Health and Economic Outcomes of Vancomycin-Resistant Enterococci

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Background: The health and economic impact of vancomycin-resistant enterococci has not been quantified.

Methods: A retrospective matched cohort study was conducted comparing the outcomes of patients with vancomycin-resistant enterococci (cases) with those of control subjects matched for length of hospital stay until inclusion in the cohort, hospital location, and calendar date. The propensity to be a vancomycin-resistant enterococci case was modeled based on patient characteristics, and included in multivariable models to adjust for confounding. Analyses included the following: (1) conditional logistic regression for mortality, surgery, intensive care unit admission, and discharge to long-term care; (2) linear regression for the logarithm of cost; and (3) accelerated failure time model for length of stay.

Results: A total of 233 cases were compared with 647 controls. Groups were similar in age (mean, 62 years), sex (female, 47%), and length of stay before inclusion in the cohort (mean, 8.1 days), but differed in primary diagnosis and comorbidities, past infection or colonization with methicillin sodium–resistant *Staphylococcus aureus* or *Clostridium difficile*, and treatment with cephalosporins or metronidazole. These variables were included in the propensity score, which had good to excellent prediction. Outcomes for cases vs controls and adjusted risks (relative risks [RRs]) were as follows: (1) case fatality rate, 17% vs 6% (RR, 2.13; *P*=.04); (2) length of stay after inclusion in the cohort, 15.1 vs 8.5 days (RR, 1.73; *P*<.001); (3) hospital costs, $52 449 vs $31 915 (RR, 1.40; *P*<.001); (4) surgery after inclusion in the cohort, 18% vs 10% (RR, 2.74; *P*=.001); (5) intensive care unit admission after inclusion in the cohort, 25% vs 14% (RR, 3.47; *P*<.001); and (6) transfer to an institution, 51% vs 35% (RR, 2.01; *P*=.001).

Conclusion: Compared with a matched hospital population, a population with vancomycin-resistant enterococci was associated with severe adverse outcomes: increased mortality, morbidity, and costs.

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ANTIBIOTIC RESISTANCE is a recognized clinical problem and a major public health threat. Infections caused by resistant bacteria are believed to result in severe adverse outcomes (increased mortality, morbidity, and medical care costs).[1-4] The reason that antibiotic resistance leads to adverse outcomes is presumably because of an increased likelihood that ineffective or suboptimal antibiotic therapy will be given. Moreover, in some organisms, the development of resistance to all available antibiotics may preclude the effectiveness of any antibiotic regimen.

Vancomycin-resistant enterococci are considered ultimate pathogens, organisms toward which no effective treatment is available (until recently). First isolated in 1987,[5,6] vancomycin-resistant enterococci have rapidly become established as important nosocomial pathogens in the United States. In intensive care units (ICUs) reporting to the National Nosocomial Infections Surveillance System in 1999, vancomycin-resistant enterococci were responsible for approximately one quarter of all enterococcal infections, an increase of 43% compared with 1994 to 1998 data. Similar trends were also observed in other hospital wards.[7]

Studies[8-11] found that bacteremia due to vancomycin-resistant enterococci was associated with increased mortality. Edmond et al[8] estimated that the attributable mortality of those with bacteremia due to vancomycin-resistant enterococci is 37%. Stosor et al[9] also found that patients with bacteremia due to vancomycin-resistant enterococci had an average additional cost of hospitalization of $27 000. Primary bacteremia due to vancomycin-resistant enterococci composes fewer than 10% of all vancomycin-resistant enterococci infections. This study quantifies the

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overall, direct, in-hospital clinical, and economic impact of vancomycin-resistant enterococci in a cohort of patients with vancomycin-resistant enterococci compared with a matched hospital population.

METHODS

SETTING, DATA COLLECTION, AND MICROBIOLOGICAL STUDIES

Beth Israel Deaconess Medical Center, West Campus, is a 320-bed urban tertiary care teaching hospital. It has 24 ICU beds, and there are approximately 12 000 patient admissions per year.

