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Treatment of Donor-derived Carbapenem-resistant *Klebsiella pneumoniae* Infection after Renal Transplantation with Tigecycline and Extended-infusion Meropenem*

Zhi-qiang WANG[1], Zhi-liang GUO[1], Hao FENG[1], Cheng FU[1], Guang-yuan ZHAO[1], Ke MA[2], Lan ZHU[1, 3#], Gang CHEN[1, 3#]
[1]*Institute of Organ Transplantation, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430030, China*
[2]*Department of Infectious Disease, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430030, China*
[3]*Key Laboratory of Organ Transplantation, Ministry of Education, Ministry of Public Health, Chinese Academy of Medical Sciences, Wuhan 430030, China*

[Abstract] Objective: Donor-derived carbapenem-resistant *Klebsiella pneumoniae* (CRKP) infection has recently emerged as a critical early complication after renal transplantation. Although CRKP is usually sensitive to tigecycline, monotherapy with this drug is often less than effective. We investigated the efficacy of a combined regimen of tigecycline with high-dose, extended-infusion meropenem in the treatment of donor-derived CRKP infection after kidney transplantation. **Methods:** From Jan. 2016 to Dec. 2017, a total of 12 CRKP isolates were detected from cultures of the organ preservation solution used for soaking the donor kidneys at our institute. Probable or possible donor-derived infection (DDI) was identified in 8 transplant recipients. Clinical data were retrospectively analyzed. **Results:** *Klebsiella pneumoniae* carbapenemase-2 (KPC-2)-producing CRKP was reported to be positive in organ preservation solution cultures at 3.5±0.9 days after transplantation, leading to surgical site (n=3), urinary tract (n=4), and/or bloodstream (n=2) infections in 8 recipients. The drug susceptibility tests showed that CRKP was sensitive to tigecycline, but resistant to meropenem. In 7 patients who received tigecycline combined with high-dose extended-infusion meropenem, DDIs were successfully cured. The length of hospital stay was 31 (18–129) days, and the serum creatinine at discharge was 105.8±16.7 μmol/L. The one remaining patient who received tigecycline combined with intravenous-drip meropenem died of septic shock. A median follow-up of 43 months (33–55) showed no recurrence of new CRKP infection in the 7 surviving recipients. **Conclusion:** It was suggested that a prompt and appropriate combination therapy using tigecycline with high-dose extended-infusion meropenem is effective in treating donor-derived KPC-2- producing CRKP infection after renal transplantation.
Key words: renal transplantation; donor-derived infection; carbapenem-resistant *Klebsiella pneumoniae*; tigecycline; meropenem

Solid-organ transplantation (SOT) is the preferred treatment for patients with end-stage organ failure. However, when organs from deceased donors are used, there is a risk of pathogen transmission during the transplantation process, which can lead to donor-derived infection (DDI)[1]. Although DDI has been significantly reduced through the microbiological screening of donors and the prophylactic use of antibiotics, it still occurs in a small number of recipients because of a failure to detect pathogens in the corresponding donors before organ procurement[2, 3]. DDI is usually more difficult to treat in transplant patients because of the high intensity of immunosuppressive therapy in the early stage after transplantation.

In recent years, carbapenem-resistant *Klebsiella pneumoniae* (CRKP) has become an emerging multi-drug-resistant Gram-negative bacterium. Given the limited treatment options, DDI caused by CRKP has become one of the most frequently fatal complications after deceased-donor organ transplantation[4]. Previous studies have reported a 3%–10% incidence of CRKP infection in SOT recipients, with a similar incidence

Zhi-qiang WANG, E-mail: wangzhiqiang891013@126.com
#Corresponding authors, Lan ZHU, E-mail: zhulan@tjh.tjmu.edu.cn; Gang CHEN, E-mail: gchen@tjh.tjmu.edu.cn
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after liver, kidney, lung, or heart transplantation[5]. A proven CRKP infection can have devastating effects on transplant recipients, including sepsis, allograft nephrectomy, and death, with a mortality rate of up to 40%[6, 7].

