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Investigation of Patients Receiving Ceftazidime-Avibactam (CZA) in an Intensive Care Unit: A Retrospective Study from a Tertiary Hospital

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ABSTRACT

Objective: This study aimed to examine the clinical characteristics and prognosis of patients receiving ceftazidime-avibactam (CZA) treatment in an intensive care unit (ICU).

Materials and Methods: This observational, cross-sectional study was conducted with patients hospitalized in the ICU between June 2021 and April 2023. Among 1,900 patients, a total of 65 were identified to have received CZA treatment. All patients receiving this treatment were included in the study. We recorded patients' demographic data and comorbid diseases. We also investigated clinical outcomes in the ICU, such as sepsis, the requirement for mechanical ventilation (MV), mortality rates, and clinical features regarding infections.

Results: Of the 65 patients, 69.2% were male, with an average age of 65±15 years. The overall mortality rate was 70.8%. The most common type of infection and the most frequently isolated pathogen were pneumonia (61.5%) and *Klebsiella pneumoniae* (73.8%), respectively. Deceased patients had clinically poorer scores on the Glasgow Coma Scale (GCS), Acute Physiology and Chronic Health Evaluation II (APACHE-II), and Sequential Organ Failure Assessment (SOFA) than survivors (p=0.006, p<0.001 and p<0.001, respectively). The rate of colistin exposure before CZA treatment was higher among dying patients (p=0.036). Multiple regression analyses indicated that factors independently associated with ICU mortality were the need for mechanical ventilation support [Odds ratio (OR): 15.155; p=0.023), development of septic shock (OR: 8.558; p=0.017), and APACHE-II score (OR: 1.146; p=0.045).

Conclusion: Our findings suggest that the development of septic shock, the requirement for mechanical ventilation (MV), and high APACHE-II and Sequential Organ Failure Assessment (SOFA) scores, and low GCS scores may be indicators of poor prognosis for patients requiring CZA.

Keywords: Carbapenem-resistant, gram-negative bacteria, ceftazidime-avibactam, intensive care unit.

INTRODUCTION

Carbapenem-resistant *Enterobacteriaceae* (CRE) have become increasingly common worldwide[1] and pose a significant global public health challenge.[2–4] While the main challenge in the early 2000s was methicillin-resistant *Staphylococcus aureus* (MRSA), today's primary concern for health professionals is treatment of multidrug-resistant (MDR) gram-negative bacteria.[5]

Currently, the antibiotic options for treating CRE are limited, and the mainstays of treatment include polymyxins, tigecycline, fosfomycin, and aminoglycosides. The increasing prevalence of pathogens producing extended-spectrum β-lactamase (ESBL) has led to the increased use of carbapenems.[4,6] Therefore, the emergence and spread of carbapenemase-producing pathogens, including carbapenem-resistant *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacteriaceae*, are of particular concern and have emphasized the urgent need for new antimicrobial agents.[2,7]

Ceftazidime-avibactam (CZA) is a new β-lactam/β-lactamase inhibitor combination. CZA has been used for complicated urinary tract infections and complicated intra-abdominal infections in the United States since February 2015, and for the treatment of hospital-associated pneumonia (HAP) and ventilator-associated pneumonia (VAP) since January 2018.[8] The use of CZA has also begun in Türkiye, especially in intensive care units (ICUs) recently. The antibacterial spectrum of CZA covers 95% of *P. aeruginosa* isolates and more than 99% of *Enterobacteriaceae*, making it one of the most commonly isolated bacteria in ICUs.[9] Combination therapy for MDR Gram-negative infections, such as the combination of colistin-polymyxin B or tigecycline with carbapenem, appears to be more successful than monotherapy and may reduce the elevation of antibiotic resistance.[10] CZA can also be administered as monotherapy or combined therapy options.[10]

In terms of the clinical use of CZA, for which experience has recently increased, the number of studies remains insufficient, especially in our country. Therefore, in the present study, we aimed to investigate the clinical characteristics of patients receiving CZA treatment and hospitalized in the ICU of an internal medicine department.

