

# Invasive *Klebsiella pneumoniae* Infections in Community-Settings and Healthcare Settings

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**Objective:** To assess clinical characteristics, outcomes and antimicrobial resistance of invasive *Klebsiella pneumoniae* (KP) infections in Chinese pediatric patients in hospital and community settings.

**Methods:** This retrospective study was conducted in the nine tertiary hospitals during 2016–2018. The 324 pediatric inpatients who had KP isolated from blood and cerebrospinal fluid and had complete medical records reviewed were included. We analyzed the risk factors, outcomes and antimicrobial resistance pattern of KP-infected patients based on comparison between healthcare-associated KP infections (HAI) and community-acquired infections.

**Results:** Of the 324 enrolled patients, 275 (84.9%) were clinically defined as HAI, including 175 (63.6%) neonates and 100 (36.4%) aged >28 days. The overall prevalence of CRKP was 38.2% (43.4% in HAI verse 8.7% in CAI,  $P < 0.05$ ). Prematurity (odds ratio (OR): 37.07, 95% CI: 8.29–165.84), hematologic malignancies (OR: 15.52, 95% CI: 1.89–127.14) and invasive mechanical ventilation (OR: 13.09, 95% CI: 1.66–103.56) were independent risk factors for HAI. Patients from rural area (OR: 1.94, 95% CI: 1.12–3.35), invasive mechanical ventilation (OR: 2.33, 95% CI: 1.25–4.33), antibiotic therapy prior to admission (OR: 2.33, 95% CI: 1.25–4.33) and prior hospital stay in the past 30 days (OR: 3.46, 95% CI: 1.87–6.41) were associated with healthcare-associated CRKP infections. Organ dysfunction was independently correlated with poor outcomes (OR: 2.92, 95% CI: 1.23–6.95).

**Conclusion:** Pediatric invasive KP infections and high prevalence of CRKP infections largely occurred in healthcare settings in China. The adequate and intensified infection control measures should be focused on high-risk hematologic patients, neonatal patients and intubated patients.

**Keywords:** *Klebsiella pneumoniae*, healthcare-associated infections, children

## Introduction

*Klebsiella pneumoniae* (KP) has been implicated in severe infections and one of the most important causes of nosocomial infections.<sup>1</sup> According to the global surveillance data, KP is the third leading bloodstream pathogen in children, and the frequency of antibiotic resistant KP has been increasing over years.<sup>2–4</sup> In recent years. Carbapenem-resistant *Klebsiella pneumoniae* (CRKP) represents a “critical concern” of the World Health Organization and poses great challenges for clinical treatment.<sup>5,6</sup> Of particular concern, the prevalence of CRKP has been sharply rising from 2.9–3% in 2005 to 25–26.3% in 2018 in China, and even reached 35.8% in neonatal patients.<sup>4,7</sup>

Currently, KP infections become an important clinical issue in pediatrics, especially in neonates, since very limited effective antibiotics are available for the

treatment choice.<sup>8,9</sup> The existing studies from other countries showed KP as a key opportunistic pathogen causing severe infections in hospitalized children.<sup>10–13</sup> So far, surveillance study and clinical data on healthcare-associated KP infections are lacking in China, although CRKP is now a pronounced problem. According to some regional surveillance studies, most of Carbapenem-resistant *organisms* (CRO) are healthcare-associated.<sup>10,14</sup> Therefore, we carried out this retrospective multicenter study to understand the current situations of invasive healthcare-associated KP infections in Chinese pediatric patients, and analyzed risk factors, outcomes and antimicrobial resistance of healthcare-associated KP and CRKP infections, aiming to identify the main problem of invasive KP infections and help find the effective solution to reduce and prevent healthcare-associated KP and CRKP infections in pediatric patients.

## Method

### Study Design and Subjects

This is a retrospective multicenter study conducted between January 2016 and December 2018 at the nine tertiary hospitals in China, including four provincial Children's Hospitals, two General Hospitals and three municipal Women and Children's Hospitals. These hospitals locate in different administrative regions of China: Five hospitals in the Southeast, three in the South and one in Central, respectively. The inclusion criteria of eligible patients were as follows: 1) hospitalized pediatric inpatients aged <18 years, 2) inpatients who had KP isolated from blood and/or cerebrospinal fluid (CSF) specimens. The patients were excluded if their clinical data collection was incomplete or their medical records were unavailable for review by the end of 2019.

