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Article

Creation of ceftazidime-avibactam utilization evaluation standards to examine physician prescribing compliance: a retrospective study

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A study was conducted to create drug utilization evaluation (DUE) standards for ceftazidime-avibactam (CZA) and evaluate CZA use at the First Affiliated Hospital of Bengbu Medical University, China, from May 26, 2020, to December 18, 2024. First, we organized an expert panel and created DUE standards for CZA. Then, we performed an observational study and evaluated the physician CZA prescribing behaviors, which were compared to the DUE standards and calculated the compliance rates. The DUE CZA standards had medication indications, management metrics, administration process, and treatment outcomes. Sixty-four patients received the CZA during the study period. There was satisfactory compliance between CZA prescription and DUE standards regarding route, solvent, incompatibility, and contraindications. However, the compliance rates for CZA indication, dosage regimen, infusion time, combination therapy, drug interaction, and duration of treatment were 68.8% (44/64), 65.6% (42/64), 29.7% (19/64), 73.3% (44/60), 43.8% (28/64), and 62.5% (40/64), respectively. The pre-CZA bacteria culture test was 96.9% (62/64). In addition, medical records and prescription authorization were 95.3% (61/64) and 71.9% (46/64) compliant, respectively. No adverse reactions were reported. In conclusion, the CZA DUE standards could be applied to identify inappropriate prescriptions for improvements.

Keywords: Ceftazidime-avibactam. Drug Utilization Evaluation. Standards. Infectious disease. Compliance

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INTRODUCTION

Ceftazidime-avibactam (CZA) is a combination medication consisting of ceftazidime, a third-generation cephalosporin, and avibactam, a β-lactamase inhibitor. In the United States (US) in 2015, it was approved to treat adults with complicated intra-abdominal infection (cIAI) (in combination with metronidazole), complicated urinary tract infection including pyelonephritis, and hospital-acquired pneumonia (HAP) or ventilator-associated pneumonia (VAP) caused by certain gram-negative microorganisms (US FDA, 2018). A multicenter retrospective cohort study including 210 US hospitals found a steady increase of CZA prescription from 0.44 to 7.7 prescriptions per 10,000 visits in the period of 2015–2017, with an 11% increase in usage per quarter (Strich *et al.*, 2021). In China, since its approval by the National Medical Products Administration on May 21, 2019, CZA has proven to be very effective in treating infections caused by multidrug- or pandrug-resistant pathogens, including *Klebsiella pneumoniae* (KP), *Escherichia coli*, *Pseudomonas aeruginosa* (PA), *Enterobacter cloacae*, or *Proteus mirabilis*. CZA has become an increasingly prescribed antibiotic against resistant bacterial infections. However, to our knowledge, there are no clinical standards or guidelines regarding the use of CZA. Establishing appropriate CZA prescribing standard can enhance its prescription efficiency and minimize overuse.

Drug utilization evaluation (DUE) is an ongoing systematic process designed to identify patterns of inappropriate prescribing practices, such as drug indications, dosage, rate, duration of treatment, adverse reactions, combination therapy, and interactions. It is a highly effective approach to gain insight into the root causes of inappropriate antimicrobial usage and promote the appropriate drug use standards during clinical practice, among other things (Arain *et al.*, 2023). The DUE program has emerged as a model of hospital pharmacy care and is essential to ongoing efforts aimed at enhancing the quality of healthcare in China. Previous studies by our department have shown that the implementation of DUE could significantly improve cefepime use and decrease adverse reactions in a cost-effective way (Qingping *et al.*, 2013). Currently, CZA has only been marketed in China for a short time, with few studies reporting on the use of CZA. We were uncertain about the appropriateness of it use in Chinese hospitals. Therefore, we aimed to establish CZA DUE standards based on the clinical practice and antibiotic guidelines recommended by relevant authorities (Ministry of Health of China 2015; Phillips *et al.*, 1996; Paulson, Albin, 2011; The Editorial Board, 2020; Bian *et al.*, 2021; Sanford, *et al*., 2021). We further evaluated the appropriate CZA use in our hospital to identify inappropriate CZA use in patients with severe infection, with the ultimate goal of improving CZA use and reducing adverse reactions.

