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ORIGINAL RESEARCH

Epidemiology and Mechanism of Drug Resistance of Multidrug-Resistant Klebsiella Pneumoniae Isolated from Patients with Urinary Tract Infection in Beijing Teaching Hospital, China

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Purpose: *Klebsiella pneumoniae* is an important pathogenic bacterium in causing urinary tract infection. With the overuse of antibiotics, bacteria resistant to quinolones combined with carbapenems are increasing. In this study, we investigated the epidemiology, molecular characteristics, drug resistance of multidrug-resistant *Klebsiella pneumoniae* (*MDR-KPN*) isolated from urine samples. It provides theoretical basis for the treatment of urinary tract infection by clinicians.

Patients and Methods: Fifty-one strains of *Klebsiella pneumonia* were obtained from urine samples collected between 2012 and 2017 in total. All the strains are multi-drug resistant bacteria. This paper used multilocus sequence typing (MLST) to determine molecular epidemiological typing. We performed antimicrobial susceptibility testing and investigated quinolones and carbapenems resistance genes.

Results: The strains which we collected were resistant to ciprofloxacin and Levofloxacin. In an epidemiological analysis using MLST, 86.27% (44/51) of isolates were confirmed to be ST11. The main carbapenem resistance gene was KPC-19, 78.43(40/51). Among the quinolone resistance genes, the major resistance genes were aac(6')-Ib-cr, oqxA and oqxB.

Conclusion: The main molecular epidemiological types we detected was ST11. The main resistance gene of carbapenems was KPC-19. The quinolone resistance genes are mainly *aac(6')-Ib-cr, oqxA and oqxB*. The experimental results can help control the use of quinolones and carbapenems, and we could provide rational drug use basis for clinicians to treat urinary tract infection. For *MDR-KPN*, a combination of multiple antibiotics is necessary.

Keywords: urinary tract infection, MLST, *Klebsiella pneumoniae carbapenemase*, quinolone resistance genes, *Klebsiella pneumoniae*

Introduction

Urinary tract infection (UTI) is a very important infectious disease, and it is the main cause of morbidity and mortality in human.[1] Klebsiella pneumoniae was the second most common cause of urinary tract infections caused by gram-negative bacteria.[2] MDR within the Enterobacterales, such as Klebsiella pneumoniae strains, have become global concern, because of inducing severe infections with increased prevalence and high mortality rates.[3,4]

Carbapenem antibiotics are recognized as the best antibiotics for the treatment of gram-negative bacterial infections. However, with its worldwide application, carbapenem-resistant bacteria have emerged. In China, the first carbapenase was reported to have been found on a plasmid of Citrobacter, in 2001.[5] It began to spread rapidly across the country. Klebsiella pneumoniae carbapenemase (KPC) was most detected in Klebsiella pneumoniae.[6] The main molecular epidemiological type in China is ST11.[7] Metallic beta-lactamase NDM-1 was first reported in 2009.[8] In a 2010 multinational study, NDM-1 was found to be mainly present in Escherichia coli and Klebsiella pneumoniae.[9] This highly resistant bacteria has also attracted worldwide attention. Quinolones are widely used in

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clinical practice because of their few side effects. With the abuse of quinolones, the situation of quinolone resistance was getting worse. Plasmid-mediated quinolone resistance mechanism was discovered in 1998.[10] Subsequently, various quinolone resistance genes were discovered one after another. Plasmid-mediated quinolone resistance gene qnrA was found in China.[11] And qnrA,qnrB and qnrS genes were discovered in France.[12] Qnr gene binds to the target enzyme and makes it impervious to drugs. Ciprofloxacin-Modifying Enzyme aac(6')-Ib-cr was found in the United States.[13] Aac(6')-Ib-cr gene could make Methylation and inactivation of the drugs. Not long after high Prevalence of Plasmid-Mediated Quinolone Resistance Genes qnr and aac(6')-Ib-cr was found in China.[14] Later Plasmid-Mediated qepA Gene was found in Japan.[15] QepA gene could reduce drug accumulation in the body through efflux. And plasmid-mediated quinolone resistance gene qnrC was found in 2009.[16] The genes for multidrug efflux pump OqxAB were found in Korea and China.[17] This gene was first discovered on the pOLA52 plasmid of Escherichia coli and it is one of the important members of the plasmid-mediated quinolone resistance gene. QnrD gene was discovered in Salmonella enterica.[18] Many resistance mechanisms have been discovered. These resistance genes also contribute to the rapid spread of quinolone resistance.

Treatment of highly drug-resistant Klebsiella pneumoniae has become a worldwide problem. But there are few studies that favor the understanding of urinary tract infections with MDR-KPN.

In this article, we mainly studied MDR-KPN in urinary tract infections, and we discuss its quinolone combined with carbapenems resistance gene. The research on the mechanism of drug resistance in urinary tract bacteria can provide better data for clinical treatment. It can provide theoretical basis for clinical drug treatment of UTI.

