Interleukin-8 in Febrile Neutropenic Children with Cancers: Its Diagnostic Value for Bacteremia/ Sepsis is Superior to that of Interleukin-6, Mannose Binding Lectin, Procalcitonin and C-Reactive Protein

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ABSTRACT

The aim of this study was to determine the predictive value of serum interleukin-6 (IL-6), interleukin-8 (IL-8), mannose binding lectin (MBL), procalcitonin (PCT) and C-reactive protein (CRP) levels for bacteremia/sepsis (B/S) at the beginning of a febrile episode in children with chemotherapy-induced febril neutropenia (FN). In a prospective study, 54 febrile neutropenic episodes from 30 pediatric cancer patients were analysed. Samples were obtained in two different clinical periods: afebrile neutropenic (AFN) period after chemotherapy and FN period (on the first day of fever). The highest levels of IL-6, IL-8, MBL and PCT were observed in cases of B/S group. However, only IL-8 levels were significantly higher in patients with B/S than those with clinically or microbiologically documented infection and those with fever of unknown origin ($p< 0.05$). While sensitivity was high for IL-6 and IL-8, specificity value was found to be quite low. The marker with the highest specificity values was PCT. While positive predictive values of all markers were generally low, their negative predictive values were higher. The high levels of IL-8 are more reliable than the levels of IL-6, MBL, CRP and PCT for prediction of B/S in pediatric cancer patients with FN. With the combined use of inflammatory markers and cytokines, the low-risk group for B/S can be determined more clearly in patients with FN at the beginning of the febrile episode.

Keywords: Febrile neutropenia, Bacteremia/sepsis, Inflammatory cytokines, Childhood cancer

INTRODUCTION

Severe infections such as bacteremia/sepsis (B/S) are among the most important causes of morbidity and mortality in pediatric patients with cancer undergoing chemotherapy.[1] In most neutropenic cases with infection, fever is the first symptom of serious infection.[2] However, there are many causes of fever in cancer patients. Apart from infection, neoplastic fever, allergic or hypersensitivity reactions to blood components or drugs are possible underlying mechanisms.[3,4] Because clinical signs of infections may be minimal in neutropenic patients, it may be difficult to identify patients with B/S at the onset of the febrile neutropenia (FN) episode. Therefore, in the past three decades, the

focus has been on the potential values of inflammatory cytokines as well as acute phase reactants measured at the onset of FN for the early diagnosis of patients with B/S or to identify high-risk patients.[5-11]

C-reactive protein (CRP) is the best known inflammatory marker in cancer patients. Its level significantly increases in inflammatory processes in response to interleukin 6 (IL-6). However, the increase in CRP levels is usually delayed and its serum level correlates with the degree of tissue damage and influenced by underlying malignant disease.[5] So, the major significance of CRP is related to its negative predictive value (NPV) for B/S. Therefore, there was a need for markers that are elevated in the early stages of B/S and are not affected by the activity of the underlying malignant disease. Procalcitonin (PCT) is a prohormone of calcitonin; it has been extensively investigated in differentiation between bacterial infection and systematic inflammation of noninfectious origin. PCT levels increase in the presence of proinflammatory cytokines and it can also regulate cytokines. In current studies PCT has been shown to be more effective than CRP in discriminating B/S from other subgroups of FN.[12] Cytokines are produced by various cells and secreted in response to bacteria and other antigens. The roles of cytokines such as IL-6, IL-8 which have been very current for many years, in the initiation of inflammation for different reasons are well known. However, their role and reliability in the early diagnosis of bacterial infections and determining the severity of infections are controversial.[5-7] Mannose binding lectin (MBL), a soluble C-type lectin which is increased during the acute phase of inflammation, is recognized as an initiator of the complement pathway. It provides lysis of bacteria by different mechanisms and regulates the immune response by playing a role in the stimulation of cytokines.[5,13] The relationship between serum level and bacterial infections tendency and the predictive value of serum level in the early period of infection are not clear.[14]

The aim of this study was to determine the predictive value of serum IL-6, IL-8, MBL, CRP, PCT levels for B/S at the beginning of a febrile episode in children with chemotherapy-induced FN.