MATERIAL AND METHODS

Study design and participant selection

We performed an observational study and reviewed medical records in patients who received intravenous CZA (brand name Zavicefta, Pfizer Ireland Pharmaceuticals) at the First Affiliated Hospital of Bengbu Medical University, China, from May 26, 2020, to December 18, 2024. The hospital is a 3,828-bed tertiary teaching care facility. This study was approved by the hospital ethics committee (protocol code 2020KY072 and date of approval August 3, 2020) and was carried out according to the relevant guidelines and regulations. All patients who received CZA were eligible for the current study.

Development of CZA DUE standards

Drugs are usually used according to medication instructions or guidelines (Bian *et al.*, 2021). The appropriateness criteria for CZA DUE were established based on guidelines from the American Society of Hospital Pharmacists (Phillips *et al.*, 1996), Zavicefta manufacturer instructions (Paulson, Albin, 2011), antimicrobial guidelines, and relevant literature and consultation

from specialists in the clinical application of special use level antibiotics. As a special use level antibiotic, CZA prescription requires formal consultation with a physician who specializes in the clinical application of special use level antibiotics. Prescriptions for CZA should not be issued directly by a physician who is/is not a member of the special use level expert pool, without formal request for consultation from specialists in the clinical application of special use level antibiotics. The final DUE standards consisted of four sections, including medication indications, management metrics, administration processes, and treatment outcomes (Table I).

TABLE I - Proposed intravenous CZA DUE standards

Sections	Items	Criteria	Outcome
Indications	Bacterial culture and drug allergy testing	Bacterial culture and drug allergy testing have been completed	0 – Yes. 1 – Others.
	Indication	Complicated intra-abdominal infection (cIAI) (in combination with metronidazole), complicated urinary tract infection including pyelonephritis, hospital-acquired or ventilator-associated pneumonia (HAP/VAP). Adult patients with serious infection caused by aerobic gram-negative bacteria and limited treatment options. Adult patients with infection caused by carbapenem-resistant organisms and limited treatment options.	0 - Adherence to the drug indication or guidelines for empirical antibiotics use. 1 - Non-compliance with drug allergy test results or guidelines for empirical antibiotics use. 2 - Not recommended by relevant guidelines (not listed as a national essential medicine).
	Contraindication	Allergies to the drug or excipients Allergies to cephalosporin Severe hypersensitivity (rapid allergic reactions or severe skin reactions) to other β-lactam antimicrobials (i.e., penicillin, monobactams, carbapenems)	0 - No contraindications. 1 – Contraindications.
Management metrics	Prescriptive authority	Consultation experts for clinical application of special-use class antimicrobial drugs	0 - Yes. 1 – Others.
	Consultation	Consult an expert out of own department in the hospital for special use of antibiotics before prescription; In case of emergency use for 24 hours, record the course of illness, and make up the relevant procedures within 24 hours	0 - Yes. 1 - Others.
	Medical records	Documentation of the basis for the medication regimen	0 - Yes. 1 - Others.
Administration process	Combination therapy	Mixed infection, drug-resistant infection, and/or severe infection not controlled by CZA alone	0 - Yes. 1 - Others.
	Route of administration	Intravenous injection	0 - Yes. 1 - Others.
	Dosage	Creatinine clearance rate (Ccr) ≥51 mL/min, 2.5 g q8h. Ccr 30–50 mL/min, 1.25 g q8h. Ccr 10–30 mL/min, 0.94 g q12h. Ccr <10 mL/min, 0.94 g q48h. Hemodialysis, 0.94 g q48h after dialysis. Continuos renal replacement therapy, 1.25 g q8h [3].	0 - Compliance with dosage and dosing intervals. 1 - Others.

