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Ceftazidime-Avibactam for the Treatment of Carbapenem-Resistant Klebsiella Pneumoniae Infection: A Retrospective, Single Center Study

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Purpose: Ceftazidime-avibactam (CZA), a novel beta-lactam/beta-lactamase inhibitor, plays an important role in the threat of emerging carbapenem-resistant Enterobacterales (CRE) infection. The study aims to analyze the clinical effectiveness and factors influencing treatment response to CZA for carbapenem-resistant *Klebsiella pneumoniae* (CRKP) infections.

Patients and Methods: From February 2020 to December 2021, patients with CRKP infection treated with CZA were enrolled in this retrospective, single-center cohort study in northern Taiwan. The primary outcome was 28-day survival rate. The secondary outcomes were clinical success, and microbiological cure. Multivariate regression analysis was used to evaluate factors associated with 28-day survival.

Results: A total of 142 patients treated with CZA alone (n=82) or in combination therapy (n=60) were included. We found 28-day survival rate, microbiological cure, and clinical success rate were 78% (111/142), 86% (87/101), and 48% (63/132), respectively. In multivariate analysis, there were no significant differences in 28-day survival between monotherapy group and combination therapy group (P=0.424). A relative lower microbiological cure rate can be observed in lower respiratory tract infection from univariate analysis (P=0.07). In addition, significantly better survival was observed in patients with creatinine clearance rate (CCr) ≥50 mL/min than CCr <50 mL/min (P=0.005).

Conclusion: CZA is an effective and important treatment option for CRKP infection even when it is treated as monotherapy. In patients with impaired renal function, a potential impact of CZA dose adjustments on poor survival outcomes has been observed, indicating the need for further research to determine optimal renal dose adjustment strategies.

Keywords: enterobacterales, *Klebsiella pneumoniae*, ceftazidime-avibactam

Introduction

Over the past two decades, carbapenem-resistant Enterobacterales (CRE) has emerged as a significant threat worldwide and has also been associated with increased mortality rate.[1]

The most common CRE in Taiwan are *Klebsiella pneumoniae* carbapenemase–producing *K. pneumoniae (*KPC-Kp) and OXA-48-like carbapenemase producing pathogens.[2,3] Ceftazidime-avibactam (CZA), a new β-lactam/β-lactamase inhibitor combination agent, is considered as a preferred treatment option for CRE in addition to colistin.[4,5] It was previously concluded that in vitro multicenter studies in Taiwan reported the susceptibility rates of CZA for *E. coli, K. pneumoniae*, and *P. aeruginosa* as 99%, 100%, 91%, respectively.[6] Even for the multidrug-resistant Enterobacterales, CZA still retained more than 90% in vitro susceptibility rates in Taiwan (96.7% in ESBL and 91.7% in KPC).[7]

Based on randomized controlled trials,[8–11] The US Food and Drug Administration (FDA) approved CZA for the treatment of complicated urinary tract infections and complicated intra-abdominal infections (cIAI) in 2015 and nosocomial pneumonia in 2018. After approval, CZA utilization has increased, accompanied by a decline in the usage of Colistin for the treatment of carbapenem-resistant gram-negative bacterial infection.[12] Real world cohort studies

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showed CZA improved the clinical response with reduced mortality in patients infected by CRE in comparison to other treatment options.[13,14] Taiwan FDA also approved CZA as the empirical treatment option for urinary tract infection (UTI), cIAI and nosocomial pneumonia in 2019.

However, there is still limited experience on the clinical use of CZA for CRE in Taiwan. The aim of this study is to evaluate the effectiveness and epidemiology of CZA for treating carbapenem-resistant *K. pneumoniae* (CRKP) infection in a single medical center in northern Taiwan.

Materials and Methods

Study Design and Patients Selection

In this retrospective, single-center cohort study, patients were included between February 20, 2020, and December 31, 2021, at Far Eastern Memorial Hospital in northern Taiwan. Patients were enrolled in this study with the following eligible criteria: (1) older than 20 years of age at admission (2) culture proved CRKP infection (3) received CZA treatment for more than 72 hours.

This study was approved by the institutional review board in Far-Eastern Memorial Hospital (IRB number 112195-E) under the ethical standards outlined in the Declaration of Helsinki and the requirement for written informed consent was waived by the IRB because the data analyzed did not contain identifiable information.

Patient and Infection Profiles

Pharmacy records and patient information were reviewed and collected using standard case record forms. Infections were defined according to the Centers for Disease Control and Prevention/National Healthcare Safety Network Surveillance Definitions for Specific Types of Infections.[15] Charlson comorbidity index and other comorbidity profiles were documented at admission.[16] Sequential Organ Failure Assessment (SOFA) score, INCREMENT-CPE score, and either the presence or absence of septic shock was assessed at infection onset (septic shock was defined as sepsis associated with hypotension and perfusion abnormalities despite the provision of adequate volume resuscitation).[17–19] The definition of acute kidney injury (AKI) was followed the latest KDIGO guideline.[20] We documented the initial clinical symptoms of each infection episode, including fever, dyspnea, purulent sputum, purulent wound discharge, abdominal pain, dysuria, as recorded in the electronic medical records. The definition of clinical success was either complete resolution or remarkable improvement of non-microbiological indicators (ie radiological imaging and laboratory tests) along with initial clinical symptoms (ie fever, dyspnea, purulent sputum, purulent wound discharge, abdominal pain and dysuria) within a 7-day period following CZA treatment. Time to active antibiotics was defined as the period from culture collection to the administration of CZA or other active antibiotics.

Microbiology and Antibiotic Regimens

Antibiotic susceptibility testing was performed by using automachine Vitek 2 system (bioMérieux Inc. Hazelwood, MO, USA), supplement by E test (bioMérieux), as indicated. Carbapenem resistance was defined as the value of minimal inhibitory concentration of imipenem or meropenem according to the criteria of CLSI guidelines.[21]

Treatment and Outcomes Statistical Analysis

CZA was administrated intravenously, given at standard dose of 2.5 g slowly infusion for 3 hours every 8 hours with renal dose adjustment based on estimated creatinine clearance rate (CCr, Cockcroft-Gault equation).[22] We defined combination therapy as treatment that includes at least one additional agent targeting Gram-negative pathogens, co-administered with CZA for more than 3 days.

