The Role of “Colonization Pressure” in the Spread of Vancomycin-Resistant Enterococci

An Important Infection Control Variable

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Objective: The spread of nosocomial multiresistant microorganisms is affected by compliance with infection control measures and antibiotic use. We hypothesized that “colonization pressure” (ie, the proportion of other patients colonized) also is an important variable. We studied the effect of colonization pressure, compliance with infection control measures, antibiotic use, and other previously identified risk factors on acquisition of colonization with vancomycin-resistant enterococci (VRE).

Methods: Rectal colonization was studied daily for 19 weeks in 181 consecutive patients who were admitted to a single medical intensive care unit. A statistical model was created using a Cox proportional hazards regression model including length of stay in the medical intensive care unit until acquisition of VRE, colonization pressure, personnel compliance with infection control measures (hand washing and glove use), APACHE (Acute Physiology and Chronic Health Evaluation) II scores, and the proportion of days that a patient received vancomycin or third-generation cephalosporins, sucralfate, and enteral feeding.

Results: With survival until colonization with VRE as the end point, colonization pressure was the most important variable affecting acquisition of VRE (hazard ratio [HR], 1.032; 95% confidence interval [CI], 1.012-1.052; P=.002). In addition, enteral feeding was associated with acquisition of VRE (HR, 1.009; 95% CI, 1.000-1.017; P=.05), and there was a trend toward association of third-generation cephalosporin use with acquisition of VRE (HR, 1.007; 95% CI, 0.999-1.015; P=.11). The effects of enteral feeding and third-generation cephalosporin use were more important when colonization pressure was less than 50%. Once colonization pressure was 50% or higher, these other variables hardly affected acquisition of VRE.

Conclusions: Acquisition of VRE was affected by colonization pressure, the use of antibiotics, and the use of enteral feeding. However, once colonization pressure was high, it became the major variable affecting acquisition of VRE.

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Infection control measures are key to preventing the spread of microorganisms within hospitals, especially in high-risk areas such as intensive care and transplant units. Hand washing is heralded as the single most important control measure, and effective hand-washing techniques have been shown to reduce the rate of nosocomial infections in several studies. However, compliance with this basic function has been reported to be as low as 22% to 42%, and achieving 100% hand-washing compliance is an elusive goal. Intensive antibiotic control programs also have been advocated as a means to decrease selective pressures that favor the emergence and persistence of antibiotic-resistant bacteria. These programs have been successful in decreasing targeted antibiotic resistance rates for specific bacteria, but published reports are limited.

In addition to compliance with infection control measures and antibiotic use guidelines, other factors may affect cross-acquisition of microorganisms. For instance, the number of patients already colonized (“colonization pressure”) may be an important factor in determining chances of cross-colonization; ie, the risk of cross-infection for a noncolonized patient probably is higher when 80% of patients are already colonized than when only 10% are colonized.

To determine the relative importance of these variables, we studied the effects of colonization pressure, compliance with infection control measures, antimicrobial use, and other risk factors on acquisition of vancomycin-resistant enterococci
MATERIALS AND METHODS

SETTING AND STUDY DESIGN

Cook County Hospital, Chicago, Ill, is a 900-bed public teaching hospital. The MICU contains 16 beds: 12 in single rooms and 4 in double rooms. As part of ongoing surveillance monitoring supervised by the hospital’s Infection Control Committee, rectal cultures were obtained daily for 19 weeks from all patients admitted to the MICU for at least 48 hours (October 26, 1994, to March 7, 1995). In addition, personnel compliance with infection control measures was monitored as described below, and demographic data and antibiotic use were recorded for all patients. At the beginning of the study and every 1 to 2 weeks thereafter, educational meetings were held with MICU nurses, house staff, and attending physicians to review infection control measures and to provide encouragement and feedback about compliance. During this period, gloves and gowns were worn during the treatment of patients in half of the unit, whereas only gloves were used for care of the patients in the other half. Personnel were required to wear clean, nonsterile gloves for all room entries and to remove the gloves and wash their hands with antibacterial soap (containing triclosan) before leaving the room. In double rooms, hands were to be washed and fresh gloves were to be put on if the health care worker moved between patients. In addition, in the 8 gloves-and-gown rooms, personnel were required to wear isolation gowns for all room entries and to remove them before leaving the room. The results of this intervention have been reported: wearing of gowns did not reduce acquisition of VRE, ie, the VRE acquisition rates were similar in the 2 groups (25.8% in the gloves-and-gown group and 23.9% in the gloves-only group). Therefore, results of acquisition for the 2 groups are combined in the analyses described below.