TABLE I - Proposed intravenous CZA DUE standards *(continue)*

Sections	Items	Criteria	Outcome
Administration process	Solvent	Reconstitution in 10 mL sterile water for injection, immediate transfer to 100 mL IV bags containing 0.9% sodium chloride for injection (9 mg/mL), 5% glucose solution for injection (50 mg/mL, glucose and sodium chloride solution for injection (2.5% glucose 25 mg/mL, 0.45% sodium chloride 4.5 mg/mL, or Ringer's lactate solution.	0 - Yes. 1 - Others.
	Infusion time	2 h for all CZA dosages (2.5 g, 1.25 g, or 0.94 g)	0 - Yes. 1 - Others.
	Duration of treatment	cIAI: 5-14 days, HAP/VAP: 7-14 days, adult patients with serious infection caused by aerobic gram-negative bacteria who had limited treatment options: determined by severity of infection, pathogen, clinical condition of the patient, and treatment outcome.	0 - Yes. 1 - Others.
	Incompatibility	Not mixed with other drugs except for solvent	0 - Yes. 1 - Others.
	Drug interactions	Combination with probenecid, chloramphenicol, or high dosage of cephalosporins or nephrotoxic drugs (i.e., aminoglycosides or potent diuretics such as furosemide) not recommended.	0 - Yes. 1 - Others.
	Treatment regimens adjustment	Treatment is tailored to microorganisms and clinical responses	0 - Yes. 1 - Others.
Treatment outcome	Adverse reactions	No adverse reactions. If adverse reactions occur, the drug should be discontinued and the adverse reactions treated accordingly.	0 - Adverse reactions monitored and minimized. 1 - Adverse reactions not monitored; no actions taken to avoid serious adverse reactions.

Unless stated otherwise, 0 indicates CZA use consistent with the proposed standard and 1 indicates inconsistency with the proposed standard. The Cockcroft and Gault formula was used to calculate Ccr (Cockcroft, Gault, 1976).

Data collections

Patients' information, including sex, age (≥ 14 years), weight, length of hospitalization, medical department, infection diagnosis, comorbidity, history of drug allergy, course of medication, extracorporeal membrane oxygenation (ECMO) and/or continuous renal replacement therapy (CRRT) status during medication use, and serum creatinine levels before and during medication use was extracted from the hospital patient information management system. Adverse reactions, including the type of reactions and time of occurrence, were also extracted from the physician medical record.

Statistical analysis

Data were analyzed using SPSS 24.0 (IBM, New York, US). Continuous data were first tested for normality. Data that followed a normal distribution were presented as the mean ± standard deviation ($\overline{x} \pm s$). Non-normally distributed data were presented as the median. Categorical data were presented as numbers

with percentage (%). Compliance rate of CZA use was presented as percentage, as the number of prescriptions consistent with the DUE standards divided by the total number of total prescriptions.

RESULTS

Patient characteristics

A total of 64 patients, including 42 males (65.6%) and 22 females (34.4%), were included in this study. The mean age was 62.4 (± 16.5) years old (ranged from 14 to 90 years) and the mean body weight was 66.8 (± 13.7) kg. The average duration of treatment was 9.8 ± 6.2 days. As shown in Table II, the patients were from seven medical departments. One patient had an allergy to levofloxacin and clotrimazole and two patients had allergic reactions to penicillin. There were 22 patients with CRRT and nine patients with ECMO. Among them, 17 patients received CRRT, and two patients received ECMO during CZA treatment.

TABLE II - Department distribution of patients who received CZA from May 26, 2020, to December 18, 2024

Departments	Numbers
Intensive Care Unit	41
Pulmonary	9
Infectious	8
Neurosurgery	3
Oncology	1
Hepatological Surgery	1
Emergency Internal Medicine	1

Underlying diseases and sites of infection

The underlying diseases and sites of infection for patients are shown in Table III.

TABLE III - Underlying diseases and sites of infection in patient received CZA from May 26, 2020, to December 18, 2024 (n=64)

Characteristics	Category	%(n)
Underlying disease	Cardiovascular disease	56.3% (36)
	Respiratory disease	56.3% (36)
	Hematologic disease	40.6% (26)
	Liver disease	39.1% (25)
	Renal disease	37.5% (24)
	Neurological disorder	31.3% (20)
	Endocrine system disease	32.8% (21)
	Digestive disorder	20.3% (13)
	Cancer	15.6% (10)
	Rheumatic and autoimmune disease	3.1% (2)
	Urologic disease	4.7% (3)
Sites of infection	Lung	93.8% (60)
	Bloodstream	31.3% (20)
	Abdomen	12.5% (8)
	Urinary tract	10.9% (7)
	Central nervous system	4.7% (3)
	Skin and soft tissue	4.7% (3)
	Chest	3.1% (2)
	Eye	1.6% (1)

Bacterial culture results

The distribution of positive bacterial culture results is shown in Figure 1. Since 43.8% of patients (28/64) had multiple-site infections, the total number of positive samples was greater than the number of patients. KP was the main pathogen that was detected in 42 patients (65.6%). Of them, 36 patients had carbapenem-resistant KP (CRKP). In addition, 27 patients (42.2%) were tested positive for PA, with carbapenem-resistant PA (CRPA) accounting for 21 of these cases. Seven (10.9%) patients were tested positive for *Escherichia coli*, with five cases of carbapenem-resistant strains. Only one (1.6%) patient was tested positive for *Proteus mirabilis*.

