

# Risk Factors for a Hospital-Acquired Carbapenem-Resistant *Klebsiella pneumoniae* Bloodstream Infection: A Five-Year Retrospective Study

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**Purpose:** This study aimed to describe trends in *Klebsiella pneumoniae* (KP) resistance in bloodstream infections (BSI) and to identify risk factors for a hospital-acquired carbapenem-resistant *Klebsiella pneumoniae* (CRKP) BSI and 28-day mortality from a hospital-acquired KP BSI.

**Patients and Methods:** We recorded the results of antimicrobial susceptibility testing of 396 KP-positive blood cultures from January 2016 to December 2020. A total of 277 patients with a KP BSI were included in this study, of which 171 had a hospital-acquired infection and 84 had a hospital-acquired CRKP BSI. Multivariate logistic regression analysis was used to identify risk factors for a hospital-acquired CRKP BSI and 28-day mortality from a hospital-acquired KP BSI.

**Results:** The proportion of hospital-acquired infections among KP BSI patients increased from 53.1% in 2016 to 72.8% in 2020. The detection rate of CRKP among KP BSI patients increased from 18.8% in 2016 to 37.7% in 2020. Multivariate logistic regression showed that  $\beta$ -lactam/ $\beta$ -lactamase inhibitor combinations (BLBLIs) exposure ( $P = 0.022$ , OR 2.863), carbapenems exposure ( $P = 0.007$ , OR 3.831) and solid organ transplantation ( $P < 0.001$ , OR 19.454) were independent risk factors for a hospital-acquired CRKP BSI. Risk factors for a 28-day mortality from hospital-acquired KP BSI were CRKP BSI ( $P = 0.009$ , OR 5.562), septic shock ( $P = 0.002$ , OR 4.862), mechanical ventilation  $> 96$  hours ( $P = 0.020$ , OR 8.765), and platelet counts  $< 100 \times 10^9/L$  ( $P = 0.003$ , OR 4.464).

**Conclusion:** The incidence of hospital-acquired KP BSI continues to rise and the proportion of CRKP BSI is also increasing. We believe that the use of the BLBLIs needs to be carefully evaluated in hospital-acquired infection. Hospital-acquired KP BSI Patients with CRKP BSI, septic shock, mechanical ventilation and deficiency of platelets are more likely to have a poor prognosis.

**Keywords:** *Klebsiella pneumoniae*, bloodstream infection, carbapenem resistance, hospital-acquired infection, risk factors

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## Introduction

Given the widespread use of carbapenems worldwide, carbapenem-resistant *Enterobacteriaceae* (CRE) has emerged all over the world.<sup>1-3</sup> Carbapenemase types of *Enterobacteriaceae* have changed greatly, *Klebsiella pneumoniae* carbapenemase (KPC) producers have an increasing prevalence in hospital acquired pathogens, most prominently among *Klebsiella pneumoniae* (KP).<sup>4</sup> Transmission of

carbapenem-resistant *Klebsiella pneumoniae* (CRKP) is largely nosocomial.<sup>5,6</sup> Urine is the main source of CRKP, which may be related to many of elderly patients.<sup>7,8</sup> However, the overall in-hospital mortality of urinary tract CRE infection is low,<sup>9</sup> while the mortality of bloodstream infection (BSI) caused by CRE is significantly higher.<sup>10,11</sup> BSI has become one of the major medical burdens worldwide,<sup>12</sup> the incidence of sepsis and BSI has risen in recent years.<sup>13</sup> The incidence of Gram-negative BSI is increasing<sup>14,15</sup> and CRKP BSI can prolong the length of hospitalization and increase patient mortality significantly,<sup>16,17</sup> which is an important clinical threat.

Previous studies have suggested that the real-time Whole Genome Sequencing (WGS) method may be helpful to monitor CRKP and improve the prognosis of patients.<sup>18</sup> The positive rate of CRKP culture in rectal swab samples is high,<sup>19,20</sup> which is helpful for the prediction of CRKP infection.<sup>21</sup> In addition to strict contact isolation,<sup>22,23</sup> previous studies have suggested that strict antibiotics restrictions can also help reduce the prevalence of CRE infection.<sup>24,25</sup> However, the specific formulation of antibiotic management plan and its impact on limiting CRE dissemination need to be more widely studied,<sup>26</sup> and the control of CRKP is still challenging due to the rapid transfer of horizontal gene of carbapenemase expressing plasmids.<sup>27</sup>

This study focused on hospital-acquired KP BSI, in particular CRKP BSI patients, described the results of antimicrobial susceptibility testing and clinical characteristics, and analyzed the risk factors for hospital-acquired CRKP BSI transmission and 28-day mortality from a hospital-acquired KP BSI.

## Study Design

This retrospective study was performed at The First Affiliated Hospital of Anhui Medical University, a 4990-bed tertiary-care teaching hospital in Anhui Province in east-central China from January 2016 to December 2020. KP BSI patients over 18 years old were included in this study. Hospital-acquired KP BSI was defined as the appearance of fevers, chills, or other infectious symptoms more than 48 hours after hospital admission, and confirmation of KP BSI by blood culture.<sup>28</sup> Patients with a history of hospital admission for BSI in the 14 days prior to the KP BSI admission were not included, and patients with a history of a KP BSI admission in the past 1 month were also excluded. The antibiotic use plan for all KP BSI patients was adjusted according to the results of

antimicrobial susceptibility testing. If the patient had multiple positive blood cultures during the study, only the first positive result was recorded. Exclusion criteria included patients younger than 18 years old, pregnant women, polybacteremia, hospitalization less than 48 hours and patients who withdrew from treatment and were difficult to follow. KP antimicrobial susceptibility testing was performed at the microbiology laboratory of the hospital. Antimicrobial resistances of KP isolated from blood samples from 2016 to 2020 were recorded. Patient clinical characteristics were collected from the medical record review system to further analyze risk factors for hospital-acquired CRKP BSI. Multivariate analysis was used to identify risk factors for developing a hospital-acquired CRKP BSI, and for 28-day mortality due to a hospital-acquired KP BSI.

## Ethics

This study protocol was approved by the institutional review committee of Anhui Medical University, the First Affiliated Hospital (Reference number: Quick-PJ 2021–09–18). The ethics committee waived informed consent because this was a retrospective study. Patient data came from the medical record system and were anonymously analyzed to preserve patient privacy. In our study, all organs were donated voluntarily with written informed consent, which was conducted in accordance with the Declaration of Istanbul.

