

Effect of Carbapenem-Resistant *Klebsiella pneumoniae* Infection on the Clinical Outcomes of Kidney Transplant Recipients

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Background: Carbapenem-resistant *Klebsiella pneumoniae* (CRKP) infection has proven to be difficult to control and typically presents with devastating effects.

Methods: This retrospective study was conducted on the renal recipients at our institution between January 2021 to January 2022. Clinical data was collected to identify factors associated with CRKP infection and clinical outcomes.

Results: There were 104 cases out of 186 total renal recipients who presented with at least one infection within 3 months after KT, and 14 cases developed unfavorable clinical outcomes. We identified 16 confirmed CRKP infected cases with the incidence of 8.60%. Possible donor derived infection (DDI) (OR = 6.743; 95% CI: 1.477–30.786; $P = 0.014$) were independent risk factors for the occurrence of CRKP infection of renal recipients in our analysis, CRKP infection (OR = 20.723; 95% CI: 3.448–124.547; $P = 0.001$) and pneumonia (OR = 28.458; 95% CI: 1.956–413.984 $P = 0.014$) were independent risk factors for the occurrence of unfavorable clinical outcomes following KT, and the occurrence of unfavorable clinical outcomes following KT were significantly associated with CRKP infection ($r = 0.535$; $P < 0.001$) and antibiotic regimen containing ceftazidime/avibactam (CZA) ($r = -0.655$; $P = 0.006$). The use of CZA was significantly different in the comparison of antibiotic regimens between the CRKP infected renal recipients with unfavorable outcomes and CRKP infected patients with favorable outcomes.

Conclusion: It is possible that DDI can lead to CRKP infection, and CRKP infection and pneumonia were closely correlated with poor prognosis. The use of CZA may play a role in avoiding the unfavorable outcomes of CRKP infected recipients.

Keywords: kidney transplant, carbapenem-resistant *Klebsiella pneumoniae*, early infections, risk factors, clinical outcomes

Introduction

Solid organ transplant (SOT) recipients receive lifelong immunosuppressive therapy, which may lead to a greater risk of severe infection compared to that in immunocompetent populations. It has been reported that 8.6% of patients died within 5 years after kidney transplantation (KT) and the proportion of deaths due to infection was 53%, which is twice that of the second most common cause of death.¹ *Klebsiella pneumoniae* (KP) is one of the most common opportunistic pathogens causing infection in immunocompromised patients.² KP infections are usually responsive to treatment with carbapenem antibiotics; however, the recent worldwide use of Carbapenem antibiotics has led to outbreaks of Carbapenem-resistant *Klebsiella pneumoniae* (CRKP) infections. Since CRKP was first identified in 2001,³ it has become one of the most lethal pathogenic infections following KT.⁴ The incidence of CRKP infection among SOT recipients ranges from 3% to 10%,⁵ and the associated mortality has been estimated to be close to 43%, which is about 3–5 times higher than that of non-CRKP-infected recipients.^{6–8} Moreover, CRKP infection in renal recipients has proven to be more

difficult to control due to limited treatment options, and it usually presents with devastating effects, such as sepsis and allograft nephrectomy. Due to their proclivity to becoming multidrug-resistant and their plasticity in drug resistance mechanisms, the emergence of drug resistance in the KP strains should be closely monitored.⁹ The high pathogenic capacity of the isolated pathotypes of KP has been reported to be related with the high prevalence of antibiotic resistance and virulence genes,¹⁰ which gives us a hopeful promise for designing effective inhibitors and antibiotics against such isolated strains.¹¹ This study was performed to analyze the clinical characteristics, outcome, and our treatment experience of CRKP infection based on the data of our center, as well as identify risk factors for CRKP infection among renal recipients.

Materials and Methods

Study Design and Patient Samples

This nested case-control observational study was retrospectively conducted from January 2021 to January 2022 at Beijing Friendship Hospital affiliated with Capital Medical University. The study protocol was approved by the Ethics Committee of Beijing Friendship Hospital and was conducted in accordance with the principles of the Declaration of Helsinki (BFHHZS20220004), and patient data confidentiality was guaranteed as all data were processed anonymously. All kidneys were donated voluntarily with written informed consent, and that the transplants were conducted in accordance with the Declaration of Istanbul. The primary endpoint of our study was the occurrence of CRKP infection within 3 months after KT. The secondary endpoint was clinical outcomes of CRKP-infected renal recipients within 6 months after KT. All patients were divided into infected and non-infected recipients based positive culture results within 3 months after KT. Patients among the infected recipients were further classified as either CRKP-infected recipients or non-CRKP infected recipients. Data from patients recruited to our study were collected and clinical outcomes were classified as favorable outcomes and unfavorable outcomes. Unfavorable outcomes comprised a composite of recurrence after a cure of infection, renal allograft loss and/or death. Favorable outcomes constituted full recovery and discharged or stable clinical condition.