### Definitions

Healthcare-associated infections (HAI) were defined as follows: 1) KP strain recovered from sterile specimens collected at least 48h after hospital admission in a patient; 2) KP culture positive within the first 48 hours of admission in a patient with prior hospital stay for a few of consecutive days in the past 30 days. Community-acquired infections (CAI) were defined as KP culture positive within 48 hours of admission in a patient without prior hospitalization within the past 30 days. Poor outcomes were considered if a patient died in hospital or

was hopelessly discharged from hospital under the request of parents based on the medical records.

### Data Collection

The following data were collected, including patient's demographics and important underlying diseases, previous history of antibiotic use and hospitalization within the 30 days prior to the admission date, ward unit during hospitalization, clinical diagnosis on admission and discharge, length of hospitalization, interval between the occurrence of KP infections (the collection date of the first KP-positive sample) and the date of admission, intravascular catheter use, mechanical ventilation, imaging findings, clinical outcomes and microbiological data.

### Microbiological Study

The first invasive KP isolate recovered from a patient was included in this study for microbiological analysis. Species identification and antimicrobial susceptibility testing were performed at local hospital laboratories by automated systems such as Vitek or Phoenix, according to the 2018 CLSI performance guideline.<sup>15</sup> Antimicrobial susceptibility testing was performed for clinical isolates using minimum inhibitory concentrations (MICs, microdilution method-based) or Kirby–Bauer disk diffusion method. The original results were classified according to the breakpoints of the 2018 CLSI standards. For polymyxin B, the criteria referred to the epidemiological cutoff value of colistin in the CLSI file (MIC  $\leq 2$   $\mu\text{g/mL}$  for wild strains; MIC  $\geq 4$   $\mu\text{g/mL}$  for non-wild strains).<sup>7</sup>

### Statistical Analysis

Data were entered and analyzed into Excel version 2016 (Microsoft, Redmond, Washington) and were analyzed using SPSS (IBM Statistics 20.0). Results were described as absolute numbers and percentage or as median and interquartile ranges. Categorical variables were compared using the Chi-square or Fisher's exact tests. Continuous variables were compared by Student's *t*-test or Mann–Whitney *U*-test according to their distribution. The risk factors were analyzed by Binary regression analysis and Multinomial regression analysis, and the results were presented as odds ratios (ORs), 95% confidence intervals (CIs) and *P* values. Significant variables with *P* value of <0.2 were then selected for multiple regression analysis to evaluate risk factors for clinical poor outcomes. A difference with *P* <0.05 was considered to be statistically significant.

## Result

### The Basic Characteristics of KP-Infected Patients

A total of 425 pediatric inpatients met the diagnosis criteria of invasive KP infections based on the hospital microbiology laboratory records, of whom, 248 (58.4%) neonates  $\leq 28$  days and 177 (41.6%) were children aged  $>28$  days on admission. Finally, 324 (76.2%) patients met the enrollment criteria and were included in this study and 101 (23.8%) were excluded due to unavailability of medical records (99 patients) and incomplete clinical data collection (2 patients).

Of the 324 enrolled patients, 299 (92.3%) had KP isolated from blood, 11 (3.4%) had KP isolated from CSF and 14 (4.3%) had KP isolated from both blood and CSF. On the clinical grounds and case definition, 275 (84.9%) patients were considered as HAI and 49 (15.1%) patients were considered as CAI.

### Clinical Features and Risk Factors of Healthcare-Associated KP Infections in Pediatric Patients

Among 275 patients with HAI, 154 (56%) were male; the median age was 0.6 months (IQR 0.17–6, range: 1 day–17 years) and the age distribution was as followings: 162 (58.9%) aged  $\leq 28$  days, 33 (12.0%) aged 29 days–2 months, 20 (7.3%) aged 3–11 months, 33 (12.0%) aged 1–5 years, 27 (9.8%) aged  $>5$  years. Of 162 neonates, 129 (79.6%) were preterm, including 13 (10.1%) at  $<28$  weeks of gestational age, 75 (58.1%) at 28–31 weeks of gestational age and 41 (31.8%) at 32–37 weeks of gestational age. Two hundred and eighteen (79.3%) patients had the accompanying focal organ infections, including pneumonia (119, 43.3%), meningitis (64, 23.3%), intra-abdominal infections (41, 14.9%), upper urinary tract infections (3, 1.1%) and osteomyelitis (4, 1.5%); 13 patients had 2 infection sites. Nine (3.3%) patients died in hospital and 30 (10.9%) patients were hopelessly discharged at the request of parents.

