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ORIGINAL ARTICLE

Attributable Costs of Enterococcal Bloodstream Infections in a Nonsurgical Hospital Cohort

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BACKGROUND. Vancomycin-resistant *Enterococcus* (VRE) bloodstream infections (BSIs) are associated with increased morbidity and mortality.

OBJECTIVE. To determine the hospital costs and length of stay attributable to VRE BSI and vancomycin-sensitive *Enterococcus* (VSE) BSI and the independent effect of vancomycin resistance on hospital costs.

METHODS. A retrospective cohort study was conducted of 21,154 nonsurgical patients admitted to an academic medical center during the period from 2002 through 2003. Using administrative data, attributable hospital costs (adjusted for inflation to 2007 US dollars) and length of stay were estimated with multivariate generalized least-squares (GLS) models and propensity score-matched pairs.

RESULTS. The cohort included 94 patients with VRE BSI and 182 patients with VSE BSI. After adjustment for demographics, comorbidities, procedures, nonenterococcal BSI, and early mortality, the costs attributable to VRE BSI were \$4,479 (95% confidence interval [CI], \$3,500–\$5,732) in the standard GLS model and \$4,036 (95% CI, \$3,170–\$5,140) in the propensity score-weighted GLS model, and the costs attributable to VSE BSI were \$2,250 (95% CI, \$1,758–\$2,880) in the standard GLS model and \$2,023 (95% CI, \$1,588–\$2,575) in the propensity score-weighted GLS model. The median values of the difference in costs between matched pairs were \$9,949 (95% CI, \$1,579–\$24,693) for VRE BSI and \$5,282 (95% CI, \$2,042–\$8,043) for VSE BSI. The costs attributable to vancomycin resistance were \$1,713 (95% CI, \$1,338–\$2,192) in the standard GLS model and \$1,546 (95% CI, \$1,214–\$1,968) in the propensity score-weighted GLS model. Depending on the statistical method used, attributable length of stay estimates ranged from 2.2 to 3.5 days for patients with VRE BSI and from 1.1 to 2.2 days for patients with VSE BSI.

CONCLUSIONS. VRE BSI and VSE BSI were independently associated with increased hospital costs and increased length of stay. Vancomycin resistance was associated with increased costs.

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Bloodstream infections (BSIs) due to vancomycin-resistant *Enterococcus* (VRE) are associated with increased morbidity, mortality, and hospital costs.¹⁻⁴ Rates of vancomycin resistance among enterococcal isolates, which are among the most common pathogens associated with nosocomial BSI,⁵ have increased substantially during the past decade.⁶ In 2003, the pooled mean proportion of enterococcal infections resistant to vancomycin among patients in intensive care units was 28.5%, as reported to the Centers for Disease Control and Prevention's National Nosocomial Infections Surveillance system.⁶ Although the incidence of infections due to VRE is higher in intensive care unit patients, VRE infections are also common among patients treated in noncritical care units. Since infection control measures to prevent transmission of VRE BSI are effective but resource intensive,⁷ accurate estimates of the attributable cost of enterococcal BSI infections

are necessary to assess the cost effectiveness of prevention strategies.

Despite the increasing prevalence of VRE in US hospitals, the financial burden of infection due to enterococcal pathogens has not been adequately explored.⁸ We are aware of only 2 published studies that estimate the hospital costs associated with VRE BSI.^{1,4} However, neither study adequately controlled for underlying severity of illness or hospital procedures that may affect the cost of care, which may have resulted in biased cost estimates. In addition, there are limited cost data regarding the independent impact of acquiring a vancomycin resistance phenotype of a particular pathogen. Estimation of the independent effects of a resistance trait or phenotype (eg, vancomycin resistance) necessitates the use of a control group of patients infected with a sensitive organism (eg, vancomycin sensitive) rather than a control group of

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uninfected patients.^{8,9} Prior studies that compared infections due to vancomycin-sensitive pathogens with infections due to vancomycin-resistant pathogens were limited by small sample size and/or inadequate adjustment for potential confounding by comorbidities.^{9,10} The purpose of our study was to estimate the hospital costs and length of stay attributable to vancomycin-sensitive *Enterococcus* (VSE) BSI and VRE BSI in a nonsurgical hospital cohort by using administrative data and 3 reproducible analytical methods. We also sought to determine the independent effect of vancomycin resistance on hospital costs.

