Clinical and Microbiological Analysis of Risk Factors for Mortality in Patients with Carbapenem-resistant *Acinetobacter baumannii* bacteremia

Hyo-Ju Son,¹,² Eun Been Cho,¹,³ Moonsuk Bae,¹ Seung Cheol Lee,⁴ Heungsup Sung,⁵ Mi-Na Kim,⁵ Jiwon Jung,¹ Min Jae Kim,¹ Sung-Han Kim,¹ Sang-Oh Lee,¹ Sang-Ho Choi,¹ Jun Hee Woo,¹ Yang Soo Kim,¹ and Yong Pil Chong¹

Departments of Infectious Diseases, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea¹

Division of Infectious Diseases, Department of Internal Medicine, Soonchunhyang University Seoul Hospital, Soonchunhyang University College of Medicine, Seoul, Korea²

Division of Infectious Diseases, Department of Internal Medicine, Chung-Ang University Hospital, Chung-Ang University College of Medicine, Seoul, Republic of Korea³

Department of Infectious Diseases and Asan Medical Institute of Convergence Science and Technology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea⁴

Department of Laboratory Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea⁵

H.-J.S and E.B.C contributed equally to this article.

Corresponding author:

Yong Pil Chong, MD, Department of Infectious Diseases, Asan Medical Center, University of Ulsan College of Medicine, 88 Olympic-ro-43-gil, Songpa-gu, Seoul, 05505, Republic of Korea

Tel: 82-2-3010-3306 Fax: 82-2-3010-6970

E-mail: drchong@amc.seoul.kr

© The Author(s) 2020. Published by Oxford University Press on behalf of Infectious Diseases Society of America.

This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs licence (http://creativecommons.org/licenses/by-nc-nd/4.0/), which permits non-commercial reproduction and distribution of the work, in any medium, provided the original work is not altered or transformed in any way, and that the work is properly cited. For commercial re-use, please contact journals.permissions@oup.com
Abstract

Background: Carbapenem-resistant Acinetobacter baumannii (CRAB) infection is associated with significant mortality, causing worldwide concern, yet there are limited data on contributing microbiological factors. This study aimed to identify clinical and microbiologic risk factors for mortality in CRAB bacteremia.

Methods: Adult patients with monomicrobial CRAB bacteremia in a 2700-bed tertiary hospital between December 2012 and December 2018 were retrospectively enrolled. Risk factors for 30-day mortality were evaluated. All isolates collected on the first day of bacteremia were subjected to colistin susceptibility testing by broth microdilution, and genotyping by multilocus sequence typing.

Results: A total of 164 patients were enrolled, and 90 (55%) died within 30 days. The most common genotype among the isolates was ST191 (49%), and 12 isolates (7%) were resistant to colistin. Genotype, colistin MIC, and colistin resistance were not significantly associated with mortality, in contrast to several clinical factors. In multivariable analysis, ineradicable or not-eradicated focus (aOR, 4.92; 95% CI, 1.95–12.42; \( P = 0.001 \)), septic shock (aOR, 4.72; 95% CI, 2.12–10.49; \( P < 0.001 \)), and inappropriate antimicrobial therapy (aOR, 2.54; 95% CI, 1.05–6.16; \( P = 0.04 \)) were independent risk factors for mortality. Among antibiotic strategies, colistin combined with tigecycline or other antibiotics were significantly associated with lower mortality after adjustment for confounding factors.

Conclusions: Clinical factors such as the nature of the infection source and source control, severity of bacteremia, and appropriateness of antibiotics, rather than microbiological factors, contribute to mortality in CRAB bacteremia. Specific antibiotic combination may help improve outcomes.

Keywords: multidrug-resistant; Acinetobacter baumannii; bacteremia; risk factors; mortality; carbapenems
Introduction

*Acinetobacter baumannii*, an aerobic, catalase-positive, oxidase-negative, gram-negative coccobacillus, causes a variety of human infections in the health care setting [1]. Two major nosocomial manifestations are bacteremia and ventilator-associated pneumonia. Others include intravascular catheter-related infection, surgical site infection, and urinary tract infection [1]. Infections with this organism have unfavorable clinical outcomes and impose a considerable economic burden [2]. *Acinetobacter* species can readily have multiple resistance mechanisms. Carbapenem resistance is an emerging concern because it is associated with high mortality [3-5]. Carbapenem-resistant *Acinetobacter baumannii* (CRAB) was classified by WHO as one of the critical priority pathogens in the global priority list of antibiotic-resistant bacteria that was intended to guide research, discovery, and the development of new antibiotics [6]. In South Korea, the carbapenem resistance rate of *A. baumannii* identified in hospitals was reported to reach 90% [7, 8]. In the report of Kor-GLASS (Korean part of the Global Antimicrobial Resistance Surveillance System), CRAB bacteremia occurred in 6.3 episodes per 10,000 patient-days in ICU, which was highest among multidrug-resistant pathogens [8].

