Clinical efficacy of cefoperazone-sulbactam in patients with acute myocardial infarction complicated with infection and effects on serum procalcitonin and serum inflammatory indicators Running tittle: Cefoperazone-sulbactam in acute myocardial infarction complicated with infection

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Abstract This study aimed to investigate clinical efficacy of cefoperazone-sulbactam in patients with acute myocardial infarction complicated by infection and effects on serum procalcitonin and serum inflammatory indicators. Prospective analysis was used in this study. A total of 109 cases of patients with acute myocardial infarction complicated with infection were collected. They were admitted to our hospital from August 2018 to September 2019 and were divided into a control group and an experimental group according to different treatment methods. Patients (53 cases) in the control group received treatment of cefoperazone, while patients (56 cases) in the experimental group received treatment of cefoperazone-sulbactam. Therapeutic effect, bacterial clearance rate and adverse reaction of the two groups were compared. Serum procalcitonin (PCT) and serum hypersensitive C-reactive protein (hs-CRP) levels were observed and compared. ROC curve was used to analyze the predictive value of PCT, hs-CRP for the treatment of acute myocardial infarction complicated by infection. Logistic regression analysis was used to analyze the risk factors for the effect of acute myocardial infarction complicated by infection. The effective rates and bacterial clearance rates of treatment in the experimental group were higher than those in the control group ($P<0.05$). After treatment, the PCT and hs-CRP levels of the experimental group were lower than those of the control group ($P<0.05$). Age, hypertension, length of hospital stay, heart failure and hs-CRP were independent risk factors affecting the effective rate of treatment for acute myocardial infarction complicated by infection. In conclusion, cefoperazone-sulbactam has good therapeutic effect on acute myocardial infarction complicated with infection. It can reduce the level of PCT and serum inflammatory indicator hs-CRP; PCT and hs-CRP have certain predictive value on the therapeutic effect, which is worthy of promotion.

Keywords: cefoperazone-sulbactam, acute myocardial infarction, infection, serum procalcitonin, serum inflammatory indicators
Tob Regul Sci.™ 2021;7(4-1): 730-740
DOI: doi.org/10.18001/TRS.7.4.1.27

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INTRODUCTION

Acute myocardial infarction refers to myocardial necrosis caused by acute and continuous coronary artery hypoxia-ischemia. It is characterized by acute attack, rapid progression, multi complications and high mortality (1). Although the treatment of acute myocardial infarction has been improved greatly in the past decade, myocardial infarction is often accompanied by pulmonary infection clinically, which brings a higher risk of death and is more difficult to treat. Therefore, when acute myocardial infarction complicated by infection occurs, infection should be actively controlled to prevent further deterioration of the condition (2-4).

According to relevant studies, acinetobacter baumannii complex and pseudomonas aeruginosa are non-fermentive gram-negative bacteria, which are common causes of clinical infection (5). β-Lactam is one of the most commonly used antibiotics in clinical practice. As an example, cefoperazone is a β-Lactam antibiotic that is used to treat various gram-positive and gram-negative infections. Sudhakar et al (6) reported in a study that for patients with acute infective endocarditis caused by P. aeruginosa, the use of β-lactam or carbapenem and aminoglycosides would be better. However, the increase in β-lactam antibiotics has led to the development of various antibiotic resistance (7,8). It has been proved that sulbactam could enhance the spectra of cefoperazone in vitro, while cefoperazone-sulbactam is a third-generation combination of cephalosporin and β-lactamase inhibitors, which is mainly used to treat severe bacterial infections (9,10). According to the study of Lai et al., sulbactam combined with cefoperazone could improve the antibacterial activity against caba-resistant enterobacteriaceae or baumannii. Moreover, their results also demonstrated that the sensitivity of cefoperazone alone in treating all different drug-resistant organisms was significantly lower than that of cefoperazone combined with sulbactam, and additional sulbactam could increase the activity of cefoperazone on most different resistant organisms (11). However, there are still few clinical reports on cefoperazone-sulbactam in acute myocardial infarction complicated by infection. Therefore, this study was conducted.

This study investigated the clinical efficacy of cefoperazone-sulbactam in patients with acute myocardial infarction complicated by infection and the influence of serum procalcitonin and serum inflammatory indicators in patients, so as to provide certain clinical reference for clinical treatment of this disease.

