The epidemiology, risk factors and outcomes of Carbapenem-resistant *Klebsiella pneumoniae* infections in the intensive care unit from 2012 to 2018

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Abstract

Background: Carbapenem-resistant Klebsiella pneumoniae (CRKP) is an increasing globally threat for human health, but the trends and clinical characteristics of CRKP infections in the intensive care unit (ICU) remain uninvestigated.

Methods: A retrospective study was conducted among ICU patients infected with KP isolates from January 2012 to December 2018. Carbapenem resistant to Klebsiella pneumoniae was defined according to Clinical and Laboratory Standards Institute (CLSI) criteria. The incidence and changing trend of CRKP were determined. CRKP patient sources, specimen types, infection sources and outcomes were investigated.

Results: There were 256 (40.13%) patients with CRKP and 382 (59.87%) patients with CSKP. The incidence of CRKP increased from 2012 (11.11%) to 2017 (63.48%) and decreased in 2018 (51.52%). The proportion of isolates not susceptible to three carbapenems increased from 0 to 98.04%. The rates of CRKP isolated from blood, wound, urine and pleural fluid were higher than that of CSKP. CRKP infections were mainly ICU acquired, rather than input acquired.

Conclusion: The incidence of CRKP was high in ICU, but showed a downward trend. Implementation of different infection control measures to different sources of patients, specimen types, and KP infections are necessary. Surveillance data will be needed for ICU patients to decrease the incidence and mortality of CRKP.

Introduction

Klebsiella pneumoniae (KP) is a gram-negative bacterial pathogen commonly causing nosocomial infection. With the widespread and unreasonable use of antibiotic, especially carbapenems, the growing prevalence of carbapenem-resistant Klebsiella pneumoniae (CRKP) has been reported worldwide, and it has become endemic in several countries[1-3], including China. China Antimicrobial Surveillance Network (CHINET) reported that the resistance rates of Klebsiella pneumoniae to imipenem have progressively rose from 3.0% in 2005 to 25% in 2018, and meropenem was 2.9% in 2005 and 26.3% in 2018[4]. Moreover, the differences among regions, hospital and wards are great[5].
Carbapenem resistance imposes difficulties in selecting the appropriate antimicrobial therapy. Especially, some cases of CRKP infection might be limited to therapeutic options. Accordingly, CRKP might evolve to cause considerable clinical problems due to their growing multidrug resistance profile, including the risks of high mortality, prolonged hospital stay, and heavy economic burden\cite{6-8}.

Intensive care patients are a group that especially susceptible to the spread of various pathogens, including CRKP. It may be partially due to the unique origin of intensive care patients, who are transferred from general wards or other hospitals, which likely facilitate the spread of pathogens. Since CRKP strains have been reported from sporadic cases in the first few years, and then outbreaks have been concentrated in the area where infection is endemic\cite{9, 10}, there is an actual increased risk for CRKP infection transmission from colonized or infected patients\cite{11}.

Several studies have reported the epidemiology, risk factors and predictors of mortality for CRKP bloodstream infections in the intensive care unit (ICU)\cite{12, 13} or in the hospital\cite{14-16}. As blood is not the main specimen type of KP, bloodstream infections does not respond well the general characteristics of CRKP infections in the ICU. Limiting progress in infection control is the absence of large-scale data on sources of CRKP patients and CRKP infections. In addition, information on prevalence and changing trends of ICU CRKP infections are scarce. To address these deficiencies, we undertook the study.

Therefore, we aimed to comprehensively investigated epidemiology and clinical characteristics in CRKP infections in the ICU from 2012 to 2018, including patient sources, specimen types and infection sources. We also determined risk factors and outcomes for CRKP infections.

Methods:
This was a retrospective, cohort study in intensive care unit (ICU) of Xiangya hospital. The hospital is a 3600-bed teaching hospital in Changsha China. Subjects were patients isolating Klebsiella pneumoniae during hospitalization in the ICU and discharged between January 2012 and December 2018. Only the first isolate was included in the study, and duplicate isolates of the same patient were not considered. Patients were excluded if they died within 48 h, or KP isolates was only isolated from
stool. Permission for collecting the information in the medical records of the patients and the Klebsiella pneumoniae isolates for research purposes was approved by the Ethics Committee of Xiangya Hospital Central South University (2018091076).

