

Clinical and Economic Evaluation of Multidrug-Resistant *Acinetobacter baumannii* Colonization in the Intensive Care Unit

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Background: The clinical and economic impact of multidrug-resistant (MDR) *Acinetobacter baumannii* colonization remains unclear. This study aimed to estimate and compare the mortality rates, length of stay (LOS), and hospitalization costs in the intensive care unit (ICU) for MDR *A. baumannii* colonized patients and a matched population.

Materials and Methods: We performed a retrospective propensity score matched cohort study comparing the outcomes of patients with MDR *A. baumannii* colonization with those of uncolonized subjects matched at the time they were admitted to the ICU between January 2012 and December 2014.

Results: During the study period, 375 (7.5%) of the 4,779 patients were colonized with MDR *A. baumannii*. One hundred and twenty-two MDR *A. baumannii* colonized patients were compared with 122 uncolonized patients using propensity score matching. MDR *A. baumannii* colonized patients were likely to have a higher mortality rate compared to uncolonized patients (49.2% vs 32.0%; odds ratio [OR], 3.64). A longer ICU LOS and total admission days were observed in the MDR *A. baumannii* colonized patient group (4.14 and 4.67 days increase, OR 1.41 and 1.19). MDR *A. baumannii* colonization patients had an average extra ICU and total admission cost of \$1,179 (₩1,261,334) and \$1,333 (₩1,422,032) according to a multivariable regression model (OR, 1.27 and 1.17). Multivariable analysis identified the factors affecting ICU cost, which included, MDR *A. baumannii* colonization (OR = 1.33 ; $P = 0.001$), ICU LOS (OR = 1.97; $P < 0.001$), valvular heart disease (OR = 1.12; $P = 0.005$), invasive devices (OR = 1.15; $P = 0.018$), and surgery (OR = 1.1; $P < 0.001$).

Conclusion: MDR *A. baumannii* colonization was associated with increased mortality, LOS, and costs in the ICU. A strict infection control program including preemptive isolation for high-risk groups would be helpful for reducing the burden of this infection.

Key Words: *Acinetobacter baumannii*; Infection control; Intensive care units

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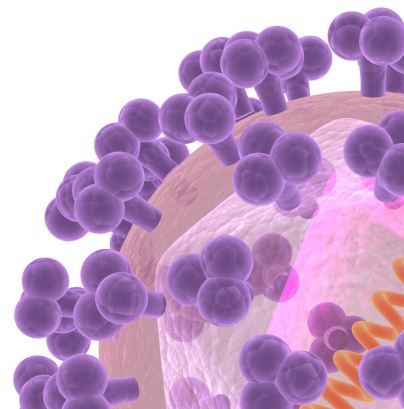
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Introduction

Antibiotic resistance is becoming increasingly problematic and is a major public health threat. Infections caused by antibiotic-resistant bacteria could have severe adverse outcomes, such as higher morbidity and mortality, a longer length of stay (LOS) in hospital, and an increased cost of medical care [1, 2].

Acinetobacter baumannii is a non-fermentive, aerobic, opportunistic, Gram-negative coccobacillary rod bacterium that is widespread in the natural environment [2]. *A. baumannii* is an opportunistic bacterial pathogen primarily associated with healthcare-related infections. *A. baumannii* infections have been found in a wide range of anatomical regions and are linked to outbreaks of nosocomial infections, such as hospital-acquired pneumonia, bloodstream infection, meningitis, battlefield trauma, and other wound infections [3]. The rapid global emergence of *A. baumannii* strains resistant to all beta-lactam antibiotics, including carbapenems, highlights the organism's ability to quickly adapt to changes caused by selective environmental pressures. The upregulation of innate resistance mechanisms and the acquisition of foreign determinants have played a critical role in *A. baumannii* becoming a multidrug-resistant pathogen [4].

The isolation of multidrug-resistant (MDR) *A. baumannii* infections is becoming more common, with an increased proportion of patients requiring critical care [3]. Intensive care units (ICUs) are high-risk settings for multidrug-resistant infection. Infection control surveillance at our healthcare institution identified a significant increase in the number of *A. baumannii* isolates from patients in the surgical ICU (SICU) [5]. The reported carbapenem-resistance rate of *A. baumannii* isolates was 82.5% in 2010, according to a survey carried out by the Korean Nosocomial Infections Surveillance System [6]. A rapid increase in the isolation rates of MDR *A. baumannii* has been observed and there have been several outbreaks of MDR *A. baumannii* in Korean ICUs [7]. However, the clinical and economic impact of multidrug resistance in patients with MDR *A. baumannii* infection has not been clearly defined. Most of all, the impact of MDR *A. baumannii* colonization itself on clinical outcome is still unclear. Detailed data regarding factors affecting medical and economical outcome are also lacking in Korea.