METHODS

Study Design

Nonsurgical patients admitted to Barnes-Jewish Hospital during the period from January 2002 through December 2003 who were hospitalized for more than 48 hours were included in the study. Surgical patients were excluded from the analysis because the distribution of costs was different for patients who incurred operating room costs. Data on demographics, inpatient mortality, microbiology results, and *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)* diagnosis and procedure codes were obtained from the hospital Medical Informatics database. *ICD-9-CM* diagnosis codes were collected for all patients who had been admitted during the past 2 years. *ICD-9-CM* procedure codes were collected only for the most recent hospitalization of each patient. Comorbidity and procedure variables were created from *ICD-9-CM* codes with guidance from the Healthcare Cost and Utilization Project Clinical Classifications Software (Agency for Healthcare Research and Quality). The presence of a central venous catheter was defined according to *ICD-9-CM* codes assigned during the 6-month period before enterococcal BSI infection for case patients or during the 6-month period before hospital discharge for uninfected control patients, with the assumption that central venous catheters inserted after diagnosis of infection were used for therapeutic purposes and that these costs needed to be captured in the costs of the infection.

Cases of enterococcal BSI were identified on the basis of positive blood culture results during hospitalization. Each patient's first episode of enterococcal BSI was analyzed. In the event of a polymicrobial BSI with both VSE and VRE organisms, the patient was classified as having a VRE BSI. Patients who had never had a BSI served as the control group. For control patients who were hospitalized more than once during the study period, 1 hospitalization per patient was randomly selected for analysis.

Hospital cost data (from the hospital payer perspective) were obtained from the Barnes-Jewish Hospital cost accounting database (Trendstar; McKesson). The departmental cost for each charge code assigned during hospitalization was calculated as the proportion of total departmental charges accounted for by the charge code multiplied by the depart-

ment's actual cost components. Departmental costs were summed to calculate total hospital costs for each hospitalization and were adjusted for inflation to 2007 US dollars according to the medical care component of the Consumer Price Index.¹¹

Statistical Analyses

Patient characteristics were compared by using the Student *t* test, the χ^2 test, or the Fisher exact test. Crude costs and hospital length of stay were compared by using the Mann-Whitney *U* test. Three methods (ie, standard regression adjustment, propensity score-weighted regression adjustment, and propensity score-matched pairs) were used to estimate total hospital costs and hospital length of stay associated with VRE BSI and VSE BSI, in order to control for the variation of many factors significantly associated with expenditures.

Standard Generalized Least-Squares Model

A generalized least-squares (GLS) regression model was fit with total cost as the dependent variable; total cost was natural log-transformed because of the highly skewed distribution of costs. The multivariate GLS model was developed by using backward stepwise regression, including all variables associated with the natural logarithm of cost in the bivariate analysis ($P \leq .05$) or biologic plausibility. Variables that applied to fewer than 10 patients were excluded from the analysis. A "feasible GLS estimator" was used to weight the observations to account for heteroskedasticity.¹² Since the GLS model used the natural logarithm of costs as the dependent variable, an intermediate regression was performed to predict costs. Each coefficient obtained in the GLS model represented the mean difference in the natural logarithm of costs between individuals with that variable and individuals without that variable, assuming all other predictors of costs remained constant. The attributable costs were calculated by solving the regression equation separately for each variable of interest (ie, VSE BSI, VRE BSI, and vancomycin resistance). Specifically, each coefficient was multiplied by the proportion of patients with that particular covariate and added to the constant, with the exception of nonenterococcal BSI. This exclusion allowed the adjusted costs of the uninfected control group to represent the "average" patient without nonenterococcal BSI. All independent variables were checked for collinearity. Models were checked for functional form misspecification by means of the Ramsey regression specification error test and for heteroskedasticity by means of the Breusch-Pagan test.¹² To assess the impact of vancomycin resistance, a second standard GLS model was fit with enterococcal BSI and vancomycin resistance as the primary independent variables. Attributable hospital length of stay was calculated by using this final model with the natural logarithm of length of stay as the dependent variable.