Definition

The criteria for infection were based on those proposed by the Centers for Disease Control and Prevention.¹² Blood and urine samples, sputum (or other respiratory secretions), and drainage from the surgical site were routinely sent for detection of infection within 2 weeks after KT. The additional culture of relevant specimens were carried out based on a clinical suspicion of infection (symptoms of fever or elevated white blood cell counts). Samples of organ preservation solution were also collected for inspection of infection from donor kidney. Types of infection were classified as bloodstream infection (BSI), surgical site infection (SSI), urinary tract infection (UTI) and pneumonia. Multiple infections were defined as infections caused by at least 2 microorganisms, and multifocal infections were defined as infections detected at different sites (involved at least 2 sites); The presence of donor-derived infection (DDI) was assessed and classified as proven, probable, possible and intervened upon without documented transmission types based on an international consensus.¹³ Possible DDI presents the same infectious disease that may be transmitted from the donor to at least one of the recipients, which is not sufficient to meet the requirements for confirmed transmission (proven and/or probable), and transmission cannot be formally excluded, it was identified when the microorganism of the recipient infection was identical to the cultured pathogen in the organ preservation solution and had the same drug sensitivity profile.¹⁴ Recurrence of infection was defined as another episode of infection within 1 month after being asymptomatic and initial resolution and isolation of pathogen culture.¹⁵ Delayed graft function (DGF) was defined as a decrease in the daily serum creatinine by less than 10% for three consecutive days during the first week after KT or serum creatinine failed to decrease to 400 mmol/L within the first postoperative week.¹⁶

Microbiological Analysis

Pathogen isolation and culture were carried out based on the *National Clinical Testing Protocols (China)*, and suspected strains were identified using a VITEK 32 automated microbial analyzer (BioMerieux, Craponne, France). Drug

susceptibility was detected using the minimum inhibitory concentration (MIC) and disk diffusion method (Oxoid Ltd, UK), and were interpreted in reference to the Clinical and Laboratory Standards Institute (CLSI, 2018). The disc diffusion assays for the following antibiotics were performed:¹⁷ imipenem (10µg), meropenem (10µg), ceftazidime (30µg), cefotaxime (30µg), cefepime (30µg), amikacin (30µg), gentamicin (10µg), tobramycin (10µg), ampicillin-sulbactam (30µg), piperacillin-tazobactam (110µg), doxycycline (30µg), ciprofloxacin (5µg) and trimethoprim-sulfamethoxazole (25µg). Resistance definition criteria for CRKP were defined as a minimum inhibitory concentration of ≥ 2 mg/mL for ertapenem and ≥ 4 mg/mL for imipenem or meropenem. Drug resistance for CRKP isolates to polymyxin B were detected using CLSI Mueller Hinton II Broth (Cation-Adjusted), and MIC was defined as 1 µg/mL. Metagenomic next-generation sequencing¹⁸ (mNGS, Dinfectome Inc., Nanjing, Jiangsu, China) was performed to detect pathogens in clinical specimens considering the possibility of a rare infection, using the following steps:¹⁹ The Generic Rapid Genomic DNA Extraction Kit (Lifefeng: DK806-02) was used for extraction of DNA, and Qubit (Thermo Fisher Scientific), NanoDrop (Thermo Fisher Scientific) were used for quantification and qualification of DNA; The preparation of DNA libraries was performed using KAPA Hyper Prep kit (KAPA Biosystems) according to the manufacturer's protocols. Agilent 2100 was used for quality control and DNA libraries were 75 bp single-end sequenced on Illumina NextSeq 550Dx (Illumina); By removing low-quality reads, adapter contamination, duplicated and short (length<36 bp) reads, high-quality sequencing data were collected. By mapping to the human reference genome (hs37d5) using Bowtie2 software, human host sequences were identified. Nonhuman sequences were retained and aligned with the microorganism genome database, which contained bacterial, fungal, viral and parasite genomic sequences (download from <https://www.ncbi.nlm.nih.gov/>), for pathogen identification; The results were considered positive under the following conditions: species detected by mNGS had a species-specific read number ≥ 1 with sequences of *Mycobacterium*, *Nocardia* and *Legionella pneumophila*; species had at least 3 nonoverlapping reads with sequences of bacteria (excluding *Mycobacterium*, *Nocardia* and *Legionella pneumophila*), fungi, viruses and parasites.

Immunosuppressive Regimen

The typical immunosuppressive regimen was methylprednisolone (1000 mg of methylprednisolone was intravenously infused on the operation day; 500, 500 mg on the first and second day after KT, respectively) and basiliximab (20 mg of basiliximab administered during operation and fourth day after surgery). The total $1.5\text{--}2.0 \text{ mg} \times \text{kg}^{-1}$ of rabbit anti-human thymocyte immunoglobulin (ATG) with the administration of methylprednisolone was administered for 3–5 days after KT in case of DGF. The routine triple maintenance immunosuppressive regimen was a composite of oral tacrolimus (or cyclosporine A), mycophenolate mofetil (MMF), and prednisone.

Anti-Infection Regimen

A 2 g ceftazidime q12h regimen was routinely administered to the recipients who received deceased donor kidney transplantation. An anti-infection regimen could be adjusted according to the drug susceptibility results of pathogen strains cultured from the clinical specimens. A combination of at least two types of the antibiotics (ceftazidime-avibactam (CZA), tigecycline, meropenem, fosfomycin, and polymyxin B) were administered to control CRKP infection. Optional antibiotic regimens were as follows: a standard dosage of CZA (2 g of ceftazidime with 0.5 g of avibactam intravenously every 8 h over 2 h) combined with fosfomycin (4 g, q8h, iv drip); tigecycline (50 mg, q12h, iv drip) with a high-dose extended infusion of meropenem (1.0 g, q8h, iv drip for 3 h/ dose) or fosfomycin (4 g, q8h, iv drip). The antibiotics regimen dosage was adjusted according to kidney function.