Prior to the approval of the new antibiotic combination of ceftazidime-avibactam (CZA) by the Food and Drug Administration (FDA), no randomized clinical study had highlighted any specific antibiotic regimen for CRKP infection. Although CRKP strains are usually susceptible to tigecycline, the clinical effects of tigecycline monotherapy in the treatment of CRKP infection are not satisfactory[8, 9]. Guidelines issued by the American Society of Transplantation recommend a combination of at least two types of the following antibiotics: colistin, tigecycline, aminoglycosides (if sensitive to the isolates), and high-dose, extended-infusion carbapenem[10]. Other studies have also shown that combined medication significantly improves the survival rate of patients when compared to monotherapy and emphasizes the importance of using carbapenem[11, 12]. In addition, double-carbapenem therapy has been reported to successfully treat CRKP infections[13]. The effect of tigecycline and carbapenem in the treatment of donor-derived CRKP infection after renal transplantation remains controversial. In this study, we have summarized our successful experience in treating early donor-derived CRKP infections after renal transplantation with tigecycline and high-dose extended-infusion meropenem.

1 MATERIALS AND METHODS

1.1 Patients and Samples

From Jan. 1, 2016 to Dec. 31, 2017, 766 patients underwent kidney transplantation from deceased donors in Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology. Urine, blood, and respiratory specimens were routinely collected for pathogen culture at the time of donor evaluation. All the kidney grafts were donated to the Red Cross Society of Hubei Province and allocated by the China Organ Transplant Response System. The study procedures were approved by the Ethics Committee at Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology and performed in accordance with the National Program of Organ Donation after Cardiac Death in China. Specimens of organ preservation solutions used for soaking the donor kidney were also sent for surveillance cultures at the time of transplantation. In recipients, the drainage from the surgical site was also collected daily for pathogen culture within 3 to 7 days after transplantation. Additional blood and urine samples were cultured when there was an indication of infection (i.e., fever or elevated white blood cell counts).

1.2 Microbiology

CRKP was identified by mass spectrometry, and drug susceptibility was tested by the disk diffusion method. The results were interpreted in reference to the M100-S27 standard issued by the Clinical and Laboratory Standards Institute. When resistance developed against meropenem and imipenem, an E test was used to determine the minimum inhibitory concentration (MIC). In addition, the β-lactamase genotypes of the CRKP strains were identified by polymerase chain reaction, followed by cloning and sequencing of the drug-resistance genes.

1.3 Definition of DDI

An international consensus has been reached on DDI[14]. DDI is mainly divided into the following types: (1) proven: clear evidence of the same infection disease in the donor and at least one of the recipients; (2) probable: strong evidence suggesting but not proving disease transmission; (3) possible: data suggest possible transmission, but are insufficient to fulfill the criteria for confirmed transmission (proven and/or probable), and transmission cannot be formally excluded; and (4) intervention without documented transmission: all or some of the recipients received an intervention (i.e., antimicrobial agent), and no disease was recognized in any of the recipients.

1.4 Anti-infection Regimen

In our hospital, the usual peri-operative antibiotic prophylaxis for deceased donor kidney transplantation in adult recipients is cefoperazone/sulbactam sodium [3 g, bid, intravenous (iv) drip] or meropenem (0.5 g, q12h, iv drip). Once CRKP was detected from the culture of an organ preservation solution and/or wound drainage fluid, the adult patient was immediately given a combined antibiotic regimen of tigecycline (50 mg, q12h, iv drip) and high-dose extended infusion of meropenem (1.0 g, q8h, iv pump for 3 h/dose). In addition, when the infection occurred in the surgical site and was difficult to heal, this regimen was supplemented with local antibiotic treatment and surgical debridement. For pediatric patients with body weight <50 kg, meropenem was given at the dose of 20 mg/kg, q8h. For pediatric patients with age <12 years old, tigecycline was given at a dose of 1.2 mg/kg, q12h.