Material and Methods

Bacterial Isolates

Urine samples were collected from the clinical department. Tenul quantitative inoculation was carried out after the microbiology laboratory received the specimens. The plates were incubated at 35°C for 18–24 h. Isolates were identified using the VITEK 2 Compact-60 system and Microbial mass spectrometer. Urine samples with concentrations greater than 10^5 colony forming units (CFU)/mL of *Klebsiella pneumoniae* were included in the article.

Antimicrobial Susceptibility Testing

VITEK-2 Compact were used for bacterial antibiotics sensitivity tests. All of the strains were multidrug-resistant bacteria. All collected strains were resistant to ciprofloxacin (MIC $\geq$ 4.0 μg/mL)and Levofloxacin (MIC $\geq$ 8.0 μg/mL). The AST results were judged according to Performance Standards for Antimicrobial Susceptibility Testing M100 (33st Edition). *ATCC 25922* and *ATCC 700323* were the quality control strain for drug susceptibility testing.

Data Analysis

Software WHONET 5.6 were used for statistical analysis.

Multilocus Sequence Typing

We used Multilocus Sequence Typing to determine molecular epidemiological typing in Klebsiella pneumonia. The DNA sequencing of seven housekeeping (*gapA, infB, MDH, pgi, phoE, rpoB, tonB*) was using PCR method. To determine the allelic numbers and STs, the nucleotide sequences were compared with the sequence in the MLST database (http://www.pasteur.fr/recherche/genopole/PF8/mlst/Kpneumoniae.html).

Detection of Quinolone and Carbapenem Resistance Genes

Genomic DNA obtained by Genomic DNA Extraction Kit. Quinolone resistance genes(*qnrA, qnrB, qnrC, qnrD, qnrS, aac(6')-Ib-cr, qepA, oqxA and oqxB*) and Carbapenem resistance genes(*KPC, NDM-1*, VIM, IPM and OXA48) were detected with polymerase chain reaction (PCR). And the products were subjected to 1.5% agarose gel electrophoresis. The positive products were validated with Sanger sequencing. The obtained nucleotide sequences were compared with the sequences in the National Center for Biotechnology Information (NCBI) database using Basic Local Alignment

Search Tool (BLAST). And we used the above methods to determine the genotype. PCR primers including sequence, annealing temperature, product length, etc. are shown in Table 1.

Results

Susceptibility of Klebsiella pneumoniae to antimicrobial agents

In Table 2, *Klebsiella pneumoniae* showed high resistance to a variety of antibiotics, and the resistance rate to colistin was the lowest. Fifty-one strains of *Klebsiella pneumoniae* were 100% Antibiotic resistance rate to the following antibiotics: ticarcillin/clavulanate, Piperacillin/tazobactam, ceftazidime, cefepime, Aztreonam, Ciprofloxacin, Levofloxacin. Rates of resistance to carbapenems was high, imipenem was 88.24%; Meropenem was 90.20%; Doripenem was 88.24%; Ertapenem was 94.12%. Doxycycline was 52.94%; Minocycline was 50.98%; Tigecycline was 27.45%; Colistin was 1.96% and its resistance rate was lowest. These strains were resistant to quinolones.

ST typing of Klebsiella pneumoniae and drug resistance of several important antibiotics:

Table 3 shows that it's resistant to several important antibiotics, and the main ST type of resistance to carbapenems was *ST11*.

Molecular epidemiological typing of *Klebsiella pneumoniae*:

In Table 4, *ST11* was the main type of molecular epidemiological typing. Five different ST classifications were detected in strains: ST11 (86.27%, 44/51), ST37 (1.96%, 1/51), ST147 (1.96%, 1/51), ST15 (3.92%, 2/51), ST273 (5.88%, 3/51).

ST typing and drug resistance gene distribution of *Klebsiella pneumoniae*:

In Table 5, We found that the main carbapenem resistance genes of *Klebsiella pneumoniae* ST11 were KPC-2 and KPC-19, and no NDM-1, VIM, IPM and OXA48 resistance genes were found. Quinolone resistance genes such as qnrA, qnrC, qnrD and qepA were not detected. Other quinolone resistance genes such as qnrB, qnrS, aac(6')-Ib-cr, oqxA, oqxB were detected in Table 5.

Distribution of Quinolone Resistance Gene of Klebsiella Pneumoniae

In Table 6, The main distribution of quinolone resistance genes in *Klebsiella pneumoniae* was *oqxA, oqxB* and *aac(6')-Ib-cr*.

Discussion

Urinary system infection refers to the inflammatory reaction caused by the invasion of pathogenic microorganisms in the urinary tract. It is a common infection in hospitalized patients.

