Infection and Drug Resistance

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ORIGINAL RESEARCH

Retrospective Analysis of Risk Factors for Cefoperazone/Sulbactam-Induced Thrombocytopenia in Adult Chinese Patients: A Six-Year Real-World Study

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Background: Drug-induced thrombocytopenia is a rare adverse reaction of drug therapy and usually underdiagnosed. Cefoperazone/sulbactam is a compound preparation composed of the third generation of cephalosporin and β-lactamase inhibitor, of which thrombocytopenia is an uncommon but serious adverse reaction. However, the existing literature on cefoperazone/sulbactam-induced thrombocytopenia remains limited, and the specific risk factors associated with this adverse effect have not been thoroughly elucidated. Consequently, this study aims to investigate the clinical characteristics and identify the risk factors for thrombocytopenia in adult patients undergoing cefoperazone/sulbactam therapy.

Methods: In this retrospective study, we reviewed patients treated with cefoperazone/sulbactam at Beijing Hospital between January 2017 and June 2023. Patients were categorized into two groups based on the presence or absence of thrombocytopenia: the thrombocytopenia group and the non-thrombocytopenia group. We collected data on demographic features, clinical characteristics, laboratory parameters, treatments, and outcomes. Subsequently, univariate and multivariate logistic regression analyses were performed to identify potential risk factors for cefoperazone/sulbactam-induced thrombocytopenia.

Results: In total, 6489 patients were included in this study, and 2.4% (155/6489) developed thrombocytopenia. The results of multivariate analysis showed that cefoperazone/sulbactam therapy duration (d) >14, PLT (10^9/L) <200, daily dose of cefoperazone/sulbactam (g) ≥6, TBil (μmoL/L) >21, AST (U/L) >35, and use of non-invasive ventilator were risk factors for cefoperazone/sulbactam-induced thrombocytopenia.

Conclusion: Despite the low incidence (2.4%), cefoperazone/sulbactam could cause serious thrombocytopenia sometimes accompanied with hemorrhage. In clinical therapy, clinicians should be vigilant in monitoring platelet count, especially for patients with risk factors of cefoperazone/sulbactam-induced thrombocytopenia.

Keywords: cefoperazone/sulbactam, risk factor, thrombocytopenia, real-world study, logistic regression analysis

Introduction

Cefoperazone/sulbactam, a compound preparation of the third generation of cephalosporin and beta-lactamase inhibitor, has been widely acknowledged to possess a broad spectrum of activity against Gram-positive, Gram-negative, and anaerobic bacteria.[1] Cefoperazone possesses bactericidal activity mainly by inhibiting biosynthesis of mucin in the cell wall of bacteria during the breeding period.[2] In clinical treatment, cefoperazone/sulbactam has been widely prescribed for the treatment of moderate-to-severe infection, such as intra-abdominal, respiratory tract, urinary tract infections, bacterial septicemia, and skin and soft tissue infection caused by susceptible organisms.[2] Considering the widespread use of cefoperazone/sulbactam, the safety of the drug has raised our concerns.

Drug-induced thrombocytopenia is a rare but probably fatal disorder characterized by the occurrence of antibodies against platelets, leading to decreased platelet level and clinical bleeding in patients.[3] Specifically, beta-lactams commonly cause thrombocytopenia, such as piperacillin, cefuroxime, and compound preparation of piperacillin/

Received: 25 April 2024
Accepted: 26 August 2024
Published: 5 September 2024

tazobactam and ampicillin/clavulanate.[4–6] In recent years, cefoperazone/sulbactam has been widely used in clinical practice, and thrombocytopenia is a rare but serious adverse event for patients administered with cefoperazone/sulbactam, sometimes leading to the discontinuation of drug treatment. Up to now, information concerning the thrombocytopenia induced by cefoperazone/sulbactam has been insufficient, and often limited to some case reports. For example, Avinash et al[7] reported a case of thrombocytopenia resulting from cefoperazone, and the platelet count dropped from 181,000 to 10,000 cells/mm^3 after the administration of cefoperazone. Additionally, the cross-reactivity between piperacillin-tazobactam and cefoperazone/sulbactam was reported to induce immune thrombocytopenia.[8] Furthermore, results of investigation of coagulation disorder or bleeding related to cefoperazone/sulbactam have been reported.[9–12] According to our knowledge of available literatures, the incidence of cefoperazone/sulbactam-induced thrombocytopenia remains undetermined, and study of the risk factors is still lacking. In clinical practice, some patients suffer serious thrombocytopenia with cefoperazone/sulbactam therapy, but it is still unclear whether demographic and clinical characteristics, type of infection, and medication are associated with the thrombocytopenia. It is necessary to investigate the risk factors for cefoperazone/sulbactam-induced thrombocytopenia with the aim to ensure the safe use of cefoperazone/sulbactam.

Data were lacking on the topic, probably because of the low incidence. To resolve the above issue, a large number of patients should be enrolled. With the help of our hospital information system, the present study analyzed nearly seven thousand patients over six years, which gave us the possibility to identify more patients who developed cefoperazone/sulbactam-induced thrombocytopenia. Based on this, we conducted univariate and multivariate analysis to investigate the relationship between clinical characteristics and thrombocytopenia, and to identify the potential risk factors for cefoperazone/sulbactam-induced thrombocytopenia.

Research Design and Methods

Ethics Approval

This study, which was in compliance with the Declaration of Helsinki, received ethical approval from the Ethics Committee of Beijing Hospital (Permit Number: 2022BJYYEC-312-02). Patient consent was not required because all the personal information of patients was de-identified prior to analysis.

