

# Ceftazidime-Avibactam as Salvage Treatment for Infections Due to Carbapenem-Resistant *Klebsiella pneumoniae* in Liver Transplantation Recipients

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**Background:** Ceftazidime-avibactam (CZA) has been approved in vitro activity against carbapenem-resistant *K. pneumoniae* (CRKP), but the experience for the treatment of CRKP in liver transplantation (LT) recipients was limited, and previous data on its efficacy in this setting are lacking.

**Methods:** LT recipients with CRKP infection who received CZA treatment were reviewed retrospectively, microbiological and clinical response, adverse events were also assessed. The primary outcome was 30-day mortality after CZA administration.

**Results:** CZA was used in 21 LT recipients (including 4 pediatric patients) with CRKP infections after failure with other antimicrobials. CZA was administered as monotherapy in 4 patients. Median time from the onset of CRKP infection until the initiation of CZA treatment was 2 days (IQR, 1–6.5), and the median treatment duration was 12 days (IQR, 8.5–18.5). The mortality at 14 days, 30 days and all-cause was 28.6%, 38.1% and 42.9%, respectively. In adult patients, clinical response of 14 days and 30 days was 70.6% (12/17) and 58.8% (10/17), respectively, while in pediatric patients the 14-day and 30-day clinical response were both 75%, respectively. The relapse rate during the treatment developed in 3 patients after 30 days with the cessation of CZA monotherapy. CZA resistance was not detected in any case and 3 (3/21, 14.3%) patients developed acute kidney injury related to uncontrolled infection.

**Conclusion:** CZA shows promising results, even in monotherapy, for the treatment of patients with severe infections due to carbapenem-resistant *K. pneumoniae* among LT recipients. The emergence of resistance to CZA was not observed.

**Keywords:** carbapenem-resistant *Klebsiella pneumoniae*, ceftazidime-avibactam, liver transplantation, intra-abdominal infection, pneumonia

## Introduction

Carbapenem-resistant *Klebsiella pneumoniae* (CRKP) infection is becoming a very serious complication, especially after liver transplantation (LT).<sup>1–5</sup> Due to limited options, CRKP infection is often associated with high morbidity and unfavorable outcomes, with overall mortality ranging from 40% to 70%.<sup>6–9</sup> The rate of CRKP infection in liver transplantation recipients is higher than general population, ranging from 6% to 13%, but in epidemic situations up to 23%.<sup>10–12</sup> Some studies have reported that carbapenem resistance was an independent risk factor for mortality, possibly due to inappropriate initial antimicrobial treatment.<sup>13–15</sup>

Effective therapeutics for carbapenem-resistant *Enterobacteriales* (CRE) infection is scarce. Recently, the antibiotics of polymyxins, tigecycline, fosfomycin and

aminoglycosides have been used against CRE infection, however, concerns remain about increased drug resistance, limited efficacy and toxicity.<sup>16–18</sup> Ceftazidime-avibactam (CZA) is a new  $\beta$ -lactam/ $\beta$ -lactamase inhibitor,<sup>19</sup> which has demonstrated in vitro activity against *Klebsiella pneumoniae* carbapenemases (KPCs) and OXA-48 producing *Enterobacterales*.<sup>20</sup> Real-world experience of CZA in the treatment of infections caused by resistant gram-negative bacilli, including CRE infections is accumulating.<sup>21–24</sup> Patients infected with CRE achieved good response to CZA treatment, with an overall success rate of about 70%.<sup>25–27</sup> Castanheira et al<sup>28</sup> showed that the sensitivity of *Enterobacterales* to CZA was 99.9%, and only 3 of 120 KPC-type carbapenemase producing strains developed resistance to CZA. Tumbarello et al reported a retrospective study from 22 hospitals in Italy for infections caused by KPC-Kp, CZA appeared to be an independent risk factor for 30-day all-cause mortality for the treatment of serious KPC-Kp infections, even when used alone.<sup>29</sup> However, most of the available data on the efficacy and safety of CZA in clinical applications were from observational studies. In addition, scarce data exists related to the efficacy of CZA for CRKP infections in patients after liver transplantation.

