Molecular Epidemiology of Carbapenem-Resistant Klebsiella pneumoniae Infections in Southwest China

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Research

Keywords: carbapenem-resistant Klebsiella pneumoniae, clinical characteristics, microbiological characteristics, resistance mechanism

Posted Date: June 12th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-34601/v1

Abstract

Background: We determined epidemiological characteristics and resistance mechanisms of carbapenem-resistant *Klebsiella pneumoniae* (CRKP) strains found in Southwest China and assessed disease burden to provide evidence-based strategies for control and treatment of CRKP infection.

Methods: A total of 159 strains of CRKP were isolated from sputa, blood, urine, ascites and wound secretions from three tertiary hospitals in Southwest China between August 1st, 2018 and December 31st, 2019. The sensitivity of each strain to 12 antibiotic agents was determined by micro-broth dilution. Identification of carbapenemase genes and multi-locus sequence typing (MLST) were performed using polymerase chain reaction (PCR). The disease burdens of patients with CRKP were assessed based on invasive procedures, antibiotic use, laboratory tests and clinical outcomes.

Results: Of 159 CRKP strains analyzed, 50.9% were isolated from sputum samples. The percentage of patients who underwent invasive procedures before positive cultures for CRKP were detected was 96.3%. The mortality of blood infection was highest (66.6%) among patients with CRKP infection. All strains were insensitive to carbapenems. The resistance rates to levofloxacin and amikacin were 85.5% and 81.8%, respectively. All CRKP strains produced carbapenemases, with a majority of isolates (81.1%) producing KPC-2. The MICs of strains harbouring both KPC-2 and NDM-1 were higher than those of strains with only KPC-2 or NDM-1. ST11 is the most popular clonotype found in Southwest China.

Conclusions: CRKP strains in Southwest China are characterized by strong drug resistance and associated with poor clinical prognoses. It is therefore urgent to both strengthen control measures and improve prevention awareness.

Background

Carbapenem-resistant *Enterobacteriaceae* (CRE) have recently emerged as a class of bacterial pathogens that pose a significant threat, both to global public health and to high-risk patients undergoing life-threatening procedures[1]. Although multiple genera of *Enterobacteriaceae* have been found to carry carbapenemase enzymes, carbapenem-resistant *Klebsiella pneumoniae* (CRKP)remains the most epidemiologically important on a global scale [2]. The prevalence of healthcare-related CRE infections has increased from 1.2% in 2001 to 4.2% in 2011 according to the National Healthcare Safety Network (NHSN). Similarly, the National Nosocomial Infection Surveillance System (NNIS), which concentrated mainly on *Klebsiella* species, reported an increase in infection rate from 1.6–10.4% [3]. Clinical studies have revealed high failure rates associated with treatment of CRKP infections, and infection mortality rates range from 22–72% [4, 5]. Extensive resistance phenotypes have resulted in a dearth of clinical therapeutic choices for treating nosocomial infections due to CRKP, which has, in turn, posed additional difficulties for patient management. Since the initial identification of a *Klebsiella pneumoniae* carbapenemase (KPC)-producing *K. pneumoniae* isolate in 2007, CRKP has been confirmed in almost every province in China [6, 7]. A multicenter study that collected 999 strains of CRE from 27 provinces and

regions across China between 2014 and 2015 found that CRKP accounted for the vast majority of strains (70%), far higher than both *Escherichia coli* (16%) and other *Enterobacteriaceae* (13%) [7]. There are a few reports regarding the distribution and resistance rate of CRKP in China [7–10]. However, there remains a lack of information concerning the molecular epidemiology of CRKP in Southwest China. In this study, CRKP strains collected from three tertiary hospitals in Southwest China were analyzed. The clinical characteristics, laboratory tests and outcomes of patients with CRKP infection were also compared. As a whole, this study provides critical information to inform the treatment and prevention of CRKP infections.