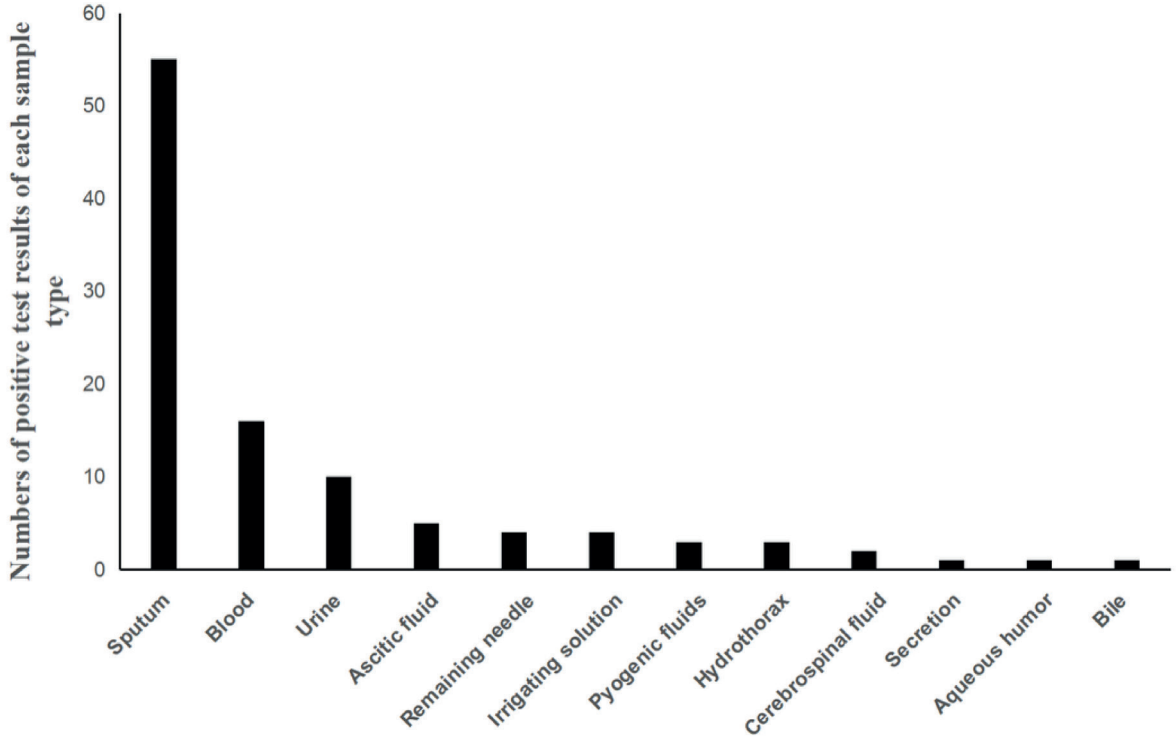

FIGURE 1 - Distribution of positive test results in terms of sample type from May 26, 2020, to December 18, 2024.

Compliance status of intravenous CZA use in our hospital

The compliance rates of intravenous CZA use in our hospital are summarized in Table IV.

TABLE IV - Compliance rates of intravenous CZA use in 64 patients

Category	Items	Compliance number	Compliance rate (%)
Indication	Indication	44	68.8
	Contraindication	64	100
	Bacterial culture	62	96.9
Administration process	Infection indicator	64	100
	Route of administration	64	100
	Solvent	64	100
	Incompatibility	64	100
	Combination therapy	44	68.8
	Dosage	42	65.6
	Duration of treatment	40	62.5
	Drug interaction	28	43.8
	Infusion time	19	29.7
	Treatment adjustment according to microorganism and clinical responses	33	51.6
Management metrics	Prescription authorization	46	71.9
	Medical records	61	95.3
	Consultation	6	9.4
Treatment outcome	Adverse reactions	64	100

Drug indication

In 96.9% of all cases (62/64), a bacterial culture test was completed before CZA use. The compliance rate of drug indication was 68.8% (44/64). The non-compliant CZA uses included: four cases of carbapenem-resistant *Acinetobacter baumannii* (CRAB); two cases of *Burkholderia cepacia* (which is naturally resistant to CZA); 12 cases of PA or KP that were sensitive to third-generation cephalosporins, ciprofloxacin/levofloxacin, aminoglycosides, combination formulations of enzyme inhibitors or carbapenems; and two cases of initial empirical use without confirmed pathogens.

