Original Article

Application of the clearance rate of inflammatory markers for evaluation of the therapeutic effect in adult bacterial bloodstream infection

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Background: Bloodstream infection (BSI) is a serious systemic infectious disease. This study aimed to investigate the application of the clearance rate of interleukin-6, procalcitonin, and C-reactive protein for the evaluation of antimicrobial efficacy in adult bacterial BSI without other inflammatory factors.

Methods: Patients with positive blood culture and without other inflammatory factors in The First Hospital of Hebei Medical University from January 2017 to December 2019, who received continuous detection interleukin-6, procalcitonin, and C-reactive protein, were selected. The clearance rate of these inflammatory markers was calculated, and the consistency test (kappa test) was performed to analyze the clinical outcomes (cure, improvement, delay, deterioration, or death).

Results: For adult patients with bacterial BSI without other inflammatory factors, the testing speculation based on the clearance rate of interleukin-6 and C-reactive protein was consistent with the clinical outcome of the patients, with kappa values of 0.784 and 0.714, respectively (P=0.000). The testing speculation based on the procalcitonin clearance rate was generally consistent with the clinical outcome, with a kappa value of 0.685 (P=0.000). The testing speculation based on the procalcitonin clearance rate showed good consistency with the clinical outcome of patients with Gram-positive cocci infection, kappa =0.813 (P=0.000); for patients with gram-negative bacilli infection, the consistency of clinical outcomes was general, kappa =0.649 (P=0.000).

Conclusions: In adult patients with bacterial BSI without other inflammatory factors, the clearance rate of interleukin-6, procalcitonin, and C-reactive protein can predict the clinical outcome within 24 hours, among which the procalcitonin clearance rate can better predict the clinical outcome of patients with Gram-negative bacilli infection. This approach can be used to evaluate the effectiveness of anti-infection treatment in early-stage BSI.

Keywords: Inflammatory markers; clearance rate; consistency test; bacterial bloodstream infection (BSI)

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Introduction

Bloodstream infection (BSI) is a serious systemic infectious disease in which pathogenic microorganisms are present in the circulating blood in a transient, intermittent, or persistent manner, which could cause damage to all organs of the body. In severe cases, BSI can induce shock, multi-organ failure, disseminated intravascular coagulation, and even death. Despite considerable advancement in the early diagnosis of patients with BSIs owing to the continuous development of modern medicine (1), longer infection durations still lead to higher disability and mortality rates in patients (2). Therefore, rapid efficacy assessment following the initial anti-infective treatment regimen can significantly improve the survival rates and quality of life of patients.

Blood cultures and procalcitonin are considered important laboratory bases in "*The International Guideline 2016 - Management of Sepsis and Septic Shock*" (1-3), and changes in the levels of interleukin-6, procalcitonin, and C-reactive protein have been used as key testing foundations for efficacy evaluation in previous literature (4-6). However, no correlation between the concentration clearance rates of the aforementioned inflammatory markers and anti-infective therapy has been reported. This study aimed to investigate the consistency between the concentration clearance rates of interleukin-6, procalcitonin, and C-reactive protein and the clinical outcome of patients, and analyze their predictive value for disease prognosis, so as to provide a theoretical basis for assessing the effectiveness of anti-infective therapy in the early stages of clinical BSI treatment. We present the following article in accordance with the MDAR reporting checklist (available at https://apm.amegroups.com/article/view/10.21037/apm-22-915/rc).

Methods

Clinical data

A total of 198 patients [aged 18 to 55 years old, 86 male patients (43.4%) and 112 female patients (56.6%)] diagnosed with bacterial BSI at The First Hospital of Hebei Medical University from January 2017 to December 2019 were enrolled in the study. All of the patients had typical clinical manifestations of infection, such as sudden chills, hyperthermia, tachycardia, and shortness of breath, and their blood cultures were positive in the bilateral bottles. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Ethics Committee of The First Hospital of Hebei Medical University (No. 20220732) and informed consent was taken from all the patients.

The inclusion criteria were as follows: (I) patients who complied with the BSI diagnostic criteria; and (II) cases in which pathogenic bacteria could be cultured in the blood. The exclusion criteria were patients with other pre-existing inflammatory factors or inflammatory diseases before the BSI, such as: (I) multiple trauma; (II) burning with large area; (III) after major surgery within 3 days; (IV) cardiac function grade III persisting for >7 days; (V) severe renal insufficiency; (VI) severe liver insufficiency; (VII) advanced solid tumor or malignant hematological disease; (VIII) pancreatitis; (IX) diabetes mellitus; (X) uncontrolled hypertension; (XI) acute stroke; (XII) pregnancy; (XIII) post-organ transplantation; (XIV) combined with rheumatic immune disease; and (XV) long-term use of hormonal or other anti-inflammatory drugs.