To improve the clinical outcome of CRAB bacteremia, identifying risk factors for mortality is crucial. The factors known to affect mortality are underlying medical condition, severity of bacteremia, and early appropriate antimicrobial therapy [9-13]. In a recent systematic review, inappropriate empirical antimicrobial treatment, septic shock, chronic liver disease, renal failure,
neutropenia, immunosuppressant use, and a high Pitt bacteremia score were risk factors for mortality in CRAB bacteremia [10]. Although there have been studies on the effects of clinical factors on mortality, few studies have examined the impact of microbiological factors. Therefore, we aimed to investigate the effect of microbiological factors including multilocus sequence type (MLST) and colistin MIC, as well as clinical factors, on mortality.

Materials and Methods

Patients and study design

All adult patients with monomicrobial CRAB bacteremia at the Asan Medical Center, a 2700-bed, tertiary hospital between December 2012 and December 2018, were retrospectively enrolled in the study. Patients were excluded if 1) they were less than 18 years old, 2) had polymicrobial bacteremia, 3) died within 24 hours of bacteremia, or 4) they had A. baumannii bacteremia within the previous three months. If patients had more than one episode of CRAB bacteremia, only the first episode was analyzed. Consecutive blood isolates that had been prospectively collected on the first day of bacteremia were used for further microbiological testing. Risk factors for 30-day mortality were evaluated through a detailed clinical and microbiological analysis of the study patients.
**Definitions**

CRAB was defined as *A. baumannii* resistant to imipenem and meropenem based on Clinical and Laboratory Standards Institute (CLSI) 2019 breakpoints [14]. CRAB bacteremia was defined as at least one blood culture positive for CRAB with clinical features compatible with infection. Empirical antimicrobial therapy was defined as treatment started no later than 24 h after blood samples for the index blood culture had been drawn. Definitive therapy was defined as treatment that was continued or commenced on the day the antibiogram results were reported to the clinicians. Antimicrobial therapy was considered appropriate if at least one antimicrobial agent with *in vitro* activity against the causative pathogen was administered. Inappropriate antimicrobial therapy was defined as inappropriate empirical therapy in patients who died before susceptibility results were available or inappropriate definitive therapy in the other patients. Combination therapy was defined as the use of one *in vitro* active antimicrobial agent combined with one or more antimicrobials with gram-negative activity, regardless of *in vitro* susceptibility. Corticosteroid therapy was the use of systemic prednisolone 20 mg equivalent or more over two weeks. A diagnosis of septic shock was made when systolic blood pressure was <90 mmHg and there was clinical evidence of peripheral hypoperfusion and the need for vasopressors [15]. Bacteremia was considered high grade if two or more blood culture sets from at least two blood culture sets drawn at the initial CRAB episode were positive. Charlson’s comorbidity index was used to score the severity of underlying disease, and the severity of illness at the time of bacteremia was assessed by Pitt bacteremia score [16, 17]. The time
interval between bacteremia and the removal of an eradicable focus was limited to 7 days to reduce potential survival bias.

Identification and susceptibility testing and treatment regimens

All blood culture samples were processed by the hospital microbiology laboratory using a standard blood culture system (BACTEC FX; Becton Dickinson, NJ, USA). A. baumannii identification and antimicrobial susceptibility tests were performed using a MicroScan WalkAway 96 Plus system and Neg Combo Panel Type 72 (Beckman Coulter, Brea, CA, USA). Colistin susceptibility was tested in triplicate using the broth microdilution method according to CLSI guidelines [18]. The results were interpreted according to the CLSI susceptibility criteria [14]. Isolates with tigecycline MIC ≤2 mg/L were considered to be susceptible to tigecycline. The dose of colistin was 5 mg/kg or 300 mg colistin base activity loading, followed by 150 mg colistin base activity every 12 hours in patients with normal renal function [19]. The dose of tigecycline was a 100 mg loading, followed by 50 mg every 12 hours.
Genotyping by MLST

MLST was performed on seven housekeeping genes (*gltA*, *gyrB*, *gdhB*, *recA*, *cpn60*, *gpi*, and *rpoD*) as described previously [20]. Isolates were assigned to sequence types (STs) using tools available on the *A. baumannii* MLST database (http://pubmlst.org/abaumannii/).

Statistical analysis

Categorical variables were compared using the χ² test or Fisher’s exact test, as appropriate, and continuous variables were compared using Student’s t-test or the Mann-Whitney U-test, as appropriate. All tests of significance were two-tailed, and *P* values <0.05 were considered statistically significant. Risk factors for 30-day mortality of patients of CRAB bacteremia were analyzed by logistic regression analysis and Cox proportional hazards regression analysis. Variables significant in the univariate analysis and other variables of clinical importance were included in a multiple logistic regression model and multivariate Cox proportional hazards model. A linear-by-linear association test was used to analyze trends among multiple groups. All statistical analyses were performed using SPSS for Windows software package, version 24 (SPSS Inc., Chicago, IL, USA).
**Patient Consent Statement**

This observational study was approved by the Institutional Review Board of the Asan Medical Center. To protect personal privacy, identifying information in the electronic database was encrypted. Informed consent was waived by the ethics committee because no intervention was involved and no patient-identifying information was included.

