The Incidence of and Clinical Variables Associated With Vancomycin-Resistant Enterococcal Colonization in Mechanically Ventilated Patients*

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Study objectives: (1) To determine in our ICU the incidence of vancomycin-resistant enterococcus (VRE) colonization in mechanically ventilated patients without a history of VRE infection or colonization; and (2) to determine the risk factors and outcome variables associated with VRE colonization in these patients.


Setting: Medical and cardiac critical care units in a tertiary care urban university hospital.

Patients: Mechanically ventilated patients without evidence of pneumonia at the onset of ventilation.

Interventions: None.

Measurements and results: Patients underwent rectal cultures by standard methods on day 1, day 3 or 4, day 6 or 7, and day 14 of intubation to detect VRE. Thirteen of 83 patients (16%) had rectal cultures positive for VRE (VRE+) at some point while being mechanically ventilated during their stay in the ICU. In comparison, approximately 15 of 2,100 medical ICU patients (0.7%) had clinical VRE infections as determined by the hospital’s infection control program during a 2-year period. VRE+ patients had a higher incidence of immunosuppression than patients who had rectal cultures negative for VRE (VRE−) (9 of 13 [69%] vs 16 of 70 [23%], respectively; p < 0.01) and neutropenia (4 of 13 [31%] vs 5 of 70 [7%], respectively; p < 0.01). Hospital length of stay (LOS) was longer in VRE+ patients than in VRE− patients (27 ± 17 days vs 17 ± 14 days, respectively; p = 0.05), whereas pre-ICU hospital LOS and ICU LOS were similar in both patient groups. Five of 67 patients (7%) were VRE+ on day 1 of intubation, suggesting colonization at a prior site of care. Three of 29 patients who had subsequent rectal cultures converted to VRE+ while in the ICU. This group had a higher incidence of immunosuppression and neutropenia, and received more vancomycin compared with the patients who remained VRE− (p < 0.01). However, there was no significant difference in the use of other broad-spectrum antibiotics (such as antipseudomonal penicillins, third-generation cephalosporins, quinolones, and clindamycin), enteral tube feedings, or sucralfate between the two groups. In addition, a topical antibiotic paste (a gentamicin, nystatin, polymixin slurry) that was placed in the oropharynx to prevent bacterial overgrowth was not found to increase the incidence of VRE colonization in this patient population.

Conclusions: The incidence of VRE colonization was surprisingly high: 16% in mechanically ventilated patients in a hospital in which VRE was not previously known to be endemic. Risk factors for the acquisition of VRE colonization included immunosuppression, neutropenia, and vancomycin use. Increased LOSs and hospital costs were seen in VRE+ patients compared to VRE− patients. Whether VRE colonization is a contributor to severe disease that leads to prolonged hospitalization and increased resource allocation or whether it is simply a marker of disease severity cannot be determined from this study. To the extent that specific antibiotic protocols are used to reduce antibiotic-resistant flora in the ICU, monitoring the incidence of VRE in the stool specimens of immunocompromised, mechanically ventilated patients can be a simple and useful tool to assess one effect of these strategies. (CHEST 1999; 115:1085–1091)

Key words: colonization; Enterococcus spp; incidence; infection control; mechanical ventilation; risk factors; vancomycin-resistant

Abbreviations: APACHE II = acute physiologic and chronic health evaluation II; GNP = gentamicin, nystatin, polymixin; LOS = length of stay; VRE = vancomycin-resistant enterococcus; VRE− = negative for vancomycin-resistant enterococcus; VRE+ = positive for vancomycin-resistant enterococcus

