Utility of Blood Markers in Early Prediction of Bacteraemia in Acute Febrile Paediatric Patients – An Observational Cohort Study in a Tertiary Care Hospital of North India

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ABSTRACT

BACKGROUND

Bacteraemia is a common cause of children presenting to the paediatric emergency with acute febrile illness. Blood cultures remain the gold standard for detection of bacteraemia but the positivity is low and also takes time to show positive results. A rapid and reliable biomarker like procalcitonin (PCT), C-reactive protein (CRP), total leucocyte count (TLC), and neutrophil-lymphocyte count ratio (NLCR) can be used to identify febrile children with greater risk for bacteraemia or serious bacterial infections. This would be very helpful to start early treatment of bacteraemia with antibiotics.

METHODS

The study was an observational cohort study conducted in the Department of Paediatrics of a tertiary care hospital in North India in children between age group 6 months to 12 years presenting with fever of > 100.4° F for 2 - 7 days. Blood samples were sent for PCT, CRP, TLC, NLCR and blood cultures.

RESULTS

The most sensitive biomarker was total leukocyte count (47.36 %) followed by the neutrophil percentage (26.32 %), C-reactive protein (21.05 %), and procalcitonin (15.79 %). The most specific biomarker was procalcitonin (75.14 %) followed by C-reactive protein (58.56 %), neutrophil percentage (22.65 %) and total leukocyte count (11.05 %). The only biomarker that was statistically significant between the bacteraemia and non-bacteraemia group in the present study was total leukocyte count (P – value < 0.05).

CONCLUSIONS

The sensitivity and specificity of each single biomarker is low and hence these cannot be used singly to predict bacteraemia. There should be a combination of biomarkers with adequate sensitivity and specificity that can be used to create an algorithm to aid in diagnosis and prognostication.

KEYWORDS

Procalcitonin, C-Reactive Protein, Blood Culture, Acute Febrile Patient

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BACKGROUND

Fever is one of the most common complaints of patients visiting to the paediatric emergency. Acute febrile illness is defined as a patient with the rectal temperature of 38° C (100.4° F) or higher at the time of presentation, persisting for 2 - 7 days.[1,2] The cause of the fever may vary and include infectious diseases, inflammatory diseases, tumours and other certain miscellaneous diseases.[1,2] However most common cause of acute febrile illness is infectious diseases (up to 30 - 40 % cases).[3] Fever is induced due to pyrogens in the body. Endogenous pyrogens are produced by bacteria, viruses, fungi, protozoa, malignancies, connective tissue disorders, certain drugs, and trauma. Common endogenous pyrogens are interleukin - 1 (IL - 1), tumour necrosis factor (TNF) and interferon. Other pyrogens are IL - 6, IL - 11, leukemia inhibitory factor (LIF), ciliary neurotrophic factor (CNTF) and onco statin-M. Exogenous pyrogens are bacterial cell wall component lipopolysaccharide (LPS), enterotoxin and exotoxin. Exogenous pyrogens can produce endogenous pyrogens.

Both pyrogens produce prostaglandins (PGs). Prostaglandin E2 is the final endogenous pyrogens which reset the hypothalamus temperature regulatory set point at the higher level. So, there is increased body temperature in comparison to normal body temperature. If this body temperature is equal to or more than 38° C (100.4° F) then it is called as fever. Bacteraemia, or severe bacterial infection is to be treated with appropriate antibiotic therapy as early as possible. Appropriate antibiotic(s) can be started on the basis of history, physical examination and availability of diagnostic modalities. However, antibiotic use may be associated with adverse event, drug resistance, drug interaction and may increase expenses.[4] Blood culture is a gold standard for definitive diagnosis of bacteraemia. Although blood cultures are routinely collected in patients with suspected infection presenting to the emergency department, their sensitivity for bacteraemia's is low, with < 10 % of cultures collected in the paediatric emergency showing growth of bacteria. Moreover, contamination limits their specificity.[5] The newer BACTEC (bioMérieux, France) method has sensitivity of 84.6 %, specificity of 94.1 %, and positive predictive value of 50 % and negative predictive value of 98.8 %.[6]