The present study continues our earlier research by including an evaluation of clinical outcome and hospital cost data [8]. This study aimed to investigate the overall, direct, in-ICU clinical, and economic impact of colonization in a cohort of patients with MDR *A. baumannii* compared with that in a

matched population.

Materials and Methods

1. Patients and study design

The Dong-A University Hospital, located in Busan, a southern 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 MDR *A. baumannii* colonization with those of uncolonized subjects. Subjects were matched at the time they were admitted to the ICU between January 2012 and December 2014. All patients with at least one MDR *A. baumannii* isolate during the study period were identified retrospectively. The definition of colonization was the presence of MDR *A. baumannii*, without signs or symptoms indicating active infection due to MDR *A. baumannii*. Of the 4,779 patients admitted to the ICUs, we identified 377 MDR *A. baumannii* colonized patients from electronic medical records. Two patients with inconclusive medical records were excluded and a final total of 375 patients were selected as the case group. The control group comprised 377 patients without MDR *A. baumannii* colonization who were hospitalized in the same unit and time period as the matched cases. We collected data on patient demographics, ICU admission route, laboratory findings, comorbidities, recent antimicrobial use (within 1 month of ICU admission), and recent prior admission (within a year). The medical record review was performed by researchers and two registered nurses in Dong-A University Hospital Regional Clinical Trial Center. Collected data were validated by the same researcher. To further control for confounding factors, we used a propensity score for MDR *A. baumannii* colonization. One hundred and twenty-two MDR *A. baumannii* colonized patients were matched with 122 uncolonized patients. This study was approved by the institutional review board (IRB) of Dong-A University Hospital.

The lengths of hospital stay and costs of hospitalization 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, as well as costs of accommodation, medication, laboratory procedures, and materials and services. The latter included the cost of catheters, implanted devices, procedures and surgeries, rehabilitation programs, respiratory care, dialysis and other special services,

physician care, nursing care, and consultations.

2. Isolation, identification, and susceptibility testing

A. baumannii was defined as multidrug resistant if it was resistant to commonly available antibiotics (antipseudomonal penicillins, antipseudomonal cephalosporins, antipseudomonal fluoroquinolones, aminoglycosides, or trimethoprim-sulfamethoxazole), but susceptible to carbapenems. Non-multiple drug resistance was defined as susceptibility to carbapenems and other alternative antipseudomonal antimicrobial agents (e.g. penicillins, cephalosporins, fluoroquinolones, or aminoglycosides) [9].

Clinical isolates underwent species identification and antibiotic susceptibility testing using the Bactec 9240 system (Becton Dickinson, Cockeysville, MD, USA). *A. baumannii* isolates were identified using both standard microbiological techniques [10] and the Vitek system (bioMérieux, Marcy l'Étoile, France). Antimicrobial susceptibility was determined using the disk diffusion technique, in accordance with the criteria established by the Clinical and Laboratory Standards Institute (formerly known as the National Committee for Clinical Laboratory Standards) [11].

3. Statistical analysis

Categorical variables were summarized by counts and relative frequencies while numeric variables were summarized by their mean \pm SD (standard deviation). Differences in patients' demographic and clinical characteristics were compared across propensity score matched groups with McNemar's test for categorical variables and a paired *t* test for numeric variables.

To reduce potential confounders in this retrospective observational study, the values of the propensity scores were adjusted for differences between the two groups (*Acinetobacter* or non-*Acinetobacter*). Propensity scores were computed as the predicted probability that a patient has *Acinetobacter* using the SAS system PROC LOGISTIC and a greedy match algorithm was used to match cases to controls. All of the variables were candidates for the model and were selected in a stepwise manner, with an entry criterion of $P < 0.20$ and a criterion to stay in the model of $P < 0.05$. Each outcome variable was later examined independently, using multivariate analysis with *Acinetobacter* status and propensity score.