Quinolones are important antibacterial drugs in the treatment of urinary tract infection. They have high urinary concentration, good antibacterial activity and tissue permeability, and are often used empirically in the treatment of urinary tract infection. The main pathogens isolated from patients with urinary tract infection were gram-negative bacteria, and the clinical treatment failure caused by drug resistance was serious. Among them, *MDR-KPN* is particularly serious. The resistance rate of *MDR-KPN* to quinolones was high and the resistance was serious. The status of multidrug-resistant *Klebsiella pneumoniae* is mostly related to the antibiotic resistance genes encoded by the plasmid.[19]

As shown in Table 3, There were 6 imipenem sensitive strains. They were 1 ST37, 2 ST15 and 3 ST11. The carbapenem antibiotic sensitivity of the two ST15 strains was the highest. It was sensitive to all carbapenem antibiotics. Three ST273 strains and one ST147 strain were resistant to carbapenems. The only colistin resistant strain was ST11, which was sensitive to doxycycline and tigecycline.

According to Multilocus Sequence Typing method, we used PCR assay to detect 7 pairs of housekeeping genes (*gapA, infB, MDH, pgi, phoE, rpoB, tonB*). The detected data was compared with the sequence in the MLST database. ST11 was a major molecular epidemiological type, it is consistent with reports from Shanghai, China.[20] The literature reports that *Klebsiella pneumoniae* subtypes ST11 and ST273 were most commonly isolated in Brazilian hospitals, which is similar to this paper.[21] In Pakistan, ST 258 and ST11 *Klebsiella pneumoniae* were predominant.[22]

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Table 1 The Primers Used to Amplify the Resistance Genes

Type	Gene	Sequence(5′-3′)	Length of amplification fragment(bp)	Annealing temperature (°C)
MLST	gap A	F:5'-GTTTTCCCAGTCACGACGTTGTATGAAATATGACTCCACTCACGG-3' R:5'-TTGTGAGCGGATAACAATTTCCTTCAGAAGCGGCTTTGATGGCTT-3'	450	50°C
	inf B	F: 5'-GTTTTCCCAGTCACGACGTTGTACTCGCTGCTGGACTATATTCG-3' R:5'-TTGTGAGCGGATAACAATTTCCGCTTTCAGCTCAAGAACTTC-3'	318	50°C
	mdh	F: 5' -GTTTTCCCAGTCACGACGTTGTACCCAACTCGCTTCAGGTTCAG-3' R:5' -TTGTGAGCGGATAACAATTTCCCGTTTTTCCCCAGCAGCAG-3'	477	50°C
	pgi	F:5'-GTTTTCCCAGTCACGACGTTGTAGAGAAAAACCTGCCTGTACTGCTGGC-3' R:5'-TTGTGAGCGGATAACAATTTCCGCGCCACGCTTTATAGCGGTTAAT-3'	432	50°C
	pho E	F:5' -GTTTTCCCAGTCACGACGTTGTAACCTACCGCAACACCGACTTCTTCGG-3' R: 5'-TTGTGAGCGGATAACAATTTCTGATCAGAACTGGTAGGTGAT-3'	420	50°C
	rpo B	F:5' -GTTTTCCCAGTCACGACGTTGTAGGCGAAATGGCWGAGAACCA-3' R:5' -TTGTGAGCGGATAACAATTTCGAGTCTTCGAAGTTGTAACC-3'	501	50°C
	ton B	F:5' -GTTTTCCCAGTCACGACGTTGTACTTTATACCTCGGTACATCAGGTT-3' R:5' -TTGTGAGCGGATAACAATTTCATTCGCCGGCTGRGCRGAGAG-3'	414	50°C
quinolone	qnr A	F:5'-AGAGGATTTCTCACGCCAGG-3'	580	55°C
		R:5'-TGCCAGGCACAGATCTTGAC-3'		
	qnr B	F:5'-TTTGCYGYYCGCCAGTCGAA-3'	264	55°C
		R:5'-GGMATHGAAATTCGCCACTG-3'		
	qnr S	F:5'-GCAAGTTCATTGAACAGGGT-3'	428	55°C
		R:5'-TCTAAACCGTCGAGTTCGGCG-3'		
	aac(6')-Ib-cr	F:5'-TTGCGATGCTCTATGAGTGGCTA-3'	482	55°C
		R:5'-CTCGAATGCCTGGCGTGTTT-3'		
	qep A	F:5'-GCAGGTCCAGCAGCGGGTAG-3'	218	60°C
		R:5'-CTTCCTGCCCGAGTATCGTG-3'		
	oqx A	F:5'-CTCGGCGCGATGATGCT-3'	392	57°C
		R:5'-CCACTCTTCACGGGAGACGA-3'		
	oqx B	F:5'-TTCTCCCCCGGCGGGAAGTAC-3'	512	64°C
		R:5'-CTCGGCCATTTTGGCGCGTA-3'		
Ambler A	KPC	F:5'-GCTACACCTAGCTCCACCTTC-3'	989	55°C
		R:5'-ACAGTGGTTGGTAATCCATGC-3'		

