (diphenoxylate, loperamide, and kaolin-pectin suspension), opiate agonists (morphine, meperidine, Vicodin [Knoll Labs; hydrocodone and acetaminophen], levorphanol, or hydromorphone), and antimotility agents (metoclopramide or cisapride); and oral and parenteral antimicrobial therapy (name of the antibiotic and duration of therapy). For stool softeners, laxatives, antidiarrheals, opiate agonists, and antimotility agents, both the duration of treatment and total daily doses were recorded. Data on all variables were collected from the date of admission to the hospital until the day before the first positive VREF culture (for case patients) and for the duration of hospitalization (for control patients).

Comorbidities were grouped and included nosocomial infection, community-acquired infection, HIV/AIDS (with and without opportunistic infections), hematologic malignancy, solid-organ malignancy, systemic hypertension, renal failure,

hepatic failure, pulmonary disease, cardiac disease, neutropenia, alcohol and/or drug dependency, psychiatric disorders, neurological disease, collagen vascular disease, arterial embolism, second- and/or third-degree burn, transplantation, shock not associated with any other condition, gastrointestinal bleeding, and other diagnoses.

Microbiology. Samples for perianal culture were obtained with sterile swabs moistened in nonbacteriostatic sterile saline. Swabs were broken off into tubes of trypticase soy broth that contained 6 μg/mL vancomycin and 8 μg/mL ciprofloxacin. The trypticase soy broth was incubated at 36°C and examined at 24 h, 48 h, and 72 h. Cloudy broths were subcultured onto Enterococcosel agar (Becton Dickinson) that contained 6 μg/mL vancomycin and 8 μg/mL ciprofloxacin. Plates were incubated at 36°C and examined at 24 h and 48 h. Microorganisms that hydrolyzed esculin were subcultured onto blood agar for confirmation and further testing. Suspect microorganisms were presumptively identified by use of the PYR test (ability to hydrolyze 1-pyrrolidonyl-β naphthylamide; PYRdisc; Remel), and further identified by using the API20STREP (bioMérieux). The E-test (antimicrobial gradient strip; AB Biodisk) was used to determine the MICs of vancomycin and teicoplanin. The *vanA* resistance phenotype was defined according to Arthur and Courvalin [27] as an MIC of ⩾64 μg/mL for vancomycin and ⩾16 μg/mL for teicoplanin. The *vanB* phenotype was defined as an MIC of 4–1000 μg/mL for vancomycin and 0.5–1 μg/mL for teicoplanin.

Data entry. Data were entered into a Microsoft Access 97 database and then entered a second time into a duplicate database. An Access module was developed that compared the 2 data sets, and the data were corrected until the 2 sets were identical. Queries were then used to create summary variables for statistical analysis.

Statistical analysis. Univariate statistical analyses were conducted for matched comparisons of case and control patients. For binary categorical variables, Mantel-Haenszel ORs and 95% CIs were computed. For continuous variables, a conditional logistic model was conducted with the case/control status as the outcome variable and the continuous variable of interest as the sole predictor variable. ORs and 95% CIs were estimated.

Conditional logistic regression with the binary outcome variable of case/control status was conducted to identify significant predictor variables for several types of models. Forward selection and backward elimination strategies were used when starting with a hypothetical model. For the forward selection procedure, the significance level for entry into the model was .10, whereas the significance level for staying in the model was .05. We performed a best-subsets analysis that included variables with $P \leqslant .2$ on univariate analysis. Variables entered the model using a criterion of $P < .10$ and were kept in the model at the $P < .05$ level. For this number of variables, the 4 subsets of variables with the highest likelihood-score statistic were identified. All reported P values are 2-sided.

An evaluation was made of the assumption that the continuous variable is linear in the logit by evaluating the fit of the squared and cubed terms. If the squared or cubed terms were significant, then the assumption of linearity was considered to be violated, and the categorical variable was used in its place. Final models included variables significant at the $P < .05$ level. All statistical analyses were performed with the PHREG and FREQ procedures using SAS statistical software (SAS Institute).