MATERIALS AND METHODS

Selection of the Patients

This cross-sectional and observational study was conducted with patients hospitalized in the 32-bed ICU of the internal medicine department at Health Sciences University, Konya City Hospital between June 2021 and April 2023. Among 1,900 patients examined, a total of 65 patients received CZA treatment. All patients treated with CZA were included in the study.

KEY MESSAGES

- Carbapenem-resistant Gram-negative bacteria are one of the most important pathogens increasing the risk of mortality, morbidity, sepsis, and septic shock in ICUs.
- The mortality rate in the recent study population was high (70.8%) and receiving colistin therapy before CZA treatment increased mortality in patients.
- In this study population, septic shock, use of steroids, receiving mechanical ventilation support, high scores of APACHE-II and SOFA, and low scores of GCS may be indicators of poor prognosis.

Ethical Board Approval

For the study, approval was obtained from the Non-Drug and Medical Device Research Ethics Committee of the Faculty of Medicine at KTO Karatay University Trade Chambers (Number: 2023/015-06 and date: 22 June 2023).

Inclusion Criteria

Patients aged 18 years or older undergoing CZA treatment in the internal ICU who had not died in the first 72 hours were included in the study.

Exclusion Criteria

Patients not receiving CZA treatment or those who started to receive CZA treatment but died within the first 72 hours were excluded from the study.

Patients' General Characteristics and Status During the Follow-ups in ICU

The demographic data and comorbid diseases of the patients were recorded. During the follow-up in the ICU, we investigated whether features such as the development of septic shock; the use of vasopressors and steroids; continuous renal replacement therapy; and the need for ventilator support occurred. Additionally, the scores from the Acute Physiology and Chronic Health Evaluation (APACHE-II) and Sequential Organ Failure Assessment (SOFA) measured on the first day of ICU admission, which are indicators of prognosis in ICUs, were recorded. Patients' pre-CZA treatment values of C-reactive protein (CRP) and procalcitonin were noted. Post-treatment CRP and procalcitonin values of those receiving CZA treatment for 14 days were also recorded. If a patient died within the treatment period of CZA before completing the treatment (3-14 days), the CRP and procalcitonin levels were noted on the day the patient died. Patients who completed CZA treatment

and were discharged from the ICU in good health, as evidenced by clinical and laboratory findings, were considered successful in terms of the treatment administered. In other words, success was indicated by decreased CRP and procalcitonin values within the laboratory reference range. Additionally, the total duration of CZA treatment was determined by recording the initial and discontinuation dates of CZA treatment. The ICU and hospital stay durations of the patients were also recorded. On the other hand, the final status of the patients in the ICU was defined as either deceased or survivors (those discharged in good health).

Clinical and Microbiologic Features of Infection

From the culture outcomes of the patients, the type of bacteria, the site of growth, and the types of infections caused by these bacteria (pneumonia, urinary tract infection, bacteremia, etc.) were investigated. Antibiotics previously received by the patients were noted (before and concomitantly with CZA treatment).

Statistical Analysis

The Standard Package for the Social Sciences for Windows, version 21.0 (SPSS, IBM Inc., IL, USA) was used for analysis. Whether numerical variables were normally distributed or not was examined using the Kolmogorov-Smirnov test. Normally distributed numerical variables were expressed as mean±standard deviation (SD), non-normally distributed numerical variables were given as median (minimum-maximum), and categorical variables were presented as numbers and percentages. For comparing numerical variables of independent groups, the Student's t-test was used for variables with normal distribution, and the Mann-Whitney U test was utilized for those with non-normal distribution. Moreover, the chi-square test or Fisher's exact test was used to compare categorical data between independent groups, where appropriate. For contingency tables larger than 2 x 2, the Fisher-Freeman-Halton Exact test was used. If 20% or more of the cells had an expected count of less than 5, or the minimum expected count was below 2, Fisher's exact test's p-value was accepted as the statistical result. Univariate and multiple binary logistic regression analyses were employed to identify factors associated with mortality in the ICU. The continuous variables in two dependent groups with skewed distributions were compared using the Wilcoxon Test (the CRP and procalcitonin levels in pre- and post-CZA treatment periods). A p-value of less than 0.05 was considered statistically significant.

