

To Determine the Role of Procalcitonin in Febrile Neutropenic Episodes of Children Undergoing Treatment for Childhood Cancers

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Abstract

Background: Infections are major cause of morbidity and mortality in children receiving cancer chemotherapy particularly when they are neutropenic, mainly due to immune deficiency. Between 48-60% neutropenic patients with fever have an underlying infection which can often be life threatening. Before putting the child on empiric antimicrobial regimes for FN, it is essential to know the spectrum of locally prevalent pathogens and their susceptibility patterns. Often these children don't manifest fever even in presence of infection and fever may be present in neutropenic patients receiving chemotherapy even in the absence of infection. Present diagnostic tools available for diagnoses in FN are often not so robust and do not differentiate between various classes of organisms causing these infections.

Procedure: Blood culture is time consuming and negative blood culture does not exclude bacteremia, which leads to the empirical use of broad-spectrum antibiotic treatment in pediatric patients with neutropenia, even where signs of infection are absent. We propose to evaluate the role of PCT, as a sensitive marker to evaluate pediatric oncology patients presenting with FN.

Results: Blood-culture was positive in 18.05% of the patients, with majority of patients having gram-negative bacterial infections. On comparison with the focus of infection, high PCT and CRP values were obtained in patients with pulmonary infection than in extra-pulmonary infections. In our study the sensitivity of PCT was high upto 73.3% at a cut-off of ≥ 0.25 ng/ml for ruling out bacteremia, when compared to blood culture and CRP in our patients.

Conclusion: The PCT value is certainly helpful in guiding the physicians in clinical decisions and thus the better approach towards the management of pediatric oncology patients with FN.

Keywords: Febrile neutropenia; Procalcitonin; Infections; Bacteremia

Introduction

Infections are a major cause of morbidity and mortality in children receiving cancer chemotherapy particularly when they are neutropenic. Neutropenia is the most important manifestation of immune deficiency. Prompt administration of empiric anti-microbial therapy for febrile neutropenic patients is considered vital and has been the standard practice for the past many decades. Before putting the child on empiric antimicrobial regimes for FN, it is essential to be aware of the spectrum of locally prevalent pathogens and their susceptibility patterns. Infections may be caused by high/low-virulence bacteria. Diagnosis is difficult because of the absence of/or changes in general signs of infection including formation of pus and leukocytosis [1]. Various foci of infection organisms implicated and antimicrobial sensitivity profile of bacteria/fungus causing blood stream/localized infections was also determined. Keeping this in mind we have planned a prospective evaluation of PCT in children undergoing chemotherapy and presenting FN and further determining various foci of infections

in these patients, spectrum and antimicrobial susceptibility pattern of bacteria causing blood stream/localized infections.

FN in patients who have undergone anti-neoplastic chemotherapy are in a state of immunosuppression that results in extreme vulnerability of the host to numerous microorganisms, which can cause lethal infections. Fever in a neutropenic patient may also be caused by non-infectious causes like chemotherapy, blood component therapy and thrombophlebitis. Cultures and clinical examination fail to detect a pathogen and/or an infectious focus in 30-60% of febrile neutropenic episodes. Major problem also arises during recurrence of fever at the end of a successful course of antimicrobial treatment for a previous infection. Blood culture remains the gold standard for identification of invasive bacterial/fungal infection. However in a previous study done at our center documented invasive bacterial and fungal infection was seen in only 27.8% and 14.2% episodes [2]. Attempts have been made to detect various infections accurately using various serological markers like CRP and IL-6; major disadvantage is their lack of specificity. There is a need to identify markers of infection which are both sensitive and specific. PCT has been explored extensively in past few years with promising data [3]. PCT is a novel peptide that is reported to be more specific and sensitive and is an early detection marker [4]. In a normal non-infected patient PCT values are very low

as, <0.05 ng/ml [4,5]. The Up-regulation of PCT in Infected patients is variously reported and is still unresolved [5,6]. In a neutropenic pediatric population, it is very important to measure an analyte which do not depend on intact cellular immune response. [3,6-9]. The rationale to perform the prospective study was to assess the diagnostic accuracy of PCT levels in predicting bacterial infections and the sensitivity of PCT as a diagnostic marker for evaluating febrile neutropenic episodes in patients undergoing treatment in our tertiary centre.