Within 7 days after the start of antimicrobial therapy, the treatment plan was affected for reasons other than the patient's affordability or medical insurance. The patients who were discharged on their own, transferred to an outside hospital for treatment, or died due to factors other than infection were classified as lost subjects, and were excluded from this study.

Study methods

Inflammatory marker testing

Venous blood was collected immediately after the clinician was informed of the positive blood culture and the antimicrobial treatment scheme. Also, blood samples were collected again five times consecutively within 24 hours, and the interval between the two consecutive tests was not less than 4 hours (to avoid detrimental patient treatment, qualified specimens collected close to the preset moment of testing for medical purposes were used for testing). Interleukin-6, procalcitonin, and C-reactive protein were measured in each blood sample.

Test speculation

The concentration-time curve was plotted and the curve regression equation was calculated using SPSS19.0 software (IBM, USA). The clearance rate was calculated by the first-order derivative (C') and second-order derivative (C") of the curve regression equation. The rates were divided into four groups according to the derivatives: C'<0, C"<0, and accelerated decrease in concentration (Cure is presumed) was defined as Group A1; C'>0, C"<0, and the decelerated

increase in concentration (Improvement is presumed) was defined as Group A2; C'<0, C">0, and the decelerated decrease in concentration (Delay is presumed) was defined as Group A3; and C'>0, C">0, and accelerated increase in concentration (deterioration or death is presumed) was defined as Group A4.

Clinical outcome follow-up

Within 7 days after the identification and implementation of the antimicrobial treatment regimen, cure was defined as the complete disappearance of the patient's clinical symptoms and signs as well as negative blood cultures for more than two consecutive times (at least 24 hours apart) (Group B1). Moreover, positive blood cultures with the decreased sequential organ failure score (SOFA) were defined as improvement (Group B2), positive blood culture with a stable SOFA change was defined as delay (Group B3), and positive blood culture with increased SOFA was defined as deterioration. Furthermore, loss of life for disseminated intravascular coagulation (DIC), shock, and severe organ failure caused by infection was defined as death, and deterioration and death were defined as Group B4.

If the antimicrobial treatment regimen was adjusted within 7 days after a comprehensive assessment by the physician, patients treated with descending ladder drugs were classified as the improvement group (Group B2), while those treated with ascending ladder drugs, increased dosage, and frequency of drugs or combination of treatments other than drug therapy were classified as the delay group (Group B3).

Statistical analysis

SPSS 19.0 statistical software was used. The consistency between the test speculation and clinical outcome was assessed by the Kappa test, which could determine the value of the rate of inflammatory markers clearance in assessing the effectiveness of antimicrobial regimens in the early treatment of BSIs. Kappa values from 0.75 to 1, 0.4 to 0.75, and 0 to 0.4 were defined as good, fair consistency, and poor consistency, respectively. P<0.05 was defined as a statistically significant difference.

Results

Pathogenic bacteria

The pathogenic bacteria obtained by blood culture were as follows: 101 cases with *Escherichia coli*, 38 cases with *Klebsiella pneumoniae*, 9 cases with *Acinetobacter baumannii*, 6 cases with *Pseudomonas aeruginosa*, 12 cases with *Coagulase-negative Staphylococcus*, 14 cases with *Staphylococcus aureus*, 9 cases with *Enterococcus spp*., and 9 cases with *Streptococci*. There were no cases of mixed infections caused by two or more pathogens.

Consistency test between the presumptive inflammatory marker of the testing speculation and clinical outcome

The consistency between the clearance rate within 24 hours and the clinical outcome of patients after 7 days were conducted using the Kappa test. Among them, the clearance rates of interleukin-6 and C-reactive protein exhibited good agreement between the test speculation and the clinical outcome of patients, with kappa values of 0.784 and 0.714, respectively (P=0.000). The clearance rates of procalcitonin showed fair agreement between the test speculation and the clinical outcome of patients, with a kappa value of 0.685 (P=0.000). The results are displayed in *Table 1*.