## Definitions

Multidrug-Resistant (MDR) was defined as acquired non-susceptibility to at least one agent in three or more antimicrobial categories.<sup>29</sup> CRKP was defined as resistance to any carbapenem. Antibiotic exposure was defined as receiving intravenous or oral antibiotics for more than 48 hours up to 90 days prior to a BSI.<sup>30</sup> The date of the collection of the first positive blood culture was considered the start of the BSI. Clinical data within 24 hours of BSI diagnosis were recorded. The Pitt bacteremia score was calculated within 24 hours of BSI diagnosis, and the highest score was recorded. Appropriate initial anti-microbial therapy was defined as the initial antibiotic regimen started after the BSI diagnosis that was consistent with the results of antimicrobial susceptibility testing.

## Antimicrobial Susceptibility Testing

Isolates were confirmed using the VITEK-2 GNI (bioMérieux Vitek Inc. in Hazelwood, Missouri, USA) and Clin-ToF-II systems<sup>31</sup> (Bioyong Technologies Inc. in Beijing, China). Antimicrobial susceptibility testing was also performed using

the microdilution method or Kirby-Bauer disk diffusion method, and drug susceptibility results were interpreted according to the standards of the Clinical and Laboratory Standards Institute (CLSI).<sup>32</sup> *Pseudomonas aeruginosa* ATCC 27853 and *Escherichia coli* ATCC 25922 were used as controls for antimicrobial susceptibility testing. All experiments were repeated three times.

## Data Collection

The following demographic and clinical data were extracted from the hospital electronic medical record system: sex, age, length of hospital stay, previous hospitalization, complicated infection site, comorbidities (diabetes, cardiovascular, kidney disease, solid tumor, hematological malignancy, solid organ transplantation, etc.), clinical invasive procedures (catheter, central venous catheter (CVC), peripherally inserted central venous catheter [PICC], arterial catheter, blood purification, endotracheal intubation, mechanical ventilation, nasogastric tube, sputum suction, catheterization, puncture, endoscope, etc.), special treatments (corticosteroids, immunosuppressants, intravenous immunoglobulin, chemotherapy, radiotherapy), antibiotic exposure, and antibiotic treatment data. The Pitt bacteremia score was used to assess the severity of the BSI. The Charlson comorbidity index (CCI) was used to quantitatively measure comorbidities.<sup>33</sup>

## Statistical Analysis

SPSS version 23.0 was used for data analysis. Continuous variables with a normal distribution were expressed as mean and standard deviation (SDS), and continuous variables with a non-normal distribution were expressed as median and interquartile range (IQR). For univariate analyses, categorical variables were compared using chi-squared or Fisher's exact tests, and continuous variables were compared using Student's *t*-test or the Mann-Whitney *U*-test. A *P* value <0.05 was considered statistically significant. Significant variables in univariate analysis (*P*<0.05) were selected for inclusion in a multivariate logistic regression. Results were reported as odds ratios (ORs) with 95% confidence intervals (CIs) and *P* values. *P* values <0.05 were considered statistically significant. The Hosmer-Lemeshow test was used to evaluate the goodness of fit of the model. The logistic regression model was reliable when the *P* value >0.05 in Hosmer-Lemeshow test.

## Results

### Characteristics of Study Participants

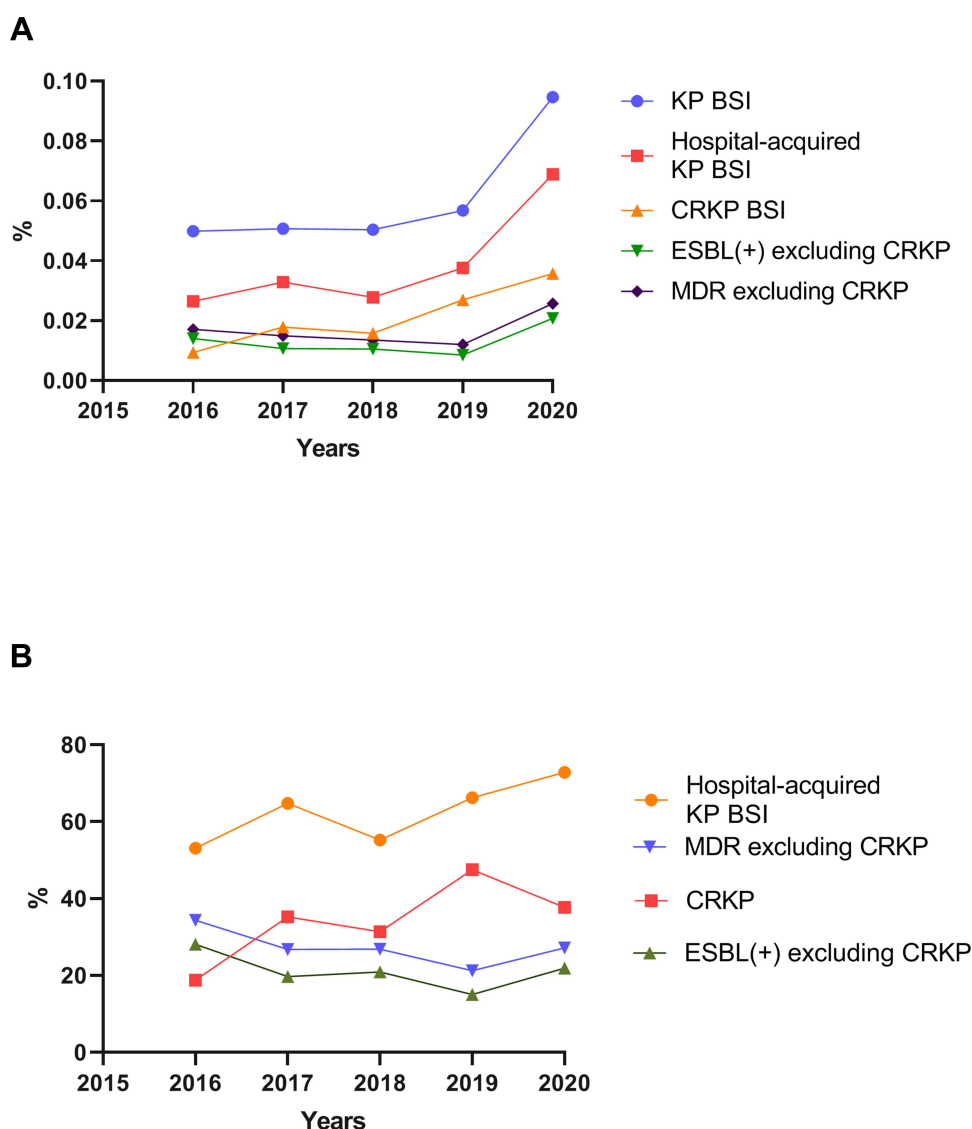
Of the 396 patients who met BSI criteria, 277 were included in this study. Of the 277 patients included in this study, 171 (61.7%) had hospital-acquired infections and 106 (38.3%) had non-hospital-acquired infections. The mortality of the hospital-acquired infection group was 33.3% (57/171), and that of the non-hospital-acquired infection group was 12.3% (13/106), which was statistically significant (*P*<0.001). The mortality rate of the CRKP group was 50.0% (47/94), while that of the carbapenem susceptible *Klebsiella pneumoniae* (CSKP) group was 12.6% (23/183), which was statistically significant (*P* < 0.001). Of the patients with a CRKP BSI, 84 had a hospital-acquired infection.