Materials and Methods

This is a prospective observational and descriptive study on patients receiving chemotherapy for malignancy and is admitted for FN from April 2015 to August 2015. We have enrolled 89 patients who have satisfied the inclusion and exclusion criteria. Ethical clearance for the study was obtained from AIIMS ethical committee. Our inclusion criteria includes, diagnosed patients of hematological /solid malignancy on follow up with the department of Pediatrics, AIIMS, presenting with documented fever (at least single reading of axillary or oral temperature ≥ 38.0 degrees Celsius) plus and having an absolute neutrophil count (polymorphonuclear forms + band forms) $<500/\mu\text{l}$ at the time of admission or within 24 hrs of admission. The Congenital Leukemia (onset of leukemia within the age of 6 weeks) and/or febrile neutropenic episodes developing in children already admitted to hospital and/or child admitted with fever, neutropenia and malignancy but fever was not documented in hospital within 24 hours of hospitalization were the major exclusion criteria.

At admission the children with hematological/solid malignancy presenting with FN with fever documented at or within 24 hours of admission, admitted from pediatric OPD/casualty/pediatric oncology clinic were enrolled. A detailed history, clinical examination and investigation are recorded throughout, till the child is discharged from hospital. A detailed clinical examination is done and any focus of infection is identified. The clinical examinations included clinically documented infection (CDI) if a focus of infection was evident. Based on clinical, microbiological and documented radiological data the patients were classified as microbiologically documented infections with bacteremia (MDIB) and microbiologically documented infections without bacteremia (MBInD). The clinically documented infections were further subdivided into respiratory tract, gastrointestinal, osteomyelitis, urinary tract, blood stream and skin infections. Blood cultures were sent for all patients at admission and at change of antibiotics. Cultures were also sent for obvious sites of infection like otitis, cellulitis or abscess. Urine examination and fungal (blood/urine) cultures were also sent. Total leucocyte count (TLC), absolute neutrophil count (ANC), hemoglobin and platelets were also recorded for all the enrolled patients. The diagnosis of fungal infections (IFD) was measured using galactomannan (Platelia)/other serological assay, CT scan of suspected site of fungal infection, microbiological diagnosis alone or in combination.

Treatment

In all patients, standard medication is initiated, and the treatment/regimen were adjusted based on the microbiological radiological and clinical data. In spite of taking anti-bacterial, if the fever still persisted beyond 72 hours, the patients were recommended for necessary investigations to rule out fungal infections and anti-fungal treatment was added as recommended by the consultant [10].

Measurement of PCT, CRP and Bacterial Culture

2 ml of blood samples were collected for each type of tests during each febrile episode. The sera for PCT were processed on day 1 of FN using VIDAS B.R.A.H.M.S PCT (Biomerieux) as per the manufacturers' instructions. The reference of >0.25 ng/mL is taken as suggestive of bacterial infection. The CRP value of >110 mg/ml is taken as suspected bacterial infection, is estimated using Dialab, turbidimetric Immunoassay Kit.

Statistical Analysis

Qualitative variables like TLC, ANC, platelets etc were compared between the culture positive and negative groups using Student's t test. When the Normality of the data was suspect, data was log transformed or non-parametric Wilcoxon rank-sum (Mann-Whitney) test was used. Odds ratios for culture positivity associated with CRP and PCT recommended cut off values were calculated using logistic regression. All tests were two tailed. Analyses performed using Stata 14.0.

Results

89 episodes of FN were enrolled during the study period, based on inclusion and exclusion criteria. Data acquired was incomplete/consent was not obtained in 7 patients; hence the analysis is representative of 82 episodes. 3 of the patients had both bacteremia and fungemia were grouped as poly-microbial infections and were included for statistical analysis. The patients having isolated fungal infections were not considered for data analysis. All patients gave written consent prior to study enrollment.