Compared to CAI patients (Table 1), the percentage of patients with underlying medical conditions was significantly greater in HAI patients, including hematologic malignancies, necrotizing enterocolitis (NEC) and prematurity (16.4% versus 2%, 9.8% versus 0%, 46.9% versus 4.1%, respectively;  $P < 0.05$ ); the percentage of patients using peripherally inserted central catheter (PICC),

invasive mechanical ventilation was significantly greater in HAI patients (29.8% versus 2%, 34.9% versus 2%, respectively,  $P < 0.01$ ). HAI patients had more episodes of meningitis than CAI patients (23.3% versus 6.1%,  $P < 0.01$ ), while CAI patients had more frequency of upper urinary tract infections than HAI patients (30.6% versus 1.1%,  $P < 0.01$ ). The isolation rate of CRKP strains was much higher in HAI patients than in CAI patients (43.4% versus 8.7%,  $P < 0.01$ ). The poor outcomes were similar between HAI and CAI patients (14.2% versus 8.2%,  $P > 0.05$ ).

Multiple regression analysis showed that prematurity ((odds ratio) OR: 37.07, 95% CI: 8.29–165.84), hematologic malignancies (OR: 15.52, 95% CI: 1.89–127.14), and invasive mechanical ventilation (OR: 13.09, 95% CI: 1.66–103.56) were independent risk factors for HAI (Table 2).

### Risk Factors of Healthcare-Associated CRKP Infections in Pediatric Patients

Compared to CSKP-infected patients (Table 3), CRKP-infected patients stayed in hospital for a longer time (38.5 days versus 30 days,  $P < 0.05$ ) and received more therapies of mechanical ventilation (45.5% versus 26.7%,  $P < 0.05$ ). More CRKP-infected patients developed organ dysfunction than CSKP-infected patients (36.1% versus 15.1%,  $P < 0.05$ ). The poor outcomes were similar between CSKP-infected and CRKP-infected patients (14.3% versus 13%,  $P > 0.05$ ).

Multiple regression analysis showed that children from rural area (OR: 1.94, 95% CI: 1.12–3.35,  $P < 0.05$ ), invasive mechanical ventilation (OR: 2.08, 95% CI: 1.12–3.88,  $P < 0.05$ ), prior antibiotic therapy before hospitalization (OR: 2.33, 95% CI: 1.25–4.33,  $P < 0.01$ ) and prior hospitalization in the past 30 days (OR: 3.46, 95% CI: 1.87–6.41,  $P < 0.01$ ) were independent risk factors for CRKP infections (Table 4).

### Risk Factors of Poor Outcomes in Pediatric Patients with Healthcare-Associated KP Infections

As shown in Table 5, univariate analysis showed that invasive mechanical ventilation, any organ dysfunction and septic shock were the significant risk factors for poor outcomes. Multiple regression analysis showed that organ dysfunction was an independent risk factor for the poor outcomes (OR: 2.92, [95% CI: 1.23–6.95],  $P < 0.05$ ).

**Table 1** Characteristics of the Children with Invasive *Klebsiella pneumoniae* Infection According to Type of Acquired Infections (HAI or CAI)