Propensity Score–Weighted GLS Model

A GLS regression model adjusted for propensity score inverse weighting was also used to estimate attributable costs.^{13,14} The predicted probabilities for development of enterococcal BSI (ie, VSE BSI and/or VRE BSI) were obtained from a multivariate logistic regression model that included all variables with P less than .20 in bivariate analysis. Each case patient was weighted by the inverse of the propensity score, and each control patient was weighted by the inverse of 1 minus the propensity score.^{13,14} The final regression model included the primary independent variables (ie, enterococcal BSI and vancomycin resistance), as well as all covariates that were unbalanced in at least 1 quintile of the propensity score. A second propensity score–weighted GLS model was also fit with enterococcal BSI and vancomycin resistance as the primary independent variables. Attributable hospital length of stay was calculated by using this final model with the natural logarithm of length of stay as the dependent variable.

Propensity Score–Matched Pairs

Propensity score–matched pairs analyses were used to estimate the attributable costs and attributable length of stay of VSE BSI and VRE BSI. The predicted probabilities for development of VSE BSI or VRE BSI were obtained from separate multivariate logistic regression models that included all biologically plausible variables associated with VSE BSI in the bivariate analysis ($P < .20$). Case patients with BSI due to VSE were matched 1 : 1 to uninfected control patients on the basis of their propensity to develop VSE BSI, and case patients with BSI due to VRE were matched 1 : 1 to uninfected control patients on the basis of their propensity to develop VRE BSI, using the nearest neighbor method within calipers of 0.25 standard deviations.^{15,16} Case patients who could not be matched with a suitable control patient were excluded from the analyses. Matched and unmatched case patients were compared by means of the χ^2 test or the Fisher exact test, with Bonferroni correction. Because of highly skewed cost data, attributable costs and attributable length of stay were presented as the median value of the difference in costs and length of stay, respectively, between matched pairs and were compared using the Wilcoxon signed rank test. Confidence intervals were calculated on the basis of the binomial distribution.

Statistical analyses were performed with SPSS, version 15.0 (SPSS), and Stata, version 9.2 (StataCorp). Approval for this study was obtained from the Washington University Human Research Protection Office.

RESULTS

During the 2-year study period, 21,154 nonsurgical patients were admitted to Barnes-Jewish Hospital and hospitalized for more than 48 hours (Table 1). Of the 276 patients (1%) identified with an enterococcal BSI, 94 (34%) had BSI due to VRE and 182 (66%) had BSI due to VSE. Enterococcal

BSI occurred significantly more often in patients with ICD-9-CM comorbidity codes for congestive heart failure, acute renal failure, *Clostridium difficile* infection, or urinary tract infection and in patients with ICD-9-CM procedure codes for bone marrow transplant, mechanical ventilation, hemodialysis, cancer chemotherapy, or placement of a central venous catheter (excluding catheters placed to administer antibiotics for treatment of enterococcal BSI). Patients with an enterococcal BSI were more likely than patients without an enterococcal BSI to have been in an intensive care unit (41 [44%] of 94 patients with VRE BSI and 62 [34%] of 182 patients with VSE BSI vs 3,330 [16%] of 20,878 patients without enterococcal BSI; $P < .001$ for both) and were more likely to die in the hospital (30 [32%] of 94 patients with VRE BSI and 31 [17%] of 182 patients with VSE BSI vs 845 [4%] of 20,878 patients without enterococcal BSI; $P < .001$ for both).

Crude costs and hospital length of stay are presented in Table 2. Patients with BSI due to VRE incurred significantly higher total crude median costs, compared with patients with BSI due to VSE ($P < .001$) and compared with patients without BSI ($P < .001$). Median departmental costs were significantly higher for patients with VRE BSI, as well as for patients with VSE BSI, compared with patients without BSI ($P < .001$ for all). The crude median costs attributable to VRE BSI were \$33,914, and those attributable to VSE BSI were \$12,703. The median hospital length of stay was significantly longer for patients with VRE BSI (14.6 days) and patients with VSE BSI (10.0 days), compared with patients without enterococcal BSI (4.0 days; $P < .001$ for both). The crude increases in length of hospital stay were 10.6 days for patients with VRE BSI and 6.0 days for patients with VSE BSI ($P < .001$ for both).