Hence, a negative blood culture does not rule out bacteraemia and on the other hand cannot differentiate between bacteraemia and contamination. In addition, blood culture needs minimum time of 24 - 48 hours to show results.[7] Considering all these factors, a rapid and reliable test as marker for bacteraemia would indeed be very helpful. For this purpose, a number of acute phase reactant proteins are utilized.[8] In the recent past, procalcitonin has been used as a rapid testing marker for bacteraemia. Several studies have established procalcitonin (PCT) levels to predict blood culture outcome in patients with pneumonia, urinary tract infections, sepsis, and acute febrile illness.[6-8] Similar data are available for C-reactive protein (CRP), neutrophil-lymphocyte count ratio (NLCR) and lymphocytopenia, with significant differences in levels of these biomarkers between bacteraemic patients and patients with negative blood cultures. Red blood cell distribution width (RDW) has also been proposed as a mortality marker for bacteraemia. Various biomarkers like procalcitonin (PCT), C-reactive protein (CRP), neutrophil-lymphocyte count ratio (NLCR) and lymphocytopenia can be used to identify early, febrile children with greater risk for bacteraemia or serious bacterial infections.

Objectives

1. To evaluate the utility of blood markers alone and in combination for their ability to predict blood culture positivity in acute febrile paediatric patients.
2. To evaluate the prognostic potential of blood biomarkers in differentiating non-bacteraemia paediatric patients from those with bacteraemia and correlating with a positive blood culture.
3. To assess the rate of bacteraemia in the acute febrile paediatric patient.

METHODS

The study was an observational cohort study conducted in the Department of Paediatrics of a tertiary care hospital in North India after clearance from institutional ethics committee (IEC No 115 / 03 / Jan / BH / 2017 dt 14 Jan 2017). Sample size was calculated to be 1000 and sampling was done by systematic random sampling. Every 10th child between age group 6 months to 12 years reporting to paediatric out-patient department or in-patient wards over a period of 06 months from December, 2017 to May, 2018 presenting with fever of $\geq$ 100.4° F for 2 - 7 days were included in the study.

Children with immune-compromised conditions (HIV, Diabetes mellitus) immune suppression (HIV infection with a CD4 count < 15 % of normal age-specific counts), undergoing chemotherapy or any immunosuppressive treatment were excluded. After taking written consent from the parents, blood samples were obtained from each patient to determine serum TLC (total Leucocyte Count), neutrophil percentage, PCT level and CRP level at the same time that the samples were obtained for blood culture.

CRP level was measured using CRP latex reagent (positive CRP > 10 mg/L). PCT level was measured via an automatic analyser, the VIDAS® B.R.A.H.M.STM PCT assay (bioMérieux, France) (positive PCT level > 0.1 ng/ml). Blood cultures were performed using a recommended 1 to 3 ml of blood in brain heart infusion broth (Aerobic/Anaerobic) and were incubated in aerobic and anaerobic conditions. Positive blood cultures were inoculated in 5 % sheep-blood and MacConkey agar plates and incubated for 2 days at 37 ℃. Gram staining, morphology of the colony, biochemical tests and automatic identification systems (VITEK 2 systems, bioMerieux, France), when needed, were used for bacterial identification.

Antibiotic susceptibility tests were performed by disc diffusion in accordance with the recommendations of clinical laboratory standards institute (CLSI). Blood cultures without any growth at the end of the 7th day were considered

negative. If we isolate microorganisms of skin flora (coagulase-negative staphylococcus, Corynebacterium species, viridans streptococcus, etc.) in a single blood culture bottle, it was considered as contamination.

Statistical Analysis

The data was analysed on statistical package for social sciences (SPSS) version 23. Male/female ratio was computed for gender distribution. All quantitative variables were described as medians and percentiles. All proportions were expressed as percentages with 95 % confidence intervals (95 % CIs). Mean ± SD was computed for all continuous variables including TLC, neutrophil percentage, CRP, procalcitonin and blood culture. Student's t-test was applied to compare mean levels of above variables between two groups. Differences were considered significant at P - value of less than 0.05.