DATA AND METHODS

General Data

A total of 109 cases of patients with acute myocardial infarction complicated by infection were collected as research subjects. They were admitted to our hospital from August 2018 to September 2019, with an age of 45-78 years old and an average age of (62.13±16.31). They were divided into a control group and an experimental group according to different treatment methods. Patients (53 cases) in the control group received cefoperazone, while patients (56 cases) in the experimental group received cefoperazone-sulbactam. This study has been approved by the ethics committee of the hospital. All patients and their families have been informed and signed informed consent.

Inclusion and exclusion criteria

Inclusion criteria were as follows: 1. Patients diagnosed with acute myocardial infarction in our hospital. 2. Patients developed signs of infection and fever 48 hours after admission. 3. Patients whose blood specimen was positive after bacterial culture. 4. Patients whose blood routine examination results showed elevation of white blood cells. Exclusion criteria were as follows: 1. Patients with malignant tumor or severe liver and kidney dysfunction. 2. Patients with previous mental illness. 3. Patients with drug allergy. 4. Patients with long-term use of antibiotics. 5. Patients with other systemic inflammatory diseases.

Methods

Patients in the control group received intravenous injection of 2.0g cefoperazone (Qilu pharmaceutical Co., Ltd., SFDA approval number: H37020569) combined with 100ml 0.9% sodium chloride, vt, q12h, for 1 week. Patients in the experimental group received intravenous injection of 2.0g cefoperazone-sulbactam (Pfizer, SFDA approval number: H10960113) combined with 100ml 0.9% sodium chloride injection, vt, q12h, for 1 week.

Observational Indexes

Therapeutic effect, bacterial clearance rate and adverse reaction of the two groups were compared. Serum procalcitonin (PCT) and serum hypersensitive C-reactive protein (hs-CRP) levels were observed and compared. ROC curve was used for analysis of PCT, hs-CRP on predictive value for the treatment of acute myocardial infarction complicated by infection, and Logistic regression analysis was used to analyze the risk factors for the effect of acute myocardial infarction complicated by infection.

Test methods

Clinical efficacy evaluation criteria

Cure: the infection-related symptoms and signs completely disappeared, with normal white blood cell level. Significant effect: the infection-related symptoms and signs of the patients basically disappeared, with significantly decreased white blood cell level. Effective: the infection-related symptoms and signs were reduced, and the white blood cell level was lower than that of admission. Invalid: patient's clinical symptoms did not improve or even aggravate after treatment. Total effective rate = (cure + significant effect + effective) / total number *100%

Bacteriological assessment

BioMerieux VITEK 2 Compact automatic bacterial identification and drug sensitivity analysis system was used for strain identification of patients on fasting blood in both groups 1 day after infection and 1 week after treatment. Specific operations were conducted by relevant professionals.

Detection of serum PCT and hs-CRP levels

Fasting blood of patients was collected 1 day after infection and 1 week after treatment, and were tested by electrochemilu minescene immunoassay. PCT and hs-CRP levels in serum were detected by ADVIA2400 automatic biochemical analyzer and supporting kit. Specific operations were conducted by relevant professionals.

Statistical Method

SPSS19.0 (Asia Analytics Formerly SPSS China) was used in this study. The enumeration data were expressed by rate, and the rate was compared by χ2. The measurement data were expressed as mean±standard deviation (mean±sd). The t test was used for comparison between the two groups. ROC curve was used for analysis of PCT, hs-CRP on predictive value for the treatment of acute myocardial infarction complicated by infection, and logistic regression analysis was used to analyze the risk factors for the effect of acute myocardial infarction complicated by infection.

RESULTS

Clinical Data

There were no differences between the two groups in age, gender, BMI, smoking and drinking history, length in bed, infection type and place of residence ($P>0.05$). More details were shown in Table I.

