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Comparison of antibiotic-associated diarrhea caused by cefoperazone/sulbactam or piperacillin/tazobactam in neurosurgery patients

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Abstract

Objective: To compare the occurrence and prognosis of antibiotic-associated diarrhea (AAD) between patients treated with cefoperazone/sulbactam and piperacillin/tazobactam in the neurosurgery department.

Methods: This study retrospectively analyzed patients who received cefoperazone/sulbactam or piperacillin/tazobactam to prevent or treat hospital-acquired infections in the Department of Neurosurgery of The First Medical Center of Chinese PLA General Hospital between October 2019 and October 2020. For patients with AAD, clinical data, antibiotic usage, the incidence of diarrhea, treatment, and prognosis were collected and analyzed.

Results: In total, 356 patients were enrolled, and 65 (18.6%) experienced AAD, 38 patients in the cefoperazone/sulbactam group and 27 patients in the piperacillin/tazobactam group. The AAD rate did not differ between the treatment arms. Conversely, the dosage, intensity, and duration of antibiotic therapy differed between the groups, whereas no differences were noted in the time to the appearance of diarrhea and prognosis. According to regression analysis, the incidence of AAD did not differ between the groups (odds ratio [OR] = 0.85, 95% confidence interval [CI] = 0.46–1.48).

Conclusion: Cefoperazone/sulbactam or piperacillin/tazobactam can lead to a similar incidence rate of AAD. The combined application of antibiotics and empiric therapy often occurs. The rational use of antibiotics should be improved.

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Introduction

Antibiotic-associated diarrhea (AAD) is a common adverse drug reaction occurring during high-intensity antibiotic therapy. AAD describes the gastrointestinal dysfunction caused by the application of antibiotics. The main symptoms of the disease including the passage of loose, watery stools three or more times a day after taking medications used to treat bacterial infections.[1] With the increasing application of broad-spectrum antibiotics, the incidence of AAD has gradually increased in recent years.[2,3] Epidemiological investigations have found that the incidence of AAD in hospitalized patients can be as high as 5% to 39%.[4] Nearly all antibiotics can cause AAD, albeit at different frequencies.[2,5] The most commonly used antibiotics in Chinese tertiary hospitals to prevent or treat hospital-acquired infections are carbapenems, combination β-lactamase inhibitors (such as cefoperazone/sulbactam and piperacillin/tazobactam), and fluoroquinolones. Cefoperazone/sulbactam and piperacillin/tazobactam are two of the most commonly used treatments in neurosurgery departments. However, few studies have compared the incidence of AAD induced by these two treatments. Thus, this study explored the incidence and prognosis of AAD induced by cefoperazone/sulbactam and piperacillin/tazobactam.

Materials and methods

This study is reported in line with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.[6] A retrospective observational analysis was performed in the Neurosurgery Department of First Medical Center of Chinese PLA General Hospital (Beijing, China). Hospital infection control measures were implemented in accordance with standard procedures and remained unchanged during the study period. The decision to use antibacterial drugs and the choice of antibacterial drugs were made by the clinician based on the patient's clinical manifestations, although most patients were treated for hospital-acquired pneumonia. All treatment plans were approved by patients or their family members. The need for ethical approval and informed consent was waived because of the retrospective nature of the study. No protected health information has been disclosed.

Inclusion and exclusion criteria

Patients who used cefoperazone/sulbactam or piperacillin/tazobactam to prevent or treat hospital-acquired infections from October 2019 to October 2020 were consecutively enrolled. The "Diagnostic Criteria for Hospital Infections" were used to diagnose AAD, patients with food poisoning, steatorrhea, irritable bowel syndrome, viral diarrhea, bacillary dysentery, salmonella diarrhea, ischemic diarrhea, and chronic diarrheal diseases were excluded.[3]

The clinical data of the patients, including demographic data (such as height, weight, age, and BMI), the incidence of AAD, anti-infective treatment dosage,

medication time, antibiotic combination, use of empiric therapy or targeted therapy, nutritional support, the time to the appearance of diarrhea, diarrhea etiology, AAD treatment (such as vancomycin and probiotics), liver and kidney function, the length of hospital stay, and prognosis, were retrospectively analyzed.

