Intensive Care Med (2002) 28:692–697
DOI 10.1007/s00134-002-1276-8

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Vancomycin-sensitive and vancomycin-resistant enterococcal infections in the ICU: attributable costs and outcomes

Accepted: 21 February 2002
Published online: 12 April 2002

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Abstract *Objectives:* To determine the economic and clinical outcomes associated with infection with vancomycin-resistant *Enterococcus* (VRE) and to compare these outcomes to those associated with infection with vancomycin-sensitive *Enterococcus* (VSE).
Methods: During a 3-month, prospective, cohort study of 117 high-risk, critically ill patients we collected complete clinical and demographic and ICU cost data from all patients during their ICU stays.
Results: After adjusting for variables in a stepwise multiple regression model VRE infections were associated with a median attributable increased ICU cost per patient of $33,251 (38,088 euros) and an increased length of hospital stay (LOS) of 22 days, while VSE infections were associated with an increased cost of $21,914 (25,102 euros) and an increased LOS of 27 days. The effect of VRE and VSE infections were not significantly different. Over the entire cohort the attributable cost per ICU patient day associated with VRE infection was $304 (348 euros).
Conclusions: The attributable cost of ICU care associated with VRE infection is $33,251 (38,088 euros) and per ICU patient day was $304 (348 euros). VRE and VSE infections do not differ in associated cost of ICU care, LOS, or mortality. Any VRE control strategy is be cost-effective if the overall cost per ICU patient-day is less than $304 (348 euros).

Keywords *Enterococcus* species · Vancomycin · Vancomycin resistance · Epidemiology · Cost · Outcome

Introduction

Since the first reports of vancomycin resistance among clinical isolates of enterococci were reported in 1988 [1], these infections have become increasingly common, particularly among critically ill patients [2, 3]. While vancomycin resistance among enterococcal isolates increased in nationally acquired hospital-wide data from 0.3% in 1989 to 7.9% in 1993, vancomycin resistance in the ICU increased to 13.6% in the same period. Although vancomycin-resistant *Enterococcus* (VRE) often are resistant to available antibiotics, enterococci are not extremely pathogenic [4], and these infections tend to occur in patients who already suffer from multiple serious medical

problems [5]. Several studies have evaluated whether vancomycin resistance per se is associated with increased mortality by comparing VRE and vancomycin-sensitive *Enterococcus* (VSE) infections. The results of these studies conflict, with some suggesting higher mortality [6, 7] in VRE than VSE infections, and others showing no such association [8, 9]. Therefore the contribution of vancomycin resistance per se to patient morbidity and mortality remains controversial.

The cost implications of VRE infection are less well known. In surgical intensive care unit (SICU) patients who survive nosocomial bloodstream infections costs attributable to these infections have been estimated to be $40,000 [10]. One study reported that patients with VRE bloodstream infections had average hospital cost more than $27,000 greater than those of patients with VSE bloodstream infections [7]. Despite the uncertainty regarding the clinical and economic significance of VRE infections the Centers for Disease Control and Prevention have advocated strict infection control measures [11].

To assess mortality, length of stay (LOS), and cost of care associated with VRE and VSE infections in critically ill patients at our institution we evaluated these outcomes in 117 consecutive high-risk patients in the Surgical (SICU) and Medical intensive care unit (MICU) at Johns Hopkins Hospital.

Materials and methods

Patients

This prospective cohort study of the epidemiology of VRE infections was carried out in all 129 patients admitted to the Johns Hopkins Hospital SICU and MICU during a 3-month period in 1996. Johns Hopkins Hospital is a tertiary and quaternary care, university-affiliated, 1000-bed teaching hospital. The SICU has 16 beds and the MICU 12 beds. The only inclusion criterion for the study was an expected LOS of 3 days or longer. Patients were included in the final analysis only if they met the 3-day LOS criterion, or if they died before spending 3 days in the ICU. The study was approved by the Johns Hopkins Joint Institutional Review Board, and informed consent was waived for this data collection. Of 129 recruited patients 117 (median age 56 years) met the eligibility criteria – 42 in the MICU, 75 in the SICU. Their baseline characteristics are summarized in Table 1.