The primary outcome was 28-day survival rate after administration of CZA. Secondary outcomes included clinical success and microbiological cure. Microbiological cure was defined as culture-confirmed eradication of the pathogen at the end of the treatment in cases with repeat cultures.

Statistical Analysis

Basic characteristics of the patients were evaluated by descriptive statistics. Discrete data were presented with numbers and percentages, and continuous data were presented with medians and interquartile ranges (IQRs). The Mann–Whitney *U*-test was used to compare continuous variables, and chi-square tests were applied for evaluating categorical variables. Two-tailed P-values of <0.05 were used to determine statistical significance. Univariate and multivariate logistic regression analysis was used to identify risk factors associated with 28-day mortality, clinical success, and microbiological cure. Variables from univariate analysis with P values of less than 0.10 were included in the multivariate model. Survival analysis was done by using the Kaplan–Meier method. All statistical analyses were performed with IBM SPSS Statistics for Windows, version 26.0 (IBMCorp., Armonk, N.Y., USA).

Results

Clinical and Microbiological Characteristics

Baseline characteristics of our subjects were summarized in Table 1 and patients stratified by monotherapy and combination therapy were compared in Table 2. A total of 142 adults with CRKP infections who received at least 72 hours of CZA therapy were included. The median age was 74 years old with range from 39 to 97 years old while 58% (83/142) of the patients were male. Only 5 patients co-infected with carbapenem-resistant *Pseudomonas aeruginosa* (CRPA), and the rest were monomicrobial CRKP infection. The major common co-morbidity was diabetes mellitus, which accounted for nearly half of the patients (69/142, 48%). Among these patients, 55% (78/142) required mechanical ventilation, and estimated 17% of them experienced septic shock (25/142). Lower respiratory tract infection (LRTI) occupied the largest proportion of infection source (65/142, 46%), followed by 20% (29/142) of them were primary bacteremia. Higher INCREMENT-CPE score (P<0.001), higher SOFA score (P=0.001), and higher percentage of septic shock (P<0.001) were observed in patients with bacteremia compared to those without bacteremia. *E* tests were performed on 22 CRKP isolates, and 21 of them (95.5%) were found to be susceptible to CZA.

Treatment Strategies and Outcomes

As shown in Table 1, the median duration of CZA therapy was 14 days (IQR, 8–18 days). About 40% of all infections were treated with combination regimen. Figure S1 showed the distribution of agents that were prescribed with CZA as combination therapy. In our patient population, the most frequently combined antimicrobial agent with CZA was colistin (37%), followed by fluoroquinolones (24%). According to Table 2, usage of combination therapy was significantly more frequent in patients with mechanical ventilation (73% vs 41%, P<0.001), and less frequent in patient with UTI (P=0.01). Patients receiving combination therapy exhibited significantly higher INCREMENT-CPE (P=0.03) and SOFA scores (P<0.001). Additionally, combination therapy group had higher incidence of AKI than monotherapy group (27% vs 9%, P=0.004).

The 28-day survival rate in our study population was 78%. Microbiological cure rate was 86% among the patients, and additionally, 46% of them achieved clinical success within 7 days of CZA treatment. There was statistically significant difference between bacteremic group and non-bacteremic group in 28-day survival rate (59% vs 83%, P=0.002). Similar result was also noticed in Kaplan–Meier survival analysis that significantly higher survival was observed in non-bacteremic group than those in bacteremic group (P=0.001) (Figure 1A). In addition, Figure 1B and C demonstrated significantly higher survival rate in patients with CCr≥50 than CCr<50 (P=0.005), and in patients with monotherapy than combination therapy (P=0.046), respectively.

Predictors Associated with 28-Day Survival Rate

Univariate and multivariate analysis for the factors associated with 28-day survival rate after administration of CZA were demonstrated in Table 3. Patient with higher SOFA score and INCREMENT-CPE score ≥8, bacteremia, received combination therapy, using mechanical ventilation, septic shock and impaired renal function were associated with non-survival. Patients without bacteremia, who received monotherapy, and those with better renal function (CCr≥50) had better survival rate.

