High-dose tigecycline for the treatment of nosocomial carbapenem-resistant *Klebsiella pneumoniae* bloodstream infections

A retrospective cohort study

Ting-Ting Geng, MM, Xin Xu, MM, Man Huang, MD

Abstract

Carbapenem-resistant *Klebsiella pneumoniae* (CRKP) bloodstream infection (BSI) has become increasingly frequent threat recently, especially in the intensive care unit (ICU). High-dose tigecycline (TGC) regimen is proposed due to the limitation of treatment options. We investigated the efficacy and safety of high-dose TGC combination regimens for treating CRKP BSI. Furthermore, the risk factors for mortality were also determined.

This was a single center retrospective cohort study conducted from 2014 to 2016. A total of 40 patients with nosocomial CRKP BSI admitted to the ICU were included; they were classified into two groups according to the treatment regimens with high-dose TGC (HD group) or not (non-HD group). In-hospital mortality rates and microbiologic responses from both groups were reviewed and compared. Besides, the survival and non-survival groups were compared to identify the risk factors of mortality.

Tigecycline was administered as 100 mg loading dose followed by 100 mg every 12 h and 17 patients constituted the non-HD group (standard dose TGC therapy as 100 mg loading dose followed by 50 mg every 12 h and other antibiotics). The in-hospital mortality was 52.2% in the HD group and 76.5% in the non-HD group ($P = .117$). The Kaplan–Meier test showed significantly longer survival times in the HD group (mean: 83 days vs 28 days; $P = .027$). Microbiological eradication was observed in 13 patients (56.5%) in the HD group and 6 patients (36.3%) in the non-HD group ($P = .844$). A smaller fraction of patients in the HD group were subjected to vasoactive therapy (52.2% vs 88.2%; $P = .016$) compared to the non-HD group. There was no significant difference in the manifestation of adverse effects between the two groups. In the multivariate analysis, multiple organ dysfunction syndrome (MODS), vasoactive therapy, and exposure to carbapenems were regarded as the independent predictors of mortality.

A therapeutic regimen consisting of a high dose of TGC was associated with significantly longer survival time and numerically lower mortality in CRKP BSI. Adverse events were not increased with the double dose therapy.

Abbreviations: ALT = alanine transaminase, APACHE II = acute physiology and chronic health evaluation, AST = aspartate transaminase, BSI = bloodstream infection, CI = confidence intervals, CRKP = carbapenem-resistant *Klebsiella pneumoniae*, CSKP = carbapenem-susceptible *Klebsiella pneumoniae*, ICU = intensive care unit, MIC = minimum inhibitory concentration, MODS = Multiple organ dysfunction syndrome, OR = Odds ratios, SD = standard deviation, SOFA = sequential organ failure assessment, TGC = tigecycline, WBC = white blood cell count.

Keywords: bloodstream infection, carbapenem resistant, high-dose tigecycline, *Klebsiella pneumoniae*