Mortality was analyzed using a conditional logistic regression model. The odds ratio (OR) for comparison of the two groups was summarized with its 95% confidence interval (CI) and *P* values using logistic regression. In a multivariate analy-

Table 1. Patients' demographic and clinical characteristics

Variables	AB colonized (n=122)	Not colonized (n=122)	<i>P</i> value ^a
Age, Mean \pm SD (years)	65.9 \pm 13.0	66.2 \pm 16.1	0.868
Male sex	81 (66.4%)	72 (59.0%)	0.235
Type of ICU			
General	56 (45.9%)	54 (44.3%)	0.858
Cardiac	25 (20.5%)	23 (18.9%)	
Neurologic	41 (33.6%)	45 (36.9%)	
Main diagnosis			
Stroke	37 (30.3%)	29 (23.8%)	0.249
Pneumonia	25 (20.5%)	21 (17.2%)	0.513
Sepsis	20 (16.4%)	24 (19.7%)	0.505
malignancy	11 (9.0%)	16 (13.1%)	0.308
Vascular injury	7 (5.7%)	4 (3.3%)	0.355
Brain injury	6 (4.9%)	5 (4.1%)	0.757
Valvular heart disease	6 (4.9%)	4 (3.3%)	0.518
Chronic heart disease	5 (4.1%)	3 (2.5%)	0.472
Other lung injury	5 (4.1%)	3 (2.5%)	0.472
Chronic kidney disease	5 (4.1%)	8 (6.6%)	0.392
COPD	4 (3.3%)	3 (2.5%)	0.701
Urinary tract infection	3 (2.5%)	3 (2.5%)	1.000
Drug intoxication	2 (1.6%)	2 (1.6%)	1.000
Myocardial infarction	1 (0.8%)	8 (6.6%)	0.017
ICU admission route			
other hospital	38 (31.1%)	31 (25.4%)	0.074
long-term care facility	11 (9.0%)	4 (3.3%)	
home	73 (59.8%)	87 (71.3%)	
Comorbidity	29 (23.8%)	31 (25.4%)	0.766
APACHE II score	16.1 \pm 5.6	16.9 \pm 5.2	0.256
Charlson score	2.2 \pm 1.8	2.3 \pm 2.0	0.737
Invasive procedure	58 (47.5%)	62 (50.8%)	0.609
Invasive devices	14 (11.5%)	14 (11.5%)	1.000
Surgery within 1 month	58 (47.5%)	62 (50.8%)	0.609
Neutropenia	4 (3.3%)	7 (5.7%)	0.355
Immunosuppressive	22 (18.0%)	28 (23.0%)	0.341

^a*P* values were derived from McNemar's test for categorical data or paired *t* test for continuous data; invasive procedure which was performed within 48 hours after the day *Acinetobacter baumannii* was identified; Invasive devices which were 1) arterial catheter, 2) abdominal drainage, 3) central venous catheter, 4) mechanical ventilation, 5) tracheostomy, 6) conventional hemodialysis & CRRT, 7) peritoneal dialysis, 8) nasogastric tube, 9) thoracic drainage, and 10) urinary catheter. AB, *Acinetobacter baumannii*; SD, standard deviation; ICU, intensive care unit; COPD, chronic obstructive pulmonary disease; APACHE, acute physiologic and chronic health evaluation.

Table 2. Outcomes and adjusted analyses for treated group versus reference group patients

Variables	AB colonized (n=122)	Not colonized (n=122)	Adjusted analyses		P-value
			OR (95% CI)	Attributable to Treat	
Mortality, n (%)	60 (49.2)	39(32.0)	3.64 (1.80-7.37)	18.8	<0.0001
ICU length of stay, mean, d	35.4±29.0	10.1±8.2	1.41 (1.20-1.66)	4.14	<0.0001
Total admission, mean, d	40.3±40.6	24.6±28.0	1.19 (1.10-1.30)	4.67	0.029
ICU cost, mean, \$ (₩)	14,114 (15,361,027)	4,367 (4,671,606)	1.27 (1.09-1.48)	1,179 (1,261,334)	0.002
Total admission cost, mean, \$ (₩)	16,087 (17,490,057)	7,840 (8,364,896)	1.17 (1.03-1.33)	1,333 (1,422,032)	0.046

AB, *Acinetobacter baumannii*; OR, odds ratio; CI, confidence interval; ICU, intensive care unit.

Table 3. Factors associated with ICU cost (linear regression model)

Parameter	Univariable			Multivariable		
	Exp (β)	95% CI	P-value	Exp (β)	95% CI	P-value
AB colonized	1.766	1.501-2.078	<.0001	1.327	1.128-1.561	0.001
VHD	1.208	1.11-1.314	0.003	1.115	1.025-1.213	0.005
Invasive device	1.242	1.065-1.448	<.0001	1.154	1.061-1.255	0.018
Surgery	0.884	0.775-1.009	0.055	1.099	1.002-1.206	0.026
ICU length of stay	2.253	1.975-2.571	<.0001	1.967	1.724-2.244	<0.0001

ICU, intensive care unit; CI, confidence interval; AB, *Acinetobacter baumannii*; VHD, valvular heart disease.

