J Infect Chemother 25 (2019) 6–11

Contents lists available at ScienceDirect

Journal of Infection and Chemotherapy

journal homepage: http://www.elsevier.com/locate/jic

Original Article

# Changes in the early mortality of adult patients with carbapenem-resistant *Acinetobacter baumannii* bacteremia during 11 years at an academic medical center☆

Seong-Ho Choi [a], Eun Been Cho [a], Jin-Won Chung [a, *], Mi-Kyung Lee [b]

[a] Division of Infectious Diseases, Department of Internal Medicine, Chung-Ang University Hospital, Chung-Ang University College of Medicine, Seoul, Republic of Korea
[b] Department of Laboratory Medicine, Chung-Ang University Hospital, Chung-Ang University College of Medicine, Seoul, Republic of Korea

ARTICLE INFO

*Article history:*
Received 19 July 2018
Received in revised form
13 September 2018
Accepted 23 September 2018
Available online 19 October 2018

*Keywords:*
Mortality
*Acinetobacter baumannii*
Bacteremia

ABSTRACT

*Background:* In the past decade, carbapenem-resistant *Acinetobacter baumannii* (CRAB) has emerged as a major pathogen of serious infections in critically ill adult patients. Despite very limited antimicrobial options, clinicians have sought to reduce the mortality of patients with serious CRAB infections. To determine whether these long-term efforts effectively lessened the mortality of such patients, we investigated changes in the early mortality of adult patients with CRAB bacteremia and related clinical factors.
*Methods:* We reviewed clinical data from 111 adult patients with monomicrobial CRAB bacteremia admitted to an academic medical center between 2006 and 2016.
*Results:* The 14-day mortality rate from 2013 to 2016 was lower than that from 2009 to 2012 (43.4% vs. 71.1%, $p = 0.01$). When the clinical characteristics of adult patients with CRAB bacteremia from 2013 to 2016 were compared to those of the patients from 2009 to 2012, chronic lung disease (6.7% vs. 24.4%, $p = 0.01$), a recent history of mechanical ventilation (38.3% vs. 57.8%, $p = 0.048$), and pneumonia (48.3% vs. 68.9%, $p = 0.04$) were less frequent in 2013–2016, while neurological disease (43.3% vs. 22.2%, $p = 0.02$), central venous catheter infection (20.0% vs. 6.7%, $p = 0.05$), and early appropriate antimicrobial therapy (46.7% vs. 24.4%, $p = 0.01$) were more frequent.
*Conclusion:* The 14-day mortality rate of adult patients with CRAB bacteremia was reduced during 2013–2016. This decrease was associated with early appropriate antimicrobial therapy and a lower proportion of patients with bacteremic pneumonia, which seemed to result from improved hospital infection control during that time period.


## 1. Introduction

Carbapenem-resistant *Acinetobacter baumannii* (CRAB) has recently emerged as a major bacterial pathogen in critically ill patients at large medical centers in South Korea [1,2]. While it causes serious infections such as pneumonia and bacteremia, frequently in patients with impaired immunity, antibacterial options for effective treatment are very limited due to the multi-drug- or pan-drug-resistant nature of many strains isolated in Korea [3,4]. Only polymyxin B, polymyxin E (colistin), and tigecycline can be used to effectively treat these strains. However, polymyxin B has rarely been used in South Korea and the clinical effectiveness of tigecycline has been questioned in clinical studies of patients with serious infections [5–8]. Thus, colistin has been regarded to be only available option for critically ill patients with CRAB infection during the past decade in South Korea. To further reduce mortality in these patients, clinicians have tried a few different colistin-related regimens, such as high-dose colistin therapy, which was developed based on new pharmacokinetic data, and combination therapy with colistin and other antimicrobial drugs, e.g., carbapenems, rifampin, and tigecyline, based on the results of several studies [9–13]. We sought to determine whether the mortality rate of adult

☆ ICMJE statement: All authors meet the ICMJE authorship criteria.
* Corresponding author. Division of Infectious Diseases, Department of Internal Medicine, Chung-Ang University Hospital, 102 Heukseok-ro, Dongjak-gu, Seoul 156-755, Republic of Korea.
*E-mail address:* drjwchung@cau.ac.kr (J.-W. Chung).

https://doi.org/10.1016/j.jiac.2018.09.011
1341-321X/

patients with serious CRAB infections has been reduced over the past decade using these limited antimicrobial strategies. Thus, we evaluated adult patients with CRAB bacteremia over an 11-year period at an academic medical center, investigated changes in the 14-day mortality rate, and identified clinical factors that might affect early mortality.