### Trends in the Prevalence of KP BSI Over the Five-Year Period

As shown in Figure 1, the prevalence of KP BSI, hospital-acquired KP BSI, and CRKP BSI in inpatients increased from 0.050%, 0.026%, and 0.0094% in 2016 to 0.095%, 0.069%, and 0.036% in 2020. Except for patients with CRKP BSI, there was smaller increase in the proportion of ESBL positive KP BSI and MDR KP BSI in the total number of hospitalized patients. The proportion of hospital-acquired infections and CRKP among KP BSI patients had an upward trend over the 5-year period, from 53.1% and 18.8% in 2016 to 72.8% and 37.7% in 2020. Except for patients with CRKP BSI, the proportion of ESBL positive KP BSI and MDR KP BSI among KP BSI had a downward trend, from 28.1% and 34.4% in 2016 to 21.9% and 27.2% in 2020.

### Detection Distribution of KP BSI by Department

KP BSI was most commonly detected in the Intensive care unit (ICU), the department of hematology, and the department of infectious disease department. The top three departments with the highest detection rates of hospital-acquired KP BSI and CRKP BSI were the ICU, the department of hematology and the department of kidney transplantation. Details are shown in Figure 2. The detection rates of KP BSI, hospital acquired KP BSI, and CRKP BSI in various departments are shown in Figure 3. Except ICU, the highest hospital-acquired infection rates of KP BSI, hospital acquired KP BSI, and CRKP BSI were in the department of kidney transplantation, with rates of 1.42%, 1.22%, and 1.09%, respectively, followed by the department of hematology and the department of liver transplantation.



**Figure 1** (A) Proportion of different categories of KP BSI in total hospitalized patients from 2016 to 2020. (B) Proportion of different categories of KP in total KPBSIs from 2016 to 2020. The detection rate of KP BSI and CRKP BSI and the proportion of hospital-acquired KP BSI among total KP BSI increased over time. Except for patients with CRKP BSI, there was smaller increase in the proportion of ESBL positive KP BSI and MDR KP BSI in the total number of hospitalized patients, while the proportion of ESBL positive KP BSI and MDR KP BSI among KP BSI had a downward trend.

**Abbreviations:** KP, *Klebsiella pneumoniae*; CRKP, carbapenem-resistant KP; BSI, bloodstream infection; MDR, multidrug resistant; ESBL, extended spectrum  $\beta$ -lactamase.

## Antimicrobial Susceptibility of KP BSI

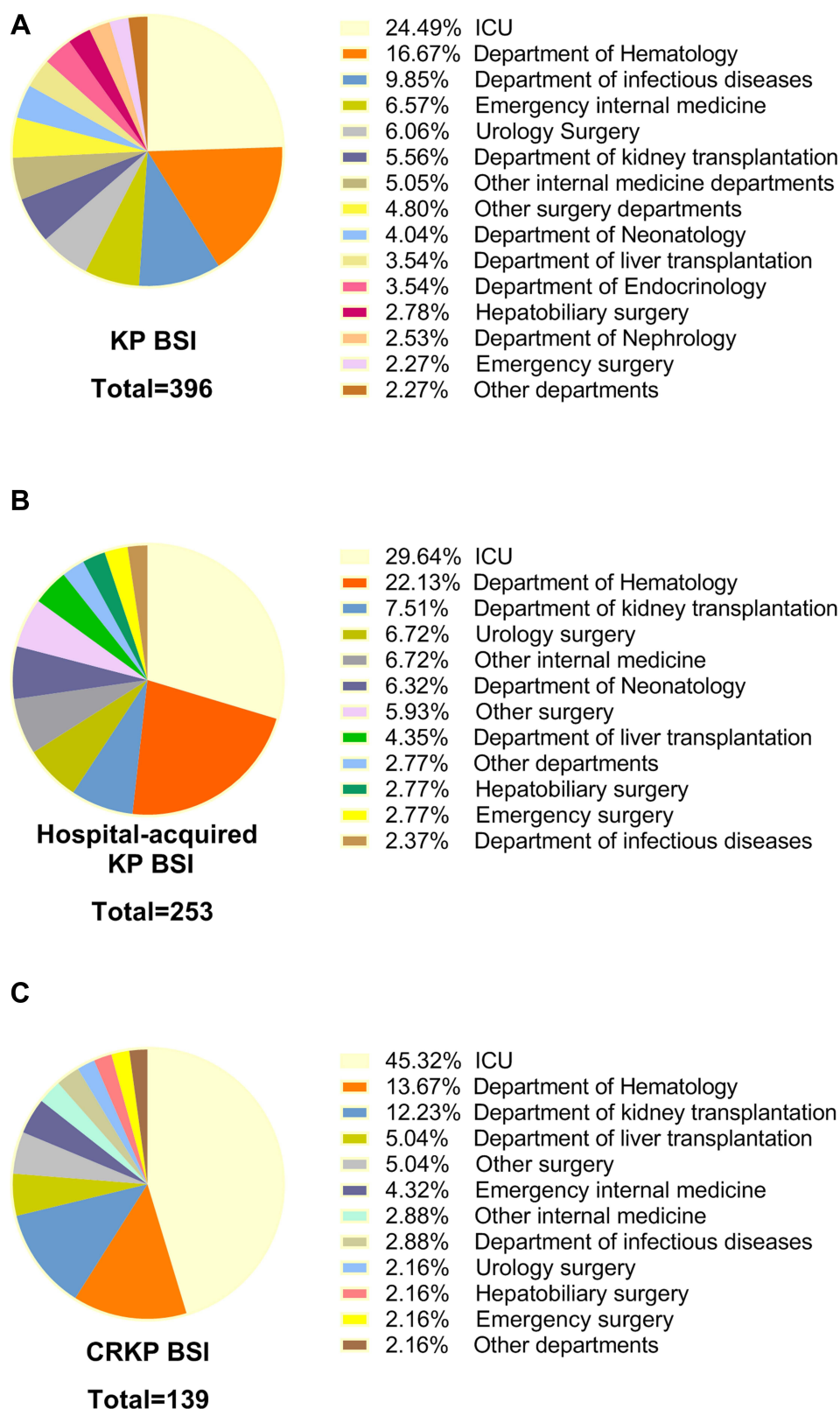
There was an upward trend in the drug resistance of KP to various antibiotics. The drug resistance rate of cephalosporins,  $\beta$ -lactam/ $\beta$ -lactamase inhibitor combinations (BLBLIs), and quinolones increased significantly in the past 5 years (details are shown in Table 1).