Clinical Data Collection

The patient demographic and clinical characteristic data were reviewed from the electronic medical record system. The variables included sex, age, comorbidities (eg, diabetes mellitus, and hypertension), time on dialysis, donor type, DGF, immune induction and maintenance regimens (eg, dose, duration, and composition of immunosuppressive drugs), type of DDI, infection type (eg, BSI, SSI, UTI and pneumonia), anti-infection regimen (eg, dose, duration, and composition of immunosuppressive drugs), acute rejection, reintervention, admission of intensive care unit (ICU) and unfavorable events (eg, recurrence after cure of infection, renal allograft loss, and/or death).

Statistical Analysis

All statistical analyses were performed using SPSS 25.0 (IBM, Armonk, NY, USA). Categorical variables were expressed as the number of individuals with the percentage of the population. Continuous variables were presented as the mean $\pm$ standard deviation or median and interquartile range (IQR) according to the normality of the distribution tested by a Kolmogorov–Smirnov test. The chi-squared test with a continuity correction was used for a comparison of categorical variables, and an independent-sample *t*-test and Mann–Whitney *U*-test were used to compare the group means for continuous variables. Univariate and multivariate logistic regression analyses were performed to examine risk factors associated with the occurrence of CRKP infection or unfavorable clinical outcomes in renal recipients using odds ratios (ORs) and 95% confidence intervals (CIs). Correlation analysis of the categorical variables were performed using Pearson correlation analysis. Statistical significance was considered at $P < 0.05$ (two-tailed).

Results

Patient Characteristics and Clinical Presentation

A total of 186 patients underwent KT at our institution between January 2021 and January 2022. Of these, 104 cases (79 males and 25 females, age range: 7–66 years) presented with at least one infection within 3 months after KT, and the total prevalence of early infections was 55.9%. KP infection was detected in 24 cases, of which CRKP was detected in 16 cases. 16 confirmed CRKP infected recipients were finally identified, there are 15 male patients and 1 female patient (age range: 16–63 years). The incidence of CRKP infection among the renal recipients in this study was 8.6%. 15 CRKP infected cases received kidneys donated by deceased donors, one CRKP infected case received a living-related kidney transplant (donor was the brother). Routine methylprednisolone and basiliximab were administered for immune induction therapy during operation. There were eight cases that received induction therapy with rabbit anti-human thymocyte immunoglobulin after KT. A total of 88 non-CRKP infected cases and 16 CRKP-infected cases were recruited in the comparative analysis study. The clinical characteristics of the recipients are listed in Table 1.

Microbial Culture and Drug Susceptibility of CRKP Strains

Among 104 infected patients within 3 months after KT in our study, 71 cases (68.3%) presented with only one type of infection: 6 cases had BSI, 32 cases had SSI, 30 cases had UTI, 3 cases had pneumonia. The remaining 33 patients (31.7%) presented with ≥ 2 types of infection; surgical site infection was the most common type of infection in the 104 infected recipients. Among 16 CRKP infected patients, 5 cases (31.3%) presented with only one type of infection; 3 patients had surgical site infection, 1 case had urinary tract infection and 1 case had pneumonia. The remaining 11 patients (68.7%) presented with ≥ 2 types of infection, the most common form of combination of infection was BBI, SSI with UTI. And CRKP infection from wound drainage fluid was detected in 1 case. 6 patients among all 16 CRKP infected patients presented as single-pathogen infections, the remaining 10 cases presented as multi-pathogen infections, and these 10 cases also presented with ≥ 2 types of infections. Among these 10 patients, there were 6 cases of multiple bacterial infections, 2 cases of bacterial infection combined with fungal infection, 1 case of bacterial infection combined with viral infection, and 1 case of bacterial infection combined with viral infection and fungal infection. Cultured bacteria were as follows: *Enterococcus faecium*, *Enterococcus faecalis*, *Hemolytic Staphylococcus*, *Staphylococcus epidermidis*, *Acinetobacter baumannii*, *Klebsiella oxytoca*. The top three bacteria were: *Enterococcus faecium*, *Acinetobacter baumannii*, *Hemolytic Staphylococcus*; Viruses included: B19 virus and JC virus; Fungi included: *Candida glabrata*.

