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ORIGINAL RESEARCH

Sulbactam Concentration in Critically Ill Patients with Hospital-Acquired Pneumonia: A Comparisons Stratified by Normal and Augmented Renal Clearance

Lin Zhang[1], Juan Zeng[1], Wenying Zhu[1], Jing Sha[1], Yue Tang[1], Bing Leng[2], Nan Guo[2], Jinjiao Jiang[1]

[1]Department of Critical Care Medicine, Shandong Provincial Hospital Affiliated to Shandong First Medical University, Jinan, People's Republic of China; [2]Department of Pharmacy, Shandong Provincial Hospital Affiliated to Shandong First Medical University, Jinan, People's Republic of China

Correspondence: Jinjiao Jiang, Department of Critical Care Medicine, Shandong Provincial Hospital Affiliated to Shandong First Medical University, No. 324 Jingwu Roud, Jinan, People's Republic of China, Email jjjsch@163.com

Purpose: To investigate the impact of varying renal function on serum sulbactam concentrations and antibiotic efficacy in critically ill patients with hospital-acquired pneumonia (HAP) who exhibit no elevation in serum creatinine levels.

Patients and Methods: A prospective observational study was conducted on 23 adult HAP patients in the ICU of Shandong Provincial Hospital who received intravenous cefoperazone/sulbactam, from January 2021 to January 2023. Renal function was estimated using serum creatinine (eGFRcreat) and cystatin C (eGFRcys). An eGFRcreat >130 mL/min or eGFRcys >80 mL/min indicated augmented renal clearance. Serum sulbactam levels were measured at 0 min (pre-dose) and 15, 30, 60, 120, 180, 360, and 480 min after the >6th dose using HPLC-MS/MS.

Results: Among all the 23 patients, 10 had an eGFRcreat above 130 mL/min and 9 had an eGFRcys above 80 mL/min. Additionally, 13 patients exhibited an eGFRcreat ranging from 47 to 123 mL/min, and 14 patients had an eGFRcys in the range of 22 to 75 mL/min. In patients with higher estimated glomerular filtration rate (eGFR), regardless of whether it was based on creatinine or cystatin C, the serum sulbactam concentration tend to decrease more rapidly after the end of administration. Patients with higher eGFR also tend to have a shorter half time and lower drug exposure (AUC). Five patients experienced antibiotic treatment failure. The median eGFRcreat and eGFRcys of these 5 patients were both higher than those patients who responded positively to antibiotic therapy, although not statistically significant.

Conclusion: Patients with higher eGFR demonstrated decreased levels of sulbactam. Despite the discrepancy in GFR estimated by creatinine and cystatin C, both the two biomarkers yielded similar predictions of variability in serum sulbactam concentration. Currently, there is no evidence in this study indicating that differences in renal function affect treatment outcomes in critically ill patients without elevated creatinine levels. Further research is warranted to explore the influence of varying renal function-related pharmacokinetic fluctuations on antibiotic efficacy.

Keywords: sulbactam, HAP, critically ill, pharmacokinetic, renal clearance, Cystatin C

Introduction

Hospital acquired pneumonia (HAP), defined as lung infection developed in hospitalized patients after at least 2 days of hospitalization, which was proved to be associated with increased in-hospital mortality, prolonged ICU and hospital-stay, as well as increased medical costs, was one of the most common reasons for intensive care unit (ICU) hospitalization.[1,2] Appropriate antibiotics administration, especially maintenance of the right degree of exposure, was the primary medical intervention to improve the outcome, as it directly targeted the cause and prevented the development of progressive organ failures.[3,4] However, due to the unique physiological characteristics of critically ill patients, such as altered fluid status, enlarged volume of distribution, hypalbuminemia, and changed hepatic and renal function, the pharmacokinetics parameters

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measured in healthy volunteers may not correctly predict the parameters in critically ill patients.[5,6] The optimal use of antibiotics in treating severe infections remains an important challenge for ICU physicians.

