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| Complete List of Authors | wang, ping; Central South University, department of pharmacy, Xiangya Hospital
Zou, Xiaocui; Central South University, Department of Pharmacy, Xiangya Hospital
zhou, boting; Xiangya Hospital Central South University, Department of Pharmacy, Xiangya Hospital
Yin, Tao; Central South University, Department of Pharmacy; Central South University |
| Keywords         | Epidemiology < TROPICAL MEDICINE, Adult intensive & critical care < INTENSIVE & CRITICAL CARE, Infection control < INFECTIOUS DISEASES, MICROBIOLOGY |
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Clinical characteristics of Carbapenem-resistant *Klebsiella pneumoniae* infection/colonization in the intensive care unit: epidemiology and sources

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Abstract:

Objectives Although risk factors for carbapenem-resistant *Klebsiella pneumoniae* (CRKP) infection/colonization in the hospital have been reported. Clinical characteristics of CRKP infection/colonization in the intensive care unit (ICU) remain scarcely investigated. We aimed to explore epidemiology and extent of *Klebsiella pneumoniae* (KP) resistance to carbapenems, sources of CRKP-positive patients and CRKP isolates, and risk factors for the development of CRKP.

Design Retrospective cohort study.

Data source Clinical data were obtained from electronic medical records.

Participants Patients isolated with KP in the ICU from January, 2012 to December, 2020.

Main outcome measures The incidence and changing trend of CRKP; the extent of KP isolates resistance to carbapenems; sources of CRKP-positive patients and CRKP isolates; the risk factors for the development of CRKP.

Results The rate of CRKP in KP isolates generally raised from 11.11% (2012) to 48.92% (2020). CRKP isolates were detected at one site in 266 patients (70.56%). The proportion of CRKP isolates not susceptible to three carbapenems increased from 0% in 2012 to 88.24% in 2020. The proportion of CRKP patients from general wards in our hospital and other hospitals gradually converged in 2020 (47.06% vs 52.94%). CRKP isolates were mainly ICU acquired (59%). Younger age (*P*= 0.024), previous admission (*P*= 0.016), previous ICU stay (*P*= 0.007), prior use of surgical drainage (*P*= 0.010) and gastric tube (*P*= 0.001), and use of carbapenems (*P*= 0.000), tigecycline (*P*= 0.006), β-lactams and β-lactamase inhibitor (*P*= 0.000), fluoroquinolones (*P*= 0.036), and antifungal drugs (*P*= 0.001) within the prior 3 months were independent risk factors for CRKP infection/colonization.

Conclusions The rate of KP resistance to carbapenems generally raised, and the extent of KP resistance to carbapenems sharply increased. The proportion of CRKP-positive patients from general wards in our hospital and other hospitals gradually approached. CRKP isolates were mainly ICU acquired, rather than input acquired. Intensive and local infection/colonization control measures are necessary for ICU patients, especially those with risk factors for the development of CRKP.

Keywords: *Klebsiella pneumoniae*; Carbapenem-resistant *Klebsiella pneumoniae*; carbapenems; intensive care unit; epidemiology

Strengths and limitations of this study

1. The study firstly reported that clinical characteristics of carbapenem-resistant *Klebsiella pneumoniae*
(CRKP) infection/colonization in the intensive care unit (ICU)

2. The study explored the extent of Klebsiella pneumoniae isolates resistance to carbapenems, trends in sources of CRKP-positive patients and CRKP isolates, and risk factors for the development of CRKP.

3. Sources of ICU patients and other epidemiology data from the general hospital may not be suitable for specialized hospitals.

4. Some information is not available in the electronic medical records, which may have potential effects on results.

**Introduction**

*Klebsiella pneumoniae* (KP) is a gram-negative pathogen commonly causing nosocomial infections. With the widespread and unreasonable use of antibiotics, especially carbapenems, the growing prevalence of carbapenem-resistant *Klebsiella pneumoniae* (CRKP) has been described. CRKP strains have been reported from sporadic cases in the first few years, then endemic outbreaks have been observed\(^1\)\(^\text{-}^2\). Now Carbapenem resistance has occurred in many countries, and become a worldwide problem\(^3\)\(^\text{-}^5\). China Antimicrobial Surveillance Network (CHINET) reported that the resistance rates of *K. 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\(^6\). Moreover, the resistance rates among regions, hospitals and wards varied greatly\(^7\)\(^\text{-}^8\).

Carbapenem-resistant pathogens impose difficulties in selecting the appropriate antimicrobial therapy\(^9\). In the intensive care unit (ICU), CRKP carriers are particularly limited to therapeutic options. Thus, CRKP might evolve to cause considerable clinical problems, including the risk of high mortality, prolonged hospital stay, and heavy economic burden\(^10\)\(^\text{-}^12\).

For long-term acute care hospital residents, high levels of CRKP colonization pressure increased the risk for horizontal transmission\(^13\). CRKP isolates may contaminate the environment, ICU staff’s hands, gloves or gowns, and then spread among environment, ICU staff and patients\(^14\). In addition, ICU patients are transferred from general wards or other hospitals, and discharged to different locations, which likely facilitate the transmission of pathogens. Thus, patients admitted to ICU actually have an increased risk of exposure to multidrug-resistant bacteria, including CRKP\(^15\).

In recent years, studies have reported the epidemiology, risk factors and outcomes of CRKP bloodstream infections in the ICU\(^16\)\(^\text{-}^17\) and hospitals\(^18\)\(^\text{-}^20\). Meanwhile, studies on CRKP infections in the ICU and hospitals\(^21\)\(^\text{-}^22\), studies on CRKP colonization in the ICU\(^23\), and studies on CRKP
infection/colonization in the hospital\textsuperscript{24--25} were presented. Given the epidemiological and clinical challenges of CRKP isolates in the ICU, a general monitoring of CRKP infection and colonization in the ICU is imperative. Moreover, CRKP bloodstream infections have been widely reported, CRKP infection/colonization of other sites also need attention. So studies of CRKP infection and colonization with all specimen types in the ICU are urgently needed. In addition, data on the extent of KP isolates resistance to carbapenems, sources of CRKP-positive patients and CRKP isolates in the ICU are limited.

Therefore, we performed a study to investigate the clinical characteristics of CRKP infection/colonization in the ICU from 2012 to 2020, including epidemiology, sources of CRKP-positive patients and CRKP isolates, and risk factors.

Methods:

Study population

This was a retrospective, cohort study in the ICU of Xiangya hospital, a teaching hospital with 3600-bed in Changsha, China. Subjects were patients with KP clinical culture and antimicrobial susceptibility testing during hospitalization in the ICU. Only the first isolate was included in the study, and duplicate isolates of the same patient were not considered. Permission for collecting the information in the medical records of patients and KP isolates for research purposes were approved by the Ethics Committee of Xiangya Hospital Central South University (2018091076).

Clinical data collection and definitions

Patient data were collected via electronic medical records and included the following: demographics (medical record number, admission and discharge dates, age, sex, bed occupied), comorbidities (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), recent invasive procedures (tracheostomy tube, surgical drainage, indwelled central venous catheter, gastric tube, urinary catheter), antibiotic administration 3 months prior to KP isolation, microbiological data (specimen types and monitoring time, the antibiotic susceptibility results).

In our hospital, KP isolates were tested for their susceptibility to carbapenems (ertapenem/imipenem/meropenem) and other antimicrobials by microbroth dilution \textsuperscript{26}. The MIC was interpreted according to the Clinical and Laboratory Standards Institute (CLSI) breakpoints.
Carbapenem-susceptible *Klebsiella pneumoniae* (CSKP) was identified when MIC was ≤1 mg/L for imipenem, meropenem, and ≤0.5 mg/L for ertapenem. KP isolates for which tested intermediate or resistant to one or more carbapenems were considered as carbapenem-resistant\(^2\). Patients were stratified into 2 groups (CRKP, CSKP) according to KP susceptibility to carbapenems. If the first isolate of KP was detected within 48 hours or prior to the ICU hospitalization, it was considered as community acquired or input acquired according to their previous admission; while if it was detected after 48 hours of ICU hospitalization, it was considered as ICU acquired.

### Statistical analysis

Descriptive statistics were conducted to describe the characteristics of the study population. Continuous variables were described as mean±standard deviation(M±SD). Univariate logistic regression was conducted to identify the potential factors. The odd radios(ORs) and the 95% confidence intervals(CIs) of each variable were calculated, and variables with a \(P\) value < 0.05 were included in multivariate logistic regression. The multivariate logistic regression used the backward method. A \(P\) value < 0.05 was considered statistically significant. All analyses were carried out by SPSS software (version 22.0, SPSS Inc., IL, USA).

### Results:

#### Epidemiology

From January 2012 through December 2020, a total of 880 patients in the ICU were isolated with KP isolates. 377(42.84%) patients were identified clinical culture with CRKP, while 503(57.16%) patients with CSKP. The trend of CRKP incidence from 2012 to 2020 was shown in Figure 1. CRKP incidence was low in 2012(11.11%) and 2013 (13.04%), but after that, the incidence of CRKP increased rapidly to peak in 2017(63.48%) , then decreased and stabilized to 48.92% in 2020.

In our study, KP isolates were obtained from various specimen types. 266 (70.56%) CRKP isolates were detected from one site, while 450(89.46%) CSKP isolates were detected from one site. In addition, the bacteria in both groups were mainly isolated from respiratory tract specimens(58.27% and 66.67%, respectively). For the specimens of KP isolated from bloodstream, urinary, wound, and catheter tip, the rates of CRKP were higher than those of CSKP(Figure 2A). KP isolates were detected from two or more sites as shown in Figure 2B. CRKP isolates could be detected from 2 to 5 sites( 19.1%, 9.28%, 0.8% and 0.27%, respectively), and CSKP isolates could be detected from 2 to 4 sites( 8.55%, 1.59% and 0.4%, respectively). There were 50 types of distribution of KP isolated sites, and 33(62%) showed
higher rate of CRKP than CSKP.

**Carbapenems non-susceptibility profiles of CRKP isolates**

Out of the 377 CRKP isolates, 294 (77.98%) were tested against three carbapenems, 70 (18.57%) were tested against two carbapenems, and 13 (3.45%) were tested against one carbapenem (Table 1). During the study period of 2012-2020, the percentage of CRKP isolates tested not susceptible to one carbapenem decreased from 66.67% to 2.94%, and two carbapenems decreased from 33.33% to 8.82%. The proportion of CRKP isolates non-susceptible to all three carbapenems increased from 0% in 2012 to 88.24% in 2020 (Figure 3).