The duration of the antibiotic treatment was based on the following criteria: (1) good toleration of the drugs without significant side-effects; (2) improved clinical and laboratory results; (3) administration for at least 2 weeks; (4) extended medication for 1 week until the negativity for CRKP was reached.

1.5 Immunosuppressive Regimen

Of the 8 recipients, 6 received induction therapy with rabbit anti-human thymocyte immunoglobulin, and 2 received baliximab. Methylprednisolone was administered to all the recipients at 500 mg/day for 3 consecutive days (day 0 to day 2). All recipients

also received triple maintenance immunosuppressive therapy with oral tacrolimus, mycophenolate mofetil (MMF), and methylprednisolone.

1.6 Data Collection

We retrospectively reviewed the characteristics of the donors and recipients, the results of microbial cultures and drug susceptibility tests, the type and manifestations of DDI, the anti-infective treatments, and the clinical outcomes (the hospital stay, recurrence of infection, the survival of kidney grafts and recipients). The follow-up data were monitored until Aug. 1, 2020.

1.7 Statistical Analysis

The data were expressed as numerical values for categorical variables. Continuous variables were presented as mean values with standard deviation (SD) if normally distributed, and as median and range in cases of non-normal distribution. Statistical analysis was performed using STATA, version 15.1 (StataCorp LLC, USA).

2 RESULTS

2.1 General Clinical Characteristics of Donors and Recipients

A total of 17 *Klebsiella pneumoniae* isolates were detected from organ preservation solution cultures in this cohort, of which 12 were CRKP. Among these 12 recipients, 8 had confirmed transmission and were enrolled in present study; the other 4 received pre-emptive intervention, and no disease transmission was recognized. The clinical characteristics of the recipients and donors are listed in table 1. The kidney grafts of the 8 recipients were from 6 deceased donors, including 4 adult donors and 2 pediatric donors with a median age of 39 years (2 months to 56 years). The causes of death were cerebral hemorrhage (3 cases), brain trauma (2 cases), and neonatal asphyxia (1 case). The length of hospital stay in the intensive care unit was 10±5.0 days for the donors. The blood and urine cultures of all donors were negative before organ procurement. The mean cold ischemia time for the donor kidneys was 6.6±3.1 h.

There were 7 adults and one pediatric patient in the recipient population, with an average age of 37.0±15.7 years. The primary diseases in these patients were chronic glomerulonephritis (4 cases), IgA nephropathy (2 cases), nephrotic syndrome (one case), and nephroblastoma (one case). The preoperative assessments of panel reactive antibodies were negative, and complement-dependent cytotoxicity tests were <10%. Before transplantation, all recipients were in stable condition, without recent fever or other symptoms of acute illness. Six recipients underwent single kidney transplantation, and the remaining one adult and one child received dual kidney transplantation with small pediatric kidneys.

2.2 Microbial Culture and Drug Susceptibility

CRKP was first reported in surveillance cultures from organ preservation solution at 3.5±0.9 days after renal transplantation. Four patients (R3, R4, R5, R6) developed probable DDI, because the same CRKP isolates were also found in cultures from another recipient whose transplant came from the same donor. In contrast, the DDI in 4 recipients (R1, R2, R7, R8) could only be categorized as possible infection because there was a lack of evidence of a corresponding infection in the donor or the contralateral renal graft (table 1). According to the infection site, 3 recipients (R3, R5, R8) had surgical site infection alone, 2 had simultaneous surgical site and urinary tract infection (UTI) (R6, R7), one had late UTI (R2), one had an early bloodstream infection (BSI) (R4), and one had delayed BSI as well as a UTI that required re-admission (R1) (table 1).

