Risk Factors Affecting Clinical Outcome in Patients with Carbapenem-Resistant *K. pneumoniae*: A Retrospective Study

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Background: The increased prevalence of carbapenem-resistant *K. pneumoniae* (CRKP) poses a great threat worldwide. Early identification of CRKP in patients is paramount. Moreover, fully understanding the risk factors affecting clinical outcome and actively providing targeted treatment can improve the cure rate of patients with CRKP. Therefore, our study aimed to describe the clinical characteristics and identify the risk factors affecting clinical outcomes in patients with CRKP.

Material/Methods: From January 2016 to September 2017, CRKP strains and clinical data from 97 hospitalized patients were collected. We first performed an antibiotic susceptibility test on CRKP strains using the Kirby-Bauer disc agar diffusion method. Logistic regression analysis was then performed to analyze risk factors.

Results: According to clinical outcome, among the 97 CRKP patients, 67 were in the effective group and 30 patients were in the noneffective group. Risk factors found to correlate with poor clinical outcome in patients with CRKP included ICU admission, arteriovenous catheterization, indwelling gastric tube, indwelling urethral catheter, tracheal intubation, mechanical ventilation, hypoproteinemia, and exposure to carbapenems. Multivariate analysis showed that hypoproteinemia (OR: 2.83, p=0.042), presence of an indwelling gastric tube (OR: 4.54, p=0.005), and exposure to carbapenems (OR: 2.77, p=0.045) negatively affected clinical outcome in patients with CRKP.

Conclusions: Adverse risk factors correlated with poor clinical outcomes in patients with CRKP were determined. This could be of help in identifying high-risk patients with whom clinicians should take extra precautions and adjust therapeutic strategy to supplement conventional basic treatment with additional measures.

MeSH Keywords: Fatal Outcome • *Klebsiella pneumoniae* • Risk Factors

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Background

*K. pneumoniae* is one of the most common gram-negative bacterial pathogens seen in hospital-acquired infections, including bloodstream infection, lower biliary tract infection, urinary tract infection, and pneumonia [1–3]. Carbapenemase-producing *K. pneumoniae* can hydrolyze carbapenems, which is a serious threat to clinical and public health. For the past few years, the global rate of resistance to carbapenem antibiotics among the *Enterobacteriaceae*, especially *Klebsiella pneumoniae*, has increased rapidly. In 2013, the Centers for Disease Control and Prevention (CDC) ranked carbapenem-resistant *Enterobacteriaceae* as the highest level of ‘urgent threat’ in the USA [4]. The first antimicrobial resistance surveillance report released by the World Health Organization (WHO), a survey of 114 countries, showed that carbapenem-resistant *Klebsiella pneumoniae* (CRKP) has appeared all over the world, and that over half of the patients with CRKP infection have received ineffective treatment in some countries [5]. In China, the prevalence of CRKP has increased rapidly, from 2.9% in 2005 to 13.4% in 2014 [6].

The rapid spread of CRKP has remained an urgent global threat, despite the efforts of researchers to control its spread [7,8]. Unfortunately, CRKP is becoming prevalent in China, bringing new challenges to clinical anti-infective treatment [9,10]. Of note, several studies have concluded that CRKP could increase the mortality rate from *K. pneumoniae* to approximately 40–50% [11,12]. High mortality rates and lack of effective treatment puts patients in a perilous situation [13]. A number of recent studies have reported that identifying the risk factors for CRKP infections could improve empiric therapy by facilitating early identification and timely intervention [14–17]. Early identification of risk factors affecting clinical outcome in patients with CRKP is essential and can help clinicians adjust treatment strategies. However, there has been little research on the clinical outcomes of patients with CRKP. Our study therefore evaluated risk factors for poor clinical outcome in patients with CRKP to provide targeted clinical strategies for patients with CRKP.

Material and Methods

Ethics approval

This study was approved by the Institutional Ethics Committee of the First Hospital of Changsha and was conducted in accordance with the Declaration of Helsinki. All enrolled participants provided written informed consent.