Table 1 Characteristics of 117 patients in cohort

	n	%
Age, median (years)	56	
APACHE II, median	21	
Gender: men/women	54/63	46/54
Race: white/black/other	76/35/6	65/30/5
Unit: SICU/MICU	75/42	64/36
Chronic obstructive pulmonary disease	18	15
Human immunodeficiency virus	7	6
Malignancy	19	16
Solid organ transplant	13	11
Steroid use	27	23
Chemotherapy	3	3
Renal failure	33	28
Surgery	60	51
Liver transplant during ICU stay	8	7
Cirrhosis	26	22

Clinical data collection

We prospectively collected clinical and demographic data, including Acute Physiology and Chronic Health Evaluation II (APACHE II) score, interventional and diagnostic procedures, use of antibiotics and immunosuppressive drugs, underlying medical conditions, and the results of all clinical cultures, biopsies, and autopsies. On enrollment to the study, twice weekly, and at discharge from the ward we obtained surveillance cultures from five sites: endotracheal aspirate, gastric fluid, oropharynx, rectum, and urine. The results of surveillance cultures were shared with patients' clinicians but were not part of infection definitions. Surveillance cultures were obtained only while patients were in the ICU. Study patients readmitted to the ICU were reenrolled and surveillance cultures were resumed.

Economic data collection

Maryland hospitals report to the Health Services Cost Review Commission. Medical services and their associated costs were extracted from the hospital billing database. Charges billed by the hospital are divided into eight categories: routine (room and board, etc), operating room, pharmacy, radiology, laboratory, supplies, "therapy" (includes physical, occupational, and respiratory therapy), and blood products/miscellaneous. Cost data from the hospital billing database were available as patient bill charges. In order to convert charges to costs we examined the cost/charge ratios among the hospital departments. The coefficient of variation of the cost/charge ratios among the individual billing departments in the hospital for 1996 was 2.8. We used the cost charge ratio for the hospital overall. All costs reported are hospital costs in 1996 U.S. dollars.

Endpoint definitions

Definitions of infection were determined before initiation of the study. A group of at least three physicians and the study coordinator evaluated each patient at his/her completion of the study to determine whether the patient met the infection definition. All infections included the presence of clinical signs of infection such as fever, white blood cell count, and the need for vasoactive agents or other organ system support consistent with infection as an underlying cause. Urinary tract infections were defined by the presence of more than 100,000 cfu/µl in a clean catch specimen or more than 10,000 cfu/µl in a catheter specimen. The presence of pyuria or leukocyte esterase was not uniformly applied in the diagnosis of infections. Bacteremia was defined as a positive blood culture, and catheter colonization as a positive vascular catheter culture with at least 15 cfu [12]. Wound infections were defined according to Centers for Disease Control criteria [13]. Colonization with VRE was defined as isolation of VRE in the absence of any of the above infection definitions. All patients with infections were treated with appropriate antimicrobial agents. This included either ampicillin (or equivalent) and vancomycin. For VRE the unit sensitivities suggested that rifampin, tetracycline, or chloramphenicol were most beneficial. High-dose ampicillin and aminoglycosides were ineffective. Quinpristin/dalpopristin and linezolid were not available. No isolate was panresistant.

Microbiology

Antibiotic susceptibility testing was performed by Mueller-Hinton agar dilution, according to the National Committee for Clinical Laboratory Standards guidelines [11]. Vancomycin resistance was defined as growth of a bacterial isolate in the presence of at least 16µg/ml vancomycin.

Statistical analysis

Data were analyzed using the Stata statistical package (version 5, College Station, Tex.,USA). Cost and LOS data were not normally distributed; however, log-transformed cost and LOS were normally distributed. Therefore in all linear regression models the data were first analyzed by using linear regression with log-transformed values as the outcome. Once the model was developed, the median values associated with the various covariates were determined by using a median regression model. Median regression is a means of model estimation that returns the median effect, rather than mean effect, of independent variables on the dependent variable, and provides large and conservative estimates of the standard errors [14]. In the stepwise regression model we used a p value of 0.25 as the threshold for inclusion in the model. Bivariate estimates of the effect of various clinical parameters on the outcomes of cost and LOS were made using the Kruskal-Wallis test. For all analyses a two tailed p value less than 0.05 was considered significant.

To examine whether day-to-day costs increased after patients became infected with VRE or VSE we used a random effects model for longitudinal data analysis [15]. The relationship between time to death and each of the clinical variables was assessed using the log-rank statistic. The Cox proportional hazards model was used to evaluate contributions of multiple independent variables on time to death. In the proportional hazards model VRE infection and VSE infection were treated as time-dependent covariates.

Fourteen patients were admitted to the ICU on more than one occasion during the study period. For patients all of their ICU time was summed, and the intervals out of the ICU were not included in analysis of events occurring in the ICU.

