Infection and Drug Resistance

Dovepress
Taylor & Francis Group

Open Access Full Text Article

ORIGINAL RESEARCH

Effectiveness and Safety of High-Dose versus Standard-Dose Cefoperazone-Sulbactam in Severe Infections: A Multicenter Retrospective Study

Cheng-Han Li[1], Chi-Kuei Hsu[2], Chih-Cheng Lai[3], Jin-Wei Liu[1], Hung-Jen Tang[1], Kuang-Ming Liao[4], Ping-Chin Chang[5], Yee-Huang Ku[5], Yu-Hsin Chiu[5], Chien-Tung Chiu[2]

[1]Division of Infectious Diseases, Department of Medicine, Chi Mei Medical Center, Tainan, 710402, Taiwan; [2]Division of Pulmonary Medicine, Department of Internal Medicine, E-Da Hospital, I-Shou University, Kaohsiung, 824005, Taiwan; [3]Division of Intensive Care Medicine, Chi Mei Medical Center, Tainan, 710402, Taiwan; [4]Department of Internal Medicine, Chi Mei Medical Center, Tainan, 722013, Taiwan; [5]Division of Infectious Disease, Department of Internal Medicine, Chi Mei Medical Center, Tainan, 736002, Taiwan

Correspondence: Chien-Tung Chiu, Division of Pulmonary Medicine, Department of Internal Medicine, E-Da Hospital, I-Shou University, Kaohsiung, 824005, Taiwan, Email chiuct168@gmail.com

Purpose: This study aimed to evaluate the clinical effectiveness and safety of high-dose versus standard-dose cefoperazone-sulbactam in patients with severe infections, particularly those caused by multidrug-resistant organisms (MDROs).

Patients and Methods: A multicenter retrospective cohort study was conducted across four hospitals from January 2020 to October 2024. Adult patients who received cefoperazone-sulbactam for severe infections, defined as admission to the intensive care unit (ICU), requirement for mechanical ventilation, or an increase in Sequential Organ Failure Assessment (SOFA) score of more than 2, or MDROs were categorized into high-dose (2 g-2 g q8h) and standard-dose (2 g-2 g q12h) groups. The primary outcome was clinical cure at day 14. Secondary outcomes included microbiological eradication, in-hospital mortality, and adverse events (AEs). Multivariate logistic regression and subgroup analyses were performed to identify treatment-associated factors.

Results: A total of 383 patients were included: 141 in the high-dose group and 242 in the standard-dose group. The high-dose group demonstrated significantly higher clinical cure rates (49.7% vs 38.8%; adjusted odds ratio [aOR]: 1.61, 95% CI: 1.05–2.50) and microbiological eradication rates (46.1% vs 20.3%; aOR: 3.85, 95% CI: 2.37–6.26). There was no significant difference in in-hospital mortality (17.7% vs 21.1%, aOR: 0.71; 95% CI: 0.41–1.25). Subgroup analyses showed greater benefit of high-dose therapy in patients with pneumonia, acute respiratory failure, ICU admission, and Charlson Comorbidity Index >4. Changes in liver function tests, renal function (serum creatinine), and coagulation parameters over the course of therapy did not differ significantly between the high-dose and standard-dose groups.

Conclusion: High-dose cefoperazone-sulbactam showed superior clinical and microbiological efficacy compared to the standard dose without increased safety concerns. These findings support the use of high-dose regimens in critically ill patients or those with MDRO infections.

Keywords: cefoperazone-sulbactam, severe infection, multidrug-resistant organism, carbapenem-resistance

Introduction

Cefoperazone-sulbactam, a combination of third-generation cephalosporins and beta-lactamase inhibitors, is widely used to treat various severe bacterial infections.[1–5] However, the emergence of resistant pathogens and complex pharmacokinetics observed in critically ill patients have raised concerns about the adequacy of standard dosing regimens in achieving optimal therapeutic outcomes. Importantly, recent clinical evidence has shown that in infections caused by extended-spectrum beta-lactamase (ESBL)-producing *Enterobacterales*, treatment outcomes with cefoperazone-sulbactam progressively worsen as minimum inhibitory concentrations (MICs) values increase, underscoring the risk of suboptimal exposure when standard dosing is applied.[1] This finding highlights the need to optimize dosing strategies.[6] Consequently, higher antibiotic doses have been proposed as a potential solution. High-dose cefoperazone-sulbactam