Thus, we conducted a retrospective study to analyze the effectiveness and safety of CZA treatment, which included 21 cases with CRKP infection after LT.

## Materials and Methods

### Study Design and Population

A retrospective study was conducted on inpatients with carbapenem-resistant *Klebsiella pneumoniae* infection after LT, who had received CZA treatment for at least 72 hours between April 2018 and August 2021. During this period, CZA was administered for infections caused by confirmed CRKP organisms. A standard dosage of CZA (2g of ceftazidime with 0.5g of avibactam intravenously every 8h over 2 hours) was administered to all included patients, with adjustments in patients with moderate or severe renal dysfunction.

### Ethics Statement

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The protocol was reviewed and approved by the institutional review committee of Renji Hospital (Approval No: 2021-061-B) and individual consent for this retrospective analysis was

waived. All livers were donated voluntarily with written informed consent. No donor organs were obtained from executed prisoners. It was conducted in accordance with the Declaration of Istanbul.

## Outcome and Explicative Variables

Primary outcome was 30-day mortality after CZA administration. Secondary outcomes were 14-day mortality, microbiological outcome and adverse events related CZA.

The recorded variables included demographic characteristics (age, sex, and weight), underlying diseases, MELD or PELD score, CZA treatment (Dosage, duration and adverse effects), microbiological resistance, prior or concomitant antimicrobial therapies, infection characteristics (SOFA score, onset of infection, and source of infection) and empirical or definitive antibiotic treatment.

## Definitions

The clinical outcomes were characterized as following: Response, complete disappearance of the patient's clinical signs and symptoms associated with infection, and/or elimination of the infection, with no recurrence within 30 days after onset of CZA treatment; Failure, continuation of signs and symptoms from baseline to the end of antibiotic treatment, and/or death due to infection and/or recurrent infection. Microbiological failure was defined as the isolation of CRKP from samples obtained from the same source of infection and/or blood cultures following  $\geq 7$  days of CZA treatment. Combination therapy was defined as combining use of two or more antibiotics for at least 48 hours, including inhaled products (only in cases of respiratory infection), regardless of in vitro activity.

CRE is defined according to centers for Disease Control criteria by phenotypic resistance to carbapenem or the presence of carbapenem hydrolases. Types of CRE infections are classified according to the National Health care safety net criteria.<sup>27</sup>

Adverse events related to CZA were defined as any adverse effect that occurred from the initiation of CZA treatment to within 30 days after discontinuation of CZA treatment.

## Isolate Collection and Microbiological Investigation

The final isolates of CRKP cultured before CZA administration from 21 patients were collected for analysis. CZA susceptibility was tested by disk diffusion or broth micro

dilution. Other antimicrobial susceptibility tests were performed with VITEK 2 compact system (Meniere, French), according to the manufacturer's instructions. Resistance to carbapenems in *Enterobacterales* was defined as imipenem and/or meropenem MIC >4 µg/mL. The type of carbapenemase of all CRKP isolates was determined by PCR using the GeneXpert System. MICs were classified according to breakpoints established by the Clinical and Laboratory Standards Institute (CLSI M100). Methods used for microbial identification and antibiotic sensitivity analysis did not change during the study period.

## Statistical Analysis

Continuous variables were expressed either as mean±standard deviation (SD) or median and interquartile range (IQR) according to whether the distribution of the variables was normal or non-normal, and compared using the Student's *t*-test or Mann–Whitney *U*-test. Variables with a *P* value <0.05 (two-tailed) were considered statistically significant. All statistical analyses were performed by the SPSS20.0.

## Results

### Clinical and Microbiological Characteristics

There were overall 72 LT recipients diagnosed with CRE infections during the study period, 21 patients with CRKP infection were included in our study from April 2018 to August 2021. Most of the strains were KPC-Kp (17/21, 81%). The mean age was 40.47 years and 66.7% (14/21) were male. The mean MELD score was 20.8 in patients older than 12 years, and PELD score was 30.7 in patients younger than 12 years. Four (4/21, 19%) patients treated with CZA were pediatric liver transplant recipients. Most of the participants received CZA therapy for KPC-Kp infection. Clinical and demographic characteristics of the patients are summarized in Table 1. The etiology of primary liver disease included acute-on-chronic liver failure (n=7, 33.3%), HBV or HCV-related cirrhosis (n=4, 19%), hepatocellular carcinoma (n=4, 19%), polycystic liver disease (n=1, 4.8%) and Wilson's disease (n=1, 4.8%). The etiology of primary liver disease for the pediatric liver transplant patients was biliary atresia.