## Antimicrobial Susceptibility of CRKP BSI

There was an high rate of the drug non-susceptibility of CRKP to various antibiotics. The non-susceptibility rates of CRKP to aminoglycoside antibiotics and fosfomycin are high (details are shown in Table 2).

## Antibiotic Exposure and Use in the Setting of Hospital-Acquired and Non-Hospital-Acquired KP BSI

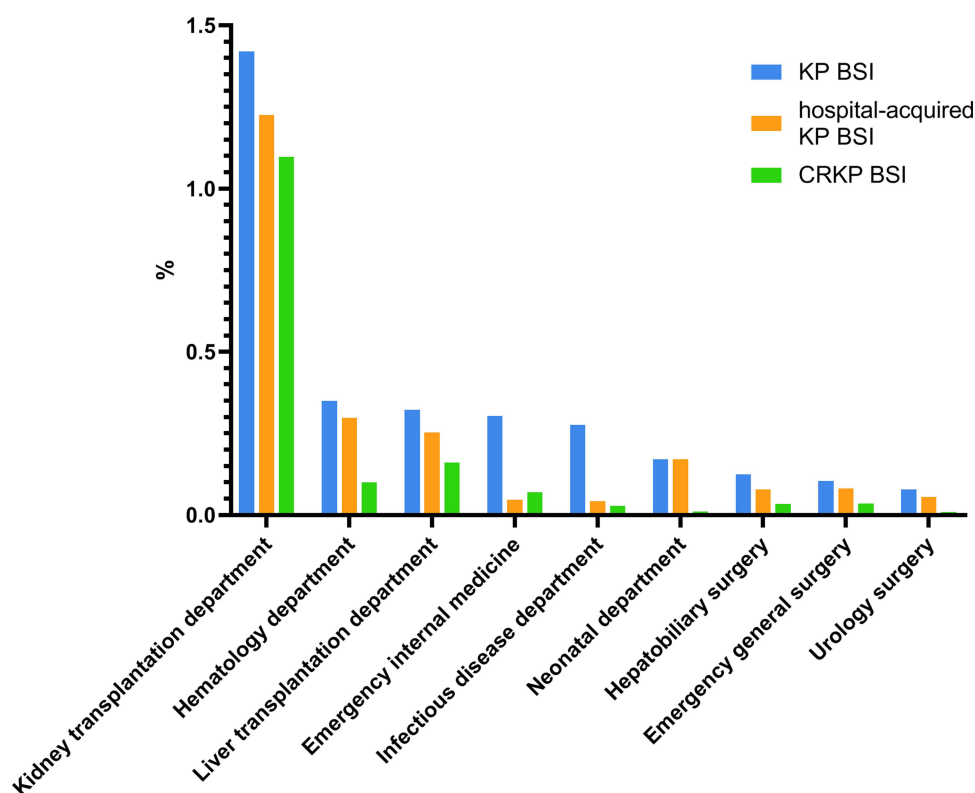
As shown in Table 3, patients with hospital-acquired KP BSI had more antibiotic exposures, especially to carbapenems, glycopeptides, cephalosporins, BLBLIs, Trimethoprim-sulfamethoxazole (TMP-SMZ) and antifungal agents. The non-hospital-acquired KP BSI group was more likely to receive the treatment regimen containing BLBLIs ( $P=0.004$ ). The non-hospital-acquired group was more likely to receive early appropriate therapy ( $P < 0.001$ ).



**Figure 2** Department distribution of KP BSI (A), hospital-acquired KP BSI (B) and CRKP BSI (C) from 2016 to 2020. The primary setting of KP BSI, hospital-acquired KP BSI and CRKP BSI was the ICU.

**Abbreviations:** KP, *Klebsiella pneumoniae*; CRKP, carbapenem-resistant KP; ICU, intensive care unit





**Figure 3** Hospital-acquired infection rates of KP BSI, hospital-acquired KP BSI, and CRKP BSI by various departments. The number of ICU inpatients was difficult to determine, so they were not included in this figure.

**Abbreviations:** KP, *Klebsiella pneumoniae*; CRKP, carbapenem-resistant KP; ICU, intensive care unit.

## Risk Factors for CRKP BSI in Hospital-Acquired KP BSI

Compared with the CSKP group, the CRKP group had a longer hospital stay time, more antibiotic exposure, were more prone to altered mental status and septic shock, and received more invasive operations. CSKP patients were older and had more 90-day readmissions. The Pitt bacteremia score of the CRKP group was higher. There were more patients with a history of chronic kidney disease, intracerebral hemorrhage, liver cirrhosis and solid organ transplantation in the CRKP group while there were more patients with hematological malignancies and solid tumors in the CSKP group. Detailed data are shown in Table 4.