RESULTS

The study included paediatric patients aged 6 months to 12 years presenting to the Department of Paediatrics of a tertiary care hospital in North India with acute febrile illness suspecting infection. Total of one thousand children took part in the study. The demographic profile is represented in Table 1.

	Characteristic	Number (%)
Gender	Male	570 (57)
	Female	430 (43)
Age	6 months – 3 years	285 (28.5)
	3 - 6 years	240 (24.0)
	6 - 9 years	335 (33.5)
	9 - 12 years	140 (14.0)
Blood culture	Positive	95 (9.5)
	True	80 (8.0)
	Contaminants	15 (1.5)
	Negative	905 (90.5)

Table 1. Patient Characteristics

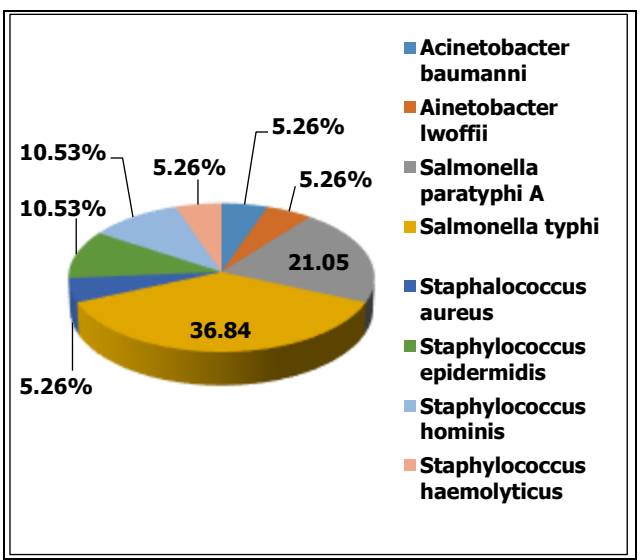

Figure 1. Profile of Organisms Grown in Blood Culture

Bacteraemia was detected in 9.5 % cases (n = 95). True bacteraemia was detected in 8 % cases (n = 80) and rest was considered to be contaminants (n = 15) (Table 1). Most common organism was identified as *Salmonella typhi* (36.84 %, n = 35) followed by *Salmonella paratyphi A* (21.05 %, n = 20). Cultures which grew *Staphylococcus haemolyticus* and *Staphylococcus epidermidis* were taken as skin contaminants (15 / 95 = 15.79 %) (Figure 1).

Out of the total 1000 acute febrile illness patients, maximum patients had respiratory tract infections of which 345 (34.5 %) were of lower respiratory tract infection and rest were upper respiratory tract infection (26 %, n = 260). Clinical profile of rest of the patients are shown in Figure 2.