The pathogenic spectrum of HAP in China was highly different from that in the US and European countries and antimicrobial resistance presented a serious challenge. A study on HAP conducted in tertiary hospitals across 13 Chinese cities showed that *Acinetobacter baumannii* and *Pseudomonas aeruginosa* were the most common pathogens of HAP, accounting for more than half of all cases. Cefoperazone-sulbactam, as a β-lactam/β-lactamase inhibitor combination that can cover some drug-resistant bacteria and has antibacterial activity against *Pseudomonas aeruginosa*, was widely used in the empirical treatment of HAP before targeted therapy.[7,8] Previous reports have demonstrated that cefoperazone is primarily excreted through bile, while sulbactam is predominantly excreted by the kidney.[9] Additionally, cefoperazone had a significantly longer half-life than sulbactam, leading to wide inter- and intra-individual pharmacokinetic variability in the ratio of cefoperazone to sulbactam in the blood over time.[9] Monte Carlo simulations of different dose combinations show that increasing sulbactam improves efficacy far more than cefoperazone. With fixed cefoperazone dose, higher sulbactam raises Pharmacokinetics/Pharmacodynamics (PK/PD) breakpoints and enhances activity against resistant bacteria. Sulbactam plays a more critical role in anti-infective therapy, especially for *Acinetobacter baumannii*.[10,11] In the context of β-lactamase-producing organisms, the efficacy of cefoperazone (when administered in combination with sulbactam) also relies on achieving a sufficiently high concentration of sulbactam to counteract β-lactamase activity. It is crucial to identify appropriate indicators for predicting potential concentrations of sulbactam.

Previous studies have shown that ~75% of intravenously administered sulbactam is excreted unchanged in urine.[12] Changes in renal function can affect the metabolism of sulbactam. As reported, alteration of renal function was very common in critically ill patients, with reported incidence of augmented renal clearance (ARC) as high as 20%–65% and AKI exceeding 50%.[13,14] In most instance, dosage adjustments of antibiotics were only recommended in patients with renal insufficiency for the risk of potential overdose toxicity. However, for antibiotics primarily eliminated through glomerular filtration and renal tubular secretion, enhanced drug elimination and subtherapeutic antibiotics concentrations were common in ARC patients and were proved to be associated with worse clinical outcomes.[15] Studies on the impact of renal clearance on serum sulbactam concentrations also mainly focused on patients with renal impairment or those receiving renal replacement therapy, and the effect of augmented renal clearance on serum sulbactam concentrations has not yet been reported. Therefore, this study aims to prospectively describe the characteristics of pharmacokinetics variability of sulbactam in critically ill patients without serum creatinine elevation and no previous kidney injury, and to investigate the possible predictive indicator of sub-therapeutic sulbactam concentration. As sulbactam is primarily renally eliminated, we assessed its relationship with GFR estimated using both serum creatinine and cystatin C, to avoid possible errors in GFR estimation caused by muscle loss in critically ill patients.

Materials and Methods

Study Design and Participants

The prospective, observational study was conducted in the intensive care unit at Shandong Provincial Hospital Affiliated to Shandong First Medical University, from January 2021 to January 2023. Eligibility of criteria for enrollment included [1] above 18 years old, [2] receiving intravenous cefoperazone/sulbactam therapy for HAP. Patients with chronic or acute kidney injury, pregnant, or lactating women, patients had undergone organ or hematopoietic stem-cell transplantation, patients receive immunosuppressants treatment, and patients receiving renal replacement therapy or extracorporeal membrane oxygenation were excluded. All patients in the study received cefoperazone/sulbactam2.0 g/1.0 g 8-hourly with an infusion duration of 2 hours.

Study Procedure

All demographic and clinical data (including age, sex, bodyweight, height, serum creatinine and cystatin C, the pathogen, the admission acute physiology and chronic health evaluation (APACHE) II score, the modified sequential organ failure assessment (SOFA) score, the length of ICU stay and hospital stay, etc.) were captured from the electronic medical system. The clinical pulmonary infection score (CPIS) was calculated as previously described.[16] The baseline characteristics were recorded close to the time of the initial cefoperazone/sulbactam administration. Empiric treatment of suspected HAP patients was determined by the attending physician according to local antibiotic practice protocol. After > 6 dose of cefoperazone/sulbactam was given, whole blood was collected in EDTA tube at 0 min (pre-dose) and 15 min, 30 min, 60 min, 120 min (end of infusion), 180 min, 360 min, 480 min after starting administration. Each sample was immediately placed on ice and centrifugated. The plasma sample was stored at −80°C until analysis. A high-performance liquid chromatography-tandem mass spectrometry (HPLC-MS/MS) assay was used to measure the plasma sulbactam concentration as previously described.[17] All assays were performed at the Pharmacology Laboratory of Shandong Provincial Hospital Affiliated to Shandong First Medical University as described.

