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Occurrence of co-colonization or co-infection with vancomycin-resistant enterococci and methicillin-resistant Staphylococcus aureus in a medical intensive care unit

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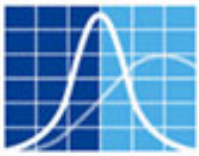

OCCURRENCE OF CO-COLONIZATION OR CO-INFECTION WITH VANCOMYCIN-RESISTANT ENTEROCOCCI AND METHICILLIN-RESISTANT *STAPHYLOCOCCUS AUREUS* IN A MEDICAL INTENSIVE CARE UNIT

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ABSTRACT

OBJECTIVE: To determine the occurrence of co-colonization or co-infection with VRE and MRSA among medical patients requiring intensive care.

DESIGN: Prospective, single-center, observational study.

SETTING: A 19-bed medical ICU in an urban teaching hospital.

PATIENTS: Adult patients requiring at least 48 hours of intensive care and having at least one culture performed for microbiologic evaluation.

RESULTS: Eight hundred seventy-eight consecutive patients were evaluated. Of these patients, 402 (45.8%) did not have microbiologic evidence of colonization or infection with either VRE or MRSA, 355 (40.4%) were colonized or infected with VRE, 38 (4.3%) were colonized or infected with MRSA, and 83 (9.5%) had co-colonization or co-infection with VRE and MRSA. Multiple logistic regression analysis demonstrated that increasing age, hospitalization during the preceding 6 months, and admission to a long-term–care facility were independently associated with colonization or infection due to VRE and co-colonization or co-infection with VRE and MRSA. The distributions of positive culture sites for VRE (stool, 86.7%; blood, 6.5%; urine, 4.8%; soft tissue or wound, 2.0%) and for MRSA (respiratory secretions, 34.1%; blood, 32.6%; urine, 17.1%; soft tissue or wound, 16.2%) were statistically different ($P < .001$).

CONCLUSIONS: Co-colonization or co-infection with VRE and MRSA is common among medical patients requiring intensive care. The recent emergence of vancomycin-resistant *Staphylococcus aureus* and the presence of a patient population co-colonized or co-infected with VRE and MRSA support the need for aggressive infection control measures in the ICU (*Infect Control Hosp Epidemiol* 2004;25:99-104).

Until the development of the oxazolidinones and quinupristin/dalfopristin, vancomycin had been the only uniformly effective antibiotic for the treatment of *Staphylococcus aureus* infections in the United States. In 1997, the first incidence of *S. aureus* with reduced susceptibility to vancomycin was described.[1] This was followed by at least eight reports of similar *S. aureus* strains in the United States.[2-6] Recently, two infections due to vancomycin-resistant *S. aureus* have been described.[7,8] Both of these isolates contained the *van*A gene, and in one of the isolates, it was identical to the *van*A gene present in *Enterococcus faecalis* cultured from the same patient.[7] These two reports suggest that the *van*A gene was acquired by *S. aureus* from vancomycin-resistant enterococci (VRE) in these two patients having prior co-colonization with methicillin-resistant *S. aureus* (MRSA) and VRE.

The occurrence of colonization with VRE and MRSA appears to be common among patients requiring intensive care.[9,10] MRSA has become the predominant form of clinically significant *S. aureus* within intensive care units (ICUs) and increasingly within some community settings as well.[9,11-15] However, there are few data indicating the frequency with which concomitant colonization or co-infection with MRSA and VRE occurs within the same patient. Given the important clinical implications of *S. aureus* developing vancomycin resistance, we performed a clinical study in which the main goal was to determine the occurrence of concomitant colonization or co-infection with VRE and MRSA among patients admitted to an ICU.

METHODS

Study Location and Patients

This study was conducted at Barnes–Jewish Hospital, a university-affiliated, urban teaching hospital with 1,400 beds. During the 28-month period from February 2000 to October 2001, all patients requiring admission to the 19-bed medical ICU for more than 48 hours were eligible for this investigation. These inclusion criteria were prospectively selected to minimize the enrollment of patients with rapidly fatal illnesses and self-

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limited conditions not requiring more prolonged intensive care. The medical ICU is a closed unit with a multidisciplinary team providing patient care under the direction of attending physicians who are board certified in critical care medicine. This study was approved by the Washington University School of Medicine Human Studies Committee.