Dosage regimen

The compliance rate of CZA dosage and dosing intervals was 65.6% (42/64).

Combination therapy

In this study, only four (6.3%) patients received CZA monotherapy. The other 60 patients received combination therapy (Figure 2), including 19 cases of combination with a single drug, 17 cases with two drugs, nine cases with three drugs, nine cases with four drugs, three cases with five drugs, and three cases with six drugs. CZA combination with two or more drugs was used to treat infections caused by multiple pathogens or multidrug/pandrug-resistant pathogens except in a few cases with unknown reasons. In several cases, the drug or its dosage used in combination with CZA did not comply with CZA DUE standards. The non-compliant combination therapies were as follows: 1) one case of combination with ceftazidime 2 g every 8 hours (q8h); 2) one case of combination with cefoperazone / sulbactam (SCF) 3g q8h; 3) one case of combination with piperacillin/sulbactam; 4) one case of CZA monotherapy for cIAI (according to CZA instructions, cIAI requires combination therapy with metronidazole); 5) one case of combination with imipenem/cilastatin for multi-site CRPA infection that was resistant to imipenem/cilastatin (MIC > 16 mg/L) but sensitive to ceftazidime, ciprofloxacin, and levofloxacin (alternatively, ceftazidime 2g q8h or ceftazidime in combination with ciprofloxacin or levofloxacin should be used); 6) one case of combination with fosfomycin for extended-spectrum β-lactamase (ESBL)-producing KP infection that was sensitive to imipenem/cilastatin, piperacillin/tazobactam, ceftazidime, amikacin, cefepime, and tobramycin (monotherapy with piperacillin/tazobactam, SCF, or carbapenems should be sufficient). 7) one case of combination with both tigecycline and ornidazole for CRKP infection (combination with tigecycline alone should be sufficient since both tigecycline and

ornidazole can be used to treat anaerobic bacterial infections). There were three cases of carbapenem-resistant Enterobacteriaceae (CRE) infection due to frequent production of New Delhi Metallo-β-lactamase (NDM) without aztreonam. Three cases were infected with KP without NDM production. Its combination with aztreonam was not appropriate. These patients were hospitalized for an extended period (> 2 days) and had non-community-acquired infections caused by atypical pathogens. Two patients with moxifloxacin and one patient with levofloxacin were not appropriate candidates for antibiotic combination.

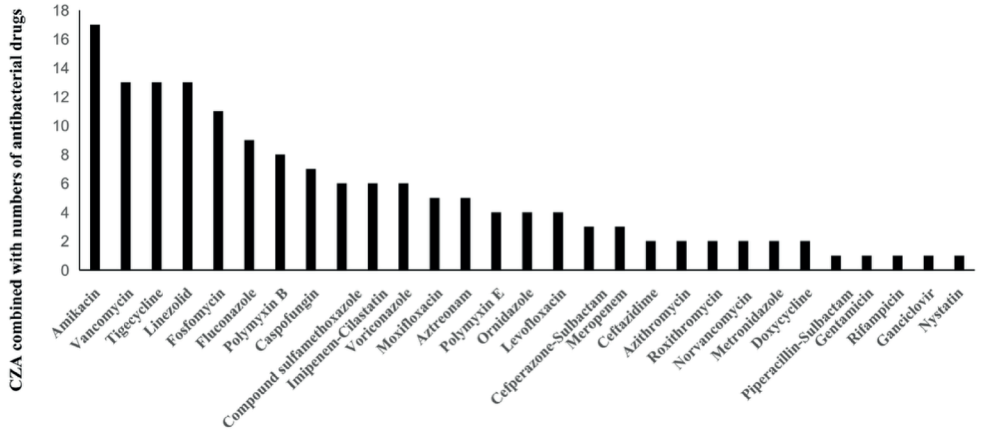

FIGURE 2 - Drugs used in combination with CZA from May 26, 2020, to December 18, 2024.