The results of the multivariate analysis are shown in Table 5. The independent risk factors for CRKP BSI in the hospital were the BLBLIs exposure ( $P = 0.022$ , OR 2.863), Carbapenems exposure ( $P = 0.007$ , OR 3.831) and solid organ transplantation ( $P < 0.001$ , OR 19.454).

## Risk Factors for 28-Day Mortality in Patients with Hospital-Acquired KP BSI

Univariate analysis of risk factors associated with 28-day mortality in patients with hospital-acquired KP BSI is shown in Table 6. Patients in the death group had more antibiotic exposures and received more invasive procedures. Comorbidities do not significantly increase the 28-day risk of death from hospital-acquired KP BSI.

The results of the multivariate analysis are shown in Table 7. Multivariate analysis suggested that the risk factors for 28-day mortality after a hospital-acquired KP BSI were CRKP BSI ( $P = 0.009$ , OR 5.562), septic shock ( $P = 0.002$ , OR 4.862), and mechanical ventilation  $>96$  hours ( $P = 0.020$ , OR 8.765), platelet (PLT) count  $<100 \times 10^9/L$  ( $P = 0.003$ , OR 4.464).

## Discussion

The incidence of KP BSI has gradually increased over the past few years, especially among hospital-acquired infections.<sup>34</sup> The overall resistance rate of various antibiotics to KP BSI is rising, as is the proportion of CRKP

**Table 1** Antimicrobial Resistances of *Klebsiella pneumoniae* Isolated from Blood Samples from 2016 to 2020

Antimicrobial Agents	2016 (n=64)	2017 (n=71)	2018 (n=67)	2019 (n=80)	2020 (n=114)
Ampicillin	63	70	66	80	114
Ampicillin-sulbactam	32	38	39	51	70
Piperacillin-tazobactam	12	25	21	38	46
Cefotetan	10	22	23	39	42
Ceftazidime	22	32	26	44	48
Cefotaxime	31	40	35	50	68
Ceftriaxone	30	39	35	50	68
Cefepime	16	31	24	39	47
Aztreonam	25	34	27	44	58
Imipenem	12	24	20	37	42
Meropenem	-	24	17	36	40
Amikacin	9	17	7	22	33
Gentamicin	19	19	20	38	49
Tobramycin	15	20	10	33	39
Ciprofloxacin	20	31	23	43	62
Levofloxacin	17	30	22	38	46
TMP-SMZ	28	23	15	22	40

**Abbreviation:** TMP-SMZ, trimethoprim-sulfamethoxazole.

**Table 2** Antimicrobial Non-susceptibility of Carbapenem-Resistant *Klebsiella pneumoniae* Isolated from Blood Samples from 2016 to 2020

Antimicrobial Agents	Susceptible(%)	Intermediate(%)	Resistant(%)	Total Number of Testing
Amikacin	55(39.6)	1(0.7)	83(59.7)	139
Gentamicin	27(19.4)	2(1.4)	110(79.1)	139
Tobramycin	27(19.4)	10(7.2)	102(73.4)	139
TMP-SMZ	80(57.6)	0	59(42.4)	139
Minocycline	101(88.6)	8(7.0)	5(4.4)	114
Tigecycline	111(97.4)	2(1.8)	1(0.9)	114
Fosfomycin	11(11.7)	11(11.7)	72(76.6)	94
Polymyxin B	47(95.9)	0	2(4.1)	49
Ceftazidime-avibactam	32(97.0)	0	1(3.0)	33

**Note:** Antibiotics with resistance rate approaching 100% are not listed in the table.

**Abbreviation:** TMP-SMZ, trimethoprim-sulfamethoxazole.

BSI.<sup>35</sup> Previous studies have shown that healthcare-associated risk factors are independently associated with gram-negative bloodstream infections.<sup>15</sup> We therefore collected the clinical data of patients with a KP BSI, recorded the results of antimicrobial susceptibility testing of KP BSI, and identified risk factors for hospital-acquired CRKP BSI and 28-day mortality from hospital-acquired KP BSI so as to provide guidance for the prevention and reasonable treatment of hospital infections.

Carbapenems are still the most commonly used antibiotics in the treatment of hospital acquired KP BSI at our hospital, and the BLBLIs are commonly used in the treatment of non-hospital-acquired KP BSIs. Although carbapenems are one of the first choice drugs for the treatment of complex urinary tract infections and severe gram-negative bacterial infections,<sup>36,37</sup> many previous studies have suggested that carbapenems exposure history is a risk factor for CRKP infection.<sup>38,39</sup> Our multivariate

**Table 3** Antibiotic Exposure and Use Histories of Patients with Hospital-Acquired and Non-Hospital-Acquired KP BSI

	Non-Hospital-Acquired (n=106)	Hospital-Acquired (n=171)	$\chi^2$	P value <sup>a</sup>
<b>Antibiotic exposure</b>				
Any antibiotics	30(28.3%)	113(66.1%)	37.399	<b>&lt;0.001</b>
Carbapenems	5(4.7%)	65(38.0%)	38.412	<b>&lt;0.001</b>
Glycopeptides	7(6.6%)	43(25.1%)	15.210	<b>&lt;0.001</b>
Quinolones	6(5.7%)	27(15.8%)	6.398	<b>0.011</b>
Cephalosporins	5(4.7%)	37(21.6%)	14.564	<b>&lt;0.001</b>
BLBLIs	7(6.6%)	75(43.9%)	43.584	<b>&lt;0.001</b>
Aminoglycosides	0	3(1.8%)	0.599	0.439
Linezolid	1(0.9%)	9(5.3%)	2.377	0.123
Tigecycline	2(1.9%)	18(10.5%)	7.291	<b>0.007</b>
Nitroimidazoles	0	5(2.9%)	1.722	0.189
TMP-SMZ	0	10(5.8%)	4.860	<b>0.027</b>
Minocycline	1(0.9%)	6(3.5%)	0.862	0.353
Antifungal agents	3(2.8%)	42(24.6%)	22.712	<b>&lt;0.001</b>
<b>Antibiotic use<sup>b</sup></b>				
Use Carbapenems	75(70.8%)	111(64.9%)	1.013	0.314
Use Quinolones	22(20.8%)	25(14.6%)	1.748	0.186
Use Cephalosporins	19(17.9%)	23(13.5%)	1.018	0.313
Use BLBLIs	65(61.3%)	74(43.3%)	8.524	<b>0.004</b>
Use Tigecycline	8(7.5%)	51(29.8%)	19.373	<b>&lt;0.001</b>
Use Amikacin	10(9.4%)	20(11.7%)	0.347	0.556
Use Minocycline	10(9.4%)	18(10.5%)	0.086	0.769
Use fosfomycin	7(6.6%)	2(1.2%)	4.540	<b>0.033</b>
Use Nitroimidazoles	8(7.5%)	5(2.9%)	2.179	0.140
Use TMP-SMZ	1(0.9%)	12(7.0%)	4.125	<b>0.042</b>
Use Ceftazidime-avibactam	0	7(4.1%)	2.945	0.086
Use polymyxin B	0	6(3.5%)	2.326	0.127
Early appropriate therapy <sup>c</sup>	94(88.7%)	102(59.6%)	26.653	<b>&lt;0.001</b>