The following information were collected from electronic medical records: demographics (medical record number, admission and discharge dates, age, sex, bed occupied), comorbidity (hepatitis/cirrhosis, hypertension, transient ischemic attack, coronary artery disease, diabetes), previous admission (the ward/hospital that the patient was admitted before this hospitalization in ICU), recent events (prior surgery, previous ICU stay), invasive procedures and antibiotics used within 90 days, microbiological information (specimen type and monitoring time, the antibiotic susceptibility results), outcomes.

All Klebsiella pneumoniae isolates were tested for their susceptibility to carbapenems (ertapenem, imipenem, or meropenem) and other antimicrobials by automated microbroth dilution testing systems[17]. Their MIC were interpreted according to the Clinical and Laboratory Standards Institute (CLSI) breakpoints. Carbapenem susceptibility was identified when MIC was ≤ 1 mg/L for imipenem, meropenem, and ≤ 0.5 mg/L for ertapenem. Klebsiella pneumoniae were classified using the most-current standard definitions: CRKP and CSKP, and Kp isolates for which tested intermediate or resistant to one or more carbapenems (ertapenem, imipenem, or meropenem) were considered as carbapenem-resistant[18]. So patients were stratified into 2 groups (CRKP and CSKP) according to their antimicrobial susceptibility testing. Clinical responses were defined according to the prognosis of patients in ICU. If the first isolate of KP was obtained from inpatients within the first 2 days of his/her hospitalization in ICU, it was considered as community/input acquired according to their previous admission; while if it was obtained from inpatients after 2 calendar days of ICU hospitalization and had no previous culture with KP within 30d, it was defined as ICU acquired. Improved and cured were defined as the complete resolution of fever, clinical symptoms and other relevant investigations of patients in ICU, failure was defined as a deterioration in infection and other clinical symptoms. Mortality was defined as death occurred during ICU admission.

Continuous variables were compared by a 2-sided t-test, categorical variables were analyzed using
the Pearson’s Chi-square ($\chi^2$). Univariate logistic regression was conducted to identify the potential factors, and variables with a P value $\leq 0.05$ were included in multivariate logistic regression. The multivariate logistic regression used the backward method. A P value $\leq 0.05$ was considered statistically significant. All analyses were carried out by SPSS software (version 22.0, SPSS Inc., IL, USA).

Results:

**Epidemiology**

During the study period, a total of 638 patients were infected by *Klebsiella pneumoniae*. The trend of CRKP incidence from 2012 to 2018 was shown in Figure 1. In 2012 and 2013, CRKP incidence were low (11.11% and 13.04%), but after that, there was a rapid increase in the incidence of CRKP to peak in 2017 (63.48%) and then the incidence decreased in 2018 (51.52%). CRKP incidence was higher than CSKP from 2016 to 2018 (51.09%, 63.48% and 51.52%).

All *Klebsiella pneumoniae* isolates were tested against three carbapenems (imipenem, meropenem, ertapenem). During the study period of 2012-2018, the percentage of isolates tested not susceptible to one carbapenem decreased from 66.67% to 1.96%. The proportion of isolates not susceptible to two carbapenems increased from 33.33% to 66.67% in the preceding two years, and then decreased from 66.67% to 0. The proportion of isolates not susceptible to all three carbapenems increased from 0 to 98.04%.

In our study, KP isolates were obtained from various specimen types. Figure 2A indicated the distribution of specimen types from 2012 to 2018. For CRKP group, the specimen types gradually diversified, rising from 3 to 8 types. The main isolates were always from respiratory specimen, but the percentage gradually decreased. For CSKP patients, the specimen types gradually decreased with the decreasing of sample size, ranging from 8 types to 5 types. The comparison of specimen types between CRKP and CSKP were shown in Figure 2B. The rates of CRKP in blood, wound, urine and pleural fluid were higher than of CSKP.

For patients infected with KP in our ICU, the incidences of CRKP and CSKP in different sources of patients were displayed in Figure 3. Most patients from community were infected with CSKP (ranging
from 66.67% to 100%) (Figure 3A). For patients from external hospitals, the incidence of CRKP increased to more than 65% gradually (Figure 3B). For patients from normal wards in our hospital, the incidence of CRKP was also on the rise, but still less than that of CSKP in 2018 (Figure 3C).