Standard GLS Model and Propensity Score–Weighted GLS Model

Both VRE BSI and VSE BSI were independent predictors of hospital costs ($P < .001$) in the standard GLS model and the propensity score–weighted GLS model after controlling for significant cost predictors, including demographics, comorbidities, procedures, nonenterococcal BSI, and early mortality. After these adjustments, nonenterococcal BSI was also associated with significantly increased costs ($P < .001$). The standard GLS model and the propensity score–weighted GLS model had adjusted coefficients of determination (R^2) of .42 and .38, respectively, indicating that approximately 40% of the variation in costs was explained by the models.

The attributable cost estimates from the GLS models are presented in Table 3. In the standard GLS model, the adjusted cost of BSI due to VRE was \$4,479 (95% confidence interval [CI], \$3,500–\$5,732), and the adjusted cost of BSI due to VSE was \$2,250 (95% CI, \$1,758–\$2,880). In the propensity score–weighted GLS model, the adjusted cost of VRE BSI was \$4,036 (95% CI, \$3,170–\$5,140), and the adjusted cost of

TABLE 1. Characteristics of Patients with and without Enterococcal Bloodstream Infection (BSI) ($N = 21,154$)

Characteristic	Case patients with VRE BSI ($n = 94$)	Case patients with VSE BSI ($n = 182$)	Control patients with no VRE or VSE BSI ($n = 20,878$)	P		
				VRE BSI vs VSE BSI	VRE BSI vs no VRE or VSE BSI	VSE BSI vs no VRE or VSE BSI
Age, median (range), years	58.3 (20.9–88.0)	65.4 (18.1–98.2)	60.1 (14.0–106.2)	.005	<.001	.004
Female sex	48 (51.1)	102 (56.0)	11,154 (53.4)	.431	.647	.481
African American	42 (44.7)	84 (46.2)	7,485 (35.9)	.816	.075	.004
Comorbidities						
Acute cerebrovascular disease	4 (4.3)	9 (4.9)	1,037 (5.0)	>.999	>.999	.989
Acute myocardial infarction	10 (10.6)	9 (4.9)	1,308 (6.3)	.077	.081	.464
Atrial fibrillation	15 (16.0)	39 (21.4)	2,603 (12.5)	.278	.307	<.001
Congestive heart failure, nonhypertensive	28 (29.8)	66 (36.3)	4,354 (20.9)	.282	.034	<.001
Pulmonary embolism and pulmonary hypertension	8 (8.5)	25 (13.7)	1,128 (5.4)	.205	.184	<.001
Chronic obstructive pulmonary disease	20 (21.3)	34 (18.7)	3,012 (14.4)	.607	.060	.104
Pneumonia	20 (21.3)	20 (11.0)	1,692 (8.1)	.021	<.001	.156
Asthma	6 (6.4)	13 (7.1)	1,390 (6.7)	.813	.915	.794
Diabetes mellitus						
Without complications	19 (20.2)	51 (28.0)	4,316 (20.7)	.158	.913	.015
With complications	12 (12.8)	29 (15.9)	1,564 (7.5)	.483	.053	<.001
Acute renal failure	37 (39.4)	46 (25.3)	2,091 (10.0)	.016	<.001	<.001
Hepatic disease	14 (14.9)	16 (8.8)	1,547 (7.4)	.123	.006	.479
Diarrhea due to <i>Clostridium difficile</i>	19 (20.2)	24 (13.2)	433 (2.1)	.127	<.001	<.001
Urinary tract infection	29 (30.9)	57 (31.3)	3,383 (16.2)	.937	<.001	<.001
Nonenterococcal BSI ^a	54 (57.4)	76 (41.8)	728 (3.5)	.013	<.001	<.001
Procedures						
Placement of central venous catheter ^b	61 (64.9)	89 (48.9)	2,677 (12.8)	.011	<.001	<.001
Hemodialysis	15 (16.0)	12 (6.6)	588 (2.8)	.013	<.001	.002
Mechanical ventilation	27 (28.7)	36 (19.8)	1,145 (5.5)	.062	<.001	<.001
Abdominal paracentesis	10 (10.6)	6 (3.3)	439 (2.1)	.013	<.001	.289
Receipt of bone marrow transplant	9 (9.6)	14 (7.7)	213 (1.0)	.592	<.001	<.001
Receipt of cancer chemotherapy	15 (16.0)	20 (11.0)	599 (2.9)	.240	<.001	<.001