**Notes:** <sup>a</sup>P values less than 0.05 are bolded; <sup>b</sup>The antibiotics selected for the first time were consistent with the antimicrobial susceptibility testing; <sup>c</sup>It refers to all antibiotics that have been used for more than 48 hours after the start of BSI.

**Abbreviations:** TMP-SMZ, trimethoprim-sulfamethoxazole; BLBLIs,  $\beta$ -lactam/ $\beta$ -lactamase inhibitor combinations.

analysis supported these hypotheses. Our multivariate analysis also found that exposure to the BLBLIs was an independent risk factor for hospital-acquired CRKP BSI, a correlation rarely mentioned in previous studies. There is an antibiotic restriction strategy (including carbapenems, Polymyxin, tigecycline and ceftazidime-avibactam) at our hospital, which leads to the use of the BLBLIs has significantly increased. A previous study suggested that a history of BLBLIs exposure may increase the risk of CRKP colonization.<sup>40</sup> A larger number of clinical studies have sought alternatives to carbapenems. Some studies have suggested that BLBLIs are not inferior to carbapenems,<sup>41</sup> and may be cost-effective.<sup>42</sup> However, these studies rarely involve hospital acquired infections and BSI. A previous randomized clinical trial<sup>43</sup> did not support piperacillin-tazobactam as an alternative to

meropenem in the treatment of ceftriaxone resistant *Escherichia coli* and KP bloodstream infections. Moreover, our univariate analysis suggested that exposure to the BLBLIs may increase the risk of 28 day mortality from hospital-acquired KP BSI. We therefore believe that the use of the BLBLIs also needs to be carefully evaluated, especially in hospital-acquired infections.

Although there is an antibiotic restriction strategy at our hospital, we found that the incidence of CRKP BSI has increased over time. Antibiotic-resistant KP cases at our hospital have gradually concentrated on CRKP. We therefore speculate that besides carbapenem abuse there are other reasons for the CRKP epidemic. In general, patients with solid tumors and hematologic malignancies are prone to infections. Our study noted similar findings. There were significantly more KPBSI patients with hematologic



**Table 4** Clinical Characteristics of the CRKP and CSKP Groups of Hospital-Acquired KP BSI

Items	CSKP (n=87)	CRKP (n=84)	Z / $\chi^2$	P value
Male	48(55.2%)	66(78.6%)	10.530	<b>0.001</b>
Age	59(49.0-68.0)	51.5(37.0-64.0)	-2.334	<b>0.020</b>
Total length of hospital stay	27(13.0-37.0)	32.5(20.0-62.0)	-3.125	<b>0.002</b>
Death in 28 days	12(13.8%)	45(53.6%)	30.430	<b>&lt;0.001</b>
Admission history within 90 days	38(43.7%)	24(28.6%)	4.220	<b>0.040</b>
Any antibiotics exposure	38(43.7%)	75(89.3%)	39.661	<b>&lt;0.001</b>
Carbapenems exposure	16(18.4%)	49(58.3%)	28.937	<b>&lt;0.001</b>
BLBLIs exposure	21(24.1%)	54(64.3%)	27.976	<b>&lt;0.001</b>
Hypertension	19(21.8%)	33(39.3%)	6.147	<b>0.013</b>
Diabetes	18(20.7%)	15(17.9%)	0.220	0.639
Chronic kidney disease	9(10.3%)	23(27.4%)	8.154	<b>0.004</b>
Coronary heart disease	9(10.3%)	7(8.3%)	0.204	0.652
Cerebral infarction	7(8.0%)	17(20.2%)	5.265	<b>0.022</b>
Intracerebral hemorrhage	3(3.4%)	15(17.9%)	9.421	<b>0.002</b>
Liver cirrhosis	2(2.3%)	9(10.7%)	5.028	<b>0.025</b>
Solid tumor	16(18.4%)	3(3.6%)	9.503	<b>0.002</b>
Hematological malignancies	27(31.0%)	13(15.5%)	5.773	<b>0.016</b>
Solid organ transplantation	3(3.4%)	25(29.8%)	21.610	<b>&lt;0.001</b>
Immunosuppressive state	34(39.1%)	37(44.0%)	0.434	0.510
CCI score>2	18(20.7%)	16(19.0%)	0.072	0.788
Admission to ICU	16(18.4%)	49(58.3%)	28.937	<b>&lt;0.001</b>
Complicated pulmonary infection	18(20.7%)	44(52.4%)	18.572	<b>&lt;0.001</b>
Mechanical ventilation > 48 hours	11(12.6%)	36(42.9%)	19.574	<b>&lt;0.001</b>
Sputum aspiration	15(17.2%)	46(54.8%)	26.219	<b>&lt;0.001</b>
Nasogastric tube	22(25.3%)	53(63.1%)	24.810	<b>&lt;0.001</b>
CVC	18(20.7%)	55(65.5%)	35.038	<b>&lt;0.001</b>
PICC	22(25.3%)	18(21.4%)	0.355	0.551
Peripheral arterial catheter	12(13.8%)	34(40.5%)	15.474	<b>&lt;0.001</b>
Blood purification	5(5.7%)	25(29.8%)	17.038	<b>&lt;0.001</b>
Bronchoscopy	1(1.1%)	9(10.7%)	5.470	<b>0.019</b>
Thoracentesis	2(2.3%)	15(17.9%)	11.554	<b>0.001</b>
Abdominal puncture	2(2.3%)	10(11.9%)	6.044	<b>0.014</b>
Bone marrow puncture	20(23.0%)	10(11.9%)	3.629	0.057
Lumbar puncture	6(6.9%)	6(7.1%)	0.004	0.950
In hospital operation	33(37.9%)	38(45.2%)	0.940	0.332
Emergency surgery	5(5.7%)	15(17.9%)	6.068	<b>0.014</b>
Altered mental status	13(14.9%)	42(50.0%)	24.073	<b>&lt;0.001</b>
Septic shock	9(10.3%)	31(36.9%)	16.824	<b>&lt;0.001</b>
Pitt bacteremia score≥4	12(13.8%)	37(44.0%)	19.135	<b>&lt;0.001</b>