## 2. Patients and methods

This study was performed at Chung-Ang University Hospital, an 850-bed tertiary care-affiliated hospital. Using the electronic medical records database of the study hospital, we identified adult patients (≥18 years of age) whose blood cultures were positive for monomicrobial CRAB bacteremia between January 2006 and December 2016. We reviewed medical charts and collected data on patient demographics, underlying diseases/conditions, infection site, severity of initial presentation, antimicrobial therapy, and 14-day mortality. Patients who had been treated for cerebrovascular diseases, Parkinsonism, or neurological sequelae were regarded to have neurological diseases. Patients who had chronic obstructive pulmonary disease, interstitial lung disease, or tuberculosis-destroyed lungs were regarded to have chronic lung disease. Patients who had an indwelling urinary catheter, central venous catheter, or mechanical ventilator therapy within 3 days prior to bacteremia were considered to have a recent history of indwelling urinary catheter, central venous catheter, or mechanical ventilation, respectively. Patients who underwent anticancer chemotherapy and neutropenia within a week prior to bacteremia were considered to have a recent history of chemotherapy or neutropenia. Patients taking immunosuppressive agents within a month prior to bacteremia were regarded to have a history of immunosuppressive therapy. The site of infection was defined as clinically or microbiologically documented. Systemic inflammatory response syndrome criteria and Pitt bacteremia score were defined as described elsewhere [14,15]. Antimicrobial therapy was considered appropriate if the identified organism was susceptible to at least one of the antimicrobial agents administered for at least three days within seven days after the onset of bacteremia. Patients who received colistin as appropriate antimicrobial therapy was further classified into high-dose and low-dose colistin groups. If the colistin dose administered was within the range of the dose described previously [16], patients were classified in the low-dose colistin group. If the dose administered was based on recent pharmacokinetic data [9], patients were classified in the high-dose colistin group. Identification and susceptibility testing of clinical isolates were performed using the Vitek II system (bioMérieux, Hazelwood, MO, USA). Antimicrobial susceptibility was determined according to CLSI criteria.

Statistical analysis was performed using SPSS software (version 18.0, SPSS, Chicago, IL, USA). Binary data were compared using a $\chi^2$ test or Fisher's exact test, and continuous data were compared using Student's *t*-test or the Mann-Whitney *U* test. Logistic regression analysis was performed to investigate independent risk factors for 14-day mortality. Variables that had a $p$ value < 0.1 on univariate analysis were included in logistic regression analysis. A backward-selection process was utilized. A $p$ value < 0.05 was considered significant. The present study protocol was reviewed and approved by the Institutional Review Board of Chung-Ang University Hospital.

## 3. Results

During the study period, 115 adult patients were diagnosed with CRAB bacteremia in the study hospital. Of these, three patients who had polymicrobial bacteremia and one whose medical information was not available were excluded from analysis; 111 were included in this study.

Table 1 presents the overall characteristics of the study patients. Nearly two-thirds (73, 65.8%) of study patients were male, and the mean age was 65.1 years (standard deviation, 15.6). Neurological disease was the most common underlying disease (32.4%), followed by diabetes mellitus (30.6%), solid tumor (26.1%), hematological malignancy (14.4%), and chronic lung disease (14.4%), among others. The majority of study patients had medical devices such as an indwelling urinary catheter (74.8%) and central venous catheter (62.2%). Less than half (45.0%) of the study patients had a history of mechanical ventilator therapy and less than a third (32.4%) had recently undergone surgery. The most common site of infection was the lungs (55.9%), followed by the central venous catheter (13.5%). Primary bacteremia was found in 13.5% of the study patients. More than half presented with septic shock (50.5%) and had a Pitt bacteremia score ≥4 (59.5%). Early administration of appropriate antimicrobial therapy was achieved in 35.1% of the study patients. The 14-day, 30-day, and 90-day mortality was 52.3%, 56.8%, and 62.2%, respectively.

Antimicrobial resistance rates of CRAB blood isolates were as follows according to antimicrobial agent: 99.1% (110/111), cefepime, ceftazidime, piperacillin/tazobactam, and ciprofloxacin; 86.1% (68/79), ampicillin/sulbactam; 85.6% (95/111), amikacin; 71.3% (57/80), trimethoprim/sulfamethoxazole and 26.0% (19/73), tigecycline. Resistance to colistin was not observed (0/80).