1. Introduction

In recent times, carbapenem-resistant *Klebsiella pneumoniae* (CRKP) associated bacterial infections have begun to emerge as a significantly important threat due to the widespread use of carbapenems in treatment. In China, CHINET reported that the rate of carbapenem resistance among *K pneumoniae* isolates increased from 2.4% in 2005 to 13.4% in 2014. CRKP are capable of producing carbapenemases, which have the ability to hydrolyze all the known cephalosporins, monobactams, carbapenems, and beta-lactamase inhibitors, thereby leading to fewer effective antibiotics at our disposal, longer lengths of stay, and higher mortality rates. An infection of the bloodstream in the host is one of the most common types of infection associated with CRKP, which approximately increases the mortality rate three-fold compared to CRKP infections occurring at other sites. Treatment options are limited, and these usually involve the use of colistin, tigecycline (TGC), carbapenems, and some aminoglycosides; but, an optimal treatment strategy is yet to be identified and clearly defined. Moreover, no listing of colistin in mainland China until now.
Disease Control and Prevention. The collection date of the CRKP
ment. Multiple organ dysfunction syndrome (MODS) was
dysfunction and persistent hypotension despite volume replace-
teriaceae set above are in accordance with the de
CRKP BSI. CRKP BSI is de
clinical signs of infection (which forms the basis of suspicion source
positive blood culture for CRKP can be obtained along with clear
during a 3-year period (January 2014
Patients
Data collection
This single center retrospective observational study was performed
in the People’s Republic of China, during a 3-year period (January 2014–December 2016). Patients
whose data were included in this study were those with a nosocomial
CRKP BSIs. CRKP BSI is defined as an infection where at least one
positive blood culture for CRKP can be obtained along with clear
clinical signs of infection (which forms the basis of suspicion source
of CRKP infection). The terms CRKP BSI and the diagnostic criteria
set above are in accordance with the definitions of the Centers for
Disease Control and Prevention.[10] The collection date of the CRKP
samples was considered as the BSI onset time in each case. Adequate
empirical antibiotic therapy refers to the regimen that involves the
administration of in vitro active antimicrobials for CRKP before the
microbiological tests are performed. The term definitive treatment
used in this report refers to the antibiotic therapy initiated within 24
hours of obtaining the microbiological results. A high-dose TGC
regimen involves the administration of a 200-mg loading dose followed by a 100-mg dose after 12 hours. BSI or intracranial
infections caused by multidrug-resistant bacteria are routinely
treated with high-dose TGC in our ICU. Sepsis was defined as an
infection that has led to a systemic inflammatory response syndrome
in a patient. Septic shock was defined as sepsis associated with organ
dysfunction and persistent hypotension despite volume replace-
Multiple organ dysfunction syndrome (MODS) was defined as the simultaneous dysfunction of at least two organ
systems in an acutely ill patient. Exclusion criteria were, patient
< 18 years old, those with BSI onset < 48 hours after ICU admission,
and those with duration of definitive treatment < 72 hours. The
primary outcome was in-hospital mortality and survival time. The
secondary outcomes were bacterial clearance based on a negative
blood culture result and the length of stay.

2.2. Data collection
Patients’ information were collected from the electronic medical
records of the hospital. Data obtained included demographic
characteristics, underlying diseases and conditions associated
with comorbidity, recent (< 30 days) surgical procedures, the use
of immunosuppressant and steroids, length of hospital stay, total
hospitalization expenses, carbapenem exposure (exposure to
carbapenems during the 30 days preceding admission to the ICU),
definitive treatment, and the duration of each course of treatment.
The severity of illness [calculated by the acute physiology and
chronic health evaluation (APACHE II) score[12] and the
sequential organ failure assessment (SOFA) score[13]] was
calculated for each patient admitted to the ICU, on admission.
Data on septic shock, inflammation markers [including white
blood cell count (WBC), procalcitonin (PCT), C-reactive protein
(CRP)], clinical outcomes, in-hospital bacterial clearance rates,
time from hospitalization to the onset of BSI, and the minimum
inhibitory concentration (MIC) were also collected. Possible
adverse effects of TGC were continuously evaluated from the
onset of TGC treatment (including empirical treatment). Serum
creatinine, total bilirubin, ALT, and AST increase means increased
more than 1.5 times baseline; fibrinogen reduce referred to
fibrinogen lower than 1.5 g/L. In this study, blinding was used
during the data collection and analysis. Furthermore, to ensure that
selection bias and information bias associated with the study were
controlled, research experts were consulted. The study was approved by an ethics committee (The Second Affiliated Hospital
of Zhejiang University School of Medicine Institutional Review
Board) prior to the commencement of the study.

2.3. Microbiological tests
Microbial identification was done using the VITEK system
(bioMérieux, Marcy l’Etoile, France). The MIC used in this
study, the determination of antimicrobial susceptibilities associ-
ated with the VITEK system, and the disk diffusion method, all
complied with the 2016 Clinical Laboratory Standards Institute
recommendations.