RESULTS

The demographic data and comorbid diseases of 65 patients in our study are listed in Table 1. The average age of the patients was 65±15 years, and 69.2% (n=45) were male. The mortality rate in the entire patient population was 70.8%. The most common type of infection and the most frequently isolated pathogen were pneumonia (61.5%) and *Klebsiella pneumoniae* (73.8%), respectively. Additionally, the majority of the patients required invasive mechanical ventilation (IMV) (72.3%). During the pre-CZA period, 69.2% and 56.9% of the patients had received carbapenem and colistin treatment, respectively. The rate of solid malignancy among dying patients (23.9%) was higher than that in survivors (p=0.03). It was determined that the rate of neurological diseases other than cerebrovascular accidents (CVA) was lower among deceased patients (p=0.02). IMV, steroid use, and the development of septic shock were statistically higher in the dying patients. Deceased patients also had clinically poorer scores of the Glasgow Coma Scale (GCS), APACHE-II, and SOFA (p=0.006, p<0.001, and p<0.001, respectively). While there was no statistically significant difference between dying and surviving patients in terms of pre- and post-CZA treatment CRP values (p=0.05 and p=0.86, respectively), procalcitonin levels were higher among deceased patients during both pre- and post-CZA treatment periods (p<0.001 for both). The follow-up period post-CZA treatment was shorter in deceased patients (p<0.001), and the detailed findings of the parameters compared between deceased and surviving patients are presented in Table 1.

In the present study, CZA treatment was primarily used for pneumonia (61.5%) and bloodstream infections (15.4%). Culture positivity was most commonly seen in endotracheal aspiration (ETA) (56.9%) and peripheral blood cultures (16.9%). The most frequently isolated pathogens were *K. pneumoniae* (73.8%) and *P. aeruginosa* (16.9%). When examining the pre-CZA treatment rates of antibiotic use, the most frequently used antibiotics were carbapenem (69.2%), tigecycline (47.7%), colistin (56.9%), and fosfomycin (41.5%), respectively. When comparing deceased and surviving patients, no statistical difference was observed between both groups in terms of sites of culture positivity, types of infections, growing pathogens, and history of using antibiotics, except for colistin. The rate of exposure to colistin before CZA treatment was found to be higher among deceased patients, and the findings are presented in Table 2.

Statistically significant parameters among the factors associated with ICU mortality in univariate analyses were included in multiple regression analyses. As a result of multiple regression analyses, it was revealed that the factors independently associated with mortality were the following: need for mechanical ventilation support [Odds ratio (OR): 15.155; p=0.023), development of septic shock (OR: 8.558; p=0.017), and APACHE-II score (OR: 1.146; p=0.045). The findings related to regression analyses are shown in Table 3.

Table 1. Comparisons of general characteristics of patients in terms of death status