Table I General data

	Control group (n=53)	Experimental group (n=56)	χ^2/t	P
Gender (n(%))			0.010	0.922
Male	27（50.94）	28（50.00）		
Female	26（49.06）	28（50.00）		
Age（years old）	61.86±15.97	62.12±16.08	0.085	0.933
BMI(kg/m2)	25.21±1.41	25.31±1.29	0.387	0.700
Smoking (n(%))			0.314	0.576
Yes	34（64.15）	33（58.93）		
No	19（35.85）	23（41.07）		
Drinking (n(%))			0.012	0.913
Yes	25（47.17）	27（48.21）		
No	28（52.83）	29（51.79）		
Length in bed (day)	8.78±1.43	9.01±1.27	0.889	0.376
Hypertesion [n(%)]			＜0.001	0.985
Yes	37（69.81）	39（69.64）		
No	16（30.19）	17（30.36）		
Diabetes [n(%)]			＜0.001	0.980

Yes	33（62.26）	35（62.50）		
No	20（37.74）	21（37.50）		
Cardiac failure [n(%)]			0.190	0.663
Yes	30（56.60）	34（60.71）		
No	23（43.40）	22（39.29）		
Residence (n(%))			0.222	0.637
Cities	26（49.06）	30（53.57）		
Countrysides	27（50.94）	26（46.43）		
Infection type [n(%)]			0.494	0.974
Upper respiratory infection	21（39.62）	19（33.93）		
Lower respiratory infection	10（18.87）	11（19.64）		
Gastrointestinal infection	13（24.53）	15（26.79）		
Urinary system infection	6（11.32）	8（14.29）		
Others	3（5.66）	3（5.35）		

Evaluation of Clinical Curative Effect

The total effective rate of the control group was 71.70%, and that of the experimental group was 91.70%. It was higher in the experimental group than that in the control group (P<0.05). More details were shown in Table II.

Table II Evaluation of clinical curative effect [n(%)]

	Control group (n=53)	Experimental group (n=56)	χ^2	P
Cure	17（32.08）	25（44.64）	1.816	0.178
Significant effect	15（28.30）	19（33.93）	0.402	0.526
Effective	6（11.32）	7（12.50）	0.036	0.849
Invalid	15（28.30）	5（8.93）	6.821	0.009
Total effective	38（71.70）	51（91.70）	6.821	0.009

Bacterial Clearance Rate

In the two groups, 109 strains of pathogens were identified by bacterial identification before treatment, of which 53 strains were in the control group, 32 strains were cleared after treatment, with the bacterial clearance rate of 60.38%. And another 56 strains were in the experimental group, 50 strains were cleared after treatment, with the bacterial clearance rate of 89.29%. The bacterial clearance rate of the experimental group was higher than that of the control group (P<0.05). As shown in Table III.

Table III Bacterial clearance rate [n(%)]

		Control group	Experimental group	χ^2	P
Pseudomonas aeruginosa	Strains	17（32.08）	18（32.14）	5.672	0.994
	Cleared strains	9（52.94）	16（88.89）	5.536	0.019
Klebsiella pneumoniae	Strains	11（20.75）	13（23.21）	0.096	0.757
	Cleared strains	6（54.55）	12（92.31）	4.531	0.033
Staphylococcus aureus	Strains	10（18.87）	11（19.64）	0.011	0.918
	Cleared strains	8（80.00）	11（100.00）	2.432	0.119
Acinetobacter baumannii	Strains	8（15.09）	8（14.29）	0.014	0.905
	Cleared strains	5（62.50）	7（87.50）	1.333	0.248
Streptococcus pneumoniae	Strains	2（3.77）	2（3.57）	0.003	0.955
	Cleared strains	1（50.00）	1（50.00）	0.000	＞0.999
Others	Strains	5（9.43）	4（7.14）	0.189	0.664
	Cleared strains	3（60.00）	3（75.00）	0.225	0.635
Total	Strains	53（100.00）	56（100.00）		
	Cleared strains	32（60.38）	50（89.29）	12.210	＜0.001

Incidence of Adverse Reactions

There were 11 cases of adverse reactions in the control group, with an incidence rate of 20.75%, and 4 cases of adverse reactions in the experimental group, with an incidence rate of 7.14%. The incidence rate of adverse reactions in the experimental group was lower than that in the control group ($P<0.05$). More details were shown in Table IV.