Table 1 Clinical characteristics of donors and kidney transplant recipients with KPC-2-producing Klebsiella pneumoniae infection

Donors				Recipients							
Case number	Age/ sex	Cause of death	ICU stay (days)	Case number	Age/ sex	Positive organ preservation solution culture	Positive drainage culture	Positive blood culture	Positive urine culture	First positive culture (days post-Tx)	DDI type
D1	56 y/M	Cerebral hemorrhage	5	R1[a]	54 y/M	Y	Y	N	N	5	Possible
				R1[b]		/	/	Y	Y	28 (recurrence)	
D2	33 y/M	Brain trauma	12	R2[a]	44 y/M	Y	Y	/	N	3	Possible
				R2[b]		/	/	/	Y	52 (recurrence)	
D3	49 y/M	Cerebral hemorrhage	19	R3	18 y/F	Y	Y	N	N	4	Probable
				R4		Y	Y	Y	/	3	
D4	45 y/M	Brain trauma	9	R5	32 y/M	Y	Y	/	N	4	Probable
				R6		Y	Y	/	Y	3	
D5	3 m/M	Neonatal asphyxia	8	R7	42 y/F	Y	Y	N	Y	4	Possible
D6	2 m/M	Cerebral hemorrhage	7	R8	11 y/F	Y	Y	N	N	2	Possible

D, donor; DDI, donor-derived infection; F, female; m, months; M, male; N, no; R, recipient; Tx, transplantation; y, years; Y, yes; [a]first admission; [b]re-admission

KPC-2 was the only resistance gene detectable in any of the CRKP isolates. The drug susceptibility tests for CRKP showed that the infection was sensitive to tigecycline but resistant to meropenem (table 2).

2.3 Anti-infection Treatment

Except for the initial course of agent in the first recipient (R1), who was on tigecycline monotherapy and developed a subsequent recurrence of DDI (including BSI and UTI), the remaining 9 infection events were treated with tigecycline combined with high-dose meropenem (table 3). The duration of treatment was 19.8±7.6 days for tigecycline and 21.9±5.9 days for meropenem. The only patient (R4) whose intravenous meropenem was not given via an extended infusion developed an uncontrollable CRKP-BSI and died as a result of septic shock on day 15 post-transplantation. In addition, 3 patients received topical medication, including one patient who underwent surgical debridement and vacuum sealing drainage (VSD). Moreover, prophylactic anti-fungal therapy was given in all recipients to prevent secondary infections.

2.4 Adjustment of Immunosuppressant

Tacrolimus was discontinued in R5 for one week because of acute liver failure but was maintained in the other 7 recipients, with a trough concentration of 6–8 ng/mL within one month after transplantation. The dose of MMF was reduced by one-half during the course of the infection.

2.5 Outcomes of Renal Grafts and Recipients

Except for the one patient (R4) who died at 15th day after transplantation, the remaining 7 patients receiving high-dose extended-infusion meropenem with tigecycline recovered, with excellent kidney graft function. Two patients were re-admitted because of a recurrence of CRKP infection, but both successfully treated. The median length of hospital stay was 31 (18–129) days, and the average serum creatinine was 105.8±16.7 μmol/L at discharge (table 3). After a median follow-up of 43 (range, 33–55) months, the graft function remained normal in the 7 recipients, and there were no recurrent episodes of CRKP infection.

2.6 Special Cases

Case 1 (R1): This was the first case of KPC-2-producing CRKP detected in cultures of the organ

Table 2 Susceptibility profile of KPC-2-producing *Klebsiella pneumoniae* isolates from kidney transplant recipients