Patients who died within 14 days of CRAB bacteremia were compared to those who survived (Table 1). While neurological disease (41.5% vs. 24.1%, $p = 0.05$) and trauma (18.9% vs. 6.9%, $p = 0.06$) tended to be more common in patients who survived than in those who died, hematological malignancies were more common in the latter group (20.7% vs. 7.5%, $p = 0.049$). A recent history of mechanical ventilation (59.6% vs. 32.1%, $p = 0.01$), chemotherapy (17.2% vs. 3.8%, $p = 0.02$), or neutropenia (15.5% vs. 1.9%, $p = 0.02$) were also more common in patients who died. An infection site within the lungs was more common in patients who died within 14 days than in those who survived (72.4% vs. 37.7%, $p < 0.001$), whereas central venous catheter (24.5% vs. 3.4%, $p = 0.001$) and biliary tract (11.3% vs. nil, $p = 0.01$) infection sites were more common in those who survived. Patients who died within 14 days had a more serious initial presentation such as septic shock (62.1% vs. 37.7%, $p = 0.01$) and Pitt bacteremia score ≥4 (77.6% vs. 39.6%, $p < 0.001$) than those who survived. The former group received early appropriate antimicrobial therapy less frequently than the latter (20.7% vs. 52.8%, $p = 0.001$).

Multivariate analysis was performed to identify risk factors for 14-day mortality. A recent history of neutropenia and a Pitt bacteremia score ≥4 were independent risk factors for 14-day mortality [adjusted odds ratio (aOR) = 17.89, 95% confidence interval (CI) = 1.49–214.28, $p = 0.02$; aOR = 6.67, 95% CI = 2.25–19.79, $p = 0.001$, respectively]. The central venous catheter as a site of infection and early appropriate antimicrobial therapy were independent preventive factors for 14-day mortality (aOR = 0.11, 95% CI = 0.02–0.63, $p = 0.01$; aOR = 0.14, 95% CI = 0.05–0.41, $p < 0.001$, respectively).

Table 2 presents the list of appropriate antimicrobial agents used and the 14-day mortality rate according to agent. Combination therapy with colistin and carbapenem was the most frequently used active regimen (53.8%), followed by colistin only (33.3%). The 14-day mortality rate did not vary among patients who received different regimens ($p = 0.63$). The mortality of patients who received combination therapy with colistin and carbapenem did not differ from the mortality of those who received either colistin alone or combination therapy with colistin and rifampin (38.1% vs. 26.7%, $p = 0.47$). The mortality of the high-dose colistin group did not differ from that of the low-dose colistin group (32.0% vs. 36.4%, $p = 1.00$).

Fig. 1 presents the change in the number of patients with CRAB bacteremia and their 14-day mortality rate, accompanied by the

**Table 1**
Clinical characteristics of adult patients with carbapenem-resistant *Acinetobacter baumannii* bacteremia (CRABB) and comparison between CRABB patients who died and survived within 14 days of bacteremia diagnosis.