Ambler B	NDM	F:5'-GGGCCGTATGAGTGA-3'	758	55°C
		R:5'-GAAGCTGAGCACCGCATTAG-3'		
	IMP	F:5'-CATGGTTTGGTGGTTCTTGT-3'	139	55°C
		R:5'-ATAATTTGGCGGACTTTGGC-3'		
	VIM	F:5'-AGTGGTGAGTATCCGACA-3	390	55°C
		R:5'-ATGAAAGTGCGTGGAGAC-3'		
Ambler D	OXA48	F:5′- TTGGTGGCATCGATTATCGG-3′	438	55°C
		R:5′- GAGCACTTCTTTTGTGATGGC-3′		

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Table 2 Resistance Rates of Klebsiella Pneumoniae to the Antibiotics

Antibacterial drugs	Klebsiella pneumoniae (n=51)	
	No. of isolate	R
Ticarcillin/clavulanate	51	100%
Piperacillin/tazobactam	51	100%
Ceftazidime	51	100%
Cefepime	51	100%
Aztreonam	51	100%
Imipenem	45	88.24%
Meropenem	46	90.20%
Doripenem	45	88.24%
Ertapenem	48	94.12%
Amikacin	28	54.90%
Tobramycin	36	70.59%
Ciprofloxacin	51	100%
Levofloxacin	51	100%
Doxycycline	27	52.94%
Minocycline	26	50.98%
Tigecycline	14	27.45%
Colistin	1	1.96%
Cotrimoxazole	29	56.86%

Carbapenem-resistant Enterobacteriaceae (CRE) are bacteria that have emerged in recent years and pose a major threat to global public health.[23] The first carbapenemase-producing *Klebsiella pneumoniae* was first reported in the United States, 2001.[24] *Carbapenem-resistant Klebsiella pneumoniae* $_{KPC}$ was spreading rapidly around the world. Understanding the mechanism of CRE resistance is important for the selection of antibiotics.[25] Two common carbapenem resistant enzymes, metalloenzymes and carbapenems, were studied in this paper. Bacteria carrying *NDM-1* are most commonly found in *Escherichia coli* and *Klebsiella pneumoniae. NDM-1* enzyme is mostly located on the plasmid, which also provides conditions for the transmission of drug resistance genes between bacteria. In Table 5, we tested NDM-1、VIM, IPM and OXA48 resistance genes of MDR-KPN, and none were detected. In our hospital, patients with urinary tract infection *MDR-KPN* were not easy to carry *NDM-1* drug resistance gene. *KPC* enzyme is the most common class A carbapenem enzyme isolated in clinical practice. We went on to study the resistance genes of *KPC*. Two *KPC* enzyme types were found, *KPC-2* and *KPC-19, KPC-2* type accounted for 9.8% (5/51), *KPC-19* type accounted for 78.43% (40/51). Klebsiella pneumoniae carbapenemase (KPC), KPC-2 and KPC-3, began to be discovered all over the world.[26] Different KPC enzyme variants are found in different countries of the world. *Klebsiella pneumoniae* $_{kpc\text{-}19}$ has been reported in liver transplant patients abroad, the molecular epidemiological type is ST1519.[27] KPC-19 showed an N291T substitution compared to the KPC-3 enzyme. At present, the KPC-19 enzyme type has not been reported much in the world, which is worth our attention. In this study, the molecular epidemiological type of *KPC-19 Klebsiella pneumoniae* was mainly ST11 (92.5%, 37/40) and ST273 (7.5%, 3/40). This kind of report was rare in domestic and foreign literature. No carbapenase was found in 6 strains that were sensitive to carbapenem antibiotics.

Quinolones are a widely used class of antibiotics, it is used to treat different bacterial infections. The targets of quinolones are DNA rotase and topoisomerase IV, which interfere with the replication and transcription process of bacterial chromosomes through the combination of drug molecules and enzymes, thus playing an antibacterial role. Plasmid mediated quinolone resistance is associated with three PMQR gene families, namely qnr gene, aac(6 ‘) -lb-cr gene, oqxAB and qepA efflux system. In this paper, the above quinolone resistance genes were detected and analyzed. Quinolone resistance genes were found in most of the strains studied.

Table 3 ST Typing of Klebsiella Pneumoniae and Drug Resistance of Several Important antibioticStrain