Received: 29 July 2025
Accepted: 17 November 2025
Published: 3 December 2025

regimens have been reported for managing severe infections and multidrug-resistant organisms, such as extended-spectrum β-lactamase (ESBL)-producing *Escherichia coli, Klebsiella pneumoniae*, and carbapenem-resistant *Acinetobacter baumannii*.[7–10] This strategy is particularly relevant in specific patient populations, including those with altered drug metabolism, impaired renal function, or impaired hepatic function, where standard doses may be insufficient to achieve therapeutic concentrations.[11,12] The standard cefoperazone-sulbactam dose is 2 g-2 g, administered every 12 h. Increasing the dose to 2 g-2 g every 8 h may enhance the time above the minimum inhibitory concentration (MIC) and improve clinical and microbiological efficacy. Additionally, physiological changes in critically ill patients, such as increased volume of distribution, augmented renal clearance, and altered protein binding, can significantly affect drug concentrations, potentially necessitating higher doses to achieve therapeutic targets.[13]

Despite the theoretical advantages of high-dose regimens, comparative data on the effectiveness and safety of high-dose versus standard-dose cefoperazone-sulbactam remain limited. Uncertainty persists regarding the optimal dosing strategy that balances maximal therapeutic effect with minimal adverse events. Moreover, the cost implications and practical considerations of implementing high-dose regimens in routine clinical practice require systematic evaluation. This study aimed to compare the effectiveness and safety profiles of high- and standard-dose cefoperazone-sulbactam in patients with severe bacterial infections. Multiple outcome parameters will be assessed, including clinical cure rates, microbiological eradication, and mortality rates. Safety outcomes will also be monitored, focusing on liver function abnormalities, coagulation disorders, and renal function changes. This study aimed to compare the effectiveness and safety profiles of high- and standard-dose cefoperazone-sulbactam in patients with severe bacterial infections.

Materials and Methods

Study Design and Population

This multicenter, retrospective cohort study was conducted at four hospitals within the Chi Mei Medical System and E-Da Hospital between January 2020 and October 2024. The study protocol was reviewed and approved by the Institutional Review Board of Chi Mei Medical Center (IRB No. 11312–013) and the Institutional Review Board of E-Da Hospital (IRB No. EMRP-113-127).

The requirement for informed consent was waived by both ethics committees due to the retrospective nature of the study involving anonymized patient data. All procedures were carried out in accordance with institutional guidelines and the ethical standards of the responsible committees, as well as the principles outlined in the Declaration of Helsinki.

Patient Selection

Adult patients aged ≥20 years who received cefoperazone–sulbactam for the treatment of severe infections, defined as admission to the intensive care unit (ICU), requirement for mechanical ventilation, or an increase in Sequential Organ Failure Assessment (SOFA) score of more than 2, or for infections caused by multidrug-resistant organisms (MDROs), excluding carbapenem-resistant *Pseudomonas aeruginosa* (CRPA), were eligible for inclusion. Infections caused by CRPA were excluded due to evidence indicating that the addition of sulbactam does not enhance the in vitro antibacterial activity of cefoperazone against carbapenem-resistant *P. aeruginosa*.[8] The type of infection was defined according to internationally recognized criteria. Pneumonia was defined based on the American Thoracic Society (ATS)/Infectious Disease Society of America (IDSA) guidelines.[14] Urinary tract infection was defined according to the IDSA guidelines.[15] Catheter-related bloodstream infection was diagnosed according to the IDSA 2009 update.[16] Primary bacteremia was defined as bloodstream infection without an identifiable primary focus of infection. Skin and soft tissue infections were defined based on the IDSA 2014 guidelines.[17] Intra-abdominal infection was defined according to the Surgical Infection Society and IDSA guidelines.[18] To ensure adequate assessment of drug exposure, patients must have received cefoperazone-sulbactam treatment for a minimum of 72 h. Additionally, the study population included patients with documented treatment failure of other antibiotics and those with MDROs who subsequently switched to cefoperazone-sulbactam therapy.

Exclusion criteria included patients under 20 years, individuals with HIV infection, pregnant or lactating women, those with creatinine clearance ≤30 mL/min, and patients with Child-Pugh class B or C liver cirrhosis. Additional

exclusions were concurrent anticoagulant therapy (warfarin or heparin), prolonged prothrombin time (INR >1.5), history of anaphylactic shock to cefoperazone-sulbactam, and documented allergies to cephalosporin antibiotics.

Intervention

Based on the clinical judgment of the treating physician, patients were categorized into two treatment groups. The standard-dose group received cefoperazone-sulbactam 2g-2 g every 12 hours, while the high-dose group received cefoperazone-sulbactam 2g-2 g every 8 hours. All other aspects of patient care followed the standard institutional protocols.