Study Population

This retrospective study was carried out on hospitalized patients in Beijing Hospital, a tertiary general hospital in China. The data of patients were obtained through the hospital information system (HIS) of Beijing Hospital between January 1, 2017 and June 30, 2023. All the subjects were identified by medical record review. In Beijing Hospital, the cefoperazone/sulbactam (made by Pfizer) used was a compound preparation consisting of cefoperazone and sulbactam in a ratio of 2:1. Patients who were aged ≥18 years and treated with cefoperazone/sulbactam were enrolled in this study. We excluded patients who met any of the following criteria: incomplete clinical records; baseline platelet count $<100\times10^9$/L before cefoperazone/sulbactam administration; cefoperazone/sulbactam therapy duration <3 days; patients who underwent major surgery with a total blood loss of more than 500 mL; tumor patients who were receiving chemotherapy treatment; patients who had autoimmune diseases (primary immune thrombocytopenia), hematological diseases (thrombocytopenia purpura, megaloblastic anemia, aplastic anemia, hematological malignancies), and acquired immune deficiency diseases.

Data Collection

We retrospectively reviewed the medical data of enrolled patients and extracted the following data for each patient: information on admission and discharge, age, gender, weight, height, comorbidities, infection type, mechanical ventilation, cefoperazone/sulbactam therapy duration, the dose and frequency of cefoperazone/sulbactam, baseline laboratory data prior to the first day of cefoperazone/sulbactam treatment (platelet [PLT], white blood cell [WBC], hemoglobin [HGB], C-reactive protein [CRP], alanine aminotransferase [ALT], aspartate aminotransferase [AST], albumin [ALB], total bilirubin [TBil], direct bilirubin [DBil], serum creatinine [SCR], blood urea nitrogen [BUN], international normalized ratio of prothrombin time [INR], prothrombin time [PT], and activated partial thromboplastin time [APTT]). During the time of this retrospective

study, PLT was measured using the sheath flow impedance method in all patients, and thus the measurement bias of PLT could be negligible. The creatinine clearance rate (CCr, mL/min) was calculated by Cockcroft–Gault formula as follows: CCr (mL/min)=(140-age)×weight (kg)/((0.818×SCR (μmoL/L)) (for female, ×0.85).[13] Body mass index (BMI) was calculated by height and weight. Many drugs have been implicated in the development of drug-induced thrombocytopenia, and herein we selected antiplatelet and heparin (including heparin sodium, dalteparin sodium, nadroparin, and low-molecular-weight heparin) as the concomitant medication. If the medication prescription periods overlapped more than one day during cefoperazone/sulbactam use, the drugs could be considered to be concomitantly administered.

The thrombocytopenia group consisted of patients who developed thrombocytopenia due to the treatment with cefoperazone/sulbactam, and the diagnosis of thrombocytopenia was defined as follows: platelet count $<100\times10^9$/L and a decrease in 20% or more from baseline of the platelet count. According to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 developed by the National Cancer Institute (NCI),[14] the thrombocytopenia was graded using the minimum blood platelet count, and the ranges of platelet count for each grade were as follows: $75–100\times10^9$/L for grade 1; $50–75\times10^9$/L for grade 2; $25–50\times10^9$/L for grade 3; $<25\times10^9$/L for grade 4. For the thrombocytopenia group, we also evaluated the time from the initiation of cefoperazone/sulbactam therapy to the development of thrombocytopenia, and the duration time of thrombocytopenia. Additionally, the symptom (coagulation disorder, increased INR, and hemorrhage), treatment (thrombopoietin receptor agonists and platelet transfusion), and outcomes in patients with thrombocytopenia were evaluated. The clinical outcomes associated with thrombocytopenia were divided into four categories: recovery, platelet count close to baseline value at discharge; death, patients who died while on treatment; improvement, platelet count got normal but lower than baseline value at discharge; sequela, platelet count lower than 100×10^9/L at discharge. The non-thrombocytopenia group included patients treated with cefoperazone/sulbactam but not diagnosed with thrombocytopenia.

Statistical Analysis

All the statistical analysis was carried out using the SPSS statistics software (version 26.0, IBM). Continuous data with normal or non-normal distribution were expressed as mean ± standard deviation (mean±SD) or M (Q25, Q75), and categorical data were presented using frequencies and percentages. Univariate analysis was conducted using the unpaired *t*-test for continuous variables with normal distribution, and Mann–Whitney *U*-test for continuous variables with non-normal distribution. Categorical variables were compared by chi-square or Fisher's exact test. The time from the first treatment of cefoperazone/sulbactam to the development of thrombocytopenia was evaluated by the cumulative incidence curve. Variables with *P*-values <0.05 in the univariate analysis were subsequently analyzed using multivariate analysis. Multivariate analysis was performed using binary logistic regression analysis. The odd ratios (ORs) and 95% confidence intervals (CI) were calculated for each variable in binary logistic regression analysis. All tests were two-sided, and *P*-values <0.05 were considered to be statistically significant.

Results

Demographic and Clinical Characteristics

With the help of patients' medical records system, we extracted hospital records for 7464 patients who received cefoperazone/sulbactam treatment between January 1, 2017 and June 30, 2023. After excluding patients who did not meet the inclusion criteria, a total of 6489 patients were finally enrolled in the present study. Among these enrolled patients, 155 patients (male: 104, female: 51) with cefoperazone/sulbactam-induced thrombocytopenia were finally identified. In this study, the incidence of thrombocytopenia was 2.4% (155/6489). The baseline characteristics, clinical features, and related treatment of patients diagnosed with thrombocytopenia are listed in Table 1. The mean age of the patients was 77.2 years, and 67.1% of the population was male. The mean duration time of thrombocytopenia was 7.6 days. The platelet count generally dropped 62.4% from the baseline. Of the 155 patients who developed thrombocytopenia, 44 patients (28.4%) had platelet count of $75–100\times10^9$/L, 61 patients (39.4%) $50–75\times10^9$/L, 41 patients (26.5%) $25–50\times10^9$/L, and 9 patients (5.8%) $<25\times10^9$/L. The main observed symptom of thrombocytopenia was hemorrhage, and different kinds of hemorrhage were detected in 67 patients. Among these, 43 patients had symptoms of gastrointestinal hemorrhage, 13 patients mucosal hemorrhage, 7 patients urethrorrhagia, 3 patients