Number	ST typing	Imipenem	Meropenem	Dolipenem(K-B)	Ertapenem(K-B)	Doxycycline	Minocycline	Tigacycline	colistin	ciprofloxacin	Levofloxacin
2853	11	R ≥16	R ≥16	R 6	R 6	S 2	S 4	S 1	S <=0.5	R ≥4	R ≥8
3373	37	S <=0.25	S <=0.25	S 27	S 23	R ≥16	R ≥16	I 4	S <=0.5	R ≥4	R ≥8
4946	11	R ≥16	R ≥16	R 6	R 6	R ≥16	R ≥16	S 2	S <=0.5	R ≥4	R ≥8
8012	11	R ≥16	R ≥16	R 6	R 6	S 4	S 4	S 2	S <=0.5	R ≥4	R ≥8
11,328	11	R ≥16	R ≥16	R 6	R 6	R ≥16	R ≥16	R ≥8	S <=0.5	R ≥4	R ≥8
11,449	11	S <=0.25	S 1	S 24	R 14	S 4	S 4	S	S <=0.5	R ≥4	R ≥8
18,284	11	R ≥16	R ≥16	R 6	R 6	S 2	S 4	S 1	S <=0.5	R ≥4	R ≥8
20,920	11	R ≥16	R ≥16	R 6	R 6	S 4	S 4	S 1	S <=0.5	R ≥4	R ≥8
16,516	147	R ≥16	R ≥16	R 6	R 6	R ≥16	R ≥16	S 2	S <=0.5	R ≥4	R ≥8
18,057	11	S 0.5	S 1	S 23	R 11	R ≥16	R ≥16	R ≥8	S <=0.5	R ≥4	R ≥8
19,425	11	R ≥16	R 8	R 12	R 9	S 4	S 4	S 1	S <=0.5	R ≥4	R ≥8
20,825	11	R ≥16	R ≥16	R 6	R 6	S 2	S 4	S <=0.5	S <=0.5	R ≥4	R ≥8
22,080	11	R ≥16	R ≥16	R 12	R 9	R ≥16	R ≥16	S 2	S <=0.5	R ≥4	R ≥8
5416	11	R ≥16	R ≥16	R 6	R 6	S 2	S 2	S <=0.5	S <=0.5	R ≥4	R ≥8
19,213	11	R ≥16	R ≥16	R 6	R 6	S 1	S <=1	S <=0.5	S <=0.5	R ≥4	R ≥8
20,170	11	R ≥16	R ≥16	R 6	R 6	S 1	S 2	S <=0.5	S <=0.5	R ≥4	R ≥8
18,077	11	R ≥16	R ≥16	R 6	R 6	S 4	S 4	S 2	S 2	R ≥4	R ≥8
23,739	11	R ≥16	R ≥16	R 8	R 6	S 4	I 8	S 2	S 2	R ≥4	R ≥8
24,633	11	R ≥16	R ≥16	R 8	R 6	R ≥16	R ≥16	R ≥8	S 2	R ≥4	R ≥8
25,150	11	R ≥16	R ≥16	R 10	R 6	S 1	S 2	S <=0.5	S <=0.5	R ≥4	R ≥8
5249	11	R ≥16	R ≥16	R 6	R 6	R ≥16	R ≥16	R ≥8	S <=0.5	R ≥4	R ≥8
5305	11	R ≥16	R ≥16	R 9	R 6	I 8	S 4	S 1	S <=0.5	R ≥4	R ≥8
6707	11	R ≥16	R ≥16	R 6	R 6	R ≥16	R ≥16	R ≥8	S <=0.5	R ≥4	R ≥8
8044	11	R ≥16	R ≥16	R 6	R 6	R ≥16	R ≥16	S 2	S <=0.5	R ≥4	R ≥8
9563	11	R ≥16	R ≥16	R 6	R 6	R ≥16	R ≥16	R ≥8	S <=0.5	R ≥4	R ≥8
16,945	11	R ≥16	R ≥16	R 6	R 6	R ≥16	R ≥16	I 4	S <=0.5	R ≥4	R ≥8
17,063	11	R ≥16	R ≥16	R 6	R 6	R ≥16	S 4	S 1	S <=0.5	R ≥4	R ≥8

(*Continued*)

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Table 3 (Continued).