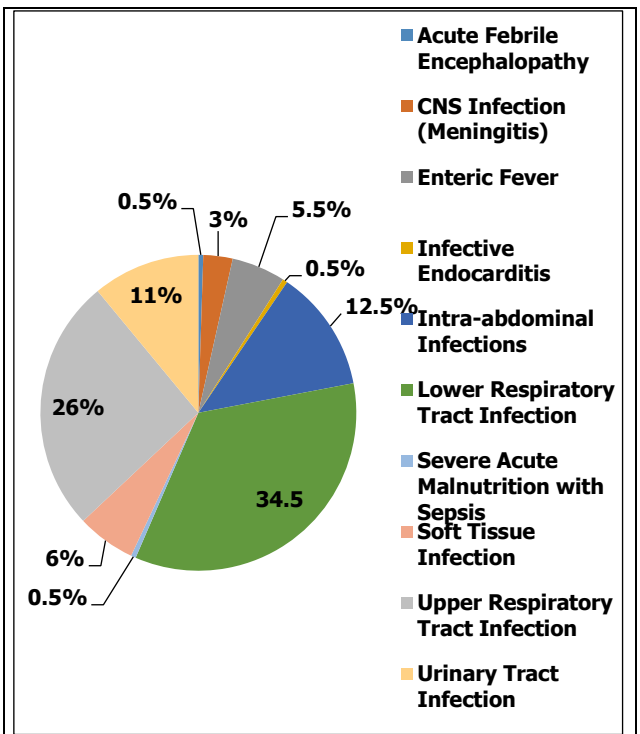

Figure 2. Clinical Profile of Patients with Infections

Biomarker		Non-Bacteraemia	Bacteraemia	P-Value
TLC (x10^9/L)	Mean ±SD	13.731+ / -2.948	9.468+ / -5.586	< 0.05
	Range	5.431 to 23.456	3.219 to 20.968	
Neutrophil %	Mean ±SD	76.796+ / -9.425	60.684 +/-16.384	> 0.05
	Range	45 to 89	41 to 88	
CRP (mg/L)	Mean ±SD	15.094+ / -11.652	10.263+ /-12.974	> 0.05
	Range	3 to 60	3 to 60	
Procalcitonin (ng/ml)	Mean ±SD	0.338+ / -0.539	0.458+ / -1.219	> 0.05
	Range	0.05 to 2.1	0.05 to 5.2	

Table 2. Mean and Standard Deviation of Biomarker

Mean total leukocyte count was 9.468 x 10^9/L in bacteraemia with standard deviation of 5.586 x 10^9/L and 13.731 x 109/L in non-bacteraemia with standard deviation of 2.948 x 10^9/L. The mean neutrophil percentage was 60.684 % in bacteraemia with the standard deviation of 16.384 % and 76.796 % in non-bacteraemia with the standard deviation of 9.425 %. Mean C-reactive protein value was 10.263 mg/L in bacteraemia with standard deviation of 12.974 and 15.094 mg/L in non-bacteraemia with standard deviation of 11.652 mg/L. Mean procalcitonin value was 0.458 ng/ml in bacteraemia with standard deviation of 1.219 ng/ml and 0.338 ng/ml in non-bacteraemia with standard deviation of 0.539 ng/ml. (Table 2).

	Sensitivity	Specificity	PPV	NPV
TLC	47.36 %	11.05 %	5.29 %.	66.67 %.
Neutrophil %	26.32 %	22.65 %	3.45 %	74.55 %.
CRP	21.05 %	58.56 %	4.49 %.	87.60 %.
Procalcitonin	15.79	75.14 %	6.25 %.	89.74 %

Table 3. Sensitivity, Specificity and Predictive Value of Laboratory Tests of Biomarkers in Acute Febrile Illness

The most sensitive biomarker was total leukocyte count (47.36 %) followed by the neutrophil percentage (26.32 %), C-reactive protein (21.05 %), and procalcitonin (15.79). The most specific biomarker was procalcitonin (75.14 %) followed by C-reactive protein (58.56 %), neutrophil percentage (22.65 %) and total leukocyte count (11.05 %). Procalcitonin had maximum positive predictive value (6.25 %) and neutrophil percentage had minimum predictive value (3.45 %). Procalcitonin had maximum negative predictive value (89.74 %) followed by C-reactive protein (87.60 %), neutrophil percentage (74.55 %) and total leukocyte count (66.67 %) (Table 3).

The only biomarker that was statistically significant between the bacteraemic and non-bacteraemic group in the present study was total leukocyte count (P – value < 0.05).

DISCUSSION

Bacteraemia was detected in 9.5 % cases (n = 95) in the present study. True bacteraemia was detected in 8 % cases (n = 80). Most common organism identified was *Salmonella typhi* (36.84 %, n = 35) followed by *Salmonella paratyphi A* (21.05 %, n = 20). Among the organisms grown, *Staphylococcus haemolyticus* and *Staphylococcus epidermidis* were skin contaminants (15 / 95 = 15.79 %). Bacteraemia rate was lower than other studies. Vyles D et al.[9] found bacteraemia of 10.3 % in a study of 735 patients in Phoenix, Arizona in 2016. In 2015, Julián-Jiménez A et al.[10] studied 328 febrile patients in Toledo, España found bacteraemia to be 13.1 %. In another study in 2013, Pereira JM et al.[11] studied 208 febrile patients in Portugal and found bacteraemia in 14 %. This difference maybe because only acute febrile illness patients who were not critically ill were considered in the present study.