The changing trends for sources of CRKP and CSKP infections were showed in Figure 4. For CRKP group, CRKP infections were mainly ICU acquired (>50%), isolates from external hospitals and normal wards in our hospital went up and down alternately, and there were no CRKP infections acquired from community (Figure 4A). Sources of CSKP infections were presented in Figure 4B. ICU acquired was the main source in most years (2013, 2014, and 2016-2018), followed by normal wards of our hospital. External hospitals input was on the rise, and community input gradually dropped to 0.

**Comparison of CRKP and CSKP patients**

A cohort of 638 patients with *Klebsiella pneumoniae* isolates were included during the study period. There were 256 (40.13%) patients with CRKP, and 382 (59.87%) patients with CSKP. A comparison of baseline characteristics between CRKP and CSKP patients was shown in Table 1. Previous admission of CRKP and CSKP patients varied significantly (*P* = 0.012). Significant differences were found for previous ICU stay, and the use of tracheostomy tube, surgical drainage, indwelled central venous catheter, and gastric tube. The previous use of carbapenem, tigecycline, glycopeptides, β-lactams and β-lactamase inhibitor, and fluoroquinolones were significantly much more in CRKP group. At the multivariate analysis, previous admission (*P* = 0.044), previous ICU stay (*P* = 0.005), the use of gastric tube (*P* = 0.011), and the use of carbapenems (*P* = 0.000), tigecycline (*P* = 0.024), β-lactams and β-lactamase inhibitor (*P* = 0.000) within 90 days were risk factors significantly associated with CRKP.

In bloodstream infections, patients with CRKP were significantly more than patients with CSKP (*P* = 0.000). CSKP patients were more likelihood to have shorter length of ICU stay (*P* = 0.000) and higher rates of improved and cured (*P* = 0.000) (Table 2).

**Risk factors associated with failure and mortality of CRKP patients**

Univariate and multivariate logistic regression were applied to analyze risk factors for failure and mortality of CRKP patients (Table 3). In the univariate analysis, risk factors associated with failure and mortality of CRKP patients were age, prior surgery, respiratory infection, blood infection, intra-
abdominal infection, tracheostomy tube, and the previous administration of carbapenems and antifungal agents. Multivariate analysis revealed age ($P=0.009$), blood infection ($P=0.000$), intra-abdominal infection ($P=0.048$), tracheostomy tube ($P=0.005$), and the previous administration of antifungal agents ($P=0.031$) as independent risk factors.

**Discussion**

In this study, we reported the rates and changing trends of CRKP infections, compared patient sources, specimen types and infection sources with CSKP and CRKP, and investigated the risk factors and outcomes for CRKP infections. Since reported studies have explored trends, characteristics and risk factors of CRKP which were isolated from blood culture in the ICU or the whole hospital, it was worth noting that we conducted the study among patients with all types of KP infections in the ICU. And changing trends of patient sources, specimen types and infection sources for critical care patients with KP infections were not reported before. So many findings in our study were reported firstly, and they provided a basis for the control of KP infections in ICU.

Few study explored changing trends of resistance rates of KP to carbapenems in the ICU, we found a study from an intensive care unit of Southern Italy that carbapenem resistant KP rates rose from 0% in 2008 to 59.2% in 2013[19], and multicenter data from CHINET described that resistance change of KP to imipenem and meropenem increased from 3.0% in 2005 to 26.3% in 2018[4]. Considering the trends of China and abroad, we predicted that the prevalence of CRKP also rose in our ICU. Here we found that an impressive increase of CRKP numbers and rates from 2012 to 2017. It showed that carbapenem resistance rate increased from 11.11% in 2012 to 63.48% in 2017. Notably, the resistance rate decreased from 2018 (51.52%), and our unpublished data also revealed that the incidence of CRKP decreased further in 2019. It may be related to the implementation of antimicrobial stewardship (AMS) in our hospital.

Uwe Koppe et al.[20] reported the number of KP isolates tested non-susceptible to 3 carbapenems (imipenem, meropenem, and ertapenem). In our study, we explored the changing trends of KP isolates resistance to 1, 2, and 3 carbapenems. We discovered that the rates of resistance to 1 and 2 carbapenems dropped significantly, and the rate of resistance to 3 carbapenems continuously
increased from 0 to 98.04%. Obviously, it posed a much more difficult challenge for the treatment of CRKP infections.

Specimen types may associate with the rates of CRKP. Among KP patients with bloodstream infection, wound infection, urinary infection, and pleural infection, the rates of CRKP were significantly higher than that of CSKP. This suggests that, the treatment regimen for CRKP infection may be necessary when KP is suspected to be the pathogen of these infections. Although bloodstream infection with CRKP were most reported, as the amount of respiratory specimen was more than the sum of other specimen types, it suggests that pulmonary infection with KP should not be ignored.