Clinical Features and Analysis of Risk Factors for CRKP Infection After KT

As shown in Table 1, the chi-squared test showed that there were significant differences in hemodialysis ($P = 0.011$), peritoneal dialysis ($P = 0.023$), possible donor derived infection ($P = 0.007$), ICU admission ($P = 0.023$), multi-focal infections ($P = 0.001$), multi-pathogen infections ($P = 0.008$) and unfavorable clinical outcomes ($P < 0.001$) between CRKP infected group and non-CRKP infected group. The univariate logistic regression analysis showed that hemodialysis, peritoneal dialysis, possible donor derived infection, and ICU admission were potential risk factors for the

Table I Clinical Characteristics and Analysis of Risk Factors for CRKP Infection in 104 Renal Recipients with Early Infection

Patient Characteristics	CRKP Infected Group (n=16)	Non-CRKP Infected Group (n=88)	t-test ^a / Chi Square tEst ^b / Mann-Whitney U-test ^c		Univariate Analysis		Multivariate Analysis	
			t/Chi Square/U	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
Median age, years, mean (standard deviation)	45.31 (13.40)	39.09 (12.91)	-1.742	0.085	1.039 (0.994–1.085)	0.088		
Male, Sex, n (percentage)	15 (93.75%)	64 (72.72%)	3.277	0.070	5.625 (0.704–44.930)	0.103		
Deceased donors, n (percentage)	15 (93.75%)	80 (90.90%)	0.138	0.710	1.500 (0.175–12.887)	0.712		
Diabetes mellitus, n (percentage)	4 (25.00%)	14 (15.90%)	0.782	0.377	1.762 (0.496–6.259)	0.381		
Hypertension, n (percentage)	16 (100%)	82 (93.18%)	1.158	0.282	-	0.999		
Types of dialysis, n (percentage)								
Hemodialysis	9 (56.25%)	74 (84.09%)	6.512	0.011	0.243 (0.078–0.761)	0.015	0.310 (0.039–2.467)	0.268
Peritoneal dialysis	5 (31.25%)	9 (10.23%)	5.136	0.023	3.990 (1.129–14.096)	0.032	2.410 (0.247–23.489)	0.449
None	2 (12.50%)	5 (5.68%)	1.003	0.317	2.371 (0.418–13.441)	0.329		
Length of dialysis time, months, median (IQR)	12 (4, 18.5)	12 (6.25, 24)	1.085	0.280	0.979 (0.941–1.018)	0.279		
Mean dosage of methylprednisolone, mg/kg, mean (standard deviation)	29.16 (6.32)	31.41 (9.34)	0.869	0.387	0.970 (0.904–1.039)	0.384		
Anti-thymocyte globulin, n (percentage)	8 (50.00%)	32 (36.36%)	1.554	0.213	2.000 (0.663–6.029)	0.218		
Mean dosage of anti-thymocyte globulin, mg/kg, median (IQR)	0 (0, 1.00)	0 (0, 1.34)	-	0.491	1.130 (0.647–1.975)	0.667		
Basiliximab, n (percentage)	15 (93.75%)	77 (87.50%)	0.518	0.472	2.143 (0.257–17.862)	0.481		
Sirolimus, n (percentage)	3 (18.75%)	15 (17.05%)	0.078	0.781	1.217 (0.306–4.845)	0.781		
Delayed graft function, n (percentage)	5 (31.25%)	12 (13.64%)	3.072	0.080	2.879 (0.850–9.750)	0.089		
Acute rejection, n (percentage)	1 (6.25%)	4 (4.55%)	0.086	0.769	1.400 (0.146–13.405)	0.770		
Possible donor derived infection, n (percentage)	5 (31.25%)	7 (7.96%)	7.198	0.007	5.260 (1.420–19.476)	0.013	6.743 (1.477–30.786)	0.014
Admission to ICU, n (percentage)	4 (25.00%)	6 (6.82%)	5.150	0.023	4.556 (1.120–18.524)	0.034	3.984 (0.742–21.408)	0.107
Multi-focal infections, n (percentage)	11 (68.75%)	22 (25.00%)	11.962	0.001				
Multi-pathogen infections, n (percentage)	10 (62.50%)	25 (28.41%)	7.047	0.008				

(Continued)

Table 1 (Continued).

Patient Characteristics	CRKP Infected Group (n=16)	Non-CRKP Infected Group (n=88)	t-test ^{a/} Chi Square tEst ^{b/} Mann–Whitney U-test ^c		Univariate Analysis		Multivariate Analysis	
			t/Chi Square/U	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
Types of infection, n (percentage)								
Bloodstream infection	5 (31.25%)	13 (14.77%)	2.568	0.109				
Surgical site infection	12 (75.00%)	50 (56.82%)	1.859	0.173				
Urinary tract infection	11 (68.75%)	48 (54.54%)	1.113	0.291				
Pneumonia	3 (18.75%)	7 (7.96%)	1.815	0.178				
Unfavorable clinical outcomes, n (percentage) ^c	9 (56.25%)	5 (5.68%)	29.718	<0.001				
Recurrence after cure of infection	7 (43.75%)	5 (5.68%)	19.222	<0.001				
Renal allograft loss	5 (31.25%)	1 (1.14%)	22.583	<0.001				
Death	2 (12.50%)	1 (1.14%)	6.241	0.012				

Notes: Data are presented in terms of mean±standard deviation, median and interquartile range (IQR) or the numbers of individuals with the percentage of the population. ^aComparison of the continuous variables in terms of mean±standard deviation were performed using two-sample t-test; ^bComparison of the categorical variables were performed using the chi-squared test; ^cComparison of the continuous variables in terms of median and IQR were performed using Mann-Whitney U-test.

occurrence of CRKP infection after KT ($P < 0.05$). The multivariate logistic regression analysis showed that possible DDI (OR = 6.743; 95% CI: 1.477–30.786; $P = 0.014$) was an independent risk factor for the occurrence of CRKP infection after KT.

