CO-CARRIAGE RATES OF VANCOMYCIN-RESISTANT *ENTEROCOCCUS* AND EXTENDED-SPECTRUM BETA-LACTAMASE–PRODUCING BACTERIA AMONG A COHORT OF INTENSIVE CARE UNIT PATIENTS: IMPLICATIONS FOR AN ACTIVE SURVEILLANCE PROGRAM

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ABSTRACT

OBJECTIVE: To assess the co-colonization rates of extended-spectrum beta-lactamase (ESBL)–producing bacteria and vancomycin-resistant *Enterococcus* (VRE) obtained on active surveillance cultures.

DESIGN: Prospective cohort study.

SETTING: Medical and surgical intensive care units (ICUs) of a tertiary-care hospital.

PATIENTS: Patients admitted between September 2001 and November 2002 to the medical and surgical ICUs at the University of Maryland Medical System had active surveillance perirectal cultures performed. Samples were concurrently processed for VRE and ESBL-producing bacteria.

RESULTS: Of 1,362 patients who had active surveillance cultures on admission, 136 (10%) were colonized with VRE. Among these, 15 (positive predictive value, 11%) were co-colonized with ESBL. Among the 1,226 who were VRE negative, 1,209 were also ESBL negative (negative predictive value, 99%). Among the 1,362 who had active surveillance cultures on admission, 32 (2%) were colonized with ESBL. Among these, 15 (47%) were co-colonized with VRE. Of the 32 patients colonized with ESBL, 10 (31%) had positive clinical cultures for ESBL on the same hospital admission. For these 10 patients, the surveillance cultures were positive an average of 2.7 days earlier than the clinical cultures.

CONCLUSIONS: Patients who are colonized with VRE can also be co-colonized with other antibiotic-resistant bacteria such as ESBL-producing bacteria. Our study is the first to measure co-colonization rates of VRE and ESBL-producing bacteria. Isolating VRE-colonized patients would isolate 47% of the ESBL-colonized patients without the need for further testing. Hence, active surveillance for VRE should also theoretically diminish the amount of patient-to-patient transmission of ESBL-producing bacteria (*Infect Control Hosp Epidemiol* 2004;25:105-108).

Extended-spectrum beta-lactamase (ESBL)–producing bacteria were first discovered in Europe in 1983,[1] and the first ESBL-producing bacteria in the United States were reported in 1989.[2] Since that time, the incidence of infections due to ESBL-producing bacteria has increased sharply. In the United States, the incidence ranges between 0% and 25%, depending on the hospital, with a national average of 3%; but these numbers are increasing.[3,4]

In 1987, the first clinical vancomycin-resistant *Enterococcus* (VRE) was isolated from patients in the United States.[5] Subsequently, the National Nosocomial Infections Surveillance System of the Centers for Disease Control and Prevention found that from 1989 to 1998, the percentage of nosocomial infections caused by VRE isolated from patients in intensive care units (ICUs) had increased from 0.4% to 22.6%.[4]

Active surveillance is defined as the periodic screening of patients at risk for antibiotic-resistant bacteria followed by the isolation of colonized patients. As an infection control technique, it has been shown to be effective for identifying patients colonized with VRE and reducing VRE infections.[6-9] Furthermore, risk factors for one antibiotic-resistant bacteria are often common risk factors for other antibiotic-resistant bacteria. Thus, patients may be co-colonized with multiple different antibiotic-resistant bacteria simultaneously.[10] Therefore, a strategy of active surveillance for VRE may also be an effective measure to prevent patient-to-patient transmission of other antibiotic-resistant bacteria. One key variable in assessing this potential added effectiveness is the co-colonization or co-carriage rate of antibiotic-resistant bacteria.

To our knowledge, this study is the first to assess the co-colonization rates of ESBL-producing bacteria and VRE. This study has several aims: (1) to determine the prevalence of ESBL-producing bacteria on admission to the ICU; (2) to determine the prevalence of ESBL co-carriage among patients colonized with VRE on admission to the ICU; (3) to determine the prevalence of VRE co-car-

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riage among patients colonized with ESBL-producing bacteria on admission to the ICU; and (4) to discuss the utility of screening and processing active surveillance cultures for other antibiotic-resistant bacteria such as ESBL-producing bacteria.