Data were extracted from patients' medical records and administrative, accounting, and laboratory computerized databases and compiled into a single data set using a relational database management system (Access; Microsoft Corp, Redmond, Wash). This informatics system has been described elsewhere.[12]

Enterococci had been identified from clinical specimens submitted to the microbiology laboratory using a gram-positive identification panel (Dade International Inc, West Sacramento, Calif). Enterococci were screened for vancomycin resistance by plating on brain-heart infusion agar with vancomycin, 6 µg/mL. Vancomycin resistance was confirmed by formal minimum inhibitory concentration testing using a microdilution broth system (MicroScan; Dade International Inc). *Enterococcus faecium* and *Enterococcus faecalis* isolates with vancomycin minimum inhibitory concentrations of 8 µg/mL or greater were classified as vancomycin-resistant enterococci according to the National Committee for Clinical Laboratory Standards guidelines.

DEFINITIONS AND STUDY DESIGN

The study was designed as a matched cohort study. All inpatients from whom vancomycin-resistant enterococci were first isolated from a clinical culture in our hospital between October 1, 1993, and December 31, 1997, were enrolled as vancomycin-resistant enterococci cases. Matching of control subjects was done based on 3 variables: hospital ward, calendar date (within 7 days), and duration of hospital stay at the time of matching (up to 3 days' difference if no exact match was available). Up to 3 appropriately matched control patients who were not positive for vancomycin-resistant enterococci (ie, specimens from the patient were cultured and no vancomycin-resistant enterococci were isolated or specimens from the patients were never cultured) were randomly selected for each case. A list of all possible controls was created, each was assigned a random number, and then the 3 highest random numbers were chosen (without replacement).

Five outcomes were examined: mortality, length of hospital stay (LOS), total hospital costs, admission to an ICU, and need for surgery (all assessed after inclusion in the cohort) or discharge to an institution (rehabilitation, nursing home, or long-term care facility).

To further control for confounding, we used a propensity score for being a vancomycin-resistant enterococci case (described later), and later we included the propensity score along with other confounding variables in the multivariate analysis examining each of the outcomes. We explored for confounding of the following variables: demographic characteristics, admitting diagnosis, comorbidities (grouped into 8 major groups and by the Charlson chronic comorbidity score[13]), being transferred from another institution, being admitted to an ICU (before inclusion in the cohort) and number of days in the ICU, undergoing a major surgical procedure, being infected with re-

sistant organisms (*Clostridium difficile* or methicillin-resistant *Staphylococcus aureus*), and antecedent treatment with different antibiotic agents.

STATISTICAL ANALYSES

Statistics were performed on Stata software (Stata Corp, College Station, Tex). A matched (conditional) logistic regression model was used to construct an explanatory model for the probability of being a vancomycin-resistant enterococci case.[14] By using the prediction probabilities of this model, a propensity score was constructed.[15-17] All the variables were candidates for the model, and were selected in a stepwise manner, with an enrollment criterion of $P<.20$ and a criterion to stay in the model of $P<.05$. Variables that were not retained in the model by this procedure were then tested for confounding by adding them one at a time to the model and examining their effects on the β coefficients. Variables that caused substantial confounding (change in the β coefficient of >10%) were included in the final model. In addition to examining statistical significance and confounding, effect modification between variables was evaluated by testing appropriate interaction terms for statistical significance. The ability of the propensity score to adjust for important covariates of treatment was evaluated by testing for differences in the covariates within quintiles of propensity.

Each outcome was later examined independently, using multivariate analysis. All the variables were candidates for these models with the procedure described previously, while forcing the vancomycin-resistant enterococci status and the propensity score into the model. Mortality, admission to an ICU, and need for surgery (all after inclusion in the cohort) or discharge to a rehabilitation or long-term care facility were examined using a matched (conditional) logistic regression model. We estimated the adjusted population-attributable fraction from the logistic regression model,[18] and used these estimates to calculate the adjusted attributable risk for the exposed. Survivorship curves of hospital LOS were examined and were appropriate for the accelerated failure time model (Weibull). Thus, an accelerated failure time model (Weibull, stratified to account for matching) was used to examine LOS. Time 0 was considered to be the date of enrollment into the cohort (the day of vancomycin-resistant enterococci isolation for cases and the matching day for controls). Patients were censored at death. The Weibull model was parameterized in the form of logarithm time, so that the coefficients that underwent exponentiation could be interpreted as multiplicative effects (MEs) on LOS. This model was also used to estimate excess number of days in the hospital, based on the value of the ME. Hospital costs were examined using logarithm-transformed hospital charges (to achieve a normal distribution) and analyzed with linear regression models, with an absorbed variable to account for matching. Coefficients from the model underwent exponentiation because of the logarithm transformation of the dependent variable and, thus, were also interpreted as MEs. All statistical tests were 2-tailed. $P\leq.05$ was considered significant.