**Note:** <sup>a</sup>P values less than 0.05 are bolded.

**Abbreviations:** ICU, intensive care unit; CCI, Charlson comorbidity index; CVC, central venous catheters; PICC, peripherally inserted central venous catheters; BLBLIs,  $\beta$ -lactam/ $\beta$ -lactamase inhibitor combinations.

diseases and solid tumors, and the proportion of CSKP BSI in these patients was higher than CRKP BSI. We hypothesize that this is related to the shorter hospital stays of these patients. Patients with hematologic diseases and solid tumors are often hospitalized for chemotherapy, which are short hospital stays. Our univariate analysis suggested that the CRKP BSI group had longer hospital

stays, which was similar to the results obtained in previous studies.<sup>44,45</sup>

We also believe that the high incidence of CRKP BSI is related to CRKP colonization. Previous studies have confirmed the association between KP colonization and bloodstream infection,<sup>46,47</sup> but the number of studies on KP nasopharynx colonization<sup>48</sup> is significantly less than

**Table 5** Multivariate Logistic Regression Analysis of Risk Factors for CRKP BSI in Patients with a Hospital-Acquired Infection

Items	P	OR	95%CI	
BLBLIs exposure	0.022	2.863	1.167	7.027
Carbapenems exposure	0.007	3.831	1.451	10.115
Solid organ transplantation	<0.001	19.454	4.552	83.139

**Note:** Hosmer-Lemeshow test:  $P=0.687$ .

**Abbreviations:** P, P value; OR, odds ratio; CI, confidence interval; BLBLIs,  $\beta$ -lactam / $\beta$ -lactamase inhibitor combinations.

that of rectal colonization.<sup>49,50</sup> The longer the hospital stay, the greater the risk of infection from colonizing bacteria. Our study found that patients with hospital-acquired CRKP BSI often also had a respiratory tract infection, which has been previously reported.<sup>51</sup> Many previous studies have shown that the use of nasogastric tubes is a risk factor for CRKP colonization and infection,<sup>52,53</sup> and that the risk of a pulmonary infection has increased significantly in these patients. Our univariate analysis found that patients who had sputum aspiration events were more likely to suffer from CRKP BSI, which was rarely reported by prior works. Sputum aspiration events can damage the respiratory mucosa, allowing CRKP colonizing the nasopharynx to enter the bloodstream. Previous retrospective studies also have shown that the lungs are prone to nosocomial infections.<sup>54</sup> Although it is difficult to ascertain if the source of the BSI in these patients is respiratory, we believe that nasopharyngeal colonization of KP merits further study in hospital-acquired infections.

In addition to polymyxin, ceftazidime-avibactam, and other new antibiotics,<sup>55</sup> previous studies proposed the feasibility of adding aminoglycosides<sup>56</sup> or fosfomycin<sup>57</sup> to treat CRKP infection. However, the antimicrobial susceptibility testing results at our hospital suggested that the rates of non-susceptibility to both drugs are high. We noted that the non-susceptibility of TMP-SMZ in blood samples was lower than that of aminoglycosides and fosfomycin. The relationship between the use of TMP-SMZ and the resistance rate in KP infection is controversial,<sup>58,59</sup> which may be related to the frequency of TMP-SMZ use.<sup>60</sup> Although TMP-SMZ is not usually used as a therapeutic drug for BSI, we propose the possibility of using TMP-SMZ in CRKP BSI patients with urinary and respiratory infections. The resistance rate of minocycline to CRKP varies greatly in different regions,<sup>61,62</sup> but the intravenous minocycline and the

treatment regimen of minocycline combined with other antibiotics<sup>63</sup> have great potential for the treatment of CRKP infection. The role of minocycline in the treatment of CRKP BSI needs to be further studied.

Our univariate analysis found that central venous catheters (CVC) may be more strongly associated with hospital-acquired CRKP BSI and hospital death from a hospital-acquired KPBSI than peripherally inserted central venous catheter (PICC). Previous studies have suggested that PICCs have a lower risk of bloodstream infections than CVCs.<sup>64</sup> However, the risk of lower extremity venous thrombosis may be higher after a PICC.<sup>65</sup> Previous studies have suggested that intravenous catheterization increased the risk of a poor prognosis in the setting of a BSI.<sup>66</sup> The choice of PICC or CVC requires further research.

According to the results of our univariate analysis, comorbidities increased the risk of a hospital-acquired CRKP BSI but did not significantly increased the 28-day mortality risk from a hospital-acquired KPBSI. The 28-day mortality of patients with hospital acquired KPBSI was significantly different in patients who underwent invasive operations or had liver, kidney or hematologic dysfunction. The results of our multivariate analysis suggest that the risk factors for 28-day mortality after a hospital-acquired KP BSI were CRKP BSI, septic shock, mechanical ventilation >96 hours, and platelet counts  $<100 \times 10^9/L$ , similar results have been reported in previous studies.<sup>67,68</sup> Our univariate analysis suggested that a high coefficient of variation of red blood cell distribution width (RDW-CV) was a risk factor for the 28-day mortality of KP BSI patients. Red blood cell distribution width (RDW) has been recently found to be a potential marker of cardiovascular disease. Studies have shown that a high RDW may be associated with adverse consequences of heart failure,<sup>69</sup> in particular long-term prognosis. With respect to infection, previous studies have shown that RDW can predict the prognosis of sepsis in patients with various non-hematologic diseases to a certain extent.<sup>70</sup> RDW-CV index is easy to obtain, and its value in infectious diseases merits further study.