Study Design and Data Collection

A prospective cohort study design was employed, with the main outcome measure being concomitant colonization or co-infection with VRE and MRSA. We also assessed secondary outcomes including the lengths of hospitalization and intensive care, the number of acquired organ system derangements, and hospital mortality.

For all patients included in the study, the following characteristics were prospectively recorded by one of the investigators: age; gender; ethnicity; severity of illness based on Acute Physiology and Chronic Health Evaluation II (APACHE II) scores[16]; the presence of congestive heart failure, chronic obstructive pulmonary disease, underlying malignancy, recent chemotherapy, seropositivity for human immunodeficiency virus, diabetes mellitus, chronic renal insufficiency, cirrhosis, and solid organ transplantation; and the administration of corticosteroids.

One of the investigators made daily rounds in the medical ICU to identify eligible patients. Patients included in the study were prospectively observed until they were discharged from the hospital or died. Discharge from the hospital was defined as transfer of a patient from the hospital to his or her home, a skilled nursing facility, or a private rehabilitative hospital. All culture results and clinical data were prospectively and independently reviewed by a board-certified infectious disease physician (VJF). Patients could not be entered into the study more than once during the same hospitalization.

Definitions

All definitions were selected prospectively as part of the original study design. We calculated APACHE II scores on the basis of the clinical data available from the first 24-hour period of intensive care.[16] The criteria for acquired organ system derangements were those used by Rubin et al.[17] One point was given for acquired dysfunction of each organ system. Renal dysfunction was defined as a twofold increase in baseline creatinine level or an absolute increase in baseline creatinine level of 2.0 mg/dL. Hepatic dysfunction was defined as an increase in total bilirubin level to more than 2.0 mg/dL. Pulmonary dysfunction was defined as one of the following: (1) a requirement for mechanical ventilation for a diagnosis of pneumonia, chronic obstructive pulmonary disease, asthma, or pulmonary edema (cardiogenic or noncardiogenic); (2) a PaO_2 level of less than 60 mm Hg while receiving a fraction of inspired oxygen of 0.50 or more; or (3) the use of at least 10 cm of H_2O of positive end-expiratory pressure. Neurologic dysfunction was defined as a new focal deficit (eg, hemiparesis after cerebral infarction) or a new generalized process (eg, seizures or coma). Gastrointestinal dysfunction was defined as gastrointestinal hemorrhage requiring transfusion, new ileus, or diarrhea lasting more than 24 hours and unrelated to previous bowel surgery. Cardiac dysfunction was defined as acute myocardial infarction, cardiac arrest, or the new onset of congestive heart failure.

Infection Control and Surveillance Protocol

Healthcare workers and visitors were required to wear both gloves and gowns before entry into rooms of patients on contact isolation or contact precautions. Contact precautions were used for patients colonized or infected with VRE, MRSA, multidrug-resistant gram-negative bacilli, or *Clostridium difficile*. Additionally, a commercially available alcohol-based disinfectant foam (Alcare Plus, Steris Corporation, St. Louis, MO) or good handwashing were required for hand disinfection prior to all patient contacts. The alcohol-based foam was dispensed from canisters placed at the entrance of every patient room. These specific infection control practices had previously been shown to reduce the acquisition of VRE in this medical ICU.[18]

In conjunction with the contact precautions described, the medical ICU employs specific protocols to reduce the occurrence of hospital-acquired infections. Protocols directed at weaning patients from mechanical ventilation,[19] reducing unnecessary sedation,[20] and providing appropriate enteral nutritional support[21] are in place and have been associated with reductions in hospital-acquired infections. Additionally, two education-based programs to reduce the occurrence of ventilator-associated pneumonia and catheter-related bloodstream infection, respectively, were employed in this ICU.[22,23]

