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Original Article

# Efficacy of short- versus prolonged-courses of antimicrobial therapy for carbapenem-resistant *Klebsiella pneumoniae* bloodstream infections: A propensity score-matched cohort study

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**KEYWORDS**
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*Klebsiella pneumoniae*;
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Short course;
Prolonged course

**Abstract** *Background:* As limited antibiotic options are available for the treatment of carbapenem-resistant *Klebsiella pneumoniae* (CRKP) bloodstream infections (BSIs), the optimal treatment duration for CRKP BSIs is unclear. Our objective was to investigate whether short courses (6—10 days) are as effective as prolonged courses (≥11 days) of active antibiotic therapy for CRKP BSIs.
*Methods:* A retrospective cohort study comprising adults with monomicrobial CRKP BSI receiving a short or prolonged course of *in vitro* active therapy at a medical center was conducted between 2010 and 2021. Comparisons of two therapeutic strategies were assessed by the logistic regression model and propensity score analysis. The primary endpoint was 30-day crude mortality. Secondary outcomes included recurrent BSIs, the emergence of multidrug-resistant organisms and candidemia during hospitalization after completing antibiotic therapy for CRKP BSIs.
*Results:* Of 263 eligible adults, 160 (60.8%) were male, and the median (interquartile range) age was 69.0 (53.0—76.0) years. Common comorbidities included diabetes (143 patients, 54.4%), malignancy (75, 28.5%), cerebrovascular accident (58, 22.1%), and hemodialysis (49, 18.6%). The 30-day mortality rate was 8.4% (22 patients). Of 84 propensity score well-

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balanced matched pairs, the 30-day mortality was similar in the short-course and prolonged-course group (6.0% and 7.1%, respectively; $P = 1.00$). However, there were less episodes candidemia in the short-course group (1.2% versus 13.1%; odds ratio, 0.08; 95% confidence interval, 0.01—0.63; $P = 0.005$).
*Conclusion:* Short courses of active therapy for CRKP BSIs demonstrate comparable clinical outcomes to prolonged courses and are associated with a lower risk of subsequent candidemia.


## Introduction

Bloodstream infections (BSIs) remain to be associated with considerable morbidity and mortality, especially carbapenem-resistant Enterobacterales (CRE) BSIs.[1—3] Infections due to *Klebsiella pneumoniae* remain a crucial and global issue, since carbapenem-resistant *K. pneumoniae* (CRKP) have spread worldwide.[4,5] Up-to-date guidelines did not provide recommended durations for the treatment of CRE bacteremia explicitly, but clinicians are advised that the duration of therapy for infections caused by organisms with resistant phenotypes should not differ that of infections caused by organisms with susceptible phenotypes.[6—8] A meta-analysis conducted by Turjeman et al. concluded that shorter courses of antibiotic therapy in suitable patients with Gram-negative bacillary BSIs may result in reduced inpatient stays, decreased antibiotic exposure, lowered costs, and no increased mortality rate or other adverse outcomes.[9] Additionally, existing clinical trials and retrospective studies, where Enterobacterales were mostly susceptible to carbapenems, revealed no significant disparities in mortality rate or recurrent bacteremia based on different antibiotic duration groups.[10—17] Similar findings were observed in a study involving patients with CRE BSIs.[18] Furthermore, prolonged antibiotic exposure is associated with an increased risk of multidrug-resistant organism (MDRO) infections due to *Clostridioides difficile*,[19] *Candida* species,[20] methicillin-resistant *Staphylococcus aureus* (MRSA),[21] or vancomycin-resistant *Enterococcus* (VRE).[22] The present study, including a larger number of cases than a published study,[18] aims to compare the clinical outcomes in propensity-matched patients with CRKP BSIs receiving a short or prolonged course of current available antibiotic therapy.