## Conclusion

CRKP threatens the control and treatment of hospital-acquired infection seriously. Hospital-acquired KP BSI Patients with CRKP BSI, septic shock, mechanical ventilation and deficiency of platelets are more likely to have a poor prognosis. Although an antibiotic restriction strategy is used, the incidence of hospital-acquired KP BSI

**Table 6** Univariate Analysis of Risk Factors Associated with 28-Day Mortality in Patients with Hospital-Acquired KP BSI

Items	Survival (n=114)	Death (n=57)	Z / $\chi^2$	P value
Male	70(61.4%)	44(77.2%)	4.263	<b>0.039</b>
Age	55.5(43.8-66.0)	56(37.5-68.5)	-0.067	0.946
Total length of hospital stay	30(17.0-52.5)	22(16.5-38.5)	-1.927	0.054
CRKP BSI	39(34.2%)	45(78.9%)	30.430	<b>&lt;0.001</b>
Early appropriate therapy <sup>a</sup>	76(66.7%)	26(45.6%)	6.997	<b>0.008</b>
Any antibiotics exposure	65(57.0%)	48(84.2%)	12.537	<b>&lt;0.001</b>
Carbapenems exposure	33(28.9%)	32(56.1%)	11.925	<b>0.001</b>
BLBLs exposure	40(35.1%)	35(61.4%)	10.688	<b>0.001</b>
Diabetes	21(18.4%)	12(21.1%)	0.169	0.681
Solid tumor	15(13.2%)	4(7.0%)	1.451	0.228
Hematological malignancies	28(24.6%)	12(21.1%)	0.261	0.609
Chronic kidney disease	23(20.2%)	9(15.8%)	0.481	0.488
Solid organ transplantation	17(14.9%)	11(19.3%)	0.534	0.465
Immunosuppressive state	48(42.1%)	23(40.4%)	0.048	0.826
CCI score>2	24(21.1%)	10(17.5%)	0.294	0.588
Admission to ICU	28(24.6%)	43(75.4%)	40.510	<b>&lt;0.001</b>
Complicated pulmonary infection	29(25.4%)	43(75.4%)	38.972	<b>&lt;0.001</b>
Septic shock	12(10.5%)	37(64.9%)	54.979	<b>&lt;0.001</b>
Altered mental status	21(18.4%)	34(59.6%)	29.603	<b>&lt;0.001</b>
Pitt bacteremia score $\geq$ 4	14(12.3%)	35(61.4%)	44.852	<b>&lt;0.001</b>
Mechanical ventilation> 96 hours	19(16.7%)	40(70.2%)	48.146	<b>&lt;0.001</b>
CVC	34(29.8%)	42(73.7%)	29.605	<b>&lt;0.001</b>
PICC	31(27.2%)	15(26.3%)	0.015	0.903
Peripheral arterial catheter	16(14.0%)	34(59.6%)	38.214	<b>&lt;0.001</b>
Blood purification	14(12.3%)	20(35.1%)	12.408	<b>&lt;0.001</b>
Bronchoscope	6(5.3%)	10(17.5%)	6.757	<b>0.009</b>
Sputum aspiration	28(24.6%)	43(75.4%)	40.510	<b>&lt;0.001</b>
Thoracentesis	9(7.9%)	13(22.8%)	7.538	<b>0.006</b>
Bone marrow puncture	23(20.2%)	12(21.1%)	0.018	0.893
Leukopenia	33(28.9%)	13(22.8%)	0.729	0.393
HGB <90g/L	55(48.2%)	36(63.2%)	3.394	0.065
RDW-CV >15	33(28.9%)	30(52.6%)	9.161	<b>0.002</b>
PLT counts <100 $\times$ 10 <sup>9</sup> /L	47(41.2%)	36(63.2%)	7.316	<b>0.007</b>
Albumin <30g/L	28(24.6%)	20(35.1%)	2.085	0.149
TBIL >2 ULN	8(7.0%)	13(22.8%)	8.794	<b>0.003</b>
Elevated serum creatinine	27(23.7%)	27(47.4%)	9.865	<b>0.002</b>
PT >16S	20(17.5%)	27(47.4%)	16.959	<b>&lt;0.001</b>

**Notes:** <sup>a</sup>P values less than 0.05 are bolded; <sup>b</sup>The antibiotics selected for the first time were consistent with the drug sensitivity results.

**Abbreviations:** ICU, intensive care unit; CRKP, carbapenem-resistant *Klebsiella pneumoniae*; BSI, bloodstream infection; CCI, Charlson comorbidity index; CVC, central venous catheters; PICC, peripherally inserted central venous catheters; HGB, hemoglobin; RDW-CV, coefficient of variation of red blood cell distribution width; PLT, platelet; TBIL, total bilirubin; PT, prothrombin time; ULN, the upper limit of normal; BLBLs,  $\beta$ -lactam- $\beta$ -lactamase inhibitor combinations.

**Table 7** Multivariate Analysis of 28-Day Mortality in Patients with Hospital-Acquired KP BSI

Items	P	OR	95%CI	
CRKP BSI	0.009	5.562	1.540	20.082
Septic shock	0.002	4.862	1.765	13.394
Mechanical ventilation > 96 hours	0.020	8.765	1.407	54.588
PLT counts <100 $\times$ 10 <sup>9</sup> /L	0.003	4.464	1.651	12.071

**Note:** Hosmer-Lemeshow test:  $P=0.432$ .

**Abbreviations:** P, P value; OR, odds ratio; CI, confidence interval; CRKP, carbapenem-resistant *Klebsiella pneumoniae*; BSI, bloodstream infection; PLT, platelet.

continues to rise and the proportion of CRKP BSI is also increasing. For patients admitted to ICU, organ transplant wards and hematology department, more resources need to be invested in the prevention of hospital-acquired KP BSI. In addition to reducing the length of hospital stay and the number of invasive operations, we believe that the use of the BLBLs needs to be carefully evaluated in hospital-acquired infections. According to the monitoring of local antimicrobial susceptibility results, TMP-SMZ and

minocycline may be potential treatment options for CRKP infection. We also believe that more attention should be paid to the relationship between respiratory tract infection and bloodstream infection.

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## Disclosure

The authors report no conflicts of interest related to this work.

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