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ORIGINAL RESEARCH

Resistance Trends of *Klebsiella pneumoniae* Causing Urinary Tract Infections in Chongqing, 2011–2019

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Purpose: To analyze the characteristics and trends of drug resistance for *Klebsiella pneumoniae* (*K. pneumoniae*), isolated from urinary tract infections (UTIs), to common antibiotics used in clinics.

Methods: This retrospective study was conducted in a teaching hospital in Chongqing from 2011 to 2019. Laboratory data of isolated bacteria were collected and analyzed.

Results: Among the 17,966 non-repetitive strains isolated from the urine sample, a total of 1543 *K. pneumoniae* isolates were identified, with an isolation frequency secondary only to *Escherichia coli* (*E. coli*) and there was a peak in the *K. pneumoniae* isolates in the year 2013. During the period, the rate of extended-spectrum β-lactamase (ESBL)-producing *K. pneumoniae* fell from 48.4% in 2011 to 32.9% in 2019, and a marked jump of resistance was seen in carbapenems from 2.2% to 18.0%. The peak of carbapenem resistance rate (22.6%) to *K. pneumoniae* was observed in 2017 along with a low ESBL-producing rate (30.9%). Piperacillin/tazobactam and cefepime resistance levels went up from 4.4% to 25.7% and from 18.2% to 30.5%, respectively. Moreover, the *K. pneumoniae* isolates resistance rate to carbapenems and amikacin gradually grew up, showing their peaks in 2017, and then dropped year by year. However, ceftazidime and aztreonam resistance levels were relatively stable, fluctuating between 21.8% and 35.6%, 32.2% and 39.4%, respectively.

Conclusion: There is a significant upward tendency in carbapenem resistance rate and a downward tendency in ESBL-production rate in *K. pneumoniae* isolates from UTIs, and continuous surveillance is necessary in the future.

Keywords: urinary tract infections, *Klebsiella pneumoniae*, carbapenem resistance, extended-spectrum β-lactamase

Introduction

Urinary tract infections (UTIs) are the most frequent bacterial infection in primary care, affecting 150 million people per year worldwide.[1] UTI is an inflammatory reaction caused by the invasion of pathogenic microorganisms in the urinary tract, which is a common infection among the inpatients in recent years, and the inappropriate use and abuse of broad-spectrum antibiotics for decolonization not only results in a decrease in the effectiveness of standard treatments, but also leads to the emergence of multidrug resistance.[2,3] A modelling study showed that about 3 million severe infections were caused by carbapenem-resistant *Escherichia coli* (*E. coli*) and *Klebsiella pneumoniae* (*K. pneumoniae*) worldwide.[4]

Accelerated emergence and effective propagation of carbapenem-resistant *K. pneumoniae* (CR-KPN) across the world have become a prominent public health challenge due to high mortality rate in healthcare-associated nosocomial

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infections.[5,6] Approximately 60%-80% of UTIs are caused by *E. coli* and 3%-10% by *K. pneumoniae*.[7–9] This last is an important pathogen that causes a wide range of infections such as pneumonia and bloodstream infections, commonly in neonates and patients admitted in intensive care units. Carbapenems is the last defense against extended-spectrum β-lactamase (ESBL)-producing *K. pneumoniae* and their frequent use has resulted in the generation and spread of CR-KPN, a clinically significant carbapenem-resistant *Enterobacteriales* (CRE).[10] Since outbreak of CR-KPN in New York hospitals in the early 2000s, this pathogen has spread throughout the United States and worldwide.[11,12] In China, CR-KPN infections prevailed from 2.9% in 2005 to 40% in 2017 and the distribution differed greatly by region, with the lowest in northeast and the highest in eastern region of China.[13–15] Here, we investigated the distribution and drug resistance trends of *K. pneumoniae* causing UTIs in a tertiary teaching hospital from 2011 to 2019 to provide reference for rational use of antibiotics.