Estimation of Renal Function and Definitions

The renal function indices estimated glomerular filtration rate based on serum creatinine (eGFRcreat) and cystatin C (eGFRcys) were calculated as previously described.[18] HAP was diagnosed by clinical symptoms, laboratory results, and meaningful positive results from microbiological tests of airway secretions. The clinical diagnosis was established when chest imaging findings showed new changes compared with previous ones, accompanied by at least 2 of the following criteria: [1] temperature exceeds 38°C; [2] purulent airway secretions; [3] the peripheral blood white blood cell count is greater than 10×10^9/L or less than 4×10^9/L.[2,7] Seventy-two hours after treatment initiation, therapeutic efficacy will be re-evaluated based on clinical symptoms and laboratory findings by the clinician in charge of this patient, with the decision to continue the current regimen determined in conjunction with etiological results. Antibiotic treatment success was defined as rapid reduction in symptoms and the absence of infection relapse following treatment. Antibiotic treatment failure was defined as persistent or worsening symptoms after 72 hours of therapy, necessitating an escalation of antimicrobial therapy. Incidence of multidrug-resistant organisms was defined as the culture of newly acquired multidrug-resistant organisms in a hospital setting. Any detection of multidrug-resistant organisms in airway secretion cultures obtained at any time after the initiation of treatment and before the patient's discharge was considered a positive result for multidrug-resistant organisms.[19] Death was considered infection-related if the patient died from direct complications of an infection or had uncontrolled infection at the time of death. Death was considered non-infection-related if patients had completed the full course of antibiotic treatment and died from a clearly identified alternative cause. In hospital death was defined as infection-related or non-infection-related death occurring during the patient's hospital stay. Half-life (T1/2) was defined as the time required for the amount of drug within the body to decrease by half. Time to peak drug concentration (Tmax) was defined as the time it took for a drug to reach the maximum concertation (Cmax). AUCall was defined as area under the curve from the time of dosing to the time of the last observation. Cavg was defined as the area under the curve for the defined interval between doses divided by dosing interval. CLss was defined as the total body clearance for intravascular administration. Vss-obs was defined as an estimate of the volume of distribution at steady state based last observed concentration. AUC0-24 was defined as area under the plasma concentration–time curve over the last 24-h dosing interval.

Statistics

Data analysis was performed using SPSS25.0 (IBM Corporation, Armonk, New York, USA). The data were expressed with mean (SD) or median interquartile ranges (IQR) for continuous variables as appropriate and presented as percentages for categorical variables. Continuous variables were compared by student t tests if they obey a normal distribution. If not, they were compared by Mann–Whitney U-tests. Categorical data were compared by Fisher's exact tests. P-values were considered statistically significant if less than 0.05 (two-sided test).

Ethical Approval

All the procedures performed in this study were in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This study was approved by the Ethics Committee of Shandong Provincial Hospital on April 14, 2022 (Ethics number: SWYX: NO.2022–150). Written informed consents were obtained from the participants or their kins.

Results

A total of 23 critically ill patients with HAP were included in this study. The median age of all the patients were 63 (46, 73) years. Among all the 23 patients, 13 patients had an eGFRcreat below 130 mL/min, 10 patients had an eGFRcreat above 130 mL/min, 14 patients had an eGFRcys below 80 mL/min, while 9 patients had an eGFRcys above 80 mL/min. The patients with eGFRcreat above 130 mL/min were much younger (44 (35, 59) versus 72 (65,81), $P < 0.05$). Although not reaching statistical significance, it was worth noting that patients with higher eGFRcys tended to be younger too. There were no significant differences in gender, body weight, BMI, APACHEIIscore, SOFA score, white blood cell count, neutrophil, procalcitonin, Interleukin −6 between the two groups. Details are shown in Table 1.