Drug interactions

The compliance rate of drug interactions was 43.8% (28/64). The non-compliant cases involved the use of drugs in combination therapy that were likely to interact with CZA and adversely affect kidney function (Figure 3), including furosemide, amikacin, vancomycin, polymyxin, gentamicin, sulfamethoxazole, high-dose SCF (3 g q8h) and ceftazidime (2 g q8h).

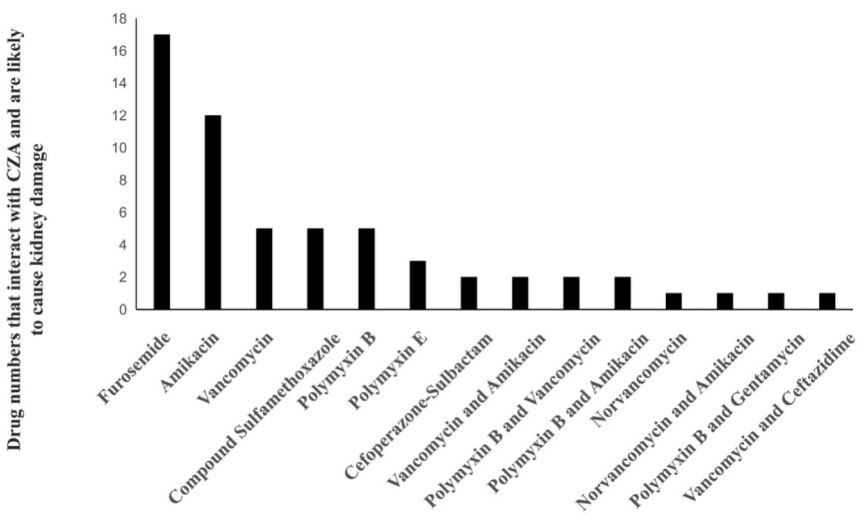

FIGURE 3 - Drugs used in combination with CZA can potentially harm kidney function from May 26, 2020, to December 18, 2024.

Adverse reactions

Consistent with previous studies (Torres *et al.*, 2018; Che *et al.*, 2019), no adverse reactions were reported in these 64 patients. There was only one case of liver impairment and one case of kidney impairment, which were not likely due to CZA use.

Other DUE metrics

Medical records were 95.3% (61/64) compliant. In the three non-compliant cases, the rationales for the use of special-grade antibiotics were not recorded. Prescription authorization was 71.9% (46/64) compliant, with the 19 non-compliant cases, involving junior or mid-level doctors in the consultation expert committee for clinical application of non-special-grade antimicrobial drugs. The compliance rate for consultation was only 9.4% (6/64). The compliance rate of infusion time was 29.7% (19/64), including 45 cases in which the infusion time was not recorded and one case in which the infusion time was one hour rather than two hours as recommended by the CZA instructions (Li *et al.*, 2020). Post-marketing clinical studies have shown that extending the infusion time to 3 h is conducive to improving the efficacy of patients with severe CRKP infection (Tumbarello *et al.*, 2021). The duration of treatment was 62.5% (40/64) compliant, with 16 non-compliant cases showing inadequate treatment duration and eight non-compliant cases showing prolonged treatment durations of 16 to 37 days. Inadequate treatment duration in 16 cases, with four (6.3%) cases adjusted according to poor clinical response, one (1.6%) case adjusted for financial reasons, three (4.7%) cases due to death, seven (10.9%) cases due to leaving against medical advice, and one (1.6%) case transferred to another hospital.

DISCUSSION

Prescription evaluation aims to evaluate the appropriateness of clinical drug use (drug indication, drug selection, route of administration, dose, drug interaction, contraindications, etc.) according to relevant laws and technical specifications. Through prescription evaluation, existing or potential problems can be identified and interventions can be developed and implemented to promote the suitability of clinical medication (Bian *et al.*, 2021). Although CZA has been increasingly used to treat drug-resistant bacterial infections, there are few studies comparing expected/approved use with real-world data. In this study, we first established CZA DUE standards based on CZA drug instructions, relevant clinical practice guidelines, and expert consensus. We then evaluated the appropriateness of CZA use in our hospital in terms of the indication, dosage regimen, outcome, and management metrics. We found that the use of CZA in our hospital was fully compliant with the standards regarding the route of administration, solvent, incompatibility, and contraindication. However, there is room for improvement in terms of drug indication, dosage regimen, infusion time, combination therapy, drug interaction, duration of therapy, bacteria culture testing, medical record administration, and prescription authorization.