RESULTS

From February 1994 through December 1998, 313 hospitalized patients with VRE were identified. According to our exclusion criteria, only 103 of these VRE-positive patients were included in the study and matched with appropriate control patients. Eighty-three case patients could be matched with 2 control patients each (166 VRE-negative control patients). Only 1 control patient could be identified for each of the remaining 20 case patients. Of the 103 VREF isolates, 93 were recovered from routine surveillance cultures (perianal swabs) and 10 were clinical isolates. Eighty-one isolates were of the *vanA* phenotype and 22 were of the *vanB* phenotype. According to CDC criteria, only 1 case patient had an infection with VREF (in the urinary tract) [26].

The results of the univariate analyses for categorical and continuous variables are shown in tables 1 and 2. For multivariable analysis, 3 different approaches were used in developing models. The first approach was based on the results of published case-control studies of VRE available at the time that our study was designed. Variables that were found to be significant on multivariable analysis in these studies were chosen for the development of our model [17–19]. These variables included the duration of hospitalization (number of days from admission to the first positive culture for case patients/duration of hospitalization for control patients) and receipt of vancomycin, third-generation cephalosporins, and enteric feedings. Table 3 shows the results of multivariable analysis when only these 4 variables were included.

We kept these variables in the model. We chose other variables with $P \leqslant .2$ on the univariate analysis or that were theoretically important variables, and we allowed them to enter the model by using forward selection and backward elimination. We deleted some of the variables from the model because of wide 95% CIs or a lack of theoretical rationale (protective effect of arterial lines and oral antibiotics). The model was repeated after removing these variables, and nonsignificant variables (i.e., intra-abdominal operations, receipt of enteric feedings, use of aminopenicillins, use of third-generation cepha-

Table 1. Categorical variables on univariate analysis in a study of vancomycin-resistant *Enterococcus faecium* in hospitalized patients.

Variable	No. (%) of case patients (n = 103)	No. (%) of control patients (n = 186)	OR (95% CI)	P
More than 5 comorbidities	37 (35.9)	40 (21.5)	2.04 (1.2–3.5)	.01
Gastrointestinal bleeding	8 (7.8)	27 (14.5)	0.4 (0.2–1.1)	.07
Nasogastric tube placement	87 (84.5)	121 (65.1)	3.9 (2.0–7.8)	.001
Dobhoff tube placement	62 (60.2)	64 (34.4)	2.9 (1.8–4.8)	.001
Receipt of enteric feedings	64 (62.1)	72 (38.7)	2.8 (1.6–4.7)	.001
Use of intravascular devices				
Arterial lines	85 (82.5)	136 (73.1)	2.4 (1.2–4.8)	.01
Central venous lines	87 (84.5)	130 (69.9)	2.6 (1.3–5.0)	.005
Intra-abdominal operations	23 (22.3)	29 (15.6)	1.6 (0.8–3.0)	.16
Use of histamine type 2 blockers	84 (81.6)	145 (78.0)	1.3 (0.7–2.4)	.44
Use of antacids	50 (48.5)	54 (29.0)	2.4 (1.4–3.9)	.001
Use of opiate agonists				
Morphine	79 (76.7)	147 (79.0)	0.8 (0.4–1.5)	.44
Meperidine	18 (17.5)	33 (17.7)	1.0 (0.5–1.8)	.91
Vicodin[a]	21 (20.4)	86 (46.2)	0.3 (0.1–0.5)	.001
Use of parenteral antimicrobial therapy	100 (97.1)	163 (87.6)	6.1 (1.7–21.6)	.005
Aminopenicillins with and without β-lactamase inhibitors[b]	33 (32.0)	44 (23.7)	1.6 (0.9–2.8)	.11
Third-generation cephalosporins[c]	59 (57.3)	70 (37.6)	2.1 (1.3–3.4)	.002
Metronidazole	23 (22.3)	15 (8.1)	3.2 (1.6–6.4)	.001
Clindamycin	34 (33.0)	46 (24.7)	1.6 (0.9–2.8)	.10
Vancomycin	68 (66.0)	66 (35.5)	3.6 (2.1–6.0)	.001
Use of oral antimicrobial therapy	28 (27.2)	81 (43.6)	0.5 (0.3–0.8)	.006