Variable	Total (n=324)	HAI (N=275)	CAI (N=49)	P value
Age (months)	0.8 (0.3–6.4)	0.6 (0.17–6)	3.0 (0.87–10)	0.54
Male	187 (57.7)	154 (56)	33 (67.3)	0.14
Rural area	178 (54.9)	156 (56.7)	22 (44.9)	0.13
Underlying disease				
Hematologic malignancies	45 (13.9)	44 (16)	1 (2)	0.02
Congenital anomalies	42 (13)	37 (13.5)	5 (10.2)	0.53
NEC	27 (8.3)	27 (9.8)	0 (0)	0.02
Prematurity	131 (40.4)	129 (46.9)	2 (4.1)	0
Solid tumors	4 (1.2)	4 (1.5)	0 (0)	1
Severe Malnutrition	12 (3.7)	11 (4)	1 (2)	0.8
Immunodeficiencies	3 (0.9)	3 (1.1)	0 (0)	1
Departments				
• Hematology-oncology ward	42 (13)	42 (15.3)	0 (0)	<0.01
• General medical ward	157 (48.5)	119 (43.3)	38 (77.6)	0
• NICU	65 (20.1)	64 (23.3)	1 (2)	0
• PICU	21 (6.5)	18 (6.5)	3 (6.1)	1
• Surgical ward	39 (12)	32 (11.6)	7 (14.3)	0.6
Length of hospitalization	28 (17–50)	33 (21–53.5)	13 (9–16)	0
Length of hospitalization before the onset of KP infections	7 (1.8–20)	10 (2–22)	1 (1–1)	0
Invasive procedures and devices				
PICC	83 (25.6)	82 (29.8)	1 (2)	0
Thoracic cavity drainage	12 (3.7)	12 (4.4)	0 (0)	0.23
Abdominal indwelling catheter	4 (1.2)	4 (1.5)	0 (0)	1
Indwelling urinary catheter	8 (2.5)	5 (1.8)	3 (6.1)	0.2
Invasive mechanical ventilation	97 (29.9)	96 (34.9)	1 (2)	0
Surgical operation	65 (20.1)	60 (21.8)	5 (10.2)	0.06
Organ dysfunction (any)	73 (22.5)	69 (25.1)	4 (8.2)	0.015
Septic shock	32 (9.9)	30 (10.9)	2 (4.1)	0.22
Mortality or hopeless discharge	44 (13.6)	39 (14.2)	5 (8.2)	0.45
Isolation of CRKP (N=304)	116 (38.2)	112 (43.4)	4 (8.7)	0
Combined organ infection				
Pneumonia	139 (42.9)	119 (43.3)	20 (40.8)	0.75
Meningitis	67 (20.1)	64 (23.3)	3 (6.1)	0
Intrabdominal infections	46 (14.2)	41 (14.9)	5 (10.2)	0.38
Upper urinary tract infections	18 (5.6)	3 (1.1)	15 (30.6)	0

**Abbreviations:** HAI, healthcare-associated infections; CAI, community-acquired infections; PICC, peripherally inserted central catheter; NEC, necrotizing enterocolitis; NICU, neonatal intensive care unit; PICU, pediatric intensive care unit; CRKP, carbapenem-resistant *Klebsiella pneumoniae*.

## Antimicrobial Susceptibility Patterns of Healthcare-Associated KP Isolates

As shown in Table 6, healthcare-associated KP strains showed high frequency of resistance to carbapenem as well as other clinical important antibiotics usually recommended for the treatment of *Enterobacteriaceae* infections, such as third-generation cephalosporins, cefepime and piperacillin/

tazobactam. Also, healthcare-associated KP strains showed significantly higher frequency of resistance to clinical important antibiotics than community-acquired KP stains. Besides, healthcare-associated KP strains showed relatively higher resistance percentage to tigecycline, amikacin, ciprofloxacin and levofloxacin (12.5–23.7%). Healthcare-associated KP strains almost remained sensitive to polymyxin B.

**Table 2** Multiple Regression Analysis of Risk Factors Associated with HAI

Variable	Total	HAI	CAI	Multi-Variate Analysis		
				P value	OR	95% CI
Underlying disease						
Hematologic malignancies	45 (13.9)	44 (16)	1 (2)	0.01	15.52	1.89–127.14
Prematurity	131 (40.4)	129 (46.9)	2 (4.1)	<0.01	37.07	8.29–165.84
Departments						
General medical ward	157 (48.5)	119 (43.3)	38 (77.6)	<0.01	0.2	0.08–0.51
NICU	65 (20.1)	64 (23.3)	1 (2)	0.11	5.82	0.68–49.89
Previous use invasive mechanical ventilation	82 (25.3)	81 (29.5)	1 (2)	0.01	13.09	1.66–103.56
Antibiotic therapy prior to admission	90 (27.8)	80 (29.1)	10 (20.4)	0.14	2.02	0.79–5.19

**Abbreviations:** NICU, neonatal intensive care unit; HAI, healthcare-associated infections; CAI, community-acquired infections.