PATIENTS AND METHODS

Patients

The single-center study was planned prospectively and approval was obtained from the Ethics Committee of Istanbul University Faculty of Medicine. Informed consent form was obtained from families. Fifty-four episodes of FN occurring in 30 pediatric cancer patients (median age 5 years, range 1-16 years; 14 female and 16 male patents) were analysed. Sixteen (53.3%) had acute lymphoblastic leukaemia (ALL), 10 (33.3%) had acute myeloid leukaemia (AML), 3 (10%) had non-Hodgkin's lymphoma (NHL) and 1 (3.3%) had neuroblastoma (NRB).

Neutropenia was defined as an absolute neutrophil count (ANC) < 0.5 x 10^9 / L at the onset of a fever. Fever was described as an axillary body temperature of > 38.5^{0}C in 1 measurement or of > 38^{0}C in 2 repeated measurements during a 6-hour period. Emergency hospitalization and empirical broad-spectrum intravenous antimicrobial therapy were routinely applied to all of patients.

According to clinical and microbiological findings, febrile episodes were classified into 3 groups: (1) clinically or microbiologically documented infection (CMDI), (2) bacteremia/sepsis (B/S), and (3) fever of unknown origin (FUO). The diagnosis of CMDI was based on positive cultures of faeces, urine and/or fever accompanied by clinical symptoms of gastrointestinal, urinary or respiratory tract infection. Bacteremia was defined as fever with positive blood cultures for bacteria from peripheral blood, with or without septic symptoms. For confirmation of coagulase-negative Staphylococcus species, 2 positive blood cultures from different sites were required.

Sampling and Laboratory Analysis

Samples were obtained in two different clinical periods: afebrile neutropenic (AFN) period after chemotherapy and FN period (on the first day of fewer). Since serum levels of IL-6, IL-8 and MBL are influenced by known promoter polymorphisms, we measured baseline levels of these cytokines from serum samples obtained AFN period. These samples were separated immediately by centrifugation at the time of admission and stored at –80^{0}C

Table 1. Site of infections of CMDI group and grown microorganisms of B/S group

The type of FN		Number of episodes	%	Site of infections and culture results
CMDI		27	50	
	CDI	24	44.5	Mucositis: 8, lung: 7, upper respiratory infections: 2, gastrointestinal system: 2, eye: 1, combine: 4
	MDI	3	5.5	Urine: 2 (*Stenotrophomonas*: 1, *Enterococcus*: 1), central venous catheter: 1 (*Klebsiella*: 1)
B/S	10	18.5		*Klebsiella*: 4, unidentified gram (-): 1, *Enterobacter*: 1, *Enterococcus*: 1, MSCNS: 1, MRSE: 1, α-*hemolitic streptococcus*:1
FUO	17	31.5		

Abbreviations: CMDI= clinically or microbiologically documented infection; CDI= clinically documented infection; MDI= microbiologically documented infection; FUO= fever of unknown origin; B/S= bacteremia/sepsis; FUO= fever of unknown origin; B/S= bacteremia/sepsis; FUO= fever of unknown origin; B/S= bacteremia/sepsis; MSCNS= Methicilline-sensitive coagulase negative *Staphylococci*; MRSE= Methicilline-resistance *Staphylococcus* epidermidis

until analysis for measurement of IL-6, IL-8 and MBL. During the period of FN, blood samples were taken for CRP, PCT, IL-6, IL-8 and MBL in addition to routine tests. Serum samples collected in FN period were also separated immediately by centrifugation and stored at –80^{0}C until analysis for measurement of IL-6, IL-8 and MBL. Additionally, routine blood counts and diagnostic blood and other appropriate cultures or diagnostic tests had been performed.

The CRP was measured by immunoturbidimetry with the Turbiquant® CRP test kit (Dade Behring, Marburg, Germany). The detection limit for CRP was 5,0 mg/L. The PCT concentration was measured by immunoluminometric assay with the commercially available Lumitest® PCT (BRAHMS Diagnostica GmbH, Berlin, Germany). The detection limit for PCT was 0.5 ng/ml. Enzyme-linked immunosorbent assay (ELISA) was used to determine the serum IL-6 (Assaypro, Cat No: EI1006-1, USA), IL-8 (Biosource International, Cat No: KHC0081, USA). Cutoff values were based on literature findings and set at 60 pg/mL for them. ELISA was also used to determine the serum MBL (Antibodyshop, Gentofte, Denmark).