The incidences of CRKP in patients from different sources were not reported before. We found that the incidence of CRKP in patients from external hospitals had increased to 65%, which was more than the incidence of CSKP in the last 3 years. It indicated that when patients from external hospitals infected with KP, CRKP would be more likely. So effective antibiotic treatment that keeping a low rate of carbapenem resistance, should be implemented.

In the study, we found that CRKP infection was mainly ICU acquired. It demonstrated that ICU admission was an important risk factor for acquiring CRKP. CSKP infection was mainly ICU acquired and normal wards in our hospital acquired. Although these findings were firstly reported and they need to be verified, it helps us tailor our surveillance actions to our circumstance, and an intensification of ICU-acquired CRKP infection control measure may be considered desirable.

Several risk factors associated with CRKP infection have been identified in previous studies. According to a CRKP BSI study, independent risk factors were ICU acquired infection, skin and tissue[14]. For a study of patients with CRKP BSI in the ICU, indwelling central venous catheter was the only independent risk factor for CRKP bacteremia[12]. Another study of a teaching hospital on CRKP infections only found that use of sputum suction was an independent risk factor[21]. In our study, we observed that previous ICU stay, gastric tube, previous use of carbapenems and β-lactams and β-lactamase inhibitor combination were risk factors for ICU patients infected with CRKP. As the scope and infection types were different among studies, the risk factors are not completely consistent, they all provided a basis for the control of CRKP in their own ICU or hospital.
In addition, we investigated the outcomes of patients with CRKP infections. Compared with CSKP, patients with CRKP had longer length of ICU stay, a higher rate of bloodstream infection, and a lower rate of improved and cured. Since the mortality was based on the number of patients who died in our ICU, we did not measure the mortality of patients transferred out of ICU who abandoned treatment due to deterioration. Therefore, the mortality in this study was lower than the actual value. We found the crude 30-day mortality in patients with CRKP infections was 7.81%, and the rate increased to 14% in patients with CRKP bloodstream infections which was also lower to studies in both China and other countries[9, 22]. So we analyzed the risk factors associated with failure and mortality of patients with CRKP infections. The result displayed that ages, bloodstream infection, and the previous use of antifungal agents were risk factors. Age, bloodstream infection were also confirmed in other studies[23, 24].

Our study has limitations. Firstly, as our hospital is a tertiary hospital that admit different kinds of critical ill patients, changing trends of patient sources and other epidemiology data maybe not suitable for specialized hospitals. Secondly, as a retrospective analysis, clinical data were obtained from electronic medical records, missing information may have potential effects on results. Nevertheless, the sample size of our study was not small and it would not hamper the statistical power of our analysis.

Conclusions
The incidence of CRKP was high in ICU, but showed a downward trend. Implementation of different infection control measures to different sources of patients, specimen types, and KP infections are necessary. It indicated that specialized surveillance data will be needed for ICU CRKP patients with different sources and specimen types to decrease the incidence and mortality of CRKP.

Declarations

Acknowledgments

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Authors’ contributions

Ping Wang and Tao Yin contributed to the concept and design of the study. Xiaocui Zou managed the
data collection. Ping Wang and Boting Zhou analysed the data. Ping Wang wrote the initial draft. All authors read and approved the final draft.

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**Availability of data and materials**

The data supporting the conclusions of the article are available from the corresponding author to the qualified researcher on reasonable request.

**Ethics approval and consent to participate**

Permission for collecting the information in the medical records of the patients and the *Klebsiella pneumoniae* isolates for research purposes was approved by the Ethics Committee of Xiangya Hospital Central South University (2018091076).

**Consent for publication**

Not applicable.

**Conflict of interest**

The authors declare no conflict of interest.