Antimicrobial agents	MIC value (μg/mL) or disk-diffusion halo (mm)[c]									
	R1[a]	R1[b]	R2[a]	R2[b]	R3	R4	R5	R6	R7	R8
Tigecycline	16[S]	16[S]	20[S]	19[S]	19[S]	19[S]	19[S]	19[S]	20[S]	19[S]
Imipenem	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32
Meropenem	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32
Cefoperazone/sulbactam	6	6	6	6	6	6	6	6	6	6
Piperacillin/tazobactam	6	6	6	6	6	6	6	6	6	6
Cefotaxime	6	6	6	6	6	6	6	6	6	6
Levofloxacin	6	6	6	6	6	6	6	6	6	6
Amikacin	6	6	6	6	6	6	6	6	6	6
Gentamicin	6	6	6	6	6	6	6	6	6	6
Ceftazidime	6	6	6	6	6	6	6	6	6	6
Cotrimoxazole	13[I]	17[S]	6	6	26[S]	26[S]	24[S]	15[I]	19[S]	24[S]
Minocycline	/	/	/	/	/	/	18[S]	19[S]	/	19[S]

MIC, minimum inhibitory concentration; [S]sensitive; [I]intermediate; [a]first admission; [b]re-admission; [c]The results for meropenem and imipenem were determined by MIC, and other drug-susceptibility results were determined by disk-diffusion halo.

Table 3 Anti-infective treatments and transplant outcomes

Case number	DDI type	Treatment duration (days)			Other treatments	Hospital stay (days)	Serum creatinine at discharge (μmol/L)	Outcome
		Tigecycline	Meropenem	Other combined antibiotics (days)				
R1[a]	Possible	6	None	None		21	102	Recovered
R1[b]		18	16	Cotrimoxazole (23)		28	122	Recovered
R2[a]	Possible	13	24	None		31	104	Recovered
R2[b]		8	18	Fosfomycin (18)		18	112	Recovered
R3	Probable	34	19	Polymyxin (5)	Surgical debridement +VSD +Topical medication	129	133	Recovered
R4	Probable	18	15	none		18	/	Death
R5	Probable	22	25	Minocycline (16)		30	75	Recovered
R6	Probable	25	25	Minocycline (22) Fosfomycin (16)	Topical medication	33	99	Recovered
R7	Possible	25	34	None	Topical medication	47	111	Recovered
R8	Possible	16	21	Minocycline (2)		63	94	Recovered

[a]first admission; [b]re-admission; DDI, donor-derived infection; VSD, vacuum sealing drainage

preservation solution and wound drainage specimens. He was given tigecycline (50 mg q12h, iv) for 6 days until no bacterial isolate could be cultured from the drainage fluid, blood, or urine. However, at only one week after discharge, the patient was re-admitted to the hospital with a sudden chill and high fever. The subsequent blood and urine cultures were both positive for CRKP. At this time, the patient was given high-dose extended-infusion meropenem with tigecycline. Three days later, the blood and urine cultures were negative, and the medication was continued for other 11 days. During this period, multiple blood and urine cultures were negative for CRKP.

Case 2 (R3): This was an 18-year-old female with the longest duration of CRKP infection and hospital stay in our study. After she had received the combined treatment with tigecycline and high-dose meropenem for 2 weeks, the regimen had to be discontinued because of a substantial increase in the serum level of total bilirubin (up to 284.9 μmol/L). The patient then received tigecycline monotherapy and extensive liver protection therapy. After the level of total bilirubin returned to normal, a significant peri-graft abscess appeared unexpectedly on day 32, and surgical debridement was thus performed. A culture of the peri-graft soft tissue was again CRKP-positive. The incision then had to be opened because of the progressive exacerbation of the localized suppurative infection. Topical debridement and dressing changes were performed daily; hydrogen peroxide and diluted iodophor were used to wash the peri-renal space, and it was smeared with sulfanilamide powder. On day 41, the patient had sudden chills and high fever, accompanied by a sharp increase in the level of C-reactive protein. After a treatment with polymyxin B (500 000 U, q12h), her body temperature gradually returned to normal. However, this drug was terminated after 5 days because of drug-related neurotoxicity and nephrotoxicity. The wound tissue culture eventually became negative on day 60 post-transplantation, and the infected tissue had been replaced by fresh granulation tissue. VSD was used to close the incision on days 70, 78, and 93, respectively. On day 107, the VSD was removed, and the incision was sutured successfully. During the whole course of the treatment, the renal graft function was temporarily impaired by the polymyxin B (serum creatinine increased from 80 to 220 μmol/L), but it gradually recovered after 1 month. The patient was discharged on day 129 with a serum creatinine level of 133 μmol/L.