**The sources of KP patients and KP isolates**

ICU patients were generally transferred from community, other hospitals, or general wards in our hospital. The patients in our study were isolated with KP isolates, and the distribution of patient sources was displayed in Figure 4. For CRKP group, patients were mainly from general wards in our hospital and other hospitals. Notably, the number of patients from other hospitals and general wards in our hospital went up and down alternately, and gradually converged in the recent 2 years. For CSKP group, patients were mainly from general wards in our hospital (59.57%-83.33%), but the trend was down.

The sources of KP isolates were summarized, including community input, other hospitals input, general wards of our hospital input and ICU acquired. Sources of CRKP and CSKP isolates were showed in Figure 5. For CRKP carriers, CRKP isolates were mainly ICU acquired (59.68%), followed by general wards in our hospital (22.02%) and other hospitals (18.30%), and there were no CRKP isolates acquired from community. For CSKP carriers, CSKP isolates most often originated in the ICU (46.72%) and general wards of our hospital (38.97%), and less frequently in other hospitals (10.93%) and community (3.38%).

**Risk factors for the development of CRKP**

A comparison of baseline characteristics between CRKP and CSKP patients was shown in Table 2. Univariate analysis showed that younger age, previous admission, previous ICU stay, and prior use of tracheostomy tube, surgical drainage, indwelled central venous catheter, and gastric tube were associated with CRKP infection/colonization. Exposure to carbapenems, tigecycline, glycopeptides, β-lactams and β-lactamase inhibitor, fluoroquinolones, aminoglycosides and antifungal drugs within the prior 3 months were significantly much more in CRKP group.
At the multivariate analysis, younger age ($P=0.024$), previous admission ($P=0.016$), previous ICU stay ($P=0.007$), prior use of surgical drainage ($P=0.010$) and gastric tube ($P=0.001$), and use of carbapenems ($P=0.000$), tigecycline ($P=0.006$), $\beta$-lactams and $\beta$-lactamase inhibitor ($P=0.000$), fluoroquinolones ($P=0.036$), and antifungal drugs ($P=0.001$) within the prior 3 months were risk factors significantly associated with CRKP infection/colonization.

Discussion

In this study, we reported clinical characteristics of CRKP infection/colonization over 9 years. Many findings in our study were reported firstly. The high incidence and growth trend of CRKP in KP isolates were observed. The high proportion of KP isolates tested resistance to 3 carbapenems mirrors the urgency of antibiotic resistance in the ICU. An important finding of this study was that CRKP isolates were mainly ICU acquired rather than input acquired, suggesting that the possible routes and effective interventions for localized acquisition need more attention.

In spite of the high prevalence of CRKP in the hospital, few study explored changing trend of resistance rate of *K. pneumoniae* to carbapenems in the ICU. We found a study from an intensive care unit of Southern Italy that carbapenem resistant *K. pneumoniae* rates rose from 0% in 2008 to 59.2% in 2013. In China, multicenter data from CHINET described that resistance change of *K. pneumoniae* to meropenem increased from 2.9% in 2005 to 26.3% in 2018. Considering the trends of China and abroad, we predicted that the rate 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 and stabilized to 48.92% in 2020. It may be related to the implementation of antimicrobial stewardship (AMS) in our hospital.

Uwe Koppe et al. reported the proportion of *K. pneumoniae* isolates non-susceptible against at least one carbapenem in hospitals of Germany. In our study, we explored the changing trends of *K. pneumoniae* isolates non-susceptible against 1, 2, and 3 carbapenems. We discovered that the rates of KP isolates non-susceptible to 1 and 2 carbapenems dropped significantly, and the rate of KP isolates non-susceptible to 3 carbapenems continuously increased from 0 to 88.24%. Obviously, our results highlight the severity of KP resistance to carbapenems in ICU, which poses a much more difficult challenge for the treatment of CRKP infections.

It is noteworthy that specimen types may be associated with CRKP and CSKP. Our findings have
practical implication for CRKP prediction according to specimen types. When the specimens of *K. pneumoniae* were isolated from bloodstream, urinary, wound, and catheter tip, the rates of CRKP were higher than that of CSKP. Although bloodstream infection with CRKP was the most reported, the amount of respiratory specimen was more than the sum of other specimen types. It suggests that pulmonary infection/colonization with *K. pneumoniae* should not be ignored.

For patients isolated with *K. pneumoniae* in the ICU, their sources were not reported before. For CRKP group, we found that the incidence of patients from other hospitals had increased to 52.94%, which was more than the rate of patients from our hospital. For CSKP group, the trend of patients from our hospital was downward. It indicated that antibiotic resistance control measures in our hospital were progressive. Special attention should be paid to patients who transferred to ICU from other hospitals.

In the study, we found that CRKP isolates were mainly ICU acquired. It confirmed ICU admission was an important risk factor for acquiring CRKP. It demonstrated that CRKP isolates may be acquired through horizontal transmission during ICU hospitalization. Studies have reported interventions to reduce transmission of carbapenem-resistant *Enterobacteriaceae*\(^{30,31}\), knowledge of local prevalence rate of CRKP and tailoring surveillance actions to local circumstance may be essential.

In our study, we observed that younger age, previous admission, previous ICU stay, prior use of surgical drainage and gastric tube, and use of carbapenems, tigecycline, \(\beta\)-lactams and \(\beta\)-lactamase inhibitor combination, fluoroquinolones, and antifungal drugs within the prior 3 months were risk factors for ICU patients isolated with CRKP. Interestingly, we found the median age of CRKP patients was younger than CSKP patients, which was consistent with the earlier studies\(^{24,25}\). Although we cannot explain this finding, it is possible that it constitutes a risk factor. For invasive procedures, prior use of surgical drainage and gastric tube were not reported as independent risk factors before. It may be due to the different types of patients in these studies or differences in sample size. Antimicrobial exposure was reported as a potential risk factor for CRKP infection/colonization. Although antibiotics identified in these studies and antimicrobial exposure time are different\(^{13,24,25}\), local and feasible antibiotic stewardship measures are all needed.

Our study has several limitations. Firstly, our hospital is a tertiary hospital that admits different kinds of critical ill patients, and the sources of patients and other epidemiology data may not be 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 rate of KP resistance to carbapenems generally raised, and the extent of KP resistance to carbapenems sharply increased. The proportion of CRKP-positive patients from general wards in our hospital and other hospitals gradually approached. CRKP isolates were mainly ICU acquired, rather than input acquired. Intensive and local infection/colonization control measures are necessary for ICU patients, especially those with risk factors for the development of CRKP.

Acknowledgments

The authors thank all of the study participants.

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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Conflict of interest

The authors declare no conflict of interest.

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication

Not applicable.

Ethical Approval

The study was approved by the Ethics Committee of Xiangya Hospital Central South University (2018091076).

Provenance and peer review

Not commissioned; externally peer reviewed.

Data availability statement

Data are available on reasonable request. All data relevant to the study are available on reasonable request to the corresponding author.

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ORCID iD

0000-0002-7939-1803
Table 1  Proportions of *K. pneumoniae* isolates non-susceptible against at least one carbapenem

<table>
<thead>
<tr>
<th>Tested carbapenem</th>
<th>Number of isolates tested</th>
<th>isolates not susceptible to one carbapenem</th>
<th>isolates not susceptible to two carbapenems</th>
<th>isolates not susceptible to three carbapenems</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meropenem/Imipenem/ Ertapenem</td>
<td>13(3.45%)</td>
<td>13(100)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Meropenem + Imipenem/ Meropenem + Ertapenem</td>
<td>70(18.57%)</td>
<td>13(18.57)</td>
<td>57(81.43)</td>
<td>-</td>
</tr>
<tr>
<td>Meropenem+Imipenem+Ertapenem</td>
<td>294(77.98%)</td>
<td>5(1.7)</td>
<td>1(0.34)</td>
<td>288(97.96)</td>
</tr>
</tbody>
</table>

Table 2. Clinical characteristics and risk factors for CRKP infection/colonization

<table>
<thead>
<tr>
<th>CRKP(n=377)</th>
<th>CSKP(n=503)</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>OR(95%CI)</td>
<td>P</td>
</tr>
<tr>
<td><strong>General characteristics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male sex</td>
<td>294(77.98)</td>
<td>363(72.17)</td>
<td>0.73(0.53-1.00)</td>
</tr>
<tr>
<td>Age(years)</td>
<td>54.43±15.51</td>
<td>57.04±16.17</td>
<td>1.01(1.00-1.02)</td>
</tr>
<tr>
<td><strong>Previous admission</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No previous admission</td>
<td>5(1.33)</td>
<td>36(7.16)</td>
<td>1.40(1.11-1.76)</td>
</tr>
<tr>
<td>Other hospitals</td>
<td>169(44.83)</td>
<td>110(21.87)</td>
<td></td>
</tr>
<tr>
<td>Same hospital</td>
<td>203(53.85)</td>
<td>357(70.97)</td>
<td></td>
</tr>
<tr>
<td><strong>Recent events</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior surgery</td>
<td>214(56.76)</td>
<td>289(57.46)</td>
<td>1.03 (0.79-1.35)</td>
</tr>
<tr>
<td>Previous ICU stay</td>
<td>111(29.44)</td>
<td>65(12.92)</td>
<td>0.36(0.25-0.50)</td>
</tr>
<tr>
<td><strong>Invasive procedures</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tracheostomy tube</td>
<td>154(40.85)</td>
<td>155(30.82)</td>
<td>0.65(0.49-0.85)</td>
</tr>
<tr>
<td>Surgical drainage</td>
<td>251(66.58)</td>
<td>285 (56.66)</td>
<td>0.66(0.50-0.87)</td>
</tr>
<tr>
<td>Indwelled central venous catheter</td>
<td>221(58.62)</td>
<td>221(43.94)</td>
<td>0.55(0.42-0.73)</td>
</tr>
<tr>
<td>Gastric tube</td>
<td>278(73.74)</td>
<td>288(57.26)</td>
<td>0.48(0.36-0.64)</td>
</tr>
<tr>
<td>Urinary catheter</td>
<td>296(78.51)</td>
<td>380(75.55)</td>
<td>0.85(0.62-1.16)</td>
</tr>
<tr>
<td><strong>Comorbidities</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>128(33.95)</td>
<td>155(30.82)</td>
<td>0.86(0.64-1.14)</td>
</tr>
</tbody>
</table>
Diabetes mellitus 60(15.92) 66(13.12) 0.80(0.55-1.18) 0.255  
Coronary 39(10.34) 61(12.13) 1.22(0.79-1.88) 0.371  
Hepatitis/cirrhosis 27(7.16) 24(4.77) 0.67(0.37-1.21) 0.187  
Chronic renal insufficiency 10(2.65) 11(2.19) 0.75(0.29-1.90) 0.538  
Malignancy 22(5.84) 31(6.16) 1.11(0.63-1.97) 0.719  
Cerebrovascular disease 24(6.37) 19(3.78) 0.58(0.31-1.07) 0.081  