Number	ST typing	Imipenem	Meropenem	Dolipenem(K-B)	Ertapenem(K-B)	Doxycycline	Minocycline	Tigacycline	colistin	ciprofloxacin	Levofloxacin
19,139	11	R ≥16	R ≥16	R 7	R 6	R ≥16	R ≥16	R ≥8	S <=0.5	R ≥4	R ≥8
19,710	11	R ≥16	R ≥16	R 6	R 8	S 4	I 8	S 2	S <=0.5	R ≥4	R ≥8
20,733	11	R ≥16	R ≥16	R 6	R 6	S 4	I 8	S 2	R ≥16	R ≥4	R ≥8
21,377	11	R ≥16	R ≥16	R 14	R 15	S 4	I 8	S 2	S <=0.5	R ≥4	R ≥8
53,746	11	R ≥16	R ≥16	R 6	R 11	I 8	I 8	I 4	S <=0.5	R ≥4	R ≥8
54,777	11	R ≥16	R ≥16	R 20	R 17	R ≥16	I 8	S 2	S <=0.5	R ≥4	R ≥8
5527	11	R 8	R ≥16	R 12	R 6	R ≥16	R ≥16	R ≥8	S <=0.5	R ≥4	R ≥8
6429	273	R ≥16	R ≥16	R 10	R 6	I 8	R ≥16	I 4	S 2	R ≥4	R ≥8
236	11	R ≥16	R ≥16	R 8	R 6	S 4	I 8	S 2	S 2	R ≥4	R ≥8
311	11	R ≥16	R ≥16	R 6	R 6	R ≥16	R ≥16	R ≥8	S <=0.5	R ≥4	R ≥8
3600	11	R ≥16	R ≥16	R 6	R 6	R ≥16	R ≥16	I 4	S <=0.5	R ≥4	R ≥8
4685	273	R ≥16	R ≥16	R 9	R 12	R ≥16	R ≥16	R ≥8	S <=0.5	R ≥4	R ≥8
6341	11	R ≥16	R ≥16	R 6	R 6	S 4	S 4	S 1	S <=0.5	R ≥4	R ≥8
6342	273	R ≥16	R ≥16	R 6	R 9	I 8	I 8	I 4	S <=0.5	R ≥4	R ≥8
6353	15	S <=0.25	S <=0.25	S 24	S 26	R ≥16	R ≥16	R ≥8	S <=0.5	R ≥4	R ≥8
6409	15	S <=0.25	S <=0.25	S 23	S 22	R ≥16	R ≥16	R ≥8	S <=0.5	R ≥4	R ≥8
6696	11	R ≥16	R ≥16	R 6	R 6	R ≥16	R ≥16	I 4	S <=0.5	R ≥4	R ≥8
8624	11	R ≥16	R ≥16	R 6	R 9	S 2	S 2	S <=0.5	S <=0.5	R ≥4	R ≥8
8846	11	R ≥16	R ≥16	R 6	R 7	R ≥16	R ≥16	R ≥8	S <=0.5	R ≥4	R ≥8
8788	11	R ≥16	R ≥16	R 11	R 9	R ≥16	R ≥16	R ≥8	S <=0.5	R ≥4	R ≥8
10,393	11	R ≥16	R ≥16	R 6	R 8	R ≥16	R ≥16	I 4	S <=0.5	R ≥4	R ≥8
50,790	11	R ≥16	R ≥16	R 6	R 6	R ≥16	R ≥16	I 4	S <=0.5	R ≥4	R ≥8
19,303–1	11	R ≥16	R ≥16	R 8	R 6	S 4	S 4	S 1	S <=0.5	R ≥4	R ≥8
16,766	11	S 1	I 2	R 27	R 19	R ≥16	R ≥16	I 4	S 2	R ≥4	R ≥8

Table 4 Molecular Epidemiological Typing of Klebsiella Pneumoniae

ST typing	Number of cases	Percentage
ST 11	44	86.27%
ST 273	3	5.88%
ST 15	2	3.92%
ST 37	1	1.96%
ST 147	1	1.96%

In tables 5 and 6, among the quinolone resistance genes, the major resistance genes were qnrB(7.84%, 4/51), qnrS (11.76%, 6/51), aac(6')-Ib-cr (41.18%, 21/51), oqxA(52.94%, 27/51), oqxB(52.94%, 27/51). Other resistance genes such as qnrA, qnrC, qnrD and qepA were not detected. In Iranian literature,[28] qnrC, qnrD and qepA resistance genes were also not detected in urinary quinolone-resistant Escherichia coli.

The four strains carrying qnrB were two ST273 and two ST15. No qnrB resistance gene was found in ST11, ST37 and ST147. Six strains carrying qnrS resistance genes were found, including ST37, ST147, ST237 and 3 ST11 strains respectively. No qnrS resistance gene was found in ST15. We found 1 ST37 strain carrying qnrS, oqxA and oqxB in urine. At the same time, a strain ST147 carrying qnrS, oqxA and oqxB was found. In the ST273 substrain, a strain carrying qnrS, oqxA and oqxB. OqxA and oqxB resistance genes were present in 27 strains. These included 20 ST11, 1 ST37, 2 ST15, 3 ST273 and 1 ST147. Aac(6 ') -lb-cr gene resistance gene was often detected. This is also similar to that reported in the Bangladeshi literature.[29] It could be detected in combination with other resistance genes, or it could be detected alone. We found 11 strains of bacteria with concurrent oqxA, oqxB and aac(6 ') -lb-cr resistance genes. The molecular epidemiological types were 9 strains ST11 and 2 strains ST15. At the same time, a ST11 genotype was found to carry qnrS, oqxA, oqxB and aac(6 ') -lb-cr resistance genes. A ST11 genotype was found to carry qnrS, aac(6 ') -lb-cr resistance genes. In cases of urinary Klebsiella pneumoniae infection in Indonesia, qnrB, qnrS, aac(6) -lb-cr are also common quinolone resistance genes, which are similar to the present study.[30] This is similar to the results of a joint study in Portugal and Spain.[31] The other two strains of ST273 carry qnrB, oqxA and oqxB. Finally, we also found that two ST15 subtypes carried qnrB, oqxA, oqxB and aac(6)-Ib-cr resistance genes. The two ST15 strains carried oqxAB resistance genes similar to those reported in China.[32] OqxA and oqxB accounted for the highest proportion of quinolone resistance genes, while the two genes often co-appeared in the ST11 molecular epidemiology genotype, while the aac(6 ') -lb-cr resistance gene occupied a secondary position in the ST11 genotype.

