Letters to the Editor

Vancomycin-Resistant Enterococci: Risk Related to the Use of Intravenous Vancomycin in a University Hospital

To the Editor:

Several case-control studies have identified clinical and epidemiological risk factors for colonization and infection with vancomycin-resistant enterococci (VRE), including the use of intravenous vancomycin.[1-8] No prospective data are available regarding the incidence of VRE colonization or infection in patients treated with intravenous vancomycin. Accordingly, we undertook this prospective study from October 1995 through February 1996 to assess the risk of acquisition of VRE in a cohort of patients receiving intravenous vancomycin in an institution where VRE are known to be prevalent.

All inpatients over the age of 18 who had received intravenous vancomycin therapy for less than 48 hours and who were not expected to be discharged from the hospital within 4 days were eligible.

A baseline (day 1) perianal culture was obtained using Culturette II swabs (Becton-Dickinson & Co, Cockeysville, MD). Perianal cultures were repeated on days 4, 7, 11, 14, and weekly thereafter throughout hospitalization. Rectal swabs were plated directly onto Enterococcosel agar (BBL, Becton-Dickinson Microbiology Systems). A 30-µg vancomycin disk was placed in the center of the plate. Plates were incubated at 35°C and examined 24 and 48 hours later for the presence of black colonies. Esculin-positive colonies were subcultured to sheep blood agar plates (BBL, Becton-Dickinson Microbiology Systems). Enterococci were identified based on colony morphology, Gram stain characteristics, and hydrolysis of L-pyrrolidonyl-β-napthylamide (PYR; Murex Diagnostics, Dartford, England). Speciation and susceptibility testing were performed using the MicroScan Pos ID type 6 panel and MicroScan Walkway-40 instrument (Dade International, Inc, West Sacramento, CA). Tests for motility and pigment production were performed to distinguish *Enterococcus faecium* from *Enterococcus gallinarum* and *Enterococcus casseliflavus.*

Demographic and clinical data were collected (Table). Patients whose initial culture grew VRE were considered to be *prevalent* cases and excluded from further analysis. Patients who grew VRE following an initial negative culture were designated as *converters.* Patients whose cultures were negative throughout their hospitalization were considered to be *nonconverters.* The evaluation of risk factors considered events prior to detection of VRE, and the duration of surveillance was similar for both

TABLE
CONVERTERS VERSUS NONCONVERTERS

Variable Subjects	Converters No. (% or SD)		Non-converters No. (% or SD)	
Continuous*				
Age in years (SD)	58	(13.6)	57	(14.4)
Length of stay in days (SD)	26.62	(20.9)	14.13	(30.4)
Duration of vancomycin therapy in days (SD)	9.1†	(9.7)	6.3	(8.5)
Categorical‡				
M/F (% male)	3/5	(37.5)	78/61	(56.1)
Prior institutionalization§	4	(50.0)	56	(40.3)
ICU stay	4	(50.0)	60	(43.2)
GI procedures‖	1	(12.5)	40	(28.8)
Tube feedings	2	(25.0)	13	(9.40)
Indwelling urinary catheter	5	(62.5)	99	(71.2)
Central catheter	4	(50.0)	28	(20.1)
Surgical drains	1	(12.5)	46	(33.1)
Diarrhea	2	(25.0)	22	(15.8)
Renal disease	3	(37.5)	6	(4.32)
Systemic steroids	1	(12.5)	43	(30.9)
Malignancy	4	(50)	40	(28.7)
Severity of illness¶				
Non-fatal	1	(12.5)	68	(48.9)
Rapidly/ultimately fatal	7	(87.5)	71	(51.0)
Clostridium difficile infection	2	(25.0)	1	(0.72)
Received cephalosporins	3	(37.5)	59	(42.4)
Received anti-anaerobic antibiotics	4	(50.0)	53	(38.1)
Service				
Medicine	6	(75.0)	28	(20.2)
Surgery	2	(25.0)	94	(67.6)
Hematology/Oncology	0		17	(12.2)

Abbreviations: GI, gastrointestinal; ICU, intensive-care unit; M/F, male/female; SD, standard deviation.
* Values expressed as means.
† Average number of days prior to conversion for converters.
‡ Values expressed as number of patients (%).
§ Overnight residence in a hospital or nursing facility within 3 months of study entry.
‖ Endoscopy, sigmoidoscopy, barrium enema.
¶ Nonfatal (not expected to die within 5 years), ultimately fatal (50% chance of dying within 5 years), rapidly fatal (50% chance of dying within 2 months).

groups. Patients were assigned a severity of illness rating by the principle investigators.[9]

Continuous variables were analyzed using the Wilcoxon's rank sum test. Discrete variables were analyzed using Fisher's Exact Test.