Major clinically The minimum and the maximum age of patients enrolled were 4 months to 14 years, with a median age of 5 years, we had 57 males and 25 females; of which majority of the patients were diagnosed with acute lymphoblastic leukemia (ALL) (51.8%) followed by acute myeloid leukemia (AML) (12.6%). Rest of the patients enrolled were diagnosed with either of the following malignancies; Hodgkin lymphoma, non-Hodgkin lymphoma, neuroblastoma, retinoblastoma, primitive neuroectodermal tumor (PNET), The patients were given specific treatments based on the primary diagnosis and were at different phases of their treatment cycle however 89% of the episodes occurred while these patients were in first cycle of chemotherapy. documented infections were pulmonary (39.02%), followed by gastrointestinal tract infection (18.29%).

Blood culture was positive in 18.05% of the patients, of which 6.64% patients were detected with gram-positive bacteria and rest had gram-negative bacteria infections. The most prevalent gram-negative bacteria was *E. coli*, other included *klebsellia* sps. and *Enterobacter* sps., the gram positive bacteria detected was *Staphylococcus* sps. Of all the patients 3 patients had poly-microbial infections reflected by blood bacterial culture positivity and positive serum galactomannan report.

We also analyzed the TLC, ANC and platelet counts in patients with culture positives versus culture negatives, none of the parameters were found to be significant amongst two groups (Table 1). The cut off values of PCT was 0.25 ng/ml, on comparison with the focus of infection, high PCT values were obtained in patients with pulmonary infection than in extra-pulmonary infections. Similarly the CRP values at a cut-off of 110 mg/ml, on comparison with the focus of infection, high CRP values were obtained in patients with pulmonary infection than in extra-pulmonary infections and with an P value of 0.002 (Figures 1 and 2).

Parameters (cells/ μ l)	Culture Positivity	Culture Negative	p value
TLC	1852.85 \pm 638	2672.37 \pm 779	0.609
ANC	646.15 \pm 428	648.07 \pm 176	0.996
Platelet	59642.86 \pm 21093	89835.71 \pm 14945	0.354

TLC: total leukocyte count, ANC: absolute neutrophil count.

Table 1: Comparative values of TLC, ANC and platelet in culture positives and culture negatives.

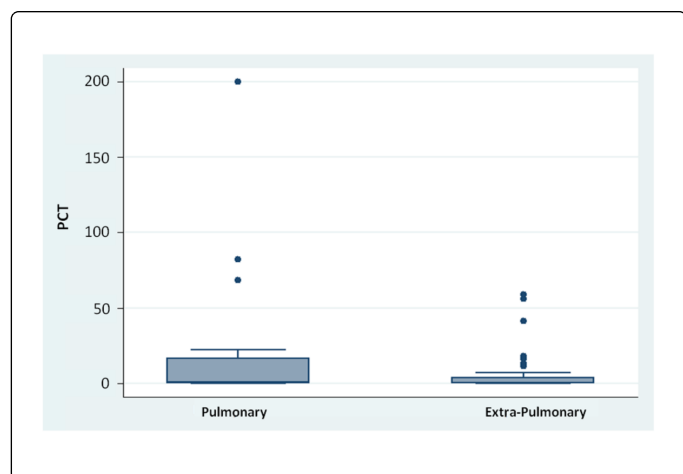


Figure 1: Distribution of serum PCT in pediatric patients with febrile neutropenia in accordance with presence or absence of pulmonary infection.