METHODS

Study Population and Sample Collection

The University of Maryland Medical System in Baltimore, Maryland, is a 747-bed, tertiary-care hospital. The medical ICU is a 10-bed unit that admits adult patients to single rooms. The patient population includes patients with hematologic and other malignancies. The surgical ICU is a 19-bed unit that admits adult patients to single rooms. The patient population includes patients with solid organ transplantation (eg, kidney, pancreas, and liver).

Patients were enrolled between September 1, 2001, and November 1, 2002. Patients in the surgical and medical ICUs had perirectal cultures performed within 72 hours of admission. The culturing technique involved swabbing the perirectal area in a circular motion from the rectum out. Cotton swabs (Staplex, Etobicoke, Ontario, Canada) were used for the surveillance cultures. Samples for cultures were obtained by nurses and nursing assistants (extenders) as part of an ongoing VRE active surveillance program. The University of Maryland Institutional Review Board approved this study.

Microbiologic Methods

Samples were concurrently processed for VRE and ESBL-producing bacteria. For VRE identification, swabs were plated on colistin–nalidixic acid agar with 10 µg/mL of vancomycin (Becton Dickinson, Sparks, MD). For ESBL identification, swabs were plated onto MacConkey agar (Remel, Lenexa, KS) with 1 µg/mL of ceftazidime as an initial ESBL screen. This selective medium with ceftazidime was chosen because it inhibits the growth of susceptible gram-negative pathogens yet still permits the isolation of ESBL-producing bacteria. Plates were incubated at 37°C for 24 to 48 hours. Each colony type with a morphology or gram-negative stain consistent with *Escherichia coli* or *Klebsiella* was then subcultured onto sheep blood agar. Species identification was determined by API 20E Identification Strips (BioMérieux Vitek, Inc., Hazelwood, MO). Gram-negative bacilli identified as *E. coli* or *Klebsiella* then underwent ESBL confirmatory testing by disk diffusion in accordance with National Committee for Clinical Laboratory Standards guidelines.[11]

RESULTS

During the study period, 1,881 patients were admitted to the surgical and medical ICUs. Among these patients, 1,555 had perirectal surveillance cultures performed within 72 hours of admission, yielding an 83% compliance rate (medical ICU compliance, 87%; surgical ICU compliance, 76%). Of the 1,555 cultures, 1,524 were performed within the first 24 hours of admission. One hundred ninety-three patients were admitted multiple times and only their first cultures were used in the subsequent analysis. Hence, 1,362 admission cultures were included in this study. The demographics of these patients were as follows: mean age, 55 years; mean Charlson score, 2.3; and average length of stay prior to surveillance culture, 4.7 days.

Among the 1,362 patients with active surveillance cultures on admission, 136 (10%) were colonized with VRE. Among those, 15 patients (positive predictive value, 11%) were co-colonized with ESBL-producing bacteria.

Among the 1,362 patients with admission cultures, 81 (6%) had isolates that were positive for ESBL on screening and 32 (2%) were colonized with ESBL-producing bacteria. Among the 32 patients colonized with ESBL-producing bacteria, 15 (47%) were co-colonized with VRE.

Twenty-one (66%) of the ESBL-producing bacteria were *E. coli* and 11 (34%) were *Klebsiella* species. Of the 32 patients colonized with ESBL-producing bacteria, 10 (31%) had positive clinical cultures during the same admission. These 10 positive clinical cultures came from multiple sources: 4 sputum, 2 urine, 1 blood, 1 abscess, and 2 miscellaneous. Of the 10 patients who had both clinical and surveillance cultures that were positive, the surveillance cultures were positive an average of 2.7 days earlier than the clinical cultures. Only 3 of the 10 patients had positive clinical cultures for ESBL-producing bacteria before or on the same day as the positive surveillance culture, and all 3 positive clinical cultures occurred on the same day as the surveillance culture. Of the 22 patients with ESBL-producing bacteria who had no ESBL clinical cultures, 12 had surveillance cultures that were negative for VRE.

The prevalence of ESBL positivity in the population was 32 of 1,362 (2.3%). The sensitivity of identifying someone with ESBL based on a positive VRE result is 15 of 32 (47%). The specificity of identifying someone without an ESBL-producing bacteria based on a negative VRE result is 1,209 of 1,330 (ie, 1209 + 121) (91%). If someone is VRE positive, the positive predictive value of also being ESBL positive is 15 of 136 (ie, 15 + 121) (11%). If someone is VRE negative, the negative predictive value of not being ESBL positive is 1,209 of 1,226 (ie, 17 + 1209) (99%) (Table).