## Materials and methods

### Study population and data collection

We reviewed the microbiology database at National Cheng Kung University Hospital (NCKUH) in southern Taiwan for the cases of *K. pneumoniae* BSIs between August 2010 and December 2021. The study was approved by the Institutional Review Board of NCKUH (B-ER-112-526). Adult aged ≥20 years with first episode of CRKP bacteremia during the study period were included. Enrolled participants were those who received *in vitro* active antibiotics at recommended doses according to the Clinical and Laboratory Standards Institute (CLSI) or the European Committee on Antimicrobial Susceptibility Testing (EUCAST) guidelines.[23,24] Moreover, those who did not survive beyond at least one day after the end of antibiotic therapy and those with polymicrobial or complicated BSIs, which was defined as the presence of endocarditis, osteoarticular infection, central nervous system infection, complicated intra-abdominal infection without adequate source control, deep abscess without drainage, or catheter-related BSIs with retained catheter, were excluded. We dichotomized the duration of antibiotic therapy to the short-course (6—10 days) and prolonged-course (≥11 days) group. The first day of therapy was referred to the day when parenteral *in vitro* active antibiotic(s) was/were administered.

### Microbiology and antimicrobial susceptibilities

Carbapenem resistance was defined as being *in vitro* resistant to at least one of ertapenem, imipenem, or meropenem, according to the current latest definition and breakpoint provided by the Centers for Disease Control and CLSI at the year of case inclusion. The VITEK 2 system (BioMérieux, Durham, NC, USA) was utilized for species identification until February 28, 2015, followed by MALDI-TOF MS (BioMérieux, Marcy l'Étoile, France) at our hospital, while minimum inhibitory concentrations (MICs) testing was determined using the broth-dilution method. MICs of the tested antibiotics, except colistin and tigecycline, were interpreted by the recommended breakpoints of the CLSI,[23] and those of colistin and tigecycline by the breakpoints of EUCAST.[24]

### Clinical evaluation and outcomes

We retrieved demographic data from medical charts of a BSI cohort by a standard record form, as prescribed previously.[2,25,26] BSI was defined as the isolation of CRKP in at least one blood culture from a patient with compatible signs of sepsis syndrome. Hospital-onset infections were defined as the infectious episodes with the first positive blood culture collected over 48 h after admission. Intensive care unit (ICU)-acquired infections were defined as the episodes with the first positive blood culture collected over 48 h after ICU admission. The rapidly fatal underlying disease was defined by the McCabe classification.[27] The

severity of BSI was assessed on the day of BSI onset using the Pitt bacteremia score, and a critical illness was defined as a Pitt bacteremia score of $\geq$4 points.[28] The primary outcome was 30-day post-bacteremia onset crude mortality after the onset of BSI. The secondary outcomes included recurrence of CRKP bacteremia with the same antibiogram, and development of candidemia, VRE BSIs, MRSA BSIs or *C. difficile* infections (CDI) after the end of antimicrobial treatment for CRKP BSI during the index hospitalization.

### Statistical analyses

Data were analyzed using the SPSS software for Windows, version 22. Categorical variables were expressed as the numbers and percentages of the specific patients and were analyzed by the Fisher exact or $\chi^2$ test, as appropriate. Continuous variables were expressed as medians and interquartile ranges and were compared by the Student's *t*-test. To identify the independent predictors for 30-day mortality, the variables with a *P* value of 0.1 or less by the univariate analyses by the above appropriate tests were included to conduct a multiple conditional logistic regression analysis. A *P* value of less than 0.05 was deemed statistically significant, with all tests being two-tailed. Given the variations in baseline characteristics inherent of the retrospective design, the propensity score matching method was employed to mitigate measured disparities between the short-course and prolonged-course groups. Propensity scores were computed via a multivariate logistic regression model, with the dependent variable being a binary indicator in the short or prolonged course. Like our previous publication,[2] covariates utilized to generate propensity scores consisted of age, gender (male), comorbidities (including diabetes mellitus, cerebrovascular accident, congestive heart failure with an ejection fraction ratio below 45%, end-stage renal disease undergoing dialysis, liver cirrhosis, chronic obstructive pulmonary disease, or immunocompromising conditions), Pitt bacteremia score, ICU stay on Day 1 of BSI, and the source of BSI. One-to-one nearest neighbor matching without replacement was conducted using a caliper width of 0.20. After propensity score matching, standardized mean biases were tested to ensure balance between the two groups.

