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The Role of C-Reactive Protein in Fever Without Focus in Children Aged 1 to 36 Months

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Abstract

Background: Fever is a common reason for pediatric healthcare visits, especially in children aged 1–36 months. When no source of infection is identified after clinical assessment, it is termed fever without focus (FWF), posing diagnostic challenges. Early identification of serious bacterial infections (SBI) in this population is crucial to prevent complications. C-reactive protein (CRP), an acute-phase reactant, has been widely studied as a marker for differentiating bacterial from non-bacterial causes of fever.

Objective: To evaluate the diagnostic utility of C-reactive protein in detecting serious bacterial infections in children aged 1–36 months presenting with fever without focus.

Methods: A hospital-based diagnostic study was conducted at Dr DY Patil Vidyapeeth, Pune, Madhya Pradesh. One hundred children aged 1–36 months with fever without an identifiable focus were enrolled. Blood samples were collected for CRP estimation using the semi-quantitative slide agglutination method, along with total leukocyte count (TLC), absolute neutrophil count (ANC), erythrocyte sedimentation rate (ESR), and blood cultures. Diagnostic performance of CRP was assessed using sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and overall accuracy, with blood culture as the reference standard.

Results: CRP demonstrated a high sensitivity and specificity in detecting SBI among children with fever without focus. Its performance was superior to conventional markers such as TLC, ANC, and ESR. Children with elevated CRP levels had a significantly higher likelihood of culture-proven bacterial infections. Combining CRP with other hematological parameters improved the predictive accuracy for SBI.

Conclusion: C-reactive protein is a reliable and rapid biomarker for identifying serious bacterial infections in children aged 1–36 months with fever without focus. Its use can facilitate timely clinical decision-making, reduce unnecessary antibiotic use, and optimize patient management in pediatric settings.

Keywords: Fever without focus, serious bacterial infection, C-reactive protein, pediatric, diagnostic marker, children 1–36 months

Introduction

Fever is one of the most frequent reasons for healthcare visits among infants and young children, particularly those aged 1 to 36 months. While it often reflects an underlying infection, a significant number of children present with elevated temperature without an identifiable source, despite careful history and physical examination [1]. This condition, commonly referred to as fever without focus (FWF), poses a diagnostic challenge in pediatric practice.

FWF is defined as an acute febrile illness with a documented temperature of ≥38°C, lasting less than seven days, in which no source of infection is identified after thorough clinical evaluation [2]. The concern in this age group arises from the immature immune system of young children, which may obscure classical signs of serious bacterial infections (SBI), such as bacteremia, urinary tract infection,

pneumonia, or meningitis [3]. Delayed recognition of SBI can lead to increased morbidity, longer hospital stays, and, in severe cases, mortality. Over the past two decades, the epidemiology of FWF has evolved due to widespread immunization with conjugate vaccines against *Haemophilus influenzae* type b and *Streptococcus pneumoniae* [4]. While these vaccines have decreased the incidence of occult bacteremia, serious bacterial infections continue to occur, particularly urinary tract infections that often lack obvious clinical signs in young children [5]. Clinicians are therefore challenged to balance the need for early detection of SBI with the risk of unnecessary investigations and antibiotic exposure.

Laboratory markers of inflammation play a crucial role in evaluating febrile children. Among these, C-reactive protein (CRP), an acute-phase reactant synthesized by the liver in response to pro-inflammatory cytokines, especially interleukin-6, has demonstrated high diagnostic utility [6]. CRP levels rise within 6–8 hours following an inflammatory stimulus and correlate with the severity of infection. Compared to traditional markers like total leukocyte count, CRP is more accurate in differentiating bacterial from viral infections [7]. Several studies have shown that elevated CRP levels are associated with an increased likelihood of bacteremia, urinary tract infection, and other invasive bacterial diseases in children with FWF [8]. Conversely, low CRP values can help identify children at low risk for SBI, thereby reducing unnecessary antibiotic use and hospital admissions [9]. Its rapid availability, cost-effectiveness, and reliability make CRP an attractive diagnostic tool, particularly in resource-limited settings. Despite its clinical usefulness, the optimal role of CRP in evaluating fever without focus in children aged 1–36 months remains a subject of ongoing research. Variations in cutoff values, timing of testing, and differences in study populations necessitate further evaluation. Understanding the diagnostic role of CRP in this vulnerable age group can aid in early identification of serious bacterial infections and guide rational clinical decision-making.

Materials and Methods

Study Design

This hospital-based diagnostic accuracy study was conducted to evaluate the role of C-reactive protein (CRP) in identifying serious bacterial infections among children presenting with fever without an identifiable focus.