Consistency test of procalcitonin clearance rate in patients infected with different pathogens

Consistency tests were conducted between the test speculations based on the procalcitonin clearance rates and the clinical outcome of patients with Gram-positive cocci infection and Gram-negative bacilli infection, respectively. The results showed good consistency of clinical outcome for patients with Gram-positive cocci infection (kappa =0.813, P=0.000), and fair consistency for patients infected with Gram-negative bacilli (Kappa =0.649, P=0.000). The results are shown in *Table 2*.

Discussion

At present, the commonly used inflammatory markers include C-reactive protein, interleukin-6, and procalcitonin, which are widely used in the diagnosis and differential diagnosis of infectious diseases (7-10). However, there are currently few domestic and international studies that have analyzed the value of inflammatory markers in the assessment of antimicrobial efficacy and prognosis. Inflammatory markers are detected to diagnose infectious diseases and assess efficacy, and the intensity of the inflammatory response is analyzed by the concentration of inflammatory markers so that the severity of infection can

Table 1 Consistency test between the presumed inflammatory marker tests and clinical outcome

Testing speculation	Clinical outcome			
	B1	B2	B3	B4
Interleukin-6				
A1	65	7	0	0
A2	5	45	6	0
A3	0	7	30	3
A4	0	0	3	27
Kappa	0.784			
P	0.000			
C-reactive protein				
A1	63	8	0	0
A2	7	42	8	0
A3	0	9	27	5
A4	0	0	4	25
Kappa	0.714			
P	0.000			
Procalcitonin				
A1	49	3	0	0
A2	19	41	3	0
A3	2	13	34	2
A4	0	2	2	28
Kappa	0.685			
P	0.000			

Table 2 Consistency test of the procalcitonin clearance rate in patients with different pathogenic infections

Test speculation	Clinical outcome			
	B1	B2	B3	B4
Gram-positive cocci infection				
A1	14	1	0	0
A2	1	11	1	0
A3	0	2	6	0
A4	0	0	1	7
Kappa	0.813			
P	0.000			
Gram-negative bacilli infection				
A1	35	2	0	0
A2	18	30	2	0
A3	2	11	28	2
A4	0	2	1	21
Kappa	0.649			
P	0.000			

be further deduced.

The concentration at the last test, the concentration at the first test, total synthesis, total clearance, and blood volume during monitoring are represented by C, C_0, C_+, C_-, and V, respectively. The equations could be presented as below:

$$CV = C_0V + C_+V - C_-V \quad [1]$$

Ignore the changes in blood volume during treatment:

$$C = C_0 + C_+ - C_- \quad [2]$$

Taking the derivative of the concentration with respect to time, the derivative form could be shown as follows:

$$C' = C_+' - C_-' \quad [3]$$

Meanwhile, the rates of change in concentration, synthesis, and clearance were represented by C', C_+', and C_-', respectively.

In this study, to ensure that only one inflammatory factor—bacterial infection—was studied, we set specific inclusion and exclusion criteria to prevent other inflammatory factors from affecting the inflammatory process (11-16) and so that the only factor affecting the synthesis of inflammatory markers was a bacterial infection. The number of bacteria was defined as B, and it was obvious that the number of bacteria was positively correlated with the rate of inflammatory marker synthesis.

It was assumed that:

$$C_+' = f(B) \quad [4]$$

The clearance of inflammatory markers would comply with the first-order kinetic, with half-life defined as T. Therefore, the formulation was obtained as below:

$$C_-' = \frac{0.693C}{T} \quad [5]$$

whereas

$$C' = f(B) - \frac{0.693C}{T} \quad [6]$$

time is derived again

$$C'' = f'(B) - \frac{0.693}{T}C' \quad [7]$$

Meanwhile, the acceleration of the change in concentration was defined as C', and the change in bacterial

inflammatory capacity was defined as f'(B). If there was no evident change in the pathogen species and pathogenicity during the monitoring period, f'(B) was only positively correlated with the number of bacteria.

It is calculated after shifting item by extracting f'(B)

$$f'(B) = C'' + \frac{0.693}{T} C' \quad [8]$$

Therefore, when a change in the bacterial number is speculated, the rate and acceleration of change of inflammatory markers should be taken into account. If the inflammatory marker concentration C' >0 and C" <0, the original treatment scheme should be maintained, this would turn to C' <0 and C" <0 and would be calculated as f'(B) <0, which indicates that the bacterial population decreases with effective anti-infective treatment, and the patient is expected to be cured. If the inflammatory marker concentration is C' <0 and C" >0, this would turn to C' >0 and C" >0 without changing the effective treatment regimen and would be calculated as f'(B) >0, which indicates that the bacterial count increases with ineffective anti-infective treatment, and the patient's condition would eventually deteriorate. In this study, it was confirmed that this method could rapidly assess the efficacy of anti-infective treatment early in adult patients with bacterial BSI without other pro-inflammatory factors by testing the consistency between the testing speculation and the clinical outcomes of the patients.