**Antibiotics used within 90 days**

<table>
<thead>
<tr>
<th>Antibiotic Class</th>
<th>Users (n, %)</th>
<th>Controls (n, %)</th>
<th>Odds Ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carapenems</td>
<td>250(66.31)</td>
<td>174(34.59)</td>
<td>0.27(0.20-0.36)</td>
<td>0.000</td>
</tr>
<tr>
<td>Tigecycline</td>
<td>88(23.34)</td>
<td>31(6.16)</td>
<td>0.22(0.14-0.33)</td>
<td>0.000</td>
</tr>
<tr>
<td>Glycopeptides</td>
<td>105(27.85)</td>
<td>95(18.89)</td>
<td>0.60(0.44-0.83)</td>
<td>0.002</td>
</tr>
<tr>
<td>β-lactams and β-lactamase inhibitor combinations</td>
<td>277(73.47)</td>
<td>284(56.46)</td>
<td>0.47(0.35-0.63)</td>
<td>0.000</td>
</tr>
<tr>
<td>3rd or 4th-cefaplosporines</td>
<td>115(30.5)</td>
<td>149(29.62)</td>
<td>0.96(0.72-1.28)</td>
<td>0.778</td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>96(25.46)</td>
<td>66(13.12)</td>
<td>0.44(0.31-0.63)</td>
<td>0.000</td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td>26(6.9)</td>
<td>17(3.38)</td>
<td>0.47(0.25-0.88)</td>
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<td>84(22.28)</td>
<td>36(7.16)</td>
<td>0.27(0.18-0.41)</td>
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### Reference


Fig.1. Incidence of CRKP over the study period (2012-2020)

729x317mm (38 x 38 DPI)
Fig. 2. Distribution of K. pneumoniae in different specimens. A. one site; B. two or more sites

187x259mm (300 x 300 DPI)
Fig. 3. Trends in the prevalence of *K. pneumoniae* isolates non-susceptible against at least one carbapenem.
Fig. 4. Trends in the sources of KP patients.

192x54mm (300 x 300 DPI)
Fig. 5. Distribution of the sources of KP isolates.

166x77mm (300 x 300 DPI)
Clinical characteristics of Carbapenem-resistant Klebsiella pneumoniae infection/colonization in the intensive care unit: a 9-year retrospective study

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<td>wang, ping; Xiangya Hospital Central South University, Department of Pharmacy; Xiangya Hospital Central South University, National Clinical Research Center for Geriatric Disorders Zou, Xiaocui; Xiangya Hospital Central South University, Department of Pharmacy zhou, boting; Xiangya Hospital Central South University, Department of Pharmacy, Xiangya Hospital; Xiangya Hospital Central South University, National Clinical Research Center for Geriatric Disorders Yin, Tao; Xiangya Hospital Central South University, Department of Pharmacy; Xiangya Hospital Central South University, National Clinical Research Center for Geriatric Disorders</td>
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Clinical characteristics of Carbapenem-resistant *Klebsiella pneumoniae* infection/colonization in the intensive care unit: a 9-year retrospective study

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Abstract: Carbapenem-resistant *Klebsiella pneumoniae* (CRKP) infection/colonization has been reported in hospitals. The clinical characteristics of CRKP infection/colonization in the intensive care unit (ICU) have received little attention. This study aims to investigate the epidemiology and extent of *K. pneumoniae* (KP) resistance to carbapenems, the sources of CRKP patients and CRKP isolates, and the risk factors for CRKP infection/colonization.

**Design** Retrospective single-centre study.

**Data source** Clinical data were obtained from electronic medical records.

**Participants** Patients isolated with KP in the ICU from January, 2012 to December, 2020.

**Main outcome measures** The prevalence and changing trend of CRKP were determined. The extent of KP isolates resistance to carbapenems, the specimen types of KP isolates, and the sources of CRKP patients and CRKP isolates were all examined. The risk factors for CRKP infection/colonization were also assessed.

**Results** The rate of CRKP in KP isolates raised from 11.11% in 2012 to 48.92% in 2020. CRKP isolates were detected in one site in 266 patients (70.56%). The percentage of CRKP isolates not susceptible to three carbapenems increased from 0% in 2012 to 88.24% in 2020. The percentage of CRKP patients from general wards in our hospital and other hospitals gradually converged in 2020 (47.06% VS 52.94%). CRKP isolates were mainly acquired in our ICU (59%). Younger age (p=0.018), previous admission (p=0.018), previous ICU stay (p=0.008), prior use of surgical drainage (p=0.012) and gastric tube (p=0.001), and use of carbapenems (p=0.000), tigecycline (p=0.005), β-lactams/β-lactamase inhibitors (p=0.000), fluoroquinolones (p=0.033), and antifungal drugs (p=0.011) within the prior 3 months were independent risk factors for CRKP infection/colonization.

**Conclusions** Overall, the rate of KP isolates resistance to carbapenems increased, and the severity of this resistance significantly increased. Intensive and local infection/colonization control measures are necessary for ICU patients, especially those with risk factors for CRKP infection/colonization.
Keywords: Carbapenem-resistant *Klebsiella pneumoniae*; carbapenems; intensive care unit; epidemiology

Strengths and limitations of this study

1. This is the first study to explore the clinical characteristics of carbapenem-resistant *Klebsiella pneumoniae* (CRKP) infection/colonization in the ICU.
2. This study takes into account the extent of *K. pneumoniae* isolates resistance to carbapenems, sources of CRKP patients and CRKP isolates in the ICU.
3. This study spans a long period of 9 years.
4. The generalisation of our findings to specialized hospitals requires further assessment.
5. Some information is not available in the electronic medical records, which may have potential effects on the results.

Introduction

*K. pneumoniae* (KP) is a gram-negative pathogen that commonly causes nosocomial infections. With the widespread and unreasonable use of antibiotics, particularly carbapenems, the prevalence of carbapenem-resistant *Klebsiella pneumoniae* (CRKP) has increased. CRKP strains have been reported from sporadic cases in the first few years, then endemic outbreaks have been observed\(^1,2\). Now Carbapenem resistance has occurred in many countries, and become a worldwide problem\(^3,4\). The China Antimicrobial Surveillance Network (CHINET) has reported that the resistance rates of *K. pneumoniae* to imipenem have increased progressively from 3.0% in 2005 to 25% in 2018, and meropenem was 2.9% in 2005 and 26.3% in 2018\(^5\). Moreover, the resistance rates vary considerably among regions, hospitals, and wards\(^7,8\).

Carbapenem-resistant pathogens impose difficulties in selecting the appropriate antimicrobial therapy\(^9\). In the intensive care unit (ICU), CRKP carriers are particularly limited in therapeutic options. Thus, CRKP may evolve to cause considerable clinical problems, including the risk of high mortality, prolonged hospital stay, and heavy economic burden\(^10-12\). In our ICU, we encounter similar issues. *K. pneumoniae* is one
of the most common bacterium detected, with drug-resistant strains prevailing. Consequently, we are interested in monitoring the occurrence and developments of CRKP in our ICU.

For residents of long-term acute care hospitals, high levels of CRKP colonization pressure increased the risk for horizontal transmission\(^{13}\). CRKP isolates may contaminate the environment, as well as hands, gloves, or gowns of ICU staffs, and then spread among the environment, ICU staff, and patients\(^{14}\). In addition, ICU patients are transferred from general wards or other hospitals, and discharged to different locations, which further facilitates the transmission of pathogens. Therefore, patients admitted to the ICU have an increased risk of exposure to multidrug-resistant bacteria, including CRKP\(^{15}\).

In recent years, studies have reported the epidemiology, risk factors, and outcomes of CRKP bloodstream infections in the ICU\(^{16, 17}\) and hospitals\(^{18-20}\). Furthermore, various studies have been presented on CRKP infections in the ICU and hospitals\(^{21, 22}\), CRKP colonization in the ICU\(^{23}\), and CRKP infection/colonization in the hospital\(^{24, 25}\). Considering the epidemiological and clinical challenges of CRKP isolates in the ICU, it is imperative to monitor CRKP infection and colonization in the ICU. Moreover, CRKP bloodstream infections have been widely reported, and CRKP infection/colonization of other sites also need attention\(^{26}\). Therefore, studies of CRKP infection and colonization with all specimen types in the ICU are urgently needed. In addition, there is limited data available on the extent of KP isolates resistance to carbapenems, sources of CRKP patients and CRKP isolates in the ICU.

Therefore, we performed a study to investigate the clinical characteristics of CRKP infection/colonization in the ICU from 2012 to 2020, including epidemiology, sources of CRKP patients and CRKP isolates, and risk factors for the development of CRKP in KP patients.

**Methods**

**Study design and population**

This was a retrospective case-control study in the ICU of Xiangya Hospital, a teaching hospital with 3600 beds in Changsha, China. Subjects were patients with
positive KP clinical culture and antimicrobial susceptibility testing during hospitalization in the ICU from January, 2012 to December, 2020. Only the first isolate was included in the study, and duplicate isolates of the same patient were not considered.

Patients were stratified into two groups, namely CRKP and CSKP, based on KP susceptibility to carbapenems. The case group included patients with positive CRKP culture, while patients with a positive culture for CSKP were in the control group. Permission for collecting the information in the medical records of patients and KP isolates for research purposes were approved by the Ethics Committee of Xiangya Hospital Central South University (2018091076).

**Clinical data collection and definitions**

Patient data were collected via electronic medical records and included the following: demographics (medical record number, admission and discharge dates, age, sex, bed occupied), comorbidities (hypertension, diabetes, coronary artery disease, hepatitis/cirrhosis, chronic renal insufficiency, malignancy, cerebrovascular disease), previous admission (the ward/hospital where the patient was admitted before this hospitalization in the ICU), recent events (prior surgery, previous ICU stay), recent invasive procedures (tracheostomy tube, surgical drainage, indwelled central venous catheter, gastric tube, urinary catheter), antibiotic administration 3 months prior to KP isolation (carbapenems, tigecycline, glycopeptides, β-lactams/β-lactamase inhibitors, 3rd/4th generation cepharosporines, fluoroquinolones, aminoglycosides, antifungal drugs), microbiological data (specimen types and monitoring time, the antibiotic susceptibility results).

In our hospital, KP isolates were tested for their susceptibility to carbapenems (ertapenem/ imipenem/meropenem) and other antimicrobials by broth microdilution. The MIC was interpreted according to the Clinical and Laboratory Standards Institute (CLSI) breakpoints. Carbapenem-susceptible Klebsiella pneumoniae (CSKP) was identified when MIC was \( \leq 1 \) mg/L for imipenem, meropenem, and \( \leq 0.5 \) mg/L for ertapenem. KP isolates that tested intermediate or resistant to one or more carbapenems were considered as carbapenem-resistant. If the first isolate of KP was
detected within 48 hours or before admission to the ICU, it was considered as community-acquired or input-acquired based on their previous admission; while if it was detected after 48 hours of ICU hospitalization, it was considered as ICU-acquired.