Table 1 Characteristics of Patients with Different Infection Sources

	All Infection (n=142)	Bacteremia (n=29)	Non-Bacteremia (n=113)	P Value (Bacteremia vs Non-Bacteremia)	LRTI (n=65)	UTI (n=26)	IAI (n=15)	SSTI (n=7)
Males	83 (58%)	15 (52%)	68 (60%)	0.16	42 (65%)	11 (42%)	9 (60%)	6 (86%)
Ages, median (IQR), yrs	74 (65–81)	74 (62–84)	74 (65–81)	0.57	76 (67.5–82.5)	76 (64.75–81.5)	68 (58–76)	58 (51–65)
Combine with CRPA infection	5 (4%)	1 (3%)	4 (4%)	0.98	2 (3%)	0	1 (7%)	1 (14%)
Comorbidities								
COPD	31 (22%)	5 (17%)	26 (23%)	0.68	19 (29%)	6 (23%)	1 (7%)	0
CHF	21 (15%)	5 (17%)	16 (14%)	0.5	15 (23%)	1 (4%)	0	0
Solid tumor	39 (27%)	12 (41%)	27 (24%)	0.06	10 (15%)	4 (15%)	9 (60%)	4 (57%)
Hematologic malignancy	4 (3%)	2 (7%)	2 (2%)	0.14	2 (3%)	0	0	0
Liver disease	26 (18%)	5 (17%)	21 (19%)	0.87	13 (20%)	3 (12%)	2 (30%)	3 (43%)
Diabetes Mellitus	69 (49%)	14 (48%)	55 (49%)	0.97	32 (49%)	14 (54%)	7 (47%)	2 (29%)
Mechanical ventilation	78 (55%)	15 (52%)	63 (56%)	0.7	46 (71%)	8 (31%)	7 (47%)	2 (29%)
Septic shock	25 (18%)	13 (45%)	12 (11%)	<0.001	10 (15%)	1 (4%)	1 (7%)	0
Severity of illness								
INCREMENT, median (IQR)	3 (3–7)	10 (6–12)	3 (3–3)	<0.001	3 (3–7)	3 (3–3)	3 (3–3)	3 (3–3)
INCREMENT≥8	26 (18%)	16 (55%)	10 (9%)	<0.001	7 (11%)	2 (8%)	1 (7%)	0
Charlson comorbidity index, median (IQR)	6 (4–7)	7 (4.5–8.5)	6 (4–7)	0.07	6 (5–7)	6.5 (4–9)	6 (4–8)	6 (3–7)
SOFA, median (IQR)	4 (2–7)	5 (3–12)	4 (2–6)	0.001	5 (3–7)	3 (1.75–4.5)	2 (1–5)	4 (0–10)
Renal function								
CCr≥50	67 (47%)	7 (24%)	60 (53%)	0.005	33 (51%)	14 (54%)	9 (60%)	4 (57%)
50>CCr≥10	45 (32%)	14 (48%)	31 (27%)	0.03	20 (31%)	7 (27%)	3 (20%)	1 (14%)
CCr<10 (without dialysis)	2 (1%)	0	2 (2%)	0.47	1 (2%)	1 (4%)	0	0
Dialysis	28 (20%)	8 (28%)	20 (18%)	0.23	11 (17%)	4 (15%)	3 (20%)	2 (29%)
CCr<30	50 (35%)	17 (59%)	33 (29%)	0.003	18 (28%)	10 (38%)	4 (27%)	1 (14%)
Therapy								
Time to active antibiotics, median (IQR), days	4 (1.75–5)	4 (1.5–5)	4 (1.5–5)	0.32	4 (1.5–5)	4 (0.75–5)	4 (0–6)	4 (4–8)
Time to CTZ-AVI, median (IQR), days	4 (4–6)	4 (3.5–6)	4 (4–6)	0.17	4 (4–6.5)	4 (3–5)	6 (4–8)	4 (4–8)
Therapy duration, median (IQR), days	14 (8–18)	15 (7–18)	14 (8–17.5)	0.74	14 (10.5–17)	8 (5.75–15)	18 (13–22)	13 (11–29)
Monotherapy	82 (58%)	17 (59%)	65 (58%)	0.92	33 (51%)	21 (81%)	7 (47%)	4 (57%)
Combination therapy	60 (42%)	12 (41%)	48 (42%)	0.92	32 (49%)	5 (19%)	8 (53%)	3 (43%)
Combine 1 agent	52 (37%)	9 (31%)	43 (38%)	0.48	27 (42%)	5 (19%)	8 (53%)	3 (43%)

Combine 2 agents	8 (6%)	3 (10%)	5 (5%)	0.22	5 (8%)	0	0	0
Combine with Colistin	24 (17%)	4 (14%)	20 (18%)	0.62	16 (25%)	1 (4%)	3 (20%)	0
Outcome								
In-hospital mortality	36 (25%)	14 (48%)	22 (19%)	0.002	15 (23%)	3 (12%)	3 (20%)	1 (14%)
14-day survival	125 (88%)	20 (69%)	105 (93%)	<0.001	60 (92%)	24 (92%)	14 (93%)	7 (100%)
28-day survival	111 (78%)	17 (59%)	94 (83%)	0.002	52 (80%)	24 (92%)	12 (80%)	6 (86%)
Microbiological cure[a]	87 (86%)	24 (96%)	63 (83%)	0.1	39 (80%)	13 (93%)	6 (75%)	5 (100%)
Clinical success[b]	63 (48%)	9 (33%)	54 (51%)	0.09	36 (56%)	13 (62%)	4 (29%)	1 (17%)
AKI	23 (20%)	7 (30%)	16 (17%)	0.15	15 (27%)	0	1 (8%)	0

Notes: [a]101 of 142 patients had culture follow up to prove microbiological negative or not, including 24 of bacteremia, 49 of LRTIs, 14 of UTIs, 8 of IAIs, 5 of SSTIs; [b]10 of 142 patients did not reach 7 days treatment.

Abbreviations: COPD, chronic obstructive pulmonary disease; CHF, congestive heart failure; LRTI, lower respiratory tract infection; UTI, urinary tract infection; IAI, intra-abdominal infection; SSTI, skin and soft tissue infection; CCr, creatinine clearance rate; IQR, interquartile range; CRPA, Carbapenem-resistant Pseudomonas aeruginosa; AKI, acute kidney injury.

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Table 2 Patients Treated with Monotherapy versus Combination Therapy

	Monotherapy (n=82)	Combination Therapy (n=60)	P value (Monotherapy vs Combination Therapy
Males	44 (54%)	39 (65%)	0.18
Ages, median (IQR), years	75 (65–82.25)	72 (63.5–79.5)	0.39
Comorbidities			
COPD	14 (17%)	7 (12%)	0.37
CHF	23 (28%)	8 (13%)	0.04
Solid tumor	17 (21%)	22 (37%)	0.04
Hematologic malignancy	2 (2%)	2 (3%)	0.75
Liver disease	15 (18%)	11 (18%)	0.99
Diabetes Mellitus	43 (52%)	26 (43%)	0.28
Mechanical ventilation	34 (41%)	44 (73%)	<0.001
Septic shock	12 (15%)	13 (22%)	0.28
Renal function			
CCr≥50	38 (46%)	29 (48%)	0.81
50>CCr≥10	27 (33%)	18 (30%)	0.71
CCr<10 (without dialysis)	1 (1%)	1 (2%)	0.82
Dialysis	16 (20%)	12 (20%)	0.94
CCr<30	28 (34%)	26 (43%)	0.76
Therapy			
Time to active antibiotics, median (IQR),days	4 (3–5)	4 (1–5)	0.44
Time to CTZ-AVI, median (IQR), days	5 (4–6)	4 (3–6)	0.02
Therapy duration, median (IQR), days	14 (8–16)	14.5 (9–20.5)	0.1
Bacteremic infections			
Bacteremia	17 (21%)	12 (20%)	0.92
Primary bacteremia	4 (5%)	1 (2%)	0.59
Secondary bacteremia	13 (16%)	10 (17%)	0.59
Primary site			
LRTI	5 (6%)	4 (7%)	0.94
UTI	4 (5%)	4 (7%)	0.65
IAI	1 (1%)	2 (3%)	0.39
SSTI	2 (2%)	0	0.19
CRBSI	1 (1%)	0	0.37
Nonbacteremic infections			
LRTI	33 (40%)	32 (53%)	0.12
UTI	21 (26%)	5 (8%)	0.01
IAI	7 (9%)	8 (13%)	0.36
SSTI	4 (5%)	3 (5%)	0.97
Severity of illness			
INCREMENT, median (IQR)	3 (3–6)	3 (3–7)	0.03
INCREMENT≥8	12 (15%)	14 (23%)	0.19
Charlson comorbidity index, median (IQR)	6 (5–7.25)	6 (4–7)	0.86
SOFA, median (IQR)	4 (2–6)	6 (3–10)	<0.001
Outcome			
In-hospital mortality	15 (18%)	21 (35%)	0.02
14-day survival	75 (91%)	50 (83%)	0.14
28-day survival	69 (84%)	42 (70%)	0.044
Microbiological cure	48 (87%)	39 (85%)	0.72
Clinical success (7 days)	41 (55%)	22 (39%)	0.07
AKI	7 (10%)	16 (32%)	0.004

