Infection and Drug Resistance

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ORIGINAL RESEARCH

Long Term Characteristics of Clinical Distribution and Resistance Trends of Carbapenem-Resistant and Extended-Spectrum β-Lactamase *Klebsiella pneumoniae* Infections: 2014–2022

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Purpose: Through long-term and large sample size statistical analysis, we revealed the pattern of *Klebsiella pneumoniae* (KP) infection and drug resistance and provided epidemiological data for the treatment and prevention and control of multidrug-resistant bacterial infection in our hospital.

Patients and Methods: Strains were identified using the BD Phoenix^{TM}100 system, minimal inhibitory concentration of antibiotics were determined by the broth method, and data were statistically analyzed using WHONET 5.6 and SPSS27.0.

Results: The isolation rate of KP from Enterobacteriaceae (26.2%, 4547/17358) in our hospital showed an increasing annual trend, ranking second only to *Escherichia coli*. Carbapenem-resistant KP (CRKP) accounted for the highest proportion of carbapenem-resistant Enterobacteriaceae (72.2%, 431/597), showing an upward trend. Infected patients had a male-to-female ratio of approximately 2:1 and were mainly >60 years of age (66.2%), with intensive care units being the most commonly distributed department. Sputum was the most common specimen type (74.0%). Compared with spring and summer, autumn and winter were the main epidemic seasons for KP and extended-spectrum β-lactamase KP (ESBL-KP). The resistance rate of KP to common antibiotics was low, but all showed an increasing trend each year. ESBL-KP was >90% resistant to piperacillin, amoxicillin/clavulanic acid, and cefotaxime and less resistant to other common antibiotics, but showed an increasing trend in resistance to most antibiotics. CRKP resistance to common antibiotics was high, with resistance rates >90%, excluding amikacin (64.1%), gentamicin (87.4%), cotrimoxazole (44.3%), chloramphenicol (13.6%), and tetracycline (30.5%).

Conclusion: KP in our hospital mainly caused pulmonary infection in older men, which occurred frequently in autumn and winter, and the isolation and drug resistance rates showed an increasing trend. Age over 70 years, admission to intensive care unit, and urinary tract infection were found to be the risk factors for CRKP and ESBL-KP-resistance.

Keywords: *Klebsiella pneumoniae*, antibacterial drugs, resistance trends, carbapenem-resistant, extended-spectrum β-lactamase, antimicrobial susceptibility surveillance

Plain Language Summary

Klebsiella pneumoniae is one of the most common pathogens causing human infections, and its rapid rise in carbapenem resistance has aroused widespread concern in recent years. Because infections caused by such species are virtually incurable, they may lead to

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a "clinical crisis". We followed up *Klebsiella pneumoniae* isolated from a large tertiary care hospital in China for up to 8 years, measured the incidence regularity and drug resistance evolution trend, and found that the isolation rate of carbapenem-resistant *Klebsiella pneumoniae* increased nearly 5-fold compared with 8 years ago, mainly causing diseases in the cold autumn and winter seasons, and most of the affected population was older male patients with pneumonia. Therefore, it is urgent to develop defense measures against the further spread of *Klebsiella pneumoniae*, which is extremely dangerous to humans, especially because of its resistance to carbapenem.

Introduction

Klebsiella pneumoniae (KP) is a common opportunistic pathogen in hospitalized patients, often causing pneumonia, urinary tract infection, and bacteremia. Gastrointestinal carriage is a risk factor for nosocomial infections.[1] KP is naturally resistant to ampicillin and can acquire resistance to multiple antibiotics. The rise in antimicrobial resistance poses a great challenge to treating infectious diseases. The World Health Organization (WHO) considers the generation of extended-spectrum β-lactamase KP (ESBL-KP) and carbapenem-resistant KP (CRKP) a serious public health threat,[2] with over 670,000 infections caused by drug-resistant bacteria each year in Europe. This resulted in approximately 330,000 deaths between 2015 and 2017, the greatest increase in CRKP infection and mortality (by 6.16 times).[3] According to the Antibiotic Resistance Study commissioned by the UK government, the annual number of deaths from antibiotic resistance worldwide is expected to be 10 million by 2050. In Europe, carbapenem resistance rates in *E. coli* and KP and vancomycin resistance rates in *E. faecium* have increased significantly between 2014 and 2020.[4] Furthermore, KP resistance to third-generation cephalosporins and carbapenems is high, and carbapenem resistance in *P. aeruginosa* is also common and higher than that of KP.[4] In China, the 2005–2022 carbapenem resistance rates of KP and *A. baumannii* showed an increasing trend, while carbapenem resistance rates of *P. aeruginosa* showed a decreasing trend.[5] Additionally, fluoroquinolones and β-lactams are considered the first line of defense against serious infections, and deaths caused by resistance to these two classes of antibiotics are estimated to account for more than 70% of the deaths caused by resistance.

Antibiotic resistance remains a major public health problem worldwide, and although high-income countries face higher levels of resistance, low-income countries are more severely impacted.[6] Urinary tract infection has become an important public health problem worldwide. The rapid increase of bacterial drug resistance makes treatment more difficult. It is necessary to use drugs appropriately according to bacterial drug sensitivity.[7] Moreover, the recent emergence of carbapenem-resistant and hypervirulent KP has aroused worldwide concern. The emergence of resistance and virulence-binding plasmids has promoted the rapid spread of virulence-coding originals in gram-negative pathogens that may cause serious infections in relatively healthy people, which are difficult to treat with current antibiotics and treatment regimens.[8] These unique clinical issues have rekindled research interest in KP. However, long-term epidemiological surveillance data are limited. In this study, we focused on the isolation rate trend, drug susceptibility results, minimal inhibitory concentration (MIC)50/90, MIC distribution, specimen type, patient age/sex/department, and seasonal distribution of KP (including ESBL-KP and CRKP) clinically isolated in our hospital for 8 years (2014–2022). We aimed to investigate the infection and drug resistance trends of KP through epidemiological studies with large sample sizes and long spans, providing the basis for future studies on the pathogenesis, clinical impact, and long-term outcome of KP determination or infection and the implementation of new prevention and control strategies against KP.

Materials and Methods

Bacterial Isolates and Antimicrobial Susceptibility Tests

In this study, we collected 5442 strains of *Klebsiella pneumoniae* from the First Affiliated Hospital of Hebei North University of China from January 1, 2014 to June 30, 2022. After removing 895 duplicate strains from the same patient, the remaining 4547 strains of KP (4547 patients) were used for research and analysis. Blood (8–10 mL), cerebrospinal fluid (1 mL), pleural fluid (1 mL), and aspirate (1 mL) were cultured in a liquid medium (Becton Dickinson and Company/FX-200, MD, USA). Urine (1 μL) and other clinical samples were streaked onto Columbia blood and MacConkey agar plates (Jinan Baibo Biological) and incubated for 24 h at 35 °C. Species identification and

determination of antimicrobial susceptibility were performed using the BD-Phoenix 100 system (Becton, Dickinson and Company, New Jersey, USA).

Susceptibility experiments were performed using the micro broth dilution method, and prior to testing, the strains were prepared as bacterial suspensions at a concentration of 0.5, McFarland standard. Following this, 25 μL of the bacterial suspension and 45 μL of the indicator were added to the broth and mixed thoroughly within 15 min of preparation of the bacterial suspension. The remaining bacterial suspension was added to the raw chemical well reaction area, the solution in the broth tube was added to the drug sensitivity reaction area, sealed with a cap, placed into the BD automatic drug sensitivity identification instrument, and incubated at 35 °C for 24 h.

CLSI - M100 ED30 breakpoints were used for the determination of drug sensitivity. An MIC ≥4 mg/L of imipenem or meropenem against KP was defined as CRKP, and an MIC ≥2 mg/L of ceftazidime, ceftriaxone, cefotaxime, or aztreonam against KP was defined as extended-spectrum β-lactamase- KP (ESBL-KP). KP QC strain ATCC700603 and *Escherichia coli* QC strain ATCC25922 were used. Supplementary Table 1 lists the classification, pharmacology, and mechanism of action of antibiotics used in this study.

Statistical Analysis

Statistical analyses were performed on the raw data using Whonet 5.6 software (WHO, Geneva, Switzerland), excluding duplicate sample submission data from the same patient. Logistic regression model was used to calculate odds ratio (OR) and 95% confidence interval (CI) for the analysis of risk factors related to CRKP and ESBL-KP infection; independent sample *t*-test or Wilcoxon rank sum test was used to compare the differences between groups. $P<0.05$ was considered statistically significant. SPSS 27.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. The Origin 2021 (OriginLab Co. MA, USA), GraphPad Prism 9.4.0 (GraphPad Software, LaJolla, CA, USA) were used for mapping.