Statistical analysis

Statistical descriptions were conducted to describe the characteristics of the study population. Continuous variables were described as mean±standard deviation(M±SD). Univariate logistic regression was conducted to identify the potential factors. Variates were chosen based on previous studies and the professional experience. The odd radios(ORs) and the 95% confidence intervals(CIs) of each variable were calculated, and variables with a p value < 0.05 were included in multivariate logistic regression. The multivariate logistic regression used the backward method. A p value < 0.05 was considered statistically significant. All analyses were carried out by SPSS software (version 22.0, SPSS Inc., IL, USA).

Patient and public involvement

Patients and the public were not involved in the design, conduct, reporting, or dissemination plans of this research.

Results

Epidemiology

From January 2012 through December 2020, a total of 880 unique patients in the ICU were separated with KP isolates(infected or colonized). 377(42.50%) patients were identified clinical culture with CRKP, while 503(57.50%) patients with CSKP. The separate rate of CRKP in KP isolates from 2012 to 2020 is shown in Table 1. CRKP rate was low in 2012(11.11%) and 2013 (13.04%), but after that, the rate increased rapidly to peak in 2017(64.35%), then decreased and stabilized at 48.92% in 2020(Table 1).

In our study, KP isolates were obtained from various specimen types. 266(70.56%) CRKP isolates were detected from one site, while 450(89.46%) CSKP isolates were detected from one site. CRKP isolates could be detected from 2 to 5 sites(19.1%, 9.28%, 0.8%, and 0.27%, respectively), and CSKP isolates could be detected from 2
to 4 sites (8.55%, 1.59%, and 0.4%, respectively) (Figure 1A). In addition, CRKP isolates were mainly isolated from respiratory tract specimens (42.67%), followed by blood (21.05%), and ascites (15.79%). CSKP isolates mainly isolated from respiratory tract specimens (57.22%), followed by ascites (15.32%), blood (8.98%) (Figure 1B).

**Carbapenems non-susceptibility profiles of CRKP isolates**

In our hospital, KP isolates were tested for their susceptibility to carbapenems (ertapenem/imipenem/meropenem). We analysed the resistance of each KP strain against ertapenem/imipenem/meropenem and tallied the resistance to 1/2/3 carbapenem(s). During the study period of 2012-2020, the percentage of CRKP isolates tested not susceptible to one carbapenem decreased from 66.67% to 2.94%, and two carbapenems decreased from 33.33% to 8.82%. The proportion of CRKP isolates non-susceptible to all three carbapenems increased from 0% in 2012 to 88.24% in 2020 (Figure 2).

**The sources of KP patients and KP isolates**

ICU patients were generally transferred from the community, other hospitals, or general wards in our hospital. The patients in our study were isolated with KP isolates, and the distribution of patient sources is displayed in Figure 3. For CRKP group, patients were mainly from general wards in our hospital and other hospitals (91.67%-100%). Notably, the number of patients from other hospitals and general wards in our hospital went up and down alternately, and gradually converged in the recent two years. For CSKP group, patients were mainly from general wards in our hospital (59.57%-83.33%), but the trend was downward.

The sources of KP isolates were summarized, including the community input, other hospitals input, general wards of our hospital input and ICU acquired. Sources of CRKP and CSKP isolates are shown in Figure 4. For CRKP carriers, CRKP isolates were mainly acquired in our ICU (59.68%), followed by general wards in our hospital (22.02%) and other hospitals (18.30%), and there were no CRKP isolates acquired from the community. For CSKP carriers, CSKP isolates most often originated in the ICU (46.72%) and general wards of our hospital (38.97%), and less frequently in other hospitals (10.93%) and community (3.38%).
Risk factors for CRKP infection/colonization

A comparison of baseline characteristics between CRKP and CSKP patients is shown in Table 2. In bivariate analysis, there were significant differences in age, previous admission, previous ICU stay, and prior use of tracheostomy tube, surgical drainage, indwelled central venous catheter, gastric tube, and exposure to carbapenems, tigecycline, glycopeptides, β-lactams/β-lactamase inhibitors, fluoroquinolones, aminoglycosides, and antifungal drugs within the prior 3 months were significantly much more in CRKP group.

In the multivariate analysis, younger age (p=0.018), previous admission (p=0.018), previous ICU stay (p=0.008), prior use of surgical drainage (p=0.012) and gastric tube (p=0.001), and use of carbapenems (p=0.000), tigecycline (p=0.005), β-lactams/β-lactamase inhibitors (p=0.000), fluoroquinolones (p=0.033), and antifungal drugs (p=0.011) within the prior 3 months were risk factors significantly associated with CRKP infection/colonization.

Discussion

In this study, we reported clinical characteristics of CRKP infection/colonization over a period of 9 years. Many findings in our study were the first reported. This study observed a high incidence and growth trend of CRKP in KP isolates, and a high proportion of KP isolates tested resistance to three carbapenems, highlighting the urgency of antibiotic resistance in the ICU. An important finding of this study was that CRKP isolates were mainly acquired in the ICU rather than input-acquired. This suggests that more attention should be given to identifying the possible routes and effective interventions for localized acquisition.

Despite the high prevalence of CRKP in the hospital, few studies explored changing trend of the resistance rate of *K. pneumoniae* to carbapenems in the ICU. We found a study from an intensive care unit in Southern Italy that carbapenem resistant *K. pneumoniae* rates rose from 0% in 2008 to 59.2% in 2013. In China, multicenter data from the CHINET described that the resistance change of *K. pneumoniae* to meropenem increased from 2.9% in 2005 to 26.3% in 2018. Considering the trends in China and abroad, we predicted that the resistance rate of *K.
*Pneumoniae* to carbapenems would increase in our ICU. As expected, we found an impressive increase in CRKP numbers and rates from 2012 to 2020. Specifically, the carbapenem resistance rate increased from 11.11% in 2012 to 64.35% in 2017, and then the resistance rate decreased and stabilized at 48.92% in 2020. It may be attributed to the implementation of antimicrobial stewardship (AMS) in our hospital.

Uwe Koppe et al.\(^\text{30}\) reported the proportion of *K. pneumoniae* isolates non-susceptible against at least one carbapenem in hospitals in Germany. In our study, we explored the changing trends of *K. pneumoniae* isolates non-susceptible against 1, 2, and 3 carbapenems. We discovered that the rates of KP isolates non-susceptible to 1 and 2 carbapenems decreased significantly, while the rate of KP isolates non-susceptible to 3 carbapenems continuously increased from 0 to 88.24%. Our results clearly indicate the severity of KP resistance to carbapenems in the ICU, which poses a much more difficult challenge for the treatment of CRKP infections.

It is noteworthy that specimen types may be associated with CRKP and CSKP. Our findings have practical implication for predicting CRKP according to specimen types. When *K. pneumoniae* specimens were isolated from the bloodstream, urinary, wound, and catheter tip, the rates of CRKP were higher than those of CSKP. Although bloodstream infection with CRKP was the most commonly reported, the number of respiratory specimen was higher than the total of other specimen types. This suggests that pulmonary infection/colonization with *K. pneumoniae* should not be ignored.

For patients isolated with *K. pneumoniae* in the ICU, their sources were not reported before. We found that the incidence of CRKP patients from other hospitals had increased to 52.94%, exceeding the rate of patients from our hospital. The trend of CSKP patients from our hospital was downward. It indicated that antibiotic resistance control measures in our hospital were progressive. Special attention should be paid to patients who transferred to the ICU from other hospitals.

In the study, we found that CRKP isolates were mainly acquired in the ICU. It confirmed ICU admission was an important risk factor for acquiring CRKP. It demonstrated that CRKP isolates may be acquired through horizontal transmission during ICU hospitalization. Previous studies have reported interventions to reduce
transmission of carbapenem-resistant *Enterobacteriaceae*\textsuperscript{31, 32}. Knowledge of local prevalence rate of CRKP and tailored surveillance actions based on local circumstance are crucial.

In our study, we observed that younger age, previous admission, previous ICU stay, prior use of surgival drainage and gastric tube, and use of carbapenems, tigecycline, \(\beta\)-lactams/\(\beta\)-lactamase inhibitors, fluoroquinolones, and antifungal drugs within the prior 3 months were risk factors for ICU KP patients isolated with CRKP. Interestingly, we found the median age of CRKP patients was younger than that of CSKP patients, which was consistent with the earlier studies\textsuperscript{24, 25}. Although we cannot explain this finding, it is possible that it constitutes a risk factor, and further studies are required to confirm the finding. For invasive procedures, prior use of surgival drainage and gastric tube were not reported as independent risk factors before. This may be due to the different types of patients in these studies or differences in sample size. Antimicrobial exposure was reported as a potential risk factor for CRKP infection/colonization. Although antibiotics identified in these studies and antimicrobial exposure time vary\textsuperscript{13, 24, 25}, local and practical antibiotic stewardship measures are necessary.

Our study has several limitations. Firstly, our hospital is a tertiary hospital that admits a variety of critically ill patients, and the sources of patients and other epidemiology data may not be suitable for specialized hospitals. Secondly, as a retrospective analysis, clinical data were obtained from electronic medical records, and missing information may have potential effects on the results. Nevertheless, the sample size of our study was not small, and did not hamper the statistical power of our analysis.

**Conclusions**

Overall, the rate of KP isolates resistance to carbapenems increased, and the severity of this resistance significantly increased. Intensive and local infection/colonization control measures are necessary for ICU patients, especially those with risk factors for CRKP infection/colonization.
Acknowledgments The authors thank all of the study participants.

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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Conflict of interest The authors declare no conflict of interest.

Patient consent for publication Not applicable.

Ethical Approval The study was approved by the Ethics Committee of Xiangya Hospital Central South University (2018091076).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are available on reasonable request to the corresponding author.