## Results

### Patient population

Overall, there were 387 patients with CRKP BSI during the study period. Of these, 263 patients met the inclusion criteria for the analysis and matching (Fig. 1). Of 263 eligible patients, 103 (39.2%) received active antibiotics for a short course (median: 10 days; interquartile range [IQR]: 9—10 days) and 160 (60.8%) with a prolonged course (median: 17 days; IQR: 15—19 days). *In vitro* antimicrobial susceptibilities of these 263 CRKP isolates were shown in Table 1. The susceptible rate for ertapenem, imipenem, and meropenem was 8.0%, 67.3%, and 81.0%, respectively. The vast majority (90.1%) were susceptible to colistin. Susceptibility testing of ceftazidime-avibactam was conducted on only nineteen available isolates, revealing that 15 (78.9%) of them were noted to be susceptible.

Of 263 cases of CRKP BSI, their median age was 69.0 (IQR: 53.0—76.0) years. The majority of the included patients (261 patients, 99.2%) were hospital-onset, and 46.0% (121 patients) had ICU-acquired BSI. The median hospital stay before the onset of BSI was 11.0 (IQR: 4.0—24.0) days. Major sources of BSIs were vascular catheter-related infections (77 patients, 29.3%) and primary BSI (66, 25.1%), followed by urinary tract infections (44, 16.7%), pneumonia

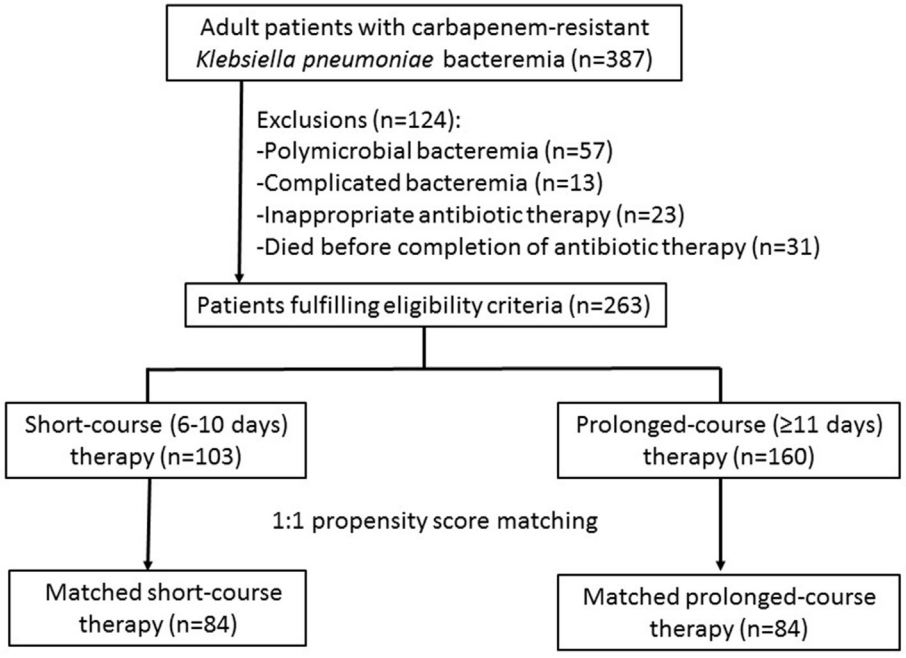


**Figure 1.** Flow diagram of study.

**Table 1** *In vitro* susceptibilities and minimum inhibitory concentrations (MICs) of 263 blood isolates of carbapenem-resistant *Klebsiella pneumoniae*.