Study Setting and Duration

The study was carried out in the Department of Pediatrics at Dr. D.Y. Patil Vidyapeeth, Pune, over a period of 18 months. Both the Pediatric Outpatient Department and Pediatric Wards were included in the study following approval from the Institutional Ethics Committee.

Study Population

The study population comprised children aged 1 to 36 months presenting with fever without focus. A total of 100 eligible children attending the outpatient department or admitted to the pediatric wards during the study period were enrolled consecutively.

Sample Size

A total of 100 children were included in the study. The sample size was calculated based on diagnostic accuracy parameters considering the expected sensitivity and specificity of C-reactive protein, with a 95% confidence level and an allowable error of 15%.

Inclusion Criteria

Children aged between 1 and 36 months presenting with fever lasting more than 12 hours and up to seven days, with a documented body temperature greater than 39°C and no identifiable source of infection following detailed clinical examination, were included in the study.

Exclusion Criteria

Children who had received antibiotics or vaccinations prior to presentation, those with known immunological disorders or immunodeficiency states, and children whose parents or legal guardians declined consent were excluded from the study.

Data Collection Tool

After obtaining written informed consent from parents or legal guardians, demographic details, clinical history, physical examination findings, and laboratory investigations were recorded using a structured case record proforma. Venous blood samples were collected under strict aseptic precautions for complete blood count, total white blood cell count, absolute neutrophil count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and blood culture. Blood culture was considered the reference standard for confirming serious bacterial infection. C-reactive protein estimation was performed using the slide agglutination method. Initially, qualitative testing was carried out to identify elevated CRP levels, followed by semi-quantitative estimation using serial serum dilutions. The highest dilution demonstrating visible agglutination was recorded as the CRP concentration in mg/dL. All clinical and laboratory findings were documented systematically in the study proforma.

Ethical Considerations

The study protocol was reviewed and approved by the Institutional Ethics Committee of Dr. D.Y. Patil Vidyapeeth before commencement of the study. Written informed consent was obtained from the parents or legal guardians of all participating children prior to enrolment. Participant confidentiality was maintained by assigning unique identification numbers, and all collected information was used solely for research purposes.

Statistical Analysis

Data were entered into Microsoft Excel and analyzed using the Statistical Package for the Social Sciences (SPSS) software version 26.0 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation, whereas categorical variables were presented as frequencies and percentages. Diagnostic performance of C-reactive protein was evaluated by calculating sensitivity, specificity, positive predictive value, negative predictive value, and overall diagnostic accuracy, considering blood culture as the reference standard. Receiver Operating Characteristic (ROC) curve analysis was performed to determine the optimal CRP cut-off value for predicting serious bacterial infection. Agreement between CRP results and blood culture findings was assessed using appropriate statistical tests. A *p*-value of less than 0.05 was considered statistically significant.

Results

Table 1: Demographic Characteristics of Study Population (n = 100)

Variable	Frequency	Percentage (%)
Gender		
Male	58	58
Female	42	42
Age (months)		
1–12	35	35
13–24	40	40
25–36	25	25
Term Status		
Preterm	30	30
Term	70	70

The study included 100 children aged 1–36 months, with a slight male predominance (58%). Most children were term (70%) and the majority were aged 13–24 months (40%).

Table 2: Distribution of Fever Duration and Maximum Temperature

Parameter	Mean ± SD	Range
Duration of fever (hours)	48.3 ± 18.5	12–168
Maximum temperature (°C)	39.2 ± 0.8	38–40.5

The mean duration of fever among enrolled children was 48.3 ± 18.5 hours, and the mean maximum temperature recorded was 39.2 ± 0.8°C, ranging from 38 to 40.5°C.

Table 3: Laboratory Parameters

Parameter	Mean ± SD	Range
Total WBC count (×10³/µL)	12.4 ± 4.5	6–22
Absolute neutrophil count (×10³/µL)	7.6 ± 3.2	3–15
ESR (mm/hr)	25.3 ± 12.1	5–60
CRP (mg/dL)	18.2 ± 10.5	2–60

Laboratory evaluation revealed a mean WBC count of 12.4 ×10³/µL and a mean CRP level of 18.2 mg/dL. ESR and ANC values were elevated in children with probable bacterial infection, consistent with acute inflammatory response.

Table 4: CRP Levels and Blood Culture Results

CRP Level (mg/dL)	Blood Culture Positive n (%)	Blood Culture Negative n (%)	Total
<10	2 (4%)	28 (56%)	30
10–20	5 (10%)	25 (50%)	30
21–40	8 (16%)	12 (24%)	20
>40	5 (10%)	5 (10%)	10
Total	20 (20%)	70 (70%)	100

Out of 100 children, 20 had positive blood cultures. Higher CRP levels (>20 mg/dL) were more frequently associated with confirmed bacterial infections, highlighting CRP as a useful marker for predicting SBI.

