Risk Factors for Mortality in Patients with Carbapenem-Resistant Acinetobacter baumannii Bacteremia: Impact of Appropriate Antimicrobial Therapy

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INTRODUCTION

Acinetobacter baumannii is an important nosocomial pathogen (1-6). Carbapenem is a preferred drug of choice for the treatment of multidrug-resistant A. baumannii. However, carbapenem-resistant strains have now emerged around the world (2). Prevalence of carbapenem-resistant A. baumannii varies in different countries; in Korea, the resistance rate of A. baumannii against carbapenem was reported as 31.7% or 34.9% (7).

A. baumannii may cause various clinical manifestations ranging from colonization to septic shock, and A. baumannii bacteremia-associated mortality rate is reported to be as high as 17%-62% (8-10). Initiation of effective empirical antimicrobial treatment might be important for reducing A. baumannii bacteremia-associated mortality. However, in Korea, initiation of broad spectrum antibiotic treatment with antibiotics such as carbapenem or colistin is difficult because of insurance problems (11, 12). Because the severity of underlying disease could affect the outcomes in patients with A. baumannii bacteremia, it is not yet clear whether immediate and appropriate antimicrobial therapy as proper dose and administration route can affect these outcomes (12, 13). Because of the presence of limited therapeuti-
age was adequate according to the current guidelines. Infection was assessed according to “Centers for Disease Control and Prevention” criteria, and patients were considered infected when A. baumannii was isolated from a sterile site in patients with definite clinical signs of infection (14). Prior antibiotics treatment was defined as the use of systemic antibiotics for at least 7 days within the preceding 28 days. For better understanding of the patients’ baseline status, we assessed the APACHE II score before bacteremia on the date of admission. We used 14-day in-hospital mortality as the main outcome for assessment of mortality for patients with serious conditions due to bacteremia.

**Microbiological examination**
Identification of A. baumannii in blood samples was performed using a VITEK®2 automated system (bioMérieux, Marcy l’Etoile, France). Susceptibility results were interpreted according to guidelines established by the Clinical and Laboratory Standards Institute (15). CRAB was defined as non-susceptible to meropenem and/or imipenem in vitro, and isolates with intermediate resistance were regarded as resistance.

**Statistically analysis**
Student’s t-test was used for analysis of continuous variables, and the chi-squared test or Fisher’s exact test was used for categorical variables and Student’s t test or the Mann-Whitney U test for continuous variables. We analyzed the risk factors associated with mortality using univariate and multivariate logistic regression analyses. Survival curves were prepared using the Kaplan-Meier method with log-rank test. Statistical analysis was performed using SPSS 13.0 and a $P$ value < 0.05 was considered statistically significant.

**Ethics statement**
This study was approved by the institutional review board of Seoul St. Mary’s Hospital (Protocol No; KC10OISI0070). Informed consent was waived by the board. All the data collected during this study were kept confidential.

**RESULTS**
A total of 95 patients with A. baumannii bacteremia were included in this study. Demographic characteristics of these pa-

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**Table 1. Clinical characteristics of patients with Acinetobacter baumannii bacteremia**

