

# Third-Generation Cephalosporins and Vancomycin as Risk Factors for Postoperative Vancomycin-Resistant *Enterococcus* Infection

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**Objective:** To examine use of third-generation cephalosporins (3GCs) alone and in association with vancomycin hydrochloride as a risk factor for vancomycin-resistant enterococcus (VRE) infection in surgical patients.

**Design:** Case-control retrospective study analyzing antibiotic use in the 30 days preceding culture of VRE or vancomycin-sensitive enterococcus from an infected site.

**Setting:** A large tertiary care teaching hospital.

**Patients:** Surgical inpatients with VRE infections between September 3, 1993, and January 29, 1997, were matched with patients with vancomycin-sensitive enterococcus infections. Matches were based on surgical procedure, initial infection site, and immunosuppression. Matches were found for 32 of 50 surgical patients with VRE. Twenty matched pairs of patients were recipients of solid organ transplants.

**Main Outcome Measures:** Multivariate logistic re-

gression analysis was done to examine 3GCs and vancomycin as risk factors for VRE infection. Univariate analysis of use of other antibiotic agents and demographic data was also performed.

**Results:** Multivariate analysis showed significant differences in the use of 3GCs both alone and concurrently with vancomycin. Univariate analysis also showed higher use of metronidazole, concurrent vancomycin and metronidazole, concurrent vancomycin and ceftazidime, and all antibiotics combined in patients with VRE infections.

**Conclusions:** This matched control study showed that use of 3GCs, alone ( $P = .05$ ) or concurrently with vancomycin ( $P = .05$ ), was a risk factor for VRE infection in surgical patients. Judicious administration of third-generation antibiotics is warranted in surgical patients with other risk factors for VRE.

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SINCE THE late 1980s, group D enterococcus (GDEN), including *Enterococcus faecalis* and *Enterococcus faecium*, has emerged as an important nosocomial pathogen.<sup>1,2</sup> Once thought to be a nonpathogen or a copathogen, GDEN has been shown to have the virulence factors necessary to cause infections in varied patient populations.<sup>3,4</sup> Strains of GDEN resistant to multiple antibiotics have been studied as clinically problematic pathogens in surgical patients.<sup>5-7</sup> Increased incidence of vancomycin-resistant enterococcus (VRE) has been identified as a serious complication in recipients of solid organ transplants.<sup>8,9</sup>

Throughout the emergence of GDEN as a recognized pathogen, antibiotic use has been cited consistently as a significant risk factor for infection.<sup>10-12</sup> As antibiotic resistance among enterococci developed and VRE became endemic in many institutions, vancomycin hydrochloride and

third-generation cephalosporins (3GCs) have been associated repeatedly with acquisition of VRE.<sup>13-15</sup> The most commonly held theory on the mechanism by which broad-spectrum antibiotics such as 3GCs select for VRE is a disruption of the patient's endogenous intestinal microbial flora.<sup>16,17</sup> This disruption allows for accelerated growth of opportunistic pathogens, such as enterococci.<sup>18</sup>

Fairview-University Medical Center, in Minneapolis, Minn, is a large (>300-bed) tertiary care teaching hospital. A marked increase in the number of surgical patients with VRE beginning on September 3, 1993, prompted the design of a 1:1 matched case-control study to investigate 3GC use as a risk factor for infection with VRE. By matching patients with VRE infections and those with vancomycin-sensitive enterococcus (VSE) infections, we sought to identify the risk factors specific for infection with VRE as opposed to infection with enterococci in general.

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## PATIENTS AND METHODS

### VRE CASE PATIENTS

Cases of VRE were defined as adult surgical inpatients (aged >18 years) who had undergone a surgical procedure within 2 to 60 days preceding VRE isolation. Only patients with clinically significant VRE cultures were included. *Clinical significance* was defined as GDEN isolation from a normally sterile site or from a diagnosed locus of infection. Significant culture sites included abdominal fluid or abscess, urine, blood, extremity tissue, bile, and sputum. In patients with multiple sites of VRE isolation, only the first clinically significant isolate of VRE was included for analysis. Patients who had been transferred from another inpatient facility were excluded.

### VSE CONTROL PATIENTS

The VSE controls were defined as adult inpatients in the surgical service with VSE isolates from clinically significant sites. The VSE controls were matched with VRE cases by culture site, immunosuppression, and primary surgery type. Surgical procedures were grouped as involving solid organ transplant, bowel, abdominal cavity (nonbowel), thoracic cavity, or extremity. When more than 1 match possibility was available, random-number generation was used to pair VSE controls and VRE cases.