Abbreviations: COPD, chronic obstructive pulmonary disease; CHF, congestive heart failure; LRTI, lower respiratory tract infection; UTI, urinary tract infection; IAI, intra abdominal infection; SSTI, skin and soft tissue infection; CCr, creatinine clearance rate; AKI, acute kidney injury; IQR, interquartile range.

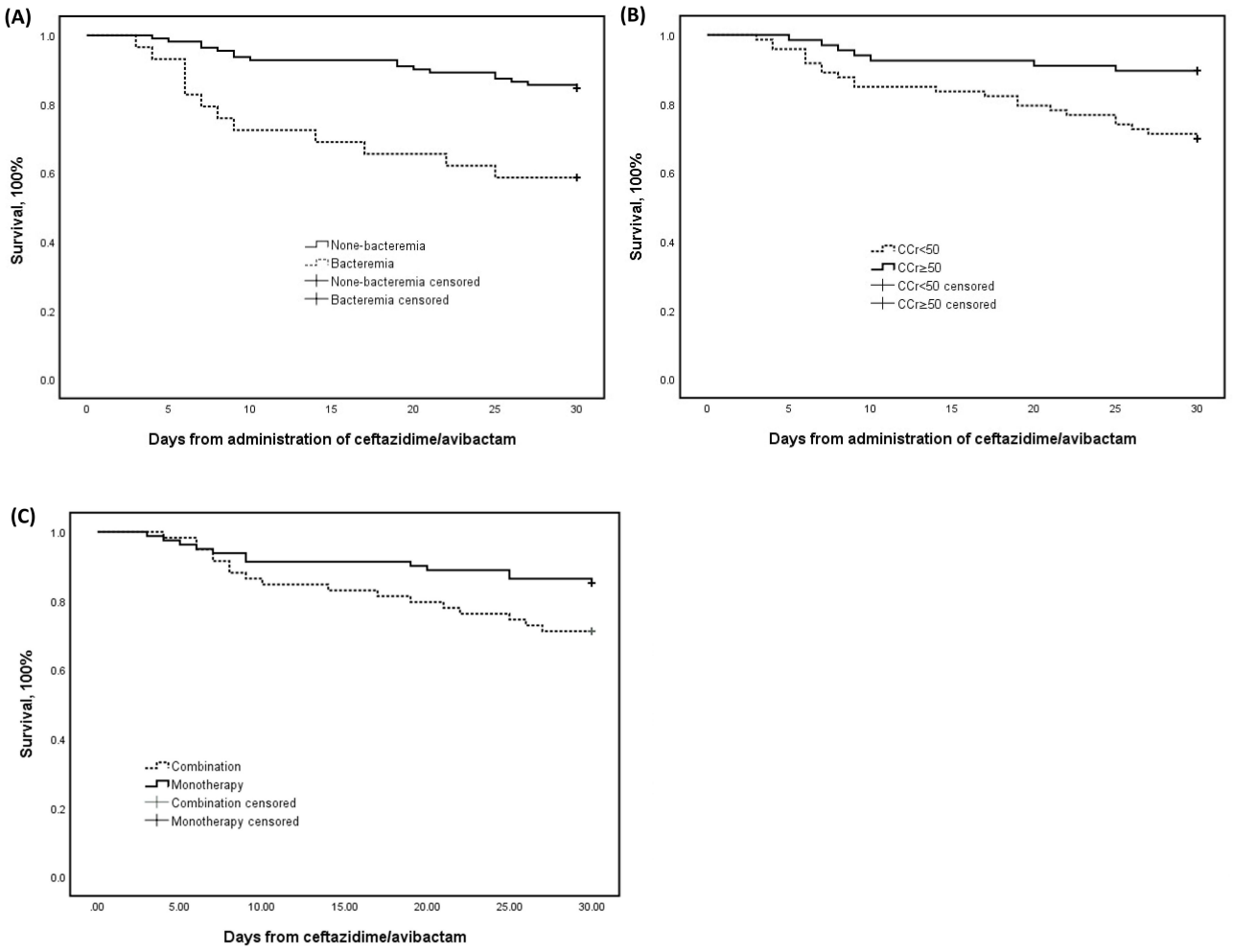

Figure 1 Kaplan–Meier Curves of Factors Associated with Survival (**A**) Kaplan–Meier curve of the impact of bacteremia or not on 30-day survival. Significantly higher mortality was observed in bacteremic group than in non-bacteremic group (P=0.001). (**B**) Kaplan–Meier curve of the impact of renal function (Cut off point: CCr 50) on 30-day survival. Significantly higher survival was observed in patients with CCr≥50 versus CCr<50 (P=0.005). (**C**) Kaplan-Meier curve of the impact of monotherapy or combination therapy on 30-day survival. Significantly higher survival was observed in patients with monotherapy versus combination therapy (P=0.046).