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Tables

Table 1. Clinical characteristics and risk factors for CRKP

| General characteristics | CRKP(n=256) | CSKP(n=382) | Univariate analysis | Multivariate analysis |
|-------------------------|------------|------------|---------------------|----------------------|
|                         |            |            | OR(95%CI)            | P                    | OR(95%CI) | P | P 5%CI |
| Male sex                | 204(79.69) | 287(75.13) | 0.77(0.53)           | 0.180                | 0.180     |
|                        | n   | n   | p-value |
|------------------------|-----|-----|---------|
| **age (years)**        |     |     |         |
| 54.02±15.70            | 1.13| 1.01| 0.099   |
| 56.16±16.31            |     |     |         |
| **previous admission** |     |     |         |
| no previous            | 5(1.95) | 30(7.85) | 1.41(1.08) | 0.012 | 1.36(0.044 |
| admission              |     |     |         |
| outside hospital       | 107(41.80) | 72(18.85) |     |     |     |
| same hospital          | 144(56.25) | 280(73.30) |     |     |     |
| **recent events**      |     |     |         |
| prior surgery          | 129(50.39) | 195(51.05) | 1.03(0.75) | 0.871 |     |
| previous ICU stay      | 63(24.61) | 34(8.90) | 0.30(0.19) | 0.000 | 0.49(0.30|
|                       |     |     |         |
| **invasive procedures**|     |     |         |
| Tracheostomy tube      | 115(44.92) | 122(31.94) | 0.58(0.42) | 0.001 | 0.73(0.50|
|                       |     |     |         |
| Surgical drainage      | 148(57.81) | 189(49.48) | 0.72(0.52) | 0.039 |     |
|                       |     |     |         |
| Indwelled central      | 134(52.34) | 161(42.15) | 0.66(0.48) | 0.011 |     |
| venous catheter        |     |     |         |
| gastric tube           | 180(70.31) | 202(52.88) | 0.47(0.34) | 0.000 | 0.62(0.42|
|                       |     |     |         |
| Urinary catheter       | 200(78.13) | 273(71.47) | 0.70(0.48) | 0.060 |     |
|                       |     |     |         |
| **comorbidities**      |     |     |         |
| Hypertension           | 87(33.98) | 108(28.27) | 0.77(0.54) | 0.125 |     |
| Diabetes mellitus      | 32(12.50) | 42(10.99) | 0.87(0.53) | 0.561 |     |
| coronary               | 25(9.77) | 47(12.30) | 1.30(0.78) | 0.322 |     |
| hepatitis/cirrhosis    | 17(6.64) | 19(4.97) | 0.74(0.38) | 0.373 |     |
| Condition                      | CRKP | CSDP | Odds Ratio (95% CI) | p-value |
|-------------------------------|------|------|--------------------|---------|
| Chronic renal insufficiency   | 7(2.73) | 8(2.09) | 0.76(0.27-2.13) | 0.602   |
| Malignancy                    | 13(5.08) | 25(6.54) | 1.31(0.66-2.61) | 0.444   |
| Cerebrovascular disease       | 16(6.25) | 15(3.93) | 0.61(0.30-1.26) | 0.185   |
| Antibiotics used within 90 days |     |      |                    |         |
| Carbapenems                   | 158(61.72) | 140(36.65) | 0.36(0.26-0.50) | 0.000   |
| Tigecycline                   | 49(19.14) | 21(5.50) | 0.25(0.14-0.42) | 0.000   |
| Glycopeptides                 | 68(26.56) | 75(19.63) | 0.68(0.46-0.98) | 0.040   |
| β-lactams and β-lactamase inhibitor combinations | 188(73.44) | 199(52.09) | 0.39(0.28-0.55) | 0.000   |
| 3rd or 4th-cepharosporines   | 95(37.11) | 134(35.08) | 0.92(0.66-1.27) | 0.600   |
| Fluoroquinolones              | 66(25.78) | 53(13.87) | 0.46(0.31-0.69) | 0.000   |
| Aminoglycosides               | 16(6.25) | 14(3.66) | 0.57(0.27-1.19) | 0.135   |
| Antifungal drugs              | 22(8.59) | 21(5.50) | 0.74(0.46-1.19) | 0.216   |