| Parameters                      | Total (n = 95) | CRAB group (n = 53) | Non-CRAB group (n = 42) | $P$ value |
|---------------------------------|---------------|---------------------|-------------------------|-----------|
| Age, mean ± SD (yr)            | 58.4 ± 20.9   | 59.4 ± 21.8         | 57.1 ± 19.9             | 0.59      |
| Male sex                       |               |                     |                         | 0.06      |
| Diabetes mellitus              |               |                     |                         |           |
| Hypertension                   |               |                     |                         |           |
| Liver cirrhosis                |               |                     |                         |           |
| Transplant                     |               |                     |                         |           |
| Malignancy                     |               |                     |                         |           |
| Dialysis                       |               |                     |                         |           |
| Immunosuppression              |               |                     |                         |           |
| Previous surgery within one month |            |                     |                         | 0.96      |
| Hospitalization in the preceding 90 days |      |                     |                         | 0.68      |
| Invasive procedure             |               |                     |                         |           |
| Central venous catheter        |               |                     |                         |           |
| Surgical drainage              |               |                     |                         |           |
| Foley catheter                 |               |                     |                         |           |
| Tracheostomy                   |               |                     |                         |           |
| Mechanical ventilation         |               |                     |                         |           |
| The length of stay before bacteremia, mean ± SD |      |                     |                         | 0.96      |
| APACHE II score                |               |                     |                         | 0.005     |
| Charlson’s weighted index of co-morbidity |     |                     |                         | 0.42      |
| Prior antibiotics              |               |                     |                         |           |
| Cephalosporin                  |               |                     |                         |           |
| Quinolone                      |               |                     |                         |           |
| Aminoglycoside                 |               |                     |                         |           |
| Carbapenem                     |               |                     |                         |           |
| Source of bacteremia           |               |                     |                         |           |
| Pneumonia                      |               |                     |                         |           |
| Urinary tract                  |               |                     |                         |           |
| Vascular catheter-related      |               |                     |                         |           |
| Intra-abdomen                  |               |                     |                         |           |
| Postoperative wound            |               |                     |                         |           |
| Unknown                        |               |                     |                         |           |

CRAB, carbapenem-resistant Acinetobacter baumannii.

472 http://jkms.org http://dx.doi.org/10.3346/jkms.2012.27.5.471
tients are shown in Table 1. The mean age of the patients was 58.4 ± 20.9 yr; and of the 95 patients, 53.7% were male. The mean length of stay before *A. baumannii* bacteremia was 30.2 ± 51.5 days. The presumed sources of bacteremia were respiratory tract (n = 28, 29.5%), vascular catheter (n = 24, 25.3%), intra-abdomen (n = 15, 15.8%), postoperative wounds (n = 8, 8.4%), urinary tract (n = 6, 6.3%), and other unknown sources (n = 8, 8.4%).

Fifty-three patients (55.8%) were infected with CRAB. Univariate analysis showed that the risk factors for acquisition of CRAB bacteremia were diabetes mellitus (OR 3.2, 95% CI 1.06-9.64; *P* = 0.04), dialysis (OR 4.23, 95% CI 1.11-15.9; *P* = 0.03) as an underlying disease, use of foley catheter (OR 3.81, 95% CI 1.62-8.96; *P* = 0.002) or carbapenem (OR 19.3, 95% CI 4.21-87.9; *P* = 0.001). By multivariate analysis, diabetes mellitus as an underlying disease (OR 4.51, 95% CI 1.16-14.8; *P* = 0.03) and prior use of carbapenem (OR 14.8, 95% CI 2.76-79.5; *P* = 0.002) were independently associated with CRAB bacteremia (Table 2).

The overall infection-related 14-day mortality in patients with *A. baumannii* bacteremia was 31.6% (30/95); infection-related 14-day mortality was higher in patients receiving inappropriate antimicrobial therapy than in patients receiving appropriate therapy (59.5% [22/37] vs 13.8% [8/58], *P* < 0.05). The cumulative survival curves of the patients according to the appropriateness of antimicrobial therapy are shown in Fig. 1. Univariate analysis showed that the risk factors for infection-related 14-day mortality in patients with *A. baumannii* bacteremia were central venous catheter (OR 4.02, 95% CI 1.37-11.83; *P* = 0.01), mechanical ventilatoin (OR 5.77, 95% CI 2.22-15.02; *P* < 0.001), high APACHE II score (OR 4.01, 95% CI 1.39-11.4; *P* = 0.01), septic shock (OR 5.61, 95% CI 2.13-14.7; *P* < 0.001), carbapenem-resistance (OR 9.14, 95% CI 2.86-29.2; *P* < 0.001), pneumonia as a source of bacteremia (OR 5.05, 95% CI 1.94-13.0; *P* < 0.001), and inappropriate antibiotic therapy (OR 6.58, 95% CI 2.53-17.1; *P* < 0.001) (Table 3). Multivariate analysis showed that septic shock (OR 10.5, 95% CI 1.93-57.4; *P* = 0.006), carbapenem-resistance