2.4. Statistical analysis
Continuous variables were expressed as mean or median while
categorical variables were expressed as absolute numbers or their
relative frequencies. Variable distributions were evaluated using
the Kolmogorov–Smirnov test. Continuous variables were
analyzed using the Student t-test (normally distributed variables)
or the Mann–Whitney U-test (non-normally distributed varia-
bles), while categorical variables were analyzed using the χ² test
or the Fisher’s test. Variables significant in the univariate analyses
(P < .1) were added to a stepwise multiple logistic regression
model to identify independent risk factors of mortality. Event-
free survival curves were constructed using the Kaplan–Meier
methods and compared using a log-rank test. Odds ratios and
95% confidence intervals were also computed. All statistical tests
conducted in the study were reported as two-tailed tests and the
P-values less than .05 were considered statistically significant.
All statistical analyses were conducted using SPSS version 23.0
(IBM Corp., Armonk, NY).

3. Results
During the course of the study, a total of 40 patients with CRKP
BSIs met the inclusion criteria and the incidence of CRKP BSI in
our ICU was 6.62%. All patients received mechanical ventilation,
central venous catheters, arterial catheters, nasogastric tubes, and
urinary catheters on ICU admission. The most common sources
Clinical characteristics

Demographic variables

The in-hospital bacterial clearance rate was 47.5%, and the median time from admission to infection was 15 days (IQR, 9.25–21 days). All patients had two or more comorbidities. There were no cases involving solid organ transplantation or receiving chemotherapy. Overall, 62.5% of patients underwent steroid therapy. Two (5%) patients received immunosuppressive therapy (cyclosporine or leflunomide) to treat systemic lupus erythematosus. The mean APACHE II score on ICU admission was 20.5 (SD ± 8) and the mean SOFA score was 5.0 (SD ± 3.12). The median duration of mechanical ventilation was 24 days (IQR, 13–39.5 days). The median hospital and ICU length of stay were 37.5 (IQR, 29–62.25) and 30 (IQR, 17.25–43.5) days, respectively. Twelve patients were transferred from the ICU to the rehabilitation wards or the medical wards while eight patients stayed in a common ward prior to the ICU admission.

Over the duration of the study, 23 patients received the high-dose TGC therapy (HD group) and the rest (17 patients) were in the non-HD group. All patients received concomitant treatment with carbapenems or beta-lactamase inhibitors or aminoglycosides; however, no significant differences occurred between the two groups. There were no significant statistical differences between the two groups with respect to demographic parameters and disease severity (Table 2). The in-hospital mortality was

Table 1

The probable source of blood stream infection.

| Probable source          | Total (%) | HD group | non-HD group | Mortality (%) |
|--------------------------|-----------|----------|--------------|---------------|
| Primary BSI              | 13 (32.5) | 8        | 5            | 46.2          |
| Lung                     | 10 (25)   | 5        | 5            | 70            |
| Intra-abdominal          | 7 (17.5)  | 3        | 4            | 57.1          |
| Urinary tract            | 4 (10)    | 2        | 2            | 75            |
| Cerebral                 | 3 (7.5)   | 1        | 2            | 100           |
| Central venous catheter  | 3 (7.5)   | 2        | 1            | 66.7          |

BSI = Blood stream infection.

Table 2

Analysis of the patients in the HD group compared with non-HD group.