| Characteristics | No. (%) of patients with CRABB (n = 111) | No. (%) of CRABB patients who died within 14 days (n = 58) | No. (%) of CRABB patients who survived for 14 days (n = 53) | *P* value |
|---|---|---|---|---|
| Male sex | 73 (65.8) | 39 (67.2) | 34 (64.2) | 0.73 |
| Mean age (standard deviation) | 65.1 (15.6) | 66.6 (13.3) | 63.4 (17.8) | 0.28 |
| Underlying diseases | | | | |
| Neurological disease | 36 (32.4) | 14 (24.1) | 22 (41.5) | 0.05 |
| Diabetes | 34 (30.6) | 21 (36.2) | 13 (24.5) | 0.18 |
| Solid tumor | 29 (26.1) | 17 (29.3) | 12 (22.6) | 0.42 |
| Hematological malignancy | 16 (14.4) | 12 (20.7) | 4 (7.5) | 0.049 |
| Chronic lung disease | 16 (14.4) | 10 (17.2) | 6 (11.3) | 0.38 |
| Trauma | 14 (12.6) | 4 (6.9) | 10 (18.9) | 0.06 |
| Congestive heart failure | 12 (10.8) | 7 (12.1) | 5 (9.4) | 0.66 |
| Liver cirrhosis | 10 (9.0) | 8 (13.8) | 2 (3.8) | 0.10 |
| Hemodialysis | 8 (7.2) | 4 (6.9) | 4 (7.5) | 1.00 |
| Chronic kidney disease | 5 (4.5) | 1 (1.7) | 4 (7.5) | 0.19 |
| Underlying conditions | | | | |
| Indwelling urinary catheter[a] | 83 (74.8) | 46 (79.3) | 37 (69.8) | 0.25 |
| Central venous catheter[a] | 69 (62.2) | 40 (69.0) | 29 (54.7) | 0.12 |
| Mechanical ventilation[a] | 40 (45.0) | 33 (59.6) | 17 (32.1) | 0.01 |
| Surgery[b] | 36 (32.4) | 14 (24.1) | 22 (41.5) | 0.05 |
| Cancer chemotherapy[c] | 12 (10.8) | 10 (17.2) | 2 (3.8) | 0.02 |
| Neutropenia[b] | 10 (9.0) | 9 (15.5) | 1 (1.9) | 0.02 |
| Immunosuppressive agents[c] | 6 (5.4) | 5 (8.6) | 1 (1.9) | 0.21 |
| Site of infection | | | | |
| Lungs | 62 (55.9) | 42 (72.4) | 20 (37.7) | <0.001 |
| Central venous catheter | 15 (13.5) | 2 (3.4) | 13 (24.5) | 0.001 |
| Unknown | 15 (13.5) | 9 (15.5) | 6 (11.3) | 0.52 |
| Biliary tract | 6 (5.4) | 0 | 6 (11.3) | 0.01 |
| Central nervous system | 4 (3.6) | 2 (3.4) | 2 (3.8) | 1.00 |
| Abdomen | 4 (3.6) | 2 (3.4) | 2 (3.8) | 1.00 |
| Urinary tract | 4 (3.6) | 1 (1.7) | 3 (5.7) | 0.35 |
| Skin/soft tissue | 1 (0.9) | 0 | 1 (1.9) | 0.48 |
| Initial severity | | | | |
| SIRS[d] criteria | | | | 0.01 |
| No SIRS[d] | 1 (1.9) | 0 | 1 (1.9) | |
| SIRS[d] | 37 (33.3) | 11 (19.0) | 26 (49.1) | |
| Severe sepsis | 17 (15.3) | 11 (19.0) | 6 (11.3) | |
| Septic shock | 56 (50.5) | 36 (62.1) | 20 (37.7) | |
| Presence of septic shock | 56 (50.5) | 36 (62.1) | 20 (37.7) | 0.01 |
| Pitt bacteremia score ≥4 | 66 (59.5) | 45 (77.6) | 21 (39.6) | <0.001 |
| Early appropriate antimicrobial therapy[e] | 39 (35.1) | 12 (20.7) | 27 (52.8) | 0.001 |

[a] Within 3 days prior to bacteremia.
[b] Within one week prior to bacteremia.
[c] Within one month prior to bacteremia.
[d] Systemic Inflammatory Response Syndrome.
[e] Appropriate antimicrobial therapy given for at least 3 days within a week after bacteremia diagnosis.

change in the number of CRAB isolates found in all specimens over 11 years. The change in the number of CRAB bacteremia patients is similar to that of all CRAB isolates – an increasing trend between 2006 and 2013, and a decreasing trend from 2014. There were several remarkable changes in the policy of hospital infection control from 2014 – introduction of ventilator-associated pneumonia (VAP) bundle care in intensive care units (ICUs), periodic monitoring/reporting of ICU infection rates including that of VAP,

**Table 2**
List of in vitro active antimicrobial agents administered to 39 adult patients with carbapenem-resistant *Acinetobacter baumannii* bacteremia for at least 3 days within 7 days of the onset of bacteremia, and 14-day mortality according to antimicrobial agent.

| Appropriate antimicrobial agents | No. (%) of patients (n = 39) | No. of 14-day mortalities/ No. of patients (%) | *P* value |
|---|---|---|---|
| All regimens | | | 0.63 |
| Colistin/carbapenem | 21 (53.8) | 8/21 (38.1) | |
| Colistin | 13 (33.3) | 3/13 (23.1) | |
| Colistin/rifampin | 2 (5.1) | 1/2 (50.0) | |
| Tigecycline | 2 (5.1) | 0/2 | |
| Levofloxacin | 1 (2.6) | 0/1 | |
| Colistin/carbapenem vs. colistin | | | 0.47 |
| Colistin/carbapenem | 21/36 (58.3) | 8/21 (38.1) | |
| Colistin or colistin/rifampin | 15/36 (41.7) | 4/15 (26.7) | |
| High-dose vs. lo- dose colistin | | | 1.00 |
| High-dose colistin | 25/36 (69.4) | 8/25 (32.0) | |
| Low-dose colistin | 11/36 (30.6) | 4/11 (36.4) | |