3 DISCUSSION

Although the incidence of donor-derived CRKP infection is not high after renal transplantation, the prognosis is poor for such patients because of a lack of specific antibiotic treatment that often results in allograft nephrectomy or death. For example, Simkins *et al* have reported 13 patients with CRKP infection after renal transplantation: after treatment with polymyxin B, tigecycline, and aminoglycosides alone or in combination, 6 of their patients (46%) died, and 2 others (15%) lost their grafts[15]. Bergamasco *et al* have detailed the treatment and prognosis of CRKP infection in 5 recipients of deceased-donor kidney transplants. In their case, after treatment with imipenem (or meropenem) and polymyxin B alone or in combination, 3 (60%) of the recipients died within a month[6]. In China, Wang *et al* found 5 cases of early bloodstream CRKP infection after kidney transplantation. After treatment with meropenem and tigecycline, 4 of these patients died, and one survived but underwent graft resection[16].

In the present study, we have used a combined regimen of tigecycline and meropenem to treat early CRKP infection in 8 recipients after renal transplantation. Most of the patients were well tolerant to the combined antibiotic therapy. Seven patients who were given meropenem via high-dose extended infusion achieved satisfactory results. The remaining patient, who was given meropenem by iv drip, died of septic shock. There are several possible reasons for the better therapeutic effects of our treatment: (1) we administered high-dose meropenem by extended infusion (at least 3 h for each infusion); (2) we highlighted early detection and early intervention, in that the treatment of CRKP generally started at 3–4 days after transplantation; (3) we utilized local antibiotic treatment and surgical debridement when the CRKP infection occurred in the surgical site and was difficult to treat; and (4) we established a multi-disciplinary collaborative team for CRKP to develop and adjust the individual medication regimens.

Because our organ procurement organization normally does not accept a donation when a blood culture from the donor is CRKP-positive, we only very rarely see “proven DDI” in our system. Of the 8 cases observed in this study, 4 were diagnosed as “probable DDI”, and the rest 4 were diagnosed as “possible DDI”. In our opinion, as compared to “donor-derived CRKP infection” (CRKP-DDI), the concept of “graft-carried CRKP infection” is more extensive, including both CRKP-DDI and the accidental contamination of donor organs with CRKP during the process of organ procurement, preservation, transportation, and pre-operative preparation. This way, even if the diagnosis of “proven DDI” cannot be achieved in the absence of positive CRKP culture of donor blood, urine, or sputum specimens, the diagnosis of “graft-carried CRKP infection” can still be assigned as long as the organ preservation solution culture was CRKP-positive. In the present study, the culture of the preservation

solution used for soaking the donor kidney was found to be positive for CRKP in all 8 patients.

We found that this kind of graft-carried CRKP infection had the following characteristics: (1) the initial bacterial load was relatively small, and if effective drugs are given to the recipients at the time of early prophylactic antibiotic use after transplantation, bacterial reproduction can be controlled without progression to infection in the recipients. Therefore, it is very important to determine whether the graft-carried CRKP is positive and to choose effective anti-microbial prophylaxis. (2) After kidney transplantation, multiple factors in the transplant recipients may contribute to the proliferation of small amounts of bacteria carried by the transplanted kidney and the subsequent infection, including low immunity caused by intensive use of immunosuppressive agents, the presence of peri-operative hyperglycemia, and the use of non-sensitive antibiotic(s). (3) Generally, infection sites consisted of the surgical site, the urinary tract, the bloodstream, and even the lung, resulting in very serious incidents, such as renal artery rupture and graft removal, and even death. We recommend that given the high mortality associated with CRKP infection, a prompt and appropriate antibiotic combination therapy should be administered for at least 2 weeks. In the meantime, continuous monitoring of the cultures is essential to determine the duration of treatment. After the culture results turn negative, further consolidation therapy for 1–2 weeks is necessary to prevent possible recurrence of the infection.