Table 3 Univariate and Multivariate Analysis of Factors Associated with 28-Day Survival

	Survivors (n=111)	Nonsurvivors (n=29)	Univariate		Multivariate	
			P value	OR (95% CI)	P value	OR (95% CI)
Males	66 (59%)	16 (55%)	0.68	1.19 (0.52–2.72)		
Age, IQR	73 (63–81)	76 (65.5–80.5)	0.35	0.98 (0.95–1.02)		
Comorbidities						
COPD	16 (14%)	3(10%)	0.57	1.46 (0.40–5.40)		
CHF	26 (23%)	5 (17%)	0.48	1.47 (0.51–4.23)		
Solid tumor	27 (24%)	12 (41%)	**0.07**	**0.46 (0.19–1.07)**	0.128	0.25(0.04–1.49)
Hematologic malignancy	2 (2%)	2 (7%)	0.17	0.25 (0.03–1.84)		
Liver disease	20 (18%)	6 (21%)	0.74	0.84 (0.30–2.34)		
Diabetes Mellitus	57 (51%)	11 (38%)	0.2	1.73 (0.75–3.99)		
Infection site						
Bacteremia	17 (15%)	12 (41%)	**0.003**	**0.26 (0.10–0.63)**	0.750	0.72(0.09–5.53)
Non bacteremia	94 (85%)	17 (59%)	0.003	3.90 (1.5–9.26)		

(*Continued*)

Table 3 (Continued).

	Survivors (n=111)	Nonsurvivors (n=29)	Univariate		Multivariate	
			P value	OR (95% CI)	P value	OR (95% CI)
LRTI	52 (47%)	11 (38%)	0.39	1.44 (0.62–3.33)		
UTI	24 (22%)	2 (7%)	**0.09**	**3.72 (0.83–16.79)**	0.915	1.12(0.14–9.16)
IAI	12 (11%)	3 (10%)	0.94	1.05 (0.28–4.00)		
SSTI	6 (5%)	1 (3%)	0.67	1.60 (0.19–13.84)		
Treatment variables						
Monotherapy	69 (62%)	12 (41%)	**0.047**	**2.33 (1.01–5.35)**	0.424	0.33(0.02–5.01)
Combination therapy	42 (38%)	17 (59%)	**0.047**	**0.43 (0.19–0.99)**		
Combine 1 agent	36 (32%)	15 (52%)	**0.06**	**0.45 (0.20–1.03)**	0.865	0.80(0.07–9.99)
Combine 2 agents	6 (5%)	2 (7%)	0.76	0.77 (0.15–4.04)		
Combine with Colistin	15 (14%)	8 (28%)	**0.08**	**0.41 (0.15–1.09)**	0.800	0.77(0.10–6.07)
Time to active antibiotics, IQR	4 (1–5)	4 (2–5)	0.56	1.04 (0.92–1.17)		
Time to CTZ-AVI, IQR	5 (4–6)	4 (3–5.5)	0.72	1.02 (0.92–1.13)		
Severity of illness						
SOFA, IQR	3 (2–5)	11 (8–14.5)	**<0.001**	**0.59 (0.49–0.71)**	**<0.001**	**0.51(0.36–0.71)**
CCI, IQR	6 (4–7)	6 (5–8.5)	**0.08**	**0.85 (0.72–1.02)**	0.372	1.18(0.82–1.70)
INCREMENT≥8	10 (9%)	15 (52%)	**<0.001**	**0.09 (0.04–0.25)**	0.691	0.46(0.01–22.22)
Mechanical ventilation	51 (46%)	25 (86%)	**<0.001**	**0.14 (0.04–0.42)**	0.316	3.15(0.33–29.81)
Septic shock	11 (10%)	13 (45%)	**<0.001**	**0.14 (0.05–0.35)**	0.645	2.48(0.05–118.02)
Renal status						
CCr≥50	60 (54%)	7 (24%)	**0.01**	**3.70 (1.46–9.36)**	0.769	1.32(0.21–8.32)
50>CCr≥10	29 (26%)	14 (48%)	**0.02**	**0.38 (0.16–0.88)**		
CCr<10 (without Dialysis)	1 (1%)	1 (3%)	0.34	0.26 (0.02–4.20)		
Dialysis	21 (19%)	7 (24%)	0.53	0.73 (0.28–1.94)		
CCr<30	35 (32%)	15 (52%)	**0.046**	**0.43 (0.19–0.99)**	0.749	1.35(0.21–8.53)

Notes: Bold text indicates statistically significant differences.

Abbreviations: COPD, chronic obstructive pulmonary disease; CHF, congestive heart failure; LRTI, lower respiratory tract infection; UTI, urinary tract infection; IAI, intra abdominal infection; SSTI, skin and soft tissue infection; CCr, creatinine clearance rate; IQR, interquartile range; OR, odds ratio; CI, confidence interval.

In the multivariate analysis (Table 3), SOFA score was the only independent factor associated with poor 28-day survival outcome (aOR: 0.51, 95% C.I: 0.36–0.71, P<0.001).

Predictors Associated with Secondary Outcomes

The secondary outcomes were defined as clinical success and microbiological cure, which were shown in Tables S1 and S2. In univariate analysis, patients with bacteremia or received monotherapy were associated with less clinical success (Table S1), but neither one reached statistical significance in multivariate analysis (Table S1).

In addition, a multivariate analysis model indicated that solid tumor was a negative predictor for clinical success (aOR: 0.34, 95% C.I: 0.14–0.82, P=0.017). As for microbiological cure (Table S2), there was no significant associated factor.