Data Collection

Comprehensive medical records were reviewed retrospectively to extract the patient data. Demographic and clinical characteristics included age, sex, underlying conditions or comorbidities, Charlson comorbidity index, and specific sites of infection. Laboratory parameters included comprehensive liver function tests, renal function profiles, coagulation parameters, and other clinically relevant biochemical markers. Disease severity was assessed using the Sequential Organ Failure Assessment (SOFA) score, while Pneumonia severity was evaluated using the CURB-65 score. The index date was defined as the first day of cefoperazone-sulbactam administration.

Microbiological Procedures

All clinical isolates were processed according to the standard operating procedures of each participating hospital. Using aseptic techniques, the samples were inoculated onto appropriate culture media and incubated at 37 °C in a 5% CO_2 atmosphere. After 18–24 hours of incubation, colony morphology, quantity, pigmentation, and odor were examined. Species identification was performed using matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS; MALDI Biotyper Microflex LT/SH, Bruker) with the Bruker MBT 8468 MSP Library. All clinical isolates underwent available cefoperazone-sulbactam antimicrobial susceptibility testing (AST) using the disk diffusion method after species identification. Antibiotic disks were purchased from BD BBL™ Sensi-Disc™. Owing to the absence of specific Clinical and Laboratory Standards Institute (CLSI) interpretive criteria, the CLSI criteria for cefoperazone alone were temporarily used to define the breakpoints for cefoperazone-sulbactam susceptibility.[19] However, routine antimicrobial susceptibility testing for cefoperazone-sulbactam was not performed at one of the participating institutions.

Outcomes

The primary outcome measure was the clinical cure rate on day 14, defined as complete resolution or significant improvement in infection signs and symptoms without the need for additional antibiotic therapy after discontinuation of cefoperazone-sulbactam. This endpoint was selected because our primary aim was to evaluate the clinical effectiveness of high-dose versus standard-dose cefoperazone–sulbactam, in line with prior retrospective studies of antibiotic therapy.[20] Secondary outcomes included microbiological eradication (elimination of the causative pathogen in follow-up cultures), all-cause mortality, and adverse events (AEs). Mortality was defined as in-hospital mortality within 28 days, and all patients were followed until discharge, with mortality status determined during the index hospitalization. Patients discharged alive before day 28 were classified as survivors. As such, no right-censored data were present for either outcome, and logistic regression was applied for statistical analysis. In cases where no follow-up culture was available, but the patient demonstrated clinical cure, eradication was classified as presumed. Presumed eradication was included in the overall microbiological eradication outcome. The AEs assessed included elevation of liver enzymes, bilirubin, serum creatinine, and coagulation abnormalities as indicated by prothrombin time (PT) and activated partial thromboplastin time (aPTT).

Statistical Analysis

Continuous variables were expressed as means and standard deviations, while categorical variables were presented as numbers and percentages. Differences between cefoperazone-sulbactam dosage groups were analyzed using chi-square tests for categorical variables and two-sample t-tests for continuous variables. Logistic regression analyses were conducted to evaluate the associations between study outcomes (ie, clinical cure rate, microbiological eradication, and in-

hospital mortality) and cefoperazone-sulbactam dosage, with the standard-dose control group defined as the reference group. A multivariate logistic model was established by selecting variables with p-values <0.05 in the univariate analysis. Subgroup analyses were performed according to sociodemographic and clinical characteristics. The association between microbiological eradication and cefoperazone-sulbactam dosage for specific microbial pathogens was evaluated using logistic regression. Changes in safety profiles on Day 7 and 14 compared to Day 0, were presented as means ± standard deviations and analyzed using two-sample *t*-test for each laboratory measure. All analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC, USA). Statistical significance was set at P <0.05.

Results

Clinical Characteristics of Included Patients

During the study period, 383 patients were included: 141 in the high-dose group and 242 in the standard-dose control group. Table 1 summarizes the clinical features of the patients. There were no significant differences between the groups in terms of age (73.7 ± 15.0 vs 74.3 ± 14.8 years, p = 0.719), sex, height, or body weight (all p > 0.05). Although the high-dose group included more ICU patients than the standard-dose group, the difference was not significant (51.1% vs 44.2%; p = 0.195). Furthermore, the Charlson Comorbidity Index, type of infection, and disease severity according to the

Table 1 Baseline Characteristics of Included Patients According to Cefoperazone/Sulbactam Dosage