Table 1 Patient Characteristics and Clinical Features in Thrombocytopenia Group (n=155)

Patient Characteristics		
Gender (n, %)	Male	104 (67.1%)
	Female	51 (32.9%)
Age (years)	Mean	77.2
	Median (range)	80 (40–96)
Severity of thrombocytopenia		
Occurrence time of thrombocytopenia from the first administration of cefoperazone/sulbactam (day)	Mean	6.5
Duration time of thrombocytopenia (day)	Mean	7.6
Percentage of platelet drop (%)	Mean	62.4%
Grade of thrombocytopenia (n, %)	Grade 1 (platelet count: 75–100×10^9/L)	44 (28.4%)
	Grade 2 (platelet count: 50–75×10^9/L)	61 (39.4%)
	Grade 3 (platelet count: 25–50×10^9/L)	41 (26.5%)
	Grade 4 (platelet count: <25×10^9/L)	9 (5.8%)
Symptoms of thrombocytopenia		
Increase in INR value (n, %)	INR >1.5	62 (40%)
Coagulation disorders (n, %)	Abnormality in PT or/and APTT	95 (61.3%)
Hemorrhage (n, %)		
	Gastrointestinal hemorrhage	43 (27.7%)
	Mucosal hemorrhage (including nose, mouth, bulbar conjunctiva, teeth, and menstruation)	13 (8.4%)
	Respiratory tract hemorrhage	1 (0.6%)
	Dermatorrhagia	3 (1.9%)
	Urethrorrhagia	7 (4.5%)
Treatment of thrombocytopenia (n)		
	Recombinant human thrombopoietin	4 (2.6%)
	Platelet transfusion	28 (18.1%)
	Recombinant human thrombopoietin + Platelet transfusion	3 (1.9%)
Clinical outcomes (n)		
	Recovery (platelet count close to baseline value at discharge)	32 (20.6%)
	Death (patients who died while on treatment)	60 (38.7%)
	Improvement (platelet count got normal but lower than baseline value at discharge)	21 (13.5%)
	Sequela (platelet count lower than 100×10^9/L at discharge)	42 (27.1%)

Abbreviations: INR, international normalized ratio of prothrombin time; PT, prothrombin time; APTT, activated partial thromboplastin time.

dermatorrhagia, and 1 patient respiratory tract hemorrhage. In addition, the INR value was elevated above 1.5 in 62 cases. In 95 cases PT and/or APTT values were elevated beyond the normal range. Among the patients with thrombocytopenia, 35 cases received treatment associated with thrombocytopenia, including 28 cases accepting platelet transfusion, 4 cases accepting recombinant human thrombopoietin, and 3 cases accepting platelet transfusion plus recombinant human thrombopoietin. As for the clinical outcomes, the platelet count of 32 cases (20.6%) returned to baseline level at discharge, suggesting that the thrombocytopenia was mild and tolerated by some patients. Notably, 60 cases (38.7%) died because of primary disease like cancer, cardiovascular event, and pulmonary infection. The cumulative incidence curve of the time to the onset of thrombocytopenia after the initiation of cefoperazone/sulbactam therapy is displayed in Figure 1. As seen, the onset of thrombocytopenia varied widely in patients, and 20 cases (12.9%) occurred rapidly within one day. In general, the overall mean time from the initiation of therapy to the development of thrombocytopenia was 6.5 days, and 81 cases (52.3%) developed thrombocytopenia within 5 days (see Figure 1).

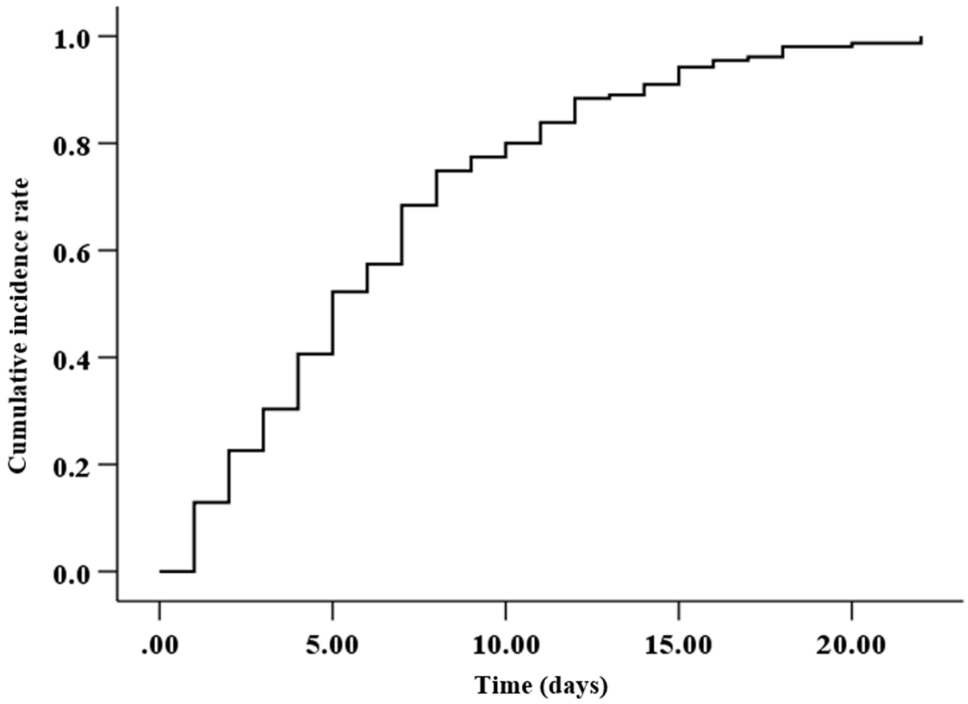

Figure 1 The cumulative incidence curve of the time to the onset of thrombocytopenia after the initiation of cefoperazone/sulbactam therapy.