**Results**

**Patient characteristics**

A total of 298 patients were diagnosed with CRAB bacteremia during the study period. Patients under 18 years (n = 27) or who died within 24 hours of bacteremia (n = 12), as well as patients with polymicrobial bacteremia (n = 90), with *A. baumannii* bacteremia within the previous three months (n = 2), and for whom no corresponding blood isolate was collected (n = 3), were excluded. A total of 164 patients with CRAB bacteremia were included in the final analysis. The mean age of these patients was 63.7 years (standard deviation [SD] 14.7 years), and 67% were male. Hematologic malignancy and solid tumor were frequent underlying diseases. Regarding treatment, 115 of the 164 patients (70%) received appropriate antimicrobial therapy. 30-day mortality was 55% (90/164), and there were no significant differences in age, gender, and Charlson comorbidity index between the surviving and deceased patients (Table 1). However, the deceased patients were significantly different in terms of underlying characteristics, site of infection, severity of infection, and
management of bacteremia. Hematologic malignancy, corticosteroid use, neutropenia, pneumonia, primary bacteremia, ineradicable or not-eradicated focus, high-grade bacteremia, septic shock, higher Pitt bacteremia score, and inappropriate definitive therapy were significantly associated with 30-day mortality. Combination antimicrobial therapy was associated with a mortality benefit.

**Microbiological characteristics**

Of the 164 CRAB isolates, 152 (93%) were susceptible to colistin (MIC ≤2.0 mg/L) (Table 2). Six of the 12 patients with colistin-resistant isolates died. In the 152 patients with colistin-susceptible CRAB isolates, 30-day mortality decreased as the colistin MIC increased (60% versus 53% versus 25%, \( P = 0.02 \)) (Figure 1). Similar trends were observed in the 93 patients treated with colistin (52% versus 48% versus 13%, \( P = 0.06 \)) (Supplementary Figure 1). Susceptibility profiles to other antibiotics are provided in Supplementary Table 1. A total of nine MLSTs were identified. ST191 was the dominant genotype, with 80 isolates (49%). 30-day mortality rates did not differ significantly between the major ST groups (\( P = 0.81 \)) (Figure 1). However, there were significant differences in rates of septic shock between them (Supplementary Figure 2).
**Risk factors for 30-day mortality**

Significant variables in the univariate analysis and other variables of clinical importance were included in a logistic regression model to identify independent risk factors for mortality. Because there were significant correlations between the variables that reflected the severity of bacteremia, we retained only septic shock. For the same reason, ineradicable or not-eradicated focus was retained, and type of infection was excluded. Because combination therapy was inversely correlated with inappropriate definitive treatment, and its benefit on mortality disappeared when patients with inappropriate definitive treatment were excluded, only the latter was retained. Finally, age, hematologic malignancy, corticosteroid use, ineradicable or not-eradicated focus, septic shock, high-grade bacteremia, and inappropriate definitive therapy were included in the logistic regression.

Multivariate analysis indicated that ineradicable or not-eradicated focus (adjusted odds ratio [aOR], 4.92; 95% confidence interval [CI], 1.95–12.42; \( P = 0.001 \)), septic shock (aOR, 4.72; 95% CI, 2.12–10.49; \( P < 0.001 \)), and inappropriate antimicrobial therapy (aOR, 2.54; 95% CI, 1.05–6.16; \( P = 0.04 \)) were independent risk factors for mortality (Table 3). Cox proportional hazards regression analysis also showed similar results indicating that ineradicable or not-eradicated focus (adjusted hazard ratio [aHR], 2.50; 95% CI, 1.18–4.85; \( P = 0.02 \)), septic shock (aHR, 2.67; 95% CI, 1.52–4.72; \( P = 0.001 \)), and inappropriate antimicrobial therapy (aHR, 3.75; 95% CI, 2.89–6.17; \( P < 0.001 \)) were independent risk factors for mortality.
Anti-CRAB strategies

We classified all anti-CRAB treatments as appropriate definitive therapy into six strategies. Of the groups with more than 10 patients, tigecycline combination without colistin had the highest 30-day mortality (6/11, 55%), followed by colistin combination without tigecycline (20/40, 50%) and colistin monotherapy (7/17, 41%). Tigecycline with colistin had the lowest 30-day mortality (10/30, 33%) (Table 1). Of 30 CRAB isolates in patients treated with tigecycline with colistin, 27 (90%) were susceptible to both antimicrobial agents, two (6%) were colistin-resistant but susceptible to tigecycline, and one colistin-resistant and tigecycline-susceptible. Different anti-CRAB strategies among patients who received appropriate definitive therapy were compared. When compared with monotherapy (using only one antibiotic except colistin), tigecycline and colistin combination (aHR, 0.26; 95% CI, 0.08–0.92; P = 0.04) and colistin combination therapy without tigecycline (aHR, 0.28; 95% CI, 0.09–0.89; P = 0.03) were significantly associated lower 30-day mortality after adjustment for confounding factors (Table 4). In addition, compared with patients receiving one in vitro active agent against CRAB, patients receiving two or more in vitro active agents tended to have lower mortality (aHR, 0.40; 95% CI, 0.16-1.04; P = 0.06).
Discussion