Study design and patients

This study was conducted at the First Hospital of Changsha, a tertiary-care teaching hospital with 1700 beds. Data on *K. pneumoniae* strains and clinical data for patients with CRKP were collected from January 2016 to September 2017. Inclusion criteria were: 1) patients diagnosed with CRKP, in compliance with the standards of the “Diagnostic Standards for Nosocomial Infections (Trial)” formulated by the Chinese Medical Association; and 2) patients who tested positive for CRKP in multiple pathogenic cultures. Exclusion criteria were: 1) patients with a positive result for *K. pneumoniae* by culture but who had received anti-infective drug treatment for less than 24 h; and 2) patients with a positive pathogenic culture result but showing no clinical symptoms of CRKP (e.g., asymptomatic bacteriuria).

Data collection and definitions

All data were collected by reviewing and recording medical histories, including: the clinical department(s) where CRKP strains were isolated; the patient’s age, sex, and length of hospital stay; comorbidities such as liver insufficiency, cardiac insufficiency, renal insufficiency, diabetes mellitus, hypertension, malignancy, and hypoproteinemia (plasma albumin <30 g/l); hospitalization (ICU, hospital history, and APACHE II score), mechanical ventilation, and invasive procedures (e.g., arteriovenous catheterization, indwelling gastric tube, indwelling urethral catheter, tracheal intubation, peripherally inserted central venous catheters, or indwelling jejunal tube); and history of antimicrobials taken in the past 90 days, including the use of carbapenems, tigecycline, and compound sulfamethoxazole.

Based on other studies [18,19], our clinical outcomes included the clinical manifestations and auxiliary examination results of patients, such as body temperature, laboratory test results for blood, liver and kidney function, coagulation function, and infection-related biomarkers (procalcitonin and C-reactive protein), as well as microbial culture results, drug susceptibility tests, and imaging results. For any patient with 2 or more positive test results, only the clinical data related to the first positive result were collected. Each patient was assigned to the effective or noneffective group after drug administration for 28 days or death.

The inclusion criteria for the effective group were as follows. 1) Full cure: all clinical signs and symptoms of the patients with CRKP had disappeared. 2) Improvement: clinical signs and symptoms of the patients with CRKP had partially disappeared, or patients were transferred from the intensive care unit (ICU) to the general ward to continue treatment, or the laboratory test results had improved. The inclusion criteria
for the noneffective group were either a worsening of clinical signs and symptoms or death.

**Antibiotic susceptibility test**

The susceptibility of CRKP strains to 18 antibiotics (ampicillin, ampicillin/subbactam, piperacillin/subbactam, cefazolin, ceftazidime pentahydrate, ceftriaxone sodium, cefepime, cefotetan, aztreonam, imipenem, ertapenem, amikacin, gentamicin, tobramycin, levofloxacin, ciprofloxacin, furadantin, and compound sulfamethoxazole) was determined by the Kirby-Bauer disc agar diffusion method. Tigecycline drug sensitivity was determined according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) standards. The rest of the antibiotic results were determined according to the standards recommended by the Clinical and Laboratory Standards Institute (CLSI) in 2017.

The extent of drug resistance was defined as follows. Multidrug resistance (MDR): resistant to 3 or more antibacterial drugs in the antibacterial spectrum. Extensive drug resistance (XDR): resistant to almost all antibacterials except 1–2 antibacterials. Pan-drug resistance (PDR): resistant to all types of antibacterial drugs [20].

**Statistical analysis**

Numbers and percentages were used to represent categorical variables. Continuous variables are expressed as mean±standard deviation (SD) (normally distributed). Chi-square test and t test or Mann-Whitney U test were employed to analyze categorical variables and continuous variables, respectively. Two-sided P<0.05 was considered statistically significant. All statistical analyses were performed with SPSS 17.0 software.

**Results**

**Characteristics of patients**

We identified a total of 97 unique cases of patients with CRKP during the study period. Isolates were obtained from different clinical samples such as: sputum (n=62, 63.92%), bronchoalveolar lavage (n=15, 15.46%), urine (n=11, 11.34%), blood (n=2, 2.06%), bile (n=1, 1.03%), pus (n=1, 1.03%), fluid (n=2, 2.06%), ascites (n=2, 2.06%), and throat swab (n=1, 1.03%). As shown in Figure 1, most of the study patients were from the Departments of Neurology, Respiratory Medicine, Critical Care Medicine, and Neurosurgery. Furthermore, we distributed patients with CRKP into effective and noneffective groups based on the clinical outcome of the patient, with 67 cases (69%) identified as effective and 30 cases (31%) identified as noneffective.