The plasma concentration–time profiles of sulbactam in patients with different eGFR levels are depicted in Figure 1, and detailed pharmacokinetic parameters are presented in Table 2. The median T1/2 of patients with eGFRcreat > 130 mL/min was 1.2 h (1.0 h, 1.5 h), which was significantly shorter than that of patients with eGFRcreat ≤ 130 mL/min (2.3 h (1.7 h, 4.5 h), $P < 0.05$). A same trend was observed in patients with eGFRcys > 80 mL/min (1.3 h (1.0 h, 1.6 h) versus 2.1 h (1.4 h, 3.0 h), $P < 0.05$). The median CLss of patients with eGFRcreat > 130 mL/min was 1.7-fold increase compared with patients with eGFRcreat ≤ 130 mL/min ($P < 0.05$). Compared with patients with eGFRcreat > 130 mL/min, patients with eGFRcreat ≤ 130 mL/min had a 1.7-fold higher Cavg ($P < 0.05$), 1.7-fold lager AUCall ($P < 0.05$), 1.9-fold larger AUC0-24 ($P < 0.05$), and 1.7-fold larger Vss_obs ($P < 0.05$). Similar trends were observed in patients stratified by eGFRcys. Increased CLss, decreased AUC, Cavg, and Vss_obs were observed in patients with eGFRcys > 80 mL/min. No significant difference was found in Cmax. Notably, the sulbactam concentration level started to decrease earlier in patients with higher eGFR levels than those with lower GFR levels after administration commencement. In patients with an eGFRcreat above 130 mL/min, sulbactam concentrations were found to be significantly lower than in those with an eGFRcreat below 130 mL/min at 3 hours after the start of administration, and this difference persisted until 8 hours after administration (Figure 1A). When renal function was evaluated by eGFRcys, serum sulbactam concentrations in patients with an eGFRcys above 80 mL/min began to be significantly lower than those in patients

Table 1 Basic Characteristics of Patients with Different eGFR

Variables	All patients (n = 23)	Subgroups			Subgroups		
		eGFRcreat ≤ 130 mL/min (n = 13)	eGFRcreat > 130 mL/min (n = 10)	P	eGFRcys < 80 mL/min (n = 14)	eGFRcys ≥ 80 mL/min (n = 9)	P
Age(years)	63 (46, 73)	72 (65, 81)	44 (35, 59)	<0.001	71 (52, 79)	59 (39, 67)	0.062
<60 y, n (%)	9 (39.1%)	1 (4.3%)	8 (34.8%)		4 (17.4%)	5 (21.7%)	
≥60y, n (%)	14 (60.9%)	12 (52.2%)	2 (8.7%)		10 (43.5%)	4 (17.4%)	
Gender				0.414			0.402
Male, n (%)	12 (52.2%)	8 (34.8%)	4 (17.4%)		8 (34.8%)	4 (17.4%)	
Female, n (%)	11 (47.8%)	5 (21.7%)	6 (26.1%)		6 (26.1%)	5 (21.7%)	
BMI (kg/m^2)	22.6 (21.1, 24.1)	22.6 (18.6, 23.4)	22.9 (21.1, 24.9)	0.456	22.5 (18.5, 23.3)	23.7 (21.0, 26.8)	0.235
APACHEIIscore	26 (17, 30)	30 (21, 31)	21 (14, 27)	0.101	30 (17, 31)	23 (17, 27)	0.124
SOFA score	7 (4, 8)	7 (5, 10)	6 (3, 5)	0.131	7 (3, 10)	6 (4, 7)	0.336
CPIS	6 (5, 7)	6 (5, 7)	6 (6, 8)	0.446	6 (5, 7)	6 (4, 9)	0.926
Serum creatinine (μmol/L)	46.2 (40.1, 61.6)	59.5 (42.6, 63.5)	43.0 (37.8, 46.9)	0.010	57.2 (42.8, 63.1)	41.0 (38.2, 47.6)	0.019
Serum cystatin C (mg/L)	1.0 (0.7, 1.5)	1.2 (1.0, 1.5)	0.8 (0.7, 1.0)	<0.001	1.3 (1.1, 1.6)	0.7 (0.6, 0.9)	<0.001
eGFRcreat (mL/min)	120.0 (80.9, 148.9)	98.8 (55.6, 115.3)	154.7 (136.2, 170.3)	<0.001	102.4 (57.9, 124.7)	137.0 (128.4, 166.8)	0.005
eGFRcys (mL/min)	62.0 (45.3, 93.2)	47.3 (34.8, 61.4)	94.0 (72.1, 111.5)	<0.001	47.2 (36.6, 58.7)	95.4 (90.8, 112.9)	<0.001
WBC (10^9/L)	12.2 (10.3, 17.6)	11.0 (6.9, 16.7)	12.6 (11.6, 18.3)	0.410	11.3 (6.6, 15.1)	12.9 (11.6, 18.5)	0.109
N (10^9/L)	10.7 (6.3, 14.8)	10.2 (6.1, 14.4)	11.5 (9.6, 15.4)	0.410	9.4 (5.8, 12.5)	12.1 (10.5, 16.3)	0.072
Procalcitonin (ng/mL)	0.4 (0.2, 0.7)	0.4 (0.3, 1.4)	0.5 (0.1, 0.6)	0.464	0.4 (0.3, 1.4)	0.5 (0.1, 0.6)	0.554
Interleukin −6 (pg/mL)	31.88 (13.8, 46.3)	34.3 (24.0, 91.7)	19.1 (10.3, 52.3)	0.186	31.1 (13.5, 87.8)	32.3 (14.0, 42.2)	0.688
ICU length of stay (days)	23 (12, 42)	19 (9, 40)	28 (13, 48)	0.020	19 (13, 40)	25 (10, 45)	0.602
Hospital length of stay (days)	25 (19, 42)	19 (12, 40)	30 (25, 48)	0.282	25 (14, 40)	25 (23, 45)	0.972