In this retrospective study, microbiological factors such as colistin MIC and genotype in addition to clinical factors were investigated to evaluate the risk factors for mortality in CRAB bacteremia. Ineradicable or not-eradicated infection focus, severity of bacteremia, and appropriate antibiotic therapy, rather than microbiological factors, were independently associated with mortality. Colistin-based combination therapy may have improved outcomes.

Previous studies reported that underlying medical conditions, severity of bacteremia, and use of early appropriate antimicrobial agents were predictors of mortality in patients with CRAB bacteremia [9-13]. Surgery before bacteremia, chronic liver disease, chronic renal disease, neutropenia, and use of corticosteroid or immune suppressants are medical conditions also had adverse effects on clinical outcome [9, 10]. Our study yielded similar results. In addition, inappropriate definitive therapy was an independent risk factor for mortality. Of importance, a relatively large proportion (29%) of our study patients did not receive appropriate antibiotic treatment, and in those patients, 30-day mortality was very high (75%). Therefore, antimicrobial stewardship for patients with CRAB bacteremia should be reinforced. Contrary to a meta-analysis emphasizing the importance of empirical therapy [10], the appropriateness of empirical antibiotics was not associated with mortality in our study. A possible explanation is that the effect of inappropriate empirical therapy is short lived (i.e. until susceptibility results are available) and can be corrected by subsequent appropriate definitive therapy.
Ineradicable or not-eradicated focus was also an important predictor of mortality. Infection source control is a variable associated with the site of infection, and pneumonia and undrainable complicated intraabdominal collections are situations in which the site of infection cannot be eliminated. A previous study also reported that mortality rate was higher in cases where the respiratory tract was the source of bacteremia [11]. In addition, we found that the mortality rate increased significantly when an eradicable focus was for any reason not removed. To reduce potential survival bias (patients who survive longer have more chance to receive source control), we limited the time interval between bacteremia and the removal of an eradicable focus to 7 days in our analysis. Therefore, in patients whose infection focus was ineradicable or challenging to eradicate, more aggressive treatment should be considered.

The optimal antibiotic choice for CRAB bacteremia is controversial. Colistin, tigecycline, and sulbactam as monotherapy or combination therapy, are the most commonly used options. Colistin is generally considered the backbone of treatment [21]. Some studies have suggested the use of tigecycline combination therapy [22-24]. On the other hand, other studies have not supported the effectiveness of combination therapy [21, 25]. In our study, after adjusting for potential confounders, colistin and tigecycline combination did increase survival, and colistin combination with other antibiotics such as carbapenem and sulbactam had a tendency to decrease mortality. However, given the high overall mortality of CRAB bacteremia (54.9%), combined therapy with colistin and tigecycline was not strikingly effective (mortality rate 39.4%). This suggests that colistin-based therapy may still be suboptimal. In view of the retrospective design of the study, it cannot be
concluded that colistin combination therapy is the best treatment option. A well-designed further study is warranted.

In the present study, colistin MIC was not associated with a significant difference in mortality. However, mortality rates declined with increasing colistin MIC within the susceptible range (≤2 mg/L), and a similar trend was evident within the colistin-treated group. However, the number of isolates with high colistin MIC was too small to conclude that high colistin MIC contributes to lower mortality. On the other hand, in a previous study of CRAB pneumonia, mortality was significantly lower when colistin MIC was below 1 mg/L [26]. However, that study differed from ours in two ways. First, it included cases of CRAB pneumonia that were non-bacteremic. Second, colistin MIC was determined using an automated system that may have yielded results that differed from the reference method. For these reasons, our study may better reflect the relationship between clinical outcome of CRAB bacteremia and colistin MIC. We infer that the tendency of mortality to decrease with increasing colistin MIC may be due to weakened virulence as CRAB gains colistin tolerance [27].