**Table 3** Characteristics of the Children with HAI According to Pattern of Carbapenem Resistance (CRKP or CSKP Isolates)

Variable	CRKP (N=112)	CSKP (N=146)	P value
Age (months)	0.53 (0.12–3.2)	0.65 (0.17–12)	0.27
Male	62 (55.4)	82 (56.2)	0.9
Rural area	74 (66.1)	72 (49.3)	<0.01
Underlying disease			
Hematologic malignancies	18 (16.1)	26 (17.8)	0.71
Congenital anomalies	19 (17)	16 (11)	0.16
Prematurity	58 (51.8)	61 (41.8)	0.11
NEC	9 (8)	15 (10.3)	0.54
Solid tumors	2 (1.8)	1 (0.7)	0.58
Severe malnutrition	7 (6.3)	4 (2.7)	0.28
Departments			
• Hematology-oncology ward	17 (15.2)	25 (17.1)	0.68
• General medical ward	56 (50)	58 (39.7)	0.1
• NICU	13 (11.6)	44 (30.1)	<0.01
• PICU	8 (7.1)	7 (4.8)	0.42
• Surgical ward	18 (16.1)	12 (8.2)	0.051
Length of hospitalization	38.5 (24–56.3)	30 (19.3–51.8)	0
Length of hospitalization before the onset of KP infections	12.5 (2–24.3)	10 (2–22)	0.02
Invasive procedures and devices			
PICC	37 (33)	43 (29.5)	0.54
Thoracic cavity drainage	6 (5.4)	6 (4.1)	0.64
Abdominal indwelling catheter	3 (2.7)	1 (0.7)	0.32
Indwelling urinary catheter	1 (0.9)	4 (2.7)	0.39
Invasive mechanical ventilation	51 (45.5)	39 (26.7)	<0.01
Surgical operation	23 (20.5)	32 (21.9)	0.79
Organ dysfunction (any)	41 (36.6)	22 (15.1)	<0.01
Septic shock	13 (11.6)	13 (8.9)	0.48
Mortality or hopeless discharge	16 (14.3)	19 (13)	0.77
Combined organ infection			
Pneumonia	54 (48.2)	60 (41.1)	0.25
Meningitis	34 (30.4)	21 (14.4)	<0.01
Intrabdominal infections	15 (13.4)	23 (15.8)	0.6
Upper urinary tract infections	2 (1.8)	1 (0.7)	0.58

**Abbreviations:** CRKP, carbapenem-resistant *Klebsiella pneumoniae*; CSKP, carbapenem-sensitive *Klebsiella pneumoniae*; KP, *Klebsiella pneumoniae*; PICC, peripherally inserted central catheter; NEC, necrotizing enterocolitis; NICU, neonatal intensive care unit; PICU, pediatric intensive care unit.



**Table 4** Multiple Regression Analysis of Risk Factors Associated with CRKP Infections in HAI

Variable	Total (N=258)	CRKP (N=112)	CSKP (N=146)	Multi-Variate Analysis	
				P value	OR (95% CI)
Rural area	146 (56.6)	74 (66.1)	72 (49.3)	0.02	1.94 (1.12–3.35)
Congenital anomalies	35	19 (17)	16 (11)	0.18	1.77 (0.78–4.01)
Prematurity	119	58 (51.8)	61 (41.8)	0.07	1.95 (0.95–4.01)
Surgical prior to admission	18 (7)	8 (7.1)	10 (6.8)	0.8	0.87 (0.29–2.57)
Antibiotic therapy prior to admission	70 (27.1)	42 (37.5)	28 (19.2)	<0.01	2.33 (1.25–4.33)
Previous use PICC	73 (28.3)	34 (30.4)	39 (26.7)	0.98	0.99 (0.46–2.15)
Previous use invasive mechanical ventilation	76 (29.5)	43 (38.4)	33 (22.6)	0.02	2.08 (1.12–3.88)
Hospital stay prior to admission in 30days	101 (39.1)	57 (50.9)	44 (30.1)	<0.01	3.46 (1.87–6.41)