Discussion

With the increasing use of CZA in CRE infection worldwide, here we reported our real-world experience of CZA for CRKP infection in Taiwan. Our result of primary outcome, 28-day survival rate 78% in CRKP infection patients treated with CZA, was similar to previous literatures ranging from 66% to 83%.[13,23,24] We also demonstrated negative associations between the SOFA scores of the patients and survival outcome.[25] The overall microbiological cure rate of our study was 86%, of which the microbiological cure rate of LRTI group (80%) was relatively lower than the other infection source (89%). This finding was also reported by a recent subgroup analysis of the Phase 3 clinical trial that only

53% patients with ventilator-associated pneumonia reached microbiological eradication, comparing with 80% of all infections.[26] Other cohort hypothesized that poor outcomes in LRTI patients treated with CZA is possibly related to drug's pharmacokinetic properties for pulmonary infection and higher INCREMENT score in their LRTI group.[27] However, another conflict result of pharmacokinetic analysis stated that enough therapeutic concentration of CZA could be achieved in the epithelial lining fluid.[28] Our study also found that, despite the LRTI group having a lower INCREMENT score compared to bacteremia group, it also displayed a lower microbiological cure rate. More evidence is needed for the relatively poor performance on microbiological cure of CZA treatment in LRTI.

The clinical success rate among our patients treated with CZA was 47%, slightly lower than reported in previous studies. In the literatures, the clinical success rate of the treatment ranges from 45% to 73%.[12,14,24,29,30] The variabilities may come from inconsistent definition and evaluation timing for clinical success, different eligible criteria, and the different species isolated. Previous research found that CZA-treated patients with pneumonia had lower clinical success rates than other infection sites (aOR: 3.09, 95% C.I: 1.03–9.34, p=0.045)[31] Furthermore, a recent retrospective observational study stated that the mortality was significantly higher among patients with LRTIs than in those with other types of infections.[27] These findings differed from our results that LRTI group are higher than bacteremia group, whether in survival rate or clinical success rate. The results may be attributed to disease severity, such as higher SOFA score and INCREMENT-CPE score among our bacteremic patients.

Before CZA became available, combination of two or more selected active antibiotics were widely used for the treatment of CRE.[32,33] However, in a recent retrospective observational multicenter study, the use of CZA monotherapy for patients with KPC-Kp infections revealed no significant difference in the 30-day mortality rate (26.1% vs 25.0%, P=0.79) when compared with the combination therapy.[27] Furthermore, from three meta-analysis, the combination therapy of CZA for carbapenem-resistant gram-negative pathogens infection (GNIs) also showed no significant difference in mortality rate when compared to CZA monotherapy (OR: 0.96, 95% CI: 0.65–1.41,[34] OR: 1.03, 95% CI: 0.79–1.34,[35] RR = 1.18, 95% CI 0.88–1.58[36]). A recent retrospective cohort study similarly showed no significant differences in clinical cure, in-hospital mortality, 30-day mortality, infection-related mortality, or microbiologic eradication between CZA combination therapy and monotherapy for treating *Pseudomonas aeruginosa* infections.[37] In our survival analysis, we found higher 28-day survival rate in patients receiving CZA monotherapy compared to combination therapy. Furthermore, our multivariate analysis did not reveal any significant survival benefits in combination therapy group. These findings suggest that monotherapy with CZA may be as effective as combination therapy in treating CRE, in consistent with previous research results. The relative lower survival rate in our combination therapy group than monotherapy group may possibly be related to higher disease severity in cases received combination regimens.

Higher incidence of AKI was observed in combination therapy of CZA than in monotherapy. The most common antimicrobial agents combined with CZA in our patients were colistin, which is known for its nephrotoxicity. A retrospective cohort study reported that incident AKI in colistin group was associated with 6.1 times higher odds (95% CI 2.53, 14.71) of mortality than in CZA group.[38] The issue that higher mortality associated with AKI in the patients treated with both CZA and colistin cannot be ignored.

Dose adjustment of CZA by renal function was usually performed when the CCr of the patient was lower than 50. From our study, survival benefit was shown in patient without dose adjustment from Kaplan–Meier survival analysis (Figures 1B and S2) and univariate regression analysis of 28-day survival rate (Table 3). According to a randomized-controlled trial, which compared CZA with meropenem for cIAI infection in clinical outcomes, less effectiveness with CZA in renal insufficiency was observed from subgroup analysis.[8] Previous studies emphasized that the possible effect of this finding may be related to inappropriate dose adjustment in critically-ill patients.[27,39] They stated that protocols for renal-dose adjustment of CZA are based mainly on data collected from individuals with stable chronic kidney disease (CKD). Moreover, they proposed deferral of dose adjustments within the first 48 hours of therapy for severe infectious events to improve outcomes. Besides, when the CCr of the patients was lower than 50, the dose of ceftazidime given in CZA was often lower than that of ceftazidime given alone. Further research may be necessary to assess the potential negative impact of CZA dose adjustments on survival outcomes, and the appropriate dosage for severe infectious chronic kidney disease (CKD) cases must be determined.

There are some limitations in our study. First of all, owing to retrospective, observational study design and limited number of patients included, the results may have been influenced by unrecognized factors. Second, only partial CRKP strains were evaluated by the *E* test for CZA, and we did not identify the resistant mechanism such as KPC or Oxa-48

like producing *Klebsiella pneumoniae* in a real-world setting, so whether treatment failure is related to ceftazidime-avibactam-resistant pathogens cannot be fully understood. In real-world practice, however, at the time of CZA available in Taiwan, the susceptibility testing such as *E* test was not yet widely adopted. Based on previous surveillance results, CZA demonstrated a remarkable susceptibility of 99.1% against *Klebsiella pneumoniae* in Taiwan.[7] Although in recent years, there has been a noticeable increase in the minimum inhibitory concentration of CZA against CRKP, it still maintains favorable susceptibility in Taiwan, especially in the early stages of its implementation.[40] Although the susceptibility of CRKP is not all available, limited isolates in our study demonstrated 95.5% susceptibility of CZA for CRKP via *E* test. The only patient in our cohort with CZA-resistant CRKP infection was switched to colistin after 4 days of CZA treatment and subsequently discharged successfully. Third, whether the patients received monotherapy or combination therapy depends on the decision of primary care clinicians and may have selection bias. Patients with higher disease severity could have higher opportunity to receive combination therapy.