| Antimicrobial agents | MIC (μg/mL) | | Numbers of susceptible isolates (%) |
|---|---|---|---|
| | $MIC_{90}$ | Range | |
| Ertapenem | 16 | 0.5 - >32 | 21 (8.0) |
| Imipenem | 8 | 0.125 - >16 | 177 (67.3) |
| Meropenem | 8 | 0.25 - >16 | 213 (81.0) |
| Amikacin | >32 | 1 - >64 | 163 (62.0) |
| Cefotaxime | >32 | 2 - >64 | 0 |
| Cefepime[a] | 32 | 2 - >64 | 173 (65.8) |
| Piperacillin-tazobactam[a] | >128 | 4 - >128 | 67 (25.5) |
| Ciprofloxacin | >2 | 0.25 - >64 | 7 (2.7) |
| Colistin[b] | 2 | 0.06 - >8 | 239 (90.1) |
| Tigecycline[b] | 2 | 0.125 - >8 | 161 (61.2) |

[a] Cefepime-susceptible and piperacillin-tazobactam-susceptible isolates include the susceptible and suceptible-dose-dependent categories, according to the CLSI criteria in 2023.

[b] *In vitro* susceptibilities and MIC are interpreted according to the breakpoints recommended by the EUCAST in 2023, and otherwise by the CLSI criteria in 2023.

(39, 14.8%), skin-soft tissue infections (31, 11.8%), and intra-abdominal infections (16, 6.1%).

Clinical characteristics of patients receiving a short-course or prolonged-course antibiotic therapy were summarized in Table 2. There were significant differences between the short-course and prolonged-course group before matching, in terms of gender (69.9% *vs*. 55.0%, $P = 0.02$), previous history of cerebrovascular accident (12.6% *vs*.28.1 %, $P = 0.004$), underlying chronic kidney disease (26.2% *vs*. 41.3%, $P = 0.02$), the need of chronic hemodialysis (11.7% *vs*. 23.1%, $P = 0.02$), and primary BSI (34.0% *vs*. 19.4%, $P = 0.01$).

## Outcomes

There were 84 propensity score—matched pairs in short-course and prolonged-course group. Baseline characteristics of two groups were well-balanced when evaluating standardized biases. Of note, the 30-day mortality rate in the short-course and prolonged-course group was 6.0% (5 patients) and 7.1% (6 patients), respectively ($P = 1.00$). In the univariate analysis, a shorter course of antibiotic therapy was not associated with an increased risk of mortality (odds ratio [OR], 0.71; 95% confidence interval [CI]: 0.28—1.79). Similarly, the in-hospital mortality rates in the short-course and prolonged-course groups were comparable (14.3% and 9.5%, respectively; $P = 0.48$). In the multivariate analysis, the presence of pneumonia as the source of BSI, and rapidly fatal underlying disease was independently associated with 30-day mortality (Table 3).

There were 5 (4.9 %) and 15 (9.4%) recurrent episodes of BSI due to CRKP with the same antibiogram in the short-course and prolonged-course group, respectively ($P = 0.54$). However, in the propensity score matching analysis, there were more BSIs due to MRSA (0%, 0/84 *vs*. 6%, 5/84) or VRE (3.6%, 3/84 *vs*. 10.7%, 9/84), CDI (0%, 0/84 *vs*. 2.4, 2/84) in the prolonged-course group. Crucially, episodes of candidemia were more frequently observed in the prolonged-course group (13.1% vs. 1.2%) with an odds ratio of 12.5 (95% CI, 1.58—99.23; $P = 0.005$) (Fig. 2).