Comparison of the Clinical Characteristics Between Thrombocytopenia Group and Non-Thrombocytopenia Group

The number of patients in the thrombocytopenia group was 155, and from the remaining 6334 patients who were not diagnosed with thrombocytopenia, 310 patients were randomly selected as the non-thrombocytopenia group. There were no significant differences in demographic characteristics between the thrombocytopenia group and the not enrolled patients (data not shown). As shown in Table 2, we compared the patients' demographic and clinical characteristics, and laboratory data between the thrombocytopenia group (n=155) and the non-thrombocytopenia group (n=310). Variables were divided into three groups on the basis of CCr (≥60 mL/min, ≥30 and <60 mL/min, and <30 mL/min), and also on the basis of cefoperazone/sulbactam therapy duration (<7 days, ≥7 days and <14 days, and ≥14 days). Univariate analysis

Table 2 Comparison of Demographic and Clinical Characteristics Between Thrombocytopenia and No-Thrombocytopenia Groups

Variables	Thrombocytopenia Group (n=155)	No-Thrombocytopenia Group (n=310)	*P*-value
Age (year), M (Q25, Q75)	80 (70, 86)	69 (61, 80)	<0.001
Gender (female), n (%)	51 (33%)	130 (42%)	0.06
Hospitalization days, M (Q25, Q75)	29.00 (20.00, 39.00)	15.00 (9.00, 22.00)	<0.001
BMI (kg/m^2), M (Q25, Q75)	22.22 (20.00, 25.09)	23.39 (20.42, 26.22)	0.005
Treatment details			
Daily dose of cefoperazone/sulbactam (g), M (Q25, Q75)	6.00 (4.50, 6.00)	6.00 (3.00, 6.00)	0.005
Cefoperazone/sulbactam therapy duration, days, M (Q25, Q75)	8.00 (5.00, 12.00)	6.00 (4.00, 9.25)	0.001
Cefoperazone/sulbactam therapy duration, days, n (%)			0.001
<7 d	60 (38.7%)	170 (54.8%)	
≥7 d and <14 d	65 (41.9%)	109 (35.1%)	
≥14 d	30 (19.4%)	31 (10%)	

(*Continued*)

Table 2 (Continued).

Variables	Thrombocytopenia Group (n=155)	No-Thrombocytopenia Group (n=310)	*P*-value
Laboratory data at the baseline			
PLT (10^9/L), M (Q25, Q75)	166.00 (135.00, 197.00)	209.00 (164.00, 255.50)	<0.001
WBC (10^9/L), M (Q25, Q75)	9.67 (6.35, 12.88)	8.27 (6.09, 11.70)	0.135
HGB (g/L), mean ± SD	98.05±22.33	110.64±23.30	<0.001
CRP (mg/L), M (Q25, Q75)	12.90 (3.30, 60.27)	8.10 (2.33, 26.31)	0.023
ALT (U/L), M (Q25, Q75)	20.00 (10.00, 37.00)	16.00 (11.00, 31.00)	0.105
AST (U/L), M (Q25, Q75)	26.00 (17.00, 47.00)	19.00 (14.00, 30.00)	<0.001
TBil (μmoL/L), M (Q25, Q75)	12.4 (8.20, 21.80)	11.00 (7.30, 16.70)	0.048
DBil (μmoL/L), M (Q25, Q75)	6.40 (4.00, 12.10)	4.60 (2.90, 7.10)	<0.001
ALB (g/L), M (Q25, Q75)	31.00 (27.00, 35.00)	34.00 (31.00, 38.00)	<0.001
SCR (μmoL/L), M (Q25, Q75)	87.00 (65.00, 157.00)	73.00 (53.75, 95.00)	<0.001
BUN (mmoL/L), M (Q25, Q75)	10.81 (6.93, 18.08)	5.65 (4.33, 7.74)	<0.001
CCr (mL/min), M (Q25, Q75)	45.15 (28.58, 73.76)	76.96 (48.47, 100.18)	<0.001
CCr (mL/min), n (%)			<0.001
≥60	53 (34.2%)	199 (64.2%)	
≥30 and <60	59 (38.1%)	77 (24.8%)	
<30	43 (27.7%)	34 (11%)	
INR, M (Q25, Q75)	1.10 (1.00, 1.24)	1.00 (0.95, 1.09)	<0.001
PT (S), M (Q25, Q75)	15.10 (13.90, 16.30)	14.00 (13.20, 15.10)	0.123
APTT (S), M (Q25, Q75)	32.8 (29.10, 36.90)	32.1 (29.8, 35.2)	0.341
Type of infection, n (%)			
Respiratory infection	111 (71.6%)	105 (33.9%)	<0.001
Hepatobiliary infection	16 (10.3%)	31 (10%)	0.913
Urinary infection	9 (5.8%)	84 (27.1%)	<0.001
Abdominal infection	7 (4.5%)	6 (1.9%)	0.112
Concomitant medications, n (%)			
Antiplatelet	38 (24.5%)	35 (11.3%)	<0.001
Heparin product	80 (51.6%)	73 (26.5%)	<0.001
Vancomycin	23 (14.8%)	22 (7.1%)	0.008
Tigecycline	40 (25.8%)	8 (2.6%)	<0.001
Comorbidities, n (%)			
CVD	63 (40.6%)	68 (21.9%)	<0.001
Respiratory disorders	18 (11.6%)	28 (9.0%)	0.380
Cancer	27 (17.4%)	77 (24.8%)	0.070
Digestive system disease	10 (6.5%)	15 (4.8%)	0.467
Diseases of urinary system	20 (12.9%)	59 (19%)	0.097
Assisted respiration, n (%)			<0.001
Non-invasive ventilator	55 (35.5%)	23 (7.4%)	
Trachea cannula	33 (21.3%)	19 (6.1%)	
No assist	67 (43.2%)	268 (86.5%)	
Blood purification, n (%)			<0.001
Hemodialysis	13 (8.4%)	11 (3.5%)	
Hemofiltration	19 (12.3%)	5 (1.6%)	
Peritoneal dialysis	3 (1.9%)	4 (1.3%)	
No purification	120 (77.4%)	290 (93.5%)	