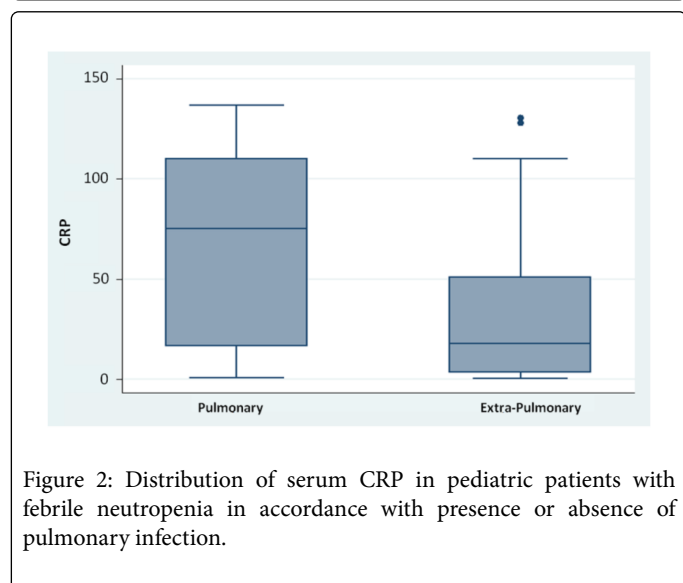


Figure 2: Distribution of serum CRP in pediatric patients with febrile neutropenia in accordance with presence or absence of pulmonary infection.

In our study the PCT values obtained for culture positives in extra-pulmonary origin of infections was very low as compared to the culture positives in pulmonary origin of infections. The PCT values in

culture negatives in pulmonary and extra-pulmonary origins were spread throughout the specified range. On the contrary the CRP values obtained for both culture positives and culture negatives were low in extra-pulmonary origin of infections as compared to the culture positives and culture negatives in pulmonary origin of infections (Figures 3 and 4). We selected 3 most significant parameters for analysis the Blood culture, CRP and PCT (Table 2). On comparison with the culture positives in the blood culture, the sensitivity of PCT at a cut-off of ≥ 0.25 ng/ml is 73.3%, but the specificity was very low in our prospective study. On the contrary the Sensitivity of CRP was low and the specificity was recorded was high up-to 77.2% at a cut-off of 110 mg/ml.

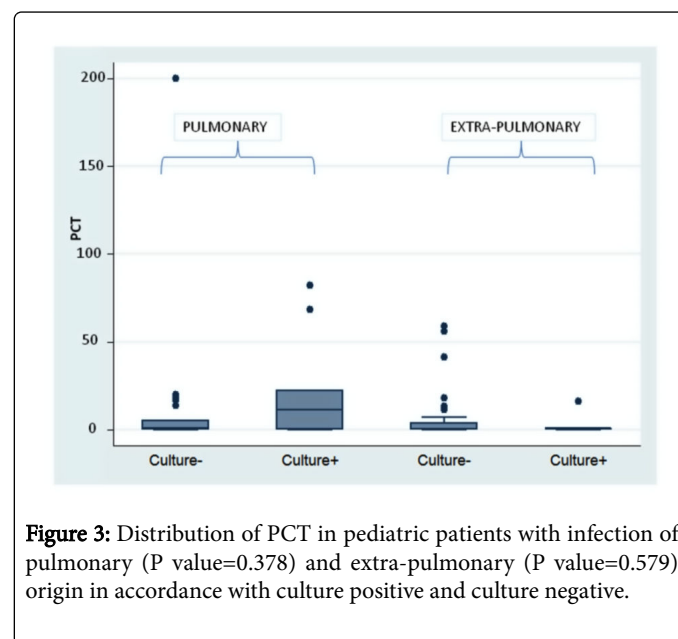


Figure 3: Distribution of PCT in pediatric patients with infection of pulmonary (P value=0.378) and extra-pulmonary (P value=0.579) origin in accordance with culture positive and culture negative.