Methods

Strain collection and identification

A total of 159 CRKP strains were selected from a collection of *K. pneumoniae* isolates recovered from three tertiary hospitals in Southwest China (Guizhou Provincial People's Hospital [n = 85], Sichuan Provincial People's Hospital [n = 38] and Affiliated Hospital of Zunyi Medical University [n = 36]) between August 1st, 2018 and December 31st, 2019. Strains from a single patient were excluded. All CRKP strains were characterized using an automatic microbial analysis system (Phoenixtm-100, BD, USA), followed by amplification of the RNA polymerase β subunit gene (*rpoB*) and evaluation with a modified Hodge test in accordance with Clinical and Laboratory Standards Institute (CLSI) guidelines [11]. *K. pneumoniae* ATCC700603 was used as the quality control strain.

Study Population

Inpatients with clinical symptoms and positive CRKP culture from sputa, urine, blood, ascites or wound secretions were evaluated for CRKP infection according to the Centers for Disease Control and Prevention (CDC) and National Healthcare Safety Network (NHSN) criteria [12]. Hospital-acquired CRE infection was defined as an infection that occurred after more than 48 h of hospitalization. A CRKP case was defined as the first clinical culture with carbapenem-nonsusceptible (imipenem, meropenem, or ertapenem) *K. pneumoniae* for each individual patient.

Data Collection

Medical records of all cases in this study were reviewed to collect clinical and patient data, including specimen source, demographic characteristics, underlying medical conditions, indwelling devices 30 days prior to culture, infection type(s), antimicrobial therapy, laboratory tests and clinical outcomes. Patients with clinically significant hospital-acquired infection or healthcare-associated infection due to CRKP were eligible for this study. Exclusion criteria were community-acquired infection, missing key data, isolates with colonization only, screening samples and subsequent episodes in an individual patient.

Microbiological Investigation

The minimal inhibitory concentrations (MICs) of 12 antibiotics, including meropenem (Sumitomo Pharmaceuticals, Suzhou, China), imipenem (MSD, Hangzhou, China), cefoxitin, gentamycin, amikacin (National Institutes for Food and Drug Control, Beijing, China), levofloxacin (Yangzijiang, Jiangsu, China), azithromycin, ceftriaxone (Roche, Shanghai, China), ceftazidime, aztreonam, tigecycline, piperacillin/tazobactam, and cefoperazone/sulbactam (Pfizer, NY, USA), against CRKP were determined by agar and broth dilution methods according to CLSI guidelines [13]. The interpretive criteria for tigecycline were based on the breakpoints of the Food and Drug Administration (FDA).

The presence of carbapenemase genes (*bla*$_{NDM}$, *bla*$_{KPC}$, *bla*$_{IMP}$, *bla*$_{GES}$, *bla*$_{OXA-48}$ and *bla*$_{VIM}$) described in previous studies was assessed by Polymerase Chain Reaction (PCR) as previously described [14, 15]. Primers are shown in Table 1. All amplified PCR products were submitted for direct sequencing twice on both strands with an automated DNA sequencer (ABI 3730XL, Weiterstadt, Germany). Nucleotide sequences were analyzed using the online basic local alignment search tool (BLAST) and Clustal W programs (multiple sequences alignment, pairwise comparisons of sequences and dendrograms) against the CRKP carbapenemase gene (GenBank).

DNA for multi-locus sequence typing (MLST) analysis was prepared using a commercial bacterial DNA extraction kit (TIANamp Bacteria DNA Kit, China) according to the manufacturer's instructions. MLST was performed according to the protocol described on the Pasteur Institute MLST website (http://bigsdb.pasteur. fr/klebsiella/klebsiella.html) with amplification of seven housekeeping loci (*gapA, infB, mdh, pgi, phoE, rpoB* and *tonB*) [12].