Parameters	Total (n=65)	Deceased (n=46)	Survivors (n=19)	p
Sex				
Male, n (%)	45 (69.2)	31 (67.4)	14 (73.7)	0.62
Female, n (%)	20 (30.8)	15 (32.6)	5 (26.3)	
Comorbidities				
DM, n (%)	20 (30.8)	16 (34.8)	4 (21.1)	0.28
COPD, n (%)	9 (13.8)	6 (13.0)	3 (15.8)	0.71
Hematological malignancy, n (%)	12 (18.5)	10 (21.7)	2 (10.5)	0.48
Solid malignancy, n (%)	11 (16.9)	11 (23.9)	0 (0.0)	**0.03**
CHF, n (%)	12 (18.5)	10 (21.7)	2 (10.5)	0.48
Neurological causes (non-CVA) , n (%)	30 (46.2)	17 (37.0)	13 (68.4)	**0.02**
CKD, n (%)	9 (13.8)	6 (13.0)	3 (15.8)	0.71
Peptic ulcer, n (%)	2 (3.1)	1 (2.2)	1 (5.3)	0.50
CAD, n (%)	17 (26.2)	13 (28.3)	4 (21.1)	0.76
PAD, n (%)	3 (4.6)	2 (4.3)	1 (5.3)	0.99
Dementia, n (%)	15 (23.1)	9 (19.6)	6 (31.6)	0.34
Connective tissue diseases, n (%)	3 (4.6)	2 (4.3)	1 (5.3)	0.99
CVA, n (%)	17 (26.2)	9 (19.6)	8 (42.1)	0.07
Respiratory support				**0.001****
IMV, n (%)	47 (72.3)	38 (82.6)	9 (47.4)	
NIMV, n (%)	3 (4.6)	3 (6.5)	0 (0.0)	
Only O_2 support, n (%)	15 (23.1)	5 (10.9)	10 (52.6)	
CVVHDF, n (%)	10 (15.4)	9 (19.6)	1 (5.3)	0.26
Steroids, n (%)	37 (56.9)	33 (71.7)	4 (21.1)	<**0.001**
Septic shock, n (%)	44 (67.7)	39 (84.8)	5 (26.3)	<**0.001**
Hospital LOS, days, median (min–max)	75 (9–613)	60.5 (9–613)	164 (14–613)	**0.03**
ICU LOS, days, median (min–max)	47 (1–508)	41.5 (1–508)	74 (2–508)	0.14
Age, years, mean±standard deviation	65±15	66±15	61±17	0.24
GCS score, median (min–max)	9 (3–15)	7.5 (3–14)	10 (4–15)	**0.006**
APACHE II score, mean±standard deviation	34.06±7.47	36.3±5.8	28.6±8.4	<**0.001**
SOFA score, mean±standard deviation	7.97±2.42	8.7±2.1	6.1±2.1	<**0.001**
CRP levels (pre-CZA treatment), mg/L, median (min–max)*	133 (11–427)	150 (20–427)	102 (11–187)	0.05
PCT levels (pre-CZA treatment), µg-L, median (min–max)*	1.78 (0.06–84.10)	3.2 (0.1–84.1)	0.6 (0.1–5.7)	<**0.001**
CRP levels (post-CZA treatment), mg/L, median (min–max)*	47 (1–397)	45 (2.5–397)	49 (1–314)	0.86
PCT levels (post-CZA treatment), µg-L, median (min–max)*	1.14 (0.07–65)	2 (0.1–65)	0.3 (0.1–4.6)	<**0.001**
Follow-up period after CZA treatment, days, median (min–max)	25 (0–411)	16 (0–377)	78 (14–411)	<**0.001**

APACHE II: Acute Physiology and Chronic Health Evaluation; CAD: Coronary Artery Disease; CHF: Congestive Heart Failure; CKD: Chronic Kidney Disease; COPD: Chronic Obstructive Pulmonary Disease; CRP: C-Reactive Protein; CVA: Cerebrovascular Accident; CVVHDF: Continuous Venous Hemofiltration; DM: Diabetes Mellitus; GCS: Glasgow Coma Scale; ICU: Intensive Care Unit; IMV: Invasive Mechanical Ventilation; LOS: Length of Stay; NIMV: Non-Invasive Mechanical Ventilation; O2: Oxygen; PAH: Peripheral Artery Disease; PCT: Procalcitonin; pre: Before CZA treatment; post: After CZA treatment; SOFA: Sequential Organ Failure Assessment; CI: Confidence Interval; *CRP levels (pre CZA treatment) vs. CRP levels (post-CZA treatment) in survivors p=0.145; PCT levels (pre-CZA treatment) vs. PCT levels (post-CZA treatment) in survivors p=0.047. CRP levels (pre-CZA treatment) vs. CRP levels (post-CZA treatment) in deceased patients p<0.001; PCT levels (pre-CZA treatment) vs. PCT levels (post-CZA treatment) in deceased patients p=0.029. An asterisk (*) indicates comparisons between pre- and post-CZA treatment CRP and PCT levels in the dependent groups, using the Wilcoxon test. Two asterisks (**) indicate the Fisher-Freeman-Halton exact test's p-values.