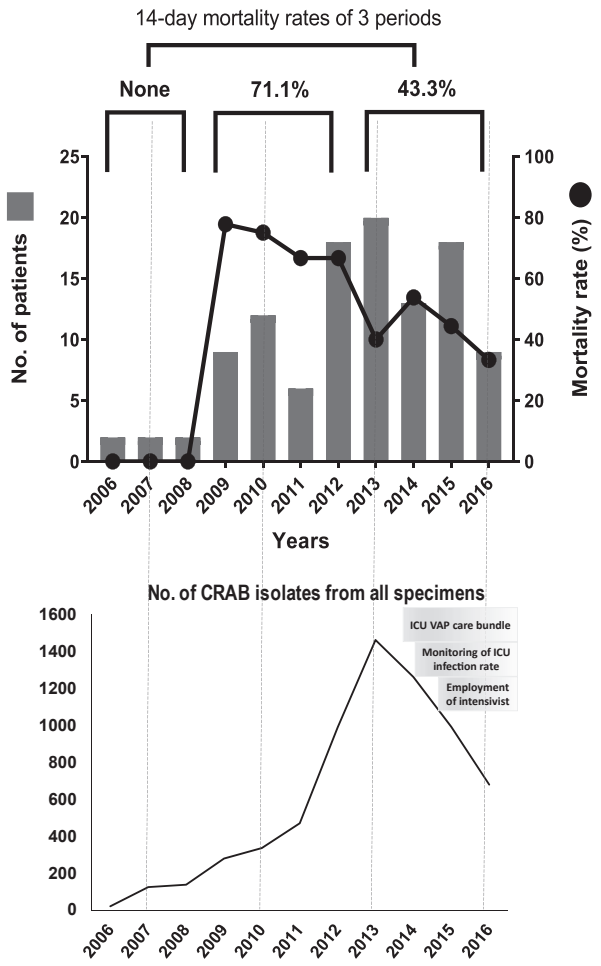


**Fig. 1.** Change in the number of patients with carbapenem-resistant *Acinetobacter baumannii* (CRAB) bacteremia (gray bar in the upper graph) and the 14-day mortality rate among those patients (black circle in the upper graph) over an 11-year period at a tertiary care center in Seoul, South Korea. The 14-day mortality rate of each period (periods 2006–2008, 2009–2012, and 2013–2016; upper graph). The change in the number of CRAB-positive specimens (lower graph). Several interventions related to hospital infection control from 2014 onward are shown in the gray boxes in the lower graph.

and employment of attending intensivists (gray boxes in Fig. 1). Regarding the 14-day mortality rate, early mortality was not observed between 2006 and 2008. This rate increased sharply from 2009 and continued to peak between 60% and 80% until 2012. From 2013 onward, there was a decreasing trend. The 14-day mortality rate from 2013 to 2016 was lower than that from 2009 to 2012 (43.3% vs. 71.1%, $p = 0.01$).

We compared the clinical characteristics of CRAB bacteremia patients admitted from 2009 to 2012 to those of patients admitted from 2013 to 2016 in Table 3. While chronic lung disease (24.4% vs. 6.7%, $p = 0.01$) and a recent history of mechanical ventilation (57.8% vs. 38.3%, $p = 0.048$) were more common in the earlier period, neurological disease was more common in the later period (43.3% vs. 22.2%, $p = 0.02$). The lungs as a site of infection were more common in the earlier period (68.9% vs. 48.3%, $p = 0.04$), while a central venous catheter infection site was more common in the later period (20.0% vs. 6.7%, $p = 0.05$). Patients in the later period received early appropriate antimicrobial therapy more frequently than those of the earlier period (46.7% vs. 24.4%, $p = 0.01$). Among patients who received colistin as an appropriate antimicrobial therapy, high-dose colistin was used more frequently in the later period than in the earlier period (81.5% vs. 33.3%, $p = 0.01$), and combination therapy with colistin and carbapenem was also used more frequently in the later period, although this difference was not statistically significant (63.0% vs. 44.4%, $p = 0.44$).

## 4. Discussion

More than a half (52.3%) of adult patients with CRAB bacteremia died within 14 days of bacteremia during the 11-year period. The 14-day mortality rate was highest during the period from 2009 to 2012. However, after the period, a decreasing trend in early mortality was noted. We suggest that two important factors were responsible for this reduction in early mortality during 2013–2016.