NOTE. Data are no. (%) of patients unless otherwise indicated. NS, nonsignificant; VRE, vancomycin-resistant *Enterococcus*; VSE, vancomycin-sensitive *Enterococcus*.

^a Defined as at least 1 blood culture result positive for a nonenterococcal pathogen or at least 2 blood culture results positive for potential skin contaminants (eg, coagulase-negative staphylococci or *Micrococcus* sp).

^b Inserted before the onset of enterococcal BSI for case patients.

VSE BSI was \$2,023 (95% CI, \$1,588–\$2,575). In the alternative models with enterococcal BSI and vancomycin resistance as the primary independent variables, vancomycin resistance was an independent predictor of hospital costs ($P = .001$). The attributable cost of vancomycin resistance ranged from \$1,713 (95% CI, \$1,338–\$2,192) with the standard GLS model to \$1,546 (95% CI, \$1,214–\$1,968) with the propensity score-weighted GLS model.

Table 3 also presents the attributable length of stay estimates. In the standard GLS model, the attributable length of stay due to VRE BSI was 2.3 days (95% CI, 1.8–2.8 days), and the attributable length of stay due to VSE BSI was 1.2 days (95% CI, 0.9–1.5 days). In the propensity score-weighted GLS model, the length of stay attributable to VRE BSI was 2.2 days (95% CI, 1.7–2.7 days), and the length of stay attributable to VSE BSI was 1.1 days (95% CI, 0.9–1.4 days). The standard GLS model and the propensity score-weighted GLS model had adjusted coefficients of determination (R^2) of 0.35 and 0.33, respectively, indicating that ap-

proximately 34% of the variation in hospital length of stay was explained by the models.

Propensity Score-Matched Pairs

On the basis of the predicted probabilities of developing VRE BSI or VSE BSI, 88 (94%) of 94 case patients with VRE BSI and 179 (98%) of 182 case patients with VSE BSI were successfully matched with uninfected control patients. Six case patients with VRE BSI and 3 case patients with VSE BSI were excluded from the analyses as a result of the absence of a suitable nearest neighbor control patient. All covariates were balanced between matched and unmatched case patients, adjusting for multiple comparisons. While there were no significant differences in median costs between unmatched and matched VSE case patients (\$23,013 vs \$20,076; $P = .417$), median costs were significantly higher for the 6 unmatched VRE case patients, compared with the 88 matched VRE case patients (\$182,763 vs \$40,140; $P = .029$).

The difference in total costs between the matched VRE BSI

TABLE 2. Crude Median Hospital Cost and Length of Stay of Patients with and without Enterococcal Bloodstream Infection (BSI)

Outcomes	Case patients with VRE BSI ^a (<i>n</i> = 94)	Case patients with VSE BSI ^a (<i>n</i> = 182)	Control patients without BSI ^b (<i>n</i> = 20,150)
Hospital length of stay, days	14.6 (7.3–28.3)	10.0 (4.9–17.6)	4.0 (2.9–6.2)
Departmental costs, 2007 US\$			
Room and board	20,213 (7,209–45,610)	10,127 (5,829–21,212)	3,976 (2,793–6,456)
Pharmacy	7,430 (3,095–20,241)	3,205 (1,397–6,925)	669 (339–1,339)
Laboratory	4,143 (1,804–10,569)	1,989 (1,172–4,716)	628 (375–1,103)
Radiology	1,942 (940–4,591)	1,222 (501–2,053)	554 (125–1,197)
Respiratory therapy	412 (0–1,510)	130 (0–719)	0 (0–152)
Physical therapy	172 (0–448)	114 (0–370)	0 (0–175)
Other ^c	3,710 (1,907–7,061)	2,193 (1,380–3,636)	1,140 (656–2,245)
Total costs	42,106 (16,310–93,870)	20,895 (11,263–41,879)	8,192 (5,615–13,495)

NOTE. All data are median values (interquartile range). VRE, vancomycin-resistant *Enterococcus*; VSE, vancomycin-sensitive *Enterococcus*.