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ORCID iD

Tao Yin http://orcid.org/0000-0002-7939-1803

Table 1 The resistance rate of K. pneumoniae isolates to carbapenems over the study period (2012-2020)

<table>
<thead>
<tr>
<th>Year</th>
<th>CRKP</th>
<th>CSKP</th>
<th>Total</th>
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<tbody>
<tr>
<td></td>
<td>n(%)</td>
<td>n(%)</td>
<td>n(%)</td>
</tr>
<tr>
<td>2012</td>
<td>9(11.11)</td>
<td>72(88.89)</td>
<td>81</td>
</tr>
<tr>
<td>2013</td>
<td>12(13.04)</td>
<td>80(86.96)</td>
<td>92</td>
</tr>
<tr>
<td>2014</td>
<td>22(30.14)</td>
<td>51(69.86)</td>
<td>73</td>
</tr>
<tr>
<td>2015</td>
<td>43(50)</td>
<td>43(50)</td>
<td>86</td>
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Table 2 Clinical characteristics and risk factors for CRKP infection/colonization

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<tr>
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<th>CSKP(n=503)</th>
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<th>Multivariate analysis</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>OR(95%CI)</td>
<td>OR(95%CI)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>P</td>
<td>P</td>
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<tr>
<td>General characteristics</td>
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</tr>
<tr>
<td>Male sex</td>
<td>294(77.98)</td>
<td>363(72.17)</td>
<td>1.37(1.00-1.87)</td>
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</tr>
<tr>
<td></td>
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<tr>
<td>Age(years)</td>
<td>54.43±15.51</td>
<td>57.04±16.17</td>
<td>0.87(0.79-0.96)</td>
<td>0.005</td>
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<td></td>
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<tr>
<td>Previous admission</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>No previous admission</td>
<td>5(1.33)</td>
<td>36(7.16)</td>
<td>0.72(0.57-0.90)</td>
<td>0.004</td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Other hospitals</td>
<td>169(44.83)</td>
<td>110(21.87)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Our hospital</td>
<td>203(53.85)</td>
<td>357(70.97)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recent events</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Prior surgery</td>
<td>214(56.76)</td>
<td>289(57.46)</td>
<td>0.97 (0.74-1.27)</td>
<td>0.838</td>
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<tr>
<td>Previous ICU stay</td>
<td>111(29.44)</td>
<td>65(12.92)</td>
<td>2.81(1.99-3.96)</td>
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<tr>
<td>Invasive procedures</td>
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<tr>
<td>Tracheostomy tube</td>
<td>154(40.85)</td>
<td>155(30.82)</td>
<td>1.55(1.17-2.05)</td>
<td>0.002</td>
</tr>
<tr>
<td>Surgical drainage</td>
<td>251(66.58)</td>
<td>285 (56.66)</td>
<td>1.52(1.16-2.01)</td>
<td>0.003</td>
</tr>
<tr>
<td>Indwelled central venous catheter</td>
<td>221(58.62)</td>
<td>221(43.94)</td>
<td>1.81(1.38-2.37)</td>
<td>0.000</td>
</tr>
<tr>
<td>Gastric tube</td>
<td>278(73.74)</td>
<td>288(57.26)</td>
<td>2.10(1.57-2.80)</td>
<td>0.000</td>
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<tr>
<td>Urinary catheter</td>
<td>296(78.51)</td>
<td>380(75.55)</td>
<td>1.18(0.86-1.63)</td>
<td>0.302</td>
</tr>
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<td>Comorbidities</td>
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<tr>
<td>Hypertension</td>
<td>128(33.95)</td>
<td>155(30.82)</td>
<td>1.17(0.88-1.56)</td>
<td>0.283</td>
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<tr>
<td>Diabetes</td>
<td>60(15.92)</td>
<td>66(13.12)</td>
<td>1.25(0.85-1.83)</td>
<td>0.255</td>
</tr>
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<td>Coronary artery disease</td>
<td>39(10.34)</td>
<td>61(12.13)</td>
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<td>24(4.77)</td>
<td>1.49(0.82-2.71)</td>
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<td>11(2.19)</td>
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insufficiency
Malignancy 22(5.84) 31(6.16) 0.90(0.51-1.59) 0.719
Cerebrovascular disease 24(6.37) 19(3.78) 1.73(0.93-3.21) 0.081

Antibiotics used within 3 months
Carbapenems 250(66.31) 174(34.59) 3.72(2.81-4.93) 0.000 2.84(2.07-3.89) 0.000
Tigecycline 88(23.34) 31(6.16) 4.64 (3.00-7.16) 0.000 2.01(1.24-3.27) 0.005
Glycopeptides 105(27.85) 95(18.89) 1.66(1.21-2.28) 0.002
β-lactams/β-lactamase inhibitors 277(73.47) 284(56.46) 2.14(1.60-2.85) 0.000 1.88 (1.35-2.63) 0.000
3rd/4th generation cephalosporines 115(30.5) 149(29.62) 1.04(0.78-1.40) 0.778
Fluoroquinolones 96(25.46) 66(13.12) 2.26(1.60-3.20) 0.000 1.54(1.04-2.29) 0.033
Aminoglycosides 26(6.9) 17(3.38) 2.12 (1.13-3.96) 0.019
Antifungal drugs 84 (22.28) 36(7.16) 2.63(1.84-3.76) 0.000 1.66(1.13-2.44) 0.011

331 REFERENCES


Cienfuegos-Gallet AV, Ocampo de Los Rios AM, Sierra Viana P, et al. Risk factors and survival of patients infected with carbapenem-resistant Klebsiella pneumoniae in a KPC
endemic setting: a case-control and cohort study. *BMC Infect Dis* 2019; **19**: 830.


Meng X, Yang J, Duan, J *et al.* Assessing Molecular Epidemiology of Carbapenem-resistant Klebsiella pneumoniae (CR-KP) with MLST and MALDI-TOF in Central China. *Scientific reports* 2019; **9**: 2271.


Figure 1 The number (A) and distribution (B) of *K. pneumoniae* isolated sites.

193x239mm (300 x 300 DPI)
Figure 2 Trends in the prevalence of *K. pneumoniae* isolates non-susceptible against at least one carbapenem.

356x167mm (300 x 300 DPI)
Figure 3 Changing trends in the sources of patients with K. pneumoniae isolates.

217x203mm (300 x 300 DPI)
Figure 4 Distribution of the sources of *K. pneumoniae* isolates.

349x154mm (300 x 300 DPI)
The RECORD statement – checklist of items, extended from the STROBE statement, that should be reported in observational studies using routinely collected health data.

<table>
<thead>
<tr>
<th>Item No.</th>
<th>STROBE items</th>
<th>Location in manuscript where items are reported</th>
<th>RECORD items</th>
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<td>1</td>
<td>(a) Indicate the study’s design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found</td>
<td>(a) Lines 1-3 and 39 (b) Lines 43-57</td>
<td>RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included. RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract. RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.</td>
<td>RECORD 1.1: Lines 40 RECORD 1.2: Lines 41-42 RECORD 1.3: Not applicable</td>
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<td><strong>Introduction</strong></td>
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<td>Objectives</td>
<td>3</td>
<td>State specific objectives, including any prespecified hypotheses</td>
<td>Lines 114-117</td>
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<td><strong>Methods</strong></td>
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<td>Study Design</td>
<td>4</td>
<td>Present key elements of study design early in the paper</td>
<td>Lines 120-121</td>
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<td>Setting</td>
<td>5</td>
<td>Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection</td>
<td>Lines 121-125</td>
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<td>Participants</td>
<td>6</td>
<td>(a) Cohort study - Give the eligibility criteria, and the</td>
<td>(a) Case-control study - Lines 126-</td>
<td>RECORD 6.1: The methods of study population selection (such as codes or</td>
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<p>| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable. | Lines 133-144 | RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided. | not applicable |
| Data sources/ measurement | 8 | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group | Lines 142-153 |  |
| Bias | 9 | Describe any efforts to address potential sources of bias | Lines 120-125 |  |
| Study size | 10 | Explain how the study size was | Line 123 |  |</p>
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<th>Quantitative variables</th>
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<th>Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why</th>
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<td>In our study, age is a quantitative variable. In the logistic analysis, we transform the continuous variable into a ordered multiclass variable. Age groups were ≤40 years old, 40-50 years old, 50-60 years old, 60-70 years old, and &gt;70 years old.</td>
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| Statistical methods | 12 | (a) Describe all statistical methods, including those used to control for confounding  
(b) Describe any methods used to examine subgroups and interactions  
(c) Explain how missing data were addressed  
(d) Cohort study - If applicable, explain how loss to follow-up was addressed  
Case-control study - If applicable, explain how matching of cases and controls was addressed  
Cross-sectional study - If applicable, describe analytical methods taking account of sampling strategy  
(e) Describe any sensitivity analyses |
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| **Results** | **Participants** | 13 | (a) Report the numbers of individuals at each stage of the study (*e.g.*, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed)  
(b) Give reasons for non-participation at each stage.  
(c) Consider use of a flow diagram  
(a) Lines 171-172 | RECORD 13.1: Describe in detail the selection of the persons included in the study (*i.e.*, study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram. | Lines 121-125 |
| **Descriptive data** | 14 | (a) Give characteristics of study participants (*e.g.*, demographic, clinical, social) and information on exposures and potential confounders  
(b) Indicate the number of participants with missing data for each variable of interest  
(c) *Cohort study* - summarise follow-up time (*e.g.*, average and total amount) | Lines 351, 170-211 |  |
| **Outcome data** | 15 | *Cohort study* - Report numbers of outcome events or summary measures over time | Lines 172-177, 220-225 |  |
Case-control study - Report numbers in each exposure category, or summary measures of exposure
Cross-sectional study - Report numbers of outcome events or summary measures

**Main results**

16
(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included.
(b) Report category boundaries when continuous variables were categorized.
(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period.

**Other analyses**

17
Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses.

**Discussion**

**Key results**

18
Summarise key results with reference to study objectives.

**Limitations**

19
Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.

**Interpretation**

20
Give a cautious overall interpretation of results.
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<td>Lines 306-307</td>
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<td>Accessibility of protocol, raw data, and programming code</td>
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Clinical characteristics of Carbapenem-resistant *Klebsiella pneumoniae* infection/colonization in the intensive care unit: a 9-year retrospective study

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<td>14-May-2023</td>
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<td>wang, ping; Xiangya Hospital Central South University, Department of Pharmacy; Xiangya Hospital Central South University, National Clinical Research Center for Geriatric Disorders Zou, Xiaocui; Xiangya Hospital Central South University, Department of Pharmacy zhou, boting; Xiangya Hospital Central South University, Department of Pharmacy; Xiangya Hospital Central South University, National Clinical Research Center for Geriatric Disorders Yin, Tao; Xiangya Hospital Central South University, Department of Pharmacy; Xiangya Hospital Central South University, National Clinical Research Center for Geriatric Disorders</td>
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Clinical characteristics of Carbapenem-resistant *Klebsiella* *pneumoniae* infection/colonization in the intensive care unit: a 9-year retrospective study

Ping Wang¹,², Xiaocui Zou¹, Boting Zhou¹,², Tao Yin¹,²*

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².National Clinical Research Center for Geriatric Disorders, Xiangya Hospital, Central South University, Changsha 410008, Hunan, China

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Abstract:

Objectives Carbapenem-resistant *Klebsiella pneumoniae* (CRKP) infection/colonization has been reported in hospitals. The clinical characteristics of CRKP infection/colonization in the intensive care unit (ICU) have received little attention. This study aims to investigate the epidemiology and extent of *K. pneumoniae* (KP) resistance to carbapenems, the sources of CRKP patients and CRKP isolates, and the risk factors for CRKP infection/colonization.