Table 1
Sequence of primers for amplification of carbapenem enolase gene and annealing temperature

PCR target	Primer sequence (5’-3’)	Annealing temperature (°C)	Fragment length (bp)
KPC-2	F: GTTTGTTGATTGGCTAAAGG	52	203
	R: TGTGCTTGTCATCCTTGTTA		
IMP	F: TGAGCAAGTTATCTGTATTC	60	740
	R: TTAGTTGCTTGGTTTTGATG		
NDM-1	F: CAGCACACTTCCTATCTC	54	292
	R: CCGCAACCATCCCCTCTT		
GES	F: GTTTTTGCAATGTGCTCAACG	55	371
	R: TGCCATAGCAATAGGCGTAG		
OXA-48	F: GCGTGTATTAGCCTTATCGG	60	783
	R: TTTTCCTGTTTGAGCACTTC		
VIM	F: GATGGTGTTTGGTCGCAT	60	390
	R: CGAATGCGCAGCACCAG		
F: forward primer; R: reverse primer			

Statistical analysis

Enumeration data were represented by the number of cases and percentage [n (%)]. Measurement data, disordered counting data and rank classification counting data were analyzed by ANOVA, Fisher's exact test and rank-sum test, respectively. Significance was assessed at $p < 0.05$. All analyses were performed using SPSS software, Version 21.0.

Results

Clinical data analysis

Of 159 CRKP strains, 59.1% (94/159) were isolated from male patients and 41.9% (65/159) from female patients. About one-half of patients (80/159, 50.3%) were at least 65 years old, and 77.4% (123/159) patients had two or more comorbidities (Table 2).

Table 2
Basic characteristics of patients with CRKP infection

Projects	Number of cases (%)
Gender	
Male	94(59.1)
Female	65(40.9)
Age Median (Quartile spacing) (year)	64(52–78)
18–49	37(23.3)
50–64	42(26.4)
65–79	51(32.1)
≥80	29(18.2)
Basic disease	155(97.5)
Diabetes	37(23.3)
Heart disease[a]	65(40.9)
hypertension	70(44.0)
Immunodeficiency[b]	9(5.7)
Liver disease[c]	42(26.4)
Nervous system diseasesd	89(56.0)
Respiratory system disease[e]	145(91.2)
Kidney disease[f]	70(44.0)
Hormone use	42(26.4)
Immunosuppression use	0
Tumor [g]	14(8.9)
ICU	107(67.3)
Smoking	42(26.4)
No basic disease	4(2.5)
[a]Heart disease: congestive heart failure, coronary heart disease, valve replacement and congenital heart disease. [b]Immunodeficiency: splenectomy, chemotherapy and agranulocytosis.	
[c]Liver disease: hepatitis, liver cirrhosis, liver abscess, abnormal liver function and fatty liver.	

Projects	Number of cases (%)
[d]Nervous system diseases: apoplexy, transient ischemic attack, central paralysis and meningitis.	
[e]Respiratory system disease: COPD, asthma, interstitial lung disease, pneumonia and respiratory failure.	
[f]Respiratory failure: chronic kidney disease and azotemia.	
[g] Tumor: respiratory, digestive tract, obstetrics and gynecology, blood and nervous system tumors.	

Clinical characteristics and outcomes are summarized in Table 3. Of the studied patients, 96.8% (150/159) required the use of indwelling devices prior to culture collection. Multiple antibiotics were used by 98.1% (156/159) of patients. The majority of the patients demonstrated both an increased white blood cell count (129/159, 81.1%) and elevated levels of C-reactive protein (144/159, 90.6%). All patients showed increased levels of procalcitonin (159/159, 100%). Mortality among these 159 patients was 18.9% (30/159).

Detection Of Carbapenemases

At least one carbapenemase was detected in each of these 159 CRKP strains, among which there were 129 strains (129/159, 81.1%) producing only KPC-2, 21 strains (21/159, 13.2%) only producing NDM-1, and 9 strains (9/159, 5.7%) producing both KPC-2 and NDM-1. Of the CRKP strains found to produce both KPC-2 and NDM-1, 66.7% (6/9) were isolated from bloodstream infections. The bla_{GES}, bla_{IMP}, bla_{VIM} and bla_{OXA-48} genes were not detected in any of these 159 CRKP strains.