Materials and Methods

Data Collection

This retrospective study data were collected in the microbiology laboratory of the First Affiliated Hospital of Chongqing Medical University using WHONET software. Strains were isolated from various patients' urine culture routinely according to the hospital laboratory procedure, and only the first isolate was included in our study. Duplicate isolates, defined as the same bacterial species from the same inpatient during the same inpatient stay, were excluded from analysis.

Antimicrobial Susceptibility Testing

A total of 1543 *K. pneumoniae* isolates recovered from urine were correctly identified by matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) (bioMérieux, MO, France), assisted with Vitek-2 compact system (bioMérieux, MO, France) according to the manufacturer's instructions. All the isolates were sub-cultured on blood agar and MacConkey agar plates for purity check to confirm species. The susceptibility testing was performed according to the Clinical and Laboratory Standards Institute (CLSI) criteria using the automated Vitek-2 compact system, and further on Mueller Hinton's agar by the Kirby-Bauer Disk Diffusion method for the following antimicrobials: aztreonam (30μg), meropenem (10μg), ciprofloxacin (5μg) and gentamicin (30μg). The ESBL test was identified by clavulanic acid synergy test, which is included in the AST-GN334 card (bioMérieux, Marcy l'Etoile, France).[16] Isolates were defined as CR-KPN if they were resistant to any one of carbapenems tested. MIC results were interpreted according to the CLSI guidelines.[17] Quality control was performed with each run using the strains *Enterobacter hormaechei* ATCC 700323 and *Escherichia coli* ATCC 25922, to ensure reproducibility of the antibiotic susceptibility testing procedure.

Results

Distribution of Strains

A total of 17,966 strains were isolated from urine culture during the 9 years of study period in our hospital in Chongqing, Southwest China. The top five species among the total identified isolates were *E. coli, K. pneumoniae, Enterococcus faecium, Enterococcus faecalis* and *Pseudomonas aeruginosa*. The annual isolation number of *K. pneumoniae* ranged from 91 to 205 during the 9 years, with 91 (7.9%) strains in the year 2011, 137 (6.7%) in 2012, 205 (9.2%) in 2013, 189 (8.4%) in 2014, 203 (8.6%) in 2015, 177 (8.0%) in 2016, 191 (9.3%) in 2017, 182 (9.6%) in 2018, and 167 (9.5%) in 2019. There was a peak in the *K. pneumoniae* isolates in the year 2018, accounting for up to 9.6% of the total isolates (Figure 1). Of note, the vast majority of the strains were isolated from the hospitalized patients (data not shown).

Characteristics of *K. pneumoniae*

Temporal trends and changes in both the rates of ESBL-production and carbapenem-resistance, and antimicrobial resistance levels in urinary *K. pneumoniae* isolates over the study period are presented in Figure 2 and Table 1. During this period, the rate of ESBL-producing *K. pneumoniae* reduced from 48.4% in 2011 to 32.9% in 2019, but a marked increase of resistance against carbapenems was seen from 2.2 to 18.0%. The peak of carbapenem resistance (22.6%) was observed in 2017 along with the low ESBL-production rate (30.9%) in *K. Pneumoniae*. (Figure 2)

Antibioresistence Profiles of *K. pneumoniae*

Antimicrobial agents checked included quinolones (ciprofloxacin and levofloxacin), sulfonamides (cotrimoxazole),