MICROBIOLOGIC METHODS

Rectal swab specimens were obtained daily from all patients in the MICU, and specimens were inoculated onto Enterococcosel agar (Becton Dickinson Microbiology Systems, Cockeysville, Md) supplemented with vancomycin, 6 µg/mL. Plates were examined after 48 hours of incubation at 35°C. Isolates were identified to the species level by API 20 STREP system (bioMerieux Vitek Inc, Hazelwood, Mo), motility, and pigmentaion. Antibiotic susceptibility was tested by standard disk diffusion and agar dilution methods.

MONITORING OF COMPLIANCE

Compliance by all health care workers was charted by unobtrusive observers (S.S. and J.V.) who monitored rooms from a raised nurses station in the center of the MICU. Observations (n=4364) were made on all shifts approximately 7 hours per week. Beds were monitored for 10 minutes in random order. Compliance with hand washing, donning gloves on entry, and removal of gloves before leaving was monitored for all beds. Because continuous monitoring was not done, compliance data were aggregated and expressed as weekly compliance rates for the entire unit.

DESIGN AND STATISTICS

OF ANALYSIS OF ACQUISITION

Design

We created a statistical model of the relative effects of colonization pressure, infection control compliance rates, antibiotic use, APACHE (Acute Physiology and Chronic Health Evaluation) II score on admission to the MICU, enteral feeding, and use of sucralfate on acquisition of VRE. All patients not colonized with VRE on admission, during the entire 19 weeks, were included in this analysis.

Definitions

Colonization on admission and acquired colonization were defined as isolation of VRE from rectal cultures obtained within or later than the first 48 hours of admission, respectively. For each study day, the point prevalence of VRE in the MICU was calculated as follows: number colonized with VRE on that day divided by the number treated in the MICU on that day. Subsequently, for each patient who was not colonized with VRE on admission, the average point prevalence of VRE for all MICU days until acquisition of VRE or until discharge (if the patient did not acquire colonization) was calculated. This calculated number reflects the colonization pressure with VRE for the period in the MICU that the patient was not colonized.

Personnel compliance rates for hand washing, donning gloves, and removing gloves were expressed as percentages per week, and this rate was attributed to each day of the week. Using these compliance rates, an attributed mean personnel compliance until acquisition of VRE or discharge was calculated for each patient. The percentage of days that noncolonized patients received vancomycin or a third-generation cephalosporin (“antibiotic pressure”) was calculated until acquisition of VRE or discharge from the ward, as were the proportion of days that patients received enteral feeding and sucralfate.

Statistical Analysis

The effects of colonization pressure, the hand-washing and gloving compliance rates, antibiotic pressure, APACHE II score on admission, and use of enteral feeding and sucralfate on acquisition of VRE were analyzed in a Cox proportional hazards regression model (SPSS for Windows, release 6.1.2, SPSS Inc, Chicago, Ill) in which the number of days until acquisition of VRE was the dependent variable. Each variable was separately analyzed in a Cox regression model, and the best-fitting model was constructed by the simultaneous inclusion of the significantly related variables. Hazard ratios (HRs) with corresponding 95% confidence intervals (CIs) were computed. An HR of a variable with 2 categories is the ratio of the 2 category-dependent probabilities for occurrence of the event. The integration of the hazard function for a certain period, eg, day by day, gives the probability of acquiring VRE in that period. The significant covariates were obtained by means of a forward stepwise selection using the P values of the likelihood ratio test. Goodness-of-fit was assessed from the 3 plots of partial residuals against time, with 1 plot for each covariate. In the plots, the points were randomly distributed.
enterococci (VRE) in a medical intensive care unit (MICU).

## RESULTS

### PATIENTS

In all, 181 patients were admitted for at least 48 hours, and 7 patients were present in the MICU when the study started. The mean±SD age of the study population was 51±15 years; the mean±SD APACHE II score on admission was 23±8, and 60% of the patients were men.