Table 2. Comparisons of clinical and microbiological characteristics of patients in terms of death status

Parameters	Total (n=65		Deceased (n=46		Survivors (n=19)		p
	n	%	n	%	n	%	
Organ/system with culture positivity							0.385*
CVC	2	3.1	1	2.2	1	5.3	
Urinary	7	10.8	4	8.7	3	15.8	
ETA	37	56.9	25	54.3	12	63.2	
Blood	11	16.9	10	21.7	1	5.3	
Pressure ulcers	5	7.7	3	6.5	2	10.5	
Empirical	3	4.6	3	6.5	0	0.0	
Type of infections							0.506*
Pneumonia	40	61.5	28	60.9	12	63.2	
UTI	7	10.8	4	8.7	3	15.8	
Blood	10	15.4	9	19.6	1	5.5	
Pressure ulcers	6	9.2	4	8.7	2	10.5	
Catheter	2	3.1	1	2.2	1	5.3	
Pathogen							0.340*
No growth	2	3.1	2	4.3	0	0.0	
Klebsiella	48	73.8	34	73.9	14	73.7	
Pseudomonas	11	16.9	6	13.0	5	26.3	
Polymicrobial	4	6.2	4	8.7	0	0.0	
History of antibiotherapy							
Penicillin							0.74
Those not receiving	53	81.5	38	82.6	15	78.9	
Those receiving pre-CZA	12	18.5	8	17.4	4	21.1	
Those receiving along with CZA	–	–	–	–	–	–	
Those taking both pre- and concomitantly with CZA	–	–	–	–	–	–	
Carbapenem							0.375*
Those not receiving	3	4.6	3	6.5	0	0.0	
Those receiving pre-CZA	45	69.2	33	71.7	12	63.2	
Those receiving along with CZA	–	–	–	–	–	–	
Those taking both pre- and concomitantly with CZA	17	26.2	10	21.7	7	36.8	
Tigecycline							0.375*
Those not receiving	25	38.5	15	33.3	10	52.6	
Those receiving pre-CZA	31	47.7	24	53.3	7	36.8	
Those receiving along with CZA	6	9.2	5	11.1	1	5.3	
Those taking both pre- and concomitantly with CZA	2	3.1	1	2.2	1	5.3	
Aminoglycoside							0.68
Those not receiving	57	87.7	41	89.1	16	84.2	
Those receiving pre-CZA	8	12.3	5	10.9	3	15.8	
Those receiving along with CZA	–	–	–	–	–	–	
Those taking both pre- and concomitantly with CZA	–	–	–	–	–	–	

Table 2 (cont). Comparisons of clinical and microbiological characteristics of patients in terms of death status

Parameters	Total (n=65		Deceased (n=46		Survivors (n=19)		p
	n	%	n	%	n	%	
Fosfomycin							0.791*
Those not receiving	35	53.8	23	50.0	12	63.2	
Those receiving pre-CZA	27	41.5	20	43.5	7	36.8	
Those receiving along with CZA	2	3.1	2	4.3	0	0.0	
Those taking both pre- and concomitantly with CZA	1	1.5	1	2.2	0	0.0	
Colistin							**0.035***
Those not receiving[1]	21	32.3	10	21.7	11	57.9	
Those receiving pre-CZA[2]	37	56.9	30	65.2	7	36.8	
Those receiving along with CZA	3	4.6	3	6.5	0	0.0	
Those taking both pre- and concomitantly with CZA	4	6.2	3	6.5	1	5.3	
Cephalosporin							0.99
Those not receiving	51	78.5	36	78.3	15	78.9	
Those receiving pre-CZA	14	21.5	10	21.7	4	21.1	
Those receiving along with CZA	–	–	–	–	–	–	
Those taking both pre- and concomitantly with CZA	–	–	–	–	–	–	
Quinolone							0.371*
Those not receiving	48	73.8	35	76.1	13	68.4	
Those receiving pre-CZA	16	24.6	11	23.9	5	26.3	
Those receiving along with CZA	–	–	–	–	–	–	
Those taking both pre- and concomitantly with CZA	1	1.5	0	0.0	1	5.3	