The most frequent source of infection was intra-abdominal (n=12) (including the four pediatric patients), followed by bloodstream infection (n=8), pulmonary infection (n=7), catheter-related bacteremia (n=2), and seven patients presented with polymicrobial infection and

two with septic shock. The mean SOFA score was 11.1 in patients due to the CRKP infection after liver transplantation. All patients with abdominal infection were treated with source control of abdominal drainage.

Based on CLSI criteria, all 21 pathogens displayed in vitro susceptibility to CZA, while they were all resistant to penicillins, extended-spectrum cephalosporins and ciprofloxacin, and minimum inhibitory concentrations (MICs) of imipenem were more than 16 µg/mL. As such, some isolates were susceptible to polymyxin B (20/21, 95.2%) tigecycline (19/21, 90.5%), Trimethoprim-sulfamethoxazole (16/21, 76.2%) and amikacin (11/21, 52.4%). Antimicrobial susceptibility of isolates is shown in Table 2.

### Antibiotic Regimens for CRKP

Prior to CZA treatment, the median (IQR) time of treatment with other agents in 21 patients was 10 days (4–31.5 days). The most common regimes prescribed prior to initiation of CZA were carbapenems (n=14), tigecycline (n=9), vancomycin (n=9) and cefoperazone-sulbactam (n=9). CZA was administered as monotherapy in 7 patients (7/21, 33.3%) and combination regimens in 14 (14/21, 66.7%) (including two pediatric patients), with meropenem (n=5), aztreonam (n=5), metronidazole (n=4), aztreonam and metronidazole (n=1), vancomycin and levofloxacin (n=1), polymyxin B, vancomycin and levofloxacin (n=1). In these 21 patients with CZA therapy, three cases developed CRKP recurrence 30 days after the cessation of CZA, and then retreated with CZA plus polymyxin B and levofloxacin or aztreonam. Patients with combination therapy showed more pulmonary infection than those with monotherapy (35.7%, 5/14 vs 28.6%, 2/7), and also higher incidence with severe sepsis (21.4%, 3/14 vs 0%, 0/7). Median number of days from the onset of CRKP infection until the initiation of CZA salvage treatment was 2 days (IQR, 1–6.5), and median duration of CZA was 12 days (IQR, 8.5–19).

### Clinical Outcomes

Among the 21 patients treated with CZA, the primary outcome of 30-day clinical response after CZA onset was reached 61.9% (13/21), respectively. Clinical response of 14-day and 30-day in adult patients was 70.6% (12/17) and 58.8% (10/17), respectively, while in pediatric patients, the 14-day and 30-day clinical response were 75%, respectively.

**Table 1** Demographic and Clinical Data of 21 Liver Transplantation Recipients Receiving CZA for KPC-Producing *Klebsiella pneumoniae* Bacterial Infection