Abbreviations: APACHE II score, acute physiology and chronic health evaluation II score; BMI, body mass index; CPIS, clinical pulmonary infection score; eGFR, estimated glomerular filtration rate; eGFRcreat, estimated glomerular filtration rate calculated based on serum creatinine; eGFRcys, estimated glomerular filtration rate calculated based on serum cystatin C; ICU, intensive care unit: SOFA score, modified sequential organ failure assessment score.

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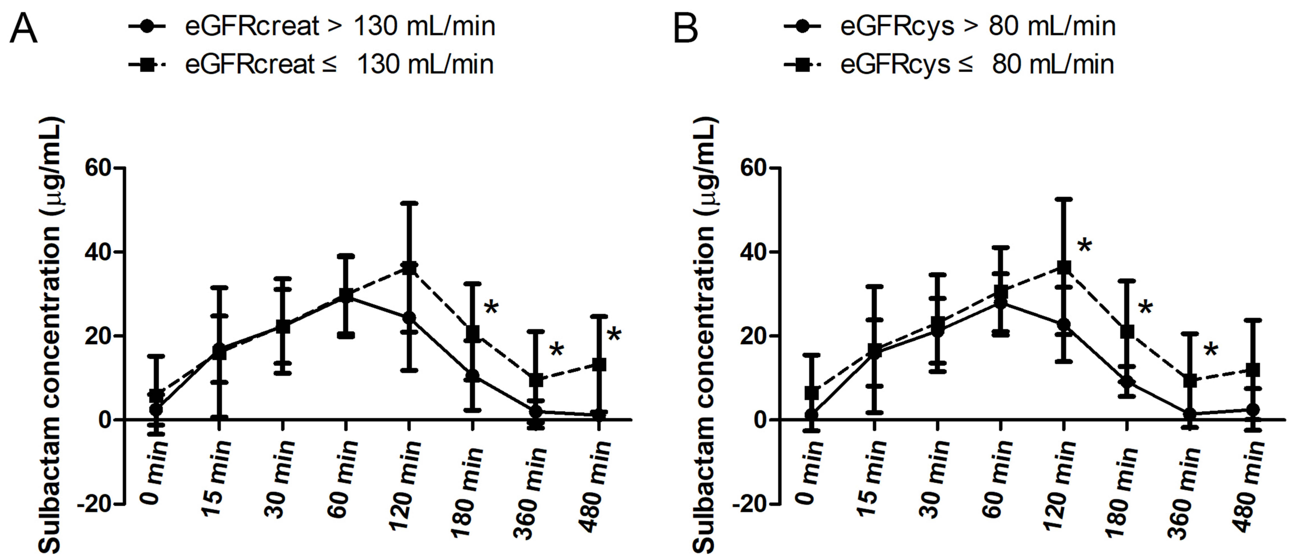