The study showed that TLC had a sensitivity of 47.36 % and specificity of 11.05 %. Positive predictive value and the negative predictive value was 5.29 % and 66.67 % respectively. Several studies have reported varying sensitivity and specificity. Bonsu et al. found that specificity is of 78 % using a lower cut-off of 5 x 10^9/L to 15 x 10^9/L.[12] Similar results were published by the study done by Galletto-Lacour in 2003.[13] They showed that WBC cut-off of 15 x 10^9/L had a poor sensitivity of 52 % and specificity of 74 %. The value of band count was even worse and extremely poor, with the sensitivity of only 11 %. Rudinsky et al. also found that the suggested cut-offs of a WBC count < 5 x 10^9/L and > 15 x 10^9/L were not an accurate and reliable predictor of SBI in children of age 3 to 24 months.[14] In Tanzania (2017), Helena H et al.[15] studied 428 febrile children and found that mean WBC was similar in children with or without bacterial illness. They found that WBC and CRP levels had limited value in identifying children with bacterial infections.

In the present study, the sensitivity of CRP was 21.05 % and specificity was 58.56 %. Franz et al. found a sensitivity of 79 % and specificity of 91 % when they considered a CRP value > 10 mg/L, in the presence of one (or more) clinical sign(s) compatible with infection, as a criterion to make a diagnosis of clinical septicaemia in neonates.[16] Galetto-Lacour et al.[13] found CRP cut-off of 40 mg/l to result in a sensitivity of 89 % and specificity of 75 % to predict serious bacterial infection (SBI). The same type of outcome was established by Galetto-Lacour two years later in a follow-up study, which showed that CRP levels were superior to WBC counts in detecting SBIs, with reported sensitivity and specificity of 79 %.[17] The study by Olaciregui et al. focused on infants aged ≤ 3 months, also showed that CRP appears to be useful in predicting SBI and recommended that it should be used in combination with other markers for management of febrile patients in this age group.[18]

Mahende C et al.[19] in a study in 2017 in Tanzania of 867 febrile children, found that CRP ≤ 20, WBC ≤ 15,000 cells/μL) and ANC ≤ 10,000 cells/μL) were observed in the majority of the patients with upper respiratory tract infection, pneumonia, acute gastroenteritis and non-specific febrile illness. Only serum CRP levels were positively correlated with positive blood cultures at a calculated cut-off value of 37.3 mg/L, giving a specificity of 77.8 % and sensitivity of 74.2 %. Bilavsky E et al.[20] in a study in Israel on 892 febrile infants out of which 102 of them had a SBI. When analyses were limited to predicting bacteraemia or meningitis only, the AUCs for CRP and WBC were 0.81 (95 % CI: 0.66 - 0.96) and 0.63 (95 % CI: 0.42-0.83), respectively. They concluded that C-reactive protein is a valuable laboratory test in the assessment of febrile infants aged < or = 3 months old and may serve as a better diagnostic marker of SBI than total WBC count.

Paran Y et al.[21] in a study in Israel on 178 febrile children found mean CRP to be 63.77 mg/L in bacteraemia and 23.2 mg/L in non-bacteraemic patients. However, they concluded CRP velocity (CRPv) improved differentiation between febrile bacterial infections and non-bacterial febrile illnesses compared with CRP alone, and could identify individuals who need prompt therapeutic intervention. Erten N et al.[22] in a study in Turkey on 36 patients who were neutropenic due to various hematologic disorders found that sensitivity and negative predictive value for CRP were higher than the values for PCT (1.00 vs. 0.40 and 1.00 vs. 0.73). They found that diagnostic value and positive likelihood ratio of CRP for severe febrile neutropenia were higher than those of PCT (71 vs. 67 and 2.32 vs. 2.00).