Strains of vancomycin-resistant enterococcus (VRE) are prominent emerging nosocomial pathogens in the United States.1,2 Treatment of these organisms is difficult because they typically are resistant to multiple antibiotics, including penicillins and aminoglycosides.3 Enterococci are now the sec-
ond most common organism isolated from sites of nosocomial infection in the United States, with a seeming increase in the fraction of isolates resistant to vancomycin. The Centers for Disease Control and Prevention reported an increase in isolation of VRE organisms as a fraction of all enterococci from infected sites from 0.3% in 1989 to 7.9% in 1993, a 20-fold increase in a 5-year period. In 1995, the incidence of VRE infection was estimated to be > 10% of all enterococcal infections in the United States. The rate of increase for VRE isolates in ICUs is reported to be even higher, rate of mortality attributable to VRE infections is significant and has been reported to be between 37% and 50%. With this increasing rate of increase for resistant organisms, strategic measures to decrease the incidence of colonization and infection by these organisms are currently being assessed in clinical trials. To facilitate such trials, information about patient populations at risk and culture methods targeted to these patient populations would be of use. Many of the studies directed at VRE colonization or infection have been retrospective or concerned small numbers of patients in local outbreaks, usually involving patient populations in which VRE infection or colonization is known to be endemic. In one interesting prospective trial of patients admitted to a Chicago ICU, Bonten and colleagues demonstrated a high incidence of VRE colonization (24%) in patients undergoing mechanical ventilation; this rate of colonization was demonstrated by obtaining cultures from six body sites. Rectal cultures alone demonstrated a 6% incidence of VRE colonization in nonmechanically ventilated patients. This surveillance study was conducted because VRE was known to be endemic in this ICU.

Surveillance for VRE infections at our own hospital identified only 15 cases in 2,100 admissions to two medical ICUs from 1995 to 1996. Nonetheless, as part of a study of prevention of ventilator-associated pneumonia, we decided to prospectively collect rectal cultures to determine the incidence of VRE colonization in our patients undergoing mechanical ventilation. In addition to defining the incidence of VRE colonization, we sought to determine associated risk factors and outcome variables.

**Materials and Methods**

This study was conducted in the medical and cardiac ICUs in a large tertiary care urban university hospital from January 1996 to March 1998. All patients were intubated, were mechanically ventilated, and lacked clinical evidence of pneumonia at the time of enrollment in the study. The patients included in this report were part of an investigation evaluating multimodality prophylaxis of ventilator-associated pneumonia. This study enrolled patients who had acute respiratory failure not associated with pneumonia within 24 h of intubation. Patients were randomized to either standard therapy, including GI hemorrhage prophylaxis with an H2 blocker, or to combination therapy to prevent ventilator-associated pneumonia using GI hemorrhage prophylaxis with sucralfate, an oropharyngeal topical antibiotic (a gentamicin, nystatin, polymixin [GNP] slurry), and kinetic bed therapy. For all results reported concerning VRE, patients were combined from both study arms, with the exception of risk analysis for the effect of the oropharyngeal topical antibiotic.

Rectal cultures were obtained using culturette swabs collected on day 1, day 3 or 4, day 6 or 7, and day 14 of intubation. Members of the ICU research team collected the rectal cultures to maintain consistency in the method of collection, and specimens were collected independently of stool output or bowel function. Once a patient was extubated, discharged from the ICU, or died, no further cultures were obtained.

Baseline demographic data, prior antibiotic usage, and previous location of care or residence were recorded for each patient on admission to the ICU. In addition, hospital length of stay (LOS), ICU LOS, and hospital cost were determined. Patients were classified as immunocompromised if they had AIDS, solid organ transplantation, solid organ malignancies undergoing chemotherapy or radiation therapy, hematologic malignancies, bone marrow transplantation, or long-term steroid use of > 20 mg prednisone daily or its equivalent. Neutropenia was defined as an absolute neutrophil count of < 1,000/mm³.

During the same time that this study was conducted, surveillance for VRE infections was performed by infection control practitioners. Clinical microbiology laboratory records were reviewed weekly to identify patients from whom VRE was isolated, and charts of those patients were examined to determine whether the positive cultures represented colonization or infection. Standard National Nosocomial Infection Surveillance definitions of infection were used. The infection control program did not perform surveillance cultures for VRE; all culture-positive cases detected by infection control practitioners were cases in which the cultures were obtained for clinical reasons.

For continuous variables, the mean ± SD was tabulated. All parametric continuous variables were compared by the Student’s t test, and nonparametric categorical variables were compared using the χ² analysis. A p value of < 0.05 was considered significant.