Table 4. Factors associated with total cost (linear regression model)

Parameter	Univariable			Multivariable		
	Exp (β)	95% CI	P-value	Exp (β)	95% CI	P-value
Type of ICU						
General	ref			ref		
Cardiac	1.132	0.839-1.526	0.073	1.078	0.912-1.274	0.053
Neurologic	1.026	0.8-1.315	0.71	0.887	0.767-1.026	0.003
Surgery	1.235	0.994-1.535	0.001	1.221	1.072-1.391	<0.0001
ICU length of stay	2.102	1.968-2.245	<0.0001	1.436	1.311-1.573	<0.0001
Total admission	2.189	2.033-2.357	<0.0001	1.629	1.46-1.819	<0.0001

CI, confidence interval; ICU, intensive care unit.

sis, ORs were also adjusted for other significant factors that were selected using a backward elimination method, with a criterion to stay in the model of $P < 0.05$. We estimated the adjusted relative risk from the logistic regression model and used these estimates to calculate the adjusted attributable risk for the exposed factors. Cost and LOS data were not normally distributed; however, log-transformed cost and LOS were normally distributed. Therefore, the data were first analyzed using linear regression with log-transformed values as the numeric outcome in all linear regression models.

P values < 0.05 were considered statistically significant. This is a retrospective study and therefore alpha was not adjusted for multiple testing. All statistical analyses were carried out using SAS version 9.4 statistical software.

Results

Demographics and clinical characteristics of MDR *A. baumannii* colonized patients and non-colonized patients that were propensity score matched are shown in Table 1. The average age of MDR *A. baumannii* colonized patients was 65.9 years, and 66.4% were men. Of the case patients, 23.8% had chronic underlying illnesses and were severely ill, as indicated by a high mean APACHE II of 16.1 and a Charlson score of 2.2; 59.8%, 31.1%, and 9% were transferred from home, another hospital, or a long term facility, respectively. The most common diagnosis on admission was stroke (30.3%).

Among the 244 cohort patients, 92 died during their hospital stay; 60 of the 122 MDR *A. baumannii* colonized patients and

39 of the non-colonized patients (mortality, 49.2% vs 32%). In a conditional logistic regression model, MDR *A. baumannii* colonization was significantly associated with mortality (OR, 3.64; $P < 0.0001$; adjusted attributable mortality, 18.8%). Results of adjusted analyses are displayed in Table 2.

A longer ICU length of stay (LOS) and total admission days were observed in the MDR *A. baumannii* colonized patients. The mean ICU LOS was 35.4 days for MDR *A. baumannii* colonized patients, compared to 10.1 days for non-colonized patients (OR, 1.41; $P < 0.0001$). The mean total admission was 40.3 days for MDR *A. baumannii* colonized patients and 24.6 days for non-colonized patients (OR, 1.19; $P = 0.029$). We estimated that average adjusted increases of 4.14 and 4.67 days were associated with ICU LOS and total admission, respectively.

All costs are expressed in 2016 U.S. dollars (Korean Won). The mean ICU cost for MDR *A. baumannii* colonization patients was \$14,114 (₩15,361,027), while the mean cost for MDR *A. baumannii* non-colonization patients was \$4,367 (₩4,671,606). MDR *A. baumannii* colonization is significantly associated with increased ICU cost in a multivariable regression model (OR, 1.27; $P = 0.002$). MDR *A. baumannii* colonization was associated with an average adjusted increase of \$1,179 (₩1,261,334). MDR *A. baumannii* colonization was also found to be a significant factor associated with increased total admission cost in a multivariable regression model (OR, 1.17; $P = 0.046$).

To adjust confounding effects of clinical factors other than MDR *A. baumannii* colonization to hospitalization cost, we included all of the clinical variables in multivariable linear regression analyses, as shown in Table 3 and 4. Notably, in multivariate analysis it was found that MDR *A. baumannii* colonization, valvular heart disease, invasive device, surgery, and ICU LOS were significantly associated with ICU cost (Table 3). It also indicated that ICU costs were significantly lower in the non-*A. baumannii* colonized group compared to those in the MDR *A. baumannii* colonized group (OR, 1.33; $P = 0.001$). However, in a multivariable model, total admission cost was not significantly associated with MDR *A. baumannii* colonization ($P > 0.05$; data not shown). Instead, total admission cost was found to be significantly associated with the type of ICU, ICU LOS, and total admission days (Table 4).

Discussion

This study assessed the outcomes of patients with MDR *A.*

baumannii colonization in the ICU. To our knowledge, it is the first to use statistical modeling to quantify the economic burden of MDR *A. baumannii* colonization in the Korean hospital setting. The strength of this study is that medical and economic outcome factors such as mortality, LOS, and cost data for patients with MDR *A. baumannii* colonization were compared.