Grouping

Patients with AAD were grouped according to the receipt of cefoperazone/sulbactam (SCF group) and piperacillin/tazobactam (TZP group).

Laboratory testing of stool samples

Fecal smear and diarrhea pathogen culture were performed by the hospital laboratory according to standard operating procedures. The pathogenic examination of diarrhea in our hospital only provides the intestinal flora distribution or clarifies the presence of fungi, and no drug susceptibility test is performed.

Statistical methods

Statistical analysis was conducted using SPSS Statistics 24 (IBM, Armonk, NY, USA). Normally distributed data were expressed as the mean ± standard deviation, and non-normally distributed data were expressed as the median (interquartile range). Cross-group comparisons were made using Student's *t*-test or the Mann–Whitney U test. Moreover, the chi-squared test was applied to compare classified variables. Bivariate correlation analysis was performed using Pearson's or Spearman's correlation tests. $P < 0.05$ indicated statistical significance. Logistic regression modeling was used to compare AAD rates between the two groups. Confounding variables were those significant at $P < 0.05$ in univariate analysis.

Results

Basic characteristics of patients

In total, 356 patients who used cefoperazone/sulbactam (n = 221) or piperacillin/tazobactam (n = 135) were enrolled in the study. Among them, 65 patients (18.26%) were diagnosed with AAD attributable to the use of these two combination drugs, including 38 (17.19%) and 27 patients (20.00%) in the SCF and TZP groups, respectively. The incidence of AAD did not significantly differ between the two groups ($P = 0.506$). Among the 65 patients with AAD, the primary disease was brain trauma in 23 patients, cerebral hemorrhage in 15 patients, and brain tumor in 28 patients. The 38 patients with AAD in the SCF group included 20 men and 18 women, and the 27 patients with AAD in the TZP group included 19 men and 8 women. There were no significant differences in gender, age, BMI, liver function, and renal function between the two groups ($P > 0.05$), as presented in Table 1.

Factors related to the occurrence of AAD

The two groups of patients had statistically significant differences in the anti-infective drug dosage, therapeutic course, and defined daily dose (DDD, 4 for "cefoperazone and β-lactamase inhibitor" and 14 for "piperacillin and β-lactamase inhibitor;" all $P < 0.05$). There were significant differences in the use of antibiotic combinations, empiric therapy, or targeted therapy; provision of nutritional support (including parenteral nutrition and parenteral nutrition assistance) and the time to the appearance of diarrhea (all $P > 0.05$), as presented in Table 2.

Treatment and outcome of AAD

Among the patients with AAD in the SCF group, 14 underwent fecal smear testing,

Table 1. Basic characteristics of the patients.

	SCF group (n = 221)	TZP group (n = 135)	*P*
AAD incidence rate	38 (18.26%)	27(17.19%)	0.506
Sex (male:female)	116:105	95:40	0.150
Age (years)	63.53 ± 15.52	61.52 ± 18.11	0.636
BMI (kg/m^2)	25.65 ± 6.30	23.84 ± 3.90	0.300
Liver function			
ALT	22.19 ± 28.64	22.20 ± 22.42	0.712
DBIL	5.19 ± 1.99	5.53 ± 1.59	0.681
Renal function			
Ccr	71.20 ± 36.67	69.65 ± 41.74	0.591

*$P < 0.05$.

SCF, cefoperazone/sulbactam; TZP, piperacillin/tazobactam; AAD, antibiotic-related diarrhea; BMI, body mass index; ALT, alanine aminotransferase; DBIL, direct bilirubin; Ccr: creatinine clearance rate.

Table 2. Factors related to the occurrence of AAD.