### MEDICAL RECORD REVIEW

Clinical and demographic information was retrospectively collected for the 60-day period preceding positive

results of VRE or VSE culture. The use of all antibiotic agents within 30 days of culture was recorded, focusing on vancomycin, 3GCs, and concurrent use of the 2 agents. Other demographic and clinical characteristics analyzed included potential nonantibiotic risk factors for VRE infection. These included age, sex, days in the hospital or intensive care unit (ICU), primary surgical procedures, number of visits to the operating room, primary disease, and Acute Physiology and Chronic Health Evaluation (APACHE) II<sup>19</sup> score at the time of culture. For patients with positive urine cultures, the number of days with an indwelling urinary catheter was noted. Information about patients undergoing peritoneal dialysis or hemodialysis was also collected. Death and the presence of an initial monomicrobial GDEN culture were tracked as outcomes rather than risk factors for infection.

### STATISTICAL METHODS

Multivariate conditional logistic regression analysis of clinical and demographic data was performed to compare 3GC use and patient characteristics of the VRE case patients and VSE controls. Infection with VRE was defined as the outcome measure. Univariate analysis of all other numerical data was carried out by means of a paired Wilcoxon signed rank test. In addition, the paired Wilcoxon univariate analysis was used to compare the groups of patients included in this study with those excluded because of a lack of matches. The McNemar test was used to analyze all factors with yes or no answers. In all instances,  $P < .05$  was considered significant.

## RESULTS

### VRE CASES AND VSE CONTROLS

Between September 3, 1993, and January 29, 1997, 116 cases of VRE were identified by the hospital laboratory. Patients admitted to services accounted for 88 cases of VRE. Clinically significant VRE was isolated from 50 of those patients. Complete medical records were available for 44 of these VRE patients, and 36 fit the criteria for inclusion. Matched controls were found for 32 patients.

The remaining 4 VRE cases, excluded because of a lack of matches, were comparable with the study group with respect to age, use of vancomycin and 3GCs, APACHE II score, and days in the hospital and ICU ( $P = .58, .54, .09, .06$ , and  $.35$ , respectively). The 25 excluded VSE controls were comparable with the VRE group with respect to age, APACHE II score, and days in the hospital ( $P = .08, .37$ , and  $.79$ , respectively). There was a significant difference only in the concurrent use of vancomycin and 3GCs and in the number of days in the ICU ( $P = .03$  and  $.006$ , respectively).

### PATIENT DEMOGRAPHICS, CHARACTERISTICS, AND ANTIBIOTIC USE

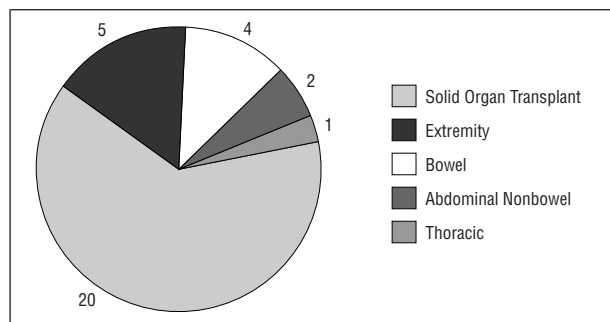
More than 60% of the patients in this study (20 of 32) were recipients of solid organ transplants (**Figure 1**). The remainder of our cases and matches had a variety of

surgical procedures, including intestinal resection, extremity vascular bypass, and exploratory laparotomy. The most common site for isolation of GDEN was from abdominal fluid (**Figure 2**). The least common site of isolation was sputum.

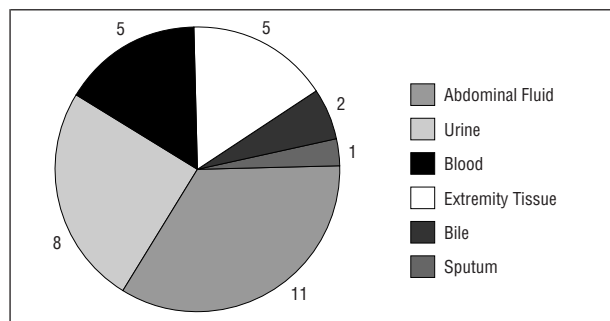
On multivariate analysis, VRE cases and VSE controls showed a significant difference in the days of use of 3GCs, both separately and concurrently with vancomycin (**Figure 3**). Relative risk for VRE infection was 1.8 for vancomycin, 1.6 for 3GCs, and 2.7 for concurrent use of 3GCs and vancomycin. There were no significant differences in age, APACHE II score, days in the hospital or ICU, or days between surgery and culture.