| Variables                                      | HD group (n = 23) | non-HD group (n = 17) | P     | OR (95% CI) |
|------------------------------------------------|-------------------|-----------------------|-------|-------------|
| Demographic variables                         |                   |                       |       |             |
| Male sex                                      | 20 (87)           | 15 (88)               | .904  | 0.89 (0.13–6.01) |
| Age, years                                    | 65.1 ± 14.3       | 61.8 ± 13.9           | .470  |             |
| Comorbidities                                 |                   |                       |       |             |
| Diabetes mellitus                             | 2 (8.7)           | 3 (17.6)              | .717  | 0.44 (0.67–3.01) |
| Hypertension                                  | 10 (43.5)         | 8 (47.1)              | .822  | 0.67 (0.25–3.05) |
| Autoimmune rheumatoid diseases                | 2 (8.7)           | 2 (11.8)              | .749  | 0.71 (0.09–5.66) |
| Coronary heart disease                        | 5 (21.7)          | 2 (11.8)              | .689  | 2.08 (0.35–12.32) |
| Malignancy                                    | 3 (13)            | 3 (17.6)              | .687  | 0.70 (0.12–3.99) |
| Trauma                                        | 12 (52.2)         | 6 (35.3)              | .289  | 2.0 (0.55–7.25) |
| Cerebral hemorrhage                           | 4 (17.4)          | 5 (29.4)              | .605  | 0.51 (0.11–2.27) |
| Clinical characteristics                      |                   |                       |       |             |
| APACHE II score on ICU admission              | 20.7 ± 9.4        | 20.2 ± 6.0            | .546  |             |
| SOFA score on ICU admission                   | 47.1 ± 3.3        | 54.8 ± 4.8            | .131  | 0.37 (0.10–1.36) |
| Occurrence of MODS after BSI                  | 8 (34.8)          | 10 (56.8)             | .016  | 0.15 (0.03–0.79) |
| Vasocative therapy after BSI                  | 12 (52.2)         | 15 (88.2)             | .145  |             |
| Time from admission to infection               | 15 (10–18)        | 16 (8–29)             | .780  |             |
| Time to bacterial clearance, days             | 15 (6–20)         | 10 (6–34)             | .564  |             |
| CRP, mg/L                                     | 210.1 ± 85.4      | 270.6 ± 121.9         | .207  |             |
| Adequate empirical therapy                    | 13 (56.5)         | 8 (47.1)              | .230  | 1.46 (0.42–5.15) |
| Duration of mechanical ventilation, d         | 22 (13–37)        | 26 (11–42)            | .330  |             |
| Total hospitalization expenses, yuan          | 20552 ± 156308    | 43440 ± 207200        | .082  |             |
| Possible adverse events                       |                   |                       |       |             |
| Hypoglycemia                                  | 3 (13)            | 3 (17.6)              | 1.0   | 0.70 (0.12–3.99) |
| Serum creatinine increase                     | 5 (21.7)          | 4 (23.5)              | 1.0   | 0.90 (0.20–4.02) |
| Total bilirubin increase                      | 11 (58.8)         | 10 (47.8)             | .491  | 0.64 (0.18–2.27) |
| ALT increase                                  | 8 (34.8)          | 5 (29.4)              | .720  | 1.28 (0.33–4.94) |
| AST increase                                  | 11 (47.8)         | 11 (64.7)             | .289  | 0.50 (0.14–1.81) |
| Fibrinogen reduce                             | 17 (73.9)         | 11 (64.7)             | .530  | 1.55 (0.40–6.03) |
| Nausea and/or vomiting                        | 0                 | 0                     | .680  | 0.76 (0.21–2.78) |
| Diarrhea                                      | 8 (34.8)          | 7 (41.2)              | .510  |             |
| Outcomes                                      |                   |                       |       |             |
| In-hospital mortality                         | 12 (52.2)         | 13 (76.5)             | .117  | 0.34 (0.08–1.34) |
| Hospital length of stay, d                    | 36 (29–69)        | 38 (29–62)            | .339  |             |
| ICU length of stay, d                         | 31 (18–42)        | 29 (16–47)            | .456  |             |
| Bacterial clearance rates                     | 13 (56.5)         | 6 (36.3)              | .184  | 2.38 (0.66–8.68) |

1 Data are number (%) or patients or median (IQR) or mean ± SD, continuous variables used Student’s t-test, categorical variables used Chi-squared test.

