RETROSPECTIVE ANALYSIS ON PATIENTS WITH INFECTION OF MULTIDRUG-RESISTANT ACINETOBACTER BAUMANNII: THE COMBINATION OF POLYMYXIN B AND TIGECYCLINE

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ABSTRACT

Introduction: *To explore the effect of the combination of Polymyxin B and tigecycline in the treatment of infection caused by multidrug-resistant Acinetobacter baumannii.*

Materials and methods: *This study retrospectively analyzed the data of patients with infection of multidrug-resistant Acinetobacter baumannii who were admitted to Nanjing Drum Tower Hospital and the First Affiliated Hospital of Nanjing Medical University from January 2016 to January 2021 and treated with the combination of Polymyxin B and tigecycline. According to the dose of polymyxin B administered, the patients were divided into the low-dose group and high-dose group. Statistical analysis was performed on the age, infection site, pre-existing diseases, liver and kidney function, inflammation-associated cytokines, liver function-associated cytokines, kidney function-associated cytokines, microbial culture results and other indicators of the patients.*

Results: *Inflammation-associated cytokines, including PCT, CRP and WBC, were significantly decreased in both groups, and the decrease in the high-dose group was significantly higher than that in the low-dose group. The kidney injury-associated cytokines, including Cre, reached the peak value on Day 10, ALB and eGFR reached on Day 5, and the three cytokines were gradually decreased in the subsequent treatment, but the speed in the high-dose group was slower than that in the low-dose group ($P<0.05$). The liver injury-associated cytokines, including ALT and AST, showed a significant rising trend in both groups, and the rising in the high-dose group was greater than that in the low-dose group ($P<0.05$). There was no statistical difference in the effective rate between the high-dose group and low-dose group, but the mortality rate in the high-dose group was higher than that of the low-dose group. The results of logistics regression analysis showed that hypertension and diabetes were significantly correlated with the occurrence of kidney injury in the two groups ($P<0.05$).*

Conclusions: *Antibiotic therapy with tigecycline combined with Polymyxin B can increase the incidence of liver and kidney injury in patients with hypertension and/or diabetes, and the resulting liver injury is irreversible, so the selection should be made with caution in clinical application.*

Keywords: *Polymyxin B, tigecycline, acinetobacter baumannii, acute kidney injury.*

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Introduction

Acinetobacter baumannii is widely distributed in the external environment and can cause wound infection, bacteremia, meningitis, respiratory system infection, and urinary system infection, as well as patient-acquired infection in inpatients, especially those in intensive care units[1, 2]. It is a serious pathogenic bacteria of nosocomial infection. The extensive use of broad-spectrum antibiotics leads to serious multidrug resistance in Acinetobacter baumannii and increases the difficulty of treatment[3]. As a result, it is usually take combined antibacterial therapy of Polymyxin B, tigecycline and other antibacterial agents in clinical treatment[4, 5]. Polymyxin B has been used for the treatment of Gram-negative bacterial infections since the 1950s, was limited to use in clinical treatment to some

extent, because it can cause serious neurological and kidney toxicity[6]. In recent years, with the increasing number of infections caused by a variety of drug-resistant Gram-negative bacteria, Polymyxin B has attracted attention again for its extremely low drag resistance and good performance to against Gram-negative bacteria, so its clinical application has increased[7]. Tigecycline, a kind of glycyl cyclic peptide antibiotic, is often used in the treatment of the infection of multidrug-resistant bacteria due to its low drug resistance rate, and common adverse reactions include nausea, vomiting, pancreatitis, hypoglycemia, and abnormal liver function[8, 9].

Studies have shown that Polymyxin B combined with tigecycline has a synergistic effect in killing Acinetobacter baumannii in vitro, and this therapeutic regimen is also common in clinical application[10]. However, there are few reports on the efficacy and safety of Polymyxin B combined with tigecycline in the antibacterial therapy[11-13]. Therefore, we performed a retrospective analysis on the data of patients with infection who were administered with tigecycline and Polymyxin B for the treatment against multidrug-resistant Acinetobacter baumannii during January 2016 to January 2021 in the two hospitals, so as to provide reference for clinicians.

Materials and methods

Study objects

In this study, we collected data of total 227 patients with infection admitted to hospital from January 2016 to January 2021 through the medical record system of the two hospitals, of which 96 patients were eventually included in the study.