[a] Knoll Labs; acetaminophen and hydrocodone.
[b] Ampicillin and ampicillin-sulbactam.
[c] Ceftriaxone and ceftazidime.

losporins, and the duration from admission to the hospital to the first positive culture for case patients/duration of hospitalization for control patients) were deleted. This resulted in the model with 5 variables shown in table 4. An increase in the protective effect of Vicodin was observed with increasing doses.

After completion of the first model, starting with risk factors from published studies, we developed a second empirical model by selecting variables from 2 groups of potential risk factors for acquisition of VRE in hospitalized patients. These 2 groups included factors that affect the host before the transmission of VRE that may make the host more susceptible to colonization with VRE and factors that affect the transmission of VRE to the patient. We reviewed the results of univariate analysis and selected variables from the latter 2 groups that we believed were theoretically most important and statistically significant on univariate analysis. The 5 variables we considered potentially most important in VRE acquisition were presence of a NGT, presence of a DHT, use of antacids, use of vancomycin, and receipt of enteric feedings. Because NGT presence and DHT presence were not found to be collinear, they were tested as individual variables in the model. The initial model that results when this approach is used is shown in table 5. We chose the variables that were significant or borderline significant in this model as our core model (NGT presence, antacid use, and vancomycin use). Then a second set of 4 variables was chosen from the potential risk factors noted above. These included gastrointestinal bleeding, comorbidities, metronidazole use, and clindamycin use. Each of the second set of 4 variables and the variable duration to the first positive culture for case patients/duration of hospitalization for control patients was added 1 at a time to the core model. These variables were also tested together by keeping the core model constant and running forward selection and backward elimination. Both the duration to first positive culture for case patients/duration of hospitalization for control patients and gastrointestinal bleeding entered the model (table 6). The 2 variables in our literature-based model that were not in the model shown in table 6 (presence of central venous lines and Vicodin use) were then tested in the latter model. These variables entered the model to the exclusion of the variables

Table 2. Continuous variables on univariate analysis in a study of vancomycin-resistant *Enterococcus faecium* in hospitalized patients.

Variable	Mean value ± SD		P
	Case patients (n = 103)	Control patients (n = 186)	
No. of days from hospital admission to the first positive culture result, for case patients, and duration of hospitalization, for control patients	22.2 ± 19.5	25.8 ± 32.9	.29
Comorbidities	4.4 ± 2.4	3.8 ± 2.4	.02
No. of nasogastric tube insertions	1.4 ± 1.2	1.0 ± 1.0	.01
No. of Dobhoff tube insertions	1.1 ± 1.4	0.7 ± 1.3	.02
No. of arterial line placements	2.1 ± 1.7	1.7 ± 1.9	.06
No. of central venous line placements	2.2 ± 1.8	1.7 ± 2.1	.02
Morphine therapy			
Duration, days	8.4 ± 9.6	8.5 ± 12.9	.80
Daily dose, mg	20.8 ± 38.0	13.1 ± 18.2	.02
Meperidine therapy			
Duration, days	1.5 ± 6.0	1.9 ± 13.5	.75
Daily dose, mg	18.6 ± 54.6	15.1 ± 40.9	.58
Vicodin therapy[a]			
Duration, days	0.6 ± 1.6	3.9 ± 11.3	.0002
Daily dose,[b] mg	3.3 ± 7.4	9.2 ± 11.9	.0001
Duration of parenteral antibiotic therapy, days			
Third-generation cephalosporins[c]	5.3 ± 7.9	4.0 ± 7.3	.25
Metronidazole	2.0 ± 5.1	0.7 ± 2.8	.02
Clindamycin	3.0 ± 6.3	2.2 ± 5.5	.26
Vancomycin	6.9 ± 10.3	5.5 ± 12.7	.38

[a] Knoll Labs; acetaminophen and hydrocodone.
[b] On the basis of the hydrocodone dose.
[c] Ceftriaxone or ceftazidime.