Interleukin-6 is secreted by a variety of cells and tissues and is elevated within 1 to 3 hours after the onset of infection; it can reach a peak at 12–24 hours and gradually decrease at 48–72 hours, with a half-life of approximately 1 hour (16-18). Numerous studies have shown that interleukin-6 is highly sensitive compared to other inflammatory markers. However, inflammation caused by other inflammatory factors can also induce elevated levels of interleukin-6, such as infection with the coronavirus disease 2019 (COVID-19) or ongoing chimeric antigen receptor T-cell immunotherapy (CAR-T). This may result in a cytokine storm with large amounts of interleukin-6 in the BSI, systemic inflammatory response (SIRS), and multiple organ dysfunction syndrome (MODS). Therefore, infectious diseases have relatively low specificity and interleukin-6 is generally not used in the clinic for the dynamic monitoring of changes in inflammatory intensity. However, this study was found that the test speculations obtained for the clearance rate of interleukin-6 and the clinical outcome of patients were in good agreement. Thus, it can be presumed that interleukin-6 is not affected by the duration and sustained intensity of inflammation due to its short half-life; it can better reflect the instantaneous change in inflammatory intensity at the time of blood collection, which is more suitable for determining the trend of bacterial population changes.

C-reactive protein is mainly secreted by liver cells and begins to increase 4–12 hours after infection, with a peak at 24–72 hours. It can maintain an elevated state for 2 weeks, with a half-life of 19 hours (12). Excepted being elevated when the organism infected, C-reactive protein is regulated by other inflammatory factors including interleukin-6, interleukin 1, and tumor necrosis factor α, so that its low sensitivity and specificity could be obtained. This was corroborated in the present study, for which the test speculations and clinical outcomes obtained based on C-reactive protein was "generally consistent". However, there is a high concentration of C-reactive protein in blood, and given its convenient detection and low cost, it is suitable for long-term clinical monitoring.

Procalcitonin is defined a specific indicator of severe bacterial infections, especially BSIs, but is also a reliable indicator of sepsis and multi-organ failure (19-22). *The International Guideline 2016 - Management of Sepsis and Septic Shock* selected procalcitonin as a laboratory basis second only to blood culture and as the parameter of choice for monitoring inflammatory activity *in vivo* (1-3). However, we found that the agreement between the test speculations obtained based on procalcitonin and the clinical outcome was the worst among the three groups. Moreover, better agreement in patients with Gram-positive cocci infection compared to patients with Gram-negative bacilli infection was also observed. The inconsistency between testing speculation and clinical outcome results in patients with Gram-negative bacilli infection was mainly found in the cure and improvement groups. We analyze the reason was that endotoxin could promote the massive release of large amounts of procalcitonin, which is a cell wall component of Gram-negative bacilli, and endotoxin was released regardless of the natural death or killing of bacteria. This could lead to elevated procalcitonin as well as a spoor correlation among inflammatory markers, inflammatory intensity, and the degree of infection (23-25).

In conclusion, the clinical outcome of adult patients with bacterial BSIs without other inflammatory factors was inferred by the clearance rates of interleukin-6, procalcitonin, and C-reactive protein, for which accurate results could be obtained within 24 hours. Among these, the procalcitonin clearance rate can better predict the clinical outcome of patients with Gram-negative bacillary infections, and the effectiveness of anti-infective therapy

in early BSIs can be rapidly assessed. The effectiveness of antimicrobial treatment regimens can be rapidly assessed in the early stage of treatment to improve the survival rate and quality of life of patients.

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Footnote

Reporting Checklist: The authors have completed the MDAR reporting checklist. Available at https://apm.amegroups.com/article/view/10.21037/apm-22-915/rc

Data Sharing Statement: Available at https://apm.amegroups.com/article/view/10.21037/apm-22-915/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://apm.amegroups.com/article/view/10.21037/apm-22-915/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Ethics Committee of The First Hospital of Hebei Medical University (No. 20220732) and informed consent was taken from all the patients.

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