### RELATIVE IMPACT OF COLONIZATION PRESSURE, INFECTIOIN CONTROL COMPLIANCE, ANTIBIOTIC USE, ENTERAL Feeding, AND USE OF SUCRALFATE ON VRE ACQUISITION RISK

One hundred fifty-three patients were not colonized with VRE on admission to the MICU, and 45 (29%) of them acquired rectal colonization with VRE after a mean±SD of 7.4±5.3 days (Table). The calculated colonization pressures for these 153 patients ranged from 9% to 67%. Compliance was monitored approximately 7 hours per week, yielding 4364 observations equally divided over the study period. Weekly compliance rates ranged from 16% to 73% for hand washing, from 59% to 91% for donning gloves, and from 60% to 100% for removing gloves. When calculated for individual patients, compliance rates ranged from 29% to 65% for hand washing, from 58% to 93% for donning gloves, and from 58% to 96% for removing gloves. The antibiotic pressure analysis focused on vancomycin and third-generation cephalosporins because these agents were prescribed most frequently and have been associated with colonization and infection with VRE.

### Table

<table>
<thead>
<tr>
<th>Colonization pressure‡</th>
<th>Patients Not Acquiring VRE (n = 108)</th>
<th>Patients Acquiring VRE (n = 45)</th>
<th>P†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vancomycin</td>
<td>29.8 ± 12.2 (29; 9-67)</td>
<td>38.0 ± 17.9 (37; 11-65)</td>
<td>.007‡</td>
</tr>
<tr>
<td>Third-generation cephalosporins</td>
<td>10.5 ± 26.3 (0; 0-100)</td>
<td>14.5 ± 26.5 (0; 0-100)</td>
<td>.03‡</td>
</tr>
<tr>
<td>Vancomycin or third-generation cephalosporins</td>
<td>42.6 ± 44.1 (27; 0-100)</td>
<td>59.4 ± 42.4 (67; 0-100)</td>
<td>.02‡</td>
</tr>
<tr>
<td>Enteral feeding§</td>
<td>47.7 ± 44.9 (39; 0-100)</td>
<td>67.6 ± 39.2 (100; 0-100)</td>
<td>.01‡</td>
</tr>
<tr>
<td>Sucralfate§</td>
<td>18.2 ± 30.3 (0; 0-100)</td>
<td>52.3 ± 38.1 (67; 0-100)</td>
<td>&lt;.001‡</td>
</tr>
<tr>
<td>APACHE II score</td>
<td>23.4 ± 37.7 (0; 0-100)</td>
<td>50.2 ± 43.7 (60; 0-100)</td>
<td>&lt;.001‡</td>
</tr>
</tbody>
</table>

§Proportion of days with use calculated per patient.
†The student t test (‡) was used for parametric variables and the Mann-Whitney U test (#) was used for nonparametric variables.
‡Mean of all daily point prevalences calculated per patient.
§Proportion of days with use calculated per patient.

When each variable was tested individually in a Cox regression analysis with duration until VRE acquisition, death, or discharge as “survival time,” each was associated with acquisition of VRE. The P values for these associations ranged from .004 for the daily point prevalence to .10 for donning gloves. When all variables were tested as covariates in a Cox regression model, a clear distinction between 3 relevant variables and the other, unrelated variables was observed. The best model included the daily point prevalence of VRE (colonization pressure (HR, 1.032; 95% CI, 1.012-1.052; P=.002), the proportion of days with enteral feeding (HR, 1.009; 95% CI, 1.000-1.017; P=.05), and the proportion of patient days with cephalosporin use (HR, 1.007; 95% CI, 0.999-1.015; P=.11). The other variables were not selected as significant risk factors because their P values were greater than .3 for the use of sucralfate and greater than .5 for the remaining variables. Analysis of vancomycin use did not add significantly to the impact of the use of third-generation cephalosporins. An HR of 1.032 for coloni-
The high prevalence of VRE colonization in our MICU may seem to be an extreme case. However, during the study only 8 patients had VRE recovered from clinical specimens, demonstrating that the number of recognized infections with VRE only represents the tip of the iceberg. Compared with the reported proportion of nosocomial gram-negative bacteria was associated with higher rates of acquisition of these bacteria, and a shorter colonization-free period, for noncolonized patients. However, compliance with infection control procedures and antibiotic pressures were not monitored in that study.

Our analyses, performed in a single MICU, demonstrate the relative impact of colonization pressure, antibiotic pressure, and other factors on acquisition of VRE. In a Cox regression analysis, colonization pressure was the most important variable affecting VRE acquisition. Antibiotic use and enteral feeding had important effects mainly when the prevalence of VRE colonization was relatively low. According to our analysis, the expected median time until acquisition of VRE is 19 days when both antibiotic pressure and colonization pressure are 25% but 6 days when colonization pressure is 75% and antibiotic pressure is 25%.