Abbreviations: BMI, body mass index; PLT, platelet; WBC, white blood cell; HGB, hemoglobin; CRP, C-reactive protein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBil, total bilirubin; DBil, direct bilirubin; ALB, albumin; SCR, serum creatinine; BUN, blood urea nitrogen; CCr, creatinine clearance rate; INR, international normalized ratio of prothrombin time; PT, prothrombin time; APTT, activated partial thromboplastin time; CVD, cardiovascular disease.

showed that there were significant differences in age (p<0.001), hospitalization days (p<0.001), BMI (p=0.005), daily dose of cefoperazone/sulbactam (p=0.005), cefoperazone/sulbactam therapy duration (p=0.001), PLT (p<0.001), HGB (p<0.001), CRP (p=0.023), AST (p<0.001), TBil (p=0.048), DBil (p<0.001), ALB (p<0.001), SCR (p<0.001), BUN (p<0.001), CCr (p<0.001), INR (p<0.001), respiratory infection (p<0.001), urinary infection (p<0.001), antiplatelet (p<0.001), heparin product (p<0.001), vancomycin (p=0.008), tigecycline (p<0.001), cardiovascular disease (p<0.001), assisted respiration (p<0.001), and blood purification (p<0.001) between the thrombocytopenia group and the non-thrombocytopenia group.

Risk Factors of Cefoperazone/Sulbactam-Induced Thrombocytopenia

In the multivariate logistic regression analysis, the following variables were included as independent factors: age, BMI, cefoperazone/sulbactam therapy duration, daily dose of cefoperazone/sulbactam, PLT, HGB, CRP, TBil, ALB, INR, AST, CCr, cardiovascular disease, assisted respiration (no-assist compared with non-invasive ventilator and trachea cannula), blood purification (no purification compared with hemodialysis, hemofiltration, and peritoneal dialysis), and concomitant medications. Considering the intrinsic relationship between DBil and TBil, TBil was chosen as an independent factor in logistic regression. For the same reason, CCr was analyzed using multivariate analysis, but SCR and BUN were not included. The significant independent variables (p<0.05) associated with thrombocytopenia are presented in Table 3. It was found that cefoperazone/sulbactam therapy duration (d) >14 (OR=5.013, 95% CI: 1.031–24.380, p=0.046), PLT (10^9/L) <200 (OR=3.902, 95% CI: 1.465–10.396, p=0.006), daily dose of cefoperazone/sulbactam (g) ≥6 (OR=5.379, 95% CI: 1.193–24.248, p=0.029), TBil (μmoL/L) >21 (OR=6.844, 95% CI: 2.049–22.858, p=0.002), AST (U/L) >35 (OR=4.594, 95% CI: 1.373–15.076, p=0.013), and use of non-invasive ventilator (OR=8.832, 95% CI: 2.266–34.428, p=0.002) were associated significantly with cefoperazone/sulbactam-induced thrombocytopenia.

Discussion

Up to now, this is the first study to investigate the prevalence and risk factors of cefoperazone/sulbactam-induced thrombocytopenia. A particular strength of this study is that patients with hematological diseases and existing thrombocytopenia, which may be confounding factors, have been excluded from the study population. Findings from the present study can help predict which patients are at risk of developing thrombocytopenia, and formulate monitoring strategies to prevent thrombocytopenia. Results showed that 2.4% of patients (155/6489) receiving cefoperazone/sulbactam treatment developed thrombocytopenia. Because this study is the first to report the incidence of cefoperazone/sulbactam-induced thrombocytopenia, no comparison can be made with other papers. Nowadays, thrombocytopenia caused by drugs has attracted increasing attention, and numerous studies have reported risk factors of thrombocytopenia in patients treated with linezolid. The incidence of linezolid-induced thrombocytopenia varies widely across studies. Zhang et al performed a systematic review involving forty observational studies and 6457 patients treated with linezolid, and linezolid-induced thrombocytopenia was estimated to occur in 37% of patients.[15] In comparison, the incidence of thrombocytopenia associated with cefoperazone/sulbactam is relatively low, and thus studies on this topic remain scarce because of low incidence.

Table 3 Binary Logistic Regression Analysis of Determinants Associated with Thrombocytopenia

Independent Variable	OR	95% CI	*P*-value
Cefoperazone/sulbactam therapy duration (d) >14	5.013	1.031–24.380	0.046
PLT (10^9/L) <200	3.902	1.465–10.396	0.006
Daily dose of cefoperazone/sulbactam (g) ≥6 g	5.379	1.193–24.248	0.029
TBil (μmoL/L) >21	6.844	2.049–22.858	0.002
AST (U/L) >35	4.594	1.373–15.076	0.013
Non-invasive ventilator	8.832	2.266–34.428	0.002

Abbreviations: PLT, platelet; TBil, total bilirubin; AST, aspartate aminotransferase; OR, odds ratio; CI, confidence interval.