Results

Basic Features

This study included ESBL-KP 1292 and CRKP 431. During the 8 years, KP accounted for 26.2% (4547/17358) of Enterobacteriaceae, ranking second only to *Escherichia coli*, and the isolation rate showed an increasing trend each year (Figure 1A); CRKP had the highest detection rate in carbapenem-resistant Enterobacteriaceae (CRE), accounting for 72.2% (431/597), and showing an increasing trend (Figure 1B); the detection rate of ESBL-KP was higher than that of CRKP, and both reached their highest value in 2018. Additionally, the detection rate of CRKP showed a rapidly increasing trend from 2014 to 2018, and then a slowly decreasing trend from 2018 to 2022, while ESBL-KP showed an initially increasing trend, followed by another decrease, then increase (Figure 1C).

KP was mainly derived from sputum (74.0%, 3364/4547), while urine (8.9%, 404/4547) and blood (6.1%, 279/4547) were the second and third sources, respectively. Other sources included secretions (3.7%, 170/4547), throat swabs (3.1%, 140/4547), drainage fluid (1.2%, 55/4547), and ascites (1.1%, 48/4547) (Figure 2A). There was little fluctuation in the proportion of sample separation among the top five samples between 2014 and 2022 (Figure 2B). In addition, KP strains isolated from urine samples was more resistant to carbapenems and cephalosporins and amtreonam than those isolated from sputum and blood samples (Supplementary Table 2).

KP, ESBL-KP, and CRKP-infected patients were mostly men, and the male-to-female ratio was approximately 2:1 ($P<0.05$) (Figure 3A). Additionally, male patients were more likely to be infected with ESBL-KP than female patients (Supplementary Table 2). Patients aged 50–80 years constituted the main infected population, and CRKP infection was also more common in patients aged <1 year (Figure 3B). Age over 70 years was found to be a risk factor for infection with CRKP and ESBL, and the risk increased with age (Supplementary Table 2). Furthermore, KP was distributed in neurology, respiratory and cardiovascular medicine departments, CRKP was mainly distributed in respiratory, nephrology, and rehabilitation medicine departments, while ESBL-KP was mostly concentrated in neurology, respiratory, and nephrology departments (Figure 4). In addition, admission to intensive care unit was a risk factor for infection with CRKP and ESBL-KP (Supplementary Table 2). KP and ESBL-KP infection seasons were mainly the third and fourth

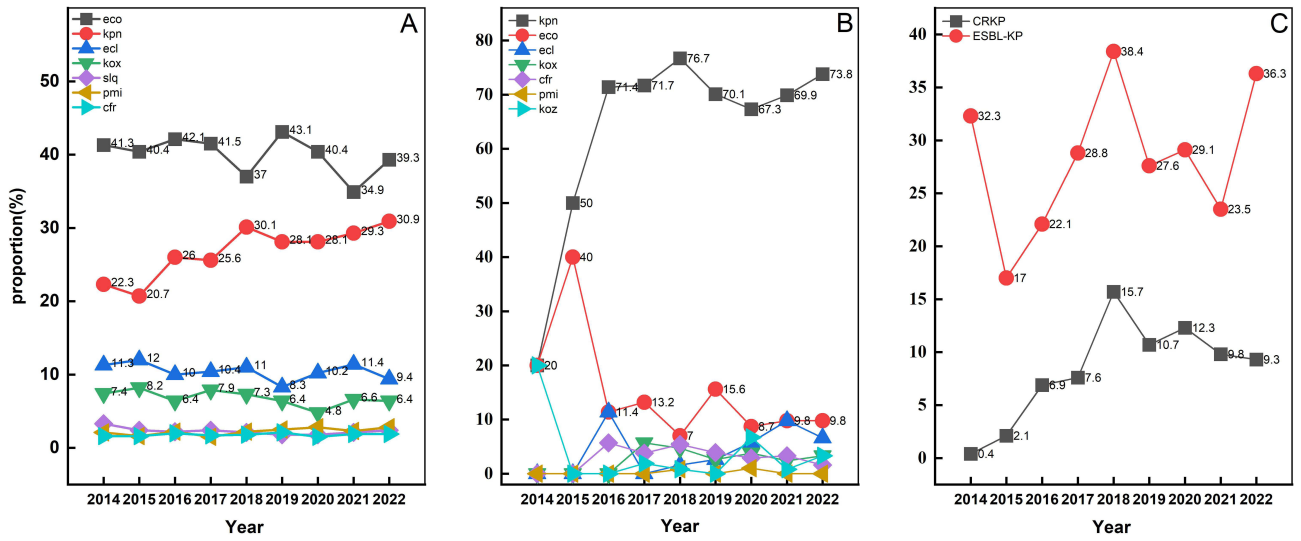

Figure 1 Isolation trend of major Enterobacteriaceae, carbapenem-resistant Enterobacteriaceae and drug-resistant *Klebsiella pneumoniae* from 2014 to 2022. (**A**) Trend of major Enterobacteriaceae isolation. (**B**) Trend of detection rate of carbapenem-resistant Enterobacteriaceae. (**C**) Trend of extended-spectrum β-lactamase-*Klebsiella pneumoniae* (ESBL-KP) and carbapenem-resistant *Klebsiella pneumoniae* (CRKP) detection rate.
Abbreviations: eco, *Escherichia coli*; kpn, *Klebsiella pneumoniae*; ecl, *Enterobacter cloacae*; kox, *Klebsiella oxytoca*; slq, *Serratia liquefaciens*; pmi, *Proteus mirabilis*; cfr, *Citrobacter freundii*; koz, *Klebsiella pneumonia ozaenae*.

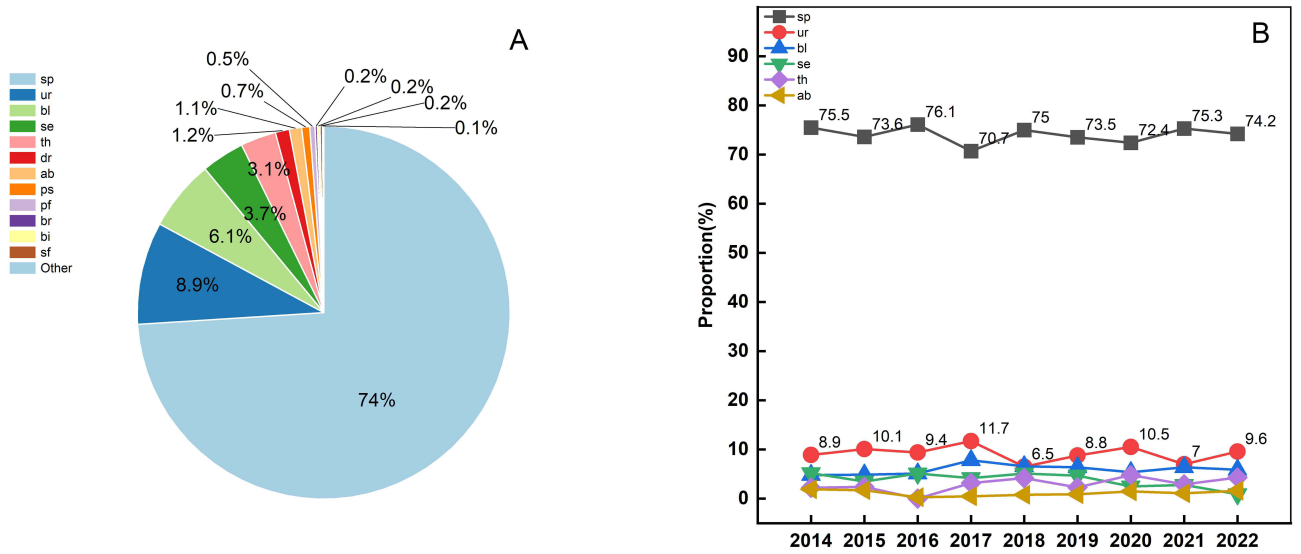

Figure 2 Distribution and trend of specimens from 2014 to 2022. (**A**) Total sample proportion classification. (**B**) Annual sample isolation rate of *Klebsiella pneumoniae*.
Abbreviations: sp, sputum; ur, urine; bl, blood; se, secretion; th, throat; dr, drainage; ab, abdominal fluid; ps, pus; pf, pleural fluid; br, bronchial; bi, bile; sf, cerebrospinal fluid.

quarters; however, there was no difference in CRKP seasonal distribution (Figure 5). In addition, KP detected in the third quarter was more susceptible to resistance to cephalosporins and amtreonam (Supplementary Table 2).