First, there were some changes in the underlying diseases of the study patients and the type of infection they experienced. From 2009 to 2012, patients vulnerable to pneumonia, such as those having chronic lung disease or those already receiving mechanical ventilation, were more commonly infected with CRAB than observed from 2013 to 2016. In the later period, such patients were less frequent and the number of central line infections was more common. Bacteremic pneumonia is one of the most fatal types of bacterial infection [17], whereas central line infection can be controlled relatively easily with early removal of infected devices [18]. In this study, central line infection was independently associated with 14-day survival. Thus, early mortality was lower from 2013 to 2016 mainly due to the reduced proportion of patients with bacteremic pneumonia. Although the reason why such changes in the type of infection remain unclear, we suggest some changes in hospital infection control during this period as one of the most plausible explanations for that. The reduction in early mortality seemed to coincide with a decrease in the number of CRAB isolates in all specimens from 2014 onward, as shown in Fig. 1. This was likely caused by the above mentioned several changes of hospital infection control programs beginning around that time in the study hospital. CRAB is most fatal through the development of pneumonia, which principally occurs in ICU patients. Thus, hospital infection control, especially focusing on VAP, may reduce early mortality rates among adult patients with CRAB bacteremia by decreasing the proportion of those with bacteremic pneumonia. With the limited antimicrobial options available to treat rapidly emerging extremely resistant bacteria, hospital infection control may play a crucial role in reducing mortality from those.

Second, patients treated from 2013 to 2016 received early appropriate antimicrobial therapy more frequently than those treated from 2009 to 2012. Early appropriate antimicrobial therapy was an independent protective factor against 14-day mortality in our analysis. Thus, it is suggested that higher use of early appropriate antimicrobial therapy in the later period may be the other factor responsible for the reduction of early mortality. It is supported by the fact that the 14-day mortality rate was reduced from 87.1% (2009–2012) to 51.7% (2013–2016) also in a subgroup of patients with bacteremic pneumonia ($p = 0.003$), regardless of the reduced proportion of the subgroup (the first factor described above). The higher use of early appropriate antimicrobial therapy in the later period may have been associated with increasing physician knowledge of CRAB and its treatment during this period. The number of physicians who were reluctant to use colistin immediately because of its potential damage to renal function might have decreased through previous experience with fatal CRAB infections and familiarity with the literature supporting aggressive use of this drug. This may also be responsible for the increasing use of high-dose colistin based on new pharmacokinetic data and of combination therapy in the later period. However, we did not find any survival benefits related to these two treatment approaches in our study, although their clinical effectiveness and survival benefit

**Table 3**
Clinical characteristics of patients with carbapenem-resistant *Acinetobacter baumannii* bacteremia (CRABB) treated from 2009 to 2012 and from 2013 to 2016.

| Characteristics | No. (%) of CRABB patients from 2009 to 2012 (n = 45) | No. (%) of CRABB patients from 2013 to 2016 (n = 60) | *P* value |
|---|---|---|---|
| Male sex | 28 (62.2) | 40 (66.7) | 0.64 |
| Mean age (SD) | 66.1 (15.8) | 65.4 (15.2) | 0.83 |
| Underlying diseases/conditions | | | |
| Neurological disease | 10 (22.2) | 26 (43.3) | 0.02 |
| Diabetes | 18 (40.0) | 16 (26.7) | 0.15 |
| Solid tumor | 14 (31.1) | 14 (23.3) | 0.37 |
| Hematological malignancy | 8 (17.8) | 8 (13.3) | 0.53 |
| Chronic lung disease | 11 (24.4) | 4 (6.7) | 0.01 |
| Hemodialysis | 4 (8.9) | 4 (6.7) | 0.72 |
| Mechanical ventilation[a] | 26 (57.8) | 28 (38.3) | 0.048 |
| Site of infection | | | |
| Lungs | 31 (68.9) | 29 (48.3) | 0.04 |
| Central venous catheter | 3 (6.7) | 12 (20.0) | 0.05 |
| Unknown | 6 (13.3) | 9 (15.0) | 0.81 |
| Biliary tract | 1 (2.2) | 3 (5.0) | 0.63 |
| Central nervous system | 1 (2.2) | 3 (5.0) | 0.63 |
| Abdomen | 0 | 2 (3.3) | 0.51 |
| Urinary tract | 3 (6.7) | 1 (1.7) | 0.31 |
| Skin/soft tissue | 0 | 1 (1.7) | 1.00 |
| Initial severity | | | |
| Pitt bacteremia score ≥4 | 32 (71.1) | 34 (56.7) | 0.13 |
| Presence of septic shock | 24 (53.3) | 32 (53.3) | 1.00 |
| Early appropriate antimicrobial therapy[b] | 11 (24.4) | 28 (46.7) | 0.01 |
| Therapy with colistin | 9/11 (81.8) | 27/28 (96.4) | 0.19 |
| High-dose colistin | 3/9 (33.3) | 22/27 (81.5) | 0.01 |
| Colistin with carbapenems | 4/9 (44.4) | 17/27 (63.0) | 0.44 |
| 14-day mortality | 32 (71.1) | 26 (43.3) | 0.01 |