## Discussion

Treating CRKP infection is challenged by their multidrug resistance and the absence of oral antibiotics for step-down therapy. Limited options underscore the need for innovative solutions to navigate this complex landscape and emphasize the urgency for new antimicrobial agents and alternative strategies in CRKP infection management. Determining optimal treatment duration for CRKP BSIs is challenging, as extended therapy seeks eradication but raises concerns about resistance and superinfections. Tailored approaches are essential to balance effectiveness and risk.[7] Our findings indicate that patients receiving a short course (6—10 days) of antibiotic therapy for uncomplicated CRKP BSIs have no higher risk of mortality in the ensuing 30 days than those receiving a longer course (≥11 days) of antibiotic therapy. Moreover, patients receiving a short-course therapy did not experience more episodes of recurrent CRKP BSIs, as compared with those receiving a prolonged-course therapy.

To enhance the generalizability of our findings to the populations susceptible to CRE infections, we included the cases of CRKP BSI, irrespective of underlying medical conditions or severity of illness. There is a common assumption that infections due to MDRO necessitate aggressive treatment, including extended therapy durations.[29] Clinicians frequently adhere to antibiotic duration recommendations based on the established guidelines,[30] often opting for a minimum of a 14-day course in the management of the cases of Gram-negative bacteremia. However, for CRE BSI, the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and the Infectious Diseases Society of America (IDSA) did not provide explicit recommendations regarding prolong treatment duration, and the Infectious Diseases Society of Taiwan (IDST) recommended a treatment course of 7—14 days that the definite treatment duration should be individualized according to infection sites, source control, the underlying comorbidities and the initial response to therapy.[6—8] A recent observational study involving 183 cases investigated the optimal duration for CRE bacteremia, and concluded 7—10 days of antibiotic therapy might be potentially sufficient.[18] Furthermore, our research enhances the persuasiveness of the argument that short courses of antibiotic therapy for CRKP BSIs can result in clinical outcomes, as prolonged courses of antibiotic therapy do.

In the present study, two recognized independent risk factors associated with 30-day mortality were rapidly fatal underlying diseases and bacteremic pneumonia. The short course of therapy, however, was not a significant prognostic variable. In contrast, a prolonged duration of antibiotic therapy did not result in reduced mortality or offer benefits in minimizing the risk of recurrent BSIs, but tended to select multidrug-resistant organisms (MDROs).[19—22] Moreover, our

**Table 2** Characteristics and outcomes of 263 adults with monomicrobial carbapenem-resistant *Klebsiella pneumoniae* bloodstream infections (BSIs).