Using multivariate analysis, we found six risk factors: cefoperazone/sulbactam therapy duration (d) >14, PLT (10^9/L) <200, daily dose of cefoperazone/sulbactam (g) ≥6, TBil (μmoL/L) >21, AST (U/L) >35, and use of non-invasive ventilator. The relative risk of thrombocytopenia for patients treated with cefoperazone/sulbactam for more than 14 days was 5.013 times higher than patients receiving cefoperazone/sulbactam for less than 7 days. This was consistent with our finding that the overall mean time from the initiation of therapy to the development of thrombocytopenia was 6.5 days, indicating that the risk of thrombocytopenia increased with cefoperazone/sulbactam therapy duration. Hence, careful dynamic monitoring of platelet counts was necessary for patients receiving cefoperazone/sulbactam therapy for more than 14 days.

Patients in the thrombocytopenia group had statistically significantly lower baseline PLT than those in the non-thrombocytopenia group (Table 2). The logistic regression analysis revealed that patients with baseline PLT (10^9/L) <200 had an approximately four times greater risk of thrombocytopenia (OR=3.902, 95% CI: 1.465–10.396) compared to patients with baseline PLT (10^9/L) >200. Thus, our finding suggests a closer monitoring of PLT for patients with baseline PLT (10^9/L) <200. The relationship between baseline PLT and cefoperazone/sulbactam-induced thrombocytopenia was first revealed in this study. Interestingly, most studies have reported that lower baseline PLT was a risk factor for thrombocytopenia in patients treated with linezolid. For instance, Choi et al demonstrated that a baseline PLT of <150 (10^9/L) was associated with thrombocytopenia occurrence, and Lima et al identified a baseline PLT of <200 (10^9/L).[16,17] The lower baseline PLT may increase the risk for thrombocytopenia, which are both found in patients treated with cefoperazone/sulbactam or linezolid.

Our study indicated that higher daily dose of cefoperazone/sulbactam was an independent risk factor for thrombocytopenia. The relative risk of thrombocytopenia for patients receiving cefoperazone/sulbactam therapy of more than 6.0 g per day (4.0 g cefoperazone and 2.0 g sulbactam) were 5.379 times higher than patients receiving cefoperazone/sulbactam therapy of less than 6.0 g per day. This result indicated that thrombocytopenia caused by cefoperazone/sulbactam was dose-dependent. According to the drug instructions, the recommended daily dose for adults was 1.5–3.0 g (1.0–2.0 g cefoperazone and 0.5–1.0 g sulbactam), and the maximum daily dose could be up to 12.0 g (8.0 g cefoperazone and 4.0 g sulbactam). Our study was consistent with the drug instructions, and patients who accepted cefoperazone/sulbactam treatment above the recommended daily dose might be more likely to develop thrombocytopenia.

According to the drug instructions, the pharmacokinetics of cefoperazone have been reported to be mainly influenced by the patient's hepatobiliary function, with 75% cefoperazone excreted through bile. Thus, liver and biliary dysfunction might affect drug metabolism and cause drug accumulation in the body.[18] In our study, TBil (μmoL/L) >21 (OR=6.844, 95% CI: 2.049–22.858, p=0.002) and AST (U/L) >35 (OR=4.594, 95% CI: 1.373–15.076, p=0.013) were defined to be a risk factor of cefoperazone/sulbactam-induced thrombocytopenia, which was consistent with the pharmacokinetic characteristic of cefoperazone/sulbactam. Therefore, for patients with hepatobiliary dysfunction, we recommended more frequent platelet monitoring when patients are treated with cefoperazone/sulbactam.

We examined the impact of renal function on the risk of thrombocytopenia by classifying patients into three groups: CCr ≥60 mL/min, CCr ≥30 mL/min and <60 mL/min, and CCr <30 mL/min. As shown in Table 2, the univariate analysis indicated a significant difference in CCr between the thrombocytopenia group and the non-thrombocytopenia group. Of the patients in the thrombocytopenia group, 38.1% had a CCr value between 30 mL/min and 60 mL/min, and 27.7% had a CCr below 30 mL/min, which were higher than in the non-thrombocytopenia group. However, the CCr was not a independent risk factor for cefoperazone/sulbactam-induced thrombocytopenia in the multivariate analysis. The drug instructions indicated that pharmacokinetic parameters of cefoperazone were more related to the patient's liver function rather than renal function. The clearance of cefoperazone/sulbactam is not affected significantly by renal insufficiency, as 75% of cefoperazone sodium is excreted mainly through bile. In this regard, our results were consistent with drug pharmacokinetics.

The mechanism of cefoperazone/sulbactam-induced thrombocytopenia is still unclear. A review of literatures showed that antimicrobial drugs have been recognized to cause thrombocytopenia. It was commonly believed that the main mechanisms of drug-induced thrombocytopenia fell into two categories: (1) decreased production of platelet by myelosuppression, and/or (2) enhanced destruction of platelet because of immune-mediated mechanism.[15,19–21] In general, the decrease of platelet production via myelosuppression tended to develop gradually over several weeks, generally after at least 10 days of antimicrobial therapy. In contrast, the immune-mediated thrombocytopenia could present earlier, mostly after 7–14 days of treatment.[22] Other research indicated that beta-lactam antibiotics commonly caused immune-mediated thrombocytopenia.[8] In our study, the thrombocytopenia occurred rapidly, with an average of