ALT = Alanine transaminase, APACHE II = acute physiology and chronic health evaluation, AST = aspartate transaminase, CRP = C reactive protein, ICU = intensive care unit, IQR = interquartile range, MODS = multiple organ dysfunction syndrome, PCT = procalcitonin, SD = standard deviation, SOFA = sequential organ failure assessment.
observed as 52.2% and 76.5% in the HD and non-HD groups, respectively ($P = 0.117$). Microbiological eradication was observed in 13 (56.5%) patients and 6 (36.3%) patients in the HD and non-HD groups, respectively ($P = 0.184$). As shown in Figure 1, survival was significantly longer in the HD group (mean: 83 days vs. 28 days; $P = .027$). The proportion of patients who required vasoactive therapy (52.2% vs 88.2%; $P = .016$) was significantly lower in the HD group after the onset of CRKP BSI. Although not statistically significant, the occurrence of MODS (34.8% vs 58.8%; $P = .131$) was lower in the HD group after the onset of CRKP BSI. Furthermore, the median length of mechanical ventilation was 22 days (IQR, 13–37 days) for patients in the HD group compared to 26 days (IQR, 11–42 days) in the non-HD group. The mean hospital expenses were lower in the HD group (mean ± SD: 290552 ± 156308 yuan vs 434403 ± 297200 yuan; $P = .082$). With respect to adverse effects, no differences were observed between the two groups in terms of glucose abnormalities (specifically hypoglycemia), serum creatinine, total bilirubin, fibrinogen, alanine transaminase (ALT), aspartate transaminase (AST), and gastrointestinal symptoms (nausea, vomiting, or diarrhea). Besides, we did not find other adverse effects, for example, allergic reaction, acute pancreatitis, jaundice, drowsiness, itchy, and pain, etc. The majority (79.5%) of isolates were susceptible in vitro to TGC (MIC ≤ 2 mg/L) with one isolate missing, the distribution of non-susceptible isolation was not significantly different between the two groups. All isolates were resistant to meropenem, but all the MICs were found to be ≤ 32 mg/L. In vitro susceptibility was found in only 10% of the isolates for amikacin and levofloxacin. All isolates were resistant to cefoperazone sodium, sulbactam sodium, imipenem, piperacillin, tazobactam, and cephalosporins. Characteristics of the survivor and non-survivor sub-groups are depicted in Table 3. Significant differences were observed between the two groups in terms of APACHE II score on ICU admission (16.1 ± 6.5 vs 19.1 ± 7.1; $P = .026$), SOFA score on ICU admission (4.0 ± 3.0 vs 6.0 ± 5.0; $P = .001$), Occurrence of MODS (4 of 15 patients vs 8 of 25 patients; $P = .050$), and Vasoactive therapy (8 of 25 patients vs 0 of 15 patients; $P = .018$).

### Table 3

| Variables                        | Non-survivors (n = 25) | Survivors (n = 15) | $P$    | OR (95% CI) |
|----------------------------------|------------------------|-------------------|--------|-------------|
| Demographic variables           |                        |                   |        |             |
| Male sex                         | 23 (92)                | 12 (80)           | .537   | 2.68 (0.42–19.62) |
| Age, y                           | 65.48 ± 14.54          | 60.80 ± 13.21     | .315   |             |
| Comorbidities                    |                        |                   |        |             |
| Diabetes mellitus                | 4 (16)                 | 1 (6.67)          | .633   | 3.86 (1.01–14.90) |
| Hypertension                     | 14 (56)                | 4 (26.67)         | .071   | 3.5 (0.87–13.66) |
| Autoimmune thyroid diseases      | 2 (8)                  | 2 (13.33)         | .691   | 1.63 (0.27–9.86) |
| Coronary heart disease           | 5 (20)                 | 2 (13.33)         | .381   | 3.5 (0.37–33.31) |
| Malignancy                       | 5 (20)                 | 1 (6.67)          | .381   | 3.5 (0.37–33.31) |
| Trauma                           | 9 (36)                 | 9 (60)            | .140   | 0.37 (1.0–1.39) |
| Cerebral hemorrhage              | 6 (24)                 | 3 (20)            | 1.0    | 1.26 (0.27–6.03) |
| Clinical characteristics         |                        |                   |        |             |
| APACHE II score on ICU admission | 21.88 ± 7.15           | 18.20 ± 9.02      | .162   |             |
| SOFA score on ICU admission      | 5.92 ± 2.71            | 3.47 ± 2.35       | .014   |             |
| Presentations with septic shock  | 22 (88)                | 5 (33.33)         | .001   | 14.67 (2.92–73.72) |
| Occurrence of MODS               | 17 (68)                | 1 (6.67)          | <.001  | 29.75 (5.31–267.40) |
| Vasoactive therapy               | 23 (92)                | 4 (26.67)         | <.001  | 31.63 (5.01–199.76) |
| Steroids therapy                 | 19 (76)                | 6 (40)            | .232   | 4.75 (1.19–18.92) |
| Immunosuppressive therapy        | 1 (4)                  | 1 (6.67)          | 1.0    | 0.59 (0.03–10.01) |
| Neutropenia                      | 1 (4)                  | 0 (0)             | .046   | 3.86 (1.01–14.92) |
| Carbenepenem exposure            | 18 (72)                | 6 (40)            | .680   | 1.31 (0.36–4.77)  |
| Surgical history                 | 15 (60)                | 8 (53.33)         | .806   | 1.31 (0.36–4.77)  |
| Days between admission and infection | 19 (8–26)          | 14 (10–16)        | .047   |             |
| Bacterial clearance time, days   | 9 (5.25–30)            | 15 (9–19)         | .943   |             |
| White blood cell count, 10^9/L   | 14.9 ± 11.86           | 11.5 ± 9.48       | .331   |             |
| CRP, mg/L                        | 247.40 ± 108.85        | 215.91 ± 103.61   | .361   |             |
| PCT, µg/L                        | 1.10 ± 3.05            | 0.45 ± 25.59      | .091   |             |
| Adequate empirical therapy       | 12 (48)                | 9 (60)            | .476   | 2.25 (0.50–10.14) |
| Duration of mechanical ventilation, d | 28 (15–42)      | 17 (11–37)        | .171   |             |
| Total hospitalization expenses, yuan | 389303.72 ± 260773.78 | 286886.58 ± 174569.5 | .150 |             |