Variable	Q12H (n=242)		Q8H (n=141)		p-value[b]
	n	%	n	%	
Age, years[a]	74.3±14.8		73.7±15.0		0.719
Sex					0.174
Female	94	38.8%	45	31.9%	
Male	148	61.2%	96	68.1%	
Height, cm[a]	160.6±8.7		161.1±8.5		0.548
Weight, kg[a]	57.1±15.2		59.0±15.0		0.246
Intensive care unit admission	107	44.2%	72	51.1%	0.195
Acute respiratory failure[c]	60	24.8%	59	41.8%	<0.001
Infection source					0.247
Primary bacteremia	15	6.2%	4	2.8%	
Pneumonia	173	71.5%	101	71.6%	
Intra-abdominal infection	9	3.7%	1	0.7%	
Urinary tract infection	25	10.3%	22	15.6%	
Catheter related blood stream infection	2	0.8%	2	1.4%	
Skin and soft tissue infection	6	2.5%	5	3.6%	
Other	12	5.0%	6	4.3%	
SOFA score					0.655
0-6	187	77.3%	105	74.5%	
7-9	40	16.5%	26	18.4%	
10-12	12	5.0%	6	4.3%	
≥13	3	1.2%	4	2.8%	
Charlson Comorbidity Index (CCI)					0.211
≤4	58	24.0%	42	29.8%	
>4	184	76.0%	99	70.2%	

(*Continued*)

Table 1 (Continued).

Variable	Q12H (n=242)		Q8H (n=141)		p-value[b]
	n	%	n	%	
CURB65 (only pneumonia cases)					0.766
≤2	127	54.5%	70	49.6%	
>2	46	19.0%	31	22.0%	
Duration of Cefoperazone-sulbactam use, days	7.8±3.7		7.7±5.6		0.875
Microbiology					
Escherichia coli	26	10.7%	18	12.8%	0.550
Klebsiella pneumoniae	26	10.7%	13	9.2%	0.634
Pseudomonas aeruginosa	21	8.7%	14	9.9%	0.682
Acinetobacter baumannii	18	7.4%	11	7.8%	0.897
Carbapenem-resistant Enterobacterales	10	4.1%	20	14.2%	<0.001
Carbapenem-resistant *Acinetobacter baumannii*	15	6.2%	8	5.7%	0.835

Notes: [a]Presented by mean±standard deviation. [b]Chi-square test was performed for categorical variables and *t*-test for continuous variables. [c]Defined as patients who required ventilation.

SOFA and CURB-65 scores for patients with pneumonia did not differ significantly (all $p > 0.05$). Compared with the standard-dose group, the high-dose group had significantly more patients with acute respiratory failure (41.8% vs 24.8%, $p < 0.001$), but treatment duration was similar (7.7±5.6 vs 7.8±3.7, $p = 0.875$).

In the high-dose group, *E. coli* (n = 18) was the most common pathogen, followed by *P. aeruginosa* (n = 14), *K. pneumoniae* (n = 13), and *A. baumannii* (n = 11). The most common pathogens in the standard-dose group were *E. coli* (n = 26) and *K. pneumoniae* (n = 26), followed by *P. aeruginosa* (n = 21) and *A. baumannii* (n = 18), this distribution did not differ significantly between the groups. Details of all cases with positive pathogen cultures, along with their corresponding infection types and specimen sources, are provided in Supplementary Table 1. The prevalence of carbapenem-resistant Enterobacterales (CRE) (defined as non-susceptibility to at least one carbapenem) was significantly higher in the high-dose group (n=20, 14.2%) compared with the standard-dose group (n=10, 4.1%; $p < 0.001$). In contrast, the number of patients with carbapenem-resistant *A. baumannii* (CRAB) was comparable between the two groups (n=8 [5.7%] vs n=15 [6.2%]; $p = 0.835$). Regarding the available susceptibility to cefoperazone-sulbactam, in the high-dose group, the susceptibility rates were 92.9% for *E. coli*, 42.9% for *K. pneumoniae*, 30.0% for carbapenem-resistant Enterobacterales, and 100% for *A. baumannii*. In the Q12H group, the corresponding rates were 85.7%, 69.6%, 42.9%, and 87.5%, respectively (Supplementary Table 2).

Primary Outcomes

The clinical cure rates on day 14 were 49.7% (70/141) and 38.8% (94/242) in the high-dose and standard-dose groups, respectively (Table 2). Compared with the standard-dose group, the high-dose group had a significantly higher clinical cure rate (adjust odds ratio [OR]: 1.55; 95% CI, 1.03–2.39) (Table 3). This trend persisted after multivariate adjustment for age, sex, acute respiratory failure, and infection with CRE (aOR: 1.61; 95% CI, 1.05–2.50). In subgroup analysis, higher clinical cure rate in the high-dose group were observed in patients with pneumonia (aOR: 2.10, 95% CI: 1.23–3.58, p=0.007), acute respiratory failure (aOR: 2.80, 95% CI: 1.30–6.07, p=0.009), those admitted to the ICU (aOR: 2.39, 95% CI: 1.24–4.61, p=0.009), and those with higher Charlson Comorbidity Index (CCI >4) (aOR: 1.76, 95% CI: 1.05–2.96, p=0.032) (Table 4). A higher clinical cure rate in the high-dose group was also observed in patients with high SOFA scores (≥10), although this difference was not statistically significant (aOR: 1.89, 95% CI: 0.71–5.05, p=0.206).