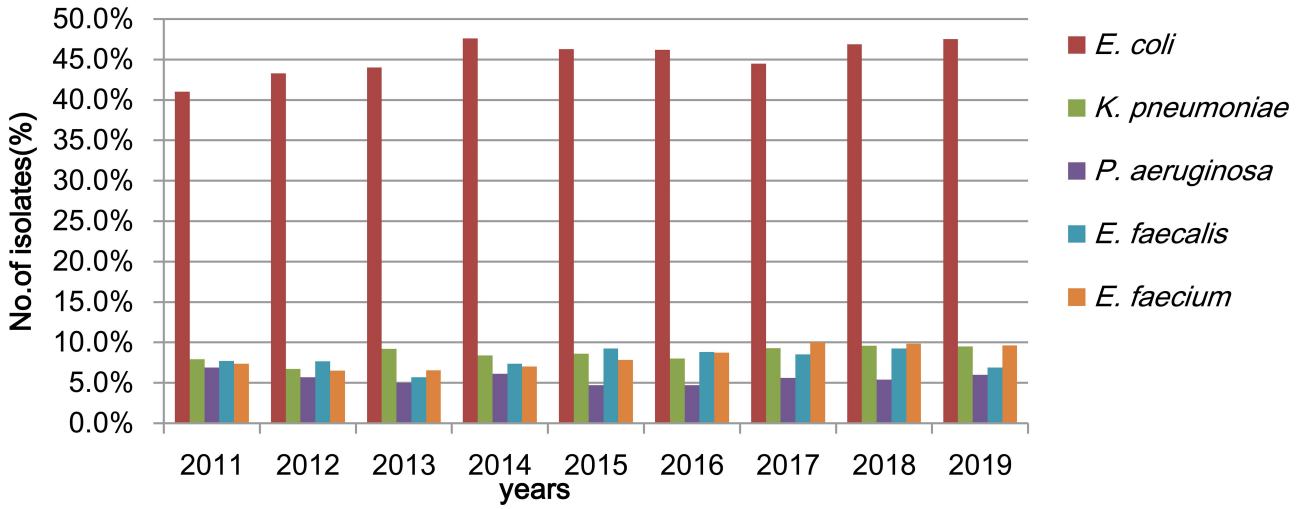

Figure 1 Distribution of strains isolated from urine for the 9-year study.
Abbreviations: *E. coli, Escherichia coli; K. pneumoniae, Klebsiella pneumoniae; P. aeruginosa, Pseudomonas aeruginosa; E. faecalis, Enterococcus faecalis; E. faecium, Enterococcus faecium.*

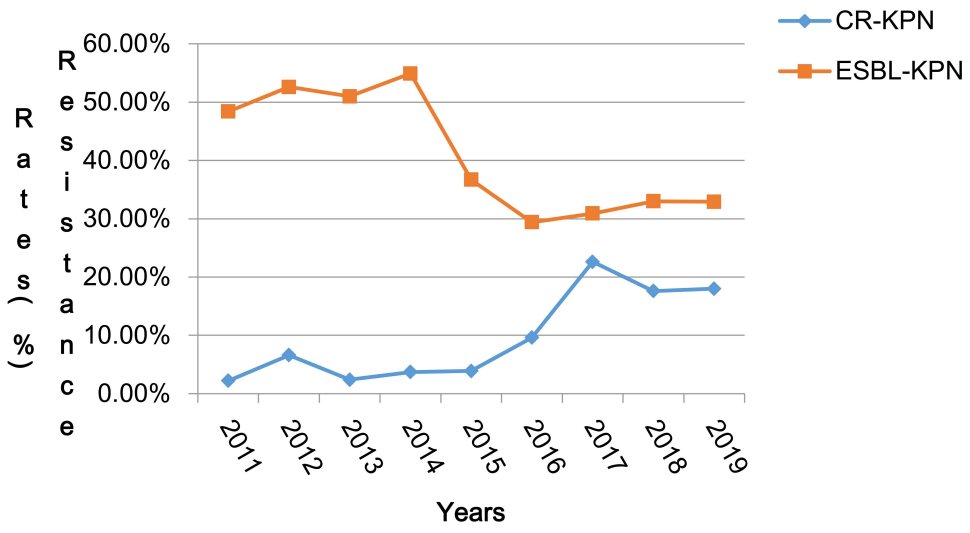

Figure 2 Rates of ESBL-producing and Carbapenem resistant-*K. pneumoniae* from 2011 to 2019.
Abbreviations: CR-KPN, carbapenem resistant-*K. pneumoniae*; ESBL-KPN, ESBL-producing *K. pneumoniae.*

third-generation cephalosporins (ceftazidime and ceftriaxone), fourth-generation cephalosporins (cefepime), cephamycins (cefoxitin and cefotetan), other penicillins (piperacillin/tazobactam), carbapenems (ertapenem, imipenem and meropenem), aminoglycosides (gentamicin, amikacin and tobramycin) and monocyclic β-lactam antibiotics (aztreonam). With regard to drug susceptibility of *K. pneumoniae*, ESBL producers accounted from 48.4% in 2011 to 32.9% in 2019 (Figure 2). ESBL-producing *K. pneumoniae* showed a high resistance rate to the antibiotics except cefoxitin, cefotetan, piperacillin/tazobactam, amikacin and carbapenems, while CRKP was highly resistant to all antibiotics (Table 2).