^a $P < .001$ for all comparisons with uninfected control group. $P < .001$ for all comparisons of patients with VRE BSI with patients with VSE BSI, with the exceptions of respiratory costs ($P = .015$) and physical therapy costs ($P = .205$).

^b Defined as patients without enterococcal or nonenterococcal BSI.

^c Defined as costs not allocated to room and board, pharmacy, laboratory, radiology, respiratory therapy, or physical therapy departments.

case and control pairs was \$9,949 (median), and the difference in total costs between the matched VRE BSI case and control pairs was \$5,282 (median) (Table 3). The median values for the difference in hospital length of stay for the matched pairs were equal to 3.5 days for VRE BSI and 2.2 days for VSE BSI ($P < .001$ for both, using the Wilcoxon signed rank test).

DISCUSSION

In this retrospective cohort of nonsurgical patients admitted to a university-affiliated tertiary care hospital, we used administrative data and readily reproducible methods to estimate the costs attributable to enterococcal BSI and vancomycin resistance. VRE BSI and VSE BSI were independently associated with significantly increased hospital costs after adjustment for other cost predictors, including demographics, comorbidities, procedures, nonenterococcal BSI, and early mortality. In addition, we determined that vancomycin resistance was independently associated with increased hospital expenditures. To our knowledge, this is the first study to report that enterococcal BSI due to vancomycin-resistant strains is independently associated with increased hospital costs. In this era of increasing antimicrobial resistance, accurate estimates of the financial burden associated with nosocomial infections are important for evaluating the cost-effectiveness of prevention strategies.

Since patients with infection often have more severe underlying diseases that are independently predictive of adverse outcomes and increased costs, adjustment for underlying severity of illness is essential for accurate cost estimation.⁸ In our cohort, patients who developed enterococcal BSI were much more likely than uninfected control patients to have risk factors for developing a BSI, including diabetes mellitus,

congestive heart failure, cancer, and receipt of a bone marrow transplant. Given that the large differences in observed covariates between patients with enterococcal BSI and patients without enterococcal BSI could lead to biased estimates of costs, we used 3 different analytical methods to adjust for the variation of factors significantly associated with expenditures. In this cohort, we calculated the crude median attributable cost of VRE BSI to be \$33,914. After adjustment for an extensive number of comorbidities and procedures that were associated with hospital expenditures, the VRE BSI cost estimates were \$4,479 in the standard GLS model and \$4,036 in the propensity score-weighted GLS model. The cost estimate generated by the propensity score-matched pairs method (\$9,949) was more than twice as large as the GLS model estimates, despite the exclusion of 6 case patients with VRE BSI (6%) who had significantly higher median costs than the 88 case patients with VRE BSI (94%) who were included in the analysis. The disparity between the cost estimates generated by the GLS models and those generated by the matched pairs may be due, in part, to different control groups. The control group in the GLS models was composed of “average” uninfected patients, because we used the mean of all covariates (except nonenterococcal BSI) to calculate attributable costs; however, the control group in the matched-pairs analysis was limited to a more severely ill subset of patients. Since patients with enterococcal BSI tend to be sicker than the average patient, the results of the matched-pairs analysis suggest that VRE BSI in sicker patients is associated with approximately \$10,000 in additional hospital costs. The matched-pairs design is an effective method for eliminating bias, but the reduction in sample size reduces the precision of cost estimates. This provides justification for the propensity

TABLE 3. Attributable Costs and Length of Stay Associated with Vancomycin-Resistant *Enterococcus* (VRE) and Vancomycin-Sensitive *Enterococcus* (VSE) Bloodstream Infections (BSIs)