Low compliance with infection control procedures and high antibiotic use have been associated with the spread of antibiotic-resistant bacteria. The analysis of the interaction of these risk factors with colonization pressure is new. In another study, one of us (M.J.M.B.) found that an increase in the number of patients colonized with nosocomial gram-negative bacteria was associated with higher rates of acquisition of these bacteria, and a shorter colonization-free period, for noncolonized patients. However, compliance with infection control procedures and antibiotic pressures were not monitored in that study.

The high prevalence of VRE colonization in our MICU may seem to be an extreme case. However, during the study only 8 patients had VRE recovered from clinical specimens, demonstrating that the number of recognized infections with VRE only represents the tip of the iceberg. Compared with the reported proportion of colonization pressure means that for each 1% that colonization pressure increased, the risk of acquisition of VRE increased by 3.2%. For each 1% increase in enteral feeding and cephalosporin use, the risk of acquisition of VRE increased by 0.9% and 0.7%, respectively.

We used this model (colonization pressure and either enteral feeding or antibiotic pressure) to calculate the median time until acquisition of VRE. Given the compliance rates observed during the present study, colonization pressure seemed to have a greater effect on acquisition of VRE than did antibiotic pressure or enteral feeding, eg, the time to acquisition was shorter with high colonization pressure and low antibiotic pressure (or enteral feeding) than with the converse condition (Figure 1, Figure 2, and Figure 3). Although the HRs may seem small, the expected duration of a noncolonized patient to remain VRE negative was 5 days when colonization pressure and antibiotic pressure were 75% and 19 days when both variables were 25%. Moreover, once colonization pressure was greater than 50%, the other variables had only a slight effect on time to acquisition of VRE (Figure 1). With a colonization pressure of 75%, the calculated duration until acquisition of VRE was 5 days when antibiotic pressure was 75% and 6 days when antibiotic pressure was 25%.

**Figure 1.** The median number of days until acquisition of vancomycin-resistant enterococci (VRE) in relation to the "colonization pressure" (prevalence) and the use of third-generation cephalosporins. The days until acquisition were calculated from the relation among acquisition of VRE, VRE colonization pressure, third-generation cephalosporin use, and enteral feeding in a Cox regression analysis according to the following formula: \( \log \left( \frac{h_i(t)}{h_0(t)} \right) = 0.0314 X_{coli} + 0.0086 X_{efi} + 0.0065 X_{cepi} \), where \( i \) indicates the index patient; \( X_{coli} \), the "VRE colonization pressure" for patient \( i \); \( X_{efi} \), the use of enteral feeding for patient \( i \); \( X_{cepi} \), the hazard; and \( h_0(t) \), the hazard of a fictitious patient with 0 for all variables. For \( X_{efi} \), the mean of the study population was used, ie, 28.2157.

**Figure 2.** The median number of days until acquisition of vancomycin-resistant enterococci (VRE) in relation to the "colonization pressure" (prevalence) and enteral feeding: \( \log \left( \frac{h_i(t)}{h_0(t)} \right) = 0.0314 X_{coli} + 0.0086 X_{efi} + 0.0065 X_{cepi} \), with 32.2353 for \( X_{coli} \), as the mean of the study population.

**Figure 3.** The median number of days until acquisition of vancomycin-resistant enterococci (VRE) in relation to the use of third-generation cephalosporins and enteral feeding: \( \log \left( \frac{h_i(t)}{h_0(t)} \right) = 0.0314 X_{coli} + 0.0086 X_{efi} + 0.0065 X_{cepi} \), with 32.2353 for \( X_{coli} \), as the mean of the study population.
nosocomial enterococcal infections caused by VRE in US hospitals (>10%-14%), our situation probably is no exception, and high rates of colonization with VRE may already be established in many hospitals, although prevalence rates may vary considerably from one geographic area to another.

**Vancomycin-resistant** enterococci are thought to be spread mainly via cross-colonization. The present study reveals additional important observations that bear on preventing the spread of VRE and possibly other nosocomial pathogens. First, rates of cross-colonization were affected by the prevalence of colonization. We suspect that this occurred because a higher prevalence of VRE colonization increased the chance for health care workers to contact a patient colonized with VRE and thus made any lapses in compliance more of a risk. These data seem to underscore observations made by Haley and coworkers studying methicillin-resistant *Staphylococcus aureus*. They found that overcrowding and understaffing, which increase the number of patient contacts for each health care worker, predisposed to the spread of methicillin-resistant *S aureus* in a neonatal ICU.