Figure 1 Mean plasma concentration–time profiles of sulbactam in patients with different eGFR. (**A**) Creatinine clearance rate was calculated based on serum creatinine levels. (**B**) Creatinine clearance rate was calculated based on serum cystatin C levels. *, $P < 0.05$.
Abbreviations: eGFR, estimated glomerular filtration rate; eGFRcreat, estimated glomerular filtration rate calculated based on serum creatinine; eGFRcys, estimated glomerular filtration rate calculated based on serum cystatin C.

with an eGFRcys below 80 mL/min at 2 hours after administration, and this situation persisted until 6 hours after administration. At 8 hours after administration, the difference still existed but is no longer statistically significant (Figure 1B).

During the cefoperazone sulbactam treatment period, 5 out of 23 patients experienced treatment failure and required medication adjustment. Among these individuals, one had eGFRcys > 80 mL/min and eGFRcreat ≤ 130 mL/min, while another had eGFRcys > 80 mL/min and eGFR > 130 mL/min. For the remaining 3 patients, their eGFRcreat values were all below 130 mL/min, and their eGFRcys values were all below 80 mL/min. The median eGFRcys of these 5 patients were 91.0 (56.2, 112.3) mL/min, which was higher than those patients who responded positively to antibiotic therapy (61.0 (41.6, 91.5) mL/min), although no statistic difference was observed. The median eGFRcreat of these 5 patients was also slightly higher (123.0 (97.45, 135.4) mL/min versus 118.3 (71.6, 162.1), $P<0.05$). Multidrug-resistant organisms were detected in 8 patients, 2 patients had eGFRcys > 80 mL/min and eGFR > 130 mL/min, while 1 patient had an eGFRcys ≤ 80 mL/min and eGFRcreat > 130 mL/min. For the remaining 5 patients, their eGFRcreat values were all below 130 mL/min, and their eGFRcys values were all below 80 mL/min. The 5 patients with antibiotic treatment failure received antibiotic escalation and other therapeutic adjustments based on their specific conditions. There was no infection-related death in this study. Details are shown in Table 3.

Table 2 Pharmacokinetic Parameters of Patients Receiving Sulbactam

Parameters	Subgroups			Subgroups		
	eGFRcreat ≤ 130 mL/min	eGFRcreat > 130 mL/min	*P*	eGFRcys ≤ 80mL/min	eGFRcys > 80mL/min	*P*
$T_{1/2}$ (h)	2.3 (1.7, 4.5)	1.2 (1.0, 1.5)	<0.001	2.1 (1.4, 3.0)	1.3 (1.0, 1.6)	0.019
Tmax (h)	2.0 (1.5, 2.0)	1 (1, 2)	0.208	2.0 (1.8, 2.0)	1 (1, 2)	0.109
Cmax (μg/mL)	38.8 (27.9, 51.4)	30.1 (27.4, 34.9)	0.313	38.9 (28.3, 53.6)	30.2 (27.0, 35.1)	0.224
AUCall (h μg/mL)	129.7 (109.8, 160.6)	77.2 (67.8, 86.6)	0.003	136.8 (108.4, 173.4)	80.4 (75.4, 91.2)	0.009
Cavg (μg /mL)	16.2 (13.7, 20.1)	9.6 (8.5, 10.8)	0.003	17.1 (13.5, 21.7)	10.0 (9.4, 11.4)	0.009
CLss (mL/h)	7707.3 (6246.3, 9159.3)	12,959.0 (11,684.0, 14,803.7)	0.003	7328.2 (5774.5, 9500.0)	12,438.7 (11,113.6, 13,260.3)	0.009
Vss_obs (mL)	20,312.9 (16,213.8, 32,310.7)	11,747.0 (11,201.0, 16,950.0)	0.005	19,809.5 (15,555.6, 27,835.8)	11,787.9 (11,650.3, 17,840.9)	0.083
AUC0-24 (h μg/mL)	149.2 (125.6, 213.8)	77.5 (68.5, 88.9)	<0.001	148.6 (111.1, 212.7)	81.2 (77.7, 106.8)	0.013

Abbreviations: AUC0-24: area under the plasma concentration–time curve over the last 24-h dosing interval; AUCall, area under the curve from the time of dosing to the time of the last observation; Cavg, the area under the curve for the defined interval between doses divided by dosing interval; CLss, the total body clearance for intravascular administration; Cmax: the maximum concertation; Tmax, time to peak drug concentration; T1/2, the time required for the amount of drug within the body to decrease by half; Vss-obs, an estimate of the volume of distribution at steady state based last observed concentration.

