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Major article

Vancomycin-resistant *Enterococcus* colonization in the intensive care unit: Clinical outcomes and attributable costs of hospitalization

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Background: The clinical and economic impact of vancomycin-resistant *Enterococcus* (VRE) colonization remains unclear. Little data are available on factors affecting hospitalization length of stay (LOS) and costs. This study aimed to estimate mortality, LOS, and hospitalization costs for VRE colonized patients compared with a matched hospital population.

Methods: We performed a retrospective propensity score matched cohort study comparing the outcomes of patients with VRE colonization with those of uncolonized subjects matched at the time they were admitted to the intensive care unit (ICU). Between January 2008 and December 2010, we obtained rectal swab cultures within 24 hours of ICU admission to detect VRE colonization.

Results: During the study period, 567 (7.2%) of the 7,703 patients were colonized with VRE. There were 199 VRE colonized patients compared with 199 uncolonized patients using the propensity score. VRE colonized patients when compared with uncolonized patients were likely to have a higher case fatality rate (24.6% vs 17.1%; OR, 2.35). Longer total admission days were observed in the VRE colonized patients (28.7 vs 21.4 days; multiplicative effect, 1.25; $P = .004$). VRE colonization is found to be a significant factor associated with increased ICU cost in the multivariable regression model ($6,065 vs $5,298; multiplicative effect, 1.22; $P = .029$). Multivariable analysis identified the factors affecting ICU cost as follows: VRE colonization (odds ratio [OR], 1.20; $P = .038$), ICU length of stay (OR, 1.93; $P < .001$), ICU type (OR, 1.51; $P = .001$), valvular heart disease (OR, 2.38; $P = .27$), hospitalization within 12 months (OR, 1.21; $P = .037$), and use of invasive devices (OR, 1.28; $P = .017$).

Conclusion: Compared with a matched hospital population, VRE colonization was associated with increased mortality, LOS, and costs. Strict infection control programs, including preemptive isolation for a high-risk group, should be helpful.

The first isolates of high-level vancomycin-resistant *Enterococci* (VRE) were reported in the United Kingdom in the late 1980s.[1] Since then, rates of VRE colonization and infection have risen steadily.[2] A recent multicenter epidemiologic study showed that 28% of enterococci cultured from 25 North American intensive care units (ICUs) were resistant to vancomycin.[3] Likewise, in the Republic of Korea, the VRE isolation rate has rapidly increased in tertiary hospitals since the first reported VRE isolation in 1992, and rectal colonization rates in ICU patients of the Republic of Korea range from 9.7%-51.9%.[4]

VRE have become important nosocomial pathogens, and it is well-known that asymptomatic VRE colonization precedes infection.[5] Susceptible hosts are at a high risk for VRE colonization.[6] These include patients who are severely ill and those receiving multiple and prolonged courses of antimicrobial agents. Importantly, the impact of VRE colonization per se on outcome is still unclear. Knowledge regarding factors affecting length of stay (LOS) and costs is also lacking.

Identification of potentially preventable risk factors for mortality, LOS and costs of hospitalization, and understanding the impact of colonization on these outcomes would improve the management of patients with VRE. Information regarding the LOS and costs of hospitalization would also facilitate evaluations of various infection control measures to minimize the spread of VRE.

The present study builds on our earlier research by including an evaluation for underlying condition and hospital cost data.[7] This

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study could qualify overall, direct, in-hospital clinical, and economic impact of colonization in a cohort of patients with VRE compared with a matched hospital population.

METHODS

Patients and study design

The Dong-A University Hospital, which is located in Busan, a south end city in Korea, is a 980-bed tertiary care hospital with a 66-bed medical and surgical ICU. We performed a retrospective propensity score matched cohort study comparing the outcomes of patients with VRE colonization with those of uncolonized subjects matched at the time they were admitted to the ICU. Between January 2008 and December 2010 we obtained rectal swab cultures within 24 hours of ICU admission to detect VRE colonization. Of the 7,703 patients admitted to the ICUs, we obtained 554 VRE colonized cases by electronic medical record search. The 504 controls, consisting of patients who were admitted to the ICU for >48 hours but were not colonized with VRE, were selected from the same ICU during the same calendar month in which VRE was isolated. We collected data for patient demographics, ICU admission route, laboratory findings, comorbidities, recent antimicrobial use (within 1 month of ICU admission), and recent prior admission (within a year). Patients' electronic medical records were reviewed to verify the information on colonization status, infection episodes, and sensitivity to vancomycin by 2 registered nurses with >5 years of experiences in ICU care. Collected data were double checked by the same researcher. To further control for confounding, we used a propensity score for VRE colonization. There were 199 VRE colonized patients matched with 199 uncolonized patients. This study was approved by the institutional review board of Dong-A University Hospital.