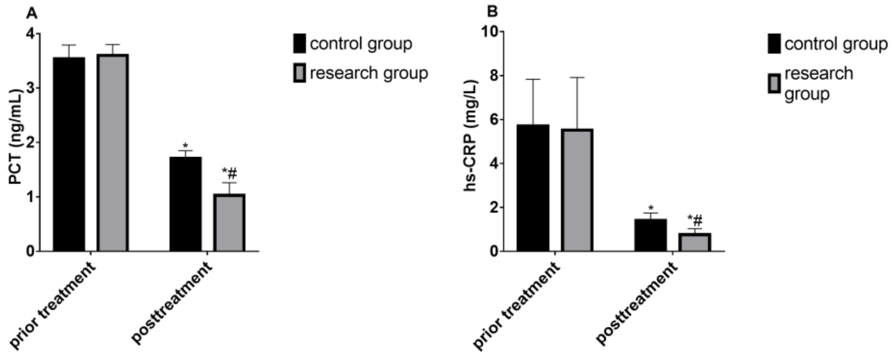
Table IV Incidence rate of adverse reactions [n(%)]

	Control group (n=53)	Experimental group (n=56)	χ^2	P
Gastrointestinal reaction	5（7.55）	2（3.57）	1.557	0.212
Headache	3（5.66）	1（1.79）	1.156	0.282
Rash	3（5.66）	1（1.79）	1.156	0.282
Total	11（20.75）	4（7.14）	4.251	0.039

Detection of Serum PCT and hs-CRP Levels

The PCT levels of the control group before and after treatment were (3.54±0.25) and (1.71±0.14) ng/mL, respectively. The PCT levels of the experimental group before and after treatment were (3.60±0.20) and (1.03±0.23) ng/mL, respectively. After treatment, the PCT level of the experimental group was lower than that of the control group ($P<0.05$). Hs-CRP levels in the control group before and after treatment were (5.70±2.13) and (1.41±0.34) mg/L, respectively. The hs-CRP levels of the experimental group before and after treatment were (5.52±2.39), (0.76±0.27) mg/L, respectively. There were no differences in the hs-CRP level between the two groups before and after treatment (P 0.05). After treatment, the hs-CRP level of the experimental group was lower than that of the control group (P<0.05), as shown in Figure 1.

Figure 1 Detection of serum PCT and hs-CRP levels



A: After treatment, the PCT level of the experimental group was lower than that of the control group. B: After treatment, the PCT level of the experimental group was lower than that of the control group. * means compared with that before treatment, P<0.05. # means compared with the control group after treatment, P < 0.05 .

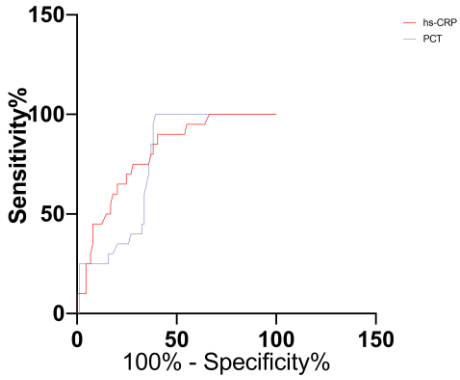
The Predictive Value of PCT and hs-CRP in Patients with Acute Myocardial Infarction Complicated by Infection

The AUC, critical level, sensitivity and specificity of PCT in predicting the efficacy of acute myocardial infarction complicated by infection were 0.753, 60.67, 100.00 and 59.55, respectively. The AUC, critical level, sensitivity and specificity of hs-CRP in predicting the efficacy of acute myocardial infarction complicated by infection were 0.801, 49.55, 90.00 and 57.30, respectively. More details were shown in Table V and Figure 2.

Table V The predictive value of PCT and hs-CRP in patients with acute myocardial infarction complicated by infection

	AUC	Critical level	95%Cl	Sensitivity%	Specificity%
PCT	0.753	60.67 ng/mL	0.6575to0.8475	100.00	59.55
hs-CRP	0.801	49.55 mg/L	0.7054to0.8962	90.00	57.30

Figure 2 The predictive value of PCT and hs-CRP in patients with acute myocardial infarction complicated by infection



The AUC of PCT and hs-CRP in predicting the efficacy of acute myocardial infarction complicated by infection was 0.753 and 0.801, respectively

Univariate Analysis of Treatment Effect of Patients

All patients were divided into effective group (n=89) and ineffective group (n=20) in accordance with effective rate of treatment. Clinical data of patients in the two groups were collected for univariate analysis, and it was found that there were no differences in gender, BMI, drinking, diabetes, place of residence and infection type (P>0.05), while there were differences in age, smoking, hypertension, length of bed rest, heart failure, PCT and hs-CRP (P<0.05), as shown in Table VI.