As part of the ICU surveillance program, nurses obtained samples for stool cultures or rectal swab cultures for VRE from the patients on admission, weekly, and at the time of discharge from the ICU.[24] Bile esculin azide agar with vancomycin (6 µg/mL; Remel, Lenexa, KS), followed by a subculture on a 30-µg vancomycin disk, was used for isolation, identification, and characterization of enteric VRE, as described elsewhere.[25] Because *van*A and *van*B fail to produce inhibition zones of greater than 6 mm, whereas *van*C isolates primarily produce inhibition zones of greater than 15 mm during subculturing on a 30-µg vancomycin disk, this method reliably differentiates clinically and epidemiologically relevant species.[25] In addition, all stool samples submitted for *C. difficile* testing were routinely tested for enteric VRE.[25,26]

A patient was considered to have enteric colonization with VRE if a clinical culture or surveillance culture of a rectal swab or stool sample was positive for VRE. Colonization or infection with MRSA was defined as a positive clinical culture. Surveillance cultures from the nares or other locations for MRSA were not routinely performed during this investigation.

Statistical Analysis

All comparisons were unpaired and all tests of significance were two-tailed. Continuous variables were com-

pared using the Student's *t* test for normally distributed variables and the Wilcoxon rank sum test for non-normally distributed variables. The chi-square or Fisher's exact test was used to compare categorical variables. The primary data analysis compared patients according to the presence or absence of colonization or infection with VRE and MRSA (alone or in combination). We performed multiple logistic regression analysis using a commercial statistical package (SPSS software, version 10.0 for Windows; SPSS, Inc., Chicago, IL).

A stepwise approach was used to enter new terms into the logistic regression model. Colonization or infection with VRE, colonization or infection with MRSA, and co-colonization or co-infection with VRE and MRSA were the three dependent outcome variables examined, and .05 was set as the limit for the acceptance or removal of new terms. Variables with a *P* value of less than .15 were entered into the multivariate analysis based on models that were judged a priori to be clinically sound.[27] This was prospectively determined to be necessary to avoid producing spuriously significant results with multiple comparisons. Results of the logistic regression analyses are reported as adjusted odds ratios (ORs) with 95% confidence intervals (CI_{95}). Values are expressed as the mean ± standard deviation (continuous variables) or as a percentage of the group from which they were derived (categorical variables). All *P* values were two-tailed, and *P* values of .05 or less were considered to indicate statistical significance.

RESULTS

Patients

A total of 878 consecutive patients requiring admission to the medical ICU for more than 48 hours were evaluated. The mean age of the patients was 59.0 ± 17.0 years (range, 15 to 102 years) and the mean APACHE II score was 23.2 ± 7.4 (range, 5 to 47). There were 431 (49.1%) male and 447 (50.9%) female patients.

Co-Colonization or Co-Infection With VRE and MRSA

Four hundred two (45.8%) of the patients had no microbiologic evidence of colonization or infection with VRE or MRSA during their stay in the ICU. Three hundred fifty-five (40.4%) of the patients had colonization or infection with VRE, 38 (4.3%) of the patients had colonization or infection with MRSA, and 83 (9.5%) of the patients had co-colonization or co-infection with VRE and MRSA. The distribution of the sites of infection is given in Table 1. VRE was cultured statistically more often from stool samples or rectal swabs compared with MRSA (86.7% vs 0.0%; $P < .001$). MRSA was isolated more often from respiratory secretions (34.1% vs 0.0%; $P < .001$) and from blood (32.6% vs 6.5%; $P < .001$). Among all of the cultures evaluated, 7 blood cultures were positive for VRE and MRSA in the same patient. Two wound cultures from the same patients were also positive for VRE and MRSA.