Clinical Features and Analysis of Risk Factors Affected to the Clinical Outcomes of Infected Renal Recipients

Of the 104 recipients infected with multiple pathogens, three cases died within 6 months after KT, recurrence of the same pathogen strain after the cure of infection were recorded in 12 cases, 6 cases developed renal allograft loss, 14 cases developed unfavorable clinical outcomes after KT, the rate of overall unfavorable outcomes in the infected cases was 13.5%. The chi-squared test showed that there were significant differences in DGF ($p = 0.004$), ICU admission ($P = 0.010$), multi-focal infections ($P < 0.001$), multi-pathogen infections ($P < 0.001$), types of infection ($P < 0.05$) and CRKP infection ($P < 0.001$) between infected renal recipients with favorable outcomes group and infected recipients with unfavorable outcomes group. A univariate logistic regression analysis showed that the potential risk factors for unfavorable clinical outcomes after KT were DGF, BSI, SSI, UTI, pneumonia, multifocal infection, multipathogen infection, admission to ICU, and CRKP infection. The multivariate logistic regression analysis showed that CRKP infection (OR = 20.723; 95% CI: 3.448–124.547; $P = 0.001$) and pneumonia (OR = 28.458; 95% CI: 1.956–413.984; $P = 0.014$) were independent risk factors for the occurrence of unfavorable clinical outcomes after KT (Table 2).

Clinical Features for Patients with Clinical Outcomes in Renal Recipients with CRKP Infection

An anti-infection regimen of ceftazidime was routinely administered to the renal recipients who received deceased donor kidney transplantation. After CRKP was detected in the clinical specimens, the anti-infection regimen was adjusted according to the drug susceptibility results. 6 cases received antibiotic regimen containing tigecycline, 4 patients among

Table 2 Clinical Features and Risk Factors Analysis for Patients with Unfavorable Clinical Outcomes in 104 Renal Recipients with Early Infection

Patient Characteristics	Unfavourable Outcomes (n=14)	Favourable Outcomes (n=90)	t-test ^a / Chi Square test ^b / Mann-Whitney U-test ^c		Univariate Analysis		Multivariate Analysis	
			t/Chi Square/U	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
Median age, years, mean (standard deviation)	40.43 (14.42)	39.99 (13.20)	-0.115	0.909	1.003 (0.961–1.046)	0.908		
Male, Sex, n (percentage)	12 (85.71%)	67 (74.44%)	0.843	0.359	2.060 (0.428–9.901)	0.367		
Deceased donors, n (percentage)	13 (92.86%)	82 (91.11%)	0.047	0.829	1.268 (0.146–10.993)	0.829		
Diabetes mellitus, n (percentage)	2 (14.29%)	16 (17.78%)	0.103	0.748	0.771 (0.157–3.786)	0.749		
Hypertension, n (percentage)	13 (92.86%)	85 (94.44%)	0.056	0.813	0.765 (0.083–7.076)	0.813		
Types of dialysis, n (percentage)								
Hemodialysis	9 (64.29%)	74 (82.22%)	2.419	0.120	0.389 (0.115–1.318)	0.129		
Peritoneal dialysis	2 (14.29%)	12 (13.33%)	0.009	0.923	1.083 (0.215–5.450)	0.923		
None	3 (21.43%)	4 (4.44%)	5.567	0.018	5.864 (1.157–29.724)	0.033		
Length of dialysis time, months, median (IQR)	12 (5.5, 12.75)	12 (6, 24)	-	0.553	0.987 (0.953–1.022)	0.452		
Mean dosage of methylprednisolone, mg/kg, mean (standard deviation)	30.82 (13.04)	31.14 (8.41)	0.116	0.908	0.996 (0.930–1.066)	0.907		
Anti-thymocyte globulin, n (percentage)	7 (50.00%)	33 (36.67%)	1.411	0.235	2.015 (0.624–6.504)	0.241		
Mean dosage of anti-thymocyte globulin, mg/kg, median (IQR)	0.42 (0, 1.10)	0 (0, 1.36)	-	0.346				
Basiliximab, n (percentage)	12 (85.71%)	80 (88.89%)	0.120	0.729	0.750 (0.146–3.847)	0.730		
Sirolimus, n (percentage)	3 (21.43%)	15 (16.67%)	0.324	0.569	1.500 (0.368–6.109)	0.571		
Delayed graft function, n (percentage)	6 (42.86%)	11 (12.22%)	8.315	0.004	5.386 (1.571–18.468)	<0.01	1.000(0.119–8.418)	1.000
Acute rejection, n (percentage)	1 (7.14%)	4 (4.44%)	0.193	0.661	1.654 (0.171–15.970)	0.664		
Multi-focal infections, n (percentage)	12 (85.71%)	21 (23.33%)	21.764	<0.001	19.714 (4.083–95.199)	<0.001	1.173 (0.004–367.490)	0.957
Multi-pathogen infections, n (percentage)	11 (78.57%)	24 (26.67%)	14.618	<0.001	10.083 (2.590–39.263)	0.001	0.543 (0.002–132.797)	0.828

(Continued)

Table 2 (Continued).