Inclusion criteria:

• Tigecycline and Polymyxin B are used as combined antibacterial therapeutic regimen;

• Multidrug-resistant Acinetobacter Baumannii infection is identified in pathogen test;

• Complete clinical data;

• Normal liver and kidney function.

Exclusion criteria:

• Age <18 years;

• Use antibiotics other than tigecycline and Polymyxin B;

• Duration of combined medication with tigecycline and Polymyxin B <48 h.

Tigecycline and Polymyxin B

Both tigecycline and Polymyxin B are administered intravenously. Tigecycline was administered at a dose of 50 mg every 12 h. Polymyxin B was administered at a dose recommended in the instructions that no higher than 50 mg every 12 h for the low-dose group, and at a dose beyond the recommended dose with more than 50 mg every 12 h for the high-dose group.

Data collection

We have collected age, gender, APACHE II score, SOFA score, main diagnosis, infection site, microbiological detection result, acute kidney injury (AKI grading), acute liver injury (Child-Pugh score), dose, course of treatment, and physiological and biochemical indicators. This was a retrospective study. All patients were monitored for liver and kidney functions during treatment, but time and frequency are different. Some patients were discharged voluntarily or died, so there was a lack of data on the recovery of liver and kidney functions after drug withdrawal.

Evaluation criteria

We made statistics on the changes of liver and kidney related physiological and biochemical indicators in patients during the medication with tigecycline and Polymyxin B and conducted correlation analysis in combination with the patients' pre-existing diseases, pathological and physiological status.

Statistical analysis

In this study, SPSS 24.0 was used for statistical analysis, measurement data was expressed as ($\bar{x}\pm S$), count data was expressed in rate (%), correlation analysis was performed with logistics regression method, with the result represented by R. $P<0.05$ indicated statistical significance.

Results

General data

A total of 227 patients were enrolled in this study, 56 in the low-dose group and 40 in the high-dose group. The general data of the patients is shown in Table 1.

Liver and kidney function and inflammatory indicators

As the treatment went on, inflammation-associated cytokines, including PCT, CRP and WBC, were significantly decreased in both groups,

and the decrease in the high-dose group was significantly higher than that in the low-dose group. The kidney injury-associated cytokines, including Cre, which reached the peak value on Day 10, ALB and eGFR reached the peak value on Day 5, and the three cytokines were gradually decreased in the subsequent treatment, but the decrease rate in the high-dose group was slower than that in the low-dose group (P<0.05). Liver injury-associated cytokines, including ALT and AST, had a significant rising trend in both groups, and the rising in the high-dose group was greater than that in the low-dose group (P<0.05).

Item	Low-Dose Group (n=56)	High-Dose Group (n=40)	P
Age/year ($\bar{x}$±S)	65.68±2.03	60.13±2.95	0.339
Male/cases (%)	37 (66.1)	30 (75)	0.637
Female/cases (%)	19 (33.9)	10 (25)	
APACHE II score	24.68±8.05	23.57±9.19	0.547
SOFA score	9.91±2.64	12.07±5.14	0.246
Course of treatment/d	11.89±1.22	9.85±1.21	0.205
Infection site	Lung (n = 53)	Lung (n = 38)	0.847
	Blood (n=8)	Blood (n=10)	
	Abdominal cavity (n=3)	Abdominal cavity (n=3)	
	Skin (n=1)	Wound infection (n=3)	
	Urinary tract infection (n=3)		
Kidney function injury AKI score	Grade 1 (n=10)	Grade 1 (n=7)	0.040
	Grade 2 (n=1)	Grade 2 (n=8)	
	Grade 3 (n=8)	Grade 3 (n=8)	
	33.9%	57.5%	
Liver function injury Child-Page score	Grade A (n=8)	Grade A (n=7)	0.001
	Grade B (n=2)	Grade B (n=6)	
	Grade C (n=2)	Grade C (n=9)	
	21.4%	55.0%	
Pre-existing diseases	Hypertension (n=29)	Hypertension (n=25)	0.673
	Diabetes (n=15)	Diabetes (n=13)	
	Atrial fibrillation (n=14)	Atrial fibrillation (n=8)	
	Lung cancer (n = 2)	Rheumatoid arthritis (n=2)	
	Cerebral hemorrhage (n=5)	Pancreatitis (n=2)	
		Cerebral hemorrhage (n=7)	
		Prostatic hyperplasia (n=2)	
Effective rate%	39 (69.6%)	26 (65.0%)	0.953
Mortality %	5 (8.9%)	10 (25.0%)	0.004

Table 1: Patient data.