Table 2 Characteristics of Study Outcomes by Cefoperazone/Sulbactam Dosage

Outcome	Q12H (n=242)		Q8H (n=141)		p-value
	n	%	n	%	
Clinical cure rate at D14	94	38.8%	70	49.7%	0.039
Microbiological eradication at D14	49	20.3%	65	46.1%	<0.001
In-hospital mortality	51	21.1%	25	17.7%	0.429

Table 3 Association of Cefoperazone/Sulbactam Dosage with Clinical and Microbiology Outcomes[a]

	Univariate[b]				Multivariate[b,c]			
	OR	95% CI		p-value	aOR	95% CI		p-value
Clinical cure rate at D14	**1.55**	**1.02**	**2.36**	**0.040**	**1.61**	**1.05**	**2.50**	**0.031**
Microbiological eradication at D14	**3.37**	**2.14**	**5.32**	**<0.001**	**3.85**	**2.37**	**6.26**	**<0.001**
In-hospital mortality	0.81	0.48	1.37	0.429	0.71	0.41	1.25	0.237

Notes: [a]The results with statistically significant were marked in bold face. [b]Patients in the Q12H group were defined as the referent group in the logistic regression models. [c]Adjustment for age, sex, acute respiratory failure and infection with carbapenem resistant *Enterobacteriaceae*.
Abbreviations: OR, odds ratio; CI, confidence interval; aOR, adjusted odds ratio.

Table 4 Stratified Analyses for Association of Dose of Cefoperazone-Sulbactam on Clinical and Microbiology Outcomes by Patients' Clinical Characteristics

	Clinical Cure at D14				In-Hospital Mortality			
	aOR[a]	95% CI		p-value	aOR[a]	95% CI		p-value
Sex								
Female (n=139)	2.17	1.03	4.57	0.042	0.80	0.27	2.36	0.685
Male (n=244)	1.38	0.80	2.38	0.245	0.66	0.34	1.28	0.220
Pneumonia (n=274)	2.10	1.23	3.58	0.007	0.72	0.39	1.36	0.317
Acute respiratory failure (n=179)	2.80	1.30	6.07	0.009	0.92	0.37	2.27	0.856
ICU admission (n=179)	2.39	1.24	4.61	0.009	1.03	0.48	2.23	0.936
Charlson Comorbidity Index (CCI)								
≤4 (n=100)	1.05	0.43	2.53	0.918	1.04	0.26	4.12	0.953
>4 (n=283)	1.76	1.05	2.96	0.032	0.69	0.37	1.28	0.236
SOFA								
0-9 (n=292)	1.56	0.95	2.56	0.082	0.41	0.18	0.92	0.030
≥10 (n=91)	1.89	0.71	5.05	0.206	1.99	0.72	5.45	0.183

Note: [a]Adjustment for age, sex, acute respiratory failure and infection with carbapenem resistant *Enterobacterales*.
Abbreviations: aOR, adjusted odds ratio; CI, confidence interval.

Secondary Outcomes

Microbiological eradication rates were also significantly higher in the high-dose group (46.1% vs 20.3%; OR, 3.37; 95% CI, 2.14–5.32). All-cause in-hospital mortality was lower in the high-dose group, although this difference was not statistically significant (17.7% vs 21.1%; OR, 0.81; 95% CI, 0.48–1.37) (Tables 2 and 3). After adjustment for age, sex, acute respiratory failure, and infection with CRE, significantly higher microbiological eradication rate (aOR: 3.85; 95% CI, 2.37–6.26) and a trend toward a lower in-hospital mortality rate (aOR: 0.71; 95% CI, 0.41–1.25) remained (Table 3). In subgroup analyses, a higher eradication rate was observed in the CR-Gram-negative bacillus (GNB) group, although this difference was not statistically significant (aOR: 2.20; 95% CI, 0.58–8.42) (Table 5). A trend toward lower in-

Table 5 Subgroup Analyses for Association Between Cefoperazone-Sulbactam Dosage and Microbiological Eradication

	Microbiological Eradication at D14			p-value
	aOR	95% CI		
Escherichia coli	2.69	0.52	13.87	0.238
Klebsiella pneumoniae	4.01	0.62	26.13	0.147
Pseudomonas aeruginosa	1.37	0.30	6.27	0.689
Acinetobacter baumannii	0.92	0.12	6.81	0.933
Carbapenem-resistant gram-negative bacillus	2.20	0.58	8.42	0.249

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval.