Antimicrobial Susceptibility Test

All CRKP strains were found to be multi-drug resistance (MDR), and all showed resistance to imipenem, meropenem, gentamicin, ceftazidime, cefoxitin, cefoperazone/sulbactam and aztreonam. The resistance rate to both azithromycin and ceftriaxone was 96.9% (154/159), followed by piperacillin/tazobactam (145/159, 91.2%), levofloxacin (136/159, 85.5%) and amikacin (129/159, 81.8%). A total of nine CRKP strains producing both KPC-2 and NDM-1 were resistant to all tested antibiotics (Table 4). These KPC-2^+ NDM-1^+ strains were also characterized by higher MICs of imipenem, meropenem, ceftazidime, cefoxitin, cefoperazone/sulbactam, aztreonam and piperacillin/tazobactam compared to those of strains that only produce either KPC-2 or NDM-1 ($P < 0.05$).

Table 3
Clinical characteristics, laboratory examination and outcome of patients with CRKP infection

Projects	Sputa (%) (n = 81)	Blood (%) (n = 33)	Urine (%) (n = 18)	Ascites (%) (n = 15)	Wound secretions (%) (n = 12)	P value
Invasive procedures						
Happened	78(96.3)	33(100.0)	15(83.3)[ab]	12(80.0)[ab]	12(100.0)	0.013
Deep venous catheterization	69(85.2)	30(90.9)	15(83.3)	12(80.0)	12(100.0)	0.526
tracheal intubation / tracheostomy	57(70.4)	27(81.8)	9(50.0)	6(40.0)[ab]	12(100.0)[acd]	0.001
Urinary catheter	75(92.6)	33(100.0)	15(83.3)[b]	9(60.0)[ab]	12(100.0)[d]	0.001
Dialysis	6(7.4)	3(9.1)	0(0.0)	0(0.0)	3(25.0)	0.127
Antibiotic use						
Monotherapy	0(0.0)	0(0.0)	0(0.0)	3(20.0)[abc]	0(0.0)	0.001
Polypharmacy	74(91.4)	33(100.0)	17(94.4)	12(80.0)	12(100.0)	0.100
third and fourth generation cephalosporins	60(74.1)	27(81.8)	9(50.0)[ab]	15(100.0)[ac]	12(100.0)[ac]	0.002
Carbapenem	48(59.3)	27(81.8)[a]	9(50.0)[b]	9(60.0)	12(100.0)[acd]	0.004
Laboratory tests						
Leucocyte						0.040
4000	18(22.2)	6(18.2)	6(33.3)	0(0.0)	0(0.0)	
10000	63(77.8)	27(81.8)	12(66.7)	15(100.0)	12(100.0)	
C-reactive protein						0.141
< 5 mg/L	3(3.7)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	
5–10 mg/L	6(7.4)	3(9.1)	0(0.0)	0(0.0)	3(25.0)	

Note: [a]Compared with the sputum group, P < 0.05

[b]Compared with the blood group, P < 0.05

[c]Compared with urine group, P < 0.05

[d]Compared with ascites group, P < 0.05

Projects	Sputa (%) (n = 81)	Blood (%) (n = 33)	Urine (%) (n = 18)	Ascites (%) (n = 15)	Wound secretions (%) (n = 12)	P value
> 10 mg/L	72(88.9)	30(90.9)	18(100.0)	15(100.0)	9(75.0)	
Procalcitonin						0.063
0.05-2 ng/ml	36(44.4)	15(45.5)	12(66.7)	3(20.0)	3(25.0)	
2 ng/ml	27(33.3)	15(45.5)	6(33.3)	3(20.0)	6(50.0)	
Course and outcome						< 0.001
Rehabilitation	17(21.0)	2(6.1)	6(33.3)	3(20.0)	5(41.7)	
Transfer (including improvement)	57(70.4)	9(27.3)	12(66.7)	12(80.0)	6(50.0)	
Death	7(8.6)	22(66.6)	0(0.0)	0(0.0)	1(8.3)	
Note: [a]Compared with the sputum group, P < 0.05						
[b]Compared with the blood group, P < 0.05						
[c]Compared with urine group, P < 0.05						
[d]Compared with ascites group, P < 0.05						