Compliance of intravenous CZA use

Different from previous studies (Yao *et al.*, 2020), this study also included the route of administration, infusion time, treatment adjustment according to the microorganism and clinical response. Compliance rates of contraindication, infection indicators, solvent, incompatibility, and adverse reactions were the same as those reported in the previous study. However, there were differences in other items, especially indication, dosage, combination therapy, duration of treatment, drug interaction, and consultation.

The clinical use of CZA was recommended to follow its indication. Our studies showed that the compliance rate for indications was 68.8% (44/64), consistent with 68% approved indications of prescriptions (Nwankwo *et al.*, 2021), but lower than 80% reported in a previous study (Wang *et al.*, 2022). Inappropriate CZA use

happened when CZA was prescribed to patients with positive culture for *Acinetobacter baumannii,* or *Burkholderia cepacia*, since these two strains were resistant to CZA (Wang *et al.*, 2020). In addition, CZA was also considered inappropriate if patients had infections from PA or KP that were sensitive to third-generation cephalosporins, ciprofloxacin/levofloxacin, aminoglycosides, combination formulations of enzyme inhibitors, or carbapenems. This inappropriate use could promote the spread of bacterial resistance (Nwankwo *et al.*, 2021).

The compliance rate of CZA dosage and dosing intervals was 65.6% (42/64). CZA does not require dose adjustment based on sex, race, or liver function (Bezprozvanny, 2009). The recommended dosing for CZA is 40 mg/kg per dose for patients aged 3 to 6 months, and 50 mg/kg per dose for those aged 6 months to 18 years. Both doses should be administered every 8 hours and infused over a period of 2 hours (Auwaerter *et al.*, 2023). In this study, there were two cases under 18 years old (specifically, 14 and 17 years old), whose body weight was 50 kg and 55 kg, respectively, for whom a dosage of 2.5g q8h was reasonable. As 80–90% of CZA is excreted unchanged in the urine, CZA blood concentration and efficacy are directly linked to renal function. Patients with moderate to severe renal impairment require dose adjustment. Whether the CZA requires dose adjustment in patients with a creatinine clearance rate (Ccr) ≥ 130 mL/min is unknown. In this study, nine patients who had high Ccr (131, 134.9, 141.4, 153.34, 159.9, 161.14, 192.4, 210.47 and 218.7 mL/min, respectively) received standard CZA dosage of 2.5 g q8h, and all showed improvements except for two cases (161.14 and 210.47) were leaving against medical advice. Meanwhile, care should be taken to avoid combining CZA with drugs that could impair renal function. For patients with borderline renal function, Ccr should be monitored daily and CZA dosage could be adjusted accordingly. As CZA can be cleared by hemodialysis, patients undergoing dialysis should receive CZA infusion (0.94 g q48 h) after the dialysis is completed. CRRT has been reported to be the sole risk factor for loss of CZA effectiveness (Vena *et al.*, 2020). In 17 patients who were on CRRT during CZA treatment in the current study, the doses of ceftazidime and avibactam were adjusted during CRRT in only four cases, which was inconsistent with the recommended CZA dosage for patients on CRRT (1.25 g q8h) (Paulson, Albin, 2011). Twelve patients did not respond to CZA while five showed improvements. The lack of response in the CRRT patients might be due to their critical conditions and/or mixed infections. A larger sample size is required to validate the effectiveness of CZA in patients on CRRT. In this study, only two patients received ECMO during CZA treatment;, the dose of CZA was not adjusted, but followed the normal dosing in ECMO patients (Bakdach *et al.*, 2022; Curtiaud *et al.*, 2024) and they also did not respond to CZA.