Antimicrobial Susceptibility

Klebsiella pneumoniae (KP)

KP susceptibility to the commonly used antibacterial agents was initially high, increasing yearly from 2014 to 2018, then decreasing yearly from 2018 to 2022. The mean resistance rate to piperacillin was greater than that to piperacillin/tazobactam (28.2% vs 18.9%), and the mean resistance rate to amoxicillin/clavulanic acid was higher (30.1%). Among cephalosporins, cefotaxime showed the highest mean resistance rate (23.4%), while ceftazidime and cefepime showed 14.7% and 19.7%, respectively. Aztreonam (monocyclic β-lactam antibiotic) showed a relatively low resistance rate, with

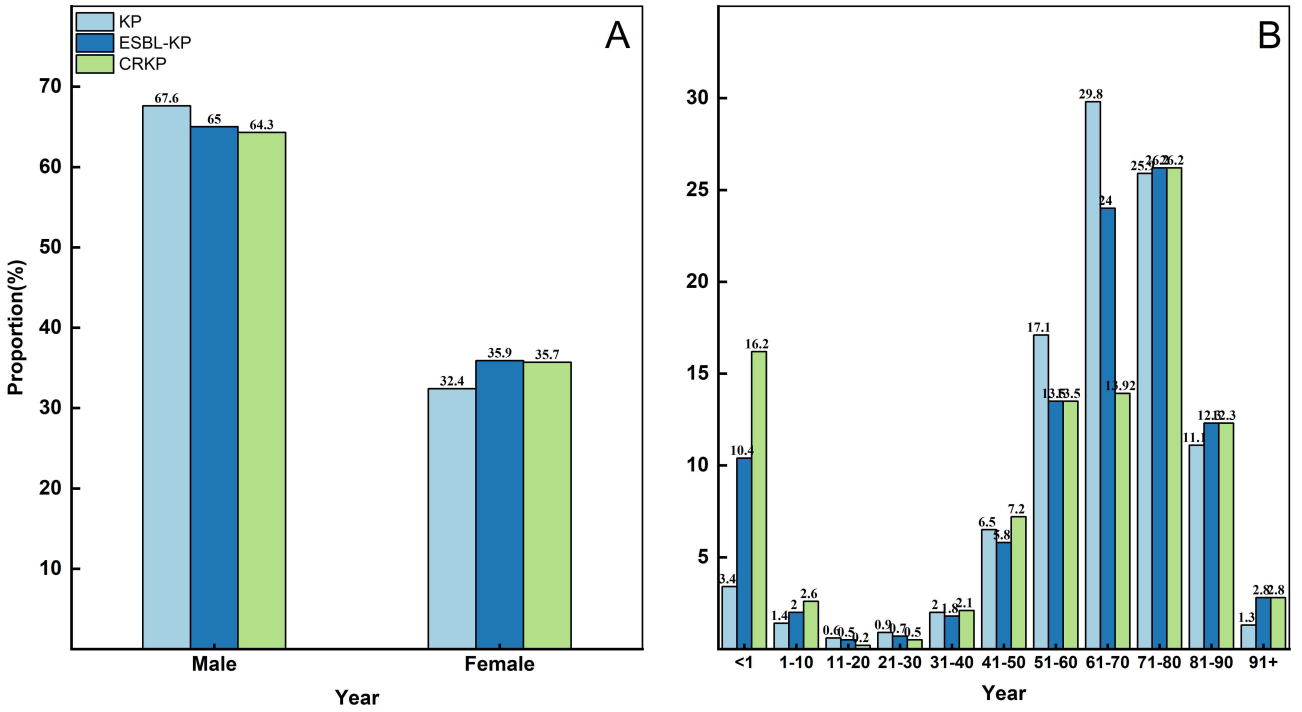

Figure 3 Sex and age distribution of *Klebsiella pneumoniae* (KP), extended-spectrum β-lactamase-*Klebsiella pneumoniae* (ESBL-KP) and carbapenem-resistant *Klebsiella pneumoniae* (CRKP). (**A**) Sex distribution of KP, ESBL-KP, and CRKP. (**B**) Age distribution of KP, ESBL-KP, and CRKP.

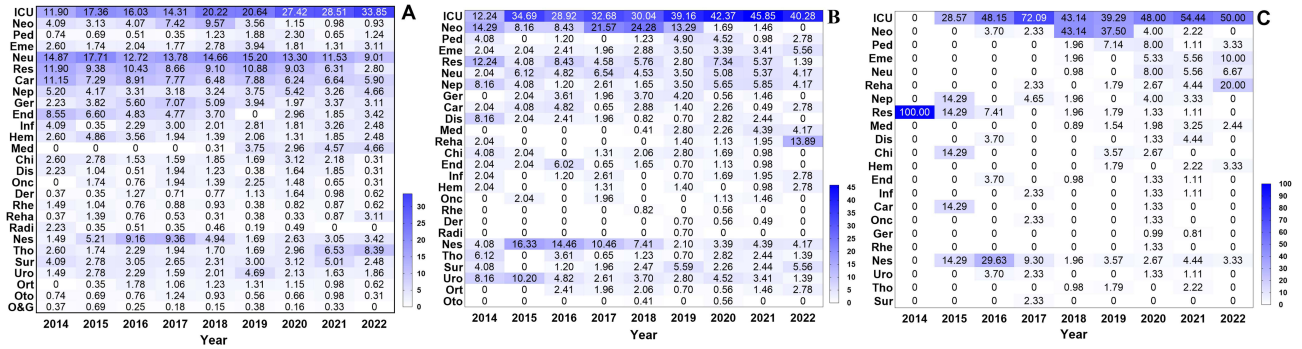

Figure 4 Departmental distribution of *Klebsiella pneumoniae* (KP), extended-spectrum β-lactamase-*Klebsiella pneumoniae* (ESBL-KP) and carbapenem-resistant *Klebsiella pneumoniae* (CRKP) from 2014 to 2022. (**A**) Departmental distribution of KP, (**B**) Departmental distribution of ESBL-KP, (**C**) Departmental distribution of CRKP.
Abbreviations: ICU, Intensive care unit; Neo, Neonatology department; Ped, Pediatrics department; Eme, Emergency department; Neu, Neurology department; Res, Respiratory department; Car, Cardiovascular department; Nep, Nephrology department; Ger, Geriatrics department; End, Endocrine department; Inf, Infectious diseases department; Hem, Hematology department; Med, General Medicine; Chi, Traditional Chinese Medicine department; Dis, Digestive department; Onc, Internal Medicine-Oncology; Ger, dermatological department; Rhe, Rheumatism Immunity Branch; Reha, Rehabilitation medicine department; Radi, Radiotherapy department; Nes, neurosurgery department; Tho, Thoracic Surgery; Sur, General surgery; Uro, Urology Surgery; Oto, Otorhinolaryngology surgery department; O&G, Obstetrics and Gynecology department.

a mean resistance rate of 17.8%. Additionally, the resistance rates to imipenem and meropenem were lower (7.7% vs 7.6%), but both showed an increasing annual trend. Among aminoglycoside antibiotics, the average resistance rate to gentamicin exceeded twice as that to amikacin (17.4% vs 6.6%). Further, among the fluoroquinolone antibiotics, the mean resistance rate to ciprofloxacin was higher than that to levofloxacin (23.3% vs 16.6%). The resistance rate to sulfamethoxazole/trimethoprim was stable and did not fluctuate, with an average resistance rate of 23.84%. Similarly, the resistance rates to chloramphenicol and tetracycline were relatively stable, with mean resistance rates of 19.5% and 23.9%, respectively (Table 1).

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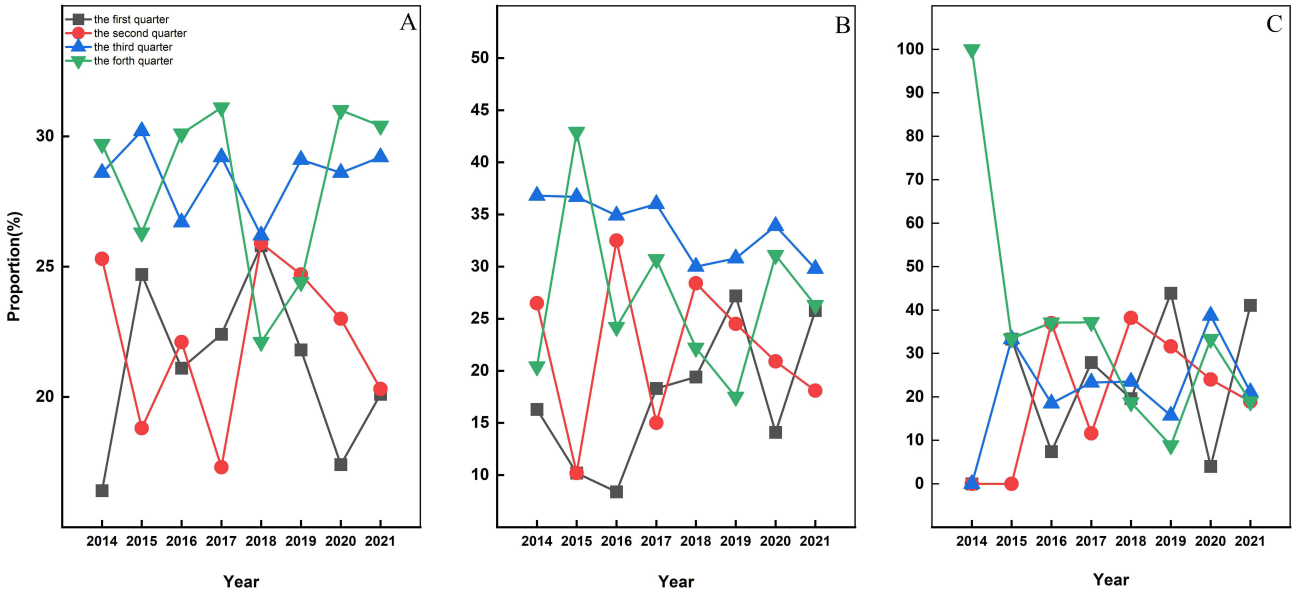

Figure 5 Seasonal distribution of *Klebsiella pneumoniae* (KP), extended-spectrum β-lactamase-*Klebsiella pneumoniae* (ESBL-KP) and carbapenem-resistant *Klebsiella pneumoniae* (CRKP) from 2014 to 2021. (**A**) Seasonal distribution of KP. (**B**) Seasonal distribution of ESBL-KP. (**C**) Seasonal distribution of CRKP.