RESULTS

During the 51 months studied, 251 vancomycin-resistant enterococci cases were identified. No appropriate control patient could be matched for 18 cases. Thus, the study cohort included 880 patients: 233 cases and 647 matched controls. The primary site of isolation was a wound in 42%, the urinary tract in 31%, an intra-abdominal infection in 17%, and a primary bloodstream infection in 9% (percentages do not total 100 because of rounding). The average age of the patients was 62 years,

and 46% were female. Patients were hospitalized for an average of 8.1 days before enrollment into the study. Many of the cohort patients had chronic underlying illnesses and were severely ill, as expressed by a high mean Charlson score of 2.9; 37% were transferred from another institution, 32% underwent a major surgical procedure, and 27% were admitted to an ICU. Many patients (33%) had diabetes mellitus, a characteristic of the overall hospital population. Characteristics of cases and controls are summarized in **Table 1**.

A multivariate logistic regression model was developed to calculate the propensity score,[14-16] a score that predicts the patient probability of being a vancomycin-resistant enterococci case. After matching for hospital location, calendar date, and duration of hospitalization, the following variables predicted being a vancomycin-resistant enterococci case (propensity score): (1) main admitting diagnosis of cardiovascular disease (0.44) or infectious condition (2.9); (2) comorbid conditions of diabetes mellitus (2.1), organ transplantation (2.6), and hepatobiliary disease (2.9); (3) infection or colonization with methicillin-resistant *S aureus* (3.5) or *C difficile* (2.0) within the past year; or (4) undergoing treatment with a third-generation cephalosporin (2.8) or metronidazole (2.1). The propensity score had an area under the receiver operating characteristic curve of 80%, indicating excellent discrimination between vancomycin-resistant enterococci cases and controls.

MORTALITY

Of the 880 cohort patients, 81 died in the hospital: 39 of the 233 vancomycin-resistant enterococci case patients and 42 of the 647 control patients (case fatality rate, 17% vs 6%; relative risk [RR], 3.49; $P<.001$; attributable mortality, 10%). In a matched logistic regression multivariable model constructed to control for confounding, being a vancomycin-resistant enterococci case was significantly associated with mortality (adjusted RR, 2.13; $P=.04$; adjusted attributable mortality, 6%). Results of adjusted analyses, and corresponding adjusted attributable risks (attributable fraction in the exposed), are displayed in **Table 2**, and subgroup analyses for mortality according to initial site of vancomycin-resistant enterococci isolation are presented in **Table 3**.

HOSPITAL LOS

The median number of days between inclusion in the cohort and discharge from the hospital was 9 for vancomycin-resistant enterococci cases (mean, 15.1 days; range, 1-107 days) and 5 for controls (mean, 8.5 days; range, 1-116 days).

The ME on the duration of stay following inclusion in the cohort (vancomycin-resistant enterococci isolation day for cases and matching day for controls) was calculated using an accelerated failure time model. Results of the analysis are displayed in Table 2. A longer duration of stay was observed in the vancomycin-resistant enterococci cases (ME, 2.06; $P<.001$). Similar results were seen in the multivariable model developed to control for confounding (ME, 1.73; $P<.001$). We estimated that being