In the present study, the CRKP strains of all 8 patients were susceptible to tigecycline; therefore, the use of tigecycline could inhibit rapid bacterial reproduction and reduce bacterial load. It has been reported that high-dose tigecycline monotherapy can successfully treat multi-drug-resistant bacterial infections[17, 18]; nevertheless, this monotherapy is rather difficult to implement in kidney transplant recipients. One of the reasons for this difficulty is that side effects of tigecycline are common, such as nausea, vomiting, elevated amylase levels, and abnormal liver function and coagulation; a high dose and prolonged course of tigecycline would be difficult for perioperative renal transplant recipients to tolerate. The second reason is that an interaction occurs between tigecycline and calcineurin inhibitors, which increases the number of side effects of the drugs, including cyclosporine-related nephrotoxicity, tacrolimus-related diarrhea, and acute pancreatitis[19, 20]. The third reason is that the recurrence rate of CRKP infection in immunosuppressed patients is as high as 40%[21], and the main pharmacological action of tigecycline is to inhibit bacterial protein synthesis rather than to exert a strong bactericidal effect. Therefore, it is difficult to effectively prevent CRKP recurrence with tigecycline monotherapy.

Although CRKP is resistant to meropenem, using high-dose extended-infusion of meropenem to treat CRKP may be effective because a portion of the drug first neutralizes the KPC-2 hydrolase produced by the bacteria, and after the hydrolase is exhausted, the remaining portion of the drug may exert a bactericidal effect on the CRKP. The combined use of ertapenem and a high-dose extended infusion of meropenem has been reported to be effective against a KPC-2-producing CRKP infection, with the possible explanation that ertapenem may neutralize the KPC-2 hydrolase first, so that the meropenem used later is no longer hydrolyzed[13].

At present, CZA, a novel combination of cephalosporin and β-lactamase inhibitor with special effects on CRKP, has been approved by the FDA[22]. Its use may simplify the treatment of CRKP. However, prior to the worldwide use of CZA, the combined regimen of tigecycline and high-dose extended-infusion meropenem used in this study provides an effective alternative for the treatment of donor-derived CRKP infection after kidney transplantation.

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Conflict of Interest Statement

All the authors declared no competing interests. The clinical activities being reported are consistent with the principles of the declaration of Istanbul as outlined in the "Declaration of Istanbul on Organ Trafficking and Transplant Tourism".

REFERENCES

1 Fishman JA, Grossi PA. Donor-derived infection--the challenge for transplant safety. Nat Rev Nephrol, 2014,10(11):663-672
2 Ison MG, Grossi P, AST Infectious Diseases Community of Practice. Donor-derived infections in solid organ transplantation. Am J Transplant, 2013,13(Suppl 4):22-30
3 Kaul DR. Donor-derived infection: epidemiology and outcomes. Curr Infect Dis Rep, 2012,14(6):676-682
4 Schwaber MJ, Carmeli Y. Carbapenem-resistant Enterobacteriaceae: a potential threat. JAMA, 2008, 300(24):2911-2913
5 Satlin MJ, Jenkins SG, Walsh TJ. The global challenge of carbapenem-resistant Enterobacteriaceae in transplant recipients and patients with hematologic malignancies. Clin Infect Dis, 2014,58(9):1274-1283
6 Bergamasco MD, Barroso Barbosa M, de Oliveira Garcia D, *et al*. Infection with Klebsiella pneumoniae carbapenemase (KPC)-producing K. pneumoniae in solid organ transplantation. Transpl Infect Dis, 2012, 14(2):198-205
7 Mularoni A, Bertani A, Vizzini G, *et al*. Outcome of Transplantation Using Organs From Donors Infected or Colonized With Carbapenem-Resistant Gram-Negative