Univariate analysis of use of all groups of oral and intravenous antibiotics was performed to identify other differences between the VRE cases and VSE controls. Significant differences were demonstrated in the use of several of these agents (**Table 1**). As expected, there was a significant difference in the use of 3GCs and vancomycin. In addition, metronidazole hydrochloride, concurrent vancomycin and metronidazole, concurrent vancomycin and ceftazidime, and total antibiotic use were significantly higher in patients with VRE infection. Use of second-generation cephalosporins was significantly lower in VRE cases than in VSE controls.

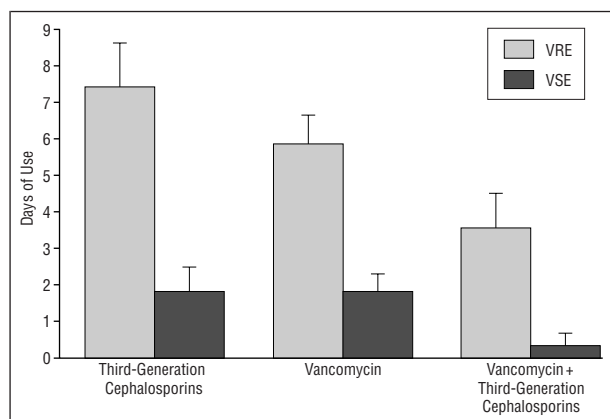
Univariate analysis of other clinical and demographic data indicated other differing factors between the VRE cases and VSE controls (**Table 2**). Patients with



**Figure 1.** Primary surgical procedures in matched pairs of vancomycin-resistant enterococcus cases and vancomycin-sensitive enterococcus controls (numbers of cases are given).



**Figure 2.** Site and frequency of group D Enterococcus isolation in matched pairs of vancomycin-resistant enterococcus cases and vancomycin-sensitive enterococcus controls (numbers of cases are given).



**Figure 3.** Duration of use of third-generation cephalosporins and vancomycin in vancomycin-resistant enterococcus (VRE) cases and vancomycin-sensitive enterococcus (VSE) controls. Within each treatment group,  $P < .05$  in multivariate analysis for VRE vs VSE. Data are shown as mean  $\pm$  SE.

VRE infection were in the hospital and ICU for longer periods than their cohorts. In addition, patients with VRE infection had slightly higher APACHE II scores at the time of positive results of culture. Initial VRE cultures were more likely to be monomicrobial than the matched results of VSE cultures from the same sites. Patients with positive VRE urine cultures had indwelling urinary catheters in place longer than their VSE counterparts.

## COMMENT

The results of this study indicate that use of 3GCs is a significant risk factor for infection with VRE, espe-

**Table 1.** Univariate Analysis of Duration of Antibiotic Use in the 30 Days Preceding Positive Results of Culture\*

	Days of Use, Mean $\pm$ SE		P
	VRE Cases	VSE Controls	
Penicillins	2.9 $\pm$ 0.8	3.1 $\pm$ 1.1	.76†
Aztreonam, imipenem/cilastatin	1.7 $\pm$ 0.9	0.5 $\pm$ 0.3	.38†
First-generation cephalosporins	0.7 $\pm$ 0.3	0.8 $\pm$ 0.4	.99†
Second-generation cephalosporins	0.9 $\pm$ 0.6	1.6 $\pm$ 0.7	.05
Third-generation cephalosporins	7.4 $\pm$ 1.3	1.8 $\pm$ 0.6	<.001
Vancomycin hydrochloride	5.8 $\pm$ 0.8	1.8 $\pm$ 0.4	<.001
Aminoglycosides	1.1 $\pm$ 0.5	0.6 $\pm$ 0.4	.59†
Erythromycin, neomycin sulfate, or clindamycin	1.3 $\pm$ 0.6	1.1 $\pm$ 0.5	.92†
Metronidazole hydrochloride	5.0 $\pm$ 1.1	0.9 $\pm$ 0.4	<.001
Quinolones	3.0 $\pm$ 1.1	1.3 $\pm$ 0.8	.06†
Trimethoprim/sulfamethoxazole	12.6 $\pm$ 2.1	11.8 $\pm$ 1.9	.65†
Antifungals	31.0 $\pm$ 4.4	22.2 $\pm$ 3.7	.07†
Antivirals	12.5 $\pm$ 2.3	11.6 $\pm$ 2.2	.64†
Vancomycin and third-generation cephalosporins	3.5 $\pm$ 0.8	0.3 $\pm$ 0.4	<.001
Vancomycin and ceftazidime	1.9 $\pm$ 0.6	0.0 $\pm$ 0.3	.002
Vancomycin and metronidazole	1.8 $\pm$ 0.6	0.0 $\pm$ 0.3	<.001
Total antibiotics	89.1 $\pm$ 9.9	56.2 $\pm$ 7.9	<.001

\*VRE indicates vancomycin-resistant enterococcus;

VSE, vancomycin-sensitive enterococcus.