Of 266 patients who met initial screening criteria, 153 gave consent and were enrolled. Cultures from 6 (3.9%) of the 153 enrolled patients revealed VRE at the time of study entry. The 147 patients who were culture-negative at the time of study entry comprised the prospective study group.

The incidence of conversion of patients from VRE culture-negative to VRE culture-positive during the study period was 5.4% (8/147). Converters and nonconverters differed significantly only in regard to presence of renal failure: 3 (37.5%) of 8 converters had renal disease, compared to 6 (4.31%) of 139 nonconverters (P=.008).

Four of eight converters had positive cultures by day 4 of the study; the remaining patients converted on days 7, 11, 42, and 49. Nonconverters received an average of 6.3 days of vancomycin (median, 3; range, 1-80) during their hospitalization, compared to 9.1 (median, 5.5; range, 1-31) days of vancomycin prior to conversion for converters (P=.26).

Our study was designed to test the correlation between duration of vancomycin exposure and development of VRE colonization, but not to test if any exposure to vancomycin would result in VRE colonization. The unanticipated low rate of conversion resulted in inadequate statistical power; hence, the difference in duration of vancomycin therapy between converters and nonconverters did not achieve statistical significance.

It should be noted that two converters had received ≤48 hours of vancomycin therapy. If these two early converters were reclassified as prevalent cases (ie, assuming that their initial negative culture represented a false-negative result), there would have been a statistically significant difference in the mean duration of vancomycin therapy between the remaining six converters and the nonconverters (11.7 vs 6.3 days, respectively; P=.03).

Although these findings are anecdotal, consideration of these data is clinically and epidemiologically instructive and raises a number of important issues regarding the risk of VRE colonization attributed to vancomycin. First, the correlation between intravenous vancomycin use and subsequent intestinal colonization with VRE may be exaggerated due to the methodological constraints of retrospective studies. For example, in our study, 6 of 153 patients had positive cultures for VRE at the time of study entry. Had we included the 6 prevalent cases for analysis, the association between vancomycin use and the acquisition of VRE would have been artificially inflated (14/153, 9.1% vs 8/147, 5.4%).

Second, screening methods used to detect gut colonization with VRE also may inflate estimates of risk. Weinstein and colleagues estimated the sensitivity of a single perianal swab to be 79%.[10] If VRE is detected after this time, potentially one in five patients erroneously will be assigned as incident, not prevalent, cases.

And finally, a third factor that may inflate the risk of VRE gut colonization being attributed to intravenous vancomycin is that the drug (as well as other antibiotics) may increase the sensitivity of the screening method.

Here, the assumption is that vancomycin exerts selective pressure on the gut, raising undetectable levels of preexisting VRE to detectable levels. In such a case, vancomycin administration does not "cause" VRE, nor does it increase the odds that the individual patient will acquire VRE. However, it results in an apparent increase in incidence. More importantly, if selection pressure is exerted by vancomycin, then those patients with preexisting VRE will increase their endogenous levels of VRE in proportion to the duration of therapy, serving as epidemiological reservoirs for further dissemination of the epidemic. Unfortunately, no recent studies have addressed the effect of intravenous vancomycin on the gastrointestinal tract to determine whether this hypothesis is true.

In support of these arguments for "risk inflation," it is interesting to note that, of the eight patients who became colonized during the study, two had received vancomycin for less than 1 week and two had received vancomycin for less than 2 days. There are several possible explanations for the presence of these organisms in these subjects, including de novo mutation of existing enterococci (highly unlikely given VRE's complex plasmid-mediated resistance factors); exposure from other patients or hospital personnel; contamination of samples in the laboratory; and limited sensitivity of screening with perianal swabs.