Results

In this cohort enterococci were the second most common group of isolates in bloodstream infections behind *Staphylococcus* spp. VRE and/or VSE infection developed in 34 of the 117 patients: only VRE in 6, only VSE in 16, and both in 6. The bloodstream was the most common site of infection with both VRE and VSE (Table 2); the distribution of infection sites did not differ between VRE and VSE infections. A total of 573 clinical and surveillance isolates obtained from the cohort during the study were positive for *Enterococcus* species, of which 302 (53%) were *E. faecium*, 132 (23%) were *E. faecalis*, 9 were *E. avium*, 3 were *E. casselliflavus*, and 128 enterococcal isolates were not specified. Of the enterococcal isolates 277 (48%) were VRE, of which 270 (97%) were *E. faecium*, 5 *E. faecalis*, and 2 *E. avium*. Thirty-one blood cultures and one catheter tip culture positive for enterococci were recovered from 13 patients – 14 VRE and 17 VSE. Because of the small numbers of overall infections and the multiple combinations of therapeutic regimens in both the VRE and the VSE group, no specific effect of antibiotic therapy could be obtained.

Table 2 Infections with VRE and VSE and their sites (percentages do not sum to 100% due to rounding)

	VRE		VSE		p[b]
	n	%	*n*	%	
Blood[a]	9	75	12	55	0.21
Urine	2	17	3	14	0.59
Wound	1	8	3	14	0.56
Abscess	0	0	4	18	0.16

[a] Bloodstream infections include one patient with a catheter colonization, >15 colonies of VRE on a vascular catheter tip
[b] VRE vs. VSE, χ^2

Cost

The 117 eligible patients spent a total of 1323 patient-days in the ICU, cost data for which were available on 1312 patient-days (99.2%). All costs are expressed in 1996 U.S. dollars. The unadjusted median cost for the entire ICU stay for the cohort was $21,521. The median ICU cost for the 6 patients with VRE infection only (excluding patients with VSE infection) was $33,224, while the median cost for the 16 patients with VSE infection only was $51,171 (Table 3). The median hospital cost for patients with neither infection was $18,863. The costs for VRE and VSE infections were both higher ($p<0.05$) than the median cost for those patients who never developed either infection; the costs associated with VRE in-

Table 3 Unadjusted cost and clinical outcomes for VRE and VSE infected patients; continuous outcomes compared using the Kruskal-Wallis test, dichotomous outcomes compared with χ^2 test

Outcome	VRE infection only[a]	VSE infection only[a]	Not infected	p
Median ICU cost (1996 dollars)	33,224 ($p=0.03$)	51,171 ($p<0.01$)	18,863	1.0
ICU mortality	5/12 (42%) ($p=0.27$)	9/22 (41%) ($p=0.14$)	21/89 (24%)	0.49
Median hospital mortality	8/12 (75%) ($p=0.01$)	10/22 (45%) ($p=0.18$)	26/89 (29%)	0.42
Median hospital length of stay (days)	57 ($p<0.001$)	52 ($p<0.001$)	17	0.80
Median ICU length of stay (days)	14 ($p<0.01$)	17.5 ($p<0.001$)	6	0.63

[a] p value vs. noninfected

Table 4 Final regression model for ICU cost (1996 dollars/2001 euros); coefficients represent median incremental cost associated with each of the covariates

Covariate	Adjusted coefficient	95% Confidence interval	*p*
VRE infection			<0.01
Dollars	33,251	20,182–46,320	
Euros	38,088	23,118–530,589	
VSE infection			<0.01
Dollars	21,914	11779–32048	
Euros	25,102	13,492–36,710	
Liver transplantation			<0.01
Dollars	29,427	13,693–22,637	
Euros	33,708	15,585–25,930	

Table 5 Effect of adjusting for length of stay on cost attributable to VRE and VSE infections; adjusted values represent median attributable costs from stepwise regression

Variable	Unadjusted change in ICU cost		Adjusted change in cost, excluding LOS	
	Median	95% CI	Median	95% CI
VRE infection				
Dollars	53,276	37,983–68,569	33,251	6,387–30,997
Euros	61,026	43,508–785,44	38,088	7,316–35,506
VSE infection				
Dollars	41,231	29,427–53,035	21914	10,103–29,321
Euros	47,229	33,708–60,750	25,102	11,572–33,587

fection and VSE infection were not significantly different from each other.