TABLE 1
SITES OF INFECTION

Site	VRE (n = 504)	MRSA (n = 139)
Blood	33 (6.5%)	42 (32.6%)
Respiratory secretions	0 (0.0%)	44 (34.1%)
Urine	24 (4.8%)	22 (17.1%)
Soft tissue or wound	10 (2.0%)	21 (16.2%)
Rectum or stool	437 (86.7%)	0 (0.0%)*

VRE = vancomycin-resistant enterococci; MRSA = methicillin-resistant *Staphylococcus aureus*.
*MRSA was not actively screened for in the rectal or stool cultures due to the presence of vancomycin-impregnated culture media.

Risk Factors for Colonization or Infection With VRE and MRSA

Compared with patients who did not have colonization or infection, patients with colonization or infection due to VRE were statistically older and more likely to have chronic obstructive pulmonary disease, chronic renal failure, outpatient hemodialysis, hospitalization during the 6 months preceding the current hospitalization, and admission to the ICU from a long-term–care facility (Table 2). Similarly, patients with colonization or infection due to MRSA were statistically older and more likely to have chronic obstructive pulmonary disease, prior hospitalization, and admission to the ICU from another hospital compared with patients who did not have colonization or infection. Patients with colonization or infection due to MRSA were statistically more likely to have underlying malignancy and admission to the ICU from another hospital and statistically less likely to have chronic renal failure compared with patients colonized or infected with VRE. Patients co-colonized or co-infected with VRE and MRSA were statistically older and more likely to have chronic obstructive pulmonary disease, prior hospitalization, and admission to the ICU from a long-term–care facility compared with patients who did not have colonization or infection with these microorganisms. Patients with co-colonization or co-infection with VRE and MRSA were statistically less likely to have chronic renal failure and outpatient dialysis compared with patients with colonization or infection due to VRE.

Multiple logistic regression analysis showed that increasing age (adjusted OR, 1.02; CI_{95}, 1.01 to 1.03), hospitalization during the 6 months preceding the current hospitalization (adjusted OR, 2.74; CI_{95}, 2.21 to 3.40), and admission from a long-term–care facility (adjusted OR, 1.30; CI_{95}, 1.14 to 1.47) were independently associated with colonization or infection due to VRE. The same three variables with similar adjusted ORs were independently associated with co-colonization or co-infection with VRE and MRSA. Prior hospitalization was the only variable independently associated with colonization or infection due to MRSA (adjusted OR, 7.35; CI_{95}, 3.96 to 13.67).

TABLE 2
PATIENT CHARACTERISTICS ACCORDING TO MICROORGANISM

Characteristic	Patients With Neither VRE or MRSA (n = 402)	Patients With VRE Only (n = 355)	Patients With MRSA Only (n = 38)	Patients With Both VRE and MRSA (n = 83)
Mean age, y (± SD)	56.3 (± 17.3)	60.4 (± 16.7)*	62.6 (± 17.4)*	63.9 (± 13.4)*
Gender				
Male	191 (47.5%)	174 (49.0%)	19 (50.0%)	47 (56.6%)
Female	211 (52.5%)	181 (51.0%)	19 (50.0%)	36 (43.4%)
Ethnicity				
White	248 (61.7%)	197 (55.5%)	27 (71.1%)	54 (65.1%)
Black	151 (37.6%)	153 (43.1%)	11 (28.9%)	26 (31.3%)
Other	3 (0.7%)	5 (1.4%)	0 (0.0%)	3 (3.6%)
Mean APACHE II score (± SD)	23.8 (± 7.4)	24.7 (± 6.7)	24.2 (± 6.2)	25.4 (± 7.7)
Surgery	30 (7.5%)	20 (5.6%)	1 (2.6%)	9 (10.8%)
Congestive heart failure	70 (17.4%)	69 (19.4%)	7 (18.4%)	16 (19.3%)
COPD	93 (23.1%)	111 (31.3%)*	15 (39.5%)*	31 (37.3%)*
Underlying malignancy	48 (11.9%)	29 (8.2%)	8 (21.1%)†	8 (9.6%)
Chemotherapy	10 (2.5%)	5 (1.4%)	2 (5.3%)	0 (0.0%)
HIV positive	14 (3.5%)	16 (4.5%)	0 (0.0%)	0 (0.0%)
Diabetes mellitus	120 (29.9%)	126 (35.5%)	14 (36.8%)	39 (47.0%)
Received corticosteroids	146 (36.3%)	142 (40.0%)	10 (26.3%)	32 (38.6%)
Chronic renal failure	99 (24.6%)	117 (33.0%)*	6 (15.8%)†	17 (20.5%)†
Outpatient hemodialysis	33 (8.2%)	56 (15.8%)*	3 (7.9%)	5 (6.0%)†
Cirrhosis	38 (9.5%)	22 (6.2%)	2 (5.3%)	6 (7.2%)
Organ transplant	21 (5.2%)	29 (8.2%)	2 (5.3%)	5 (6.0%)
Prior hospitalization	138 (34.3%)	205 (57.7%)*	22 (57.9%)*	41 (49.4%)*
Admission location				
Other hospital	105 (26.1%)	63 (17.7%)*	16 (42.1%)*,†	19 (22.9%)*,‡
Hospital ward	161 (40.0%)	184 (51.8%)	7 (18.4%)	33 (39.8%)
Home	126 (31.3%)	73 (20.6%)	13 (34.2%)	19 (22.9%)
Long-term–care facility	10 (2.5%)	35 (9.9%)	2 (5.3%)	12 (14.5%)