Statistical Analysis

Data were analyzed using SPSS for Windows (version 16.0, SPSS Inc., Chicago, IL). The data of this study were evaluated using descriptive statistical methods (mean ± standard deviation, median, frequencies and percentages). The Mann-Whitney U test and Kruskal-Wallis test were used for comparison of independent variables and the Wilcoxon test for comparison of dependent variables. Spearman's correlation coefficient was used to assess relationships between CRP, PCT, IL-6 and IL-8 levels. A receiver operating characteristic (ROC) curve was used to determine a cut-off level for each marker. To evaluate the diagnostic test properties of CRP, PCT, IL-6 and IL-8, we determined the sensitivity (true positives), specificity (true negatives), positive predictive value (PPV) and NPV with the corresponding 95% confidence intervals (CI, calculated by the exact method). A two-tailed p value less than 0.05 was considered statistically significant.

RESULTS

Twenty two episodes in 16 ALL patients, 24 episodes in 10 AML patients, 7 episodes in 3 NHL patients and an episode in a NRB patient had occurred. Twenty seven (50%) episodes were CMDI [CDI= 24 (44.5%) and MDI= 3 (5.5%)], 17 (31.5%) episodes were FUO and 10 (18.5%) episodes were B/S (Gram-negative= 6, gram-positive= 4). There were no significant differences between the three groups in age, sex or neutrophil count. Details were shown in Table 1. None of patients had died due to CMDI or B/S.

In AFN period, median level of IL-6 of patients

Table 2. Differences between levels of IL-6, IL-8, PCT, CRP and MBL in various types of FN

Markers		FUO (n= 17)	CMDI (n= 27)	B/S (n= 10)	p
CRP (mg/L)	Median	57	45	37.3	0.981
	Mean	58,2	78,3	67	
PCT (ng/ml)	Median	0.39	0.62	4	0.068
	Mean	2	1,2	16,5	
IL-6 (pg/ml)	Median	90	135	330	0.071
	Mean	250	198,2	570	
IL-8 (pg/ml)	Median	167	194	375	0.021
	Mean	213	282,3	444	
MBL (ng/ml)	Median	335.8	385.3	458.8	0.46
	Mean	429	411.52	482.6	

Abbreviations: CRP= C-reactive protein; PCT= procalcitonin; IL-6/IL-8= interleukin-6/-8; MBL= mannose binding lectin; CMDI= clinically or microbiologically documented infection; FUO= fever of unknown origin; B/S= bacteriemia/sepsis; FN= febrile neutropenic; AFN= afebrile neutropenic

was 12±31 pg/mL (mean: 32, min: 5, max: 98 pg/mL), median level of IL-8 was 78.4±66.6 pg/ml (mean: 104.2, min: 22.8, max: 282 pg/mL) and median level of MBL was 302.26 ng/ml (mean: 311.51, min: 19.12, max: 631.71).

At during the FN episodes, CRP levels were similar in all types of FN. The highest levels of IL-6, IL-8, PCT and MBL were observed in cases of B/S group. However, only IL-8 levels were significantly higher in B/S group compared to the CMDI (p= 0.038) and FUO groups (p= 0.012). Serum levels of IL-6, IL-8, CRP, PCT and MBL in subgroups of FN were summarized in Table 2 and were presented in Figure 1 (A-E).

In all patients, IL-6, IL-8 and MBL levels during FN period were significantly higher than levels during AFN period (p< 0.001). In the subgroup analysis, IL-6, IL-8 and MBL values in the B/S and CMDI groups during the FN period were found to be statistically significantly higher than the values in the AFN period (p< 0.001). In FUO, there was no significant difference between IL-6, IL-8 and MBL values of the AFN and the values of the FN period (Table 3).