Design Retrospective single-centre study.

Data source Clinical data were obtained from electronic medical records.

Participants Patients isolated with KP in the ICU from January, 2012 to December, 2020.

Main outcome measures The prevalence and changing trend of CRKP were determined. The extent of KP isolates resistance to carbapenems, the specimen types of KP isolates, and the sources of CRKP patients and CRKP isolates were all examined. The risk factors for CRKP infection/colonization were also assessed.

Results The rate of CRKP in KP isolates raised from 11.11% in 2012 to 48.92% in 2020. CRKP isolates were detected in one site in 266 patients (70.56%). The percentage of CRKP isolates not susceptible to imipenem increased from 42.86% in 2012 to 98.53% in 2020. The percentage of CRKP patients from general wards in our hospital and other hospitals gradually converged in 2020 (47.06% VS 52.94%). CRKP isolates were mainly acquired in our ICU (59%). Younger age (p=0.018), previous admission (p=0.018), previous ICU stay (p=0.008), prior use of surgical drainage (p=0.012) and gastric tube (p=0.001), and use of carbapenems (p=0.000), tigecycline (p=0.005), β-lactams/β-lactamase inhibitors (p=0.000), fluoroquinolones (p=0.033), and antifungal drugs (p=0.011) within the prior 3 months were independent risk factors for CRKP infection/colonization.

Conclusions Overall, the rate of KP isolates resistance to carbapenems increased, and the severity of this resistance significantly increased. Intensive and local infection/colonization control measures are necessary for ICU patients, especially those with risk factors for CRKP infection/colonization.
Keywords: Carbapenem-resistant *Klebsiella pneumoniae*; carbapenems; intensive care unit; epidemiology

Strengths and limitations of this study

1. This is the largest study to explore the clinical characteristics of carbapenem-resistant *Klebsiella pneumoniae* (CRKP) infection/colonization in the ICU.

2. This study takes into account the extent of *K. pneumoniae* isolates resistance to carbapenems, as well as the sources of CRKP patients and CRKP isolates in the ICU.

3. This study spans a long period of 9 years.

4. The generalisation of our findings to specialized hospitals requires further assessment.

5. Some information is not available in the electronic medical records, which may have potential effects on the results.

Introduction

*K. pneumoniae* (KP) is a gram-negative pathogen that commonly causes nosocomial infections. With the widespread and unreasonable use of antibiotics, particularly carbapenems, the prevalence of carbapenem-resistant *Klebsiella pneumoniae* (CRKP) has increased. CRKP strains have been reported from sporadic cases in the first few years, then endemic outbreaks have been observed. Now Carbapenem resistance has occurred in many countries, and become a worldwide problem. The China Antimicrobial Surveillance Network (CHINET) has reported that the resistance rates of *K. pneumoniae* to imipenem have increased progressively from 3.0% in 2005 to 25% in 2018, and meropenem was 2.9% in 2005 and 26.3% in 2018. Moreover, the resistance rates vary considerably among regions, hospitals, and wards.

Carbapenem-resistant pathogens impose difficulties in selecting the appropriate antimicrobial therapy. In the intensive care unit (ICU), CRKP carriers are particularly limited in therapeutic options. Thus, CRKP may evolve to cause considerable clinical problems, including the risk of high mortality, prolonged
hospital stay, and heavy economic burden. In our ICU, we encounter similar issues. *K. pneumoniae* is one of the most common bacteria detected, with drug-resistant strains prevailing. Consequently, we are interested in monitoring the occurrence and developments of CRKP in our ICU.

For residents of long-term acute care hospitals, high levels of CRKP colonization pressure increased the risk for horizontal transmission. CRKP isolates may contaminate the environment, as well as hands, gloves, or gowns of ICU staffs, and then spread among the environment, ICU staff, and patients. In addition, ICU patients are transferred from general wards or other hospitals, and discharged to different locations, which further facilitates the transmission of pathogens. Therefore, patients admitted to the ICU have an increased risk of exposure to multidrug-resistant bacteria, including CRKP.

In recent years, studies have reported the epidemiology, risk factors, and outcomes of CRKP bloodstream infections in the ICU and hospitals. Furthermore, various studies have been presented on CRKP infections in the ICU and hospitals, CRKP colonization in the ICU, and CRKP infection/colonization in the hospital. Considering the epidemiological and clinical challenges of CRKP isolates in the ICU, it is imperative to monitor CRKP infection and colonization in the ICU. Moreover, CRKP bloodstream infections have been widely reported, and CRKP infection/colonization of other sites also need attention. Therefore, studies of CRKP infection and colonization with all specimen types in the ICU are urgently needed. In addition, there is limited data available on the extent of KP isolates resistance to carbapenems, as well as the sources of CRKP patients and CRKP isolates in the ICU.

Therefore, we performed a study to investigate the clinical characteristics of CRKP infection/colonization in the ICU from 2012 to 2020, including epidemiology, sources of CRKP patients and CRKP isolates, and risk factors for the development of CRKP in KP patients.

**Methods**

**Study design and population**

This was a retrospective cohort study in the ICU of Xiangya Hospital, a teaching
hospital with 3600 beds in Changsha, China. Subjects were patients with positive KP clinical culture and antimicrobial susceptibility testing during hospitalization in the ICU from January, 2012 to December, 2020. Only the first isolate was included in the study, and duplicate isolates of the same patient were not considered. Permission for collecting the information in the medical records of patients and KP isolates for research purposes were approved by the Ethics Committee of Xiangya Hospital Central South University (2018091076).

Clinical data collection and definitions

Patient data were collected via electronic medical records and included the following: demographics (age, sex, bed occupied, admission and discharge dates), comorbidities (hypertension, diabetes, coronary artery disease, hepatitis/cirrhosis, chronic renal insufficiency, malignancy, cerebrovascular disease), previous admission (the ward/hospital where the patient was admitted before this hospitalization in the ICU), recent events (prior surgery, previous ICU stay), recent invasive procedures (tracheostomy tube, surgical drainage, indwelled central venous catheter, gastric tube, urinary catheter), antibiotic administration 3 months prior to KP isolation (carbapenems, tigecycline, glycopeptides, β-lactams/β-lactamase inhibitors, 3rd/4th generation cephalosporins, fluoroquinolones, aminoglycosides, antifungal drugs), microbiological data (specimen types and monitoring time, the antibiotic susceptibility results).

In our hospital, KP isolates were tested for their susceptibility to carbapenems (ertapenem/imipenem/meropenem) and other antimicrobials by bioMerieux VITEK-2 (bioMerieux) 27. The MIC was interpreted according to the Clinical and Laboratory Standards Institute (CLSI) breakpoints. Carbapenem-susceptible Klebsiella pneumoniae (CSKP) was identified when MIC was ≤1 mg/L for imipenem, meropenem, and ≤0.5 mg/L for ertapenem. KP isolates that tested intermediate or resistant to one or more carbapenems were considered as carbapenem-resistant28. If the first isolate of KP was detected within 48 hours or before admission to the ICU, it was considered as community-acquired or input-acquired based on their previous admission; while if it was detected after 48 hours of ICU hospitalization, it was
considered as ICU-acquired.

**Statistical analysis**

Statistical descriptions were conducted to describe the characteristics of the study population. Continuous variables were described as mean ± standard deviation (M ± SD). Univariate logistic regression was conducted to identify the potential factors. Variates were chosen based on previous studies and the professional experience. The odds ratios (ORs) and the 95% confidence intervals (CIs) of each variable were calculated, and variables with a p value < 0.05 were included in multivariate logistic regression. The multivariate logistic regression used the backward method. A p value < 0.05 was considered statistically significant. All analyses were carried out by SPSS software (version 22.0, SPSS Inc., IL, USA).

**Patient and public involvement**

Patients and the public were not involved in the design, conduct, reporting, or dissemination plans of this research.

**Results**

**Epidemiology**

From January 2012 through December 2020, a total of 880 unique patients in the ICU were separated with KP isolates (infected or colonized). 377 (42.50%) patients were identified clinical culture with CRKP, while 503 (57.50%) patients with CSKP. The separate rate of CRKP in KP isolates from 2012 to 2020 is shown in online supplemental table A1. CRKP rate was low in 2012 (11.11%) and 2013 (13.04%), but after that, the rate increased rapidly to peak in 2017 (64.35%), then decreased and stabilized at 48.92% in 2020.

In our study, KP isolates were obtained from various specimen types. 266 (70.56%) CRKP isolates were detected from one site, while 450 (89.46%) CSKP isolates were detected from one site. CRKP isolates could be detected from 2 to 5 sites (19.1%, 9.28%, 0.8%, and 0.27%, respectively), and CSKP isolates could be detected from 2 to 4 sites (8.55%, 1.59%, and 0.4%, respectively) (Figure 1A). In addition, CRKP isolates were mainly isolated from respiratory tract specimens (42.67%), followed by blood (21.05%), and ascites (15.79%). CSKP isolates mainly isolated from respiratory
tract specimens (57.22%) , followed by ascites (15.32%), blood (8.98%) (Figure 1 B).

Carbapenems non-susceptibility profiles of CRKP isolates

In our hospital, all KP isolates were tested for their susceptibility to at least one carbapenem, and we analysed the resistance of each KP strain against ertapenem, imipenem, and meropenem. During the study period of 2012-2020, the rate of CRKP isolates tested not susceptible to imipenem increased from 42.86% to 98.53%, and the non-susceptible rates to meropenem and ertapenem remained steadily close to or reached 100%. Since 2017, the rates of CRKP isolates non-susceptible to meropenem, imipenem, and ertapenem have all approached or reached 100% (Figure 2).

The sources of KP patients and KP isolates

ICU patients were generally transferred from the community, other hospitals, or general wards in our hospital. The patients in our study were isolated with KP isolates, and the distribution of patient sources is displayed in Figure 3. For CRKP group, patients were mainly from general wards in our hospital and other hospitals (91.67%-100%). Notably, the number of patients from other hospitals and general wards in our hospital went up and down alternately, and gradually converged in the recent two years. For CSKP group, patients were mainly from general wards in our hospital (59.57%-83.33%), but the trend was downward.