	SCF group (n = 221)	TZP group (n = 135)	*P*
Dosage (mg/kg/day)	54.0 (36.0–105.8)	94.5 (63.0–182.2)	/
Therapy course (day)	8 (6–11)	14 (8–21)	0.001*
Number of DDDs used	1.4 (1.0–1.5)	1.0 (0.9–1.0)	<0.001*
Empiric therapy	167 (76.32%)	105 (77.78%)	0.890
Targeted therapy	52 (23.68%)	30 (22.22%)	
Combined antibiotics	111 (50.23%)	80 (59.26%)	0.461
Nutrition support	167 (76.32%)	125 (92.59%)	0.165

*$P < 0.05$.

SCF, cefoperazone/sulbactam; TZP, piperacillin/tazobactam; AAD, antibiotic-related diarrhea; DDD, defined daily dose.

and 4 patients (28.57%) had fungal pseudohyphae all patients had cocci/bacilli ratio imbalance. In patients with AAD in the TZP group, 15 underwent fecal smear testing tested, and 3 patients had fungal pseudohyphae (20.00%). Moreover, 14 patients had cocci/bacilli ratio imbalance (93.33%). None of the patients stopped anti-infective treatment, and all received anti-diarrheal therapy. Oral vancomycin and probiotics were sometimes used as treatment. There was no significant difference in the use of vancomycin and probiotics between the two groups (both $P > 0.05$). Regarding the outcome, there were no significant differences in the time to the appearance of diarrhea, the length of hospitalization, and patient prognosis between the two groups ($P > 0.05$), as presented in Table 3.

Table 4 presents the results of logistic regression analysis comparing the incidence of AAD between the two groups. After adjusting for confounding factors such as the treatment course and DDD, the adjusted OR was 0.85 (95% CI = 0.46–1.58, $P = 0.61$), indicating that the incidence of AAD did not differ between the groups.

Discussion

Among all hospitalized patients, neurosurgery patients have among the highest intensities of antibiotic treatment. As such, antibiotic-related adverse reactions have become an important concern.

Table 3. Treatment and outcome of AAD.

AAD	SCF group (n = 38)	TZP group (n = 27)	*P*
Vancomycin	4 (10.53%)	7 (25.93%)	0.103
Probiotics	24 (63.16%)	18 (66.67%)	0.771
Time to the appearance of diarrhea (days)	4.97 ± 2.57	4.11 ± 2.82	0.205
Length of stay (days)	31.50 (21.00–49.25)	43 (28.00–83.00)	0.085
Outcome: cured	33 (86.84%)	24 (88.89%)	>0.99

SCF, cefoperazone/sulbactam; TZP, piperacillin/tazobactam.

Table 4. Logistic regression analysis of the incidence of AAD between the two groups.

Item	AAD
SCF group	38 (18.26%)
TZP group	27 (17.19%)
crude OR (95% CI)	0.84 (0.48–1.45)
crude *P*	0.525
adj. OR (95% CI)	0.85 (0.46–1.58)
P (Wald's test)	0.61

AAD, antibiotic-related diarrhea; SCF, cefoperazone/sulbactam; TZP, piperacillin/tazobactam; OR, odds ratio; CI, confidence interval.

Cefoperazone/sulbactam and piperacillin/tazobactam are two commonly used antibiotic regimens in neurosurgery departments, and few studies have compared the incidence of AAD induced by these treatments. In the present study, the incidence of AAD was 18.26, and the incidence did not differ between the treatment groups (OR = 0.85, 95% CI = 0.46–1.58, $P = 0.61$) Treatment and prognosis also did not differ between the groups.