In FN period, there was a strong correlation between the levels of IL-6 and IL-8 (Spearman's

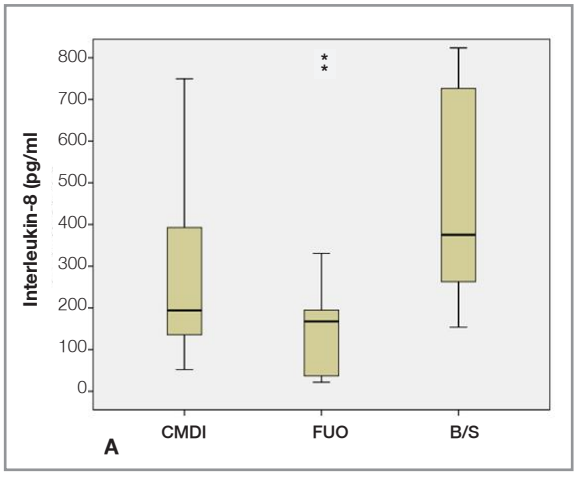

Figure 1A. Levels of IL-8 in three groups of neutropenic patients with hematological malignancies. The line represents the median in each group

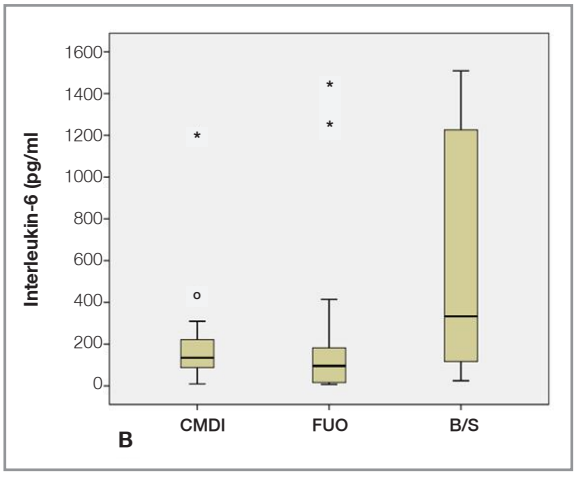

Figure 1B. Levels of IL-6 in three groups of neutropenic patients with hematological malignancies. The line represents the median in each group

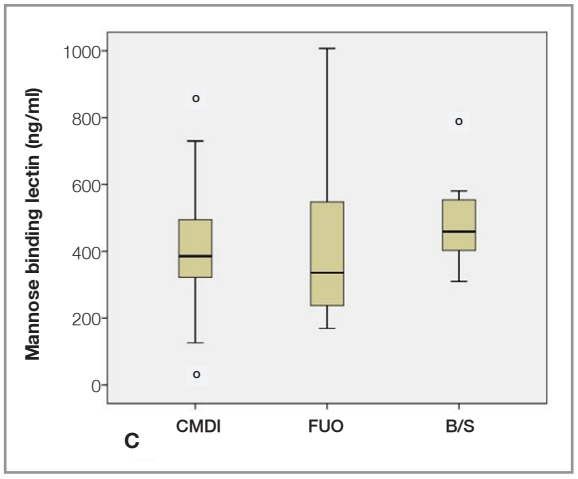

Figure 1C. Levels of MBL in three groups of neutropenic patients with hematological malignancies. The line represents the median in each group

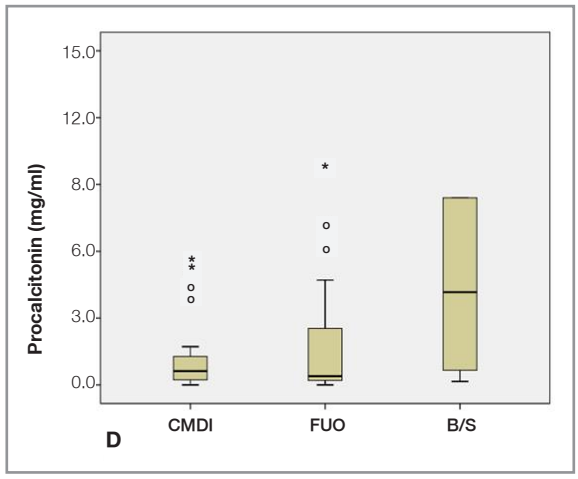

Figure 1D. Levels of PCT in three groups of neutropenic patients with hematological malignancies. The line represents the median in each group

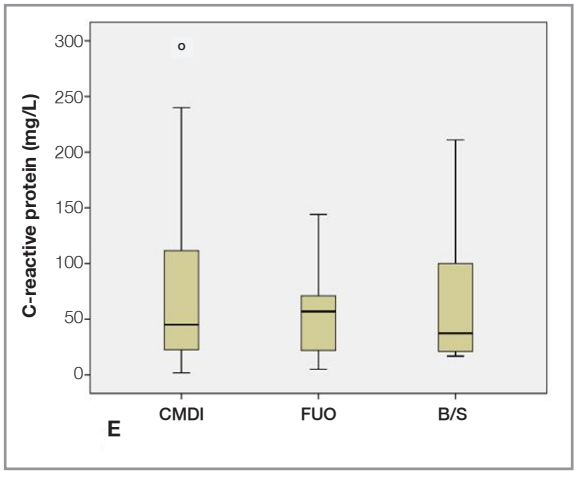

Figure 1E. Levels of CRP in three groups of neutropenic patients with hematological malignancies. The line represents the median in each group