NGT placement and duration to first positive culture for case patients/duration of hospitalization for control patients, giving rise to the same model as that developed by the literature-based approach (table 4).

As a third approach to multivariable analysis, we used variables from univariate analysis and conducted a best-subsets analysis according to the likelihood-score statistic. The computer algorithm created 4 models, each of which included 5 variables. The model with the best score was exactly the same as the literature-based model and empirical model (table 4).

DISCUSSION

Our data were analyzed by use of multivariable techniques, but we believe that other elements of study design were equally important in the accurate identification of risk factors for the acquisition of VRE. These included the precise determination of the time of acquisition of VRE, to avoid collecting data on risk factors after the occurrence of the outcome, and the use of control patients who had negative cultures for VRE. In 5 (group 1) of the 10 published studies analyzed by use of multivariable techniques, the time of acquisition of VRE was not accurately determined [16–18, 21, 23]. In 2 of the studies, VSE-positive patients were used as control subjects [17, 23]; in 2 studies, patients who were culture-negative for VRE were used as control subjects [16, 21]; and in the other study, control patients were not clearly defined [18]. In the remaining 5 case-control studies (group 2), the time of acquisition of VRE was

Table 3. Findings of the initial literature-based model in a study of vancomycin-resistant *Enterococcus faecium* in hospitalized patients.

Variable	OR (95% CI)	P
No. of days from hospital admission to the first positive culture result, for case patients, and duration of hospitalization, for control patients	0.97 (0.96–0.99)	.0009
Vancomycin use	3.6 (1.8–7.1)	.0003
Use of third-generation cephalosporins	1.8 (0.96–3.5)	.07
Receipt of enteric feeding	2.5 (1.3–4.9)	.008

Table 4. Findings of the final model on multivariable analysis in a study of vancomycin-resistant *Enterococcus faecium* in hospitalized patients.

Variable	OR (95% CI)	*P*
Vancomycin use	3.2 (1.7–6.0)	.0003
Gastrointestinal bleeding	0.26 (0.08–0.79)	.02
Presence of central venous lines	2.2 (1.04–4.6)	.04
Antacid use	2.9 (1.5–5.6)	.002
Mean daily dose of Vicodin[a]		
100 mg acetaminophen/1 mg hydrocodone	0.93 (0.90–0.97)	.0003
500 mg acetaminophen/5 mg hydrocodone	0.71 (0.59–0.85)	
1000 mg acetaminophen/10 mg hydrocodone	0.50 (0.34–0.73)	
1500 mg acetaminophen/15 mg hydrocodone	0.35 (0.20–0.62)	
2000 mg acetaminophen/20 mg hydrocodone	0.25 (0.12–0.53)	

[a] Knoll Labs; acetaminophen and hydrocodone.

precisely determined, and patients who had negative cultures for VRE were used as control subjects [19, 20, 22, 24, 25].

We studied most medications that affect gastrointestinal function. We identified use of antacids as a risk factor and use of Vicodin (hydrocodone and acetaminophen) as a protective factor against the acquisition of VRE. We confirmed antacid use as a risk factor after we had identified it as a risk factor for the acquisition of VRE in an outbreak in our burn unit [28]. By decreasing gastric acidity, antacids may create a medium suitable for colonization by VRE. On the other hand, H_2 blockers have a similar effect on gastric pH, and they were not found to be significantly associated with the acquisition of VRE in either our study or the study by Slaughter et al. [19]. It is also possible that other effects of antacids may increase the risk of colonization by VRE, and this possible relationship needs further investigation.