KPC enzyme is currently considered to be the main cause of bacterial resistance to penicillins, cephalosporins and carbapenems. Timely monitoring of the above multi-drug resistant bacteria and taking effective control measures are effective ways to reduce the spread of multi-drug resistant bacteria. At present, urinary tract infections caused by drug-resistant gram-negative bacteria have attracted more and more attention. We should use antibiotics more wisely according to the principles of applied antimicrobial management. Knowledge of common pathogens of urinary tract infections is essential to determine appropriate experiential treatment. Resistance to quinolones is high and increasing, so they are not recommended as first-line treatment.[33] Treatment regimens with fluoroquinolones was no longer appropriate for patients with *MDR-KPN* in urinary tract infections. No carbapenem resistance genes were detected in carbapenem antibiotic-sensitive strains. Carbapenem antibiotics can still be used as clinical therapeutic drugs for the treatment of urinary tract infections in these patients. For carbapenemase-producing *MDR-KPN*, a combination regimen of aminoglycosides, colistin, and tigecycline is recommended for the treatment of *MDR-KPN* caused by urinary tract infection.[34] The presence of drug-resistant bacteria has an important impact on patient morbidity and mortality. We hope to provide data support for patients with urinary tract infection through the above articles and provide favorable conditions for clinicians to use antibiotics more rationally.

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Table 5 ST Typing and Drug Resistance Gene Distribution of Klebsiella Pneumoniae

Strain number	ST typing	qnrA	qnrB	qnrC	qnrD	qnrS	aac	qepA	oqxA	oqxB	KPC	NDM-1	VIM	IPM	OXA48
2853	11	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	KPC-2	(-)	(-)	(-)	(-)
3373	37	(-)	(-)	(-)	(-)	qnrS1	(-)	(-)	(+)	(+)	(-)	(-)	(-)	(-)	(-)
4946	11	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	KPC-19	(-)	(-)	(-)	(-)
8012	11	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	KPC-19	(-)	(-)	(-)	(-)
11,328	11	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	KPC-19	(-)	(-)	(-)	(-)
11,449	11	(-)	(-)	(-)	(-)	qnrS1	(+)	(-)	(+)	(+)	(-)	(-)	(-)	(-)	(-)
18,284	11	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	KPC-19	(-)	(-)	(-)	(-)
20,920	11	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	KPC-19	(-)	(-)	(-)	(-)
16,516	147	(-)	(-)	(-)	(-)	qnrS1	(-)	(-)	(+)	(+)	KPC-2	(-)	(-)	(-)	(-)
18,057	11	(-)	(-)	(-)	(-)	qnrS1	(+)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
19,425	11	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(+)	(+)	KPC-19	(-)	(-)	(-)	(-)
20,825	11	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	KPC-19	(-)	(-)	(-)	(-)
22,080	11	(-)	(-)	(-)	(-)	(-)	(+)	(-)	(+)	(+)	KPC-19	(-)	(-)	(-)	(-)
5416	11	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(+)	(+)	KPC-2	(-)	(-)	(-)	(-)
19,213	11	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(+)	(+)	KPC-19	(-)	(-)	(-)	(-)
20,170	11	(-)	(-)	(-)	(-)	(-)	(+)	(-)	(+)	(+)	KPC-19	(-)	(-)	(-)	(-)
18,077	11	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(+)	(+)	KPC-19	(-)	(-)	(-)	(-)
23,739	11	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(+)	(+)	KPC-19	(-)	(-)	(-)	(-)
24,633	11	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	KPC-19	(-)	(-)	(-)	(-)
25,150	11	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(+)	(+)	KPC-19	(-)	(-)	(-)	(-)
5249	11	(-)	(-)	(-)	(-)	(-)	(+)	(-)	(-)	(-)	KPC-19	(-)	(-)	(-)	(-)
5305	11	(-)	(-)	(-)	(-)	(-)	(+)	(-)	(+)	(+)	KPC-19	(-)	(-)	(-)	(-)