VRE = vancomycin-resistant enterococci; MRSA = methicillin-resistant *Staphylococcus aureus*; SD = standard deviation; APACHE = Acute Physiology and Chronic Health Evaluation; COPD = chronic obstructive pulmonary disease; HIV = human immunodeficiency virus.
*$P < .05$ for comparison with the group who had neither organism cultured.
†$P < .05$ for comparison with the group who had VRE identified in culture.
‡$P < .05$ for comparison with the group who had MRSA identified in culture.

Secondary Outcomes

Patients with colonization or infection due to VRE had statistically longer hospital stays compared with uninfected patients (Table 3). Patients with co-colonization or co-infection with VRE and MRSA had statistically longer stays in the hospital and in the ICU, longer duration of mechanical ventilation, and a greater likelihood of hospital discharge to a long-term–care facility compared with patients who did not have colonization or infection with VRE and MRSA.

DISCUSSION

We demonstrated that co-colonization or co-infection with VRE and MRSA was common among patients admitted to a medical ICU, occurring in 9.5%. Increasing patient age, hospitalization during the preceding 6 months, and admission to the ICU from a long-term–care facility were identified as independent risk factors for co-colonization or co-infection with VRE and MRSA. Co-colonized or co-infected patients also had statistically longer stays in the hospital and ICU and were statistically more likely to require admission to a long-term–care facility following hospital discharge compared with patients who did not have VRE and MRSA colonization or infection.

Despite the widespread presence of patients colonized or infected with VRE and MRSA in ICUs, no previous study has examined the occurrence of co-colonization or co-infection with these gram-positive bacteria within the same patient in this clinical setting. Previous investigations among hospitalized patients and patients in skilled-care facilities suggest that those colonized with VRE are at increased risk for colonization or infection

TABLE 3
CLINICAL OUTCOMES

Outcome Variable	Patients With Neither VRE or MRSA (n = 402)	Patients With VRE Only (n = 355)	Patients With MRSA Only (n = 38)	Patients With Both VRE and MRSA (n = 83)
Mean no. of acquired organ system derangements (± SD)	1.8 (± 1.1)	1.8 (± 1.0)	1.6 (± 1.0)	1.7 (± 1.0)
Mean hospital stay, d (± SD)	22.1 (± 22.8)	28.3 (± 29.4)*	27.8 (± 27.2)	29.4 (± 24.2)*
Mean ICU stay, d (± SD)	9.1 (± 8.0)	9.8 (± 8.6)	10.1 (± 7.4)	13.3 (± 10.3)*,†
Mean duration of mechanical ventilation, d (± SD)	10.6 (± 12.0)	12.3 (± 14.3)	10.6 (± 8.1)	17.8 (± 20.8)*,†
Disposition of hospital survivors				
Home	182 (60.7%)	119 (52.9%)	15 (55.6%)	22 (40.0%)*
Long-term–care facility	102 (34.0%)	96 (42.7%)	11 (40.7%)	31 (56.4%)*
Outside hospital	16 (5.3%)	10 (4.4%)	1 (3.7%)	2 (3.6%)