Table 3. Changes in serum IL-6, IL-8 and MBL levels of patients during FN and AFN periods in subgroups of FN

	Difference in AFN and in FN period		
	IL-6	**IL-8**	**MBL**
All patients	p< 0.001	p< 0.001	p< 0.001
B/S	p= 0.007	p= 0.007	p= 0.005
CMDI	p< 0.001	p= 0.003	p= 0.037
FUO	p= 0.063	p= 0.056	p= 0.063

Abbreviations: IL-6/IL-8= interleukin-6/-8; B/S= bacteriemia/sepsis; MBL= mannose binding lectin; CMDI= clinically or microbiologically documented infection; FUO= fever of unknown origin; FN= febrile neutropenic; AFN= afebrile neutropenic

rho= 0.53; p< 0.001). There was a weak correlation between the levels of IL-6 and PCT (Spearman's rho= 0.25; p= 0.04) and between the levels of CRP and PCT (Spearman's rho= 0.25; p= 0.04).

Table 4 shows the sensitivity, specificity, PPV and NPV of CRP, PCT, IL-6, IL-8 and MBL to discriminate patients with B/S from the other groups of patients according to ROC curve cut-off levels. Overall, all markers at the low cut-off levels showed high sensitivity and a low specificity. As the cut-off value increased, sensitivity decreased and specificity increased. The marker with the highest specificity values was PCT. While sensitivity was high for IL-6 and IL-8, specificity value was found to be quite low. While PPV of all markers were generally low (except cut-off level 10 ng/ml for PCT and 50 pg/ml for IL-8), their NPV values were higher (range: 77% - 100%).

DISCUSSION

In neutropenic patients, fever is considered to be due to bacterial causes and treatment is started. However, the rate of B/S is less than 30% in episodes of FN.[15] By excluding B/S or determining that the risk of B/S is low, the duration of antibiotic therapy may be shorter, patients can be discharged earlier, and ultimately their quality of life can be

Table 4. Sensitivity, specificity, PPV and NPV values of inflammatory markers for the prediction of B/S group versus the other groups according to ROC curves cutoff levels

Cut-off value	Prediction of B/S			
	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
CRP (mg/L)				
10	100	14	20	100
50	40	47	14	77
100	30	72	20	82
PCT (ng/ml)				
0.5	80	47	25	91
1	70	65	31	90
5	40	88	44	86
10	20	100	100	84
IL-6 (pg/ml)				
20	100	12	22	100
50	80	22	20	81
100	80	40	25	88
IL-8 (pg/ml)				
50	100	12	100	84
100	100	22	24	100
200	80	65	36	92
MBL /ng/ml)				
300	100	34	25	100
400	80	59	31	93
500	40	73	25	84

Abbreviations: B/S= bacteremia/sepsis; PPV= positive predictive value; NPV= negative predictive value; IL-6/IL-8= interleukin-6/-8; CRP= C-reactive protein; PCT= procalcitonin; ROC= Receiver operating characteristic

Note: Sensitivity: percentage of patients with B/S above threshold; specificity: percentage of patients with febrile episodes without B/S below threshold; positive predictive value: percentage of patients above threshold with febrile episodes wiyh B/S; negative predictive value: percentage of patients below threshold with febrile episodes without B/S

improved. Unfortunately, there are no reliable tests that clearly demonstrate that antibiotic treatment is unnecessary in neutropenic patients without bacterial growth in cultures and in persistent fever.[6]

In this single-center prospective study, we obtained promising results for IL-8, its serum levels were significantly higher in patients with B/S than in those with CMDI and FUO. Despite the highest levels of IL-6, PCT and MBL were also observed in the B/S subgroup, statistical significance was not detected. CRP levels were similar in all types of FN. Therefore, it was concluded that serum levels of CRP could not distinguish between an infectious and a non-infectious inflammatory response, as in previous studies.[16]