**Antibiotic susceptibility test**

The drug resistance rates for aminoglycosides, β-lactams, carbapenems, quinolones, and sulfa drugs among the 97 CRKP isolates are summarized in Table 2. The drug sensitivity results demonstrated that compound sulfamethoxazole had the lowest resistance rate (21.65%), followed by amikacin (48.45%), gentamicin (59.79%), tobramycin (63.92%), levofloxacin (94.85%), and ciprofloxacin (94.85%). The remaining antibiotics had resistance rates of 100%. The percentages of MDR, XDR, and PDR were 94%, 3%, and 3%, respectively (Table 3). The most frequently isolated MDR strains, from the Neurology Department, are shown in Table 3.
To identify risk factors for poor clinical outcomes in patients with CRKP, we conducted a retrospective study. Clinical variables are listed in Table 1. Firstly, we performed a univariate analysis of these clinical variables. In this univariate analysis, the following factors were negatively correlated with good clinical outcomes: ICU admission (OR: 3.39, p=0.011), exposure to arteriovenous catheterization (OR: 3.06, p=0.017), indwelling gastric tube (OR: 3.19, p=0.013), indwelling urethral catheter (OR: 3.87, p=0.023), tracheal intubation (OR: 2.90, p=0.019), mechanical ventilation (OR: 3.44, p=0.017), hypoproteinemia (OR: 2.47, p=0.049), and exposure to carbapenems (OR: 3.25, p=0.012).

The multivariate analyses of the effective and noneffective groups were carried out with the adjustment of the logistic regression model for 8 variables, wherein the risk factors dramatically differed from the univariate analyses. As shown in Table 5, hypoproteinemia (OR: 2.83, p=0.042), presence of an indwelling gastric tube (OR: 4.54, p=0.005), and exposure to carbapenems (OR: 2.77, p=0.045) were found to be independent risk factors for poor clinical outcomes in patients with CRKP.

### Discussion

Currently, carbapenem-resistant Enterobacteriaceae, especially CRKP, are an urgent public health challenge worldwide [21–24].
Antibiotics, particularly carbapenem and tigecycline antibiotics, have been recommended for the treatment of CRKP, and have had a degree of therapeutic effect. However, the treatment process for CRKP is still a challenge. On the one hand, CRKP has a certain resistance to existing antibacterial drugs, which leads to a high mortality rate in patients with CRKP. On the other hand, CRKP strains are either MDR, XDR, or PDR, resulting in limited treatment options available for patients with CRKP [25]. Identification of the risk factors for poor clinical outcome in patients can provide guidance for the treatment of CRKP. In this study, our findings demonstrated that exposure to carbapenems, hypoproteinemia, and presence of an indwelling gastric tube were negatively correlated with good clinical outcome in patients with CRKP.

Table 2. Drug sensitivity of CRKP strains.

| Antimicrobial agent            | Number of resistant strains | Drug resistance rate (%) |
|--------------------------------|-----------------------------|--------------------------|
| Ampicillin                     | 97                          | 100.00                   |
| Ampicillin/sulbactam           | 97                          | 100.00                   |
| Piperacillin/sulbactam         | 97                          | 100.00                   |
| Cefazolin                      | 97                          | 100.00                   |
| Ceftazidime pentahydrate       | 97                          | 100.00                   |
| Ceftriaxone sodium             | 97                          | 100.00                   |
| Cefepime                       | 97                          | 100.00                   |
| Cefotetan                      | 97                          | 100.00                   |
| Aztreonam                      | 97                          | 100.00                   |
| Imipenem                       | 97                          | 100.00                   |
| Amikacin                       | 47                          | 48.45                    |
| Gentamicin                     | 58                          | 59.79                    |
| Tobramycin                     | 62                          | 63.92                    |
| Levofloxacin tablets           | 92                          | 94.85                    |
| Ciprofloxacin                  | 92                          | 94.85                    |
| Furadantin                     | 97                          | 100.00                   |
| Compound sulfamethoxazole      | 21                          | 21.65                    |