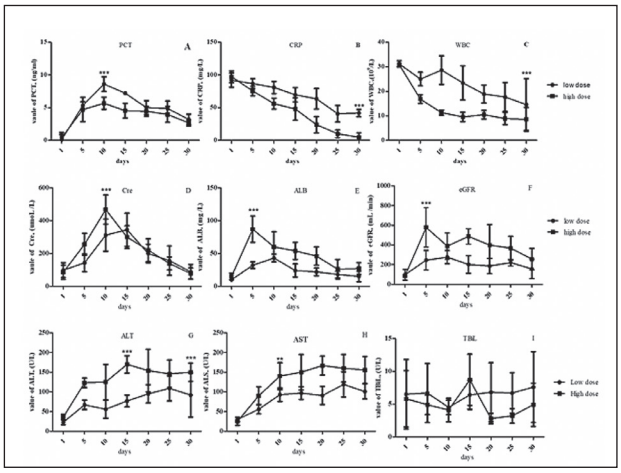

Figure 1: Liver and kidney function and inflammatory indicators. (A) Procalcitonin, PCT; (B) C-reactive protein, CRP; (C) White blood cell, WBC; (D) Creatinine, Cre; (E) Albumin, ALB; (F) Glomerular filtration rate, eGFR; (G) Glutamate-pyruvate transaminase, ALT; (H) Aspartate aminotransferase, AST; (I) Total bilirubin, TBIL.
*Notes: ***means significant difference, P<0.001.*

Logistics regression analysis

We incorporated the patient's pathological data, including age, gender, course of treatment, APACHE II score, SOFA score, pre-existing diseases and other information into the Logistics regression model, and conducted regression analysis with the patient's kidney and liver injury respectively in Table 2.

Item	Low-Dose Group				High-Dose Group			
	Kidney injury		Liver injury		Kidney injury		Liver injury	
	R	P	R	P	R	P	R	P
Age	0.127	0.353	0.080	0.623	0.114	0.304	0.115	0.479
Gender	0.257	0.056	0.159	0.327	0.112	0.411	0.024	0.884
Course of treatment	0.089	0.514	0.144	0.274	0.083	0.542	0.143	0.377
APACHE II score	0.320	0.537	0.209	0.196	0.010	0.941	0.109	0.503
SOFA score	0.052	0.705	0.124	0.446	0.207	0.123	0.160	0.325
Hypertension	0.270*	0.044	0.016	0.920	0.954*	0.008	0.202	0.212
Diabetes	0.266*	0.048	0.246	0.125	0.467*	0.098	0.407	0.771

Table 2: Logistics regression analysis.
**.at 0.05 (double ends), significant relevance.*

Pre-existing diseases include hypertension, diabetes, pre-existing diseases of the cardiovascular system, pre-existing diseases of the nervous system, and tumors. Due to the diversity and complexity of the types and data of pre-existing diseases of the enrolled patients, only two pre-existing diseases (hypertension and diabetes) with a large number of patients were analyzed in this study.

The results showed that hypertension and diabetes were significantly correlated with kidney injury (low-dose group: P=0.044, 0.048; high-dose group: P=0.008, 0.098). Hypertension and diabetes mellitus were not significantly correlated with liver injury (low-dose group: P=0.920, 0.125; high-dose group: P=0.212, 0.771).

Discussion

The patients enrolled in our study were mostly elderly (age: low-dose group, 65.68±2.03; high-dose group, 60.13±2.95; P=0.339). They all suffered from pre-existing diseases of different degrees, including hypertension, diabetes, cerebral hemorrhage, tumor, etc. Such chronic pre-existing diseases have a negative impact on the overall health of patients. The more pre-existing diseases may lead to the worse recovery of the body and the worse tolerance to drugs in the occurrence of infection and other major diseases[14-16]. The study results showed that age, gender, course of treatment, APACHE II score and SOFA score had no significant correlation with the occurrence of kidney and liver injury in the two groups (P>0.05). The results of logistics regression analysis showed that hypertension and diabetes were significantly correlated with the occurrence of kidney injury (R=0.270, 0.266, P=0.044, 0.048), and were independent risk factors for kidney injury.