CZA: Ceftazidime-Avibactam; CVC: Central Venous Catheter; ETA: Endotracheal Aspiration; N/A: Not Applicable; UTI: Urinary Tract Infection. *: Indicate p-values from the Fisher-Freeman-Halton exact test. 1: The p-value was 0.005 when comparing patients who did not receive colistin (n=21) with those who received colistin (n=44) (pre-, along with, or both pre- and concomitantly with CZA) between deceased and survivors. 2: The p-value was 0.036 when comparing patients who received colistin therapy pre-CZA (n=37) with others (n=28) (those not receiving, along with, or both pre- and concomitantly with CZA) between deceased and survivors.

DISCUSSION

In our study, it was observed that the patients treated with CZA were predominantly older and male; the most common culture positivity was detected in ETA and blood cultures; the most common types of infection were pneumonia and bacteremia; and the most common pathogen was *K. pneumoniae*. In this patient group, exposure to colistin was determined to be higher among deceased patients than among those surviving. Among our patient group receiving CZA treatment, respiratory support, being in septic shock, and a high APACHE-II score were found to be independently associated factors for ICU mortality.

Nosocomial infections are among the significant health challenges addressed by the World Health Organization (WHO) in the Antimicrobial Resistance Global Action Plan published in 2015. In the 2015 action plan, WHO identified the increasing incidence of nosocomial infections led by *Enterobacteriaceae* pathogens, such as *K. pneumoniae*, *Escherichia* spp., or *Pseudomonas* spp., as a public health challenge.[11]

Most of these pathogens have a broad spectrum of antimicrobial resistance based on carbapenemase and beta-lactamase enzymes. These factors make the treatment of nosocomial infections difficult and also increase the failure of treatment modalities and the rate of mortality.[12,13]

In our study, the mortality rate was found to be higher, especially in those with pneumonia, bloodstream infections, septic shock, and receiving steroid treatment. As the requirement for respiratory support by patients increased, the rate of mortality also increased, and the most frequently isolated bacteria were *K. pneumoniae*, followed by *P. aeruginosa*. It was observed that the post-CZA treatment survival time of the patients was as short as 29 days.

Table 3. Determination of intensive care unit (ICU)-mortality-related parameters through logistic regression analysis

Parameters	Univariate analyses			Multiple analyses		
	OR	95% CI	p	OR	95% CI	p
Neurological causes (non-CVA)	0.271	0.087–0.844	0.02*			
CVA	0.334	0.104–1.074	0.07			
Mechanical ventilation support[1]	9.111	2.499–33.212	0.001*	15.155	1.457–157.660	0.023
Steroids	9.519	2.657–34.103	0.001*			
Septic shock	15.600	4.252–57.240	<0.001*	8.558	1.460–50.171	0.017
Age, years	1.021	0.986–1.059	0.24			
GCS score	0.776	0.643–0.936	0.008			
APACHE-II score	1.219	1.086–1.368	0.001*	1.146	1.003–1.310	0.045
SOFA score	1.814	1.308–2.516	<0.001			
CRP levels (pre-CZA treatment), mg/L	1.009	1.000–1.017	0.04*			
PCT levels (pre-CZA treatment), µg-L	1.398	1.032–1.893	0.03			
PCT levels (post-CZA treatment), µg-L	2.266	1.171–4.384	0.02			
Colistin therapy2	4.950	1.569–15.618	0.006*			