Extended-Spectrum β-Lactamase-*Klebsiella pneumoniae* (ESBL-KP)

ESBL-KP has a high resistance rate to penicillin, β_lactam/β_lactamase inhibitors, and cephalosporins and a low resistance rate to carbapenems, amikacin, tetracycline, and sulfamethoxazole/trimethoprim. The mean resistance rate of ESBL-KP to piperacillin was higher than that to piperacillin/tazobactam (98.4% vs 56.1%); however, the resistance rate to amoxicillin/clavulanic acid showed an increasing trend annually, with a mean resistance rate of 97.9%, which was higher than that to piperacillin/tazobactam (P<0.05) (Supplementary Figure 1C). Among cephalosporins, the cefotaxime resistance rate was high (98.2%) and 76.4% had high-level resistance (≥ 64 mg/mL). The mean resistance rate to ceftazidime was low (60.3%). The drug resistance rate of cefepime was higher than that of ceftazidime, but the drug resistance rate of both showed an upward trend (Figure 6A), and the difference in the drug resistance rate of the three drugs was statistically significant (P<0.05) (Supplementary Figure 1B). The average resistance rate to aztreonam was 72.2%, which showed an increasing trend each year. The average resistance rates to carbapenem antibiotics were low, with 29.6% and 29.0% for imipenem and meropenem, respectively; however, both the resistance rates showed an increasing trend, with a rapid increase from 2014 to 2018 and a slow increase from 2018 to 2022 (Figures 6C and 7). Among aminoglycosides, the average resistance rate of ESBL-KP to gentamicin was approximately twice as that to amikacin (65.0% vs 25.6%) (P<0.05) (Supplementary Figure 1D). The amikacin resistance rate showed a trend of increasing and then decreasing, and the resistance rate of gentamicin was stable (Figure 8A). Furthermore, the fluoroquinolones resistance rates showed an increasing trend, with levofloxacin resistance increasing faster than ciprofloxacin resistance (Figure 8C), and the mean resistance rate to ciprofloxacin was higher than that to levofloxacin (78.3% vs 55.5%) (P<0.05) (Supplementary Figure 1E). The resistance rate to sulfamethoxazole/trimethoprim showed a trend of increasing and then decreasing, with an average resistance rate of 68.2%. The chloramphenicol resistance rate showed a decreasing trend, with an average resistance rate of 39.7%. The resistance rate to tetracycline showed an increasing trend annually, with an average resistance rate of 64.32% (Table 2).

Carbapenem-Resistant *Klebsiella pneumoniae* (CRKP)

The resistance rate of CRKP to common antibiotics is remarkably high. For β_lactam/β_lactamase inhibitors, it was almost 100%, and the average resistance rates to amoxicillin/clavulanic acid and piperacillin/tazobactam were 96.8% and 97.7%, respectively. The resistance rates to cephalosporins were also high; the average resistance rates to ceftazidime, cefotaxime, and cefepime were 93.6%, 95.3%, and 98.0%, respectively, and the resistance rate of cefotaxime showed an increasing annual trend (Figure 6B). The resistance rate to aztreonam initially decreased then increased, with an average

Table 1 Rates (%) of *Klebsiella pneumoniae* Resistance to Antimicrobial Agents from 2014 to 2022

Antibiotic	2014		2015		2016		2017		2018		2019		2020		2021		2022		All	
	N	R	N	R	N	R	N	R	N	R	N	R	N	R	N	R	N	R	N	R
Piperacillin	268	27.6	287	20.9	392	25.0	566	31.4	648	40.3	533	28.3	603	32.2	918	23.9	317	24.0	4532	28.2
Amoxicillin/clavulanic acid	266	28.2	287	23.3	393	27.2	566	33.9	648	41.8	533	30.2	607	32.9	919	26.1	322	27.0	4541	30.1
Piperacillin/tazobactam	265	14.0	287	11.8	393	16.5	566	22.6	648	27.5	533	18.9	607	22.1	917	17.3	322	19.3	4538	18.9
Ceftazidime	268	6.7	287	7.7	393	11.2	566	17.0	648	23.6	526	15.4	609	18.7	918	15.3	322	16.5	4537	14.7
Cefotaxime	268	18.3	287	16.0	392	19.1	566	25.4	648	35.8	533	26.5	609	27.6	919	20.9	322	21.1	4544	23.4
Cefepime	266	14.3	287	14.3	393	15.3	566	22.3	648	28.2	531	22.2	607	23.2	919	17.8	321	19.9	4538	19.7
Aztreonam	269	10.8	287	10.8	393	15.0	566	19.6	648	26.4	533	19.1	607	21.7	919	17.6	322	19.3	4544	17.8
Imipenem	266	0.4	287	2.1	393	5.9	565	6.7	645	14.4	528	10.6	606	11.2	914	8.9	320	8.8	4524	7.7
Meropenem	269	0.4	287	2.1	393	5.1	566	7.2	645	14.6	533	10.3	604	10.9	913	8.7	320	8.8	4530	7.6
Amikacin	268	1.1	287	1.7	393	6.6	566	7.4	648	13.1	533	10.1	609	9.2	919	7.2	322	3.4	4545	6.6
Gentamicin	269	10.8	287	13.2	393	15.3	566	17.5	648	29.5	533	19.3	609	20.7	919	15.5	322	14.9	4546	17.4
Ciprofloxacin	267	14.2	287	16.0	390	19.7	562	23.1	642	34.9	530	26.6	607	28.2	915	25.1	321	22.1	4521	23.3
Levofloxacin	261	6.5	285	9.1	392	11.7	562	14.6	639	26.8	532	18.6	500	23.6	775	22.1	321	16.8	4267	16.6
Sulfamethoxazole/trimethoprim	269	24.2	287	21.6	393	20.6	566	28.6	648	29.8	533	19.5	609	26.9	918	24.1	322	19.3	4545	23.8
Chloramphenicol	269	22.3	286	19.6	393	19.6	566	20.1	648	24.2	520	16.5	556	18.5	859	17.6	292	17.5	4389	19.5
Tetracycline	265	25.3	287	21.6	391	21.7	566	26.1	647	28.9	532	23.7	609	23.3	919	21.2	322	23.0	4538	23.9

Abbreviations: N, number; R, drug resistance rate (%).