Table 6 Evaluation of Safety Profiles by Cefoperazone-Sulbactam Dosage

	Q12H (n=242)		Q8H (n=141)		p-value
	n	Mean±SD	n	Mean±SD	
Change between Day 7 and Day 0					
AST	85	−14.60±107.86	75	−8.59±118.39	0.737
ALT	118	17.38±356.89	103	−7.88±76.86	0.455
Bilirubin	52	0.34±3.54	56	0.56±5.37	0.807
PT	59	0.34±2.46	62	1.58±9.08	0.303
APTT	53	2.22±15.92	45	4.96±19.85	0.450
Creatinine	167	−0.05±0.73	113	−0.76±6.90	0.284
Albumin	69	−0.10±0.52	31	−0.07±0.50	0.848
Change between Day 14 and Day 0					
AST	49	−22.57±140.66	41	9.83±67.74	0.158
ALT	74	−21.38±244.81	61	−0.48±91.67	0.499
Bilirubin	22	1.05±5.59	32	−0.08±1.21	0.361
PT	24	3.68±13.97	23	1.77±4.58	0.529
APTT	23	6.17±20.42	20	3.05±11.03	0.529
Creatinine	105	0.00±1.17	81	−1.04±8.20	0.259
Albumin	32	1.63±8.97	22	0.17±0.39	0.366

Abbreviations: AST, Aspartate aminotransferase; ALT, Alanine aminotransferase; PT, Prothrombin time; APTT, Activated partial thromboplastin time.

hospital mortality was also observed in the pneumonia, acute respiratory failure, and high CCI score subgroups and was statistically significant in the group with a lower SOFA score (Table 4).

Regarding laboratory examinations, the changes in PT, aPTT, creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), bilirubin, and albumin levels from day 0 to day 7 or 14 did not differ between the groups (all $p > 0.05$) (Table 6).

Discussion

This study compared the clinical effectiveness and safety of high-dose cefoperazone-sulbactam in treating patients with severe bacterial or MDRO infections. The results demonstrate that high-dose cefoperazone-sulbactam offers enhanced clinical effectiveness without compromising safety. First, patients treated with high-dose cefoperazone-sulbactam exhibited a significantly higher clinical cure rate than those treated with the standard dose, despite the greater proportion of patients with respiratory failure in the high-dose group. Second, the high-dose group achieved a superior microbiological eradication rate. These findings remained robust even after adjusting for potential confounders. Third, in subgroup analysis, a higher clinical cure rate was observed in patients with pneumonia, acute respiratory failure, ICU

admission, and a high CCI score. A trend towards higher microbiological eradication rates was also observed in the CR-GNB group. These findings are consistent with those of a previous study that compared cefoperazone-sulbactam 2 g-2 g twice daily with a dose adjusted according to renal function in patients with chronic kidney diseases (CKD).[12] The group receiving a higher dose demonstrated a higher clinical response rate (80.0% vs 65.0%) and a lower treatment failure rate (4.0% vs 23.8%).[12] In summary, these findings suggest a potential role for high-dose cefoperazone-sulbactam in the treatment of severe bacterial or MDRO infections.

The findings of this study can be attributed to the pharmacodynamic advantage of higher doses, which results in sustained concentrations of the free drug above the minimum inhibitory concentration (%fT > MIC).[11,21] This effect may be due to the increased daily dose of sulbactam, which enhances its activity against multidrug-resistant pathogens. The 2024 IDSA guidelines recommend a sulbactam dose of 9 g daily for the treatment of carbapenem-resistant *A. baumannii* (CRAB).[22] Higher sulbactam doses have been associated with improved microbiological eradication rates and reduced mortality during the treatment of CRAB infections.[23] For multidrug-resistant *Enterobacterales*, an elevated sulbactam-to-cefoperazone ratio reduces the MIC of ESBL-producing and CRE.[9] Additionally, in vitro studies have demonstrated that formulations with higher sulbactam content exhibit improved susceptibility to high-inoculum ESBL-producing *K. pneumoniae* and *E. coli*.[7] Collectively, these mechanisms explain the enhanced efficacy of high-dose cefoperazone-sulbactam in clinical settings.

This study also evaluated the safety profile of high-dose cefoperazone-sulbactam and found no significant differences in the prolongation of PT, APTT, liver function, or renal function compared with the standard-dose regimen. These results align with the findings of previous studies, including those involving patients with CKD.[12,24] These studies compared the adverse effects of 2 g-2 g every 12 h and 1 g-1 g every 12 h in patients with CKD and renal replacement therapy and found no significant between-group differences in AEs, including prolonged PT.[12,24] Although an association between cefoperazone use and coagulopathy has been reported,[25] the administration of vitamin K1 effectively mitigates coagulation abnormalities.[26] At our institution, prophylactic vitamin K1 was administered to patients receiving cefoperazone-sulbactam, resulting in no significant prolongation of PT or evidence of bleeding. In summary, our findings demonstrate that high-dose cefoperazone-sulbactam is well tolerated in patients with sepsis and MDRO infections, and can be safely used in critically ill patients without raising additional safety concerns.