APACHE-II: Acute Physiology and Chronic Health Evaluation; CI: Confidence Interval; CRP: C-Reactive Protein; CVA: Cerebrovascular Accident; GCS: Glasgow Coma Scale; HR: Hazard Ratio; PCT: Procalcitonin; pre: Before CZA treatment; post: After CZA treatment; SOFA: Sequential Organ Failure Assessment. "Mechanical ventilation support" was categorized into two groups: -Absent: Patients not needing mechanical ventilation support, given only oxygen (reference group). - Present: Patients given mechanical ventilation support using either non-invasive mechanical ventilation (NIMV) or invasive mechanical ventilation (IMV) devices. "Colistin therapy" was categorized into two groups: - Absent: Patients who did not use colistin therapy (reference group). - Present: Patients who used colistin therapy either before or concomitantly with CZA treatment. Since all patients with solid tumors passed away and there were no survivors, they were not included in the regression analysis model. Parameters marked with an asterisk (*) were included in the multiple binary logistic regression analysis. The SOFA score and GCS were not included in the multiple analyses because the APACHE-II score evaluates similar clinical parameters, such as GCS, creatinine levels, mean arterial blood pressure, and PaO_2 and FiO_2 levels, more comprehensively than the SOFA score. Since the missing values in PCT parameters were high (12 patients), we added only the CRP levels to the multiple analyses. Binary logistic regression was analyzed using the backward method. In the final step (step 3), the statistically significant findings are presented in Table 3. For this step, the p-values of the Omnibus test and the Nagelkerke R square were found to be <0.001 and 0.671, respectively.

In a study conducted by Carlo-Garcia et al.[14] in Spain, it was determined that the most frequently isolated bacteria in patients receiving CZA treatment was *K. pneumoniae* (68.3%), as with our study findings. In the study, *Escherichia coli* was found to be the second most common agent (11%). In another study carried out by Jiaxin Yu et al.[15] in China, the most frequently isolated bacteria in the cultures of those treated with CZA were detected to be multiple carbapenem-resistant Gram-negative bacteria (55.8%) and *K. pneumoniae* (34.9%). In a multicentric study performed in Spain, Balandin et al.[16] found that the most common agents for which CZA treatment was administered were *Enterobacterales* (79.4%) and *P. aeruginosa* (19.1%). In the study done by Alraddadi et al.[17] in Saudi Arabia, the researchers stated that the most common bacteria isolated was *K. pneumoniae*. In the study conducted by Santevecchi et al.[18] in the United States, *P. aeruginosa* was also found as the most frequently isolated pathogen in the patients treated with CZA (n=8/21, 38%). In another multicentric study performed in Italy by Vena et al.,[19] while *P. aeruginosa* was detected to be the most frequently isolated bacteria in patients treated with CZA (80.5%), extended-spectrum beta-lactamase (ESBL)-producing *Enterobacteriaceae* was reported to be the second most common agent (9.8%). However, in the study conducted by Pietrantonio et al.[20] in Italy, *K. pneumoniae* and *P. aeruginosa* were found as the most common and the second most common agents, respectively. In light of the findings reported in previous studies and those in our study, it can be asserted that *K. pneumoniae* and *P. aeruginosa* are likely to be the most frequently encountered pathogens in the treatment with CZA.

In our study, the most common foci of the infections in patients receiving CZA treatment were identified as pneumonia (61.5%) and bacteremia (15.4%). In the study conducted by Carlo-Garcia et al.,[14] however, CZA treatment was most commonly initiated due to intra-abdominal infections (31.7%), with pneumonia being the second most common cause for CZA treatment (20.6%). In the study by Jiaxin Yu et al.,[15] CZA treatment was most commonly initiated due to pulmonary infections (88.4%) and infections in the blood circulatory system (39.5%). However, in another study, Balandin et al.[16] reported the main foci of the infections in patients treated with CZA as respiratory tract infections (33.8%), intra-abdominal infections (22.1%), and urinary tract infections (10.3%), and also identified blood circulatory system infections in 22 cases (32.4%). In the study carried out by Alraddadi et al.,[17] CZA treatment was most commonly used due to pneumonia. Santevecchi et al.[18] also

stated that CZA treatment was most commonly administered due to pneumonia. In their study, Vena et al.[19] stated that pneumonia and bacteremia ranked first and second as the most responsible culprits for CZA treatment. In the study conducted by Pietrantonio et al.,[20] the most common and second most common types of infections were reported to be pneumonia and bacteremia, respectively. Based on the findings in these studies, it has been shown that CZA has been used safely in the treatment of pneumonia, bacteremia, urinary tract infections, and intra-abdominal infections.