Hypertension and diabetes are chronic influencing factors for kidney diseases, and the long-term effects of such diseases on the human body lead to increased kidney load and ultimately kidney damage[17, 18]. There are two main types of kidney injuries caused by hypertension. One is renal arteriolar sclerosis caused by hypertension, resulting in insufficient blood supply to the kidney and loss of partial tissue function. The other is ischemic lesions in renal tubule caused by hypertension, with the earliest symptoms of increased nocturia and decreased urinary concentration, followed by proteinuria and glomerular lesions[19, 20]. The results of the study by Sisay showed that the incidence of kidney injury was about 48% when Polymyxin B was administered alone, and the elderly, high daily dose, underlying diseases such as diabetes, and the use of nephrotoxic drugs were independent risk factors for nephrotoxicity[21]. The results of our study showed that the incidence (57.5%) of acute kidney injury in the high-dose group of Polymyxin B was higher than that in the low-dose group (33.9%), and the difference was statistically significant (P=0.04). In addition, a multicenter randomized clinical study showed an incidence of kidney injury in the antibiotic therapy with Polymyxin B combined with Tigecycline was about 20%[22]. The results of our study showed that the incidence of kidney injury was higher than the above results. This may be related to the fact that about 33% of tigecycline was excreted in the urine, Polymyxin B itself has strong renal toxicity and about 60% was excreted via kidney, the increasing dose of Polymyxin B and the combined use of tigecycline increased the burden of renal drug metabolism, and thus increased the risks of kidney injury[23, 24]. Another possible reason is hypertension already resulted in extreme injury of the kidney function, and the use of drugs excreted through the kidney induced the occurrence of kidney injury. Clinically, early kidney injury was defined as negative protein and normal BUN and Scr in routine urine examination, with no obvious clinical symptoms. In this study, more sensitive Cre, ALB and eGFR were selected as the detection indicators of kidney injury[25].

As shown in Figure 1, the values of all three indicators showed a rising trend in the early stage of treatment and showed a gradual decrease with the ending of antibacterial treatment, which indicated that the kidney injury caused by the combination of Polymyxin B and tigecycline was reversible. However, either the high dose or low dose of Polymyxin B, there is no significant correlation between hypertension and diabetes and the occurrence of liver injury (P>0.05). Previous studies have shown that the toxicity of Polymyxin B was mainly manifested as nephrotoxicity and neurotoxicity[21, 24]. However, the results of our study showed an incidence of liver injury of 55.0% in the high-dose group, which was much higher than 21.4% in the low-dose group. The safety analysis of tigecycline by Su showed that the incidence of liver injury caused by tigecycline was 37.5%, which was higher than 21.4% in the low-dose group, but they were all lower than 55.0% in the high-dose group (P=0.001). Liver function-associated cytokines, including ALT and ALS, were significantly increased in both groups, and the high-dose group was higher than that in the low-dose group (P<0.05), indicating that the liver injury caused by the combination of Polymyxin B and tigecycline was dose-dependent; the ALT and ALS did not decrease with discontinuation of Polymyxin B and tigecycline. Therefore, the liver injury caused by the combination of Polymyxin B and tigecycline was irreversible. Considering that

tigecycline was metabolized mainly through biliary tract and faeces, Polymyxin B was mainly through the kidney[23]. Their metabolic pathways were different. In vitro study by Dai showed that Polymyxin B combined with tigecycline can synergistically induce hepatocyte autophagy[26]. Therefore, we speculate that Polymyxin B and tigecycline may also play a synergistic role in inducing autophagy in liver cells in vivo, resulting in irreversible liver injury. We will conduct further study on this hypothesis.

In conclusion, this study observed the patients with severe infection with multidrug-resistant Acinetobacter baumannii who were treated with the combination of Polymyxin B and tigecycline, and found that the combination of Polymyxin B and tigecycline significantly reduced the inflammation-associated cytokines in a measurement correlated manner; There was no significant difference in the effective rate, but the mortality in the high-dose group was higher. The injury to kidney function of patients with hypertension and diabetes was reversible, but the injury to liver function was irreversible and dose-dependent. This study provides valuable clinical experiences for the treatment with the Polymyxin B combined with tigecycline, and provide clinical support for the patients with serious infection with multidrug-resistant Acinetobacter baumannii to select rational antimicrobial therapy.

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