Table 3 Detail Clinical Data of Enrolled Patients

Patients No.	Age	Gender	APACHE II score	SOFA score	eGFRcys > 80 (mL/min)	eGFRcreat > 130 (mL/min)	Response to Antibiotic Therapy	Multidrug-Resistant Organisms	Infection-Related Death	In-Hospital Death
1	72	Male	30	8	No	No	Success	No	No	No
2	70	Male	29	7	No	No	Success	Yes	No	No
3	66	Female	27	4	Yes	No	Failure	No	No	No
4	74	Female	30	7	No	No	Failure	No	No	No
5	63	Male	33	11	No	No	Success	Yes	No	No
6	63	Male	8	3	No	No	Success	No	No	No
7	82	Male	15	3	No	No	Success	Yes	No	Yes
8	48	Female	20	12	No	No	Failure	No	No	Yes
9	83	Female	30	8	No	No	Drop out	No	No	No
10	87	Male	31	6	No	No	Success	Yes	No	No
11	79	Male	31	10	No	No	Success	No	No	Yes
12	73	Male	21	6	Yes	No	Success	No	No	No
13	72	Male	30	9	No	No	Failure	Yes	No	No
14	42	Female	11	3	No	Yes	Success	No	No	No
15	21	Male	17	3	Yes	Yes	Success	No	No	No
16	53	Male	17	3	No	Yes	Success	No	No	No
17	60	Female	10	3	Yes	Yes	Success	No	No	No
18	67	Female	29	7	Yes	Yes	Success	Yes	No	Yes
19	46	Female	26	7	Yes	Yes	Success	No	No	No
20	40	Male	24	8	Yes	Yes	Success	No	No	No
21	59	Male	15	4	Yes	Yes	Failure	No	No	No
22	26	Female	35	7	No	Yes	Success	Yes	No	No
23	38	Female	18	5	Yes	Yes	Success	Yes	No	No

Abbreviations: APACHEIIscore, acute physiology and chronic health evaluation II score; eGFRcreat, estimated glomerular filtration rate calculated based on serum creatinine; eGFRcys, estimated glomerular filtration rate calculated based on serum cystatin C; SOFA score, modified sequential organ failure assessment score.

Discussion

In the present study, we found that the serum sulbactam concentration was lower in patients with augmented renal clearance, no matter the patients' renal function was grouped by eGFRcreat or eGFRcys. In patients with eGFRcys > 80 mL/min, sulbactam concentration became significantly lower after the end of drug infusion, and the difference would last for at least 4 hours. In patients with eGFRcreat > 130 mL/min, the sulbactam concentration became lower than that in the other patients at 1 hour after the end of administration, and this difference persisted throughout the rest dosing interval. However, the clinical outcomes of patients did not seem to be impacted by the differences in renal clearance capacity and sulbactam concentration. Among the 5 patients who experienced antibiotic treatment failure, their eGFR levels were slightly higher than those of other patients, but this difference of eGFRcys did not reach statistical significance. Regarding the 8 patients with multidrug-resistant organisms, no relation was observed between the detection of such microorganisms and renal clearance capacity. Based on the existing results, we found that renal clearance capacity has a significant impact on the serum sulbactam concentration, especially after the end of administration. However, its impact on antibiotic efficacy and pathogen resistance remains inconclusive, probably due to the small sample size or the confounding factors needed to be corrected, such as different pathogens, the severity of infection and immune statuses of patients.