Table 2. Comparison of infection types and outcomes between CRKP and CSDKP group
| Variables                        | CRKP(n=256)          | CSKP(n=382)          | $\chi^2/t$ | $P$  |
|---------------------------------|----------------------|----------------------|------------|------|
| type of infection               |                      |                      |            |      |
| respiratory infection           | 217(84.77)           | 301(78.80)           | 3.58       | 0.059|
| bloodstream infection           | 71(27.73)            | 48(12.57)            | 23.24      | 0.000|
| intra-abdominal infection       | 42(16.41)            | 48(12.57)            | 1.87       | 0.172|
| surgical site infection         | 9(3.52)              | 18(4.71)             | 0.54       | 0.462|
| intracranial infection          | 13(5.08)             | 20(5.24)             | 0.01       | 0.930|
| urinary tract infection         | 16(6.25)             | 21(5.50)             | 0.16       | 0.690|
| outcomes                        |                      |                      |            |      |
| 30day mortality                 | 20(7.81)             | 21(5.24)             | 1.64       | 0.200|
| length of ICU stay              | 22.86±20.26          | 16.16±15.07          | 4.76       | 0.000|
| improved and cured              | 156(60.94)           | 313(81.94)           | 35.12      | 0.000|
| failure                         | 74(28.91)            | 48(12.57)            |            |      |
| mortality                       | 26(10.16)            | 21(5.50)             |            |      |

**Table 3. Regression analysis of factors associated with failure and mortality of patients with CRKP**

| Variables | Univariate analysis | Multivariate anal |
|-----------|---------------------|-------------------|
|           | OR(95%CI)           | $P$               | OR(95%CI)   |
| age(years)| 1.02(1.00-1.04)     | 0.035             | 1.03(1.01-1.04) |
|                                | Hazard Ratio (95% CI) | p-value |
|--------------------------------|-----------------------|---------|
| male sex                       | 0.63 (0.34-1.16)      | 0.137   |
| previous admission             | 1.04 (0.65-1.66)      | 0.867   |
| Source of pathogens            | 1.01 (0.94-1.08)      | 0.854   |
| number of pathogens detected   | 1.08 (0.95-1.22)      | 0.237   |
| number of infected sites       | 1.21 (0.98-1.48)      | 0.072   |
| number of comorbidities        | 1.03 (0.82-1.30)      | 0.804   |
| number of antibiotics used within 90 days | 1.03 (0.89-1.20)      | 0.692   |
| number of invasive procedures  | 0.87 (0.74-1.02)      | 0.082   |
| prior surgery                  | 0.57 (0.35-0.95)      | 0.032   |
| previous ICU stay              | 0.95 (0.53-1.70)      | 0.856   |
| type of infection              |                       |         |
| respiratory infection          | 0.43 (0.22-0.87)      | 0.018   |
| bloodstream infection          | 1.94 (1.46-2.58)      | 0.000   |
| intra-abdominal infection      | 1.29 (1.03-1.61)      | 0.025   |
| surgical site infection        | 0.66 (0.39-1.11)      | 0.116   |
| intracranial infection         | 1.05 (0.87-1.27)      | 0.592   |
| urinary tract infection        | 0.91 (0.77-1.07)      | 0.242   |
| invasive procedures            |                       |         |
| Tracheostomy tube              | 0.36 (0.21-0.61)      | 0.000   |
| Surgical drainage              | 0.72 (0.44-1.20)      | 0.213   |
| Indwelled central venous catheter | 0.98 (0.59-1.62)    | 0.930   |
| gastric tube                   | 0.98 (0.56-1.69)      | 0.930   |
| Urinary catheter               | 0.82 (0.45-1.49)      | 0.511   |
| Antibiotics used within 90 days |                       |         |
| Carbapenems                    | 2.44 (1.41-4.21)      | 0.001   |
| Tigecycline                    | 1.10 (0.58-2.07)      | 0.780   |
| Glycopeptides                  | 0.56 (0.31-1.02)      | 0.059   |
| Category                          | Ratio     | p-value | Figure 1 |
|----------------------------------|-----------|---------|----------|
| Polymyxin B                      | 0.77(0.19-3.17) | 0.721    |          |
| Aminoglycosides                  | 0.34(0.094-1.23) | 0.099    |          |
| β-lactams and β-lactamase inhibitor | 0.64(0.36-1.12) | 0.116    |          |
| Fluoroquinolones                 | 1.31(0.74-2.32) | 0.347    |          |
| Antifungal agents                | 2.45(1.12-5.36) | 0.024    | 2.57(1.09-6.05) |

**Figures**

![Figure 1](image)

**Figure 1**

Incidence of CRKP over the study period (2012-2018)
Figure 2
The distribution of the specimen types of Klebsiella pneumoniae. A. Annual distribution; B. Distribution of various types.

Figure 3
Changing trends of the sources of ICU patients. A. Community; B. External hospitals; C. Normal wards in our hospital.

Figure 4
Changing trends of the sources of CRKP infections. A. CRKP group; B. CSKP group.