Bacteria. Am J Transplant, 2015,15(10):2674-2682
8 Qureshi ZA, Paterson DL, Potoski BA, *et al*. Treatment Outcome of Bacteremia Due to KPC-Producing Klebsiella pneumoniae: Superiority of Combination Antimicrobial Regimens. Antimicrob Agents Chemother, 2012,56(4):2108-2113
9 Bai XR, Liu JM, Jiang DC, *et al*. Efficacy and safety of tigecycline monotherapy versus combination therapy for the treatment of hospital-acquired pneumonia (HAP): a meta-analysis of cohort studies. J Chemother, 2018,30(3):172-178
10 van Duin D, van Delden C, Practice ASTIDCo. Multidrug-resistant gram-negative bacteria infections in solid organ transplantation. Am J Transplant, 2013, 13(Suppl 4):31-41
11 Tumbarello M, Viale P, Viscoli C, *et al*. Predictors of mortality in bloodstream infections caused by Klebsiella pneumoniae carbapenemase-producing K. pneumoiae: importance of combination therapy. Clin Infect Dis, 2012,55(7):943-950
12 Qureshi ZA, Paterson DL, Potoski BA, *et al*. Treatment outcome of bacteremia due to KPC-producing Klebsiella pneumoniae: superiority of combination antimicrobial regimens. Antimicrob Agents Chemother, 2012,56(4):2108-2113
13 Souli M, Karaiskos I, Masgala A, *et al*. Double-carbapenem combination as salvage therapy for untreatable infections by KPC-2-producing Klebsiella pneumoniae. Eur J Clin Microbiol Infect Dis, 2017, 36(7):1305-1315
14 Garzoni C, Ison MG. Uniform definitions for donor-derived infectious disease transmissions in solid organ transplantation. Transplantation, 2011,27;92(12):1297-300
15 Simkins J, Muggia V, Cohen HW, *et al*. Carbapenem-resistant Klebsiella pneumoniae infections in kidney transplant recipients: a case-control study. Transpl Infect Dis, 2014,16(5):775-782
16 Wang Y, Lei H, Zhang Y, *et al*. Epidemiology of carbapenem-resistant Klebsiella pneumoniae bloodstream infections after renal transplantation from donation after cardiac death in a Chinese hospital: a case series analysis. Antimicrob Resist Infect Control, 2018, 7:66
17 Cunha BA, Baron J, Cunha CB. Monotherapy with High-Dose Once-Daily Tigecycline is Highly Effective Against Acinetobacter baumanii and other Multidrug-Resistant (MDR) Gram-Negative Bacilli (GNB). Int J Antimicrob Agents, 2018,52(1):119-120
18 Baron J, Cai S, Klein N, *et al*. Once Daily High Dose Tigecycline Is Optimal: Tigecycline PK/PD Parameters Predict Clinical Effectiveness. J Clin Med, 2018,9;7(3):49
19 Srinivas NR. Tigecycline and cyclosporine interaction-an interesting case of biliary-excreted drug enhancing the oral bioavailability of cyclosporine. Eur J Clin Pharmacol, 2009,65(5):543-544
20 Pavan M, Chaudhari AP, Ranganth R. Altered bioavailability of tacrolimus following intravenous administration of tigecycline. Am J Kidney Dis, 2011, 57(2):354
21 Bias TE, Malat GE, Lee DH, *et al*. Clinical outcomes associated with carbapenem resistant Klebsiella pneumoniae (CRKP) in abdominal solid organ transplant (SOT) recipients. Infect Dis, 2018,50(1):67-70
22 van Duin D, Lok JJ, Earley M, *et al*. Antibacterial Resistance Leadership G. Colistin Versus Ceftazidime-Avibactam in the Treatment of Infections Due to Carbapenem-Resistant Enterobacteriaceae. Clin Infect Dis, 2018,66(2):163-171

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