| | Crude analysis | | | Propensity score matched analysis | | |
|---|---|---|---|---|---|---|
| | Short-course group, n = 103 | Prolonged-course group, n = 160 | *P* value | Short-course group, n = 84 | Prolonged-course group, n = 84 | Standardized mean difference |
| **Characteristics** | | | | | | |
| Age, median (IQR), year | 69 (55–77) | 69 (53–75) | 0.55 | 69 (55.0–76.5) | 69 (49–76) | 0.09 |
| Gender, male | 72 (69.9) | 88 (55.0) | 0.02 | 57 (67.9) | 57 (67.9) | 0 |
| Hospital stay before BSI, median (IQR), day | 8 (4–24) | 12 (5.0–23.5) | 0.94 | 12 (3.5–24.0) | 12 (4.5–26.5) | 0.01 |
| ICU acquired | 44 (42.7) | 77 (48.1) | 0.45 | 34 (40.5) | 38 (45.2) | 0.09 |
| Comorbidity | 102 (99.0) | 156 (97.5) | 0.65 | 83 (98.8) | 82 (97.6) | 0.09 |
| Diabetes mellitus | 53 (51.5) | 90 (56.3) | 0.45 | 44 (52.4) | 46 (54.8) | 0.05 |
| Cerebrovascular accident | 13 (12.6) | 45 (28.1) | 0.004 | 13 (15.5) | 15 (17.9) | 0.06 |
| Congestive heart failure | 15 (14.6) | 28 (17.5) | 0.61 | 13 (15.5) | 13 (15.5) | 0 |
| Chronic hemodialysis | 12 (11.7) | 37 (23.1) | 0.02 | 11 (13.1) | 14 (16.7) | 0.1 |
| Liver cirrhosis | 11 (10.7) | 11 (6.9) | 0.36 | 10 (11.9) | 7 (8.3) | 0.1 |
| Malignancy | 33 (32.0) | 42 (26.3) | 0.33 | 26 (31.0) | 26 (31.0) | 0 |
| Rapidly fatal underlying illness (McCabe classification) | 6 (5.8) | 14 (8.8) | 0.48 | 5 (6.0) | 9 (10.7) | 0.16 |
| Critical illness (Pitt bacteremia score, ≥4 points) | 26 (25.2) | 38 (23.8) | 0.88 | 20 (23.8) | 20 (23.8) | 0 |
| Source of BSI | | | | | | |
| Vascular catheter-related infection | 27 (26.2) | 50 (31.3) | 0.41 | 25 (29.8) | 23 (27.4) | 0.05 |
| Primary BSI | 35 (34.0) | 31 (19.4) | 0.009 | 20 (23.8) | 23 (27.4) | 0.08 |
| Intra-abdominal infection | 5 (4.9) | 11 (6.9) | 0.60 | 4 (4.8) | 7 (8.3) | 0.15 |
| Pneumonia | 14 (13.6) | 25 (15.6) | 0.72 | 13 (15.5) | 13 (15.5) | 0 |
| Skin and soft-tissue infection | 11 (10.7) | 20 (12.5) | 0.70 | 11 (13.1) | 7 (8.3) | 0.15 |
| Urosepsis | 16 (15.5) | 28 (17.5) | 0.74 | 16 (19.0) | 14 (16.7) | 0.06 |
| Combinational definitive therapy | 48 (46.6) | 60 (37.5) | 0.16 | 39 (46.4) | 34 (40.5) | 0.06 |
| **Outcomes** | | | | | | |
| 30-day mortality | 7 (6.8) | 15 (9.4) | 0.504 | 5 (6.0) | 6 (7.1) | 0.05 |
| In-hospital mortality | 16 (15.5) | 24 (15.0) | 1.000 | 12 (14.3) | 8 (9.5) | 0.1 |
| Recurrent BSI | 5 (4.9) | 15 (9.4) | 0.235 | 4 (4.8) | 7 (8.3) | 0.1 |

Data are given as numbers (percentages), unless otherwise specified. IQR, interquartile range; ICU, intensive care unit.

**Table 3** Multivariate logistic regression analysis of risk factors of 30-day crude mortality among 263 adults with monomicrobial carbapenem-resistant *Klebsiella pneumoniae* bloodstream infections.

| Variables | Survivors (n = 241) | Non-survivors (n = 22) | Univariate analysis | | Multivariate analysis | |
|---|---|---|---|---|---|---|
| | | | OR (95% CI) | *P* values | OR (95% CI) | *P* values |
| Age; median (IQR), years | 69 (55–75) | 63.5 (49–83) | | 0.82 | | |
| Gender, male | 145 (60.2) | 15 (68.2) | 1.42 (0.56–3.61) | 0.50 | | |
| Cerebrovascular accident | 57 (23.7) | 1 (4.5) | 0.15 (0.02–1.17) | 0.06 | 0.356 (0.03–3.41) | 0.36 |
| Rapidly fatal underlying disease | 15 (6.2) | 5 (22.7) | 4.43 (1.44–13.66) | 0.02 | 6.19 (1.26–30.40) | 0.03 |
| Pneumonia | 32 (13.3) | 7 (31.8) | 3.05 (1.15–8.05) | 0.03 | 5.00 (1.32–18.96) | 0.02 |
| Pitt bacteremia score ≥4 points | 49 (20.3) | 15 (68.2) | 8.40 (3.25–21.72) | <0.001 | 2.42 (0.65–9.02) | 0.19 |
| Short-course therapy | 96 (39.8) | 7 (31.8) | 0.71 (0.28–1.79) | 0.50 | | |

Data are given as numbers (percentages), unless otherwise specified. Ellipses indicate not available.
OR, odds ratio; CI, confidence interval; IQR, interquartile range.
Variables with a *P* value of 0.1 or less in the univariate analysis were included in the multivariate analysis.