Moreover, piperacillin/tazobactam and cefepime resistance levels increased from 4.4% to 25.7% and from 18.2% to 30.5%, respectively (Table 1). The resistance rate of carbapenems and amikacin gradually rose from 2011 to 2017, reaching its peaking in 2017, and then went down year by year. However, ceftazidime and aztreonam resistance levels were stable, fluctuating between 21.8% and 35.6%, 32.2% and 39.4%, respectively (Table 1).

Discussion

Our study highlights the decreasing detection rate of ESBL-producing coupled with rising resistance rates of

Table 1 Resistance Rates (%) of Urine *K. pneumoniae* Isolates to Antimicrobial Agents

Antibiotics	2012		2013		2014		2015		2016		2017		2018		2019	
	n = 137		n = 205		n = 189		n = 203		n = 177		n = 191		n = 182		n = 167	
	n	R%	n	R%	n	R%	n	R%	n	R%	n	R%	n	R%	n	R%
SAM	137	62.0	205	56.1	183	59.0	188	49.5	172	55.8	188	60.6	182	50.5	/	/
TZP	137	4.4	205	1.5	183	2.2	188	5.9	172	11.6	188	23.4	182	13.7	167	25.7
CAZ	137	31.4	205	28.8	183	26.8	188	21.8	172	27.3	188	35.6	182	28.0	167	29.3
CRO	137	56.9	205	56.6	183	53.0	188	43.1	172	43.6	190	53.7	182	45.6	167	46.7
FEP	137	18.2	205	17.6	183	15.3	188	11.2	172	19.2	188	30.9	182	22.0	167	30.5
CTT	137	2.9	205	0.5	183	2.7	188	4.3	172	11.0	188	19.1	182	15.4	/	/
FOX	/	/	/	/	/	/	155	13.5	158	24.7	180	28.9	181	28.7	136	28.7
ATM	137	35.8	205	36.6	183	36.6	188	32.4	172	32.6	188	39.4	180	32.2	145	34.5*
ETP	133	6.0	200	2.0	182	3.3	182	4.4	171	9.9	190	22.6	182	17.0	167	16.8
IPM	137	1.5	205	0	183	0.5	188	4.3	172	8.7	190	20.0	182	13.7	167	11.4
MEM	/	/	/	/	/	/	163	4.3*	159	8.2*	184	18.5*	181	13.8*	153	11.1*
AMK	137	7.3	205	6.8	175	6.3	175	6.9	164	10.4	181	21.5	182	15.4	167	10.8
GEN	137	42.3	205	51.7	183	41.5	188	33.5	175	38.3	190	45.8	182	34.1	51	23.5
TOB	137	14.6	204	21.1	183	22.4	188	14.9	172	16.9	188	33.0	182	19.8	/	/
CIP	137	55.5	205	51.2	183	59.0	188	48.9	172	54.1	188	58.5	182	52.2	/	/
LVX	137	38.0	205	35.6	183	41.0	188	37.8	172	39.0	188	38.3	182	40.1	167	36.5
SXT	50	54.0	205	53.2	183	60.1	187	46.0	172	54.7	188	50.5	181	41.4	167	43.1

Notes: *The data are results using Kirby-Bauer method; /, the data are not detected.

Abbreviations: SAM, ampicillin/sulbactam; TZP, piperacillin/tazobactam; CAZ, ceftazidime; CRO, ceftriaxone; FEP, cefepime; CTT, cefotetan; FOX, cefoxitin; ATM, aztreonam; ETP, ertapenem; IPM, imipenem; MEM, meropenem; AMK, amikacin; GEN, gentamicin; TOB, tobramycin; CIP, ciprofloxacin; LVX, levofloxacin; SXT, sulfamethoxazole/trimethoprim.