Conclusion

In conclusion, we found that CZA is an effective and important treatment option for CRKP infection even when used as monotherapy. SOFA score is an independent factor associated with worse 28-day survival. In addition, poor survival outcome has been observed among patients with impaired renal function which, is consistent with previous cohort studies. Additional research is needed to determine optimal renal-dose adjustment strategies.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Tzouvelekis LS, Markogiannakis A, Psichogiou M, Tassios PT, Daikos GL. Carbapenemases in Klebsiella pneumoniae and other Enterobacteriaceae: an evolving crisis of global dimensions. *Clin Microbiol Rev*. 2012;25(4):682–707. doi:10.1128/CMR.05035-11
2. Jean SS, Lee NY, Tang HJ, Lu MC, Ko WC, Hsueh PR. Carbapenem-Resistant Enterobacteriaceae Infections: Taiwan Aspects. *Front Microbiol*. 2018;9:2888. doi:10.3389/fmicb.2018.02888
3. Lee YL, Lu MC, Shao PL, et al. Nationwide surveillance of antimicrobial resistance among clinically important Gram-negative bacteria, with an emphasis on carbapenems and colistin: results from the Surveillance of Multicenter Antimicrobial Resistance in Taiwan (SMART) in 2018. *Int J Antimicrob Agents*. 2019;54(3):318–328. doi:10.1016/j.ijantimicag.2019.06.009
4. Paul M, Carrara E, Retamar P, et al. European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines for the treatment of infections caused by multidrug-resistant Gram-negative bacilli (endorsed by European society of intensive care medicine). *Clin Microbiol Infect*. 2022;28(4):521–547.
5. Sy CL, Chen PY, Cheng CW, et al. Recommendations and guidelines for the treatment of infections due to multidrug resistant organisms. *J Microbiol Immunol Infect*. 2022;55(3):359–386. doi:10.1016/j.jmii.2022.02.001
6. Liao CH, Lee NY, Tang HJ, et al. Antimicrobial activities of ceftazidime-avibactam, ceftolozane-tazobactam, and other agents against Escherichia coli, Klebsiella pneumoniae, and Pseudomonas aeruginosa isolated from intensive care units in Taiwan: results from the Surveillance of Multicenter Antimicrobial Resistance in Taiwan in 2016. *Infect Drug Resist*. 2019;12:545–552. doi:10.2147/IDR.S193638
7. Jean SS, Lu MC, Shi ZY, et al. In vitro activity of ceftazidime-avibactam, ceftolozane-tazobactam, and other comparable agents against clinically important Gram-negative bacilli: results from the 2017 Surveillance of Multicenter Antimicrobial Resistance in Taiwan (SMART). *Infect Drug Resist*. 2018;11:1983–1992. doi:10.2147/IDR.S175679
8. Mazuski JE, Gasink LB, Armstrong J, et al. Efficacy and Safety of Ceftazidime-Avibactam Plus Metronidazole Versus Meropenem in the Treatment of Complicated Intra-abdominal Infection: results From a Randomized, Controlled, Double-Blind, Phase 3 Program. *Clin Infect Dis*. 2016;62(11):1380–1389. doi:10.1093/cid/ciw133
9. Carmeli Y, Armstrong J, Laud PJ, et al. Ceftazidime-avibactam or best available therapy in patients with ceftazidime-resistant Enterobacteriaceae and Pseudomonas aeruginosa complicated urinary tract infections or complicated intra-abdominal infections (REPRISE): a randomised, pathogen-directed, phase 3 study. *Lancet Infect Dis*. 2016;16(6):661–673. doi:10.1016/S1473-3099(16)30004-4
10. Wagenlehner FM, Sobel JD, Newell P, et al. Ceftazidime-avibactam Versus Doripenem for the Treatment of Complicated Urinary Tract Infections, Including Acute Pyelonephritis: RECAPTURE, a Phase 3 Randomized Trial Program. *Clin Infect Dis*. 2016;63(6):754–762. doi:10.1093/cid/ciw378
11. Torres A, Zhong N, Pachl J, et al. Ceftazidime-avibactam versus meropenem in nosocomial pneumonia, including ventilator-associated pneumonia (REPROVE): a randomised, double-blind, phase 3 non-inferiority trial. *Lancet Infect Dis*. 2018;18(3):285–295. doi:10.1016/S1473-3099(17)30747-8
12. Almangour TA, Ghonem L, Aljabri A, et al. Ceftazidime-Avibactam versus Colistin for the Treatment of Infections Due to Carbapenem-Resistant Enterobacterales: a Multicenter Cohort Study. *Infect Drug Resist*. 2022;15:211–221. doi:10.2147/IDR.S349004
13. Tumbarello M, Trecarichi EM, Corona A, et al. Efficacy of Ceftazidime-Avibactam Salvage Therapy in Patients With Infections Caused by Klebsiella pneumoniae Carbapenemase-producing K. pneumoniae. *Clin Infect Dis*. 2019;68(3):355–364. doi:10.1093/cid/ciy492
14. Shields RK, Nguyen MH, Chen L, et al. Ceftazidime-Avibactam Is Superior to Other Treatment Regimens against Carbapenem-Resistant Klebsiella pneumoniae Bacteremia. *Antimicrob Agents Chemother*. 2017;61(8). doi:10.1128/AAC.00883-17