In their study, Carlo-Garcia et al.[14] reported that the mortality rate was higher among the patients admitted to the ICU due to bacteremia. In another study, Jiaxin Yu[15] also reported a mortality rate of 39.5% and found that bacteremia increased mortality. In the study carried out by Balandin et al.,[16] the mortality rates in the hospital and ICU were reported as 32.4% and 41.2%, respectively. Balandin et al.[16] also stated that mortality displayed a positive correlation among those with bacteremia, using steroids, and requiring life support. Even so, in the study where Alraddadi et al.[17] investigated the efficacy of CZA in the treatment of infections due to carbapenem-resistant *Enterobacteriaceae*, the mortality rate was found to be 50% in their patient group. The researchers attributed such a high mortality rate to the high comorbidity index in the patients and the complexity and seriousness of these infections. In the study where CZA treatment was investigated for antibiotic-resistant organisms other than *K. pneumoniae* by Santevecchi et al.,[18] the mortality rates were found to be higher in bacteremia (50%) and intra-abdominal infections (50%) than in pneumonia (33%). However, Vena et al.[19] reported the mortality rate as 10% and emphasized that receiving continuous renal replacement therapy was the biggest determinant of mortality. In another study, Pietrantonio et al.[20] stated that pneumonia and IMV support may be the indicators of mortality. In their study, the researchers also highlighted that surgical patients achieved more clinical success with CZA treatment and stated the need to operate frequently to control the infections at surgical sites and the focus of infections as the reason.

In our study, the mortality rate in all patient groups was found to be 70.8%, which is high. Such factors as the higher average age of our patients (65±15 years) (although the mean age was not significantly different between deceased and survivors), higher requirements for IMV support (72.8%), and the fact that most patients were in septic shock (67.7%) may have contributed to a higher mortality rate in our study. On the other hand, no tests (antibiograms) investigating the sensitivity to CZA on culture results are routinely performed in our hospital. In our clinical practice, if the growing pathogen is sensitive to any antibiotic, that antibiotic is administered first; during the follow-up of patients, when the condition involves a MDR pathogen, the susceptibility test to CZA is performed, and if sensitive, CZA treatment is initiated. Therefore, CZA is initiated in patients developing MDR microorganisms in our practice. Performing sensitivity tests to CZA and initiating CZA treatment at an earlier period, especially in those requiring IMV support and/or being in septic shock, may reduce mortality rates.

Our study also has several limitations. The fact that we conducted the study in a single center with a limited number of patients and its retrospective design can be considered limitations. Since CZA treatment was administered to those with a relatively severe clinical course and likely to have a high ICU mortality, we consider that further studies examining the condition in cases where the treatment was initiated earlier and whose prognosis may be better are needed. On the other hand, CZA was launched for use in our country in April 2021, and the number of studies investigating CZA treatment in our country is increasing. However, despite the relatively small number of patients, to the best of our knowledge, this study was the first to investigate clinical and prognostic values in patients receiving CZA in the ICU in Türkiye.

CONCLUSION

Carbapenem-resistant Gram-negative bacteria are the most important pathogens increasing the risk of mortality, morbidity, sepsis, and septic shock in ICUs. We consider that the sensitivity to CZA should be investigated at earlier stages in cultures of patients treated in ICUs, and it would be more appropri-ate to begin the treatment at an earlier period. We found that receiving colistin therapy before CZA treatment increased mortality in patients. In our patient population, it was determined that the devel-opment of septic shock, use of steroids, receiving mechanical ventilation support, high scores of APACHE-II and SOFA, and low scores of GCS may be the indicators of poor prognosis.

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