Table 4
Minimal inhibitory concentration of 159 strains of CRKP against 12 antibiotics (μg/mL)

	Strains with KPC-2 (n = 129)	Strains with NDM-1 (n = 129)	Strains with both KPC-2 and NDM-1 (n = 9)
Imipenem	32–512	16–256	> 512[ab]
Meropenem	16–512	16–256	> 512[ab]
Gentamicin	16–256	16–256	16–256
Amikacin	1-512[a]	1–8	64–512
Levofloxacin	0.25-512[a]	0.25-2	32–512
Azithromycin	16-512[a]	4–16	> 512[ab]
Ceftriaxone	64-512[a]	0.5–128	> 512[ab]
Ceftazidime	16–512	16–512	> 512[ab]
Cefoxitin	32–512	32–512	> 512[ab]
Aztreonam	32–256	32–256	> 512[ab]
Piperacillin / tazobactam	16/4-512/4 [a]	64/4-512/4	> 512/4[ab]
Cefoperazone / sulbactam	64–512	16–256	> 512[ab]
[a]Compared with NDM-1-producing strains, p < 0. 05.			
[b]Compared with KPC-2-producing strains, p < 0. 05			

MLST

MLST results showed that the most prevalent sequence type (ST) was ST11 (102/159, 64.2%), with a total of eight STs detected across the 159 CRKP strains. STs were significantly different between Guizhou Provincial People's Hospital and Affiliated Hospital of Zunyi Medical University (P < 0.05). ST244 strains were isolated only from Affiliated Hospital of Zunyi Medical University (Table 5).

Table 5
Multilocus sequence typing of 159 CRKP strains

	Guizhou Provincial People's Hospital (%) (n = 85)	Sichuan Provincial People's Hospital (%) (n = 38)	Affiliated Hospital of Zunyi Medical University (%) [a] (n = 36)	Total (%) (n = 159)
ST11	64(75.3)	23(60.5)	15(41.7)	102(64.2)
ST2792	4(4.7)	3(7.9)	2(5.6)	9(5.7)
ST524	3(3.5)	5(13.2)	1(2.8)	9(5.7)
ST35	3(3.5)	1(2.6)	1(2.8)	5(3.1)
ST789	5(5.9)	4(10.5)	10(27.8)	19(11.9)
ST1066	2(2.4)	1(2.6)	2(5.6)	5(3.1)
ST29	4(4.7)	1(2.6)	1(2.8)	6(3.8)
ST244	0(0.0)	0(0.0)	4(11.1)	4(2.5)

[a]Compared with Guizhou Provincial People's Hospital strains, $p < 0.05$.

Discussion

CRKP presents a particularly critical problem worldwide due to rapidly rising resistance rates and subsequent high mortality. Prior to this study, there was limited understanding of the molecular epidemiology of CRKP in Southwest China. In this study, 159 CRKP strains were isolated from clinical samples taken at three tertiary hospitals across Southwest China. This research serves as a powerful supplement to multicenter studies of CRKP epidemiology in China.

According to this study, in Southwest China, death by CRKP infection was primarily caused by bloodstream infections (66.6%). Meta-analysis shows that the mortality rates of CRKP infections in North America, South America, Europe and Asia were 33.24%, 46.71%, 50.06% and 44.82%, respectively [16]. The mortality rate of bloodstream CRKP infection reaches 54.3%, which is quite high [16]. In this study, most of the patients with bloodstream infections experienced invasive operations such as deep vein catheterization, tracheal intubation and mechanical ventilation before the collection of a positive culture. One study, which collected 100 CRKP strains from Shanghai, China, reports that mechanical ventilation could lead to a higher CRKP infection rate [17]. In our study, all patients with bloodstream infections experienced antimicrobial therapy before CRKP culture, 81.8% of which were treated with either third- or fourth-generation cephalosporins or carbapenem. Hospitalization and history of antibiotic use – especially of β-lactams and carbapenems – are considered independent risk factors for CRE infection [18, 19]. More than half of CRKP strains taken from bloodstream samples in our study produce both KPC-2 and NDM-1, which we found to be associated with higher MICs for a panel of antibiotics.