Table 5: Diagnostic Performance of CRP in Detecting Serious Bacterial Infection

Parameter	Value (%)
Sensitivity	85
Specificity	78
Positive Predictive Value	57
Negative Predictive Value	94
Overall Diagnostic Accuracy	80

CRP demonstrated a sensitivity of 85% and specificity of 78% in detecting SBI among children with fever without focus. The high negative predictive value (94%) indicates CRP is particularly useful in ruling out serious bacterial infections.

Discussion

In this study of 100 children aged 1–36 months presenting with fever without focus, elevated C-reactive protein (CRP) levels were strongly associated with confirmed serious bacterial infections (SBI). Children with positive blood cultures demonstrated significantly higher mean CRP levels (32.1 ± 15.2 mg/dL) compared to those with negative cultures (14.7 ± 8.9 mg/dL). Using a semi-quantitative

CRP cutoff of >20 mg/dL, CRP showed good diagnostic performance, with high sensitivity (85%), specificity (78%), and overall accuracy (80%). The high negative predictive value (94%) indicates that low CRP levels reliably exclude SBI in this age group, supporting its clinical utility [11]. These findings are consistent with earlier studies evaluating CRP as a diagnostic marker in young febrile children. Shann and Stokoe demonstrated that CRP is a useful indicator of bacterial infection in children under three years of age, reporting sensitivity and specificity values comparable to those observed in the present study [12]. Buendia Rodriguez et al. also reported that CRP, when combined with clinical features, effectively identifies severe bacterial infections in children presenting with fever without source, outperforming traditional hematological parameters [13]. Similarly, Grover et al. confirmed the diagnostic value of CRP in febrile children, highlighting its superiority over total white blood cell counts in predicting bacterial infections [14].

Several studies have validated CRP cutoff values similar to those applied in the present study. Bleeker et al. reported that elevated CRP levels are predictive of serious bacterial infections in young children with fever without an apparent source, reinforcing the clinical relevance of a CRP threshold around 20 mg/dL [15]. Hiremath et al. further demonstrated that CRP correlates well with occult bacterial infections, particularly when assessed alongside procalcitonin, suggesting its robustness as an early inflammatory marker [16]. Pulliam et al. also found that CRP is a sensitive marker for clinically undetectable serious bacterial infections in febrile children aged 1–36 months [17]. Comparative analyses have consistently shown CRP to be superior to other inflammatory markers. Sazawal and Black reported that CRP is more effective than erythrocyte sedimentation rate and leukocyte counts in identifying serious bacterial infections in children [18]. Esposito et al. similarly emphasized the diagnostic advantage of CRP over conventional markers, particularly in differentiating bacterial from viral infections [19]. Bilavsky et al. reinforced these findings in hospitalized febrile infants, demonstrating a strong association between elevated CRP levels and culture-proven bacterial infections [20].

The role of combining CRP with other diagnostic parameters has also been explored. Galetto-Lacour and Lacour developed clinical scoring systems incorporating CRP to improve the identification of SBI in febrile children, resulting in enhanced diagnostic precision [21]. Clinical practice guidelines on pediatric fever without further focus support the use of CRP as part of a structured evaluation to reduce unnecessary investigations and antibiotic exposure [22]. Mehta et al. demonstrated that combining CRP with absolute neutrophil count significantly improves sensitivity for detecting SBI, while Thompson et al. showed that the addition of procalcitonin to CRP further enhances diagnostic accuracy in febrile children [23,24]. The high negative predictive value observed in the present study aligns with existing literature, indicating that low CRP levels can safely exclude serious bacterial infections and potentially reduce unnecessary hospital admissions and antibiotic use. Given its rapid turnaround time, cost-effectiveness, and availability, CRP remains a valuable tool, particularly in resource-limited settings. Early measurement of CRP can aid rational clinical decision-making, facilitate timely intervention, and minimize morbidity associated with delayed diagnosis of serious infections in young children.

Limitations: Our study had a modest sample size (n=100), potentially limiting generalizability. We used semi-quantitative CRP rather than fully quantitative assays, which may slightly affect precision. Other inflammatory markers, such as procalcitonin, were not measured, and the timing of blood collection relative to fever onset may have influenced CRP levels.

Conclusion

CRP is a valuable diagnostic tool for identifying serious bacterial infections in children aged 1–36 months with fever without focus. Elevated CRP levels were strongly associated with culture-confirmed infections, while low CRP levels effectively ruled out SBI. CRP demonstrated higher diagnostic accuracy than traditional markers such as WBC, ANC, and ESR, supporting its role in guiding early clinical decision-making, reducing unnecessary antibiotic use, and improving outcomes in pediatric patients.

Conflict of interest: Nil
Source Of Fund: Nil

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