No.	Age(y) / Sex	Diagnosis	MELD Score/ PELD Score	Procedure	Infection	SOFA Score	T from CRKP Onset to LT (d)	Carbapenemase	Prior Antibiotics	Source Control	Septic Shock	Sepsis	Prior Antibiotics Time (d)	T from CRKP Onset to CZA Initiation(d)	Concomitant Tx	Tx Duration (d)	M/O	C/O
1	48/M	HBV-LC	15	DDLT	BSI, IAI, PI	13	1	KPC-2	Initial: CPZ/ SBT, CAZ, IMP, VAN, FOS, MEM, TGC; Second: MEM, POL	YES	YES	YES	32	10	Initial: MEM, second: POL+LEV +VAN	Initial: 6, Second:17	P	Die
2	45/M	HCC	7	DDLT	BSI, IAI	12	62	KPC-2	IMP FOS, MEM, TGC, AMI, VAN, CAZ	YES	NO	YES	33	30	MEM	5	P	Die
3	54/M	HCV-LC	11	DDLT	BSI	17	3	KPC-2	CAZ	NO	NO	NO	5	3	MEM	19	E	Die
4	37/M	ACLF	35	DDLT	PI	15	1	KPC-2	CAZ, MEM, VAN	NO	NO	NO	13	10	VAN+LEV	8	P	Improve
5	41/M	ACLF	28	DDLT	IAI, PI	8	55	KPC-2	Initial: IMP Second: AMI, LEV, VAN, CPZ/ SBT, PIP/ TAZ	YES	NO	NO	36	1	Initial: MET; second: AZM+ MET	Initial: 13, Second:10	P	Die
6	46/F	PLD	10	DDLT	CRBSI	2	6	KPC-2	MEM, TGC, VAN	NO	NO	NO	19	7	-	6	E	Improve
7	67/M	ACLF, ALD	21	DDLT	IAI, CRBSI	14	3	KPC-2	CAZ, IMP, VAN	YES	NO	NO	31	1	AZM	11	E	Improve
8	50/M	HBV-LC	18	DDLT	IAI	19	56	KPC-2	CPZ/ SBT	YEA	NO	NO	9	6	AZM	9	E	Improve
9	65/M	HCC, HBV-LC	11	DDLT	BSI	5	81	KPC-2	CAZ	NO	NO	NO	4	1	-	9	E	Die
10	68/M	ACLF	24	DDLT	BSI, IAI, PI	15	3	KPC-2	Initial: MOX, LEV, CPZ/ SBT, MEM Second: CPZ/ SBT, TGC, VAN, MEM	YES	NO	YES	16	1	Initial: MEM, PIP/ TAZ Second:-	Initial: 31 Second:4	P	Die
11	39/F	Wilson's disease	32	DDLT	PI	14	5	KPC-2	CAZ, PIP/TAZ	NO	NO	NO	10	1	AZM	13	E	Improve
12	47/M	ACLF	41	DDLT	BSI, IAI	17	3	KPC-2	CAZ, LEV	YES	NO	NO	3	2	MEM	19	E	Improve

13	65/M	HCC	8	DDLIT	BSI	8	4	KPC-2	CAZ, MET, CPZ/ST	NO	NO	NO	5	4	-	11	E	Improve
14	59/M	HCC	6	DDLIT	PI	9	45	KPC-2	MEM, MOX, LIN, VAN, IMP	NO	NO	NO	13	2	-	8	P	Die
15	55/M	ACLF	24	DDLIT	PI	9	3	KPC-2	MEM, VAN, TGC	NO	NO	NO	5	1	MET, POL	13	E	Improve
16	19/M	Carol's syndrome	20	LDLT	IAI	13	34	NDM-1	MEM, VAN, CPZ/ST	YES	NO	NO	31	3	MET	10	P	Die
17	30/M	ACLF	35	DDLIT	BSI	11	7	KPC-2	CPZ/ST, TEI	NO	NO	NO	5	1	-	9	E	Improve
18	1/F	BA	23	LDLT	PI, IAI	12	3	NDM-1	PIP/TAZ, MEM, TGC, CPZ/ST	YES	YES	NO	27	26	-	3	P	Die
19	2/F	BA	7	LDLT	IAI	9	2	NDM-1	TEI, TGC, MEM, CPZ/ST	YES	NO	NO	33	32	AZM	18	E	Improve
20	12/F	BA	28	DDLIT	IAI	4	29	KPC-2	CEF, MEM, LNI, VAN, TGC	YES	NO	NO	33	3	MET	14	E	Improve
21	0.5/F	BA	62	LDLT	IAI	7	7	NDM-1	MEM, TGC, CAZ	YES	NO	NO	37	9	-	7	E	Improve

**Abbreviations:** T, time; Tx, treatment; HBV/LC, hepatitis B-related liver cirrhosis; HCC, hepatocellular carcinoma; ACLF, acute-on-chronic liver failure; ALD, alcoholic liver disease; PLD, polycystic liver disease; BA, biliary atresia; DDLIT, deceased donor liver transplantation; LDLT, living donor liver transplantation; BSI, bloodstream infection; VAP, ventilator-associated pneumonia; IAI, intraabdominal infection; CRBSI, catheter-related bloodstream infection; PI, pulmonary infection; AMI, amikacin; LIN, linezolid; POL, polymyxin; LEV, levofloxacin; MOX, moxifloxacin; AZM, aztreonam; CAZ, ceftazidime; MET, meropenem; CPZ/ST, ceftazidime-sulbactam; PIP/TAZ, piperacillin and tazobactam; LNI, linezolid; TEI, teicoplanin; CEF, cefepime; E, eradication; P, persistence; M/O, microbiological outcome; C/O, clinical outcome.