Patient Characteristics	Unfavourable Outcomes (n=14)	Favourable Outcomes (n=90)	t-test ^a / Chi Square test ^b / Mann–Whitney U-test ^c		Univariate Analysis		Multivariate Analysis	
			t/Chi Square/U	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
Types of infection, n (percentage)								
Bloodstream infection	6 (42.86%)	12 (13.33%)	7.379	0.007	4.875 (1.438–16.522)	0.011	2.709 (0.295–24.865)	0.378
Surgical site infection	13 (92.86%)	49 (54.44%)	7.425	0.006	10.878(1.365–86.706)	0.024	15.588 (0.442–550.231)	0.131
Urinary tract infection	12 (85.71%)	47 (52.22%)	5.536	0.019	5.489 (1.162–25.942)	0.032	7.024 (0.234–211.036)	0.262
Pneumonia	5 (35.71%)	5 (5.56%)	12.680	<0.001	9.444 (2.289–38.966)	<0.01	28.458 (1.956–413.984)	0.014
Possible donor derived infection, n (percentage) ^c	3 (21.43%)	9 (10.00%)	1.550	0.213	2.455 (0.575–10.469)	0.225		
Admission to ICU, n (percentage)	4 (28.57%)	6 (6.67%)	6.689	0.010	5.600 (1.347–23.283)	0.018	1.938 (0.145–25.834)	0.617
CRKP infection	9 (64.29%)	7 (7.78%)	29.718	<0.001	21.343 (5.600–81.345)	<0.001	20.723 (3.448–124.547)	0.001

Notes: Data are presented in terms of mean±standard deviation, median and interquartile range (IQR) or the numbers of individuals with the percentage of the population.

^aComparison of the continuous variables in terms of mean±standard deviation were performed using two-sample t-test; ^bComparison of the continuous variables in terms of median and IQR were performed using Mann–Whitney U-test; ^cComparison of the categorical variables were performed using the chi-squared test.

these 6 cases received regimen of tigecycline and meropenem, 5 cases received antibiotic regimen of polymyxin B and fosfomycin, 4 patients received CZA, and 1 case was treated with aztreonam based on the result that CRKP strain is sensitive to aztreonam, the remaining 1 case underwent surgical debridement of abdominal wound without any antibiotic treatment. 9 patients eventually recovered without any unfavorable outcomes, event of renal graft loss occurred in 5 patients and death occurred in 2 patients. 7 patients presented recurrence after cure of infection. Significant differences were observed in the use of CZA between CRKP infected renal recipients with favorable outcomes group and with unfavorable outcomes group (chi-square test, $P = 0.009$). The same result was also found in the comparison between recipients with recurrence after cure of infection subgroup and without recurrence after cure of infection subgroup ($p = 0.042$). While no significant difference was observed in the antibiotic regimens of tigecycline and meropenem or containing polymyxin ($P > 0.05$) (Table 3).

Correlation Analysis of Clinical Characteristics, Antibiotic Regimens, CRKP Infection and Unfavorable Clinical Outcomes

The correlation analysis results (Table 4) of clinical characteristics and CRKP infection showed that multi-focal infections ($r = 0.339$; $P < 0.001$) and multi-pathogen infections ($r = 0.260$; $P = 0.008$) were significantly related to CRKP infection, but there were no significant correlation between age ($P = 0.085$), sex ($P = 0.071$) and CRKP infection. The correlation analysis results of clinical characteristics, antibiotic regimens, CRKP infection and unfavorable clinical outcomes showed that antibiotic regimen containing CZA ($r = -0.655$; $P = 0.006$), CRKP infection ($r = 0.535$; $P < 0.001$), multi-focal infections ($r = 0.457$; $P < 0.001$) and multi-pathogen infections ($r = 0.375$; $P < 0.001$) were significantly related to occurrence of unfavorable clinical outcomes, but there were no significant correlation between age ($P = 0.909$), sex ($P = 0.363$), antibiotic regimen containing tigecycline and meropenem ($P = 0.417$) and antibiotic regimen containing polymyxin B ($P = 0.223$) and occurrence of unfavorable clinical outcomes.

Discussion

Since CRKP was first reported in 2001,³ the multidrug-resistant (MDR) gram-negative bacterial strain has spread globally. In addition, the incidence of CRKP infection has gradually increased over the past decade²⁰ and emerged as

Table 3 Clinical Characteristics and Antibiotic Regimens in 16 Renal Recipients with CRKP Infection