15. CDC/NHSN surveillance definitions for specific types of infections. *National Healthcare Safety Network (NHSN) patient safety component manual 2023 Chapter 17*. 2023.
16. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40(5):373–383. doi:10.1016/0021-9681(87)90171-8
17. Gutiérrez-Gutiérrez B, Salamanca E, de Cueto M, et al. Effect of appropriate combination therapy on mortality of patients with bloodstream infections due to carbapenemase-producing Enterobacteriaceae (INCREMENT): a retrospective cohort study. *Lancet Infect Dis*. 2017;17(7):726–734. doi:10.1016/S1473-3099(17)30228-1
18. Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA*. 2016;315(8):801–810. doi:10.1001/jama.2016.0287
19. Vincent JL, Moreno R, Takala J, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. *Intensive Care Med*. 1996;22(7):707–710. doi:10.1007/BF01709751
20. Khwaja A. KDIGO clinical practice guidelines for acute kidney injury. *Nephron Clin Pract*. 2012;120(4):c179–184. doi:10.1159/000339789
21. CLSI. Performance Standards for Antimicrobial Susceptibility Testing. 28th ed. CLSI supplement M100. 2023.
22. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron*. 1976;16(1):31–41. doi:10.1159/000180580
23. Jorgensen SCJ, Trinh TD, Zasowski EJ, et al. Real-World Experience With Ceftazidime-Avibactam for Multidrug-Resistant Gram-Negative Bacterial Infections. *Open Forum Infect Dis*. 2019;6(12):ofz522. doi:10.1093/ofid/ofz522
24. Shi Y, Hu J, Liu P, et al. Ceftazidime-Avibactam-Based Versus Tigecycline-Based Regimen for the Treatment of Carbapenem-Resistant Klebsiella pneumoniae-Induced Pneumonia in Critically Ill Patients. *Infect Dis Ther*. 2021;2021:1–14.
25. Jones AE, Trzeciak S, Kline JA. The Sequential Organ Failure Assessment score for predicting outcome in patients with severe sepsis and evidence of hypoperfusion at the time of emergency department presentation. *Crit Care Med*. 2009;37(5):1649–1654. doi:10.1097/CCM.0b013e31819def97
26. Mazuski JE, Wagenlehner F, Torres A, et al. Clinical and Microbiological Outcomes of Ceftazidime-Avibactam Treatment in Adults with Gram-Negative Bacteremia: a Subset Analysis from the Phase 3 Clinical Trial Program. *Infect Dis Ther*. 2021;10(4):2399–2414. doi:10.1007/s40121-021-00506-7
27. Tumbarello M, Raffaelli F, Giannella M, et al. Ceftazidime-Avibactam Use for Klebsiella pneumoniae Carbapenemase-Producing K. pneumoniae Infections: a Retrospective Observational Multicenter Study. *Clin Infect Dis*. 2021;73(9):1664–1676. doi:10.1093/cid/ciab176
28. Dimelow R, Wright JG, MacPherson M, Newell P, Das S. Population Pharmacokinetic Modelling of Ceftazidime and Avibactam in the Plasma and Epithelial Lining Fluid of Healthy Volunteers. *Drugs R D*. 2018;18(3):221–230. doi:10.1007/s40268-018-0241-0
29. Di Pietrantonio M, Brescini L, Candi J, et al. Ceftazidime-Avibactam for the Treatment of Multidrug-Resistant Pathogens: a Retrospective, Single Center Study. *Antibiotics (Basel)*. 2022;11(3). doi:10.3390/antibiotics11030321
30. Kuang H, Zhong C, Wang Y, et al. Clinical characteristics and outcomes of patients with multidrug-resistant Gram-negative bacterial infections treated with ceftazidime/avibactam. *J Glob Antimicrob Resist*. 2020;23:404–407. doi:10.1016/j.jgar.2020.10.023
31. Shields RK, Nguyen MH, Chen L, Press EG, Kreiswirth BN, Clancy CJ. Pneumonia and Renal Replacement Therapy Are Risk Factors for Ceftazidime-Avibactam Treatment Failures and Resistance among Patients with Carbapenem-Resistant Enterobacteriaceae Infections. *Antimicrob Agents Chemother*. 2018;62(5). doi:10.1128/AAC.02497-17
32. Daikos GL, Tsaousi S, Tzouvelekis LS, et al. Carbapenemase-producing Klebsiella pneumoniae bloodstream infections: lowering mortality by antibiotic combination schemes and the role of carbapenems. *Antimicrob Agents Chemother*. 2014;58(4):2322–2328. doi:10.1128/AAC.02166-13
33. Giannella M, Trecarichi EM, Giacobbe DR, et al. Effect of combination therapy containing a high-dose carbapenem on mortality in patients with carbapenem-resistant Klebsiella pneumoniae bloodstream infection. *Int J Antimicrob Agents*. 2018;51(2):244–248. doi:10.1016/j.ijantimicag.2017.08.019
34. Fiore M, Alfieri A, Di Franco S, et al. Ceftazidime-Avibactam Combination Therapy Compared to Ceftazidime-Avibactam Monotherapy for the Treatment of Severe Infections Due to Carbapenem-Resistant Pathogens: a Systematic Review and Network Meta-Analysis. *Antibiotics (Basel)*. 2020;9(7):1.
35. Li D, Fei F, Yu H, et al. Ceftazidime-Avibactam Therapy Versus Ceftazidime-Avibactam-Based Combination Therapy in Patients With Carbapenem-Resistant Gram-Negative Pathogens: a Meta-Analysis. *Front Pharmacol*. 2021;12:707499. doi:10.3389/fphar.2021.707499
36. Onorato L, Di Caprio G, Signoriello S, Coppola N. Efficacy of ceftazidime/avibactam in monotherapy or combination therapy against carbapenem-resistant Gram-negative bacteria: a meta-analysis. *Int J Antimicrob Agents*. 2019;54(6):735–740. doi:10.1016/j.ijantimicag.2019.08.025
37. Almangour TA, Ghonem L, Alassiri D, et al. Novel β-lactam-β-lactamase inhibitors as monotherapy versus combination for the treatment of drug-resistant Pseudomonas aeruginosa infections: a multicenter cohort study. *J Infect Chemother*. 2024;30(10):1008–1014. doi:10.1016/j.jiac.2024.03.015
38. Doremus C, Marcella SW, Cai B, Echols RM. Utilization of Colistin Versus β-Lactam and β-Lactamase Inhibitor Agents in Relation to Acute Kidney Injury in Patients with Severe Gram-Negative Infections. *Infect Dis Ther*. 2021;2021:1–13.
39. Jorgensen SCJ, Trinh TD, Zasowski EJ, et al. Evaluation of the INCREMENT-CPE, Pitt Bacteremia and qPitt Scores in Patients with Carbapenem-Resistant Enterobacteriaceae Infections Treated with Ceftazidime-Avibactam. *Infect Dis Ther*. 2020;9(2):291–304. doi:10.1007/s40121-020-00288-4
40. Lee JA, Du SH, Lee TF, et al. Rapid emergence of ceftazidime-avibactam resistance among carbapenem-resistant Enterobacterales in a tertiary-care hospital in Taiwan. *J Infect*. 2023;86(1):66–117. doi:10.1016/j.jinf.2022.10.003