Table 3. Departments from which CRKP strains with MDR, XDR, and PDR were isolated.

| Clinical department          | MDR | XDR | PDR |
|------------------------------|-----|-----|-----|
| Neurology                    | 27  | 1   |     |
| Respiratory Medicine         | 23  | 1   |     |
| Department of Critical Care Medicine | 13  |     |     |
| Neurosurgery                 | 11  | 1   | 1   |
| Department of Rehabilitation Medicine | 5   |     |     |
| Endocrinology                | 2   | 2   |     |
| Cardiology                   | 1   | 2   |     |
| AIDS                         | 3   |     |     |
| Department of General Surgery | 4   |     |     |
| Total                        | 91  | 3 (3%) | 3 (3%) |

MDR – multidrug resistance; XDR – extensive drug resistance; PDR – pan-drug resistance.
In the present study, we found that clinical outcome was associated with various factors, including ICU stay, exposure to arteriovenous catheterization, indwelling gastric tube, indwelling urethral catheter, tracheal intubation, mechanical ventilation, hypoproteinemia, and exposure to carbapenems. Among these, presence of an indwelling gastric tube, hypoproteinemia and exposure to carbapenems were independent risk factors for poor clinical outcome in patients with CRKP in multivariate analyses. These findings indicated that clinicians should attach great importance to appropriate antibiotic use and aseptic invasive procedures.

In our study, we found that CRKP had a low resistance rate to compound sulfamethoxazole (21.65%), which was similar to the findings in a previous report [26].

| Variable                                | Effective (n=67) | Noneffective (n=30) | Univariate analysis |
|-----------------------------------------|-----------------|---------------------|---------------------|
| Age                                     | 75 (61–84)      | 78 (60–83)          | OR (95% CI) P        |
| Male                                    | 16              | 19                  | 0.379               |
| APACHE2 score                           | 11 (8–14)       | 15 (10–20)          | 0.094               |
| Length of hospitalization (days)        | 29 (15–66)      | 32 (18–57)          | 0.329               |
| ICU                                     | 30 (45.78)      | 22 (73.33)          | 3.39 (1.323–8.697) 0.011 |
| Surgical                                | 24 (35.82)      | 16 (53.33)          | 0.108               |
| History of antimicrobials in the past 90 days | 39 (58.21) | 19 (63.33)          | 0.635               |
| Hospital history in the past 90 days    | 29 (43.28)      | 17 (56.66)          | 0.224               |
| Multisite infection                     | 34 (50.74)      | 13 (43.33)          | 0.5                 |
| Mixed infection                         | 45 (67.16)      | 21 (70.00)          | 0.782               |
| Hypertension                            | 45 (67.16)      | 16 (53.33)          | 0.195               |
| Diabetes mellitus                       | 14 (20.89)      | 6 (20.00)           | 0.920               |
| Hypohepatia                             | 19 (28.35)      | 12 (40.00)          | 0.258               |
| Cardiac insufficiency                   | 37 (55.22)      | 15 (50.00)          | 0.634               |
| Renal insufficiency                     | 11 (16.41)      | 9 (30.00)           | 0.131               |
| Malignancy                              | 1 (1.49)        | 2 (6.67)            | 0.213               |
| Hypoproteinemia                         | 30 (44.77)      | 20 (66.67)          | 2.47 (1.004–6.061) 0.049 |
| Mechanical ventilation                  | 36 (53.73)      | 24 (80.00)          | 3.44 (1.248–9.508) 0.017 |
| Arteriovenous catheterization           | 29 (43.28)      | 21 (70.00)          | 3.06 (1.221–7.659) 0.017 |
| Indwelling gastric tube                 | 16 (23.88)      | 15 (50.00)          | 3.19 (1.283–7.917) 0.013 |
| Indwelling urethral catheter            | 42 (62.68)      | 26 (86.67)          | 3.87 (1.209–12.383) 0.023 |
| Tracheal intubation                     | 25 (37.31)      | 19 (63.33)          | 2.90 (1.189–7.084) 0.019 |
| Peripherally inserted central venous catheters | 17 (25.37) | 10 (33.33)          | 0.42                |
| Indwelling jejunal tube                 | 14 (5.97)       | 5 (16.6)            | 0.165               |
| Exposure to carbapenems                 | 28 (41.79)      | 21 (70.00)          | 3.25 (1.296–8.151) 0.012 |
| Exposure to tigecycline                 | 4 (5.97)        | 4 (13.33)           | 0.235               |
| Exposure to compound sulfamethoxazole   | 3 (4.47)        | 1 (3.33)            | 0.794               |