Patient Characteristics	Recurrence After Cure of Infection		t-test ^a /Chi Square test ^b		Unfavourable Outcomes		T/Chi Square test	
	Yes (n=7)	No (n=9)	t/Chi Square value	P-value	Yes (n=9)	No (n=7)	T/Chi Square value	P-value
Median age, years, mean (standard deviation)	41.43 (15.84)	48.33 (13.30)	0.948	0.359	43.22 (14.28)	48.00 (15.21)	0.646	0.529
Male, Sex, n (percentage)	6 (85.71%)	9 (100%)	1.371	0.242	8(88.89%)	7 (100%)	0.830	0.362
Deceased donors, n (percentage)	6 (85.71%)	9 (100%)	1.371	0.242	8(88.89%)	7 (100%)	0.830	0.362
Diabetes mellitus, n (percentage)	2 (28.57%)	2 (22.22%)	0.085	0.771	2 (22.22%)	2 (28.57%)	0.085	0.771
Hypertension, n (percentage)	7 (100%)	9 (100%)	-	-	9 (100.00%)	7 (100%)	-	-
Types of dialysis, n (percentage)								
Hemodialysis	5 (71.43%)	4 (44.44%)	1.165	0.280	5 (55.56%)	4 (57.14%)	0.004	0.949
Peritoneal dialysis	1 (14.29%)	4 (44.44%)	1.667	0.197	2 (22.22%)	3 (42.86%)	0.780	0.377
None	1 (14.29%)	1 (11.11%)	0.036	0.849	2 (22.22%)	0 (0%)	1.778	0.182
Length of dialysis time, months, mean (standard deviation)	14.43 (16.94)	15.29 (8.73)	-0.119	0.907	13.50 (9.53)	16.67 (17.39)	0.438	0.669
Mean dosage of methylprednisolone, mg/kg, mean (standard deviation)	25.76 (7.67)	31.72 (3.84)	1.916	0.079	27.07 (7.82)	31.26 (3.90)	1.268	0.229
Anti-thymocyte globulin, n (percentage)	4 (57.14%)	4 (44.44%)	0.077	0.782	5 (55.56%)	3 (42.86%)	0.579	0.447
Basiliximab, n (percentage)	6 (85.71%)	9 (100%)	1.371	0.242	8 (88.89%)	7 (100%)	0.830	0.362
Sirolimus, n (percentage)	1 (14.29%)	2 (22.22%)	0.069	0.792	1 (11.11%)	2 (28.57%)	0.603	0.438
Delayed graft function, n (percentage)	3 (42.86%)	2 (22.22%)	0.780	0.377	4 (44.44%)	1 (14.29%)	1.667	0.197
Acute rejection, n (percentage)	1 (14.29%)	0 (0%)	1.371	0.242	1 (11.11%)	0 (0%)	0.830	0.362
Possible donor derived infection, n (percentage)	2 (28.57%)	3 (33.33%)	0.042	0.838	2 (22.22%)	3 (42.86%)	0.780	0.377
Admission to ICU, n (percentage)	3 (42.86%)	1 (11.11%)	2.116	0.146	4 (44.44%)	0 (0%)	4.148	0.042
Antibiotic regimen containing tigecycline and meropenem, n (percentage)	1 (14.29%)	3 (33.33%)	0.762	0.383	3 (33.33%)	1 (14.29%)	0.762	0.383
Antibiotic regimen containing polymyxin B, n (percentage)	3 (42.86%)	2 (22.22%)	0.780	0.377	4 (44.44%)	1 (14.29%)	1.667	0.197
Antibiotic regimen containing ceftazidime/avibactam, n (percentage)	0 (0%)	4 (44.44%)	4.148	0.042	0 (0%)	4 (57.14%)	6.857	0.009

Notes: Data are presented in terms of mean±standard deviation or the numbers of individuals with the percentage of the population. ^aComparison of the continuous variables in terms of mean±standard deviation were performed using two-sample t-test; ^bComparison of the categorical variables were performed using the chi-squared test.

one of the most common opportunistic infections causing lethal events in SOT recipients in recent years.⁶ CRKP infection has also attracted worldwide attention given its characteristics of multidrug resistance, high transmissibility, and elevated mortality.²¹ The proportion of CRKP isolates in KP strains was reported to have steadily increased from 10.8% in 2012 to 17.9% in 2016. In addition, the resistance rate of *K. pneumoniae* strains to imipenem and meropenem rose steadily from 3.0% and 2.9% in 2015 to 20.9% and 24.0% in 2016 based on the China Antimicrobial Surveillance Network (CHINET) data. Due to a lack of appropriate antibiotics and immunosuppression of SOT recipients, a CRKP infection is more difficult to control once it occurs in SOT recipients compared with the immunocompetent population.

Table 4 Correlation Analysis of Clinical Characteristics, Antibiotic Regimens, CRKP Infection and Unfavorable Clinical Outcomes in 104 Renal Recipients with Early Infection

Patient Characteristics	CRKP Infection		Unfavorable Clinical Outcomes	
	r	P	r	p
Age	0.170	0.085	0.011	0.909
Sex	0.178	0.071	0.090	0.363
Multi-focal infections	0.339	<0.001	0.457	<0.001
Multi-pathogen infections	0.260	0.008	0.375	<0.001
Antibiotic regimen containing tigecycline and meropenem	-	-	0.218	0.417
Antibiotic regimen containing polymyxin B	-	-	0.323	0.223
Antibiotic regimen containing ceftazidime/avibactam			-0.655	0.006
CRKP infection	1	-	0.535	<0.001

Notes: Correlation analysis of the categorical variables were performed using Pearson correlation analysis.

A CRKP infection typically presents with devastating effects, including sepsis, allograft nephrectomy, and death. The mortality rate of CRKP infection in SOT recipients was estimated to be close to 43%, which poses substantial challenges to both clinicians and patients. The epidemiology, clinical characteristics, and treatment experiences (to some extent) of CRKP infection have been previously described. We conducted this study to estimate the incidence and risk factors for developing CRKP infection after KT, assess our treatment experiences of CRKP infection in this population, as well as to determine the risk factors that affect the clinical outcome of infected renal recipients.