**Abbreviation:** PICC, peripherally inserted central catheter.

**Table 5** Multiple Regression Analysis of Risk Factors Associated with Poor Outcomes in HAI

Variable	Survived N=236	Poor Outcome N=39	Univariate Analysis		Multi-Variate Analysis	
			P value	OR (95% CI)	P value	OR (95% CI)
Age (months)	0.6 (0.1–4.8)	1.0 (0.4–6.7)	0.75	1.0 (0.99–1.0)		
Male	132 (55.9)	22 (56.4)	0.96	1.02 (0.52–2.02)		
Rural area	132 (55.9)	24 (61.5)	0.51	1.26 (0.63–2.52)		
Underlying disease						
Hematologic malignancies	39 (16.5)	5 (12.8)	0.56	0.74 (0.27–2.02)		
Congenital anomalies	31 (13.1)	6 (15.4)	0.7	1.2 (0.47–3.1)		
NEC	22 (9.3)	5 (12.8)	0.5	1.43 (0.51–4.03)		
Prematurity	3 (1.3)	1 (2.6)	0.92	0.97 (0.49–1.9)		
Solid tumors	3 (1.3)	1 (2.6)	0.54	2.04 (0.21–20.16)		
Severe malnutrition	9 (3.8)	2 (5.1)	0.7	1.36 (0.28–6.56)		
Immunodeficiencies	2 (0.8)	1 (2.6)	0.36	3.08 (0.27–34.79)		
Length of hospitalization before the onset of BSI	10 (2–12)	10 (2–11)	0.44	0.99 (0.97–1.01)		
Invasive procedures and devices						
PICC	69 (29.2)	13 (33.3)	0.61	1.21 (0.59–2.49)		
Thoracic cavity drainage	11 (4.7)	1 (2.6)	0.56	0.54 (0.07–4.29)		
Abdominal indwelling catheter	3 (1.3)	1 (2.6)	0.54	2.04 (0.21–20.16)		
Indwelling urinary catheter	4 (1.7)	1 (2.6)	0.71	1.53 (0.17–14.03)		
Invasive mechanical ventilation	77 (32.6)	19 (48.7)	0.05	1.96 (0.99–3.89)	0.88	0.93 (0.39–2.21)
Operation	51 (21.6)	9 (23.1)	0.84	1.09 (0.49–2.44)		
Organ dysfunction (any)	50 (21.2)	19 (48.7)	0	3.53 (1.75–7.13)	0.02	2.92 (1.23–6.95)
Septic shock	21 (8.9)	9 (23.1)	0.01	3.07 (1.29–7.33)	0.08	2.29 (0.9–5.85)
Isolation of CRKP (N=304)	96 (35.7)	16 (45.7)	0.25			
Combined organ infection						
Pneumonia	98 (41.5)	21 (53.8)	0.15	1.64 (0.83–3.25)	0.58	1.22 (0.59–2.53)
Meningitis	53 (22.5)	11 (28.2)	0.43	1.36 (0.63–2.91)	0.31	0.52 (0.15–1.85)
Intrabdominal infections	38 (16.1)	3 (7.7)	0.18	0.43 (0.13–1.48)		
Upper urinary tract infections	3 (1.3)	0 (0)	-	-		

**Abbreviations:** HAI, healthcare-associated infections; PICC, peripherally inserted central catheter; NEC, necrotizing enterocolitis; NICU, neonatal intensive care unit; PICU, pediatric intensive care unit; CRKP, carbapenem-resistant *Klebsiella pneumoniae*.