**Rectal Cultures**

Swab specimens were taken from stool or directly from the rectum, were held in aerobic transport media, and were plated onto Columbia CNA agar containing 5% sheep blood (Becton Dickenson Microbiology Systems; Cockeysville, MD) by means of the four-quadrant streaking technique. Plates were incubated aerobically at 35°C for up to 72 h. From each plate, six isolates with colony morphology characteristics of enterococci were initially identified by appearance with Gram’s stain, catalase reaction, and pyrrolidonyl peptidase activity (Murex Diagnostics Limited; Norcross, GA). Each isolate presumptively identified as Enterococcus sp was tested for vancomycin resistance by the Kirby-Bauer disk diffusion method using interpretive standards according to National Committee for Clinical Laboratory Standards guidelines. Each VRE isolate was further identified to species level using tube biochemical testing.
RESULTS

One hundred twenty-three rectal cultures were obtained from 83 patients; 67 cultures were obtained on day 1, 33 on day 3 or 4, 19 on day 6 or 7, and 8 on day 8. Of the 67 cultures obtained on day 1, VRE was isolated from 5. Twenty-nine patients who initially had rectal cultures negative for VRE (VRE2) had subsequent rectal cultures. Three of these patients acquired VRE. No patient converted from having rectal cultures positive for VRE (VRE1) to VRE2 during the period of observation (Fig 1).

Thirteen of 83 patients (16%) were VRE1 at some point while being mechanically ventilated during their stay in the ICU. Five of these patients were VRE1 on day 1; five patients had no culture on day 1 but were VRE1 on the first day that a specimen was obtained; and three patients converted from VRE2 on day 1 to VRE1 sometime thereafter.

Demographic data and patient characteristics for VRE1 patients and VRE2 patients are presented in Table 1. VRE1 patients had a higher incidence of immunosuppression than VRE2 patients (69% vs 23%, respectively; p < 0.01). In addition, VRE1 patients had a higher incidence of neutropenia than VRE2 patients (31% vs 7%, respectively; p < 0.01). Hospital LOS was longer in VRE1 patients than in VRE2 patients (27 ± 17 days vs 17 ± 14 days, respectively; p = 0.05). ICU LOS was similar in both patient groups. In addition, the total hospital cost was increased in the VRE1 group compared with the VRE2 group ($86,091 ± $51,760 vs $47,422 ± $44,086; p = 0.03; Table 1). There was a

Table 1—Comparison of VRE+ Patients and VRE− Patients

<table>
<thead>
<tr>
<th></th>
<th>VRE+ Patients</th>
<th>VRE− Patients</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>49 ± 15*</td>
<td>58 ± 17</td>
<td>0.06</td>
</tr>
<tr>
<td>Gender</td>
<td>5 M/8 F</td>
<td>27 M/43 F</td>
<td>0.99</td>
</tr>
<tr>
<td>APACHE II</td>
<td>22 ± 8</td>
<td>23 ± 8</td>
<td>0.70</td>
</tr>
<tr>
<td>Immunosuppression</td>
<td>9 (69%)</td>
<td>16 (23%)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>4 (31%)</td>
<td>5 (7%)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Hospital charges, $</td>
<td>86,091 ± 51,760</td>
<td>47,422 ± 44,086</td>
<td>0.03</td>
</tr>
<tr>
<td>Hospital LOS, d</td>
<td>27 ± 17</td>
<td>17 ± 14</td>
<td>0.05</td>
</tr>
<tr>
<td>ICU LOS, d</td>
<td>290 ± 192</td>
<td>217 ± 183</td>
<td>0.22</td>
</tr>
<tr>
<td>Mortality</td>
<td>8 (62%)</td>
<td>25 (36%)</td>
<td>0.08</td>
</tr>
</tbody>
</table>

*Values are the mean ± SD.
†M = male; F = female.
‡Values are number of patients that are affected in the group (percentage of group).
trend toward increased mortality in the VRE+ patients compared with the VRE− patients, although this trend did not reach statistical significance (p = 0.08). Mortality attributable to VRE colonization was not assessed in this study.