PCT and IL-6 are the most frequently compared markers with CRP in several studies, but the results were somewhat inconsistent. In most circumstances, the overall diagnostic efficacy of PCT was higher than CRP.[12,17] Some researches has found that the diagnostic accuracy of IL-6 is higher than PCT.[18] There are studies indicating that IL-6 and IL-8 [19-21] are very valuable in the early diagnosis of B/S, as well as studies indicating the opposite.[8,22,23] On the other hand, there are also studies indicating that IL-6 and PCT are equivalent [24,25] or even more reliable than IL-8 in predicting bacterial infection.[9] Moreover, in another study, IL-8 was also found not to be able to predict bacterial infections in children with FN.[7,26] The predictive role of MBL levels in the early diagnosis of bacterial infection or B/S during the FN period was also examined. Similarly, studies investigating whether low MBL

levels increase the risk of bacterial infection in oncology patients have reached opposite results in the literature.[14,27,28]

In these studies, the comparison of the results may cause inconsistent interpretations due to the heterogeneity of the patient populations, the different clinical conditions of the patients, year of publication, positivity threshold of biomarkers, and the difference in blood sampling times. The results obtained from non-neutropenic patients and/or adult patients may not be valid for pediatric neutropenic patients. In cases where there are many heterogeneous studies and very different results are emphasized, evaluation should be made with meta-analyzes. In the meta-analysis in which 25 studies (incorporating 50933 suspected bloodstream infections episodes) were evaluated, it was shown that PCT was more valuable than CRP in the diagnosis of gram-negative B/S and there was no significant difference either in threshold or in accuracy between PCT and IL-6.[24]

In the present study, all markers at the low cut-off levels showed high sensitivity and a low specificity. As the cut-off value increased, sensitivity decreased and specificity increased. In predicting B/S, the optimum PCT cut-off level was 10 ng/ml with a high specificity (100%), high PPV (100%) and high NPV (84%). In the meta-analysis in which 41 studies (8319 episodes from 4843 patients) were evaluated, it was shown that PCT at a threshold of 0.5 ng/mL appears the most suitable admission biomarker to predict adverse outcomes.[11] In our study, while PPV of all markers were generally low (except cut off level 10 ng/ml for PCT and 50 pg/ml for IL-8), their NPV values were higher (range: 77%-100%). But in predicting B/S, the optimum IL-8 cut-off level was 200 pg/mL with a high sensitivity (80%) and moderate specificity (65%) and high NPV (92%). The optimum MBL cut-off level was 400 ng/mL with a high sensitivity (80%), moderate specificity (59%) and high NPV (93%). IL-8 levels are more specific in diagnosing bacterial infections in FN and has a higher NPV for B/S.[16] Bal et al. also published IL-8 had greater sensitivity and specificity in determination of gram-negative bacterial infections with a higher NPV.[29]

Our data showed that IL-6, IL-8 and MBP levels in children increased compared to basal level in FN subgroups other than FUO, which is in agreement with other reports.[30,31] Since serum levels of IL-6, IL-8 and MBL are affected by known promoter polymorphisms, our determination of basal levels during the AFN period has increased the value of our study. However, our study has some limitations. If we could take more consecutive samples for biomarkers from more patients, the level changes in the FN subgroups of biomarkers could be better detected and a significant relationship could be detected in other markers in addition to IL-8 in the early diagnosis of B/S.

The use of IL-8 in combination with other markers such as IL-6 or PCT has been found to be more reliable for early diagnosis of B/S [11,25,32] and/or identification of low-risk patients.[33] In order for these tests to be used widely, the tests should be performed in hospitals at low cost and with rapid results. Today, unlike IL-8 and MBL, CRP, PCT and IL-6 measurements can be performed in many hospitals at low cost and around the clock. The use of comprehensive marker sets will enter our clinical practice in the near future.

Conclusion

Early diagnosis of B/S in children with FN remains difficult due to non-specific clinical and laboratory signs. We obtained promising results for IL-8. With the combined use of inflammatory markers, cytokines and endotoxin tests, the low-risk group for B/S can be determined more clearly in patients with FN at the beginning of the febrile episode. In this way, intravenous antibiotic treatment can be terminated early, the risk of development of antibiotic-resistant bacteria and the cost of treatment can be reduced.

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