**Table 6** Resistance Patterns of *Klebsiella pneumoniae*

Antimicrobial Drugs	Percentage Rate (%) of Resistance <sup>a</sup> (Number of Isolates Resistant/Number of Isolates Tested)			
	Total	HAI	CAI	P value
Ampicillin	93.8 (227/242)	96.6 (199/206)	77.8 (28/36)	0
Ampicillin/Sulbactam	75.6 (205/271)	81.5 (190/233)	39.5 (15/38)	0
Cefepime	55.3 (167/302)	60.5 (155/256)	26.1 (12/46)	0
Ceftriaxone	59.8 (76/127)	70.2 (73/104)	13 (3/23)	0
Ceftazidime	62.7 (188/300)	69.4 (177/255)	24.4 (11/45)	0
Cefuroxime	58.6 (17/29)	66.7 (16/24)	20 (1/5)	0.13
Piperacillin/tazobactam	43 (128/298)	48.6 (124/255)	9.3 (4/43)	0
Gentamicin	30.6 (92/301)	34.5 (88/255)	8.7 (4/46)	0
Amikacin	14.2 (43/302)	16.4 (42/256)	2.2 (1/46)	0.02
Ciprofloxacin	20.8 (63/303)	23.7 (61/257)	4.3 (2/46)	<0.01
Levofloxacin	18.2 (55/303)	21 (54/257)	2.2 (1/46)	<0.01
Imipenem	36.2 (110/304)	41.5 (107/258)	6.5 (3/46)	0
Meropenem	40.5 (96/237)	45.4 (93/205)	9.4 (3/32)	0
Tigecycline	10.5 (2/19)	12.5 (2/16)	0 (0/3)	1
Polymyxin B	0.6 (1/169)	0.7 (1/148)	0 (0/21)	1

**Note:** <sup>a</sup>*Klebsiella pneumoniae* isolates displaying intermediate susceptibility were not categorized as resistance in this study.

**Abbreviations:** HAI, healthcare-associated infections; CAI, community-acquired infections.

## Discussion

This multicenter retrospective study first revealed that most episodes of invasive KP infections were healthcare-associated in pediatric patients in China. We further demonstrated that the high percentage of CRKP infections usually occurred in healthcare setting (40.4%) rather than in community setting (10.2%). Of particularly concern, 58.9% of pediatric invasive healthcare-associated KP infections occurred in neonates. KP infections impose a health threat to hospitalized neonates and children.

According to the surveillance in Chinese adults, KP was the second common pathogen in hospital-associated bloodstream infections.<sup>16</sup> Our recent study revealed that KP was the second common pathogen of bloodstream bacterial infections in Chinese pediatric patients.<sup>4</sup> Our present study further showed that 84.9% of invasive KP infections were hospital-associated. Thus, it is feasible to prevent and reduce invasive KP infections through a bundle of effective infection prevention and control (IPC) measures. Identifying some key risk factors is essential to formulate the targeted measures. In this study, hematologic malignancies, prematurity, and invasive mechanical ventilation were identified as the independent risk factors for HAI. The available evidences have demonstrated that IPC practices and procedures can effectively prevent the occurrence and the spread of HAI in healthcare facilities.<sup>17,18</sup> Thus, reinforcement of IPC at high-risk

pediatric units, such as hematological units, pediatric and neonatal intensive care units, is key to prevent invasive healthcare-associated KP infections. Healthcare-associated KP infections in preterm neonates are of particular concern because 58.9% of invasive healthcare-associated KP occurred in neonate and the odds ratio for prematurity is highest. Prematurity is a common risk factor of any nosocomial infections in neonatal units.<sup>19,20</sup> Our results further support this finding and emphasize prematurity as the most key risk factor of severe invasive nosocomial KP infections. Therefore, hospitalized preterm neonates should be placed on the highest priority group for whom IPC practice should be strengthened and improved. Besides, we noticed that 43.3% of children with hospital-associated KP infections had accompanying pneumonia and 34.9% of patients received mechanical ventilation therapy. Thus, part episodes of invasive healthcare-associated KP infections were likely to be secondary to ventilation-associated pneumonia.

We noticed that the high prevalence of CRKP in hospital setting but low prevalence of CRKP in community setting in pediatric patients. CRKP indeed represents a clinical and economic impact on pediatric patients and tertiary pediatric hospital in China. In this study, previous antibiotic therapy prior to hospitalization, previous mechanical ventilation, and prior hospital stay within the past 30 days were independent risk factors for acquisition of healthcare-associated CRKP infections, which is

consistent with most of previous studies conducted in children and adults.<sup>21–23</sup> In addition, we found that children from rural area were an independent risk factor for invasive healthcare-associated CRKP infections in Chinese children. In China, it is usual for rural patients to delay seeking medical consultation, furthermore, severe rural patients usually cannot have access to the tertiary hospitals for initial treatment, and they have to experience the hospital referral for advanced treatment. Inappropriate treatment is unavoidable before referral to the tertiary hospitals. Thus, rural children are at higher risk of acquiring HAI. Unlike most previous single-center or specific-unit studies,<sup>23,24</sup> we did not find that patients with hematologic malignancies were an independent risk factor of invasive CRKP infections. This difference is possibly owing to the selected bias of study hospitals and enrolled patients.