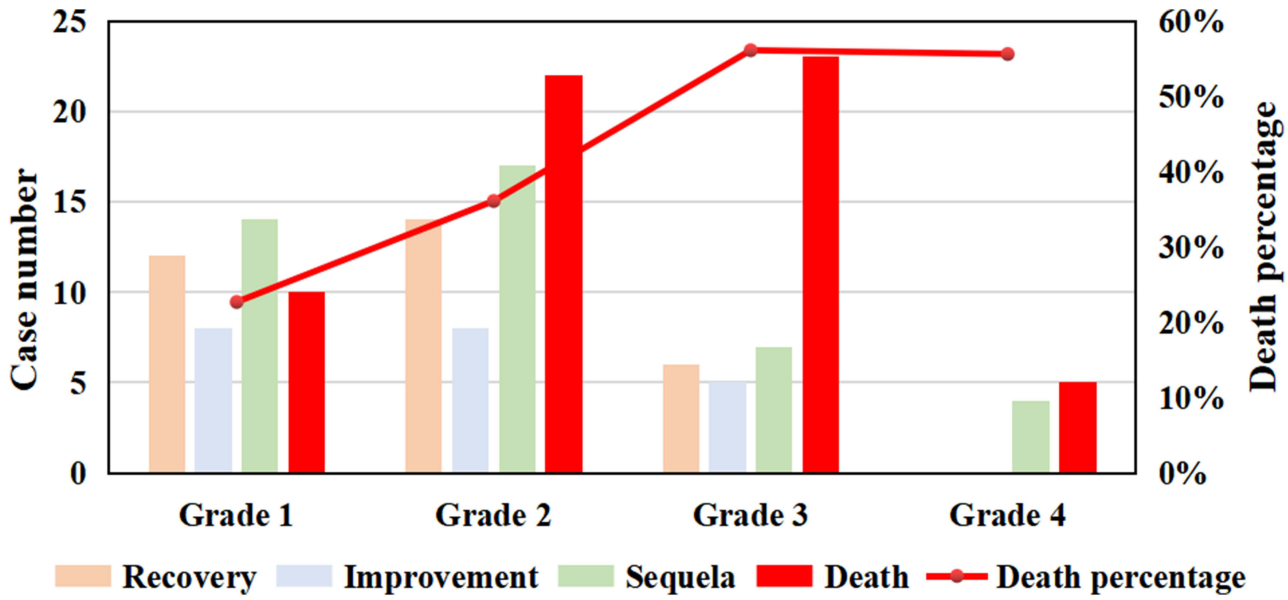

Figure 2 The relationship between the thrombocytopenia grade and clinical outcomes of patients in the thrombocytopenia group (n=155).

6.5 days after administration of drugs. Having considered the above-mentioned issues, we speculate that cefoperazone/sulbactam-induced thrombocytopenia might be related to the immune system, but further studies are required for the verification at the cellular and molecular level.

Continued use of cefoperazone/sulbactam after the occurrence of thrombocytopenia might be not the optimal choice for every patient. Herein, we further investigated the relationship between thrombocytopenia grade and clinical outcomes. Figure 2 compares the clinical outcomes of patients developing different grades of thrombocytopenia, as well as death percentage in each grade. Overall mortality in the thrombocytopenia group was 38.7%, with increased mortality in grade 3 (56.1%) and 4 (55.6%) compared to those in grade 1 (22.7%) and 2 (36.1%). The severity of thrombocytopenia may be a marker of poor outcomes, although none of the patients directly died from thrombocytopenia. Previous studies have identified the relationship between thrombocytopenia and poor clinical outcomes in several diseases, including acute coronary syndrome,[23] leukemia,[24] and in intensive care unit patients.[25] In our study, the association between thrombocytopenia and clinical outcomes may follow the same reasons in the aforementioned studies. Thus, we suggested that physicians should follow the patient-centered approach and balance the risk and benefits of continuing therapy of cefoperazone/sulbactam.

Several limitations of this study should be acknowledged. Firstly, this study is retrospective, and we are unable to confirm the accuracy of the data or to ascertain missing data. Secondly, this single-center study was conducted in one large tertiary general hospital in Beijing, and our results may not be generalizable to all Chinese patients. However, the study's sample size is large, containing nearly seven thousand enrolled patients across the country. Our findings will be helpful in predicting the risk factors for the thrombocytopenia induced by cefoperazone/sulbactam, and also in establishing an appropriate drug usage strategy when using cefoperazone/sulbactam treatment.

Conclusion

Up to now, this is the first paper to study the incidence and related risk factors of thrombocytopenia induced by cefoperazone/sulbactam. Through the retrospective analysis of hospitalized patients in the past six years, we finally identified 155 patients of cefoperazone/sulbactam-induced thrombocytopenia from the nearly seven thousand enrolled patients. In comparison, the incidence of thrombocytopenia caused by cefoperazone/sulbactam (2.4%) was relatively lower than that caused by linezolid. In general, the overall mean time from the initiation of therapy to the development of thrombocytopenia was 6.5 days, and the mean duration time of thrombocytopenia was 7.6 days. The multivariate analysis showed that patients treated with cefoperazone/sulbactam for more than 14 d, with baseline PLT (10^9/L) below 200, daily

dose of cefoperazone/sulbactam more than 6 g, baseline TBil and AST values above the normal range, or with non-invasive ventilator use were at increased risk of developing thrombocytopenia. The severity of thrombocytopenia was probably a marker of poor outcomes of patients. Prompt evaluation and management of underlying risk factors are important to mitigate the risk of developing thrombocytopenia during the treatment with cefoperazone/sulbactam. We recommend that in patients with risk factors for cefoperazone/sulbactam-induced thrombocytopenia the platelet count should be closely monitored when receiving cefoperazone/sulbactam treatment.

Data-Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request. Some data may not be made available because of privacy or ethical restrictions.

Consent for Publication

All authors approved the final manuscript and the submission to this journal.

Funding

This manuscript was supported by funding from National High Level Hospital Clinical Research Funding (BJ-2022-173).

Disclosure

All authors have no conflicts of interest to report in this work.