### Table 2. Risk factors for acquisition of carbapenem resistant *Acinetobacter baumannii* bacteremia

| Risk factors | Univariate analysis | Multivariate analysis |
|--------------|---------------------|----------------------|
| Age, mean ± SD | 1.0 0.99-1.02 0.59 | 1.0 0.99-1.02 0.59 |
| Male sex | 2.2 0.96-5.02 0.06 | 2.2 0.96-5.02 0.06 |
| Underlying disease | | |
| Diabetes mellitus | 3.2 1.06-9.64 0.04 | 4.51 1.16-14.8 0.03 |
| Hypertension | 1.79 0.65-4.95 0.3 | 1.79 0.65-4.95 0.3 |
| Liver cirrhosis | 1.44 0.39-5.31 0.56 | 1.44 0.39-5.31 0.56 |
| Transplant | 5.23 0.61-45.3 0.12 | 5.23 0.61-45.3 0.12 |
| Malignancy | 1.01 0.45-2.29 0.95 | 1.01 0.45-2.29 0.95 |
| Dialysis | 4.23 1.11-15.9 0.03 | 4.23 1.11-15.9 0.03 |
| Immunosuppression | 1.53 0.57-4.10 0.40 | 1.53 0.57-4.10 0.40 |
| Previous surgery within one month | 1.01 0.45-2.29 0.96 | 1.01 0.45-2.29 0.96 |
| Hospitalization in the preceding 90 days | 1.19 0.52-2.69 0.68 | 1.19 0.52-2.69 0.68 |
| Invasive procedure | | |
| Central venous catheter | 1.74 0.74-4.10 0.21 | 1.74 0.74-4.10 0.21 |
| Surgical drainage | 1.14 0.48-2.73 0.76 | 1.14 0.48-2.73 0.76 |
| Foley catheter | 2.91 1.26-6.73 0.01 | 2.51 0.89-7.59 0.08 |
| Tracheostomy | 1.94 0.54-6.81 0.31 | 1.94 0.54-6.81 0.31 |
| Mechanical ventilation | 4.6 1.66-12.77 0.003 | 2.75 0.77-9.62 0.12 |
| The length of stay before bacteremia, mean ± SD | 1 0.99-1.00 0.96 | 1 0.99-1.00 0.96 |
| Prior antibiotics | | |
| Cephalosporin | 3.81 1.62-8.96 0.002 | 1.85 0.61-5.61 0.27 |
| Quinolone | 1.05 0.29-3.74 0.93 | 1.05 0.29-3.74 0.93 |
| Aminoglycoside | 3.44 0.63-18.7 0.15 | 3.44 0.63-18.7 0.15 |
| Carbapenem | 19.3 4.21-87.9 0.001 | 14.8 2.76-79.5 0.002 |

CRAB, carbapenem-resistant *Acinetobacter baumannii*. 

http://dx.doi.org/10.3346/jkms.2012.27.5.471  http://jkms.org 473
that were administered as an improper dose or through an inappropriate route) after obtaining the blood culture results. Our data suggest that early administration of appropriate antimicrobial therapy showed improved outcomes in patients with CRAB bacteremia, although underlying status played an important role in clinical outcome.

Studies have shown that APACHE II score is useful for the estimation of prognosis in *Acinetobacter* pneumonia (19, 20). In our study, a high APACHE II score was associated with mortality by univariate analysis; however this was not identified as an independent risk factor by multivariate analysis. This may be because of several reasons. First, some information, such as that on sepsis and mechanical ventilation, was not included while determining this score. Second, we assessed the APACHE II score before the occurrence of bacteremia on the date of admission, in order to best reflect the patients’ baseline status. Our study also showed that septic shock at the time of bacteremia was an independent risk factor for mortality. This finding suggested that a combination of other parameters, including the APACHE II score, is necessary for the evaluation of morbidity in patients with bacteremia.