[a] Within 3 days prior to bacteremia.
[b] Appropriate antimicrobial therapy administered for at least 3 days within a week after bacteremia onset.

have been suggested in other studies [9–13]. Recent studies have proposed that clinical data are not yet sufficient for clinicians to reach a clear consensus on clinical effectiveness [19–21]. From our study results, early administration of appropriate antimicrobial therapy should be the top priority for clinicians who manage adult patients suspected of having serious CRAB infections. Consequently, novel laboratory methods for the early detection of CRAB may be very useful.

This study has a few important limitations. First, clinical data were retrospectively collected. Unrecognized clinical factors may have resulted in biases in the study analysis. Second, because of the limited number of the study patients, this study may not draw any conclusion on the clinical effectiveness of high-dose colistin or combination therapy with colistin and carbapenem, compared to that of colistin.

In conclusion, we observed a reduction in the 14-day mortality rate of adult patients with CRAB bacteremia treated from 2013 to 2016 at an academic medical center. This decrease was associated with early administration of appropriate antimicrobial therapy and a decreased proportion of patients with bacteremic pneumonia, which may have resulted from the institution of stricter hospital infection control strategies.

## Acknowledgment

**Funding:** There was no external funding in this study.

**Conflict of interest:** All authors have no potential conflicts of interest to disclose.

## References

[1] Lee K, Kim MN, Kim JS, Hong HL, Kang JO, Shin JH, et al. Further increases in carbapenem-, amikacin-, and fluoroquinolone-resistant isolates of *Acinetobacter* spp. and *P. aeruginosa* in Korea: KONSAR study 2009. Yonsei Med J 2011;52:793–802. https://doi.org/10.3349/ymj.2011.52.5.793.

[2] Kang CI, Song JH. Antimicrobial resistance in Asia: current epidemiology and clinical implications. Infect Chemother 2013;45:22–31. https://doi.org/10.3947/ic.2013.45.1.22.

[3] Wong D, Nielsen TB, Bonomo RA, Pantapalangkoor P, Luna B, Spellberg B. Clinical and pathophysiological overview of *Acinetobacter* infections: a century of challenges. Clin Microbiol Rev 2017;30:409–47. https://doi.org/10.1128/CMR.00058-16.

[4] Kim D, Ahn JY, Lee CH, Jang SJ, Lee H, Yong D, et al. Increasing resistance to extended-spectrum cephalosporins, fluoroquinolone, and carbapenem in gram-negative bacilli and the emergence of carbapenem non-susceptibility in Klebsiella pneumoniae: analysis of Korean antimicrobial resistance monitoring system (KARMS) data from 2013 to 2015. Ann Lab Med 2017;37:231–9. https://doi.org/10.3343/alm.2017.37.3.231.

[5] Choi YH. Treatment of drug resistant bacteria: new bugs, old drugs, and new therapeutic approaches. J Korean Med Assoc 2014;57:837–44. https://doi.org/10.5124/jkma.2014.57.10.837.

[6] Freire AT, Melnyk V, Kim MJ, Datsenko O, Dzyublik O, Glumcher F, et al. Comparison of tigecycline with imipenem/cilastatin for the treatment of hospital-acquired pneumonia. Diagn Microbiol Infect Dis 2010;68:140–51. https://doi.org/10.1016/j.diagmicrobio.2010.05.012.

[7] Prasad P, Sun J, Danner RL, Natanson C. Excess deaths associated with tigecycline after approval based on noninferiority trials. Clin Infect Dis 2012;54:1699–709. https://doi.org/10.1093/cid/cis270.