DISCUSSION

In this study, we assessed the co-carriage rates of VRE and ESBL-producing bacteria among patients admitted to the medical and surgical ICUs of a tertiary-care hospital in the United States. A unique feature of the study was the use of identical perirectal surveillance cultures. From an infection control perspective, this limits the effort and cost of performing surveillance cultures. Theoretically, the same surveillance culture could be used to screen for many other antibiotic-resistant bacteria including methicillin-resistant *Staphylococcus aureus*.

The 10% prevalence of VRE among patients admitted to an ICU is consistent with other studies performed in the United States.[3,4] Our study revealed a 2% prevalence

of ICU patients who had ESBL-producing bacteria. The prevalence of ESBL in an adult population of ICU patients in the United States has not been assessed. Several European studies done in the early 1990s demonstrated a higher rate.[12,13] The smaller prevalence of ESBL versus VRE illustrates the fact that at this point in time, VRE has a higher endemic prevalence than ESBL in our ICUs. A limitation of our study is that the sensitivity of perirectal stool culture for detecting patients colonized with ESBL-producing bacteria has not been studied.

A co-carriage rate of VRE and ESBL has not been previously described. Among patients who had VRE, 11% were co-carriers of ESBL-producing bacteria. Among patients who had ESBL-producing bacteria, 47% had VRE. This high co-carriage rate is not unexpected in that risk factors for ESBL-producing bacteria are similar to risk factors for VRE.[13-16] Risk factors such as comorbidity, colonization pressure, time at risk, and antibiotic exposure are common for both VRE and ESBL and likely other antibiotic-resistant bacteria such as methicillin-resistant *S. aureus* and multidrug-resistant *Pseudomonas*. We can only speculate as to what the co-carriage rates of these other resistant bacteria are in our cohort. Antibiotics may be common risk factors because they disturb the intestinal flora and increase a patient's susceptibility to colonization and subsequent infection by many kinds of resistant bacteria.

The cost-effectiveness of active surveillance for VRE is still debated.[17,18] The strategy of passive surveillance for VRE has been shown to miss the 90% of patients who are colonized but do not manifest infection.[19-21] The isolation of patients who are colonized with VRE also likely leads to the isolation of patients who are co-colonized with other antibiotic-resistant bacteria. Hence, active surveillance for VRE should theoretically also lead to a decrease in patient-to-patient transmission of other antibiotic-resistant bacteria.

An important feature of a cost-effectiveness analysis is the microbiological cost of active surveillance. This topic is also debated.[22,23] Published costs for laboratory and technologist time for active surveillance for VRE are $4.59 for positive results and $13.77 for negative results.[22] These costs would be higher if specimens were processed for both VRE and ESBL-producing bacteria.

Our study demonstrates that the strategy of passive surveillance for ESBL-producing bacteria misses 69% of patients who are colonized but do not have positive clinical cultures either before or after the surveillance culture. Another benefit of active surveillance for ESBL-producing bacteria is that the active surveillance culture was positive an average of 2.6 days prior to the clinical culture among patients who had positive clinical cultures, so that patients could be isolated sooner.

Another important finding of this study is the negative predictive value of 99% in patients who were negative for VRE colonization. Of all patients negative for VRE colonization on admission to the ICU, only 1% are colonized with an ESBL-producing *E. coli* or *Klebsiella*. This suggests that future cost-effectiveness analyses may find that testing for ESBL-containing organisms is cost-effective only if patients are already colonized with VRE and only if infection control interventions would differ between those solely colonized with VRE and those co-colonized.

TABLE
VANCOMYCIN-RESISTANT *ENTEROCOCCUS* AND EXTENDED-SPECTRUM BETA-LACTAMASE–PRODUCING BACTERIA CO-COLONIZATION MATRIX

	No. of Patients Who Were ESBL Positive	No. of Patients Who Were ESBL Negative
VRE positive	15	121
VRE negative	17	1,209

ESBL = extended-spectrum beta-lactamase; VRE = vancomycin-resistant *Enterococcus*.

Patients who are colonized with VRE can also be co-colonized with other antibiotic-resistant bacteria such as ESBL-producing bacteria. Hence, active surveillance for VRE should also theoretically diminish the amount of patient-to-patient transmission of ESBL-producing bacteria. However, the marginal gain of active surveillance above the utility of clinical cultures for gram-negative resistant bacteria is slightly less than that for VRE. The cost-effectiveness of active surveillance for ESBL-producing bacteria and other antibiotic-resistant gram-negative bacteria has yet to be determined.

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