The distribution of sequence types (STs) varies regionally [28-32]. ST191 is known as the dominant ST in South Korea [30, 31]. In our case, ST191 was also the most common type and accounted for about half of the total. Certain clonal types were found to be associated with poor outcome in previous studies [9, 28]. Mortality did not differ between STs in our study, but rates of septic shock did differ significantly; thus, genotype may influence the early clinical manifestations of bacteremia. However, further research is needed to elucidate the effect of the genotype of CRAB on clinical outcomes.
This study has several limitations. First, it was a single-center study, and clinical data were retrospectively collected. Unrecognized clinical factors may have resulted in biases. However, a thorough chart review was done, and we included a relatively large number of patients to compensate for the limited study design. Second, the small number of patients who received tigecycline monotherapy and sulbactam-based therapy made it difficult to evaluate the effectiveness of those treatments. Third, because of the confusing nature of kidney injury due to decreased organ perfusion during bacteremia and the adverse effect of colistin, we could not evaluate nephrotoxicity during colistin use. However, despite such limitations, our data have important clinical implications because we analyzed the effect of microbiological factors such as colistin MIC and STs on mortality in CRAB bacteremia, which has rarely been done before.

In conclusion, ineradicable or not-eradicated focus, septic shock, and inappropriate definitive therapy are independent risk factors for mortality in CRAB bacteremia. There was no significant mortality difference according to microbiological factors. In the treatment of CRAB bacteremia, it is important to eliminate eradicable foci such as catheters and intraabdominal complicated fluid collections and to administer timely appropriate antibiotics. Colistin combination therapy may contribute to a better treatment outcome.
Funding

This research was supported by a grant from the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare, Republic of Korea (grant number: HI17C2052).

Potential Conflicts of Interest

All  No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

Author Contributions

HJS, EBC, YPC conceived the ideas; HJS, EBC, SCL collected and analyzed the data; HJS, YPC wrote the manuscript and created tables; HJS, EBC, YPC, MB, HSS, JJ, MJK, SHK, SOL, SHC, YSK, JHW reviewed, revised and approved the manuscript.
References

1. Hochman S, Phillips M. Acinetobacter Species. In: Bennett JE, Dolin R, Blaser MJ, eds. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. 9th ed. Philadelphia: Elsevier; 2020. 2718-24.

2. Nelson RE, Schweizer ML, Perencevich EN, et al. Costs and mortality associated with multidrug-resistant healthcare-associated Acinetobacter infections. Infect Control Hosp Epidemiol 2016; 37:1212-8.

3. Lemos EV, de la Hoz FP, Einarson TR, et al. Carbapenem resistance and mortality in patients with *Acinetobacter baumannii* infection: systematic review and meta-analysis. Clin Microbiol Infect 2014; 20:416-23.

4. Sheng WH, Liao CH, Lauderdale TL, et al. A multicenter study of risk factors and outcome of hospitalized patients with infections due to carbapenem-resistant *Acinetobacter baumannii*. Int J Infect Dis 2010; 14:e764-9.

5. Park SY, Choo JW, Kwon SH, et al. Risk factors for mortality in patients with *Acinetobacter baumannii* bacteremia. Infect Chemother 2013; 45:325-30.

6. Organization WH. Global priority list of antibiotic-resistant bacteria to guide research, discovery, and development of new antibiotics. 2017; https://www.who.int/medicines/publications/global-priority-list-antibiotic-resistant-bacteria/en/. Accessed 28 February 2020.

7. Kim D, Ahn JY, Lee CH, 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.

8. Lee H, Yoon EJ, Kim D, et al. Antimicrobial resistance of major clinical pathogens in South Korea, May 2016 to April 2017: first one-year report from Kor-GLASS. Euro Surveill 2018; 23.
9. Nutman A, Glick R, Temkin E, et al. A case-control study to identify predictors of 14-day mortality following carbapenem-resistant *Acinetobacter baumannii* bacteraemia. Clin Microbiol Infect 2014; 20:O1028-34.

10. Du X, Xu X, Yao J, et al. Predictors of mortality in patients infected with carbapenem-resistant *Acinetobacter baumannii*: A systematic review and meta-analysis. Am J Infect Control 2019; 47:1140-5.

11. Liu CP, Shih SC, Wang NY, et al. Risk factors of mortality in patients with carbapenem-resistant *Acinetobacter baumannii* bacteremia. J Microbiol Immunol Infect 2016; 49:934-40.

12. Kim T, Park KH, Yu SN, et al. Early intravenous colistin therapy as a favorable prognostic factor for 28-day mortality in patients with CRAB bacteremia: a multicenter propensity score-matching analysis. J Korean Med Sci 2019; 34:e256.

13. Park SY, Lee EJ, Kim T, et al. Early administration of appropriate antimicrobial agents to improve the outcome of carbapenem-resistant *Acinetobacter baumannii* complex bacteraemic pneumonia. Int J Antimicrob Agents 2018; 51:407-12.

14. Institute CaLS. Performance standards for antimicrobial susceptibility testing: 29th informational supplement M100-S25. Clinical and Laboratory Standards Institute, Wayne, PA. 2015.

15. Singer M, Deutschman CS, Seymour CW, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). Jama 2016; 315:801-10.

16. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987; 40:373-83.

17. Chow JW, Fine MJ, Shlaes DM, et al. Enterobacter bacteremia: clinical features and emergence of antibiotic resistance during therapy. Ann Intern Med 1991; 115:585-90.