Of the 67 patients who had rectal cultures performed on day 1 of their intubation, 5 of 67 of these patients (7%) were VRE+. Demographic data and pre-ICU characteristics are shown in Table 2. The VRE+ patients were slightly younger than the VRE− patients (46 ± 9 years vs 57 ± 17 years, respectively; p = 0.05). Of significance, VRE+ patients had a higher incidence of neutropenia on admission to the ICU than the VRE− patients (2 of 5 [40%] vs 4 of 62 [6%]; p < 0.01). The rate of broad-spectrum antibiotic use, including third-generation cephaplorins, antipseudomonal penicillins, clindamycin, and quinolones as well as vancomycin, during the week before intubation was not increased in the group with VRE colonization on the first day of intubation. In addition, there was no significant difference between the two groups in the location of intubation. In addition, there was no significant difference between the two groups. In the group with VRE colonization on the first day of intubation was not significantly different between the two groups.

Three of 29 patients converted from VRE− to VRE+ while intubated at some time during their stay in the ICU. The baseline characteristics of these patients and the characteristics of their ICU stay compared to the other patients with subsequent rectal cultures that remained negative are shown in Table 3. Interestingly, the patients with VRE colonization had a lower acute physiology and chronic health evaluation II (APACHE II) score compared with the patients without VRE colonization (21 ± 0.6 vs 24 ± 8.0, respectively; p = 0.04) All three patients were immunosuppressed and receiving broad-spectrum antibiotics, and two patients were receiving vancomycin during their ICU stay. The VRE+ patients had a higher incidence of immunosuppression and neutropenia than the VRE− patients (p < 0.01). Of the four VRE+ patients, neutropenia had been present 1, 8, 22, and 35 days before their positive culture. More VRE+ patients received vancomycin than did VRE− patients (p < 0.01). However, there was no significant difference in the use of other broad-spectrum antibiotics, enteral tube feedings, or sucralfate between the two groups. In addition, a topical antibiotic paste (a GNP slurry) that was placed in the oropharynx to prevent bacterial overgrowth was not found to increase the incidence of VRE colonization in this patient population. There was no difference in the mortality rate between the two groups.

From 1995 to 1996, the hospital’s infection control program, using the results of cultures obtained for clinical reasons, identified 15 patients in the medical ICU with VRE infection and 4 with VRE colonization. Because approximately 2,100 patients are admitted to our medical ICUs each year, the incidence of VRE infection and colonization in our ICUs detected by routine cultures is approximately 0.7% and 0.2% per year, respectively.

### Discussion

In the mid-1980s, the first clinical isolate of VRE was discovered in Europe. Since that time, VRE...
has become a prominent organism both in Europe and, more recently, in the United States. Documented infections may represent a “tip of the iceberg” phenomenon with a large reservoir of colonized patients in critical care units and other health care environments.6,7 Because the GI tract is a large reservoir that is not often clinically assessed for these organisms, it is possible that it is involved in the nosocomial spread of these organisms. In this study, we found the incidence of GI tract VRE colonization to be 16%, which is higher than the 7 to 10% that has been previously described for all patient populations.6,7 The high incidence of colonization that we encountered is comparable to the incidence rate in mechanically ventilated patients reported by Bonten and colleagues,20 but it could be documented with much simpler culture techniques (single-site rectal cultures as opposed to culturing at six body sites). It is also notable that their study was conducted in an ICU known to have endemic colonization with VRE; our own study began at a time when recent routine culture data suggested an incidence of infection or colonization with VRE of only 0.9%. Admittedly, one interpretation of our results is that the monitoring of routine culture data that was obtained for clinical purposes is not an adequate means of surveillance for VRE, and that the culturing of high-risk patients by protocol may find the organism to be endemic when more casual monitoring had not.