The sources of KP isolates were summarized, including the community input, other hospitals input, general wards of our hospital input and ICU acquired. Sources of CRKP and CSKP isolates are shown in Figure 4. For CRKP carriers, CRKP isolates were mainly acquired in our ICU (59.68%), followed by general wards in our hospital (22.02%) and other hospitals (18.30%), and there were no CRKP isolates acquired from the community. For CSKP carriers, CSKP isolates most often originated in the ICU (46.72%) and general wards of our hospital (38.97%), and less frequently in other hospitals (10.93%) and community (3.38%).

Risk factors for CRKP infection/colonization

A comparison of baseline characteristics between CRKP and CSKP patients is shown in Table 1. In bivariate analysis, there were significant differences in age, previous admission, previous ICU stay, and prior use of tracheostomy tube, surgical drainage,
indwelled central venous catheter, gastric tube, and exposure to carbapenems, tigecycline, glycopeptides, β-lactams/β-lactamase inhibitors, fluoroquinolones, aminoglycosides, and antifungal drugs within the prior 3 months were significantly much more in CRKP group.

In the multivariate analysis, younger age (p=0.018), previous admission (p=0.018), previous ICU stay (p=0.008), prior use of surgical drainage (p=0.012) and gastric tube (p=0.001), and use of carbapenems (p=0.000), tigecycline (p=0.005), β-lactams/β-lactamase inhibitors (p=0.000), fluoroquinolones (p=0.033), and antifungal drugs (p=0.011) within the prior 3 months were risk factors significantly associated with CRKP infection/colonization.

Discussion

In this study, we reported clinical characteristics of CRKP infection/colonization over a period of 9 years. Many findings in our study were the first reported. This study observed a high incidence and growth trend of CRKP in KP isolates, and since 2017, the rates of CRKP isolates non-susceptible to meropenem, imipenem, and ertapenem have all approached or reached 100%. An important finding of this study was that CRKP isolates were mainly acquired in the ICU rather than input-acquired. This suggests that more attention should be given to identifying the possible routes and effective interventions for localized acquisition.

Despite the high prevalence of CRKP in the hospital, few studies explored changing trend of the resistance rate of K. pneumoniae to carbapenems in the ICU. We found a study from an intensive care unit in Southern Italy that carbapenem resistant K. pneumoniae rates rose from 0% in 2008 to 59.2% in 2013. In China, multicenter data from the CHINET described that the resistance change of K. pneumoniae to meropenem increased from 2.9% in 2005 to 26.3% in 2018. Considering the trends in China and abroad, we predicted that the resistance rate of K. pneumoniae to carbapenems would increase in our ICU. As expected, we found an impressive increase in CRKP numbers and rates from 2012 to 2020. Specifically, the carbapenem resistance rate increased from 11.11% in 2012 to 64.35% in 2017, and then the resistance rate decreased and stabilized at 48.92% in 2020. It may be
attributed to the implementation of antimicrobial stewardship (AMS) in our hospital.

Uwe Koppe et al.\textsuperscript{30} reported 99.9\% of the \textit{K. pneumoniae} isolates were tested against at least one carbapenem in hospitals in Germany. In our study, all \textit{K. pneumoniae} isolates were tested against at least one carbapenem. We discovered that the rate of CRKP isolates that were not susceptible to imipenem increased significantly from 42.86\% to 98.53\%. Meanwhile the non-susceptible rates to meropenem and ertapenem remained steadily close to or reached 100\%. The results clearly indicate the severity of KP resistance to carbapenems in the ICU, which poses a much more difficult challenge for the treatment of CRKP infections.

It is noteworthy that specimen types may be associated with CRKP and CSKP. Our findings have practical implication for predicting CRKP according to specimen types. When \textit{K. pneumoniae} specimens were isolated from the bloodstream, urinary, wound, and catheter tip, the rates of CRKP were higher than those of CSKP. Although bloodstream infection with CRKP was the most commonly reported, the number of respiratory specimen was higher than the total of other specimen types. This suggests that pulmonary infection/colonization with \textit{K. pneumoniae} should not be ignored.

For patients isolated with \textit{K. pneumoniae} in the ICU, their sources were not reported before. We found that the incidence of CRKP patients from other hospitals had increased to 52.94\%, exceeding the rate of patients from our hospital. The trend of CSKP patients from our hospital was downward. It indicated that antibiotic resistance control measures in our hospital were progressive. Special attention should be paid to patients who transferred to the ICU from other hospitals.

In the study, we found that CRKP isolates were mainly acquired in the ICU. It confirmed ICU admission was an important risk factor for acquiring CRKP. It demonstrated that CRKP isolates may be acquired through horizontal transmission during ICU hospitalization. Previous studies have reported interventions to reduce transmission of carbapenem-resistant \textit{Enterobacteriaceae}\textsuperscript{31, 32}. Knowledge of local prevalence rate of CRKP and tailored surveillance actions based on local circumstance are crucial.

In our study, we observed that younger age, previous admission, previous ICU stay,
prior use of surgical drainage and gastric tube, and use of carbapenems, tigecycline, β-lactams/β-lactamase inhibitors, fluoroquinolones, and antifungal drugs within the prior 3 months were risk factors for ICU KP patients isolated with CRKP. Interestingly, we found the median age of CRKP patients was younger than that of CSKP patients, which was consistent with the earlier studies\textsuperscript{24, 25}. Although we cannot explain this finding, it is possible that it constitutes a risk factor, and further studies are required to confirm the finding. For invasive procedures, prior use of surgical drainage and gastric tube were not reported as independent risk factors before. This may be due to the different types of patients in these studies or differences in sample size. Antimicrobial exposure was reported as a potential risk factor for CRKP infection/colonization. Although antibiotics identified in these studies and antimicrobial exposure time vary\textsuperscript{13, 24, 25}, local and practical antibiotic stewardship measures are necessary.

Our study has several limitations. Firstly, our hospital is a tertiary hospital that admits a variety of critically ill patients, and the sources of patients and other epidemiology data may not be suitable for specialized hospitals. Secondly, as a retrospective analysis, clinical data were obtained from electronic medical records, and missing information may have potential effects on the results. Nevertheless, the sample size of our study was not small, and did not hamper the statistical power of our analysis.

Conclusions
Overall, the rate of KP isolates resistance to carbapenems increased, and the severity of this resistance significantly increased. Intensive and local infection/colonization control measures are necessary for ICU patients, especially those with risk factors for CRKP infection/colonization.

Acknowledgments The authors thank all of the study participants.

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.
Funding  This research received no specific grant from any funding agency in the public, commercial
or not-for-profit sectors.

Conflict of interest  The authors declare no conflict of interest.

Patient consent for publication  Not applicable.

Ethical Approval  The study was approved by the Ethics Committee of Xiangya Hospital Central
South University (2018091076).

Provenance and peer review  Not commissioned; externally peer reviewed.

Data availability statement  All data relevant to the study are available on reasonable request to the
corresponding author.

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ORCID iD
Tao Yin  http://orcid.org/0000-0002-7939-1803

Figure captions:

Figure 1: The number (A) and distribution (B) of *K. pneumoniae* isolated sites.

Figure 2: Trends in the prevalence of *K. pneumoniae* isolates non-susceptible to
imipenem, meropenem, and ertapenem.

Figure 3: Changing trends in the sources of patients with *K. pneumoniae* isolates.

Figure 4: Distribution of the sources of *K. pneumoniae* isolates.
### Table 1 Clinical characteristics and risk factors for CRKP infection/colonization

<table>
<thead>
<tr>
<th>General characteristics</th>
<th>CRKP (377)</th>
<th>CSKP (503)</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>294 (77.98)</td>
<td>363 (72.17)</td>
<td>1.37 (1.00-1.87)</td>
<td>0.050</td>
</tr>
<tr>
<td>Age (years)</td>
<td>54.43 ± 15.51</td>
<td>57.04 ± 16.17</td>
<td>0.87 (0.79-0.96)</td>
<td>0.005</td>
</tr>
<tr>
<td>Previous admission</td>
<td>CRKP</td>
<td>CSKP</td>
<td>OR (95%CI) P</td>
<td>OR (95%CI) P</td>
</tr>
<tr>
<td>No previous admission</td>
<td>5 (1.33)</td>
<td>36 (7.16)</td>
<td>0.72 (0.57-0.90)</td>
<td>0.004</td>
</tr>
<tr>
<td>Other hospitals</td>
<td>169 (44.83)</td>
<td>110 (21.87)</td>
<td>0.87 (0.78-0.98)</td>
<td>0.018</td>
</tr>
<tr>
<td>Our hospital</td>
<td>203 (53.85)</td>
<td>357 (70.97)</td>
<td>0.73 (0.56-0.95)</td>
<td>0.018</td>
</tr>
<tr>
<td>Recent events</td>
<td>CRKP</td>
<td>CSKP</td>
<td>OR (95%CI) P</td>
<td>OR (95%CI) P</td>
</tr>
<tr>
<td>Prior surgery</td>
<td>214 (56.76)</td>
<td>289 (57.46)</td>
<td>2.81 (1.99-3.96)</td>
<td>0.000</td>
</tr>
<tr>
<td>Previous ICU stay</td>
<td>111 (29.44)</td>
<td>65 (12.92)</td>
<td>1.69 (1.15-2.47)</td>
<td>0.008</td>
</tr>
<tr>
<td>Invasive procedures</td>
<td>CRKP</td>
<td>CSKP</td>
<td>OR (95%CI) P</td>
<td>OR (95%CI) P</td>
</tr>
<tr>
<td>Tracheostomy tube</td>
<td>154 (40.85)</td>
<td>155 (30.82)</td>
<td>1.55 (1.17-2.05)</td>
<td>0.002</td>
</tr>
<tr>
<td>Surgical drainage</td>
<td>251 (66.58)</td>
<td>285 (56.66)</td>
<td>1.52 (1.16-2.01)</td>
<td>0.003</td>
</tr>
<tr>
<td>Indwelled central venous catheter</td>
<td>221 (58.62)</td>
<td>221 (43.94)</td>
<td>1.81 (1.38-2.37)</td>
<td>0.000</td>
</tr>
<tr>
<td>Gastric tube</td>
<td>278 (73.74)</td>
<td>288 (57.26)</td>
<td>2.10 (1.57-2.80)</td>
<td>0.000</td>
</tr>
<tr>
<td>Urinary catheter</td>
<td>296 (78.51)</td>
<td>380 (75.55)</td>
<td>1.73 (1.25-2.39)</td>
<td>0.001</td>
</tr>
<tr>
<td>Comorbidities</td>
<td>CRKP</td>
<td>CSKP</td>
<td>OR (95%CI) P</td>
<td>OR (95%CI) P</td>
</tr>
<tr>
<td>Hypertension</td>
<td>128 (33.95)</td>
<td>155 (30.82)</td>
<td>1.17 (0.88-1.56)</td>
<td>0.283</td>
</tr>
<tr>
<td>Diabetes</td>
<td>60 (15.92)</td>
<td>66 (13.12)</td>
<td>1.25 (0.85-1.83)</td>
<td>0.255</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>39 (10.34)</td>
<td>61 (12.13)</td>
<td>0.82 (0.53-1.27)</td>
<td>0.371</td>
</tr>
<tr>
<td>Hepatitis/cirrhosis</td>
<td>27 (7.16)</td>
<td>24 (4.77)</td>
<td>1.49 (0.82-2.71)</td>
<td>0.187</td>
</tr>
<tr>
<td>Chronic renal insufficiency</td>
<td>10 (2.65)</td>
<td>11 (2.19)</td>
<td>1.34 (0.53-3.41)</td>
<td>0.538</td>
</tr>
<tr>
<td>Malignancy</td>
<td>22 (5.84)</td>
<td>31 (6.16)</td>
<td>0.90 (0.51-1.59)</td>
<td>0.719</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>24 (6.37)</td>
<td>19 (3.78)</td>
<td>1.73 (0.93-3.21)</td>
<td>0.081</td>
</tr>
<tr>
<td>Antibiotics used within 3 months</td>
<td>CRKP (377)</td>
<td>CSKP (503)</td>
<td>OR (95%CI) P</td>
<td>OR (95%CI) P</td>
</tr>
<tr>
<td>Carbapenems</td>
<td>250 (66.31)</td>
<td>174 (34.59)</td>
<td>3.72 (2.81-4.93)</td>
<td>0.000</td>
</tr>
<tr>
<td>Tigecycline</td>
<td>88 (23.34)</td>
<td>31 (6.16)</td>
<td>4.64 (3.00-7.16)</td>
<td>0.000</td>
</tr>
<tr>
<td>Glycopeptides</td>
<td>105 (27.85)</td>
<td>95 (18.89)</td>
<td>1.66 (1.21-2.28)</td>
<td>0.002</td>
</tr>
<tr>
<td>β-lactams/β-lactamase inhibitors</td>
<td>277 (73.47)</td>
<td>284 (56.46)</td>
<td>2.14 (1.60-2.85)</td>
<td>0.000</td>
</tr>
</tbody>
</table>