**Table 2** Susceptibility Testing Results of *Klebsiella pneumoniae* Isolates to Antimicrobial Agents

Antimicrobial Agent	<i>Klebsiella pneumoniae</i> (n=21)		
	S	I	R
Amikacin	11 (52.4%)	0	10 (47.6%)
Ampicillin	0	0	21 (100%)
Piperacillin-tazobactam	0	0	21 (100%)
Imipenem	0	0	21 (100%)
Meropenem	0	0	21 (100%)
Cefoperazone-sulbactam	0	1 (4.8%)	20 (95.2%)
Cefepime	0	0	21 (100%)
Aztreonam	0	0	21 (100%)
Levofloxacin	0	0	21 (100%)
Trimethoprim-sulfamethoxazole	16 (76.2%)	0	9 (42.8%)
Tigecycline	19 (90.5%)	0	2 (9.5%)
Polymyxin B	20 (95.2%)	0	1 (4.8%)
Ceftazidime Avibactam	21 (100%)	0	0

Six cases of 14-day clinical failure were attributed to organ failure (n=4) and uncontrolled infection (n=2). Of the eight patients with 30-day clinical failure was due to CRKP recurrence in the same location (n=2), persistence of symptoms and signs of infection (n=3) and organ failure (n=3), but 2 patients showed a 14-day clinical response. The all-cause mortality rate was 42.9% (n=9/21), including one child. Infection-related all-cause mortality was 83.3% (5/9), comprising three cases with recurrent intra-abdominal and pulmonary infection and two cases with uncontrolled pulmonary infection, while gastrointestinal hemorrhage contributed 11.1% of all-cause mortality in one patient, three others died from organ failure. The nine patients who experienced clinical failure are summarized in Table 3.

## Microbiology Outcomes

Microbiologic failures occurred in 42.9% (9/21) of episodes due to relapsing CRKP infections (n=3), death (n=4) and respiratory colonization (n=2). The recurrence episode happened in the same location as the previous. One case developed a second intra-abdominal infection 34 days after CZA monotherapy, and retreated with CZA combined with aztreonam. One case presented a relapse in pulmonary after 30 days of completing infection with

CZA monotherapy, and retreated with CZA combined with polymyxin B. Another case was relapsed in pulmonary after 44 days of combination with meropenem, and retreated with CZA monotherapy. In these cases, the CRKP isolates remained susceptible to CZA, although the clinical and microbiological cures were failure after retreatment with CZA monotherapy or plus with other agents.

## Adverse Events

Three patients develop acute renal failure, perhaps due to progressive infection during treatment period (285umol/L to 451umol/L, 81umol/L to 823umol/L and 36umol/L to 243umol/L, respectively), and two patients received hemodialysis after CZA treatment. One of these patients had combined polymyxin B treatment, which primarily contributed to renal dysfunction.

Two patients developed alanine aminotransferase (ALT) (67U/L to 189U/L and 17U/L to 152U/L) and aspartate aminotransferase (AST) (34U/L to 99U/L and 25U/L to 77U/L) increased, one concomitant with tigecycline, and the other with voriconazole. No adverse reactions occurred in the skin, subcutaneous tissue, gastrointestinal system or nervous system in our study.

For the four pediatric recipients, no adverse events such as renal dysfunction, rash, diarrhea, vomiting or neurotoxicity were found in this study.