Table 1. Characteristics of the Case and Control Patients*

Variable	Case Patients (n = 233)	Control Patients (n = 647)	P Value
Age, mean, y	61.7	62.3	.76
Female sex	114 (49)	292 (45)	.34
Main admitting diagnosis			
Orthopedic condition	15 (6)	53 (8)	.81
Cardiovascular condition	49 (21)	236 (36)	<.001
Endocrine disorder	6 (3)	13 (2)	.60
Gastrointestinal disorder	77 (33)	160 (25)	.005
Genitourinary disorder	18 (8)	35 (5)	.21
Infectious disease	26 (11)	19 (3)	<.001
Hematological disease	5 (2)	12 (2)	.70
Neurological disease	18 (8)	69 (11)	.30
Pulmonary disease	19 (8)	49 (8)	.80
Comorbidities			
Cardiovascular disease	160 (69)	460 (71)	.36
Lung disease	32 (14)	88 (14)	.95
Diabetes mellitus	127 (55)	162 (25)	<.001
Organ transplantation	39 (17)	45 (7)	<.001
Renal disease	57 (24)	103 (16)	.01
Cancer	25 (11)	93 (14)	.18
AIDS	2 (1)	8 (1)	.70
Hepatobiliary disease	65 (28)	97 (15)	<.001
Charlson chronic comorbidity score, mean	3.2	2.7	.003
Transfer from an institution	84 (36)	243 (38)	.56
Surgery	67 (29)	211 (33)	.01
ICU admission	65 (28)	169 (26)	.38
Past year infection or colonization			
Methicillin sodium–resistant *Staphylococcus aureus*	28 (12)	26 (4)	<.001
Clostridium difficile	17 (7)	20 (3)	.006

*Data are given as number (percentage) of patients unless otherwise indicated. AIDS indicates acquired immunodeficiency syndrome; ICU, intensive care unit.

a vancomycin-resistant enterococci case was associated with an average adjusted increase of 6.2 days in hospital LOS. Subgroup analyses for LOS according to initial site of vancomycin-resistant enterococci isolation are presented in Table 3.

SURGERY

Forty-one of the 233 vancomycin-resistant enterococci case patients and 66 of the 647 control patients underwent a major surgical procedure after being included in the cohort (18% vs 10%; RR, 1.96; $P=.004$; attributable need for surgery, 7%). After adjusting for confounding using the propensity score and multivariate modeling, being a vancomycin-resistant enterococci case was associated with a significantly higher likelihood of undergoing major surgery after being included in the cohort (RR, 2.74; $P=.001$; adjusted attributable risk, 10%). The subgroup analyses for surgery according to initial site of vancomycin-resistant enterococci isolation are presented in Table 3.

ADMISSION TO THE ICU

Fifty-nine of the 233 vancomycin-resistant enterococci case patients and 92 of the 647 control patients re-

Table 2. Outcomes and Adjusted Analyses for Case Patients vs Matched Control Patients*

| Outcome | Case Patients (n = 233) | Control Patients (n = 647) | Adjusted Analyses | | *P* Value |
			RR (95% CI)	Attributable to Vancomycin-Resistant Enterococci	
Mortality, %	17	6	2.13 (1.05-4.37)	6	.04
Length of stay, mean, d	15.1	8.5	1.73 (1.43-2.10)†	6.2	<.001
Cost, mean, $	52 449	31 915	1.40 (1.26-1.59)†	12 766	<.001
Surgery, %	18	10	2.74 (1.52-4.92)	10	.001
ICU admission, %	25	14	3.47 (1.75-6.85)	11	<.001
Discharge to long-term care, %	51	35	2.01 (1.34-3.02)	16	.001

*RR indicates relative risk; CI, confidence interval; and ICU, intensive care unit.
†The multiplicative effect is given vs the RR.

Table 3. Subgroup Adjusted Analyses of Outcomes for Case Patients With Vancomycin-Resistant Enterococci vs Matched Control Patients According to the Initial Site of Vancomycin-Resistant Enterococci*