†Not significant.

**Table 2.** Patient Demographics and Clinical Data\*

	VRE Cases (n = 32)	VSE Controls (n = 32)	P
Hospital days	31.1 $\pm$ 3.1	19.5 $\pm$ 2.2	<.001
ICU days	6.7 $\pm$ 2.4	3.1 $\pm$ 1.7	.03
APACHE II score	12.0 $\pm$ 0.8	10.2 $\pm$ 0.8	.04
Age, y	49.2 $\pm$ 2.8	52.4 $\pm$ 2.6	.18†
OR visits	2.1 $\pm$ 0.3	1.5 $\pm$ 0.1	.06†
Urinary catheter days‡	20.6 $\pm$ 2.2	7.2 $\pm$ 1.1	.04
Mortality, No. (%)	6 (19)	1 (3)	.13†
Peritoneal dialysis, No. (%)	5 (16)	3 (9)	.69†
Hemodialysis, No. (%)	10 (31)	7 (22)	.51†
Monomicrobial culture, No. (%)	15 (47)	5 (16)	.009

\*VRE indicates vancomycin-resistant enterococcus;

VSE, vancomycin-sensitive enterococcus; ICU, intensive care unit;

APACHE II, Acute Physiology and Chronic Health Evaluation II; and

OR, operating room. Data are mean  $\pm$  SE unless otherwise specified.

†Not significant.

‡Patients with urinary tract infections only; n = 8.

cially when combined with vancomycin (relative risk, 2.7 for vancomycin and 3GCs together). The incidence of use of 3GCs, either independently or concurrently with vancomycin, was higher in surgical patients with VRE than in matched patients with similar VSE infections.

In addition, metronidazole was significantly associated with VRE acquisition in the univariate analysis, whereas second-generation cephalosporins were associated with VSE rather than VRE infection. As in any study involving a small sample and variables that are substantially correlated, univariate analyses serve to point out potentially important factors but lack the ability to iden-

tify which ones will be significant when the entire complex system is taken into account.

Previous publications from our institution have examined the course of VRE outbreaks in hospitalized recipients of solid organs. In patients with pancreas transplants, previous use of vancomycin and metronidazole was found to be a risk factor for VRE infection.<sup>20</sup> Furthermore, a separate prospective study found that recognized fecal colonization preceded VRE infection in 50% of cases.<sup>21</sup> This lends credence to the theory that VRE infections arise from a patient's endogenous microbial flora. At the same time, the 50% figure reminds us that infection control procedures still have a substantial role in suppression of further VRE dissemination.

A recent matched, 1:1 control study of 145 patients also supported the theory that 3GCs, alone or with vancomycin, are associated with VRE infection.<sup>22</sup> Colonized and infected patients from both medical and surgical services were included. In addition, VRE cases were matched to VSE controls by date of GDEN culture only. While this helps to equalize the risk of VRE acquisition from contaminated health care workers, we believed that a match by surgery type, culture site, and immunosuppression represented the infected surgical patient more accurately.

On the basis of the obvious connection between vancomycin and VRE infection, many institutions have implemented restriction policies for glycopeptide administration. Unfortunately, control of vancomycin use has shown less than ideal efficacy in the suppression of VRE infection development and dissemination.<sup>23</sup> Judicious restriction of 3GCs has been shown to reduce significantly the incidence of enterococcal stool carriage in hospitalized patients.<sup>24</sup> This, in conjunction with our study and the growing evidence that use of 3GCs commonly precedes VRE infection in surgical patients, suggests that controlled use of specific cephalosporins may be necessary to minimize the growing nosocomial VRE dilemma.

Both the Surgical Infection Society<sup>25</sup> and Hospital Infection Control Practices Advisory Committee<sup>26</sup> have previously recommended vancomycin restriction to delay the emergence of VRE infection. We suggest that conservative or restricted use of 3GCs be added to these recommendations. On the basis of our study, the restriction of ceftazidime in surgical patients with multiple risk factors for VRE acquisition or infection is warranted. This, in conjunction with continued vigilant environmental precautions and isolation protocols, may help moderate the spread of VRE infection.

Since the initiation of this study, several cases of *Staphylococcus aureus* infection have emerged in the United States with intermediate resistance to vancomycin.<sup>27</sup> In multiple laboratory experiments, VRE has been proved capable of transferring resistance plasmids to *S aureus*.<sup>28</sup> Although this has not been proved to occur in vivo, the mere possibility should serve as another extremely persuasive reason to do all that is possible to control VRE infection development and propagation.

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