Statistical method	Costs, US\$ (95% CI)		Length of stay, days (95% CI)	
	VRE BSI	VSE BSI	VRE BSI	VSE BSI
GLS regression model, mean value	\$4,479 (3,500–5,732)	\$2,250 (1,758–2,880)	2.3 (1.8–2.8)	1.2 (0.9–1.5)
GLS regression model with IPW, mean value ^a	\$4,036 (3,170–5,140)	\$2,023 (1,588–2,575)	2.2 (1.7–2.7)	1.1 (0.9–1.4)
Matched pairs ^{a,b}	\$9,949 (1,579–24,693)	\$5,282 (2,042–8,043)	3.5 (2.1–7.3)	2.2 (1.0–3.5)

NOTE. CI, confidence interval; GLS, generalized least squares; IPW, inverse probability weighting.

^a The variables in the logistic regression model used to create the propensity score for development of VSE BSI or VRE BSI include demographic variables (age [by 5-year intervals], nonwhite race, and sex), medical conditions (pneumonia, aspiration pneumonitis, chronic obstructive pulmonary disease and bronchiectasis, nonhypertensive congestive heart failure, pulmonary heart disease, coronary atherosclerosis, cardiac dysrhythmias not including atrial fibrillation, hypertension with complications and secondary hypertension, heart valve disorders, cardiac arrest and ventricular fibrillation, atrial fibrillation, atrial flutter, conduction disorders, peri-, endo-, and myocarditis, hyperlipidemia, diabetes mellitus without complications, diabetes mellitus with complications, chronic renal failure, acute renal failure, solid tumor malignancy, leukemia, non-Hodgkin's lymphoma, multiple myeloma, human immunodeficiency virus infection, *Clostridium difficile* diarrhea, urinary tract infection, infective arthritis and osteomyelitis, rheumatoid arthritis, agranulocytosis [neutropenia], peritonitis and intestinal abscess, graft-vs-host disease, chronic ulcer of the skin, deficiency and other anemias, hypovolemia, later complications after transplant of whole organ, complications of transplanted and reattached limbs, depression, methicillin-sensitive *Staphylococcus aureus* infection [before VRE BSI or VSE BSI], methicillin-resistant *S. aureus* infection [before VRE BSI or VSE BSI], antibiotic-sensitive gram-negative rods infection [before VRE BSI or VSE BSI], antibiotic-resistant gram-negative rods infection [before VRE BSI or VSE BSI], and BSI not due to *Enterococcus*, *S. aureus*, or gram-negative rods [before VRE BSI or VSE BSI]), and procedures (hemodialysis, mechanical ventilation for >96 hours during hospitalization, mechanical ventilation for <96 hours during hospitalization, gastrostomy [temporary and permanent], bone marrow transplant, cancer chemotherapy, and insertion of central venous catheter [during the 6-month period before enterococcal BSI infection for case patients or during the 6-month period before hospital discharge for uninfected control patients]).

^b Data are the median values of the difference between case-control pairs, and corresponding 95% CIs are based on the binomial distribution.

score-weighted GLS model, which allows for analysis of the full cohort with the advantages of propensity score adjustment to reduce confounding.

The wide variability in published cost estimates about VRE BSI is due in part to differences in study designs, case definitions, control groups, sample sizes, and adjustment for confounders. Stosor et al⁴ reported that patients with VRE BSI incurred crude mean hospitalization costs \$27,000 higher than the crude mean costs of patients with VSE BSI. Song et al¹ estimated the excess difference in median costs between patients with VRE BSI and patients without BSI to be \$77,558. Song and colleagues¹ calculated median costs by using pairs matched by age, year of hospital admission, days of hospitalization prior to the diagnosis of BSI, principal diagnosis and primary procedure (according to *ICD-9-CM* codes), and the all-patient refined diagnosis-related group complexity level; however, a number of important cost drivers also associated with infection were not included in the analysis. Additional cost estimates from studies involving other VRE infections (ie, colonization or infection at sites other than the bloodstream) range from \$8,936 to \$38,669.^{9,10,17-19}