## Discussion

This case series study is firstly evaluating effectiveness of treatment with CZA in LT recipients due to infection with CRKP. Even with the limitation of small sample size, it demonstrated the clinical benefit of CZA for the treatment of CRE infection. In our experience, the 14-day and 30-day mortality rates were 28.6% and 38.1%, respectively, consistent with a recently published report which observed a 34.1% of 30-day mortality.<sup>22</sup> In Tumbarello et al's study, the 30-day all-cause mortality was 25.3%, the mortality between patients managed with CZA alone and those treated with combination was no statistically significant difference, but CZA administration by prolonged infusion significantly reduced mortality.<sup>29</sup> It is also in line with the all-cause in-hospital mortality rate of 39.5% reported in other patients who were managed with CZA salvage therapy.<sup>30</sup> However, in a recent prospective cohort study, the group of patients (96% of them with KPC-Kp infections) received first-line treatment with CZA, a very low 30-day mortality rate was observed (8%).<sup>31</sup> Compared



**Table 3** Description of Patients Infected by Carbapenem-Resistant *Klebsiella Pneumoniae* Who Experienced Clinical Failure

Age/ Sex	Underlying Condition	Type of Infection	Clinical Presentation	Prior Therapy to CZA	Dose of CZA	CRRT	Combined Antibiotics	Reason for Clinical Failure
48/M	HBV-LC	BSI, IAI, HAP	Septic shock, sepsis	Initial: CPZ/SBT for 9d, IMP/VAN for 5d, TGC / MEM/FOS for 6d, Second: MEM/POL for 30d	Initial:2.5g q12h for 6d; Second:1.25g q12h for 17d	YES	Initial: MEM; Second: POL+ LEV	Recurrent infection; Death
45/M	HCC	BSI, IAI	Sepsis	IMP for 4d, MEM/FOS / TGC for 18d, IMP/FOS / TGC for 10d	2.5g q12h for 5d	NO	MEM	Respiratory failure, Death
54/M	HCV-LC UGIB	BSI	No sepsis	CAZ for 1d	2.5g q12h for 19d	YES	MEM	Gastrointestinal bleeding, Hemorrhagic shock, Death
41/M	HBV-LC	IAI HAP	No sepsis	Initial: IMP for 2d, Second: AMI/CPZ/SBT for 17d, LEV 7d, VAN /PIP/TAZ for 10d	Initial:2.5g q12h for 4d; Second:2.5g q12h for 7d	NO	Initial:MET; Second: AZM+MET	Recurrent infection; Death
65/M	HBV-LC, HCC	BSI	No sepsis	CAZ for 1d	2.5g q12h for 10d	NO	NO	Hepatic failure, Death
68/F	ACLF	BSI IAI PI	Sepsis	Initial: MOX for 5d, LEV for 2d, CPZ/SBT for 4d, MEM for 20d Second: PIP/TAZ for 6d, CPZ/SBT for 14d, TGC for 19d, VAN for 16d, MEM for 16d	Initial:2.5g q8h for 6d, 2.5g q12h for 25d; Second:2.5g q12h for 4d	NO	Initial:MEM, PIP/TAZ; Second: NO	Multiple organ failure, Recurrent infection, Death
59/M	HCC	HAP	No sepsis	MEM for 3d, MOX for 9d, LIN for 3d, VAN for 8d, IMP for 2d	2.5g q8h for 8d	NO	NO	Severe pulmonary infection, Gastrointestinal bleeding, Death
18/M	LC	IAI	No sepsis	MEM for 20d, VAN for 28d, CPZ/SBT for 8d	2.5g q8h for 10d	NO	MET	Recurrent infection, Severe pulmonary infection, Death
1/F	BA	HAP IAI	Septic shock	PIP/TAZ for 3d, MEM for 22d, TGC for 24d, CPZ/ SBT for 5d	0.3g q8h for 3d	NO	NO	Multiple organ failure, Septic shock, Death

**Abbreviations:** IMP, imipenem; MEM, meropenem; TEI, teicoplanin; TMP-SMZ, trimethoprim-sulfamethoxazole; VAN, vancomycin; TGC, tigecycline; AMI, amikacin; LIN, linezolid; POL, polymyxin; LEV, levofloxacin; AZM, aztreonam; CAZ, ceftazidime; MET, metronidazole; CPZ/SBT, cefoperazone-sulbactam; PIP/TAZ, piperacillin and tazobactam.

with our series, CZA was started in most of LT patients owing to failure of previous anti-bacterial regimens.