This study has several limitations. First, the number of included patients was limited; therefore, a significant difference was observed only in the overall population and not in all subgroup analyses. Accordingly, our findings should be interpreted not only in terms of statistical significance but also by considering the effect sizes and the possibility of both type I and type II errors. Although subgroup analyses were underpowered, the overall sample size (n=383) was adequate to detect clinically meaningful differences between high-dose and standard-dose groups, consistent with prior studies that reported similar effect estimates with comparable sample sizes.[2] Second, because antimicrobial susceptibility tests for cefoperazone-sulbactam was not consistently available across all centers, resulting in missing susceptibility data, which may limit the generalizability of the susceptibility analysis. Third, because this was a retrospective study, the inability to control for biases and confounding variables may have compromised the validity of our findings, such as time to appropriate therapy and immune status. Fourth, we acknowledge that mortality is often considered a primary endpoint in retrospective studies; however, given the study aim to evaluate treatment effectiveness beyond survival, we selected clinical cure rate as the primary endpoint, consistent with prior observational studies.[20] Further large-scale studies are required to clarify this issue.

Conclusion

High-dose cefoperazone-sulbactam demonstrated superior clinical effectiveness and microbiological eradication compared with the standard dose, without additional safety concerns. These findings suggest that high-dose regimens may be beneficial for selected patients with severe infections or MDROs, but prospective trials are warranted to validate these observations.