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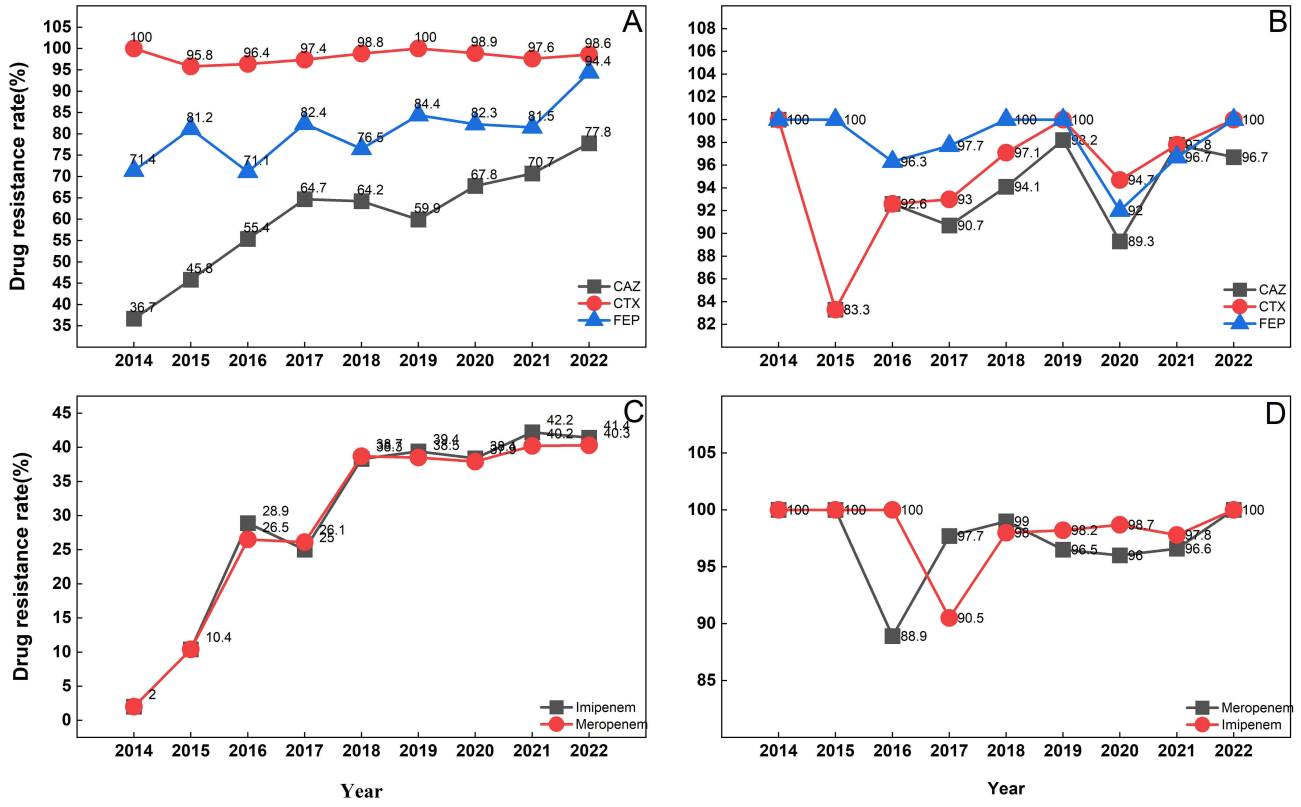

Figure 6 Trends of resistance of carbapenem-resistant *Klebsiella pneumoniae* (CRKP) and extended-spectrum β-lactamase-*Klebsiella pneumoniae* (ESBL-KP) to carbapenes and cephalosporins from 2014 to 2022. (**A**) Trend of resistance rate of ESBL-KP to cephalosporin. (**B**) Trend of resistance rate of CRKP to cephalosporin. (**C**) Trend of resistance rate of ESBL-KP to carbapenems. (**D**) Trend of resistance rate of CRKP to carbapenems.
Abbreviations: CAZ, Ceftazidime; CTX, Cefotaxime; FEP, Cefepime.

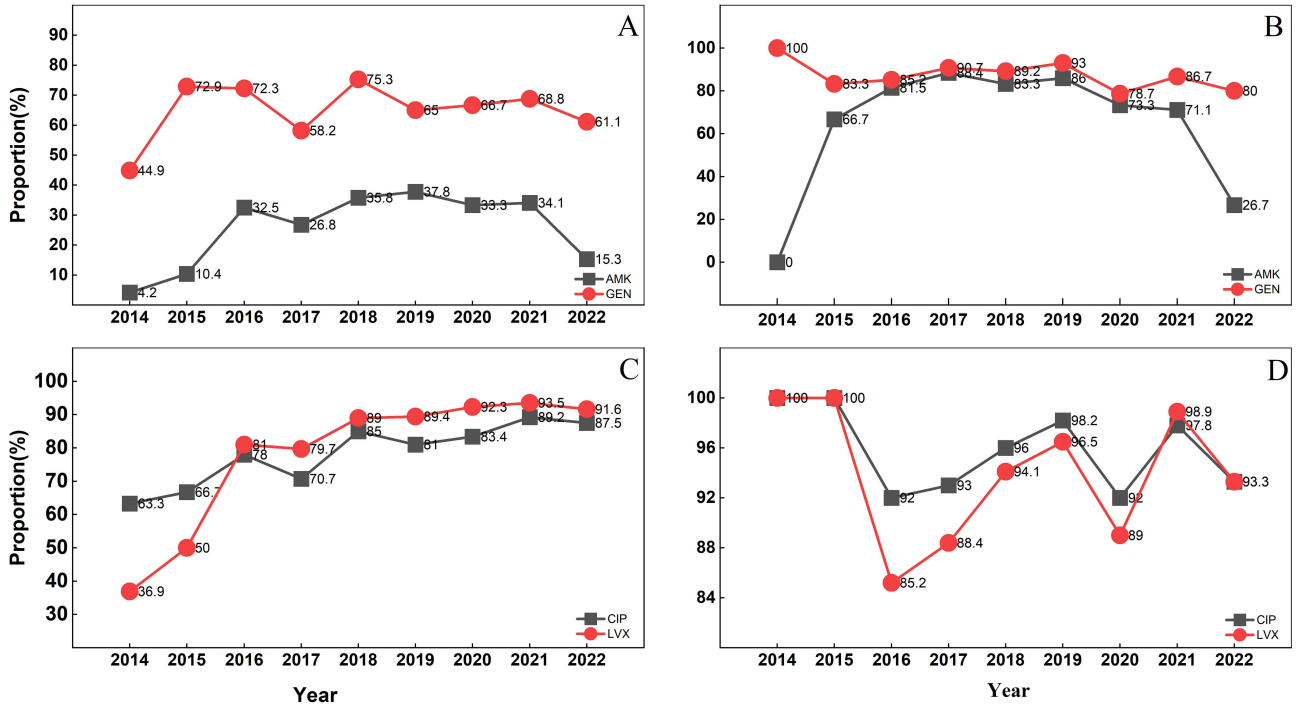

Figure 7 Trends of resistance of extended-spectrum β-lactamase-*Klebsiella pneumoniae* (ESBL-KP) and carbapenem-resistant *Klebsiella pneumoniae* (CRKP) to aminoglycosides and fluoroquinolones from 2014 to 2022. (**A**) Trend of resistance of ESBL-KP to aminoglycosides. (**B**) Trend of resistance of CRKP to aminoglycosides. (**C**) Trend of resistance of ESBL-KP to fluoroquinolones. (**D**) Trends of resistance of CRKP to fluoroquinolones. AMK, Amikacin; GEN, Gentamicin; CIP, Ciprofloxacin; LVX, Levofloxacin.

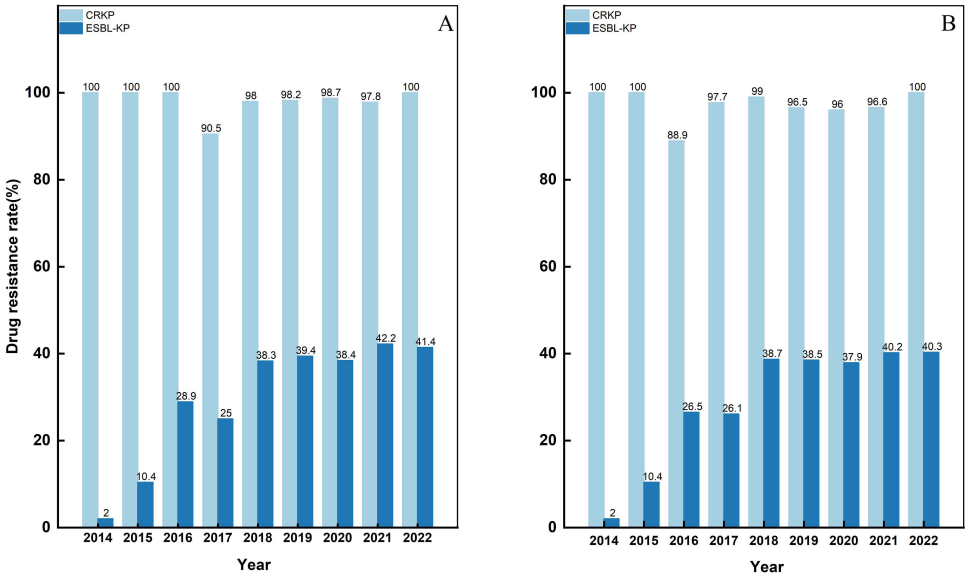

Figure 8 Comparison of drug resistance trends of carbapenem-resistant *Klebsiella pneumoniae* (CRKP) and extended-spectrum β-lactamase-*Klebsiella pneumoniae* (ESBL-KP) to imipenem and meropenem from 2014 to 2022. (**A**) Comparison of imipenem resistance rates between CRKP and ESBL-KP. (**B**) Comparison of meropenem resistance rates between CRKP and ESBL-KP.

resistance rate of 97.7%. The resistance rates to carbapenem antibiotics (imipenem and meropenem) were high, showing an upward trend (Figures 6D and 7). Aminoglycosides (amikacin and gentamicin) showed an initial increase, followed by a decrease, with a greater fluctuation for amikacin (Figure 8B), where the average resistance rates were 64.1% and 87.4%, respectively (P<0.05) (Supplementary Figure 2D). Fluoroquinolones (ciprofloxacin and levofloxacin) showed fluctuating trends of increasing and decreasing resistance rates (Figure 8D), with average resistance rates of 95.8% and 93.9%, respectively (P<0.05) (Supplementary Figure 2E). The resistance rate to sulfamethoxazole/trimethoprim decreased between 2014 and 2019 and increased again between 2019 and 2022. The average resistance rate was 44.3%, and the lowest resistance rate was only 10.5%. The resistance rate to chloramphenicol showed a downward trend, with an average resistance rate of 30.4%. The resistance rate of tetracycline first decreased and then increased, with an average resistance rate of 41.5% and the lowest resistance rate of 10.8% (Table 3).