The lengths of hospital stay and costs of hospitalization, given in US dollars ($) and Korean Won (₩), were compared between case patients and control patients. Data on the costs of hospitalization were retrieved from the central financial service at Dong-A University Hospital and included information about the total cost of each hospital stay and costs of accommodation, medication, laboratory procedures, and materials and services. The latter included the cost of catheters, implanted devices, procedures and operations, rehabilitation programs, respiratory care, dialysis and other special services, physician care, nursing care, and consultations.

Statistical analysis

Categorical variables were summarized by counts and relative frequencies; numerical variables were summarized by their mean ± SD. Differences in patients' demographic and clinical characteristics were compared across propensity score matched groups with a McNemar test for categorical variables and a paired *t* test for numerical variables.

To reduce potential confounders in this retrospective observational study, the values of the propensity scores were used to adjust for differences between the 2 groups (VRE or non-VRE). Propensity scores were computed from the predicted probability that a patient has VRE using the SAS system PROC LOGISTIC (SAS Institute, Cary, NC), and a greedy match algorithm was used to match cases to controls (SAS macro code: http://www2.sas.com/proceedings/sugi26/p214-26.pdf).[8] All the variables were candidates for the model and were selected in a stepwise manner, with an entry criterion of $P < .20$ and a criterion to stay in the model of $P < .05$. Each outcome variable was later examined independently, adjusting for matching strata and the propensity score.

Mortality was examined using a matched (conditional) logistic regression model. Odds ratios (OR) for comparison of 2 groups were summarized with 95% confidence intervals (CIs) and *P* values using logistic regression. We estimated the adjusted OR from the logistic regression model and used these estimates to calculate the adjusted attributable risk for the exposed using maximum likelihood estimates as proposed by Greenland and Drescher.[9] 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 with log-transformed values as the numerical outcome adjusting for matching strata. Coefficients that underwent exponentiation could be interpreted as multiplicative effects (MEs) on ICU LOS, total admission days, and hospital costs.

P values lower than .05 were considered statistically significant. This is a retrospective study; therefore, the alpha was not adjusted for multiple testing. All statistical analyses were carried out using SAS version 9.2 statistical software (SAS Institute, Cary, NC).

RESULTS

From January 2008 to December 2010, of the 7,703 patients admitted to the ICUs, 567 (7.2%) patients were colonized with VRE. The study cohort included 398 participants: 199 VRE colonized patients were matched with 199 noncolonized patients using a propensity score matching method. The average age of VRE colonized patients was 62 years, and 60% were men. Many (54%) of the cohort patients had chronic underlying illnesses and were severely ill as expressed by a high mean APACHE II score of 14.9 and Charlson score of 4.7; 59%, 39%, and 2% of the participants were transferred from another institution, emergency department, and outpatient clinic, respectively. Among the admitting diagnoses, most patients (17%) were malignant. Demographics and clinical characteristics of VRE colonized patients and noncolonized patients that were propensity score matched are shown in Table 1.

Among the 398 cohort patients, 83 died during hospital admission, which included 49 of the 199 VRE colonized patients and 34 of the uncolonized patients (case fatality rate, 24.6% vs 17.1%). In a matched (conditional) logistic regression model, VRE colonization was significantly associated with mortality (adjusted OR, 2.35; $P = .012$; adjusted attributable mortality, 11%). The OR was adjusted for the matching strata and propensity score and attributable risk of VRE colonization using maximum likelihood estimates as proposed by Greenland and Drescher.[9] Results of adjusted analyses are displayed in Table 2.

Logistic regression analysis was performed for mortality because mortality is a binary response variable (dead: 1, alive: 0). However, LOS and cost were continuous data; therefore, the regression analysis was used. All LOS and cost variables were log transformed because they were nonnormally distributed. LOS and cost of hospitalization data were log transformed in all linear regression models in this article. Therefore, exponentiated coefficient values, Exp(β), were interpreted as MEs on LOS and cost. All linear regression models for LOS and cost were adjusted for matching strata and propensity score. Results of the analysis are displayed in Table 2. The mean of the ICU LOS was 7.6 days for VRE colonized patients compared with 8.8 days for noncolonized patients. This difference was not significant. Longer total admission days were observed in the VRE colonized patients (ME, 1.25; $P = .004$). We estimated that VRE colonized patients were associated with an average adjusted increase of 5.4 days.

All costs are expressed in 2014 US dollars (Korean Won). The mean ICU cost for VRE colonization was $6,065 (₩6,430,236), whereas the mean cost for VRE noncolonization was $5,298 (₩5,617,253). VRE colonization is found to be a significant factor