Monotherapy is commonly recommended for CZA (Sousa *et al.*, 2018; De la Calle *et al.*, 2019; Jorgensen *et al.*, 2019; Tang, Cui, 2021). However, in critically ill, mechanically ventilated patients with severe carbapenem-resistant infections, combination therapy outperformed monotherapy for saving lives (Pogue *et al.*, 2019; Tsolaki *et al.*, 2020). Our study showed that only four (6.3%) patients were treated with CZA monotherapy, significantly lower than the 23.3% reported previously (Wang *et al.*, 2022). In these four patients, three showed improvements or completely recovery and one died. Unlike previous studies of combination therapy (76.7%) with the most commonly combined agent of polymyxin B (Wang *et al.*, 2022), our study showed that combined therapy was administrated in 93.8% (60/64) patients and the most commonly combined medication was amikacin (26.6%, 17/64), followed by vancomycin, tigecycline, linezolid (13, 20.3% for each); fosfomycin (17.2%, 11/64); fluconazole (14.1%, 9/64); polymyxin B (12.5%, 8/64); caspofungin (10.9%, 7/64); compound sulfamethoxazole, imipenem-cilastatin, voriconazole (6, 9.4% for each); and moxifloxacin and aztreonam (7.8%, 5/64). Although CZA combined with amikacin, polymyxin B, tigacycline, fosfomycin, amtronam, and

carbapenem all have synergistic against infections caused by CRKP and reduced the MIC to less than the susceptibility breakpoint (Manning *et al.*, 2018; Mikhail *et al.*, 2019; Ojdana *et al.*, 2019), we recommend that combination therapy should be used to treat infections caused by CRE or CRKP, and the susceptibility to specific combinations should be evaluated *in vitro* to guide the selection of the appropriate drug combination.

The main reason for the low consultation rate might be linked to the fact that most CZA users were authorized by a doctor who worked in the same department and was a member of the consultation expert committee for the clinical application of special-grade antimicrobial drugs. The clinicians didn't know that they still had to place a formal consultation request to the consultation expert committee for appropriate use of CZA. This might show the inadequate supervision of ceftazidime and avibactam in our hospital, which was different from previous studies, in which nearly all targeted use of CZA rely heavily on supervision and guidance of infectious disease specialists (Strich *et al.*, 2021).

This study was limited by a single-center, observational design with a small sample size. We also had no information on the types of carbapenemases carried by the pathogens detected in patients.

In this study, we created CZA DUE standards and evaluated real-world prescribing patterns. We found that most clinicians had poor prescribing practices of CZA. Indication, consultation, infusion time, drug interaction, duration of treatment, dose optimization, combination therapy, and treatment adjustment according to microorganism and clinical responses will be the next targeted interventions for antimicrobial stewardship. With the increasing use of CZA in the clinic, there is an urgent requirement for better prescribing practice on this antibiotic. More education, training, and administrative intervention are necessary to standardize and promote the appropriate and safe use of CZA to maximize treatment effectiveness and minimize potential adverse outcomes.

LIST OF ABBREVIATIONS

CZA: ceftazidime: avibactam
cIAI: complicated intra: abdominal infection
HAP: hospital: acquired pneumonia
VAP: ventilator: associated pneumonia
KP: *Klebsiella pneumoniae*
PA: *Pseudomonas aeruginosa*
DUE: Drug Utilization Evaluation
WHO: World Health Organization
CRRT: continuous renal replacement therapy
ECMO: extracorporeal membrane oxygenation
CRKP: carbapenem-resistant *Klebsiella pneumoniae*
CRPA: carbapenem-resistant *Pseudomonas aeruginosa*
CRAB: carbapenem-resistant *Acinetobacter baumannii*
SCF: cefoperazone/sulbactam
ESBL: extended-spectrum β-lactamase
CRE: carbapenem-resistant Enterobacteriaceae
NDM: New Delhi Metallo-β-lactamase
ICU: intensive care unit
DTR: difficult-to-treat resistance
Ccr: Creatinine clearance rate

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This work was approved by the Ethics Committee of the First Affiliated Hospital of Bengbu Medical University (protocol code 2020KY072 and date of approval: August 3, 2020). All methods were carried out according to relevant guidelines and regulations. All patients provided written informed consent to participate.

PATIENT CONSENT FOR PUBLICATION

Not applicable

AVAILABILITY OF DATA AND MATERIALS

The datasets generated and/or analyzed during the current study are not publicly available due to limitations of ethical approval involving patient data and anonymity, but are available from the corresponding author upon reasonable request.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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AUTHOR CONTRIBUTIONS

NZ and TC: Writing —original draft, conceptualization, investigation, Writing —review and editing; JY and JF: Investigation; CL and HW: Resources; ZL, YX, ZW, JL and RS: Writing—review and editing; All authors have read and approved the final version of the manuscript for publication.

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