MIC50 and MIC90

The MIC90/50 ratios ranged from 1 to 128 for KP, 128 for cefotaxime, and 1 for carbapenems, amikacin, and levofloxacin (Table 4); the MIC distribution ranges were wide at 0.064–32, and the proportions of imipenem and meropenem MICs ≤0.5 were 82.1% and 92.2%, respectively, (Figure 9).

The MIC90/50 ratio for ESBL-KP ranged from 1 to 32, and the MIC 90/50 ratio for most antibiotics was 1 or 2, with carbapenems having a ratio of 32 (Table 4); the MIC distribution range was mainly 0.064–32, with imipenem and meropenem having MIC ranges of 0.25–16 and 0.064–16, respectively, and the proportion with MIC ≤0.5 was 68.5% and 69.2%, respectively (Figure 9).

The MIC90/50 ratio for CRKP was 1, excluding chloramphenicol and tetracycline with a ratio of 2 and 4, respectively (Table 4). The MIC range was 0.25–32, and that of imipenem and meropenem was 0.5–16 (MIC ≥8, 92% and 96.4% respectively). The MIC range of cefotaxime shifted to the right compared to that of cefepime and ceftazidime (Figure 9).

Discussion

We found that in our hospital, KP commonly caused pulmonary infection in older men, which occurred frequently in autumn and winter, and the isolation and drug resistance rates showed an increasing trend. KP is already a major public health threat globally, with high morbidity and mortality,[9,10] and the emergence of CRKP has made the problem even more difficult because carbapenems are the drugs of choice for the treatment of ESBL-KP infections, and currently

Table 2 Rates (%) of Extended-Spectrum β-Lactamase-*Klebsiella pneumoniae* Resistance to Antimicrobial Agents from 2014 to 2022

Antibiotic	2014		2015		2016		2017		2018		2019		2020		2021		2022		All	
	N	R	N	R	N	R	N	R	N	R	N	R	N	R	N	R	N	R	N	R
Piperacillin	87	95.8	49	100.0	87	97.6	163	98.7	249	99.2	147	99.3	177	98.3	216	98.0	117	98.6	1292	98.4
Amoxicillin/clavulanic acid	87	89.8	48	100.0	83	98.8	153	99.3	243	99.2	143	97.9	176	98.9	205	98.5	72	98.6	1210	97.9
Piperacillin/tazobactam	87	32.7	48	41.7	83	55.4	153	65.4	243	61.7	143	54.5	175	62.3	204	62.7	72	68.1	1208	56.1
Ceftazidime	87	36.7	48	45.8	83	55.4	153	64.7	243	64.2	137	59.9	177	67.8	205	70.7	72	77.8	1205	60.3
Cefotaxime	87	100.0	48	95.8	83	96.4	153	97.4	243	98.8	143	100.0	177	98.9	205	97.6	72	98.6	1211	98.2
Cefepime	87	71.4	48	81.2	83	71.1	153	82.4	243	76.5	141	84.4	175	82.3	205	81.5	71	94.4	1206	80.6
Aztreonam	87	55.1	48	62.5	83	67.5	153	71.9	243	70.8	143	72.0	176	78.4	205	81.5	72	90.3	1210	72.2
Imipenem	87	2.0	48	10.4	83	28.9	152	25.0	243	38.3	142	39.4	177	38.4	204	42.2	70	41.4	1206	29.6
Meropenem	87	2.0	48	10.4	83	26.5	153	26.1	243	38.7	143	38.5	177	37.9	204	40.2	72	40.3	1210	29.0
Amikacin	87	4.2	48	10.4	83	32.5	153	26.8	243	35.8	143	37.8	177	33.3	205	34.1	72	15.3	1211	25.6
Gentamicin	87	44.9	48	72.9	83	72.3	153	58.2	243	75.3	143	65.0	177	66.7	205	68.8	72	61.1	1211	65.0
Ciprofloxacin	87	63.3	48	66.7	82	78.0	150	70.7	240	85.0	142	81.0	175	83.4	203	89.2	72	87.5	1199	78.3
Levofloxacin	87	31.1	46	37.0	82	52.4	150	44.0	236	66.9	142	59.9	163	66.3	195	75.9	71	66.2	1172	55.5
Sulfamethoxazole/trimethoprim	87	79.6	48	79.2	83	68.7	153	74.5	243	59.3	143	42.7	177	68.9	205	76.6	72	63.9	1211	68.2
Chloramphenicol	87	59.2	48	52.1	83	39.8	153	30.7	243	38.3	136	33.8	148	33.1	176	35.8	58	34.5	1132	39.7
Tetracycline	49	65.3	48	81.2	83	66.3	153	68.0	243	56.4	143	56.6	177	51.4	205	62.9	72	70.8	1173	64.3

Abbreviations: N, number; R, drug resistance rate (%).

Table 3 Rates (%) of Carbapenem Resistant *Klebsiella pneumoniae* Resistance to Antimicrobial Agents from 2014 to 2022

Antibiotic	2014		2015		2016		2017		2018		2019		2020		2021		2022		All	
	N	R	N	R	N	R	N	R	N	R	N	R	N	R	N	R	N	R	N	R
Piperacillin	1	100.0	6	100.0	27	100.0	43	97.7	102	100.0	57	100.0	72	98.6	90	97.8	30	100.0	428	99.3
Amoxicillin/clavulanic acid	1	100.0	6	100.0	27	92.6	43	95.3	102	98.0	57	100.0	75	96.0	90	97.8	30	100.0	431	96.8
Piperacillin/tazobactam	1	100.0	6	100.0	27	100.0	43	100.0	102	99.0	57	100.0	75	96.0	90	96.7	30	100.0	431	97.7
Ceftazidime	1	100.0	6	83.3	27	92.6	43	90.7	102	94.1	57	98.2	75	89.3	90	97.8	30	96.7	431	93.6
Cefotaxime	1	100.0	6	83.3	27	92.6	43	93.0	102	97.1	57	100.0	75	94.7	90	97.8	30	100.0	431	95.4
Cefepime	1	100.0	6	100.0	27	96.3	43	97.7	102	100.0	57	100.0	75	92.0	90	96.7	30	100.0	431	98.1
Aztreonam	1	100.0	6	100.0	27	96.3	43	97.7	102	98.0	57	98.2	75	89.3	90	97.8	30	96.7	431	97.1
Imipenem	1	100.0	6	100.0	27	100.0	42	90.5	102	98.0	57	98.2	75	98.7	90	97.8	30	100.0	430	98.1
Meropenem	1	100.0	6	100.0	27	88.9	43	97.7	102	99.0	57	96.5	75	96.0	89	96.6	30	100.0	430	97.2
Amikacin	1	0.0	6	66.7	27	81.5	43	88.4	102	83.3	57	93.0	75	73.3	90	71.1	30	26.7	431	64.1
Gentamicin	1	100.0	6	83.3	27	85.2	43	90.7	102	89.2	57	98.2	75	78.7	90	86.7	30	80.0	431	87.4
Ciprofloxacin	1	100.0	6	100.0	25	92.0	43	93.0	101	96.0	57	98.2	75	92.0	90	97.8	30	93.3	428	95.8
Levofloxacin	1	100.0	6	100.0	27	85.2	43	88.4	102	94.1	57	96.5	73	89.0	88	98.9	30	93.3	427	93.9
Sulfamethoxazole/trimethoprim	1	100.0	6	66.7	27	25.9	43	18.6	102	11.8	57	10.5	75	56.0	90	65.6	30	43.3	431	44.3
Chloramphenicol	1	100.0	6	33.3	27	18.5	43	23.3	102	22.5	55	20.0	60	18.3	80	20.0	22	18.2	396	30.5
Tetracycline	1	100.0	6	66.7	27	25.9	43	18.6	102	10.8	57	19.3	75	24.0	90	37.8	30	70.0	431	30.5

Abbreviations: N, number; R, drug resistance rate (%).