Previous studies on antibiotic metabolism in critically ill patients have demonstrated that those with augmented renal clearance are likely to have insufficient antibacterial drug concentrations, thereby requiring adjustments to dosage or administration regimens.[20,21] Most of these investigations were concentrated in antibiotics metabolized by the kidneys, only a few involving β-lactamase inhibitors, and there were no reported studies on sulbactam at all. Our research found that serum sulbactam concentrations are indeed significantly lower in patients with augmented renal clearance, but the available data do not support the possibility that this situation may affect the antibiotic efficiency. Similar findings have been reported in studies on other drugs. A study conducted on 215 patients with augmented renal clearance showed that renally metabolized β-lactam antibiotics generally have relatively lower serum drug concentrations. This study also failed to conduct an in-depth analysis of the relationship between drug concentrations and clinical mortality.[22] Another study involving 100 patients reached similar conclusions: augmented renal clearance was associated with low drug concentrations, but no direct correlation was found between augmented renal clearance and clinical treatment failure.[23] This may be because the treatment of critically ill patients is an extremely complex process, the scope of infection, pathogens, drug resistance, patients' immune status, organ function, and nutritional status may all affect treatment efficacy and clinical outcomes. In our study, we also attempted to evaluate whether augmented renal clearance and low sulbactam concentrations were related to the subsequent drug-resistance. Similarly, no conclusion can be drawn. A more definitive conclusion might be drawn if the analysis could be combined with pathogen minimum inhibitory concentration (MIC) and infection load. However, it is very regrettable that our hospital uses the disk diffusion method for susceptibility testing of cefoperazone-sulbactam, which cannot yield MIC values, so our current research cannot proceed to this level for the time being.

Assessing the renal function of critically ill patients has always been an important issue that ICU physicians need to address. The traditionally used Cockroft-Gault and MDRD equations were developed based on the general characteristics of patients with stable chronic renal failure. As such, conditions like edema and muscle wasting in ICU patients can lead to inaccurate results, a phenomenon that is particularly pronounced in elderly patients.[24,25] Moreover, collecting urine for 24-hour creatinine clearance testing had problems such as cumbersome operations, long time required to obtain results, and the condition of critically ill patients changes on a daily basis, making it impossible to be widely carried out in actual diagnosis and treatment work.[25] Previous studies have shown that cystatin C, as a small molecule stably expressed in all nucleated cells, was less affected by muscle levels and nutritional status, and can be used to calculate glomerular filtration rate and evaluate renal function.[26] In a prior study involving elderly patients with pneumonia, the concentration of ampicillin showed a stronger correlation with GFR estimated from serum cystatin C than with that estimated from serum creatinine, making it more reliable for adjusting dosing regimens of ampicillin/sulbactam in elderly patients.[18] Our findings indicated that eGFRcys was significantly lower than eGFRcreat in nearly all patients, particularly among the elderly. This discrepancy may be attributed to variations in muscle mass and nutritional status. Recent studies on critically ill patients have demonstrated a greater disparity between eGFRcys and eGFRcreat with prolonged ICU stays, suggesting that serum creatinine tends to overestimate kidney function due to muscle loss during extended critical illness.[27] Further research with a larger sample size is necessary to substantiate these findings.

This study has several limitations. First, it was a single-center study with a small sample size, restricted the ability to make meaningful comparisons and draw clear conclusions regarding clinical outcomes. Second, the drug susceptibility testing of cefoperazone-sulbactam was performed using the disk diffusion method, the MIC values could not be determined. Consequently, we were unable to analyze the percentage of time above MIC for each patient to clarify whether the reduced sulbactam plasma concentrations caused by enhanced renal clearance would affect antibacterial efficacy. Third, serum creatinine can be influenced by factors such as muscle mass and dietary protein intake, while serum cystatin C can be affected by inflammation and certain medications.[28,29] Consequently, the estimated GFR may not accurately reflect actual renal function, and our findings may not fully capture the true pharmacokinetic characteristics of sulbactam in critically ill patients with varying renal function. These limitations should be considered when interpreting the results.

Conclusion

In conclusion, patients with higher renal function tended to exhibit lower sulbactam concentrations in our study. Although the GFR estimated using serum creatinine and serum cystatin C were not parallel, the same lower sulbactam concentration was observed in patients with higher eGFR according to both indicators. Within this study, the GFR of patients who experienced antibiotic treatment failure was slightly higher, but there was no significant difference. Based on the data obtained from the current study, enhanced renal clearance had no impact on the outcomes of anti-infective treatment, subsequent pathogen resistance, or in-hospital mortality. Further studies are needed to address these issues.

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Disclosure

The authors report no conflicts of interest in this work.

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