K. pneumoniae to carbapenems. Isolates of *K. pneumoniae* are becoming increasingly resistant to antibiotics and subsequently may become even more difficult to be treated.[18] Overall, we found a significant reduction of ESBL detection rate for the *K. pneumoniae* in UTIs from 2011 to 2019. Fortunately, from 2011 onwards, there is a requirement for all hospitals in China to form an antibiotic administrative group with the aim to enforce formulary restrictions and total inpatient consumption of antibiotics (>40 defined daily doses/100 inpatient days).[19] The outbreaks of CR-KPN have become increasingly common in China,[20,21] and we found a growing prevalence of CR-KPN in the UTIs through retrospective analysis, consistent with findings from previous large surveillance studies.[13]

We found that the detection of CR-KPN isolates from UTI patients reached its peak in 2017, accompanied by the high resistance rates to carbapenems and amikacin. While piperacillin/tazobactam and cefepime resistance levels increased year after year, ceftazidime and aztreonam resistance levels were relatively stable. Of note, CR-KPN was almost resistant to all the antibiotics tested. High rates of bacterial resistance are often correlated with high rates of antibiotic use and intra- and inter-hospital spread of antibiotic-resistant bacteria.[22] In addition, increasing consumption of β-lactam/β-lactamase inhibitors may also increase the frequency of carbapenem-resistant *Klebsiella* spp.[23–25]

K. pneumoniae can cause serious, life-threatening infections in humans in endemic and epidemic settings.[26] Resistance to carbapenems in *Enterobacteriales* is primarily linked to different mechanisms, in particular the production of carbapenemases.[10] Carbapenems are the main defense against ESBL-producing pathogens, the overuse of which has resulted in the generation and spread of CR-KPN, which is a clinically significant CRE. A series of molecular epidemiology studies on CRE in China have shown that the outbreaks caused by KPC-2-producing *K. pneumoniae* in these regions were due to the spread of the predominant clone ST11, which is a variant of international clone ST258.[26–30] ST258 is strongly associated with KPC production and multidrug resistance, but it may have inherent traits which are responsible for its high rate of transmissibility that results from two distinct genetic clades with a hot spot for DNA recombination.[31]

Table 2 Resistance Rates of Urine *K. pneumoniae* Isolates with Diverse Characteristics to Antimicrobial Agents