| Outcome | Site | | | |
	Bloodstream Infection	Wound	Urinary Tract	Intra-abdominal Infection
Mortality				
Adjusted RR	12.30	2.00	4.28	3.75
Attributable to vancomycin-resistant enterococci, %†	25	6	9	3
P value	.02	.13	.005	.04
Length of stay				
Adjusted ME	2.06	1.78	1.75	1.42
Attributable to vancomycin-resistant enterococci, mean, d†	15.0	6.2	5.4	2.6
P value	.07	<.001	<.001	.06
Cost				
Adjusted ME	1.23	1.51	1.27	1.63
Attributable to vancomycin-resistant enterococci, mean, $†	13 537	13 884	6665	22 896
P value	.30	<.001	.02	.01
Surgery				
Adjusted RR	1.90	4.83	1.01	5.30
Attributable to vancomycin-resistant enterococci, %†	. . .	15	. . .	11
P value	.38	.001	.90	.08
ICU admission				
Adjusted RR	20.30	2.54	2.70	1.56
Attributable to vancomycin-resistant enterococci, %†	35	. . .	. . .	. . .
P value	.01	.11	.11	.48
Discharge to long-term care				
Adjusted RR	0.45	3.40	3.20	0.56
Attributable to vancomycin-resistant enterococci, %†	. . .	21	8	. . .
P value	.29	.005	.001	.30

*RR indicates relative risk; ME, multiplicative effect; ICU, intensive care unit; and ellipses, data not available.
†Attributable fraction in the exposed adjusted for confounding in multivariate models.

quired ICU care for at least 24 hours after being included in the cohort (25% vs 14%; RR, 3.1; *P*<.001; attributable risk for ICU admission, 11%). After adjusting for confounding using multivariate modeling (the propensity score and admission to the ICU before inclusion in the cohort), being a vancomycin-resistant enterococci case was associated with a significantly higher likelihood for ICU admission at some time after being included in the cohort (adjusted RR, 3.47; *P*<.001; adjusted attributable risk, 11%). Subgroup analyses for admission to the ICU according to initial site of vancomycin-resistant enterococci isolation are summarized in Table 3.

DISCHARGE TO LONG-TERM CARE

Of the 799 surviving cohort patients, 312 (39%) were discharged to long-term care. Among the vancomycin-resistant enterococci cases, 99 were discharged to long-term care compared with 213 controls (51% vs 35%; RR, 1.98; *P*<.001). After adjusting for confounding (propensity and being transferred from an institution), being a vancomycin-resistant enterococci case was associated with a higher rate of being discharged to long-term care (RR, 2.01; *P*=.001; attributable risk, 16%). Subgroup analyses for discharge to long-term care according to initial site of vancomycin-resistant enterococci isolation are presented in Table 3.

Antimicrobial resistance is a growing public health threat. Infections due to antibiotic-resistant pathogens are believed to be associated with greater mortality, morbidity, and costs than infections due to susceptible organisms. The national costs of antimicrobial resistance for the United States have been estimated between $100 million and $30 billion annually. The Office of Technology Assessment of Congress has estimated the minimal hospital cost associated with nosocomial infections caused by antibiotic-resistant bacteria to be $1.3 billion per year (in 1992).[3] However, despite the existence of these global estimates and the growing alarm about the problem of resistance, few studies that quantitatively examine the health and cost impact of resistant organisms have been performed.

Studies of the impact of antibiotic resistance must rely on observational data rather than randomized trials. Thus, to estimate the effect of resistance, patients with resistant organisms are compared with patients without resistant organisms for outcome measures such as cost and LOS. The problem with this simple comparison is that sicker patients with long LOSs are more likely to acquire resistant organisms, leading to substantial confounding bias. We addressed this problem by applying study design and analytic methods to control as much as possible the other factors besides antibiotic resistance that contributed to adverse outcomes. Patients without vancomycin-resistant enterococci (controls) were matched to patients with vancomycin-resistant enterococci (cases) so that all controls were still hospitalized on the day when the vancomycin-resistant enterococci were detected in cases. Primary diagnoses and comorbidities that distinguished vancomycin-resistant enterococci cases from their matched controls were accounted for by the propensity score method. Additional confounding variables were identified and included in the final multivariable models. We believe that the careful attention to the problem of confounding in our analysis bolsters the validity of the conclusions. Another strength of this study is that multiple outcome end points were examined, providing a more complete picture of the impact of vancomycin-resistant enterococci.