Second, degree of compliance with infection control measures has been associated with risk of transmission of nosocomial pathogens. In the present analysis, the weekly hand-washing compliance rates ranged from 16% to 73%, and compliance rates ranged from 59% to 100% for glove use. Albert and Condie found compliance rates with hand washing of 28% and 41% in ICUs in a university and a private hospital, respectively. Simmons and coworkers found a compliance rate with hand washing of 22%, which was increased to 30% without affecting infection rates. More recently, Doebbeling and coworkers studied hand washing during a total of 152 hours with 1233 observations and found a compliance rate of 42%. Reaching compliance rates of 100% seems elusive, and even with 100% compliance, there still is a possibility of acquisition of VRE via contaminated environmental sources.

The fact that compliance rates were not significantly related to acquisition of VRE in our Cox regression analyses may be a result of the relatively small range of compliances. However, our analyses on compliance with infection control measures have 2 limitations. First, the data on compliance were calculated from all observations made in the MICU each week. Therefore, despite 4364 observations, compliance data are not patient specific. This also may have led to the small differences in compliance rates between patients who acquired and those who did not acquire colonization with VRE. However, without truly continuous personnel compliance monitoring, unit-wide compliance rates may be the best measure of infection control activity in the MICU each week. Second, we did not monitor staffing ratios and, therefore, could not relate changes in staffing ratios to acquisition of VRE.

Third, the risk for acquisition of VRE may be affected by the differences in antibiotic use. Vancomycin and third-generation cephalosporins have been associated with increased infection rates with VRE, and antibiotic use was a significant variable in the Cox regression analysis. Overall, third-generation cephalosporin use (58% of all patient-days) is high in our MICU. In a general ICU in a Dutch university hospital, where neither VRE nor methicillin-resistant *S aureus* have been found, the use of vancomycin and cephalosporins during 1994 were 4% and 5% of the patient-days, respectively. However, in a 1-day point prevalence infection surveillance study of 1417 ICUs in 17 European countries, 62.3% of 10,038 patients were receiving antibiotics on the day of study, and 43.6% of the patients taking antibiotics received cephalosporins. Preliminary observations suggest that reducing use of cephalosporin antibiotics may result in decreased rates of acquisition of VRE.

Finally, enteral feeding proved to be significantly related to acquisition of VRE. Because cultures of enteral feeding were consistently negative, it seems likely that enteral feeding introduced a risk for acquisition of VRE either because of a more frequent need for hands-on care of patients by the nursing staff or because of alterations of the intestinal microenvironment. An association between enteral feeding and nosocomial acquisition of ampicillin-resistant enterococci and VRE has been reported previously. In another study, enteral feeding had a protective effect against the spread of β-lactamase-producing aminoglycoside-resistant *Enterococcus faecalis* in an infant-toddler surgical ward. However, this finding was regarded as an epiphenomenon of patients with intact gastrointestinal tract function who could better resist colonization by the bacteria. In contrast to excessive antibiotic use, administration of enteral feeding should not be limited. There are good reasons to feed critically ill patients as soon as possible, and enteral feeding has obvious advantages compared with parenteral feeding. However, it may be possible that different modes of administration of enteral nutrition (such as intermittent instead of continuous feeding or intrajejunual instead of intragastric feeding) have different effects on colonization with VRE. More studies are needed to confirm if, and to elucidate why, enteral feeding promotes colonization with VRE and if alternative ways of feeding affect this process.

In conclusion, what can be done to minimize cross-colonization when VRE colonization pressure is high, as in our setting? Compliance with hand washing and the use of gloves is important, but, under the circumstances tested, even above-average hand-washing compliance and a high rate of glove use, as in the present study, were insufficient to control spread. Reducing movement of health care workers between colonized and noncolonized patients may be achieved by creating cohorts of either patients or nursing staff and by limiting the number of physicians entering patient rooms during rounds. In many studies, the presence of VRE is related to the use of antibiotics, such as vancomycin and third-generation cephalosporins. Because these agents provide VRE with a selective growth advantage, restricted and prudent use is probably essential to control further spread of VRE. Moreover, controlling antibiotic use has been easier logistically and more
readily achieved than improving hand-washing compliance. Hospitals that currently have a low prevalence of VRE should be aggressive with surveillance and control measures now rather than waiting until the colonization pressure is high.

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