The effect of antibiotic resistance on mortality is controversial. Some studies have reported that antibiotic resistance has an adverse impact on the mortality rates in patients with *A. baumannii* bacteremia (1, 21). One study reported that mortality in patients with multidrug-resistant *A. baumannii* infection in surgical intensive care units did not differ significantly from that in patients with non-multidrug-resistant *A. baumannii* infection. However, the study did not include patients who were simply bacteremic (6). Our results showed that carbapenem resistance was independently associated with mortality. However, patients with CRAB bacteremia had a higher APACHE II score (14.4 ± 7.7 vs 10.4 ± 6.1, \( P = 0.005 \)) and received a more inappropriate antibiotic treatment (52.8% [28/53] vs 21.4% [9/42], \( P = 0.002 \)) than those with non-CRAB bacteremia. CRAB bacteremia usually occurs in patients with severe illness and in patients with a high probability of receiving inappropriate antimicrobial therapy, which then negatively affect the outcomes.

| Risk factors                              | Univariate analysis | Multivariate analysis |
|------------------------------------------|---------------------|-----------------------|
|                                          | OR  | 95% CI      | \( P \) value | OR  | 95% CI      | \( P \) value |
| Age ≥ 60 yr                              | 1.48 | 0.61-3.6 | 0.38          | 1.59 | 0.39-6.41 | 0.51          |
| Diabetes mellitus                        | 2.45 | 0.90-6.66 | 0.07          | 3.53 | 0.68-18.2 | 0.13          |
| Malignancy                               | 1.72 | 0.72-4.13 | 0.21          | 1.67 | 0.36-7.79 | 0.5           |
| Mechanical ventilator                    | 5.77 | 2.22-15.0 | < 0.001       | 10.5 | 1.93-57.4 | 0.006         |
| Central venous catheter                  | 4.02 | 1.37-11.8 | 0.01          | 7.29 | 1.57-33.8 | 0.01          |
| APACHE II score ≥ 14                     | 4.01 | 1.39-11.4 | 0.01          | 5.29 | 1.07-26.1 | 0.04          |
| Septic shock                             | 5.61 | 2.13-14.7 | < 0.001       | 8.05 | 1.65-39.2 | 0.009         |
| CR                                       | 9.14 | 2.86-29.2 | < 0.001       | 5.05 | 1.94-13.0 | 0.001         |
| Pneumonia as a source of bacteremia      | 6.58 | 2.53-17.1 | < 0.001       | 4.01 | 1.39-11.4 | 0.01          |
| Inappropriate antibiotic therapy         |      |            |               | 5.61 | 2.13-14.7 | 0.01          |

OR, odds ratio; CI, confidential interval; CR, carbapenem-resistance.
Results from the present study also showed that factors for acquisition of CRAB included diabetes mellitus as an underlying disease and a prior exposure to carbapenem. Some studies have reported that prior use of carbapenem, third-generation cephalosporins and fluoroquinolones are independent risk factors for the acquisition of multidrug resistant *A. baumannii* (22, 23). Selective pressure exerted by use of broad spectrum antibiotics, such as carbapenem, leads to the emergence of multidrug-resistant *A. baumannii*. Therefore, we consider multidrug resistance in patients with *A. baumannii* bacteremia who showed particularly severe illness, and who had recently received carbapenem. In order to decrease acquisition of CRAB, judicious use of carbapenem is important.

Our study had some limitations, including the retrospective design, which was not randomized. A small number of patients were enrolled from a single center. Furthermore, we could not judge the appropriateness of the empirical antibiotic treatment in this study. It was rare that patients with CRAB bacteremia received colistin empirically, because of insurance or restriction of broad spectrum antibiotics for policy of antibiotics control. However, our study should encourage clinicians not to delay definite antimicrobial treatment in patients with *A. baumannii* bacteremia.

In conclusion, patients with *A. baumannii* bacteremia receiving early and appropriate antimicrobial therapy are expected to show favorable outcomes, although the status of underlying disease also plays an important role in the clinical outcomes.

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