Although a few of studies suggested HAI was a risk factor for mortality of KP infections based on univariate analyses,<sup>25–27</sup> we found no statistical difference in clinical outcomes of invasive KP infections between HAI and CAI patients. This discrepancy is probably owing to loss to follow-up in discharged patients in this cohort. However, HAI patients were more likely to develop organ dysfunction, which was the only independent risk factor of poor outcomes. Most episodes (79.3%) of invasive healthcare-associated KP infections are accompanied by focal organ involvement, of which, pneumonia (43.3%) and meningitis (23.3%) were the common manifestations. Of note, KP-associated meningitis almost occurred in HAI patients. HAI patients usually had underlying diseases or were immunocompromised, thus, those patients were more likely to develop meningitis secondary to bloodstream infection or primary site infection, especially premature infants. These findings add our understanding of clinical presentation of invasive healthcare-associated KP infections, which will be helpful to predict the possible source and secondary complications of invasive KP infections and select appropriate antibiotic regimen. In African countries, the mortality rate of bloodstream KP infections in pediatric patients was reported to reach as high as 21.6%–56.5%,<sup>8,11,28</sup> significantly higher than our rough estimation (13.6%) in Chinese children. This could reflect the regional difference in accessibility of tertiary pediatric medical resource and capacity of pediatric critical intensive care for pediatric patients. On the other hand, virulence factors of endemic KP isolates are also a contributing factor of the fatal outcomes.<sup>29,30</sup> We need to

further characterize the virulence profile of KP strains in the next step to understand KP pathogenicity well.

Of particular concern is that healthcare-associated KP strains displayed higher prevalence of resistance to the tested antibiotics than community-acquired KP isolates, especially to extended-spectrum cephalosporin and carbapenem. The frequency of ceftriaxone-resistant healthcare-associated KP and community-acquired KP was 70.2% and 13.0%, respectively, and the frequency of meropenem-resistant healthcare-associated KP and meropenem-resistant community-acquired KP was 45.4% and 9.4%, respectively. The high prevalence of KP resistance in hospital setting makes it difficult to empirically and definitely select antibiotic therapy for invasive healthcare-associated KP infections in pediatric patients because the prescription of polymyxin B and tigecycline, which are almost sensitive to KP, are strictly restricted to use in children due to safety consideration, especially in neonates.<sup>31</sup>

Our study first described important profiles of healthcare-associated KP infections in Chinese pediatric patients and adds some knowledge and understanding of invasive KP and CRKP infections in children. Although this study is a retrospective study, the enrolled patients from all pediatric units of the nine tertiary children's hospitals are representative, and all episodes of invasive KP infections are culture-proven. However, our study has two major limitations. Firstly, retrospective data collection probably resulted in clinical information missing, such as prior healthcare history, prior previous antibiotic therapy and PICC utilization. Second, there is a potential estimation bias of clinical outcomes because KP-associated death post discharge was not captured. Further prospective studies are needed to trace the potential transmission source of KP in hospital setting and explain the disease severity based on integration clinical data with molecular mechanisms of carbapenemases and virulence factors of KP strains. The efforts will help to take intensified and effective IPC measures to reduce healthcare-associated KP infections and CRKP infections in pediatric patients.

## Conclusion

Pediatric invasive KP infections and high prevalence of CRKP infections largely occurred in healthcare settings in China. Of particular note, we found prematurity is the most key risk factor for healthcare-associated KP infections, and children from rural area were also an independent risk factor for CRKP infections. Overall, organ



dysfunction is independently correlated with poor outcomes. The adequate and intensified infection control measures should be focused on high-risk hematologic patients, premature neonatal patients and intubated patients.

## Ethical Approval

This study was reviewed and approved by the Ethics Committee of Fudan Children's Hospital (ethics approval number: 2020471). Informed consent from patients was not required by the Ethics Committee, because there was no contact with patients and all data were deidentified. This study was conducted in accordance with the Declaration of Helsinki.

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## Disclosure

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