18. Clinical and Laboratory Standards Institute (CLSI). Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically; approved standard-tenth edition, CLSI document M07-A10. Wayne, PA: CLSI; 2015.

19. Garonzik SM, Li J, Thamlikitkul V, 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.
20. Bartual SG, Seifert H, Hippler C, Luzon MA, Wisplinghoff H, Rodriguez-Valera F. Development of a multilocus sequence typing scheme for characterization of clinical isolates of *Acinetobacter baumannii*. J Clin Microbiol **2005**; 43:4382-90.

21. Giannella M, Bartoletti M, Gatti M, Viale P. Advances in the therapy of bacterial bloodstream infections. Clin Microbiol Infect **2019**.

22. Kim NH, Hwang JH, Song KH, et al. Tigecycline in carbapenem-resistant *Acinetobacter baumannii* bacteraemia: susceptibility and clinical outcome. Scand J Infect Dis **2013**; 45:315-9.

23. Piperaki ET, Tzouvelekis LS, Miriagou V, Daikos GL. Carbapenem-resistant *Acinetobacter baumannii*: in pursuit of an effective treatment. Clin Microbiol Infect **2019**; 25:951-7.

24. Chusri S, Singkhamanan K, Wanitsuwan W, et al. Adjunctive therapy of intravenous colistin to intravenous tigecycline for adult patients with non-bacteremic post-surgical intra-abdominal infection due to carbapenem-resistant *Acinetobacter baumannii*. J Infect Chemother **2019**; 25:681-6.

25. Amat T, Gutierrez-Pizaraya A, Machuca I, et al. The combined use of tigecycline with high-dose colistin might not be associated with higher survival in critically ill patients with bacteraemia due to carbapenem-resistant *Acinetobacter baumannii*. Clin Microbiol Infect **2018**; 24:630-4.

26. Choi IS, Lee YJ, Wi YM, et al. Predictors of mortality in patients with extensively drug-resistant *Acinetobacter baumannii* pneumonia receiving colistin therapy. Int J Antimicrob Agents **2016**; 48:175-80.

27. Beceiro A, Tomás M, Bou G. Antimicrobial resistance and virulence: a successful or deleterious association in the bacterial world? Clin Microbiol Rev **2013**; 26:185-230.

28. Liu CP, Lu HP, Luor T. Clonal relationship and the association of the ST218 strain harboring blaOXA-72 gene to mortality in carbapenem-resistant *Acinetobacter baumannii* bacteremia. J Microbiol Immunol Infect **2019**; 52:297-303.

29. Tavares LCB, de Vasconcellos FM, de Sousa WV, et al. Emergence and persistence of high-risk clones among MDR and XDR *A. baumannii* at a Brazilian teaching hospital. Front Microbiol **2018**; 9:2898.
30. Gurung M, Rho JS, Lee YC, et al. Emergence and spread of carbapenem-resistant *Acinetobacter baumannii* sequence type 191 in a Korean hospital. Infect Genet Evol 2013; 19:219-22.

31. Selasi GN, Nicholas A, Jeon H, et al. Genetic basis of antimicrobial resistance and clonal dynamics of carbapenem-resistant *Acinetobacter baumannii* sequence type 191 in a Korean hospital. Infect Genet Evol 2015; 36:1-7.

32. Huang G, Yin S, Gong Y, et al. Multilocus sequence typing analysis of carbapenem-resistant *Acinetobacter baumannii* in a Chinese Burns Institute. Front Microbiol 2016; 7:1717.
Figure Legends

**Figure 1.** 30-day mortality according to (A) colistin MIC and (B) genotype of CRAB blood isolates
Table 1. Clinical characteristics and management of CRAB bacteremia, according to 30-day mortality