In summary, our data suggest that the current incidence of VRE colonization in our hospital and elsewhere is higher than can be explained by vancomycin use. Accordingly, limitations on intravenous vancomycin use may not be a panacea. However, if intravenous vancomycin restriction does not directly decrease VRE incidence, it may indirectly decrease the overall prevalence of VRE by limiting the biological reservoir of the bacteria.

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Hepatitis C Virus and Professional Risk in Anesthesia and Intensive Care: A Case Report

To the Editor:

Hepatitis C virus (HCV) is an RNA virus discovered in 1989, which is responsible for most non-A, non-B hepatitis.[1] HCV infection is serious; it becomes chronic in 80% of cases, leads to cirrhosis in 20%, and rarely can lead to a hepatocellular carcinoma.[2-4] Transmission predominantly is parenteral. Infection due to professional exposure is thought to be unusual.[4]

Through the case of a physician infected by HCV while on duty, the authors wish to remind readers of the need for all medical staff, especially emergency room personnel, to take appropriate precautions to avoid exposure to blood-transmitted infectious diseases.

A 33-year-old male Tunisian anesthesiologist was in training abroad. He had no medical or surgical history and was HCV seronegative in April 1995. In May 1996, while on duty in the emergency room, he attended a traffic accident victim. When the patient's anti-shock trousers were taken off, a bleeding wound appeared. The physician, who already had taken his gloves off, instinctively tried to stop the bleeding with his bare hands, but his fingers had minor cuts.

Blood tests for HCV carried out on the patient were positive, and 3 months later the physician developed jaundice, asthenia, and hepatitis with serum transaminases 20 times normal. The liver ultrasound scan was negative.

Serology was negative for A, B, and E hepatitis, as well as for cytomegalovirus, human immunodeficiency virus, and herpes. Hepatitis C antibody was positive for serotype 1, using both enzyme-linked immunosorbent assay and recombinant immunoblot assay techniques with a positive polymerase chain reaction.

Interferon therapy was started in September 1996, with 3 million units administered three times per week. After 6 months of treatment, transaminases failed to return to normal and HCV polymerase chain reaction remained positive. Ribavirine was added but without response, and treatment was interrupted after 1 year.

Blood transmission of HCV is well documented and recognized.[5] For medical personnel, the risk of occupational infection by HCV is low but real. In most cases, it is due to accidental needlesticks. The best prevention consists in strict compliance with Universal Precautions. Healthcare workers should not engage in such hazardous maneuvers as recapping needles; it is important to provide special containers for used needles, use disposable supplies, and wear gloves, glasses, and other protective gear.[4,6]

Hepatitis C is serious and, despite the promising results obtained through treatment by interferon, prevention remains the best and most effective protection since no vaccine is yet available.[4-6]

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Age-Specific Rates of Serological Immunity in Patients With a Negative History for Varicella Infection

To the Editor:

With the licensure of the chickenpox vaccine (Varivax, Merck & Co, West Point, PA) in March 1995, the question of the true population rate of immunity to the varicella-zoster virus (VZV) has become an important issue in designing immunization strategies. This is particularly true in hospital work forces, where a chickenpox exposure necessitates major workforce modifications.

Three recent serological studies have examined populations of hospital workers.[1-3] They found that from 90% to 95% of the workers were immune. They also found that from 72%[1] to 90%[3] of those workers who had no history of varicella had protective antibodies to VZV. McKinney et al found age to be a significant variable.[2] They tested 241 hospital workers, 93 of whom were younger than 35 years. In that age group, 7 (64%) of 11 workers who had no history of VZV infection were in fact immune. All workers over age 35 who were tested were immune, whether they had a history of varicella or not. While this is a limited, nonrandom sample with small size, it would be expected to reflect the general population.

Kelley et al have studied antibody levels to many childhood illnesses in Army recruits.[4] They found that the seronegativity rate for varicella, adjusted to the 15- to 24-year-old US population in 1980, was 6.9%. Varicella susceptibility was significantly greater in females and blacks. In an unadjusted analysis, 11.8% of the female population was seronegative, compared with 7.7% of males. Of the 1,048 recruits who had a positive history of varicella, 27 (2.6%) were negative. Of the 211 recruits who had a negative history for varicella infection, 33 (11.5%) were negative. There was a trend to higher seropositivity with older age in this group. Importantly, Kelley documented that 97.4% of people who believe they are immune to varicella are so. Thus, the issue for assuring immunity within a population or work force is what per-