VRE = vancomycin-resistant enterococci; MRSA = methicillin-resistant *Staphylococcus aureus*; SD = standard deviation; ICU = intensive care unit.
*Comparison with the group who had neither organism cultured.
†Comparison with the group who had VRE identified in culture.

with MRSA and *S. aureus* displaying intermediate resistance to vancomycin.[28-30] The clinical importance of co-colonization or co-infection with these pathogens is highlighted by the recent description of vancomycin-resistant *S. aureus* occurring as a result of the transfer of the *van*A gene from VRE.[7,8] Although the acquired vancomycin-resistant genes *van*A, *van*B, *van*D, *van*E, *van*F, and *van*G have been reported in VRE, transfer of the *van*A gene to *S. aureus* appears to be a rare event.[7] This suggests that the transfer requires specific conditions as suggested by the difficulty encountered attempting in vitro conjugate transfer of the *van*A gene from enterococci to *S. aureus.*[31]

Although recommended measures to control the spread of VRE and MRSA in hospitals have been promoted for several years, surveillance data suggest that the existence of these recommendations has not appreciably slowed the increasing rate of infection or colonization with either of these organisms in the United States.[32,33] The reasons for this lack of effect are unclear and under debate. In some institutions, the recommended measures may be ineffective or poorly followed or implemented. However, increasing evidence suggests that well-targeted intervention programs implemented within motivated healthcare environments can reduce the occurrence of colonization as well as infection with these antibiotic-resistant, gram-positive bacteria.

Our study has several limitations. First, it was performed within a single ICU with relatively high rates of colonization or infection with VRE, especially among patients admitted from other healthcare settings. Therefore, the results may not be generalizable to ICUs and hospitals with different sources of patient referral. However, the escalating rates of VRE and MRSA in the United States suggest that co-colonization or co-infection with these bacteria is likely to be a more widespread occurrence. Second, we did not differentiate colonization from infection in this study. This was purposefully done because our intent was to identify the coexistence of VRE and MRSA among the same patients. Third, we did not specifically examine the use of antibiotics as a risk factor for the acquisition of VRE and MRSA as has been previously reported.[32] However, recent investigations have found that patients with healthcare-acquired sources of infection have bacterial pathogens associated with infection that are similar to those seen in hospital-acquired infection, and that antibiotic exposure is common among these patients.[34]

Another important potential limitation of our study is that we examined only clinical cultures for MRSA, and although we performed active surveillance of VRE, we used a selective medium for stool cultures containing vancomycin to select out for VRE. Therefore, we likely underestimated the occurrence of colonization and infection with MRSA in this population. This underreporting bias also limits the accuracy of the risk factors for infection and colonization with MRSA identified in this analysis. Other investigators have estimated that approximately 55% of patients colonized with MRSA are detected by clinical cultures alone compared with clinical cultures combined with active surveillance.[35,36] With the use of this approximation, it is likely that the true incidence of co-colonization or co-infection with VRE and MRSA is closer to 15% or 20%. Finally, we did not differentiate between patients colonized or infected with MRSA and VRE on admission to the ICU and patients who acquired these pathogens during their stay in the ICU. As a result, the risk factors identified for colonization or infection with these organisms may not be applicable to specific patient subgroups (eg, patients acquiring VRE, MRSA, or both while in the ICU).

Despite these limitations, we demonstrated that co-infection with VRE and MRSA is common among critically ill patients. Clinicians should be aware of the potential for co-infection with VRE and MRSA in the ICU setting. Appropriate infection control practices should be in place to limit the horizontal transmission of VRE and MRSA to minimize the future potential for concomitant colonization or co-infection and the transfer of resistance genes among these pathogens.

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