Table VI Univariate analysis

	Effective (n = 89)	Invalid (n = 20)	χ^2/t	P
Gender (n(%))			0.202	0.653
Male	44（49.44）	11（55.00）		
Female	45（50.56）	9（45.00）		
Age （years old）			20.670	＜0.001
≥60	20（22.47）	15（75.00）		
＜60	69（77.53）	5（25.00）		
BMI(kg/m2)			0.029	0.864
≥25	25（28.09）	6（30.00）		
＜25	64（71.91）	14（70.00）		
Smoking (n(%))			2.435	0.119
Yes	60（67.42）	17（85.00）		
No	29（32.58）	3（15.00）		
Drinking (n(%))			0.522	0.470
Yes	41（46.07）	11（55.00）		
No	48（53.93）	9（45.00）		
Length in bed rest (day)			25.200	＜0.001
≥10	14（15.73）	14（70.00）		
＜10	75（84.27）	6（30.00）		
Hypertension [n(%)]			4.770	0.029
Yes	58（65.17）	18（90.00）		
No	31（34.83）	2（10.00）		
Diabetes [n(%)]			0.059	0.808
Yes	56（62.92）	12（60.00）		
No	33（37.08）	8（40.00）		
Cardiac failure [n(%)]			4.578	0.032
Yes	48（53.93）	16（80.00）		
No	41（46.07）	4（20.00）		
Residence (n(%))			0.399	0.528
Cities	47（52.81）	9（45.00）		
Countrysides	42（47.19）	11（55.00）		
Infection type [n(%)]			0.353	0.552

Respiratory tract infection	51（57.30）	10（50.00）		
Others	38（42.70）	10（50.00）		
PCT(ng/Ml)	0.98±0.21	1.84±0.43	13.220	＜0.001
hs-CRP（mg/L）	0.53±0.18	1.58±0.22	22.600	＜0.001

Multivariate Analysis of the Effective Rate of Treatment in Patients

The indicators with differences in univariate analysis were included in assessment (the assessment table was shown in Table VII). Logistic regression analysis showed that age, hypertension, length of hospital stay, heart failure and hs-CRP were independent risk factors affecting the effective rate of treatment for acute myocardial infarction complicated by infection, as shown in Table VIII

Table VII Assignment table

Factors	Assignment
Age	≥60=0，＜60=1
Smoking	Yes=0, No=1
Hypertension	Yes=0, No=1
Length of stay	≥10=0.＜10=1
Cardiac failure	Yes=0, No=1
PCT	Continuous variables date are analyzed by original data
hs-CRP	Continuous variables data are analyzed by original data

Table VIII Logistic multivariate analysis of treatment effect

	B	S.E,	Wals	df	Sig.	Exp (B)	95% C.I. Of Exp (B)	
							Lower limit	Upper limit
Age	-0.243	0.533	0.208	1	0.049	0.984	0.276	2.229
Smoking	0.648	0.529	1.502	1	0.22	2.912	0.678	5.389
Hypertension	-0.605	0.54	1.253	1	0.026	0.646	0.189	1.575
Length of stay	-0.403	0.577	0.489	1	0.044	1.068	0.216	2.069
Cardiac failure	0.046	0.519	0.008	1	0.033	1.047	0.379	2.892
PCT	-0.064	0.424	0.019	1	0.127	0.943	0.471	1.942
hs-CRP	-0.015	0.316	0.542	1	0.018	0.742	0.463	1.834

DISCUSSION

In the context of chronic atherosclerotic vascular disease, infectious diseases may cause acute coronary syndrome through acute inflammation, biomechanical stress and vasoconstriction. Various acute respiratory tract infections may be associated with increased risk of acute myocardial infarction, so the infection control would be particularly important (12,13).