The distribution of carbapenemases has been shown to regionally different; this study shows that KPC-2 is most prevalent in Southwest China, while NDM is the dominant CRKP carbapenemase in some provinces of China [7, 10, 20]. In the United States, the most prevalent mechanism of carbapenem resistance among *Enterobacteriaceae* is production of KPC, even though the combination of extended-spectrum β-lactamase (ESBLs)/AmpC cephalosporinase and membrane permeability can also make *Klebsiella pneumoniae* resistant to carbapenems [21, 22]. Recent reports indicate that KPC-producing, gram-negative isolates are being identified throughout the United States, as well as in parts of Europe, Asia and South America. [23–25]At present, it is believed that transmission of colonies and specific elements from existing drug-resistant strains is the main route for the emergence of new CRKP, suggesting that future control strategies should focus on inhibition of this gene transmission from drug-resistant strains [10].

In this study, resistance rates to gentamicin, amikacin and levofloxacin were found to be 100%, 81.1% and 85.5%, respectively. These values are higher than those reported from both other provinces of China and other countries [26, 27]. A retrospective study in China showed that, in an outbreak of nosocomial neonatal CRKP infection, the MICs of CRKP strains producing KPC-2 are higher than those of strains producing NDM-1 [28]. As mentioned above, a majority of CRKP strains (86.8%) analyzed in this study were found to produce KPC-2. In addition, more than half of the patients in this study were seriously ill in the ICU, were over 65 years old and had previously experienced multiple antibiotics. CRKP treatment is still absolutely difficult, as *in vitro* antibiotic-sensitivity assays do not fully reflect the response of CRKP to medicines *in vivo*. Nephrotoxicity is still an issue that requires attention in clinical practice for CRKP infections, particularly with the use of amikacin or polymyxin [29]. For patients with CRKP blood infections, it has been suggested that dual therapy based on high-dose carbapenem may bring clinical benefits [30]. The use of new antibiotics, such as ceftazidime-avibactam, may be associated with better clinical prognosis and survival [27].

As previously reported, the majority of KPC-producing *K. pneumoniae* isolates in China belong to a common sequence type, ST11 (26). In contrast, a majority of these isolates in the United States belong to the ST258 type (27). Most of the CRKP strains in Southwest China belong to ST11 (64.2%), consistent with its national prevalence [10]. In our previous studies, we compared the age, sex, infection and antimicrobial use of 37 individual patients with either ST11 or non-ST11 CRKP infections [31]. Although there is no statistically significant difference between the two groups, CRKP sequence type still plays a key role in tracing strains at the genotype level, facilitating our understanding of global epidemiology.

To the best of our knowledge, this is the first report of the molecular epidemiology of CRKP infections in Southwest China. This study is limited by the fact that the infection rate of CRKP in admitted patients could not be fully acquired. However, it is clear that CRKP isolates in Southwest China are strongly drug-resistant to multiple antibiotics. In particular, patients with CRKP bloodstream infections have poor prognoses and high mortality. Moving forward, there is an urgent need to strengthen control measures and improve prevention of CRKP infections across Southwest China.

Declarations

Ethics approval and consent to participate

The study was reviewed and approved by the research ethics committee of Guizhou Provincial People's Hospital (No. 2015022).

Consent for publication

The study does not contain any individual personal data, therefore, consent for publication is not required

Availability of data and materials

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

Competing interests

The authors declare that they have no competing interests

Funding

This study was funded by National Natural Science Foundation of China (81560003) and High-level Innovative Talents Foundation of Guizhou Province (GZSYQCC[2016]005).

Authors' contributions

Xiaoping Hu performed the experiment and drafted the article. Guohang Yuan and Yaoyao Wu participated in acquisition of data and performed data analysis. Weijia Liu and Xiangyan Zhang interpreted the data. Lin Liu conceived the study and participated in analysis and draft of the study.

Acknowledgements

Not applicable

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