CRKP – carbapenem-resistant *Klebsiella pneumoniae*; OR – odds ratio; CI – confidence interval.
The multivariate analyses showed that exposure to carbapenems, hypoproteinemia, and an indwelling gastric tube were independent risk factors for poor clinical outcome in patients with CRKP. Emerging evidence has indicated that carbapenem administration is an independent risk factor for CRKP infection, as well as for *Pseudomonas aeruginosa* and *Acinetobacter baumannii* infection/colonization [16,34–36]. Our study demonstrated that patients with CRKP who used carbapenems had worse clinical outcomes. This phenomenon was probably caused by the very high MIC of carbapenems (>16 µg/ml) against CRKP. This result supports the importance of choosing the right antibacterials in light of drug sensitivity results and promptly implementing antibiotic de-escalation to avoid similar incidents [37]. Moreover, medical invasive devices, such as an indwelling gastric tube, greatly increase the chance of bacterial infection [38], which to some extent increases the difficulty of treatment and negatively affects the clinical outcome of patients with CRKP. Of note, our results showed that the presence of an indwelling gastric tube increased the risk for poor clinical outcome by 4.53-fold; therefore, hospitals should strictly implement disinfection and isolation measures and strengthen monitoring of the hospital environment. In addition, hypoproteinemia was also an adverse independent risk factor for clinical outcome in patients with CRKP. Serum albumin level and plasma colloid osmotic pressure were decreased in patients with hypoproteinemia, affecting the function of various organs and tissues in the body [39]. This would serve to significantly reduce the body's resistance and increase the incidence of poor clinical outcomes in patients with CRKP. For such patients, among the most beneficial measures is improvement of nutritional status to increase albumin levels. Overall, nosocomial transmission and the selection of appropriate antimicrobial therapy, as well as patient nutrition, can play critical roles in the clinical outcome of CRKP-infected patients.

## Conclusions

We found that the presence of an indwelling gastric tube, hypoproteinemia, and exposure to carbapenems were risk factors for poor clinical outcome in patients with CRKP. These findings...

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**Table 5. Multivariate analysis of risk factors for poor clinical outcome in patients with CRKP.**

| Risk factor                          | OR value | 95% CI      | p-Value |
|--------------------------------------|----------|-------------|---------|
| Age                                  | 2.56     | 0.901–7.246 | 0.078   |
| Male                                 | 1.38     | 0.462–4.096 | 0.567   |
| ICU                                  | 1.14     | 0.331–3.887 | 0.840   |
| Hypoproteinemia                       | 2.83     | 1.040–7.704 | 0.042   |
| Mechanical ventilation                | 1.96     | 0.622–6.165 | 0.25    |
| Arteriovenous catheterization        | 2.12     | 0.726–6.196 | 0.169   |
| Indwelling gastric tube               | 4.54     | 1.567–13.12 | 0.005   |
| Indwelling urethral catheter         | 1.67     | 0.42–6.652  | 0.465   |
| Tracheal intubation                   | 0.88     | 0.230–3.368 | 0.851   |
| Exposure to carbapenems              | 2.77     | 1.022–7.495 | 0.045   |

CRKP – carbapenem-resistant *Klebsiella pneumoniae*; OR – odds ratio; CI – confidence interval.
may provide a theoretical foundation for the adjustment of clinical therapeutic strategies. Clinicians should pay close attention to the condition of CRKP-infected patients and ensure rational use of carbapenems. In addition, strengthened monitoring of the hospital environment could improve the prognoses of patients with CRKP.

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