Antibiotics	ESBL(+)-KPN		ESBL(-)-KPN		CR-KPN		CSE-KPN	
	R (%)	S (%)	R (%)	S (%)	R (%)	S (%)	R (%)	S (%)
SAM	85.3 (480/563)	2.8 (16/563)	34.5 (268/777)	60.6 (471/777)	100.0 (122/122)	0 (0/122)	50.8 (599/1180)	40.6 (480/1180)
TZP	6.6 (41/617)	83.6 (516/617)	13.6 (120/884)	82.4 (728/884)	79.2 (118/149)	9.4 (14/149)	3.2 (42/1314)	91.2 (1198/1314)
CAZ	43.6 (269/617)	50.2 (310/617)	18.3 (162/885)	80.5 (712/885)	96.6 (144/149)	3.4 (5/149)	20.5 (269/1314)	75.9 (997/1314)
CRO	95.8 (591/617)	3.4 (21/617)	17.8 (158/886)	81.6 (723/886)	98.7 (147/149)	1.3 (2/149)	44.3 (583/1316)	55.1 (725/1316)
FEP	25.6 (158/617)	70.5 (435/617)	12.2 (108/885)	86.9 (769/885)	85.9 (128/149)	8.7 (13/149)	10.3 (135/1314)	88.1 (1158/1314)
CTT	1.8 (10/563)	96.4 (543/563)	11.7 (91/777)	86.5 (672/777)	76.2 (93/122)	14.8 (18/122)	0.5 (6/1180)	98.6 (1163/1180)
FOX	22.9 (64/279)	71.3 (199/279)	25.8 (138/534)	71.2 (380/534)	99.1 (111/112)	0.9 (1/112)	12.8 (85/664)	82.8 (550/664)
ATM	62.6 (382/610)	35.7 (218/610)	15.0 (131/872)	84.5 (737/872)	92.3 (132/143)	7.0 (10/143)	28.0 (364/1300)	71.0 (923/1300)
ETP	4.2 (26/615)	94.6 (582/615)	13.5 (119/880)	85.8 (755/880)	100.0 (149/149)	0 (0/149)	0 (0/1316)	100.0 (1316/1316)
IPM	0.6 (4/617)	98.9 (610/617)	11.5 (102/886)	88.0 (780/886)	71.8 (107/149)	22.8 (34/149)	0 (0/1316)	100.0 (1316/1316)
MEM	1.4 (4/287)	97.2 (279/287)	16.2 (90/557)	83.5 (465/557)	80.0 (92/115)	15.7 (18/115)	0 (0/686)	100 (686/686)
AMK	8.2 (49/597)	91.6 (547/597)	12.2 (106/868)	87.8 (762/868)	66.9 (97/145)	33.1 (48/145)	4.3 (55/1284)	95.6 (1228/1284)
GEN	64.8 (378/583)	34.1 (199/583)	23.0 (190/826)	76.3 (630/826)	76.3 (100/131)	22.9 (30/131)	36.5 (451/1235)	62.9 (777/1235)
TOB	26.3 (148/563)	29.3 (165/563)	16.1 (125/777)	71.9 (559/777)	76.2 (93/122)	10.7 (13/122)	14.6 (172/1180)	58.8 (694/1180)
CIP	51.1 (313/613)	40.6 (249/613)	27.5 (241/876)	70.2 (615/876)	91.7 (133/145)	6.9 (10/145)	30.7 (400/1305)	64.2 (838/1305)
LVX	38.9 (240/617)	54.0 (333/617)	24.1 (213/884)	73.0 (645/884)	87.2 (130/149)	11.4 (17/149)	23.2 (305/1314)	71.6 (941/1314)
SXT	80.4 (456/567)	19.6 (111/567)	32.8 (277/846)	67.2 (569/846)	60.6 (87/143)	39.4 (56/143)	51.0 (630/1236)	49.0 (606/1236)

Abbreviations: ESBL(+)-KPN, ESBL-producing *K. pneumoniae*; ESBL(-)-KPN, non ESBL-producing *K. pneumoniae*; CR-KPN, carbapenem-resistant *K. pneumoniae*; CS-KPN, carbapenem-sensitive *K. pneumoniae*; SAM, ampicillin/sulbactam; TZP, piperacillin/tazobactam; CAZ, ceftazidime; CRO, ceftriaxone; FEP, cefepime; CTT, cefotetan; FOX, cefoxitin; ATM, aztreonam; ETP, ertapenem; IPM, imipenem; MEM, meropenem; AMK, amikacin; GEN, gentamicin; TOB, tobramycin; CIP, ciprofloxacin; LVX, levofloxacin; SXT, sulfamethoxazole/trimethoprim.

There are some limitations of this work. This study is retrospective in nature, so some potential confounders, such as the length of stay, patients from different wards, and time of collection of urine samples, could not be ascertained while observing the trends. At the same time, ESBLs production was not detected by molecular biological methods, so there may be lower detection rates due to the influence of carbapenem production in the CR-KPN isolates on ESBLs detection.

Conclusion

Taken together, our data demonstrated that there was a significant rise in the prevalence of carbapenem resistance and a decline in ESBL production in *K. pneumoniae* isolates from the patients with UTIs in our hospital. Further work and continuous surveillance are needed to advance the rational and judicious use of antimicrobial agents.

Data Sharing Statement

The data sets used and analyzed during the current study are available from the corresponding author on reasonable request.

Ethical Approval

The samples were part of the routine hospital laboratory procedure, not collected for this study, so an institutional review board will not be required.

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Author Contributions

All authors read and approved the final manuscript. 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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