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Table 4 Ratio of MIC90 to MIC50 for the *Klebsiella pneumoniae(KP)*, Extended-Spectrum β-Lactamase-Klebsiella pneumoniae (ESBL-KP) and Carbapenem-Resistant *Klebsiella pneumoniae* (CRKP) (Fold)

Antibiotic	*KP*	ESBL-KP	CRKP
Piperacillin	16	1	1
Amoxicillin/clavulanic acid	8	2	1
Piperacillin/tazobactam	8	2	1
Ceftazidime	32	2	1
Cefotaxime	128	1	1
Cefepime	16	1	1
Aztreonam	16	1	1
Imipenem	1	32	1
Meropenem	1	32	1
Amikacin	1	16	1
Gentamicin	16	1	1
Ciprofloxacin	16	1	1
Levofloxacin	1	2	1
Sulfamethoxazole/trimethoprim	16	1	1
Chloramphenicol	16	2	2
Tetracycline	16	1	4

available therapeutic alternatives are limited. The development of antibiotic resistance is a natural phenomenon caused by mutations in bacterial genes or the acquisition of exogenous resistance genes carried by mobile genetic elements that can spread horizontally between bacteria. The most important resistance mechanism of CRE is via carbapenemase production, and the common carbapenemases include *Klebsiella pneumoniae* carbapenemase (KPC), New Delhi metallo-β-lactamase (NDM), imipenemase (IMP), Verona-integron-encoded metallo-β-lactamase (VIM), and oxacillinase-48 (OXA-48).[11] KPC is the most prevalent carbapenemase in KP. However, a hospital in Iran showed that the incidence rates of KPC and NDM in KP were almost the same.[12] New β_lactam/β_lactamase inhibitors are optional therapeutic agents for treating infections. Unfortunately, resistance to ceftazidime - avibactam has emerged in many countries, which has posed a new clinical challenge in recent years.[13] Continued surveillance information provides the foundation for developing and implementing antimicrobial stewardship programs as well as for enhancing the development of new antimicrobial agents.

In our hospital, CRKP increased rapidly, the isolation rate showed an increasing trend annually, and the detection rate was the highest in CRE. The detection rate of ESBL-KP initially increased and then decreased, and the detection rate of ESBL-KP was higher than that of CRKP (Figure 1C). Data from the China Antibiotic Surveillance Network (CHINET) showed that the isolation rate of KP from gram-negative bacilli in China increased from 14.0% in 2005 to 20.7% in 2018, and 2018–2022 showed a decreasing trend.[5] In Europe, ESBL-KP isolation rate is approximately 30%; in North America, approximately 10%; and in Southeast Asia, 40%.[14] In the United States (US), the isolation rate of ESBL-KP is approximately 3–35%, and a survey study between 2012 and 2017 showed that ESBL was the only pathogen with an increasing incidence (53% increase), while the incidence of CRKP did not change significantly.[15] Data from the China Antimicrobial Resistance Surveillance System showed that the detection rate of CRKP had an increasing trend every year, from 4.9% in 2013 to 10.9% in 2020, whereas the detection rate of third-generation cephalosporin-resistant KP showed a decreasing trend year by year, from 36.9% in 2014 to 31.1% in 2020.[16] ESBL-KP infection rate showed a downward trend from 2008 to 2018 in a hospital of Zhejiang Province in China.[17] KP infection is the leading cause of nosocomial pneumonia in China; however, it is one of the most common causes of hospital-acquired urinary tract infections in the United States.[18] In this study, KP mainly caused pneumonia, followed by urinary tract and bloodstream infections. However, KP isolated from urine samples was more resistant to carbapenems and

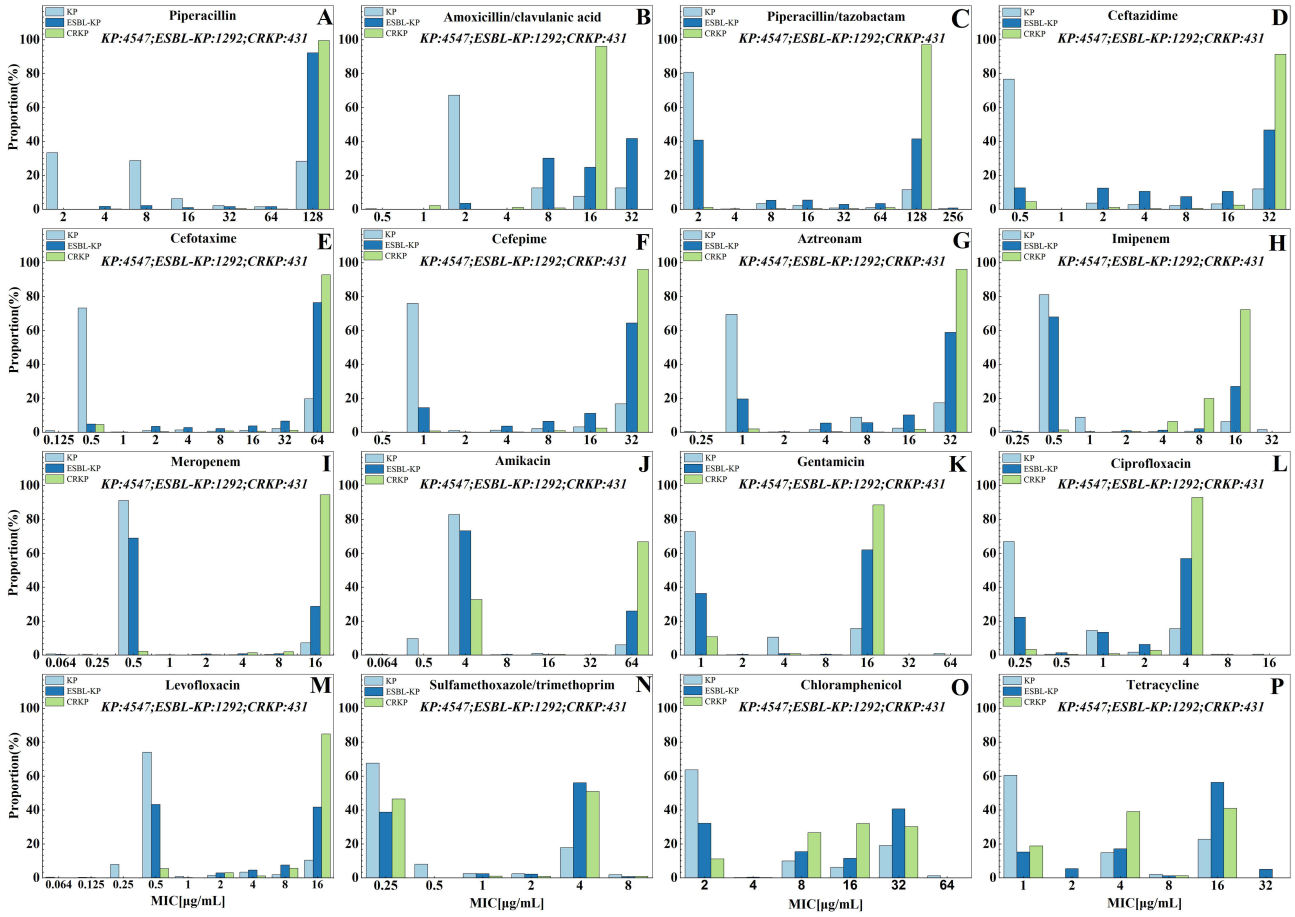

Figure 9 Minimum inhibitory concentration (MIC [μg/mL]) distribution of *Klebsiella pneumoniae* (KP), extended-spectrum β-lactamase-*Klebsiella pneumoniae* (ESBL-KP) and carbapenem-resistant *Klebsiella pneumoniae* (CRKP). (**A**–**P**) Piperacillin, Amoxicillin/clavulanic acid, Piperacillin/tazobactam, Ceftazidime, Cefotaxime, Cefepime, Aztreonam, Imipenem, Meropenem, Amikacin, Gentamicin, Ciprofloxacin, Levofloxacin, Sulfamethoxazole/trimethoprim, Chloramphenicol, Tetracycline of KP/ESBL-KP and CRKP.