It has previously been reported that the prevalence of CRKP infection ranged from 3% to 11.2%,^{7,15} and variables (eg, DGF, diabetes, and mechanical ventilation [MV] > 48 h)^{22–24} have been identified as risk factors associated with CRKP infections in previous studies. In this study, there were 16 recipients who had CRKP infections, and the incidence of CRKP infection was 8.6%, which was consistent with the results of previous studies. However, a significant association between CRKP infection with factors, including DGF, diabetes were not demonstrated in our analysis. Instead, only factor of possible DDI was found to be statistically significant in univariate and multivariate analysis, indicating that possible DDI associated with a higher risk of CRKP infection in the cases we included. The finding can be explained by the high incidence of possible donor-derived CRKP infection in our study. The incidence in our centre was 31.25% (5/16), which is higher than that in other study.²⁵

In our study, multi-focal infections ($r = 0.339$; $P < 0.001$) and multi-pathogen infections ($r = 0.260$; $P = 0.008$) were significantly related to CRKP infection, and multi-focal infections ($r = 0.457$; $P < 0.001$) and multi-pathogen infections ($r = 0.375$; $P < 0.001$) were also significantly related to occurrence of unfavorable clinical outcomes, suggesting that the occurrence of CRKP infection is usually accompanied by multi-pathogen infections and multi-focal infections. We should not ignore other types of infection while treating CRKP infection. There were nine CRKP infected cases that developed unfavorable clinical outcomes at the rate of 56.3%, and four cases presented with ≥ 2 clinical outcome events. Being consistent with previous study,^{24,26,27} the occurrence of unfavorable clinical outcomes following KT was significantly associated with factor of CRKP infection ($r = 0.535$; $P < 0.001$), suggesting that CRKP infection may be the cause of poor prognosis in the early infected renal recipients in our research. But unlike previous research results, pneumonia was also an independent risk factor for unfavorable clinical outcomes following KT. A possible reason for this result is that when a patient develops pneumonia during the early period after KT, especially the primary manifestation of infection is SSI, UTI rather than pneumonia, it usually means the occurrence of severe infection or deterioration of the condition, which increases the risk of unfavorable clinical outcomes.

Out of the total of 16 cases with CRKP infection in our study, 7 patients presented recurrence after cure of infection, the incidence of infection relapse was 43.75%. Many factors may contribute to the recurrence of CRKP infection after cure in the previous report, such as the use of immunosuppressive regimen, failed antibacterial treatment, ineffective control of infection

source, and the adaptability of pathogen strains to host environment,¹⁵ while there are very limited studies on the analysis of the factors that influence the recurrence of CRKP infection after cure. Based on our research results (Table 3), demographic and clinical characteristics of the CRKP infected patients with unfavorable outcomes (especially the event of recurrence after cure) and CRKP infected patients with favorable outcomes were similar. In terms of the use of tigecycline combined with meropenem or polymyxin B, no significant difference between these groups was observed, and there were no significant statistical correlation between antibiotic regimen containing tigecycline combined with meropenem ($P = 0.417$) and antibiotic regimen containing polymyxin B ($P = 0.223$) and occurrence of unfavorable clinical outcomes. CRKP isolates are prone to drug resistance following long-term antibiotic treatment, even with a beneficial inhibitory or sterilization effect.^{28,29} Which reminds us that in addition to the adequate duration of antibiotics treatment, it is also vital to timely adjust the regimen in clinical practice. The use of CZA was significantly different in the comparison of antibiotic regimens between these groups, and antibiotic regimen containing CZA ($r = -0.655$; $P = 0.006$) was also significantly correlated with the occurrence of unfavorable clinical outcomes, demonstrated that CZA may play a role in improving the prognosis of patients, as a potential protective factor against the unfavorable outcomes. The promising efficacy of CZA, usually selected as salvage treatment, for the control of CRKP infection were also observed in the previous reports.^{25,30,31}

The present study has some limitations. The total sample size of CRKP-infected cases was limited, and this retrospective study was conducted at a single institute; thus, the conclusions reached may not be applicable to other institutions. In the comparison of factors for clinical outcomes of CRKP infected renal recipients, univariate and multivariate analysis cannot be performed to evaluate risk factor for occurrence of unfavorable outcomes; Larger prospective multicenter studies are required to better inform our understanding of the epidemiological risk factors, clinical prognosis, and management strategy of CRKP infection in KT recipients.

Conclusions

CRKP infection may be primarily caused by possible DDI in our study. Moreover, CRKP infection and pneumonia were identified as independent risk factors for the occurrence of unfavorable clinical outcomes in early infected renal recipients. The use of CZA may play a role in improving the prognosis of CRKP infected recipients.

Abbreviations

CRKP, carbapenem-resistant *Klebsiella pneumoniae*; KP, *Klebsiella pneumoniae*; SOD, solid organ transplant; KT, kidney transplantation; BSI, bloodstream infection; SSI, surgical site infection; UTI, urinary tract infection; DDI, donor-derived infection; DGF, delayed graft function; CZA, ceftazidime-avibactam.

Ethics Approval and Consent to Participate

The study protocol was approved by the Ethics Committee of Beijing Friendship Hospital and was conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent has been provided by the patients to have the case details and any accompanying images published.

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Disclosure

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