| Characteristic or treatment                          | Deceased patients (n = 90) | Surviving patients (n = 74) | Total (n= 164) | P value |
|------------------------------------------------------|-----------------------------|-----------------------------|----------------|---------|
| Age, mean years ± SD                                 | 62.1 ± 16.0                 | 65.6 ± 12.7                 | 63.7 ±         | 0.12    |
| Male gender                                          | 58 (64)                     | 53 (72)                     | 111 (67)       | 0.33    |
| Site of acquisition                                  |                             |                             |                | 0.01    |
| Community-onset healthcare-associated infection      | 0 (0)                       | 6 (8)                       | 6 (4)          |         |
| Hospital-acquired infection                          | 90 (100)                    | 68 (92)                     | 158 (96)       |         |
| Underlying disease/condition                         |                             |                             |                |         |
| Hematologic malignancy                               | 33 (37)                     | 13 (18)                     | 46 (28)        | 0.01    |
| Solid tumor                                          | 18 (20)                     | 26 (35)                     | 44 (27)        | 0.03    |
| Chronic kidney disease                               | 10 (11)                     | 14 (19)                     | 24 (15)        | 0.16    |
| Chronic obstructive pulmonary disease                | 8 (9)                       | 4 (5)                       | 12 (7)         | 0.39    |
| Recent chemotherapy                                  | 30 (33)                     | 15 (20)                     | 45 (27)        | 0.06    |
| Recent surgery                                       | 20 (22)                     | 18 (24)                     | 38 (23)        | 0.75    |
| Immunosuppressant use                                | 13 (14)                     | 15 (20)                     | 28 (17)        | 0.46 (28)0.32 |
| Corticosteroid use                                   | 31 (34)                     | 15 (20)                     | 46 (28)        | 0.04    |
| Neutropenia                                          | 32 (36)                     | 7 (10)                      | 39 (24)        | <0.001  |
| Ventilator care                                      | 46 (51)                     | 36 (49)                     | 82 (50)        | 0.75    |
| Charlson comorbidity, median (IQR)                  | 3 (2–5)                     | 4 (2–7)                     | 3 (2–6)        | 0.09    |
| Type of infection                                     |                             |                             |                |         |
| Catheter-related infection                           | 7 (8)                       | 16 (22)                     | 23 (14)        | 0.01    |
| Intra-abdominal infection                            | 10 (11)                     | 8 (11)                      | 18 (11)        | 0.95    |
| Biliary tract infection                              | 2 (2)                       | 19 (26)                     | 21 (13)        | <0.001  |
| Pneumonia                                            | 49 (54)                     | 20 (27)                     | 69 (42)        | <0.001  |
| Skin & soft tissue infection                         | 4 (4)                       | 3 (4)                       | 7 (4)          | 0.99    |
| Primary bacteremia                                   | 18 (20)                     | 6 (8)                       | 24 (15)        | 0.03    |
| Eradicable focus                                     | 14 (16)                     | 41 (55)                     | 55 (34)        | <0.001  |
| Removal of eradicable focus within 7 days            | 9/14 (64)                   | 38/41 (93)                  | 47/55 (85)     | 0.02    |
| Days from diagnosis to focus removal, median (IQR)   | 1 (0–2)                     | 2 (0–4)                     | 1 (0–4)        | 0.33    |
| Ineradicable or not-eradicated focus                 | 81 (90)                     | 36 (49)                     | 117 (71)       | <0.001  |
| Intensive care unit                                  | 70 (78)                     | 38 (51)                     | 108 (66)       | <0.001  |
| Septic shock                                         | 67 (74)                     | 20 (27)                     | 87 (47)        | <0.001  |
| Pitt bacteremia score, median (IQR)                  | 4 (2–8)                     | 2 (0–3)                     | 3 (0–5)        | <0.001  |
| High grade CRAB bacteremia                           | 65 (72)                     | 38 (51)                     | 103 (63)       | 0.01    |
| Inappropriate empirical therapy                      | 61 (68)                     | 47 (64)                     | 108 (66)       | 0.57    |
| Inappropriate antimicrobial therapy                   | 36 (40)                     | 13 (18)                     | 49 (30)        | 0.002   |
| Combination antimicrobial therapy                    | 43 (48)                     | 47 (64)                     | 90 (55)        | 0.04    |
| Anti-CRAB strategies                                  | 47                          | 61                          | 108            |         |
| Therapy                                | CRAB  | SD   | IQR   | CRAB  | SD   | IQR   |
|----------------------------------------|-------|------|-------|-------|------|-------|
| Tigecycline monotherapy                | 3 (6) | 3 (5)| 6 (6) | >0.99 |      |       |
| Tigecycline combination\(^d\)          | 6 (13)| 5 (8 )| 11 (10)| 0.53  |      |       |
| Tigecycline with colistin              | 10 (21)| 20 (33)| 30 (28)| 0.19  |      |       |
| Colistin combination\(^e\)             | 20 (43)| 20 (33)| 40 (37)| 0.30  |      |       |
| Colistin monotherapy                   | 7 (15)| 10 (16)| 17 (16)| 0.83  |      |       |
| Sulbactam-based therapy\(^f\)         | 1 (2)| 2 (3) | 3 (3) | >0.99 |      |       |

Data are presented as number of patients (with the corresponding percentage in parentheses) unless otherwise specified.

CRAB, carbapenem-resistant *Acinetobacter baumannii*; SD, standard deviation; IQR, interquartile range

\(^a\) High-grade CRAB bacteremia was defined when two or more blood culture sets were positive from at least two blood culture sets drawn.

\(^b\) Defined as not using at least one antibiotic susceptible to the causative isolate.

\(^c\) Among patients who received appropriate definitive therapy.

\(^d\) Tigecycline combination was defined as tigecycline combination therapy without colistin.

\(^e\) Colistin combination was defined as colistin combination therapy without tigecycline.