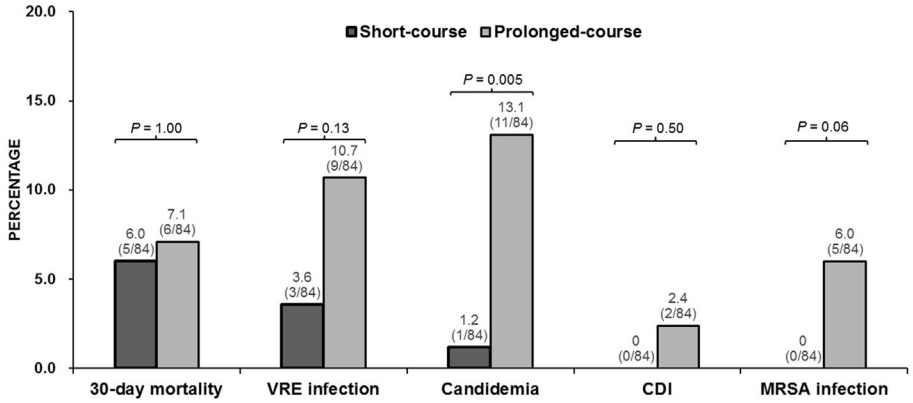


**Figure 2.** Clinical outcomes in matched patient receiving definitive short-course or prolonged-course antibiotic therapy.

work revealed a higher incidence of sequential infections caused by MDROs, esp. candidemia, in the prolonged-course group. This outcome indirectly supports the notion of disruptions in the human gut microbiome by systemic antibiotic therapy and the intestinal dysbiosis can provoke the development of MDRO infections.[31]

There were several limitations in our work. First, the design of a retrospective observational study would be confounded due to unmeasured variables. Nevertheless, this study demonstrated consistent results through both multivariate logistic regression and propensity score matching analyses. When well-designed, the propensity score matching method may offer an approach approximating the validity of randomized controlled trials for BSI.[32] Nevertheless, we cannot entirely rule out the possibility of additional unmeasured confounding factors in generating propensity scores. If the propensity score fails to effectively assess and balance these unmeasured factors, the outcomes of propensity score matching can be misleading.[33] Second, the findings did not apply to patients with complicated or polymicrobial BSIs, since the inclusion of the cases of polymicrobial BSIs is likely to introduce research bias due to the complexity of the virulence and resistance profiles of concurrent pathogens. Third, only clinical data related to the hospitalization period were available, and the long-term outcomes in two study groups remained undefined. Finally, despite the recent introduction of several antimicrobial agents for the treatment of CRE infections,[7] few patients were treated by ceftazidime-avibactam, which was available in our hospital during the last year of this observational study. However, the stewardship intervention program constantly proceeded during the study period,[34,35] and the prescriptions of antibiotic therapy for CRKP bacteremia would be optimized by the infectious disease specialists.

## Conclusion

This study suggests that a short course of active antibiotic treatment for CRKP bacteremia is not associated with a higher risk of crude mortality or recurrent CRKP bacteremia, and may provide a prognostic benefit in mitigating the consequences of superinfections by MDROs, particularly candidemia.

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## CRediT authorship contribution statement

**Tian-Yu You:** Data curation, Formal analysis, Writing — original draft. **Ching-Lung Lo:** Data curation. **Wen-Chia Tsai:** Data curation. **Hao-En Jan:** Data curation. **Wen-Chien Ko:** Conceptualization, Writing — review & editing. **Nan-Yao Lee:** Conceptualization, Formal analysis, Writing — review & editing.

## Declaration of competing interest

All authors: no interest conflicts.

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