References

1. Kogilathota Jagirdhar GS, Rama K, Reddy ST, et al. Efficacy of cefoperazone sulbactam in patients with Acinetobacter infections: a systematic review of the literature. *Antibiotics*. 2023;12(3). doi:10.3390/antibiotics12030582
2. Ji XW, Zhu X, Li Y, et al. Model-informed drug development of new cefoperazone sodium and sulbactam sodium combination (3:1): pharmacokinetic/pharmacodynamic analysis and antibacterial efficacy against Enterobacteriaceae. *Front Pharmacol*. 2022;13:856792. doi:10.3389/fphar.2022.856792
3. Visentin GP, Liu CY. drug-induced thrombocytopenia. *Hematol Oncol Clin North Am*. 2007;21(4):685–696. doi:10.1016/j.hoc.2007.06.005
4. Chen A, Basit M, Monogue ML. A large-scale retrospective study on thrombocytopenia associated with beta-lactam antibiotics. *AMIA Annu Symp Proc*. 2023;2022:359–367.
5. Beaulieu C, Kurczewski L, Yajnik V. Cefepime challenge after piperacillin/tazobactam-induced thrombocytopenia. *J Thromb Thrombolysis*. 2019;48(1):167–170. doi:10.1007/s11239-019-01848-3
6. Patel S, Levin-Epstein R, Kobashigawa J. Piperacillin-induced thrombocytopenia in a dual heart and kidney transplant patient: a case report. *Transplant Proc*. 2017;49(7):1672–1674. doi:10.1016/j.transproceed.2017.02.043
7. Avinash A, Kunder SK, Magazine BC, Bairy KL, Adiga S, Patil N. Cefoperazone: a rare cause of thrombocytopenia. *J Appl Pharm Sci*. 2016;6 (12):190–191. doi:10.7324/japs.2016.601227
8. He X, Huang W, Wan X, Li X, Chang Q, Ding L. Cross-reactivity between piperacillin-tazobactam and cefoperazone-sulbactam in drug-induced immune thrombocytopenia. *J Int Med Res*. 2023;51(3):030006052311624. doi:10.1177/03000605231162434
9. Wang W, Liu Y, Yu C, et al. Cefoperazone-sulbactam and risk of coagulation disorders or bleeding: a retrospective cohort study. *Expert Opin Drug Saf*. 2020;19(3):339–347. doi:10.1080/14740338.2020.1713090
10. Miao W, Guo J, Cheng H, Zhao Q. Risk factors for cefoperazone/sulbactam-induced coagulation disorder. *Infect Drug Resist*. 2023;16:6277–6284. doi:10.2147/IDR.S429706
11. 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 (VK1) preventive intervention: a single-center, retrospective analysis. *Med Sci Monit*. 2023;29:e939203. doi:10.12659/MSM.939203
12. Zhang L, Cai X, Peng F, et al. Comparison of bleeding risk and hypofibrinogenemia-associated risk factors between tigecycline with cefoperazone/sulbactam therapy and other tigecycline-based combination therapies. *Front Pharmacol*. 2023;14:1182644. doi:10.3389/fphar.2023.1182644
13. Hanai Y, Matsuo K, Ogawa M, et al. A retrospective study of the risk factors for linezolid-induced thrombocytopenia and anemia. *J Infect Chemother*. 2016;22(8):536–542. doi:10.1016/j.jiac.2016.05.003
14. National Cancer Institute, Cancer therapy evaluation program. common terminology criteria for adverse events v5.0. http://www.cancer.gov/. Accessed 10, Feb 2017.
15. Zhang D, Xu Y, Wang X, et al. Risk factors for thrombocytopenia in patients receiving linezolid therapy: a systematic review and meta-analysis. *Eur J Clin Pharmacol*. 2023;79(10):1303–1314. doi:10.1007/s00228-023-03542-z
16. Choi GW, Lee JY, Chang MJ, et al. Risk factors for linezolid-induced thrombocytopenia in patients without haemato-oncologic diseases. *Basic Clin Pharmacol*. 2019;124(2):228–234. doi:10.1111/bcpt.13123
17. Lima LS, Brito EDCA, Mattos K, Parisotto EB, Perdomo RT, Weber SS. A retrospective cohort study to screen linezolid-induced thrombocytopenia in adult patients hospitalized in the Midwestern region of Brazil. *Hematol Transf Cell*. 2020;42(3):230–237. doi:10.1016/j.htct.2019.07.004
18. Zeng J, Zou M, Min M, Xu M. Characteristics and influencing factors of coagulation dysfunction caused by cefoperazone/sulbactam. *Altern Ther Health Med*. 2024:AT9327. PMID: 38290444.

19. Inoue Y, Takekuma Y, Miyai T, et al. Use of Japanese big data from electronic medical records to investigate risk factors and identify their high-risk combinations for linezolid-induced thrombocytopenia. *Eur J Clin Pharmacol*. 2023;79(3):415–425. doi:10.1007/s00228-023-03455-x
20. Zhang L, Yan Y, Liao R, Dong H. Effect of platelet parameters on linezolid-related thrombocytopenia in hospitalized patients. *Infect Drug Resist*. 2023;16:6145–6154. doi:10.2147/IDR.S408102
21. Han X, Wang J, Zan X, Peng L, Nie X. Risk factors for linezolid-induced thrombocytopenia in adult inpatients. *Int J Clin Pharm Net*. 2022;44(2):330–338. doi:10.1007/s11096-021-01342-y
22. Loo AS, Gerzenshtein L, Ison MG. Antimicrobial drug-induced thrombocytopenia: a review of the literature. *Semin Thromb Hemost*. 2012;38(8):818–829. doi:10.1055/s-0032-1328882
23. Wang TY, Ou FS, Roe MT, et al. Incidence and prognostic significance of thrombocytopenia developed during acute coronary syndrome in contemporary clinical practice. *Circulation*. 2009;119(18):2454–2462. doi:10.1161/CIRCULATIONAHA.108.827162
24. Rozman C, Montserrat E, Felíu E, et al. Prognosis of chronic lymphocytic leukemia: a multivariate survival analysis of 150 cases. *Blood*. 1982;59(5):1001–1005. doi:10.1182/blood.v59.5.1001.1001
25. Vanderschueren S, De Weerdt A, Malbrain M, et al. Thrombocytopenia and prognosis in intensive care. *Crit Care Med*. 2000;28(6):1871–1876. doi:10.1097/00003246-200006000-00031