When selecting potential risk factors for inclusion in the study, we chose use of Vicodin and other drugs that decrease gastrointestinal motility, reasoning that slowed motility might promote colonization with VRE. However, both univariate and multivariable analyses revealed that Vicodin had a protective effect. We were unable to find information about hydrocodone in the literature that could explain this observation. Because Vicodin is a combined preparation of acetaminophen and hydrocodone, we also investigated a possible effect of acetaminophen. Acetaminophen has been shown to be a scavenger of superoxide radicals [29]. There are ⩾2 published reports that have described enterococcal cell extracts and whole microorganisms that generate superoxide radicals [30, 31]. Under appropriate conditions, superoxide radicals can lead to the generation of powerful oxidants, such as hydrogen peroxide and hydroxide radicals [32]. The role of superoxide production in the pathogenicity of enterococci has not yet been established. However, in a study designed to investigate whether superoxide production by enterococci augments the pathogenicity of these microorganisms, results suggested that there was an association between invasiveness and extracellular superoxide production [33]. Taking these observations into consideration, it might be speculated that acetaminophen, acting as a scavenger for superoxide radicals, may antagonize or prevent VRE colonization. There might also be an unknown interaction between acetaminophen and hydrocodone that provides a protective effect against VRE colonization. This finding needs further investigation.

The protective effect of gastrointestinal bleeding on VRE acquisition may be related to the strong cathartic effect of blood in the intestinal lumen. Ours is the first study to have shown that gastrointestinal bleeding is a protective factor against VRE acquisition; this needs to be supported by further studies.

In spite of many similarities in design between our study and those in group 2, we noted a significant association between vancomycin use and acquisition of VRE, whereas only 1 of the 5 studies in the latter group observed such an association. In a meta-analysis that assessed the association between treatment with vancomycin and acquisition of VRE in the hospital, Carmeli et al. [34] concluded that one could account for the reported strong association between treatment with vancomycin and hospital acquisition of VRE by selection of an inappropriate reference group (e.g., patients colonized or infected with VSE) and failure to control for confounding due to the duration of

Table 5. Findings of the initial empirical model in a study of vancomycin-resistant *Enterococcus faecium* in hospitalized patients.

Variable	OR (95% CI)	*P*
Dobhoff tube placement	1.4 (0.5–3.4)	.51
Nasogastric tube placement	2.2 (0.94–5.2)	.07
Antacid use	1.9 (1.1–3.6)	.03
Vancomycin use	2.8 (1.5–5.3)	.002
Receipt of enteric feeding	1.0 (0.4–2.6)	.94

Table 6. Results of forward selection and backward elimination with the variables hospital days for case patients/control patients, gastrointestinal bleeding, comorbidities, metronidazole use, and clindamycin use, from the empirical model.

Variable	OR (95% CI)	*P*
Nasogastric tube placement	2.9 (1.2–6.7)	.01
Antacid use	2.0 (1.05–3.8)	.04
Vancomycin use	2.6 (1.3–4.9)	.005
Gastrointestinal bleeding	0.2 (0.07–0.6)	.003
No. of days from hospital admission to the first positive culture result, for case patients, and duration of hospitalization, for control patients	1.01 (1.001–1.02)	.04

hospitalization. However, all of the studies in group 2 and our study used the same type of control patients (i.e., patients with negative cultures for VRE), and each study controlled for the duration of hospitalization. Furthermore, the duration of hospitalization was longer for our control patients than it was for our case patients.

Ours is the first study in the literature in which the presence of central venous lines has been identified as an independent risk factor for VRE acquisition. We used central venous lines as a surrogate for an increased level of contact between patients and health care workers. Although it had an OR of 2.2 (95% CI, 1.0–4.6) in the final model, the lower bound of the 95% CI was 1; thus, this is not a very strong predictor for the acquisition of VRE.

We believe that our multivariable model is robust, given the convergence to the same model by 3 different approaches used in the analysis. However, one potential weakness in our study was the possible exclusion of the sickest patients, because patients with multiple admissions to the hospital were not included if the exact time of VRE acquisition could not be determined. This could have resulted in some selection bias. However, we accepted this risk, because we believed that it was more important to be certain of the time of the outcome (VRE acquisition) to avoid collecting risk-factor data after occurrence of the outcome.

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