* Data are number (%) or patients or median (IQR)

APACHE II = Acute physiology and chronic health evaluation, CI = Confidence intervals, CRP = C reactive protein, ICU = Intensive care unit, IQR = Interquartile range, MODS = Multiple organ dysfunction syndrome, OR = Odds ratios, PCT = Procalcitonin, SD = Standard deviation, SOFA = Sequential Organ Failure Assessment.
between survivors and non-survivors with respect to SOFA scores on ICU admission ($P=0.14$), presentation with septic shock ($P=0.001$), occurrence of MODS ($P<0.001$), vasoactive therapy ($P<0.001$), steroid therapy ($P=0.023$), carbapenems exposure ($P=0.046$), time from admission to infection ($P=0.047$), white blood cell count ($P=0.031$), and bacterial clearance ($P=0.011$). Moreover, compared to the survivor group, the non-survivor group showed significant differences in terms of the following characteristics, older average age, higher APACHE II score, time, and higher hospitalization costs. In the multivariate logistic regression analyses, MODS ($P=0.021$), the requirement and duration of vasoactive therapy ($P=0.005$), and carbapenems exposure ($P=0.047$) were independent predictors of in-hospital mortality (Table 4).

4. Discussion

In this study, 40 CRKP BSI cases were studied. The incidence of CRKP BSI in the ICU was 6.62%, which is higher than previously reported. This discrepancy could be because Zhejiang Province has one of the highest prevalences of CRKP infections in China. This depicts the seriousness of the condition of patients included in this study. All the patients who participated in this study required variety invasive procedures. Moreover, the APACHE II scores of the patients were quite high indicating a more or less severe form of the disease. All patients in this study also underwent treatment using multiple antibiotics prior to their participation in this study, which increased the possibility of CRKP infection. The ICU stay was reported as an independent risk factor of CRKP acquisition. Since patients have a high risk of CRKP infection in ICU, empirical therapy plays an important role in their prognosis. In our study, 52.5% of the patients received adequate empirical therapy.