Sensitivity and specificity of procalcitonin was 15.79 % and 75.14 % respectively using a cut of 0.1 ng/ml in the present study. In 2003, Galetto-Lacour et al. published the results of their prospective research confirming the superiority of PCT.[13] A PCT cut-off of 0.5 ng/ml resulted in a sensitivity of 93 % and specificity of 74 %, similar to the author's previous findings. CRP was less sensitive and specific: the proposed optimum cut-off of 40 mg/L was 52 % sensitive and 74 % specific. Gendrel et al. found that PCT, at the cut-off of 2 ng/mL, had a very high sensitivity (96 %) and specificity (87 %) in detecting invasive bacterial

infection and performed much better than CRP at different cut-offs.[23]

Nelson[24] in his study in Pune found a PPV of 98 % for CRP and 57 % for PCT while an NPV of 53 % for CRP and 100 % for PCT. In another study by Khorvash[25] in Iran found a PPV of 19.3 % for CRP and 46.2 % for PCT and an NPV of 92.5 % for CRP and 92.7 % for PCT. Lopez in Spain studied 445 children who were treated for fever in paediatric emergency department.[26] The PCT offers better specificity than CRP for differentiating between the viral and bacterial aetiology of the fever with similar sensitivity. PCT offers better sensibility and specificity than CRP to differentiate between invasive and non-invasive infection. PCT is confirmed as an excellent marker in detecting invasive infections in ED and can even make early detection possible of invasive infections if the evolution of the fever is < 12 h.

However, the present study showed a positive predictive value and negative predictive value of C-reactive protein as 4.49 % and 87.60 % respectively. Positive predictive value and negative predictive value of PCT was 6.25 % and 89.74 % respectively. Thus, there are wide variations in using CRP and PCT both for PPV as well as for NPV.

In this study, the only biomarker levels that was statistically significant between the bacteraemic and non-bacteraemic group was total leukocyte count (P – value < 0.05). Even though various other studies, like Oksuz L in Turkey[27] and Jeong S in Republic of Korea,[28] found the values of CRP and PCT to be statistically significant between the bacteraemic and non-bacteraemic groups (P < 0.0001). In the study, all these biomarkers are within the normal limit in bacteraemia caused by *Salmonella typhi* and *Salmonella paratyphi* infection. So, they are not useful for early prediction of bacteraemia caused by *Salmonella typhi* and *Salmonella paratyphi* infection. Therefore, blood culture is the gold standard test for these infections.

Even though these biomarkers are positive in case of bacteraemia caused by *Acinetobacter baumannii*, *Acinetobacter lwoffii*, *Staphylococcus aureus* and *Staphylococcus hominis,* their prediction of bacteraemia is not statistically significant. Therefore, blood culture again remains the gold standard investigation to confirm bacteraemia.

CONCLUSIONS

The sensitivity and specificity of each single biomarker is low and hence these cannot be used singly to predict bacteraemia. There is a pressing requirement to have a single effective biomarker tool to lessen the dependence on blood culture and microbiology resources in India as these take a long time to give positive result. Till such an effective biomarker is found, a combination of biomarkers with adequate sensitivity and specificity can be used to create an algorithm to aid in diagnosis and prognostication. Also, further well-designed studies are required to predict definite cut off values of these biomarkers for the diagnosis and also time of de-escalation of antibiotics in paediatric patients with bacteraemia.

Limitation

This study has some limitations. Firstly, the sample size was small and the validity and reliability of the study can be improved if done on a larger sample size. Secondly the study was conducted in a single centre. Hence it may not be applicable to other centres and other demographic areas. The most common organism is *Salmonella typhi* and *Salmonella paratyphi* which is less related to biomarker variability.

There were very few patients with positive blood culture results. Therefore, the validity of the cut-off levels of the biomarkers (TLC, neutrophil percentage, CRP and PCT) level could not be fully evaluated. Besides, as the types of infection were very varied, it was difficult to predict the utility of the biomarkers for specific infectious diseases.

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