Because of the greater number of VRE+ cultures obtained in this study compared with those VRE+ cultures obtained by routine patient management in our medical ICU, underrecognition of VRE colonization may precipitate further spread and potential infection by resistant organisms. In addition, new studies involving the rotation of antibiotics are currently being done to optimize antibiotic strategies and to decrease the rate of increase for resistant organisms.14,25 Because studies have shown that alternating antibiotic therapies has been successful in reducing resistant organisms recovered from episodes of bacteraemia and ventilator-associated pneumonia, surveillance rectal cultures for VRE colonization in targeted patient populations may provide another end point to use during the implementation of these strategies.

The five patients who were VRE+ on arrival to the medical ICU had a significantly higher incidence of neutropenia compared with VRE− patients. In addition, all 13 patients who were colonized with VRE had a significantly higher incidence of immunosuppression and neutropenia compared with patients who were not colonized with VRE. Although previous studies have identified underlying hospital diagnosis, admission to a hematology/oncology ward, and immunosuppression as risk factors associated with VRE colonization, to our knowledge neutropenia has never been specifically identified.11,26–29 One may speculate that neutropenia is typically associated with a hematology/oncology diagnosis and therefore may be associated with VRE colonization. However, in our patients, there were several underlying diagnoses making it impossible to correlate neutropenia with any specific oncologic diagnosis. Although previously recognized risk factors for VRE colonization including immunosuppression and vancomycin administration may be associated with neutropenia, a multivariate analysis was not performed to determine whether a correlation was present owing to the small number of patients enrolled in this study.

Interestingly, one of the patients colonized with VRE arrived in the ICU from home taking no antibiotics. She had a diagnosis of polymyositis and had been previously on low-dose methotrexate. This patient had been discharged from a long-term facility approximately 8 months before admission. Although the pattern of antibiotic use at this facility is unknown, the most likely source of VRE in this patient is via nosocomial transmission during her stay at this facility. VRE colonization has been described to persist for up to 1 year. It is unlikely that she became colonized from the environment, as there have been no reports of de novo VRE colonization or infection outside the hospital setting in the United States. This is clearly different in Europe where VRE has been isolated from sewage, animal sources, and healthy volunteers without prior hospitalizations.29–33

We demonstrated an increase in hospital LOS, increased hospital costs, and a trend toward increased hospital mortality in VRE+ patients compared with VRE− patients. VRE colonization previously has been associated with longer hospital stays, which is suggestive of increased exposure to VRE.26,34 In this study, although VRE colonization was associated with prolonged hospital stays, this increased LOS did not occur before acquiring VRE, suggesting that VRE colonization was not a result of increased hospital LOS. This association between VRE colonization and increased hospital LOS may reflect a contribution of VRE colonization to worsening disease processes leading to a prolonged hospital course. On the other hand, it may simply reflect that VRE is a surrogate marker of disease severity. This distinction cannot be made from this study.

Scoring for severity of illness as determined by the APACHE II score on admission to the ICU was not increased in VRE+ patients and was even decreased in the patients who converted to VRE+ compared with the patients who remained VRE−. Therefore, APACHE II scores may not reliably identify patients who are colonized with VRE or those who are at risk for acquiring VRE colonization as reported in previ-
eous studies. In addition, APACHE II scores did not correlate with increased hospital stays and increased hospital costs in the VRE+ patient population.

We recognize that there are drawbacks of this study. The number of patients who were either initially colonized with VRE or subsequently became colonized with VRE is small and therefore may not provide the necessary power to determine differences between these two patient populations for certain variables. In addition, it is not possible to perform a multivariate analysis on such a small patient population to detect any associations between variables. Because only a subset of mechanically ventilated patients in our ICU were cultured for VRE, it is impossible to assess the incidence of VRE+ cultures in our entire ICU patient population. Accordingly, risk factors and nosocomial transmission by cross-contamination of VRE cannot be determined from this study.

In summary, the incidence of VRE colonization in a patient population without previously described VRE colonization was found to be high in this study. We identified neutropenia and immunosuppression, as well as vancomycin use, as risk factors for acquiring VRE colonization. Conceivably, surveillance cultures targeted to such high-risk populations could assist in tracking the pattern of VRE colonization in the ICU. A restriction on antibiotics, specifically on vancomycin, and a more resolute implementation of infection control policies are recommended to curb the rate of increase in VRE colonization in these patients.

**References**