The best treatment regimen for CRKP infections is yet to be determined. Combination therapy with two or more active drug agents under in vitro conditions is widely accepted. The use of TGC combination therapy for serious infections is somewhat controversial and still under debate. The efficacy of TGC in BSI has been questioned because of its low-serum concentrations. Recent meta-analyses and retrospective studies show that TGC is not associated with higher survival and may even cause more deaths and other serious side effects in severe forms of infectious disease. The FDA in particular, warned against the use of TGC for serious infections in 2010. In contrast, other studies have shown that TGC therapy, when administered as a constituent of combination therapy, (especially high-dose TGC-based therapy), can be effective and can reduce the mortality associated with the severe forms of infectious disease. Another retrospective study involving 15 patients receiving different doses of TGC for severe CRKP infections has been reported. The favorable clinical response reported in the above-mentioned study was 87.5%. The overall 30-day mortality rate was 33.3% and 20% for daily doses of 100 mg and 200 mg, respectively. Besides, De Pascale et al. reported that high doses of TGC can be administered without undue toxicity for the treatment of serious infections in critically ill patients. In the current study, the mortality was 24.3% lower in HD patients compared to the non-HD group. Moreover, the group where a high dosage of TGC was administered displayed significantly longer survival times ($P=0.027$) and less requirement of vasoactive therapy ($P=0.016$). We think requirement for vasoactive therapy is partly an outcome indicator for septic shock, but there are many factors to influence the outcome and our sample size was small, so our results need further large simple study to be confirmed.

The safety and tolerability of the high dosage TGC therapy are of great concern. Nausea and vomiting are the most often reported manifestations of intolerance. It was reported that these adverse effects of the gastrointestinal system, were dose-dependent and increased in frequency with increasing TGC dosage. A randomized phase-2 trial showed that the incidence of gastrointestinal adverse effects was higher in patients treated with the high TGC dosage. As for the safety, renal, hepatic, and hematological toxicity associated with TGC should be evaluated. However, in some articles, no adverse effects were found in patients receiving high-dose TGC therapy compared with standard dose. Similarly, our study reported no case of nausea or vomiting; this was probably due to the fact that all patients included in this study were breathing with the aid of mechanical ventilation, and were also under sedation. No other adverse effects were observed in HD patients. Therefore, we believe that the treatment regimen consisting of the double dose TGC is not associated with more adverse events.

The mortality rates associated with CRKP BSI have been widely reported and they range from 40% to 70%. These rates were reported to be significantly higher compared to carbapenem susceptible $K$ pneumoniae (CSKP) BSI. Additionally, the duration of hospitalization was also found to be significantly longer with CRKP BSI. In a retrospective study, the in-hospital mortality was 42.4% for CRKP BSI, compared to 19.8% in patients with CSKP BSI and the median length of hospitalization for patients with the CRKP BSI and CSKP BSI were 30 and 24 days, respectively. All of these results were statistically significant.

Earlier studies have evaluated the benefits of inadequate empirical therapy, immunosuppression, corticosteroid use, septic shock, the effect of age, high SOFA, APACHE II scores, poor functional status, and the duration of ICU stay as predictors of mortality in CRKP infections. The results obtained from our analysis on the risk factors for mortality were similar to those obtained from previous studies. Carbapenem exposure has been reported as an independent risk factor for CRKP infections. Analogously, we find that carbapenem exposure (exposure to carbapenems during the 30 days preceding admission to the ICU) is an independent predictor of mortality. However, we did not find a relationship between immunosuppression and mortality, which could probably be due to the small sample size in the current study.

There were several limitations associated with this study. First, the current study was a retrospective, single center study with a limited sample size. Second, we did not exclude polymicrobial infection cases. Finally, carbapenemase types were not assessed, thereby leading to the loss of some data associated with the microbial sensitivity test.

| Table 4 Multivariate analysis of risk factors for mortality. |
|-----------------|-----------------|-----------------|
| Variable         | OR (95% CI)     | P               |
| MODS             | 49.96 (1.78–1399)| .021            |
| Vasoactive therapy| 60.89 (4.33–1081)| .005            |
| Carbapenems exposure| 15.56 (1.04–232.89)| .047            |

$\text{OR} =$ odds ratios.
5. Conclusion
In the present study, the incidence and mortality rates of CRKP BSI were high in critically ill patients. The high dosage TGC therapy was associated with significantly longer survival time and numerically lower mortality. Moreover, adverse events were not increased with the double dose therapy. The independent factors of mortality were MODS, vasoactive therapy, and exposure to carbapenems. Further prospective studies are needed to confirm the results put forth by this study.

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