6707	11	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	KPC-19	(-)	(-)	(-)	(-)
8044	11	(-)	(-)	(-)	(-)	(-)	(+)	(-)	(-)	(-)	KPC-19	(-)	(-)	(-)	(-)
9563	11	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	KPC-19	(-)	(-)	(-)	(-)
16,945	11	(-)	(-)	(-)	(-)	(-)	(+)	(-)	(-)	(-)	KPC-19	(-)	(-)	(-)	(-)
17,063	11	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	KPC-19	(-)	(-)	(-)	(-)
19,139	11	(-)	(-)	(-)	(-)	(-)	(+)	(-)	(+)	(+)	KPC-19	(-)	(-)	(-)	(-)
19,710	11	(-)	(-)	(-)	(-)	(-)	(+)	(-)	(-)	(-)	KPC-19	(-)	(-)	(-)	(-)
20,733	11	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(+)	(+)	KPC-19	(-)	(-)	(-)	(-)
21,377	11	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	KPC-19	(-)	(-)	(-)	(-)
53,746	11	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(+)	(+)	KPC-19	(-)	(-)	(-)	(-)
54,777	11	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	KPC-19	(-)	(-)	(-)	(-)
5527	11	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(+)	(+)	KPC-19	(-)	(-)	(-)	(-)
6429	273	(-)	(-)	(-)	(-)	qnrS1	(-)	(-)	(+)	(+)	KPC-19	(-)	(-)	(-)	(-)
236	11	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(+)	(+)	KPC-19	(-)	(-)	(-)	(-)
311	11	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	KPC-19	(-)	(-)	(-)	(-)
3600	11	(-)	(-)	(-)	(-)	(-)	(+)	(-)	(-)	(-)	KPC-19	(-)	(-)	(-)	(-)
4685	273	(-)	qnrB4	(-)	(-)	(-)	(-)	(-)	(+)	(+)	KPC-19	(-)	(-)	(-)	(-)
6341	11	(-)	(-)	(-)	(-)	(-)	(+)	(-)	(+)	(+)	KPC-19	(-)	(-)	(-)	(-)
6342	273	(-)	qnrB4	(-)	(-)	(-)	(-)	(-)	(+)	(+)	KPC-19	(-)	(-)	(-)	(-)
6353	15	(-)	qnrB10	(-)	(-)	(-)	(+)	(-)	(+)	(+)	(-)	(-)	(-)	(-)	(-)
6409	15	(-)	qnrB10	(-)	(-)	(-)	(+)	(-)	(+)	(+)	(-)	(-)	(-)	(-)	(-)
6696	11	(-)	(-)	(-)	(-)	(-)	(+)	(-)	(-)	(-)	KPC-2	(-)	(-)	(-)	(-)

(*Continued*)

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Table 5 (Continued).

Strain number	ST typing	qnrA	qnrB	qnrC	qnrD	qnrS	aac	qepA	oqxA	oqxB	KPC	NDM-1	VIM	IPM	OXA48
8624	11	(-)	(-)	(-)	(-)	(-)	(+)	(-)	(+)	(+)	KPC-2	(-)	(-)	(-)	(-)
8846	11	(-)	(-)	(-)	(-)	(-)	(+)	(-)	(-)	(-)	KPC-19	(-)	(-)	(-)	(-)
8788	11	(-)	(-)	(-)	(-)	(-)	(+)	(-)	(+)	(+)	KPC-19	(-)	(-)	(-)	(-)
10,393	11	(-)	(-)	(-)	(-)	(-)	(+)	(-)	(-)	(-)	KPC-19	(-)	(-)	(-)	(-)
50,790	11	(-)	(-)	(-)	(-)	qnrS1	(-)	(-)	(-)	(-)	KPC-19	(-)	(-)	(-)	(-)
19,303–1	11	(-)	(-)	(-)	(-)	(-)	(+)	(-)	(+)	(+)	KPC-19	(-)	(-)	(-)	(-)
16,766	11	(-)	(-)	(-)	(-)	(-)	(+)	(-)	(+)	(+)	(-)	(-)	(-)	(-)	(-)

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Table 6 Distribution of Quinolone Resistance Gene of Klebsiella Pneumoniae

Quinolone resistance gene	Number of cases	Percentage
qnrA	0	/
qnrB	4	7.84%
qnrC	0	/
qnrD	0	/
qnrS	6	11.76%
aac(6)-Ib-cr	21	41.18%
qepA	0	/
oqxA	27	52.94%
oqxB	27	52.94%
oqxA+ oqxB	27	52.94%
oqxA+ oqxB+ aac(6)-Ib-cr	11	21.56%
qnrS+ oqxA+ oqxB	4	7.84%
qnrS+ oqxA+ oqxB+ aac(6)-Ib-cr	1	1.96%
qnrS+ aac(6)-Ib-cr	1	1.96%
qnrB+ oqxA+ oqxB	2	3.92%
qnrB+ aac(6)-Ib-cr+ oqxA+ oqxB	2	3.92%

Conclusion

The resistance rate of *MDR-KPN* to quinolones was serious. Fifty-one strains were resistant to quinolones. ST11 is a major molecular epidemiological type. The main carbapenem resistance gene was KPC-19. We found that the major quinolone resistance genes were *aac(6')-Ib-cr, oqxA, oqxB*. The remaining quinolone resistance genes *qnrA, qnrC, qnrD* and *qepA* were not detected. For *MDR-KPN*, a combination of multiple antibiotics is necessary.

Data Sharing Statement

The data used to support the findings of this study are included within the article.

Ethics Approval and Consent to Participate

The strains in this study are part of the routine diagnosis and treatment procedures in hospitals. The use of these samples has been applied for no informed consent by the Ethics Committee of Beijing Shijitan Hospital, without the informed consent of patients. The informed consent was waived by the ethics committees of the Beijing Shijitan Hospital. The ethical approval number was No.26 of 2018. This study was carried out in accordance with the Declaration of Helsinki.

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Disclosure

The authors report no conflicts of interest in this work.

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