In this study, the effective rate of cefoperazone-sulbactam was significantly higher in the experimental group than that in the control group, suggesting that cefoperazone-sulbactam had a better therapeutic effect. We compared the safety of the two treatments and found that the rate of adverse reactions was lower in the experimental group, indicating that cefoperazone-sulbactam was safer than cefoperazone alone. According to report of Peng et al. (14) on the treatment of sepsis with cefoperazone-sulbactam, cefoperazone-sulbactam has a significant therapeutic effect on sepsis and can improve the therapeutic effect, which is safe and effective. Moreover, Song, Sun et al. (15,16) also showed in their study that cefoperazone-sulbactam was more effective in treating stroke comorbid with infection and nosocomial infection, which was consistent with our results, indicating that cefoperazone-sulbactam had a better effect on post-infection treatment. Subsequently, we investigated the bacterial clearance rate of cefoperazone-sulbactam after acute myocardial infarction complicated by infection, and found that the bacterial clearance rate of the experimental group was higher than that of the control group, indicating that cefoperazone-sulbactam was more sensitive to bacteria than cefoperazone alone. Ali et al. (17) studied the present situation of bacterial susceptibility to respiratory tract infection in people of all ages in Punjab, Pakistan, and explored the sensitivity of various antibiotics to bacteria. It was found that the highest sensitivity of cefoperazone-sulbactam to gram-negative bacteria was 91.39%, which confirmed the feasibility of the results of this study. However, our results show that the streptococcus clearance rate of patients treated with cefoperazone-sulbactam did not exceed 50%, but the combination of β-lactam antibiotics and aminoglycosides has a synergistic antibacterial effect (18), which means that the treatment plan for patients with acute myocardial infarction complicated with infection needs to be improved.

PCT is widely originated from endotoxin or mediator released by bacterial infection, and CRP is an inflammatory marker that predicts the risk of various cardiovascular outcomes, including acute myocardial infarction (19,20). In this study, the levels of these two biomarkers were detected before and after cefoperazone-sulbactam treatment for acute myocardial infarction complicated by infection. It was found that the two biomarkers in the experimental group were lower than those in the control group, which is consistent with the results of Chen et al. (21) on the changes of two biomarkers in the treatment of acinetobacter baumannii severe pneumonia. We could conclude that cefoperazone-sulbactam in treatment of acute myocardial infarction complicated by infection could reduce the levels of PCT and hs-CRP and other inflammatory markers. According to recent studies, inflammation after acute myocardial infarction could clear wounds, promote wound healing and scar formation, however, excessive inflammation can lead to left ventricular remodeling and heart failure. Markers of systemic inflammatory response are predictors of adverse clinical outcomes such as death in patients with acute myocardial infarction, recurrent myocardial infarction and heart failure (22). Therefore, we investigated the predictive value of PCT and hs-CRP for cefoperazone-sulbactam in the treatment of acute myocardial infarction complicated by infection, and found that the sensitivity of PCT in predicting the efficacy of acute myocardial infarction complicated by infection was 100.00%. According to the study of Vitkon-Barkay et al. (23), the best criterion for the identification of PCT as a differential diagnostic indicator is 0.09 ng/dl (with sensitivity of 94.4%). Serum PCT and CRP had a good ability to distinguish infected AMI patients from non-infected AMI patients, and it should be used as an auxiliary test when inflammation signs appeared in AMI patients. Moreover, Sun et al. (24) also reported in the study that serum PCT level of patients was correlated with myocardial infarction complicated by pulmonary infection, suggesting that PCT level could be used as an important diagnostic indicator of this complication, which was consistent with our results. Therefore, we speculated that PCT could be used as an easily detectable biological indicator to assess the prognosis of acute myocardial infarction complicated by infection.

Finally, logistic regression was used to analyze the risk factors affecting the therapeutic effect of acute myocardial infarction, and it was found that age, hypertension, length of stay, heart failure and hs-CRP were independent risk factors affecting the therapeutic effect of acute myocardial infarction. According to the study of Jie-yu et al. (25), age, length of stay, hypertension and heart failure were all risk factors for acute myocardial infarction complicated by infection. There were also some relevant reports supporting that elevation of hs-CRP was an important risk factor for cardiovascular diseases (26). Pokharel et al. (27) pointed out that elevation of hs-CRP at 30 days after acute myocardial infarction was associated with deterioration of health status. These results suggested that we should pay special attention to these aspects in the treatment of acute myocardial infarction complicated by infection to improve the therapeutic effect(28).

In conclusion, cefoperazone-sulbactam has a good therapeutic effect on acute myocardial infarction complicated by infection. It can reduce the level of PCT and serum inflammatory indicator hs-CRP; PCT and hs-CRP have certain predictive value for their therapeutic effect, which is worthy of promotion.

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