In both the standard GLS model and the propensity score-weighted GLS model, vancomycin resistance was a highly significant independent predictor of hospital costs, indicating that expenditures for BSI due to resistant enterococci were significantly higher than expenditures for BSI due to sensitive enterococci. The costs attributable to vancomycin resistance were \$1,713 in the standard GLS model and \$1,546 in the propensity score-weighted GLS model. Of 4 published studies that used multivariate methods to estimate the costs of van-

comycin resistance,^{1,9,10,17} only 2 studies attempted to assess the independent financial impact of the acquisition of a resistance determinant.^{9,10} Pelz et al¹⁰ did not find a significant difference between the median costs of 117 ICU patients with VRE (\$33,251) or VSE (\$21,914) urinary, wound, abscess, or bloodstream infections (including catheter colonization). However, the null result is likely due to small sample size (12 cases of VRE infection and 22 cases of VSE infection). Kaye et al⁹ reported that vancomycin resistance was a significant predictor of increased costs among patients with enterococcal wound infection, with an attributable cost of \$8,936. Our estimates were substantially lower than the estimate by Kaye et al,⁹ which may be related to our exclusion of surgical patients from the study population because of a markedly higher distribution of costs for patients with operating room costs compared with other hospitalized patients. It is also possible that the costs attributable to vancomycin resistance vary according to infection site.

Our finding that vancomycin resistance was independently associated with increased hospital costs has a few possible explanations. In our cohort, room and board costs made up the highest percentage of total crude costs, accounting for approximately one-half of total crude costs regardless of BSI infection status. The positive correlation between the incremental increases in crude room and board costs (\$20,213 for VRE BSI vs \$10,127 for VSE BSI vs \$3,976 for no BSI) and crude length of stay (14.6 days for VRE BSI vs 10.0 days for VSE BSI vs 4.0 days for no BSI) indicates that length of stay was the major driver of increased costs. Pharmacy costs were the second largest contributor to total

crude costs, making up 18%, 15%, and 8% of the total costs for case patients with VRE BSI, case patients with VSE BSI, and uninfected control patients, respectively. Antibiotic resistance frequently leads to a delay in the administration of appropriate antimicrobial therapy, which may be associated with adverse outcomes.^{1,2,8,20-24} In addition, appropriate antimicrobial agents for treatment of VRE BSI cost significantly more per day than antimicrobials typically used to treat VSE BSI.⁸

Recent increases in rates of antibiotic-resistant infections⁶ highlight the need to standardize the methods for cost studies of nosocomial infections. The use of readily available administrative data is advantageous because they are relatively inexpensive to obtain and are available at all hospitals in the United States, facilitating the analysis of large cohorts.²⁵ Our study of 21,154 hospital inpatients has excellent power and provides results that are generalizable to university-affiliated tertiary care hospitals in the United States. It is important to note that our data were restricted to a single institution. We created comorbidity and procedure variables from ICD-9-CM code data by using the Healthcare Cost and Utilization Project Clinical Classifications Software as a guide, a standardized process that can improve comparability of cost estimates across studies. Compared with medical record data, comorbidities are underreported in administrative data.²⁵ Nevertheless, studies comparing diagnoses and procedures reported in administrative data with those reported in medical records and self-reporting have revealed good levels of agreement.²⁶ Furthermore, comorbidity adjustment by means of diagnoses identified from claims data does not differ markedly from comorbidity adjustment by means of diagnoses identified from medical records.²⁶⁻²⁸

The significantly higher hospital costs of VRE BSI that we identified in this study suggest that effective control of vancomycin-resistant pathogens would result in cost savings. Recent empirical evidence-based guidelines for the prevention of VRE transmission recommend the use of active surveillance cultures to identify the reservoir of the pathogen and the use of the Centers for Disease Control and Prevention's long-recommended contact precautions to decrease transmission.⁷ Other prevention strategies include the education of healthcare workers, hand hygiene, judicious antimicrobial use policies, and enhanced environmental cleaning.^{7,29,30} Our estimates of the cost of vancomycin resistance can also be used to help assess the cost-effectiveness of interventions to reduce transmission of resistant organisms in hospitals.

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