Clinical manifestations and treatment of AAD

With the widespread use of antibiotics, the incidence of AAD is increasing annually, and AAD has become one of the most common intestinal diseases.[4] More than 90% of the intestinal bacteria belong to the genus *Bacteroides*. Because of antibacterial drug use, most of the sensitive bacteria in the intestine are inhibited, whereas the resistant bacteria multiply and grow in the intestine.[5] Etiological examinations can reveal cocci/bacilli ratio imbalance. In severe cases, pseudohyphae formation or *Clostridium difficile* (CD) infection (CDI) might be present.[7] Unlike other studies, CD was not detected in the pathogenic evaluation in this study. It is reported that China has a lower rate of CDI and fewer toxic strains than the United States. Although not all patients with AAD underwent etiological examinations of diarrhea, cocci/bacilli ratio imbalance was the most common manifestation in the etiological examination. According to the guidelines, vancomycin is the drug of choice for the treatment of AAD caused by CD.[8] In our study, vancomycin was used less frequently than expected, and its use did not differ between the two groups. In this study, probiotics were used more frequently, but there was no significant difference in their use between the two groups, probably because CD was not detected and cocci/bacilli ratio imbalance was the primary manifestation of AAD. Several studies reported that the use of probiotics can reduce symptoms and shorten the duration of diarrhea, which are conducive to improving patient prognoses.[8,9] However, the specific composition of probiotics remains controversial.[11] Termination of the antibiotic(s) that induced AAD is the preferred first step of AAD treatment.[8] In the real world, this is sometimes impossible or ignored by the surgeon. None of our patients terminated

antibiotic therapy after a diagnosis of AAD. Consider the long treatment course and high ratio of empiric therapy in our study, more efforts must be focused on antimicrobial stewardship (AMS) to promote the rational use of antibiotics in the neurosurgery department.

Influence of the use of cefoperazone/sulbactam or piperacillin/tazobactam on the incidence of AAD

Although several reports stated that different antibiotics induce AAD at different frequencies, no studies compared the incidence of AAD associated with cefoperazone/sulbactam and piperacillin/tazobactam. To our knowledge, few studies directly compared the incidence of AAD among β-lactam/β-lactamase inhibitor regimens in China. The mechanism of AAD is mainly believed to be related to antibiotics' direct or indirect influence on the intestinal flora. Different antibiotics have different effects on the intestinal flora.[8,11] β-lactam antibiotics can significantly inhibit the growth and reduce the diversity of the intestinal flora and simultaneously induce the massive growth of clostridia.[13] Among them, cefoperazone is excreted through the liver and gallbladder, and it can inhibit the conversion of bile acid to dehydroxylated bile acid in the intestine and reduce the inhibitory effect of hypobile acid on CD, thereby increasing the risk of CDI.[12] However, in our study, the incidence of AAD and the time to appearance of diarrhea did not differ between the groups, meaning that the route of excretion is not the only factor influencing this adverse drug reaction. Existing studies have not clarified which β-lactam/β-lactamase inhibitor combination is most likely to cause AAD.[2] It is necessary to expand the sample size and population to conduct further research.

Limitations

Our study had some limitations. First, the high ratio of empiric therapy and relatively low etiological examination submission rate may have affected the result. However, in the neurosurgery department, antibiotics are typically used as preventative and empiric therapy, which makes it difficult to detect pathogens. Second, most patients were previously healthy with mild AAD symptoms, and thus, the interpretation of the outcome might differ in other patient populations, such as older and less healthy patients. Finally, cefoperazone/sulbactam is one of the three most commonly used drugs in China but not in the US, and thus, few studies have compared this treatment with other regimens. Our study compared two commonly used antibiotics in terms of AAD risk, and we hope the findings provide useful information for clinical treatment.

In summary, cefoperazone/sulbactam and piperacillin/tazobactam were not associated with significant differences in the occurrence and prognosis of AAD. The incidence rate of AAD was 18.26% in the study. Oral vancomycin and probiotics can be used to treat AAD. Considering the long treatment course, high rate of empiric therapy, low rate of treatment discontinuation after a diagnosis of AAD, and relatively low rate of etiological examination in our study, more efforts regarding AMS are required to promote the rational use of antibiotics in the neurosurgery department.

Declaration of conflicting interest

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