The rapid onset of CZA resistance was the most concerning events by Shields et al, which reporting a rate of recurrences in 17% (5/37) patients and a rate of 10% (8/

77) patients developed CZA resistance after a median of 15 days of CZA treatment.<sup>26</sup> Another study also showed 13.5% (5/37) patients had experienced recurrence.<sup>21</sup> Consistent to these studies, in our series we found 3 patients with intra-abdominal and pulmonary infection

observed recurrence in the same location. We did not observe CRKP isolates acquiring in vitro resistance to CZA during or after treatment. Indeed, no resistant CRE strains have been isolated in our center so far, although other studies have demonstrated that the KPC-3 or KPC-2 strains have developed resistance to CZA.<sup>21,26,30</sup>

In accordance with previous reports, CZA combination therapy was not associated with a reduced risk of clinical failure.<sup>21,22,25,26</sup> Among 14 CZA-based combination group in our cohort, eight patients died. However, we cannot draw a definitive conclusion as for the small samples. One of explanations maybe that the patients who received CZA combination therapy suffered more severe infection than those patients who did not. These data are in contrast to previous studies which showed that the combination of two or more in vitro active drugs was associated with lower mortality than monotherapy, especially in the most of patients with the most severe infections.<sup>14,32,33</sup> CZA monotherapy presumably associated with decreasing the rate of adverse events, particularly acute kidney injury, which frequently emerged during the treatments based on combinations with aminoglycosides or colistin.<sup>21,33</sup> In our series, three patients developed acute renal failure, and two patients received hemodialysis during the treatment. All these three patients received combination therapy with meropenem (n=2) or polymyxin B (n=1). In contrast, renal impairment was not detected during or after the treatment with CZA. Further studies should be conducted to determine whether combination therapy with CZA could improve prognosis of patients with serious CRKP infections.

In our study, four pediatric liver transplantation patients were treated with CZA for abdominal infection due to CRKP, with a mortality of 25%. CZA was expanded the approval to include pediatric patients aged  $\geq 3$  months by the FDA for treatment of complicated intra-abdominal infection as well as complicated urinary tract infections, including pyelonephritis, used in combination with metronidazole till March 2019. However, safety and effectiveness have not been evaluated in pediatric liver transplantation patients with CRKP infectious. The recent INFORM Surveillance program (USA 2011–2015) reported a highly in vitro-activity of ceftazidime/avibactam against *K. pneumoniae* isolated from pediatric patients.<sup>34</sup> In this study, a total of 8461 gram-negative strains collected from hospitalized pediatric patients in the United States Medical Center were confirmed to ceftazidime avibactam was in vitro activity against >99.9% of

*Enterobacterales* and 99.1% of *P. aeruginosa* strains. In a randomized Phase II study of 95 patients aged 3 months to 18 years with complicated urinary tract infection (cUTI), CZA was well tolerated in these children and the safety profile was in line with ceftazidime monotherapy in pediatric patients. Also, CZA appeared effective in the treatment of pediatric cUTI caused by Gram-negative pathogens, with favorable clinical and microbiologic response rates observed against the predominant cUTI pathogen (*E. coli*), including ceftazidime-non-susceptible isolates.<sup>35</sup> Although CZA has shown safety and efficacy in pediatric liver transplantation patients in our study, however, it is impossible to draw a specific conclusion due to the small number of pediatric liver transplantation patients in this study, more clinical studies were needed to confirm the results.

This study had several limitations by the small samples and retrospective design, which hindered the ability to make definitive conclusion about utility of LT patients with CRKP infection by CZA. On the other hand, all of patients received CZA as salvage therapy; hence, it may not be generalized to patients who can get first-line treatment of CZA. Nonetheless, our experience suggested CZA may be an available alternatively in the treatment of CRKP infections in advance and with less toxic.

In conclusion, data on this study indicate that CZA is a promising option, even in monotherapy, for the treatment of patients with severe infections due to Carbapenem-resistant *K. pneumoniae* among LT recipients. The emergence of resistance to CZA was not observed.

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## Disclosure

The authors report no conflicts of interest in this work.

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