Page 13 of 26
For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml
<table>
<thead>
<tr>
<th>Category</th>
<th>Cases (Frequency)</th>
<th>Controls (Frequency)</th>
<th>Odds Ratio (95% CI)</th>
<th>P Value</th>
<th>NRI (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3rd/4th generation</td>
<td>115 (30.5)</td>
<td>149 (29.62)</td>
<td>1.04 (0.78-1.40)</td>
<td>0.778</td>
<td></td>
</tr>
<tr>
<td>Cephalosporins</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>96 (25.46)</td>
<td>66 (13.12)</td>
<td>2.26 (1.60-3.20)</td>
<td>0.000</td>
<td>1.54 (1.04-2.29)</td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td>26 (6.9)</td>
<td>17 (3.38)</td>
<td>2.12 (1.13-3.96)</td>
<td>0.019</td>
<td></td>
</tr>
<tr>
<td>Antifungal drugs</td>
<td>84 (22.28)</td>
<td>36 (7.16)</td>
<td>2.63 (1.84-3.76)</td>
<td>0.000</td>
<td>1.66 (1.13-2.44)</td>
</tr>
</tbody>
</table>

REFERENCES


10. Saeed NK, Alkhawaja S, Azam N, et al. Epidemiology of...


22 Cienfuegos-Gallet AV, Ocampo de Los Rios AM, Sierra Viana P, *et al.* Risk


Figure 1 The number (A) and distribution (B) of *K. pneumoniae* isolated sites.

193x239mm (300 x 300 DPI)
Figure 2 Trends in the prevalence of *K. pneumoniae* isolates non-susceptible to imipenem, meropenem, and ertapenem

342x167mm (300 x 300 DPI)
Figure 3 Changing trends in the sources of patients with *K. pneumoniae* isolates.

217x203mm (300 x 300 DPI)
Figure 4 Distribution of the sources of *K. pneumoniae* isolates.

349x154mm (300 x 300 DPI)
**Supplementary Table A1** The resistance rate of *K. pneumoniae* isolates to carbapenems over the study period (2012-2020)

<table>
<thead>
<tr>
<th>KP</th>
<th>CRKP</th>
<th>CSKP</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>2012</td>
<td>9 (11.11)</td>
<td>72 (88.89)</td>
<td>81</td>
</tr>
<tr>
<td>2013</td>
<td>12 (13.04)</td>
<td>80 (86.96)</td>
<td>92</td>
</tr>
<tr>
<td>2014</td>
<td>22 (30.14)</td>
<td>51 (69.86)</td>
<td>73</td>
</tr>
<tr>
<td>2015</td>
<td>43 (50)</td>
<td>43 (50)</td>
<td>86</td>
</tr>
<tr>
<td>2016</td>
<td>47 (51.09)</td>
<td>45 (48.91)</td>
<td>92</td>
</tr>
<tr>
<td>2017</td>
<td>74 (64.35)</td>
<td>41 (35.65)</td>
<td>115</td>
</tr>
<tr>
<td>2018</td>
<td>52 (52.53)</td>
<td>47 (47.47)</td>
<td>99</td>
</tr>
<tr>
<td>2019</td>
<td>50 (48.54)</td>
<td>53 (51.46)</td>
<td>103</td>
</tr>
<tr>
<td>2020</td>
<td>68 (48.92)</td>
<td>71 (51.08)</td>
<td>139</td>
</tr>
<tr>
<td>Total</td>
<td>377 (42.50)</td>
<td>503 (57.50)</td>
<td>880</td>
</tr>
</tbody>
</table>
The RECORD statement – checklist of items, extended from the STROBE statement, that should be reported in observational studies using routinely collected health data.

<table>
<thead>
<tr>
<th>Item No.</th>
<th>STROBE items</th>
<th>Location in manuscript where items are reported</th>
<th>RECORD items</th>
<th>Location in manuscript where items are reported</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Title and abstract</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>(a) Indicate the study’s design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found</td>
<td>(a) Lines 1-3 and 39 (b) Lines 43-57</td>
<td>RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included. RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract. RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.</td>
<td>RECORD 1.1:line 40 RECORD 1.2:lines 41-42 RECORD 1.3:not applicable</td>
</tr>
<tr>
<td><strong>Introduction</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Background rationale</td>
<td>2</td>
<td>Explain the scientific background and rationale for the investigation being reported</td>
<td>Lines 77-113</td>
<td></td>
</tr>
<tr>
<td>Objectives</td>
<td>3</td>
<td>State specific objectives, including any prespecified hypotheses</td>
<td>Lines 114-117</td>
<td></td>
</tr>
<tr>
<td><strong>Methods</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study Design</td>
<td>4</td>
<td>Present key elements of study design early in the paper</td>
<td>Lines 120-121</td>
<td></td>
</tr>
<tr>
<td>Setting</td>
<td>5</td>
<td>Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection</td>
<td>Lines 121-125</td>
<td></td>
</tr>
<tr>
<td>Participants</td>
<td>6</td>
<td>(a) Cohort study - Give the eligibility criteria, and the</td>
<td>(a) Cohort study - Lines 122-125</td>
<td>RECORD 6.1: The methods of study population selection (such as codes or</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Variables</td>
<td>7</td>
<td>Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.</td>
<td>Lines 130-141</td>
<td></td>
</tr>
<tr>
<td>Data sources/measurement</td>
<td>8</td>
<td>For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group</td>
<td>Lines 145-155</td>
<td></td>
</tr>
<tr>
<td>Bias</td>
<td>9</td>
<td>Describe any efforts to address potential sources of bias</td>
<td>Lines 121-125</td>
<td></td>
</tr>
<tr>
<td>Study size</td>
<td>10</td>
<td>Explain how the study size was determined</td>
<td>Line 122-124</td>
<td></td>
</tr>
<tr>
<td>Section</td>
<td>Page</td>
<td>Description</td>
<td>Lines</td>
<td></td>
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<tr>
<td>--------------------------------</td>
<td>------</td>
<td>-----------------------------------------------------------------------------</td>
<td>-------</td>
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</tr>
<tr>
<td>Quantitative variables</td>
<td>11</td>
<td>Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>In our study, age is a quantitative variable. In the logistic analysis, we transform the continuous variable into a ordered multiclass variable. Age groups were ≤40 years old, 40-50 years old, 50-60 years old, 60-70 years old, and &gt;70 years old.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Statistical methods           | 12   | (a) Describe all statistical methods, including those used to control for confounding  
(b) Describe any methods used to examine subgroups and interactions  
(c) Explain how missing data were addressed  
(d) Cohort study - If applicable, explain how loss to follow-up was addressed  
Case-control study - If applicable, explain how matching of cases and controls was addressed  
Cross-sectional study - If applicable, describe analytical methods taking account of sampling strategy  
(e) Describe any sensitivity analyses | 154-162 |
| Data access and cleaning methods | ..   | RECORD 12.1: Authors should describe the extent to which the investigators had access to the database | 130-141 |
| Linkage | .. | RECORD 12.3: State whether the study included person-level, institutional-level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided. | not applicable |

<table>
<thead>
<tr>
<th><strong>Results</strong></th>
<th></th>
<th></th>
</tr>
</thead>
</table>
| **Participants** | 13 | (a) Report the numbers of individuals at each stage of the study (e.g., numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed)  
(b) Give reasons for non-participation at each stage.  
(c) Consider use of a flow diagram | (a) Lines 168-169  
RECORD 13.1: Describe in detail the selection of the persons included in the study (i.e., study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.  
Lines 121-125 |
| **Descriptive data** | 14 | (a) Give characteristics of study participants (e.g., demographic, clinical, social) and information on exposures and potential confounders  
(b) Indicate the number of participants with missing data for each variable of interest  
(c) **Cohort study** - summarise follow-up time (e.g., average and total amount) | Lines 168-207,334 |
| **Outcome data** | 15 | **Cohort study** - Report numbers of outcome events or summary measures over time | Lines169-170, 216-221 |
| Main results | 16 | (a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included. (b) Report category boundaries when continuous variables were categorized. (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period. | Lines209-221 |
| Other analyses | 17 | Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses. | not applicable |

**Discussion**

| Key results | 18 | Summarise key results with reference to study objectives. | Lines223-228 |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias. | Lines285-291 | RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported. Lines287-291 |

**Interpretation**

<p>| 20 | Give a cautious overall interpretation of results. | Lines 293-296 |</p>
<table>
<thead>
<tr>
<th><strong>Generalisability</strong></th>
<th>21</th>
<th>Discuss the generalisability (external validity) of the study results</th>
<th>Lines 285-287</th>
</tr>
</thead>
</table>

**Other Information**

| **Funding** | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | Lines 302-303 |


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