In bivariate analyses of the effect on ICU cost of all of the clinical variables in Table 1 the only factors found to be associated with increased ICU cost were liver transplantation and infection with VRE and VSE. APACHE II score was not significantly associated with ICU cost. In fact, increasing APACHE II score showed a nonsignificant inverse relationship with ICU cost, which is likely explained by the fact that APACHE II score was associated with increased mortality, and hence shorter length of ICU stay.

To verify that clinical factors other than VRE and VSE infection do not make an independent contribution to ICU cost we included all of the clinical variables in Table 1 in forwards and backwards stepwise linear regression on log-transformed costs. In both models the independent variables significantly associated with an increase in log dollars of ICU cost were VRE infection, VSE infection, and liver transplantation ($p<0.05$ for all). The incremental ICU cost associated with VRE and VSE infection was $33,251 and $21,914, respectively (Table 4). The incremental cost associated with liver transplantation was $29,427. Assuming an attributable ICU cost of $33,251 for each of the 12 VRE infections in this cohort, the cost across both infected and uninfected patients, per patient day, for the entire ICU 1312 patient days is $304.

In bivariate analysis the service categories that were associated with a statistically significant increase in cost among patients with VRE infection were room and board, pharmacy, laboratories, supplies, and therapy. VSE infection was also associated with increased cost for radiology services.

The variable with the greatest effect on ICU cost was LOS (Table 5). To examine whether becoming infected with VRE or VSE increased cost on a day-to-day basis we examined the effect of various clinical variables on ICU cost, using a random-effects model. In this analysis the only variables associated with daily ICU cost were cirrhosis and being in the SICU as opposed to the MICU. VRE and VSE infections were not associated with daily ICU cost.

Mortality

The overall in-hospital mortality in the study cohort was 33%, with an ICU mortality of 28%. The overall in-hospital mortality for VRE infected patients was 75%, compared to 45% for patients infected with VSE, while the ICU mortality figures were 42% and 41%, respectively (Table 3). The clinical factors showing a statistically significant association with hospital mortality in a bivariate analysis were APACHE II score, VRE infection, cirrhosis, and being in the SICU vs. the MICU. These variables were included in a stepwise logistic regression analysis, and all four remained significant ($p<0.05$). In a Cox proportional hazards model VRE infection was associated with a relative hazard of in-hospital mortality of 2.18 ($p=0.016$). VSE infection was not associated with either ICU mortality or hospital mortality in the Cox model.

Length of stay

The median hospital LOS for the cohort was 18 days, with a median ICU LOS of 8 days, with either VRE or VSE infection having a statistically greater LOS. However, LOS was similar in VRE and VSE infected patients. The independent variables found to have a significant ($p<0.05$) association with increasing length of hospital stay were VRE infection, VSE infection, solid organ transplantation, and renal failure (Table 1). The variables found to be significantly ($p<0.05$) associated with increased length of hospital stay in the stepwise model were VRE infection (22 days), VSE infection (27 days), liver transplantation (28 days), renal failure (9 days), and surgery during the ICU admission (6 days). VRE infec-

tion was associated with an increased ICU LOS of 8 days, compared to 11 days with VSE. This difference in length of between VRE and VSE infected patients was not significant.

Discussion

We have demonstrated that infection with VRE in critically ill patients is associated with greater ICU cost, in-hospital mortality, length of hospital stay, and length of ICU stay than uninfected, contemporaneous critically ill ICU patients. These associations are independent of multiple potentially confounding clinical variables, including antibiotic therapy. However, none of these associations was significantly different from the association found between these outcomes and infection with VSE.

The increased cost associated with enterococcal infections appears to be due predominantly to the increased LOS among infected patients. Furthermore, in a random-effects model daily ICU cost did not change after patients became infected with VRE or VSE, again suggesting that increased LOS rather than increased daily ICU cost is responsible for the association between enterococcal infection and ICU cost.

The point estimates from the multiple linear regression model suggest that the median increased cost per patient-day associated with VRE infection was $304. This could be considered the "break-even point" for the cost-effectiveness of any infection control strategy designed to limit the spread of VRE infections.

We evaluated the financial impact of VRE and VSE infections from the perspective of the hospital, and have assumed the acquisition costs to be those reported to the Health Services Cost Review Commission and derived from hospital charges. We have not, however, evaluated costs to society, such as lost wages, or the impact on quality adjusted years of life lost. Consideration of such costs is likely to substantially increase the economic impact of nosocomial enterococcal infection.