cephalosporins, which is consistent with the research of Rong et al.[17] Furthermore, the 2022 CHINET data showed that KP was the first major isolate in respiratory tract samples, which accounted for the largest proportion of all types of samples (38.6%), but showed a slow downward trend, from 50.1% in 2006 to 38.6% in 2022, while *Escherichia coli* was the most common isolate in sterile body fluids. In Singapore, KP commonly causes bacteremia, followed by pneumonia, urinary tract infections, and liver abscesses. From 1994 to 2017, bacteremia mortality varied from 20% to 26%.[19] The incidence of urinary tract infections caused by ESBL-KP has steadily increased in the US, and it has been shown that KP isolates from blood and urine are more carbapenem-resistant than sputum culture isolates.[17,20] In this study, CRKP patients were mainly concentrated in the population aged ≥70 years (80.9%) and neonates <1 year (16.2%). In addition, age over 70 years old was shown as a risk factor for CRKP and ESBL-KP infection. In the US, most CRKP patients are aged ≥75 years,[21] whereas in Europe, KP-infected patients are predominantly aged ≥65 years, with approximately twice as many men as women. According to a study on bloodstream infections caused by *Klebsiella pneumoniae* in China, the proportion of middle-aged patients (41–65 years, 49.4%) and older patients (>65 years, 33.9%) is higher, with male patients accounting for 66.11%.[22] The infection rate of CRKP and ESBL-KP in intensive care unit (ICU) wards is higher than that in other departments, which is consistent with our provincial and national reports.[23] The morbidity and mortality of CRKP patients infected in the ICU are much higher than those in other departments, in China. Studies have shown that KP isolates from ICU have a higher rate of resistance to imipenem than isolates from outpatients and non-ICU patients,[17,24] suggesting that admission to the ICU may be a risk factor for KP infection. This indicates that pathogens contaminate the environment or the tables in the hospital ward and may cause transmission between patients and the environment; hence, the focus should be on risk factors for infection in ICU patients. Previous studies have

suggested that KP infection may be seasonal and that the infection rate is higher in summer than in winter,[25,26] which is consistent with another study in China.[17] Our research showed that the prevalence rates in autumn and winter were higher than those in spring and summer, which may be related to the geographical location of our hospital. Our city is in a high-altitude area in northern China, where the climate is cold-dry, the wind and sand are large, and chronic respiratory diseases in older people are common endemic diseases and seem to increase the risk of KP infection, especially the infection of ESBL-KP.

Antibiotic resistance remains a major public health concern for the WHO, and data from the European Antimicrobial Resistance Surveillance System showed the highest rates of KP resistance to third-generation cephalosporins (33.9%), followed by resistance to fluoroquinolones (33.8%), aminoglycosides (23.7%), and carbapenems (10%). Carbapenem resistance rates showed a significant upward trend from 2016 to 2020, while aminoglycoside resistance rates showed a significant downward trend during the same period (excluding the United Kingdom). Between 2014 and 2017, Poland and Slovakia's CRKP resistance rates showed an increasing trend but remained at a low level (<7%); Romania, Italy, and Greece were the three countries with the highest carbapenem resistance rates (27.5%, 32.5%, and 64.0%, respectively). The resistance rate in Italy showed an annual decreasing trend, while Greece showed no significant change, and the resistance of CRKP isolated in France to fluoroquinolones and aminoglycosides showed a decreasing trend.[4] CHINET data showed that the resistance rate of CRKP increased annually, and resistance to imipenem and meropenem increased from 3.0% and 2.9% in 2005 to 25.0% and 26.3% in 2018, respectively, while the resistance rate showed a decreasing trend from 2019 to 2021. The tigecycline resistance rate also showed a decreasing trend, decreasing from 10.5% in 2010 to 4.2% in 2021.

Our study found that the resistance rate of KP was generally low, β_lactam/β_lactamase inhibitors had the highest resistance rate, and the resistance rate to most common antibiotics showed an increasing trend (Table 1). Ahmadi et al showed that KP had the highest resistance rate to cephalosporins.[12] CRKP usually exhibits high resistance to many antibiotics (Table 3). ESBL-KP has a high sensitivity to carbapenems and amikacin (Table 2) and a high resistance rate to the third-generation cephalosporin cefotaxime with an increasing trend.

For invasive bacterial infections, prompt treatment with effective antibiotics is particularly important and is one of the most effective interventions to reduce the risk of fatal consequences. Carbapenem resistance leads to limited clinical availability of drugs, and the selection of new alternatives is imminent. For CRKP, tigecycline and colistin have good in vitro activity;[27,28] however, resistance problems arise during treatment, which poses a significant challenge to public health, and colistin resistance is mainly associated with genetic alterations in lipid A modification.[29] Gentamicin is superior to amikacin and tobramycin in treating KPC-producing KP infections.[30] This may lead to a higher resistance rate to gentamicin than to amikacin. In this study, the drug resistance rates of KP to ciprofloxacin and levofloxacin were 23.3% and 16.6% respectively. In Iran, the drug resistance rate of *Klebsiella pneumoniae* to ciprofloxacin was 19%,[31] which was roughly the same as that in our hospital. Due to the overproduction of β-lactamases and the production of other inhibitors that affect their activity, there are clear geographic differences in the resistance rate of ESBL-KP to β-lactam inhibitors.[32] Compared with carbapenems, TZP has no significant advantage in treating bloodstream infections caused by ESBL-KP, while for urinary tract infections caused by ESBL-KP; TZP may be a reasonable alternative to carbapenem therapy and can reduce the resistance rate of carbapenems compared with carbapenems.[33,34] In this study, the drug resistance rate to TZP was lower than that to AMX ($P<0.05$), which will help optimize the treatment plan for urinary tract infection in our hospital. Routine use of carbapenems for CRKP is not recommended; in certain circumstances, dual carbapenems (doripenem or meropenem combined with ertapenem) may be considered.[35,36] In this study, the drug resistance rate to tetracycline was relatively low, while the study of Ahmadi et al showed that the drug resistance rates to tetracycline and erythromycin in urine samples were the highest.[37] A Spanish study showed that cotrimoxazole was synergistic with polymyxins and that lower doses of colistin enhanced the antibacterial activity of cotrimoxazole.[38] The high resistance rate of CRKP and ESBL-KP to cephalosporins in our hospital has led to limited treatment options. Therefore, there is an urgent need to develop new treatments and dosing systems to improve clinical treatment outcomes. Although the etiology of urinary tract infection is complex and diverse, the adhesive characteristics of the pathogens of urinary tract infection have accelerated the development of non-antibiotic alternative strategies for anti-adhesion.[39]

The MIC90 of CRKP for most drugs equals the MIC50, and the resistance rate is high. CRKP strains vary in their degree of resistance to carbapenems, and combinations of two or three carbapenem-containing agents are recommended when the MIC for carbapenems is ≤8 mg/L; however, combinations of carbapenems are no longer recommended when the MIC is >8 mg/L.[40] For KPC-2 and KPC-3 producing KP, MIC 2–8 mg/L or low-level resistance (MIC 16–32 mg/L), clinical efficacy was better maintained when high-dose meropenem (2 g/8 h) was combined with colistin.[27]

This study had the following limitations: First, this study involved a single-center data analysis, which only represents the epidemiological data within the region, and the representativeness is relatively limited. Second, there was a lack of data on CRKP resistance mechanism and ST typing studies; in the future, we will obtain all CRKP strains for studying carbapenem resistance gene (KPC, NDM, VIM, IPM, OXA-48) amplification and sequencing, in addition, MLST genotyping will be performed for all CRKP strains, and whole genome sequencing will be performed when necessary.

Conclusion

This study showed that the detection rate of ESBL-KP in our hospital was higher than that of CRKP, and KP isolates from urine samples were more resistant to carbapenem and cephalosporin. Admission to ICU and age >70 years were found to be the likely risk factors for infection with CRKP and ESBL-KP, and the older the age, the higher the risk factors. The resistance rate of CRKP to conventional antibiotics was generally high. ESBL-KP was highly susceptible to most common antibiotics, but attention should be paid to cefotaxime. Our hospital needs to establish a multidisciplinary collaborative mechanism to manage CRKP and ESBL-KP-induced infections and jointly curb the spread of bacterial resistance. Moreover, the sensing gateway should be moved forward to effectively curb the epidemic dissemination of drug-resistant strains; and increase the susceptibility testing of some antibiotics with low resistance rates, such as colistin, tigecycline, and ceftazidime-avibactam. For CRKP, carbapenemase detection should be conducted, and clinical practice should be reported. In the face of the high transmission and mortality of CRE, the WHO should actively strengthen international collaborations to study and develop new antibiotics against third generation cephalosporins and CRE to jointly curb the spread of multi-drug resistance.

Abbreviations

CHINET, China Antibiotic Surveillance Network; CRE, carbapenem-resistant *Enterobacteriaceae*; CRKP, carbapenem-resistant *Klebsiella pneumoniae*; ESBL-KP, extended spectrum β-lactamase producing *Klebsiella pneumoniae*; ICU, intensive care unit; IMP, imipenemase; KP, *Klebsiella pneumoniae*; KPC, *Klebsiella pneumoniae* carbapenemase; MIC, minimum inhibitory concentration; NDM, New Delhi metallo-β-lactamase; OXA, oxacillinase; QC, quality control; TZP, piperacillin-tazobactam; VIM, Verona-intergona-encoded metallo-β-lactamase.

Data Sharing Statement

Data of this study can be available upon request from the author.

Ethics Approval and Informed Consent

The study was approved by the Ethics Committee of the First Affiliated Hospital of Hebei North University (ethical approval No. K2019147), which waived the requirement of written informed consent from patients. All strains are part of the routine laboratory procedures of the hospital and do not involve any human genetic resources. This study was conducted in accordance with the principles outlined in the Declaration of Helsinki.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically

reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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