\(^f\) Sulbactam-based therapy was sulbactam monotherapy or sulbactam combination without tigecycline and colistin.
| Characteristic of blood isolates | Deceased patients (n = 90) | Surviving patients (n = 74) | Total (n= 164) | P value |
|----------------------------------|---------------------------|----------------------------|----------------|---------|
| **Colistin susceptibility**      |                           |                            |                |         |
| MIC ≤0.5 mg/L                    | 55 (61)                   | 36 (49)                    | 91 (56)        | 0.11    |
| MIC 1.0 mg/L                     | 26 (29)                   | 23 (31)                    | 49 (30)        | 0.76    |
| MIC 2.0 mg/L                     | 3 (3)                     | 9 (12)                     | 12 (7)         | 0.03    |
| MIC ≥4.0 mg/L                    | 6 (7)                     | 6 (8)                      | 12 (7)         | 0.72    |
| **Multilocus sequence type (MLST)** |                         |                            |                |         |
| ST191                            | 43 (48)                   | 37 (50)                    | 80 (49)        | 0.78    |
| ST451                            | 13 (14)                   | 10 (14)                    | 23 (14)        | 0.86    |
| ST784                            | 13 (14)                   | 9 (12)                     | 22 (13)        | 0.67    |
| ST369                            | 8 (9)                     | 6 (8)                      | 14 (9)         | 0.86    |
| Others                           | 13 (14)                   | 12 (16)                    | 25 (15)        | 0.70    |

Data are presented as number of patients (with corresponding percentage in parenthesis).
Table 3. Univariate and multivariate analysis of risk factors for mortality in patients with CRAB bacteremia

| Risk factor                                      | Univariate analysis result |          | Multivariate analysis result |          |
|--------------------------------------------------|----------------------------|----------|------------------------------|----------|
|                                                  | OR (95% CI)                | P value  | Adjusted OR (95% CI)         | P value  |
| Age                                              | 0.98 (0.96 – 1.01)         | 0.13     |                              |          |
| Hematologic malignancy                           | 2.72 (1.30 – 5.67)         | 0.01     |                              |          |
| Steroid use                                      | 2.07 (1.01 – 4.22)         | 0.05     |                              |          |
| Ineradicable or not-eradicated focus             | 9.50 (4.16 – 21.70)        | <0.001   | 4.92 (1.95 – 12.42)          | 0.001    |
| Septic shock                                     | 7.87 (3.91 – 15.81)        | <0.001   | 4.72 (2.12 – 10.49)          | <0.001   |
| High grade CRAB bacteremia                       | 1.57 (1.14 – 2.17)         | 0.01     |                              |          |
| Inappropriate antimicrobial therapy              | 3.13 (1.50 – 6.51)         | 0.002    | 2.54 (1.05 – 6.16)           | 0.04     |

OR, odds ratio.

The model fitted the data well in terms of discrimination (C-statistic = 0.84) and calibration (Hosmer-Lemeshow goodness of fit statistic = 9.62, P = 0.29).
Table 4. Univariate and multivariate analysis of associations between different definitive antibiotic strategies and 30-day mortality in patients with CRAB bacteremia (n = 108)

| Risk factor                              | Univariate analysis | Multivariate analysis<sup>a</sup> |
|------------------------------------------|---------------------|-----------------------------------|
|                                          | HR (95% CI)         | P value                           | Adjusted HR (95% CI) | P value |
| Monotherapy other than colistin<sup>b</sup> (ref) | –                   | –                                 | –                   | –       |
| Tigecycline combination<sup>c</sup>       | 0.30 (0.09 – 1.05)  | 0.06                              | 0.28 (0.08 – 1.04)  | 0.06    |
| Tigecycline with colistin                | 0.22 (0.07 – 0.72)  | 0.01                              | 0.26 (0.08 – 0.92)  | 0.04    |
| Colistin combination<sup>d</sup>         | 0.25 (0.09 – 0.76)  | 0.01                              | 0.28 (0.09 – 0.89)  | 0.03    |
| Colistin monotherapy                     | 0.25 (0.07 – 0.95)  | 0.04                              | 0.28 (0.06 – 1.36)  | 0.12    |

HR, hazard ratio.

<sup>a</sup> Adjusted HRs and 95% CIs were calculated by Cox proportional hazards regression among patients receiving appropriate definitive therapy, adjusted for age, hematologic malignancy, ineradicable or not-eradicated focus, septic shock, and CRAB isolation from more than two bottles.

<sup>b</sup> Monotherapy was defined as using only one antibiotic except colistin.

<sup>c</sup> Tigecycline combination was defined as tigecycline combination therapy without colistin.

<sup>d</sup> Colistin combination was defined as colistin combination therapy without tigecycline.
Figure 1

(A) 30-day mortality (%)

- ≤ 0.5 (n = 91)
- 1 (n = 49)
- 2 (n = 12)
- ≥ 4 (n = 12)

Colistin MIC (mg/L)

P = 0.02

P = 0.13

(B) 30-day mortality (%)

- ST191 (n = 80)
- ST451 (n = 23)
- ST784 (n = 22)
- ST369 (n = 14)
- ST357 (n = 11)
- Others (n = 14)

P = 0.81