Disclosure

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

1. Chen CH, Tu CY, Chen WC, et al. Clinical efficacy of cefoperazone-sulbactam versus piperacillin-tazobactam in the treatment of hospital-acquired pneumonia and ventilator-associated pneumonia. *Infect Drug Resist*. 2021;14:2251–2258. doi:10.2147/IDR.S313828
2. Lan SH, Chang SP, Lai CC, Lu LC, Tang HJ. Efficacy and safety of cefoperazone-sulbactam in empiric therapy for febrile neutropenia: a systemic review and meta-analysis. *Medicine*. 2020;99(8):e19321. doi:10.1097/MD.0000000000019321
3. Lan SH, Chao CM, Chang SP, Lu LC, Lai CC. Clinical efficacy and safety of cefoperazone-sulbactam in treatment of intra-abdominal infections: a systematic review and meta-analysis. *Surg Infect*. 2021;22(8):763–770. doi:10.1089/sur.2020.468
4. Liu JW, Chen YH, Lee WS, et al. Randomized noninferiority trial of cefoperazone-sulbactam versus cefepime in the treatment of hospital-acquired and healthcare-associated pneumonia. *Antimicrob Agents Chemother*. 2019;63(8):e00023–19. doi:10.1128/AAC.00023-19
5. Chou CC, Shen CF, Chen SJ, et al. Recommendations and guidelines for the treatment of pneumonia in Taiwan. *J Microbiol Immunol Infect*. 2019;52(1):172–199. doi:10.1016/j.jmii.2018.11.004
6. Chen RZ, Lu PL, Yang TY, et al. Efficacy of cefoperazone/sulbactam for ESBL-producing *Escherichia coli* and *Klebsiella pneumoniae* bacteraemia and the factors associated with poor outcomes. *J Antimicrob Chemother*. 2024;79(3):648–655. doi:10.1093/jac/dkae022
7. Chang PC, Chen CC, Lu YC, et al. The impact of inoculum size on the activity of cefoperazone-sulbactam against multidrug-resistant organisms. *J Microbiol Immunol Infect*. 2018;51(2):207–213. doi:10.1016/j.jmii.2017.08.026
8. Lai CC, Chen CC, Lu YC, Chuang YC, Tang HJ. In vitro activity of cefoperazone and cefoperazone-sulbactam against carbapenem-resistant *Acinetobacter baumannii* and *Pseudomonas aeruginosa*. *Infect Drug Resist*. 2019;12:25–29. doi:10.2147/IDR.S181201
9. Lai CC, Chen CC, Lu YC, Lin TP, Chuang YC, Tang HJ. Appropriate composites of cefoperazone-sulbactam against multidrug-resistant organisms. *Infect Drug Resist*. 2018;11:1441–1445. doi:10.2147/IDR.S175257
10. Sheu MJ, Chen CC, Lu YC, et al. In vitro antimicrobial activity of various cefoperazone/sulbactam products. *Antibiotics*. 2020;9(2):77. doi:10.3390/antibiotics9020077
11. Dong Y, Li Y, Zhang Y, et al. Cefoperazone/sulbactam therapeutic drug monitoring in patients with liver cirrhosis: potential factors affecting the pharmacokinetic/pharmacodynamic target attainment. *Basic Clin Pharmacol Toxicol*. 2019;125(4):353–359. doi:10.1111/bcpt.13245
12. Chao CM, Lai CC, Lee CH, Tang HJ. Optimal dose of cefoperazone-sulbactam for acute bacterial infection in patients with chronic kidney disease. *Antibiotics*. 2022;11(5):610. doi:10.3390/antibiotics11050610
13. Veiga RP, Paiva JA. Pharmacokinetics-pharmacodynamics issues relevant for the clinical use of beta-lactam antibiotics in critically ill patients. *Crit Care*. 2018;22(1):233. doi:10.1186/s13054-018-2155-1
14. Kalil AC, Metersky ML, Klompas M, et al. Management of adults with hospital-acquired and ventilator-associated pneumonia: 2016 clinical practice guidelines by the infectious diseases society of America and the American thoracic society. *Clin Infect Dis*. 2016;63(5):e61–e111. doi:10.1093/cid/ciw353
15. Hooton TM, Bradley SF, Cardenas DD, et al. Diagnosis, prevention, and treatment of catheter-associated urinary tract infection in adults: 2009 international clinical practice guidelines from the infectious diseases society of America. *Clin Infect Dis*. 2010;50(5):625–663. doi:10.1086/650482
16. Mermel LA, Allon M, Bouza E, et al. Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 update by the infectious diseases society of America. *Clin Infect Dis*. 2009;49(1):1–45. doi:10.1086/599376
17. Stevens DL, Bisno AL, Chambers HF, et al. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the infectious diseases society of America. *Clin Infect Dis*. 2014;59(2):e10–e52. doi:10.1093/cid/ciu296
18. Solomkin JS, Mazuski JE, Bradley JS, et al. Diagnosis and management of complicated intra-abdominal infection in adults and children: guidelines by the surgical infection society and the infectious diseases society of America. *Clin Infect Dis*. 2010;50(2):133–164. doi:10.1086/649554
19. Clinical and Laboratory Standards Institute (CLSI). *Performance Standards for Antimicrobial Susceptibility Testing—Thirty-Second Edition: M100*. Wayne, PA: CLSI; 2022.
20. Lai CC, Chen WC, Kuo LK, et al. The clinical efficacy of cefoperazone-sulbactam versus piperacillin-tazobactam in the treatment of severe community-acquired pneumonia. *Medicine*. 2023;102(28):e34284. doi:10.1097/MD.0000000000034284
21. Wang X, Xiong L, Yu W, et al. Evaluation of piperacillin/sulbactam, piperacillin/tazobactam and cefoperazone/sulbactam dosages in Gram-negative bacterial bloodstream infections by Monte Carlo simulation. *Antibiotics*. 2023;12(2):363. doi:10.3390/antibiotics12020363
22. Tamma PD, Heil EL, Justo JA, Mathers AJ, Satlin MJ, Bonomo RA. Infectious diseases society of America 2024 guidance on the treatment of antimicrobial-resistant Gram-negative infections. *Clin Infect Dis*. 2024;ciae403. doi:10.1093/cid/ciae403
23. Ungthammakhun C, Vasikasin V, Simsiriporn W, Juntanawiwat P, Changpradub D. Effect of colistin combined with sulbactam: 9 g versus 12 g per day on mortality in the treatment of carbapenem-resistant *Acinetobacter baumannii*pneumonia: a randomized controlled trial. *Int J Infect Dis*. 2024;149:107267. doi:10.1016/j.ijid.2024.107267
24. Tai CH, Tang HJ, Lee CH. Clinical outcomes and adverse effects in septic patients with impaired renal function who received different dosages of cefoperazone-sulbactam. *Antibiotics*. 2022;11(4):460. doi:10.3390/antibiotics11040460
25. Park GH, Kim S, Kim MS, et al. The association between cephalosporin and hypoprothrombinemia: a systematic review and meta-analysis. *Int J Environ Res Public Health*. 2019;16(20):3937. doi:10.3390/ijerph16203937
26. Shao X, Ren Y, Xie N, et al. Effect of cefoperazone/sulbactam on blood coagulation function in infected emergency department patients and the necessity of vitamin K1 preventive intervention: a single-center, retrospective analysis. *Med Sci Monit*. 2023;29:e939203. doi:10.12659/MSM.939203