[8] Liou BH, Lee YT, Kuo SC, Liu PY, Fung CP. Efficacy of tigecycline for secondary *Acinetobacter* bacteremia and factors associated with treatment failure. Antimicrob Agents Chemother 2015;59:3637–40. https://doi.org/10.1128/AAC.04987-14.

[9] Garonzik SM, Li J, Thamlikitkul V, Paterson DL, Shoham S, Jacob J, et al. Population pharmacokinetics of colistin methanesulfonate and formed colistin in critically ill patients from a multicenter study provide dosing suggestions for various categories of patients. Antimicrob Agents Chemother 2011;55:3284–94. https://doi.org/10.1128/AAC.01733-10.

[10] Falagas ME, Rafailidis PI, Ioannidou E, Alexiou VG, Matthaiou DK, Karageorgopoulos DE, et al. Colistin therapy for microbiologically documented multidrug-resistant Gram-negative bacterial infections: a retrospective cohort study of 258 patients. Int J Antimicrob Agents 2010;35:194–9. https://doi.org/10.1016/j.ijantimicag.2009.10.005.

[11] Bassetti M, Repetto E, Right E, Boni S, Diverio M, Molinari MP, et al. Colistin and rifampicin in the treatment of multidrug-resistant *Acinetobacter baumannii* infections. J Antimicrob Chemother 2008;61:417–20. https://doi.org/10.1093/jac/dkm509.

[12] Zusman O, Avni T, Leibovici L, Adler A, Friberg L, Stergiopoulou T, et al. Systematic review and meta-analysis of in vitro synergy of polymyxins and carbapenems. Antimicrob Agents Chemother 2013;57:5104–11. https://doi.org/10.1128/AAC.01230-13.

[13] Kim WY, Moon JY, Huh JW, Choi SH, Lim CM, Koh Y, et al. Comparable efficacy of tigecycline versus colistin therapy for multidrug-resistant and extensively drug-resistant *Acinetobacter baumannii* pneumonia in critically ill patients. PLoS One 2016;11, e0150642. https://doi.org/10.1371/journal.pone.0150642.
[14] Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM consensus Conference Committee. American College of chest physicians/Society of critical care medicine. Chest 1992;101:1644–55.
[15] Peterson DL, Ko WC, Gottberg AV, Mohapatra S, Cassellas JM, Goossens H, et al. International prospective study of *Klebsiella pneumoniae* bacteremia: implications for extended-spectrum beta-lactamase production in nosocomial infections. Ann Intern Med 2004;140:26–32.
[16] Park JH, Choi SH, Chung JW. The impact of early adequate antimicrobial therapy in 14-day mortality in patients with monomicrobial *Pseudomonas aeruginosa* and *Acinetobacter baumannii* bacteremia. J Infect Chemother 2013;19:843–9. https://doi.org/10.1007/s10156-013-0571-3.
[17] Magret M, Lisboa T, Martin-Loeches I, Máñez R, Nauwynck M, Wrigge H, et al. Bacteremia is an independent risk factor for mortality in nosocomial pneumonia: a prospective and observational multicenter study. Crit Care 2011;15:R62. https://doi.org/10.1186/cc10036.
[18] Freire MP, de Oliveira Garcia D, Garcia CP, Campagnari Bueno MF, Camargo CH, Kono Magri ASG, et al. Bloodstream infection caused by extensively drug-resistant *Acinetobacter baumannii* in cancer patients: high mortality associated with delayed treatment rather than with the degree of neutropenia. Clin Microbiol Infect 2016;22:352–8. https://doi.org/10.1016/j.cmi.2015.12.010.
[19] Benatter YD, Omar M, Zusman O, Yahav D, Doron YZ, Altunin S, et al. The effectiveness and safety of high-dose colistin: prospective cohort study. Clin Infect Dis 2016;63:1605–12. https://doi.org/10.1093/cid/ciw684.
[20] Durante-Mangoni E, Signoriello G, Andini R, Mattei A, Cristoforo MD, Murino P, et al. Colistin and rifampicin compared with colistin alone for the treatment of serious infections due to extensively drug-resistant *Acinetobacter baumannii*: a multicenter, randomized clinical trial. Clin Infect Dis 2013;57:349–58. https://doi.org/10.1093/cid/cit253.
[21] Zusman O, Altunin S, Koppel F, Benattar YD, Gedik H, Paul M. Polymyxin monotherapy or in combination against carbapenem-resistant bacteria: systematic review and meta-analysis. J Antimicrob Chemother 2017;72:29–39. https://doi.org/10.1093/jac/dkw377.