Our major findings were that vancomycin-resistant enterococci culture positivity was associated with the following: (1) 2-fold increased odds of mortality, (2) 2.7-fold increased odds of a major surgical procedure, (3) 3.5-fold increased odds of admission to the ICU, (4) a 1.7-fold increase in hospital LOS, (5) a 1.4-fold increase in cost of hospitalization, and (6) 2-fold increased odds of discharge to a long-term care facility. The latter finding suggests that the impact of vancomycin-resistant enterococci on costs likely extends beyond the period of hospitalization.

The corresponding estimates of vancomycin-resistant enterococci–attributable effects, within the vancomycin-resistant enterococci case population, were as follows: mortality, 6%; major surgical procedure, 10%; ICU admission, 11%; and discharge to long-term care, 16%. Cases had an average extra cost of $12 766, attributable to vancomycin-resistant enterococci. This trans-

lates to 15 cases of in-hospital death, 22 major operations, 26 ICU admissions, 1445 additional hospitalization days, and excess costs of $2 974 478, during the study period. These figures represent estimates of the impact of vancomycin-resistant enterococci after adjustment for confounding; however, the limitations of drawing causal inferences from a single observational study need to be emphasized. As with all studies of this nature, there may have been residual confounding bias from unmeasured variables. Another source of bias may come from classification bias, because some of the control patients may be undetected vancomycin-resistant enterococci carriers. This type of misclassification would have led to an underestimate of the true impact of vancomycin-resistant enterococci.

Our estimates of the attributable mortality and cost related to bacteremia due to vancomycin-resistant enterococci (25% and $13 537, respectively) are somewhat lower than those estimated by Edmond et al[8] and Stosor et al[9] (37% and $27 000, respectively). This may indicate that our methods of adjusting for confounding yielded more conservative effect sizes. Differences between study results likely also relate to variation between institutions and patient populations. In the study described herein, patients with vancomycin-resistant enterococci were compared with patients without vancomycin-resistant enterococci, whereas in the study by Stosor et al, patients with vancomycin-resistant enterococci were compared with patients with bacteremia due to vancomycin-susceptible enterococci. However, differences in choice of control group probably do not account fully for differences in attributable costs. A study of outcomes associated with wound infections due to vancomycin-resistant enterococci compared with wound infections due to vancomycin-susceptible enterococci has been conducted (Y.C., E.M., and M.S., unpublished data, 2002). The results of that analysis indicated effects that were similar in magnitude to those reported herein.

The many vancomycin-resistant enterococci cases examined made it possible to perform subgroup analyses and identify variations in effect, according to the initial source of vancomycin-resistant enterococci. A relationship with mortality was seen when the blood, urinary tract, or abdomen was the initial source of vancomycin-resistant enterococci but not when the source was a wound. Most of the wound infections were limb infections. Thus, the nidus of infection could be removed by amputation or extensive debridement. Indeed, when the wound, but not the urinary tract or blood, was the source of vancomycin-resistant enterococci, patients had an increased rate of surgery. Intra-abdominal infections were associated with increased mortality and an increased rate of surgery. It is reasonable to assume that the mortality rate would have been higher had operations not been performed. This is in accordance with previous observations[19] on multidrug-resistant *Pseudomonas aeruginosa*. The increased cost of care is related primarily to a longer hospital stay, but the increased rate of ICU admissions and major surgical procedures performed undoubtedly further contributed to the increased cost. Indeed, bloodstream, wound, and intra-abdominal sites, all associated with an increased ICU admission rate or access in

surgical procedures, were associated with a higher vancomycin-resistant enterococci–attributable cost than the urinary tract, which was associated only with an increased LOS.

Our cost estimates represent most closely the direct hospital perspective. Effects on third-party payers, and other societal perspectives, extend beyond hospitalization and are underestimated by this study. In addition, we believe that the hospital perspective is also underestimated because we did not account for extra costs to the institution at large caring for patients with vancomycin-resistant enterococci, such as surveillance cultures, isolation supplies, and loss of beds due to the need to isolate a patient.

The results of this study provide a strong rationale for the development of effective interventions to minimize the impact of vancomycin-resistant enterococci. These efforts should be directed toward limiting the spread of vancomycin-resistant enterococci and toward better treatment of infections due to vancomycin-resistant enterococci.

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