Our major findings were that MDR *A. baumannii* colonization was associated with the following: 1) 3.64-fold increased odds of mortality, 2) 1.41-fold increased odds of ICU LOS, 3) 1.19-fold increased odds of total admission days, 4) 1.27-fold increased odds of ICU cost, and 5) 1.17-fold increased odds of total admission cost. The corresponding estimates of MDR *A. baumannii* colonization-attributable effects were as follows: an 18.8% increase in mortality; a 4.14-day increase in length of ICU stay; a 4.67-day increase in the total number of admission days; and an average extra ICU and total hospitalization cost of \$1,179 (₩1,261,334) and \$1,333 (₩1,422,032), respectively. These could be converted into 23 cases of in-hospital deaths, 505 additional ICU days, 570 additional total hospitalization days, and excess costs of \$143,838 (₩153,882,748) and \$162,626 (₩173,487,904) for ICU and total admission during the study period.

An outbreak of MDR *A. baumannii* can cause a multitude of infections among hospitalized patients. A spectrum of severe illness due to *A. baumannii* infection acquired in the healthcare setting has been described, from sources including contaminated ventilator equipment, humidifiers, and overuse of specific antimicrobials [12, 13]. Although awareness of antimicrobial resistance is growing and knowledge on the clinical and economic impact of antimicrobial resistance is useful in healthcare programs, limited data exist on the related cost to the healthcare system. Young *et al.* found that MDR *A. baumannii* infection resulted in additional patient charges of more than \$60,000, and was associated with prolonged hospitalization by nearly 2 weeks [5]. We have shown that MDR *A. baumannii* colonization was associated with additional patient charges, and it prolonged the LOS. However, this evaluation does not include additional costs such as infection control investigation time, materials and staff needed to care for patients in isolation, physician charges, and home healthcare or outpatient therapy. Therefore, control of an MDR *A. baumannii* outbreak is crucial both from the point of view of preventing significant morbidity due to nosocomial infection and minimizing excess healthcare costs.

In Korean hospitals, control of MDR *A. baumannii* transmission in the healthcare environment can be difficult. A ma-

major restriction was the high cost per bed in an isolation room, which was related to an uncompensated care burden from the medical insurance [14]. A study has shown that antibiotic resistance in nosocomial Gram-negative bacteremia was not responsible for the increased need for hospital resources and did not cause a poor outcome for critically ill patients [15]. However, the findings of that study were limited and underpowered because of biased assessment using cause of death as the primary outcome measure and the results were not adjusted for disease severity. Therefore, information about outcomes associated with infection caused by drug-resistant organisms could be very useful in influencing programs and behavior in infection control, guiding policy makers and funding agencies, and promoting the development of measures to track and prevent the spread of antimicrobial-resistant organisms.

Colonization, which does not cause any symptoms, may last for long periods and serve as a reservoir for the transmission of MDR *A. baumannii* to other patients [16, 17]. Within hospitals, the ratio of infection to colonization may differ widely depending on the patient group [18-20]. Therefore, tracking colonization with MDR *A. baumannii* through active surveillance in high-risk units is important for preventing further transmission. The Society for Healthcare Epidemiology of America (SHEA) Board of Directors recommended routine screening cultures to identify and isolate MDR carriers [21]. However, it is very difficult to maintain appropriate infection control measures. Huskin *et al.* revealed that simply improving the identification of colonized patients and expanding the use of barrier precautions are not likely to be sufficient [22]. SHEA and the Association for Professionals in Infection Control and Epidemiology (APIC) do not support the legislation as a means to mandate any specific infection control strategy, including the use of active surveillance cultures [23].

The results of this study represent the impact of MDR *A. baumannii* colonization after adjustment for confounding variables; however, the inherent limitations of all studies of this nature should be considered. There may be additional confounding factors, which were not included in the models. To avoid confounding factors in case-control studies, it is critical to select the appropriate reference group by matching control patients on the basis of length of hospital stay and the severity of comorbidities before admission. As another source of bias, classification bias may occur because some of the control patients may be unidentified MDR *A. baumannii* carriers.

In conclusion, MDR *A. baumannii* colonization is associated with prolonged hospitalization, increased medical costs,

and an increased mortality rate in the ICU. The results of this study highlight the need for effective interventions to minimize the impact of MDR *A. baumannii* colonization, such as active MDR *A. baumannii* surveillance culture and isolation. It is also necessary to preemptively isolate patients with risk factors affecting MDR *A. baumannii* colonization in the ICU.

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Conflicts of Interest

No conflicts of interest.

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