While we have demonstrated an association between enterococcal infection and outcomes such as LOS and ICU cost, the cause-effect relationship between the two has not been established. Enterococcal infection could occur because of underlying medical condition or result from an increased period at risk of infection due to a prolonged stay in the ICU or because of some other underlying condition leads both to enterococcal infection and increased LOS. In contrast to our findings, Linden et al. [5] showed that infection with VRE is associated with higher mortality, more frequent recurrence of infection, more invasive procedures, and longer LOS than matched controls infected with VSE. Although that study included many more VRE infections than did ours, it was a retrospective study, and, as recognized by the authors, cases were not strictly matched to controls. Further, that study did not control for any validated index of severity of illness, such as the APACHE II score. In contrast, several authors [8, 9, 16, 17, 18] did not find a significant difference in mortality associated with VRE and VSE, especially when controlling for severity of illness.

Two studies have reported the costs associated with VRE infections [7, 19]. In a retrospective comparison of 20 VRE infections and 31 VSE infections occurring over a 4-year period throughout a university-affiliated hospital the average cost associated with VRE bacteremia was $27,000 more per episode than the cost per episode of VSE bacteremia. The authors evaluated the effect of VRE infection on mean cost, rather than median cost, which could result in misleading conclusions, since cost data typically are not normally distributed. Furthermore, because these data were acquired over a 4-year period during which VRE infections became more common, most of the VSE infections occurred early in the study, while most of the VRE infections occurred later. As a result the increased cost associated with VRE infection could simply reflect inflation in health care costs over the course of their evaluation period. The authors did not address this effect, and did not adjust for it in their analysis. Finally, the authors did not adjust for any other clinical variables, such as severity of illness. The second study concludes that patients with less severe illness and VRE have increased costs, while those with severe underlying disease regardless of vancomycin resistance incur similar hospitalization costs [19].

One potential weakness of the present study is that, unlike most studies of outcomes of VRE infection, we included infections at sites other than the bloodstream, raising the possibility that the VRE infections under study were not comparable to the VSE infections. Our results might then be due simply to differences in the infection sites, rather than the effect of the pathogen itself. These infections, however, were prospectively defined, using accepted criteria for nosocomial infections. Furthermore, the majority of both the VRE and VSE infections were bloodstream infections, and the distributions of infection sites in the two groups were not significantly different.

The primary limitation of this study is its small number of infections with VRE and VSE. Of the 12 VRE-infected and 22 VSE-infected patients 6 were infected with both pathogens during their stay in the ICU. Therefore only 6 patients had only VRE infection, and only 16 patients had only VSE infection. This could obscure the effect of either pathogen alone, and substantially decreases the power to compare outcomes in the two groups. However, we included infection with both pathogens in all of our multiple regression models in order to control for the effects of each pathogen. Because simultaneous infection with VRE and VSE appears to be common, it will be important that future studies of the impact of VRE control for concurrent VSE infection. An addi-

tional problem raised by the small number of patients is the possibility that one or more outliers with very high or very low ICU cost or LOS could strongly influence the conclusions of our analyses. We attempted to avoid this by using conservative, nonparametric methods of analysis that should be resistant to outliers. Nonetheless the comparison of uninfected and patients infected with VRE or VSE remains valid, and demonstrates the important cost associated with ICU enterococcal infection.

One unique strength of this study is that it is prospective, which avoids the difficulty of the retrospective identification of suitable controls. In addition, because we limited our study to the ICU setting, the patients are comparable to each other in many respects. We have demonstrated that surgical patients appear to be at increased risk of infection and have a poorer outcome. This may be related to the inevitable violation of the epithelial barriers that occur in surgical patients. The disadvantage of studying a specific patient population such as ICU patients is that the study results may lack generalizability to patients in other clinical settings. We feel that the possible lack of generalizability is of little concern in the present case since VRE infections are a problem primarily of the critically ill patients defining the population under study.

In summary, this prospective observational nested cohort study of infection with VRE and VSE in the ICU setting shows that VRE and VSE infections both have a statistically significant association with LOS and cost of ICU care when compared with contemporaneous uninfected similarly ill ICU patients. However, the magnitudes of these associations were not different for the two pathogens. VRE infection, unlike VSE infection, appears to have an independent and statistically significant association with increased hospital mortality. However, VSE infection was associated with a statistically nonsignificant increase in mortality, and the magnitudes of the effects of VRE and VSE on hospital mortality are not different from one another. We find no evidence that among patients with *Enterococcus* infections, vancomycin resistance per se confers a worse outcome on ICU patients in terms of cost, LOS, or mortality.

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