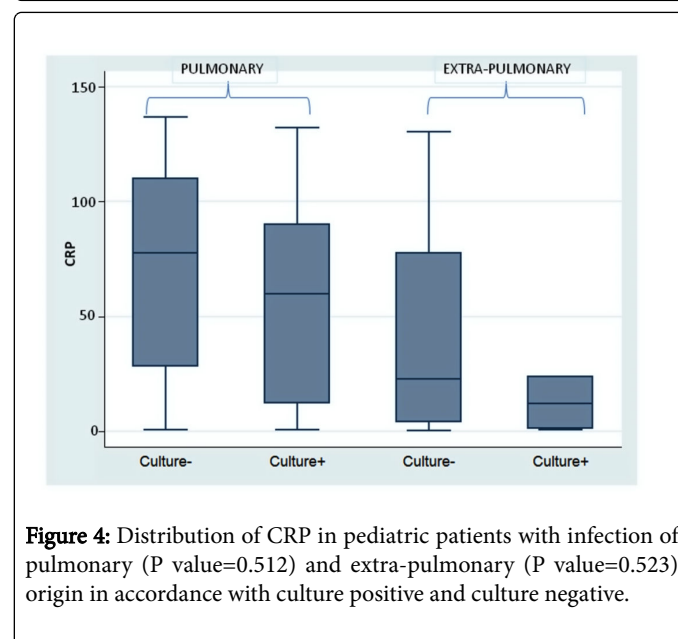


Figure 4: Distribution of CRP in pediatric patients with infection of pulmonary (P value=0.512) and extra-pulmonary (P value=0.523) origin in accordance with culture positive and culture negative.

Variables	OR (at 95%CI)	Sensitivity%	Specificity%	PPV%	NPV%
PCT \geq 0.25	1.15 (0.33-4.03)	73.3	29.4	18.6	83.3
CRP \geq 110	0.52 (0.10-2.61)	13.3	77.2	13.3	77.2

Table 2: The sensitivity and specificity profile of CRP and PCT.

Discussion

In pediatric oncology patients receiving chemotherapy are often seen admitted due to FN, there is ultimate need for sensitive marker for bacteremia. The prevalence of severe bacterial infection in children is very high due to the immune-suppressive drugs. Missed diagnosis can often cause delay in selection and administration of antibiotics, which affects the morbidity and mortality in pediatric oncology patients. In this prospective study PCT has emerged a promising biomarker and has the potential to differentiate bacterial from non-bacterial infection and also correlates directly with the clinical observations. There had been always a debate on having good biomarker for bacteremia; CRP is the earliest discovered biomarkers used to diagnose infection. CRP is an acute-phase reactant, produced by hepatocytes in infections or tissue injuries. CRP production is triggered by cytokines (IL-1, IL-6 and TNF- α) and levels increase and peaks at around 36-50 hours, with a short half-life of 4-7 hours. CRP has been reported as marker for sepsis in neonates, the data was not promising and were nonspecific. The poor specificity, sensitivity always prompted the researchers like us for a selection of a panel of biomarkers for bacteremia. Elevated levels of plasma CRP are often documented in patients with malignant diseases and PCT levels contribute to the blood stream infections in febrile neutropenic episodes. It is well documented that inflammation can be caused by high tumor load, malignant cell lysis, drug administration and infections, in all the cases CRP is elevated and it becomes very necessary to distinguish between infectious inflammation and non-infectious inflammation in a patient with hematological conditions [10,11]. Recent studies have been focusing on use of PCT as a marker for bacteremia. PCT is known as a precursor for hormone calcitonin, and regulates serum calcium concentrations. Literatures have been supporting that PCT levels are increased in children with sepsis and bacterial infection. The rise in PCT levels can be detected and documented at an earlier time point than CRP. Several studies have shown the sensitivity and specificity of PCT as a diagnostic marker for detecting bacteremia. So the advantage of PCT is early detection, early selection of treatment and early recovery. C-reactive protein is an acute phase protein released specifically by the liver in response to systemic inflammation caused by infectious or noninfectious diseases. In many literature leukocytes are also reported as nonspecific marker of systemic infection, tissue damage [12]. In our study we found PCT to be very sensitive in detecting bacterial infection and responsive in children with hematological conditions. Fleischhack et al. [13] also reported that PCT may be a more useful diagnostic inflammatory parameter than CRP, IL-6, IL-8, sIL-2, and sTNFRII in febrile neutropenic pediatric cancer patients [14]. The culture positives in non-Indian studies are variously reported to be as high as 40%. In our prospective study, as majority of the patients already receive immediate antibiotics and the sampling for all lab investigations are done within 6-8 hrs of receiving emergency care, which might have reflected in low culture positives (~18%), but PCT was still very sensitive to pick the inflammations due to infections. We have also correlated the

conventional C-reactive protein and absolute neutrophil count, which was not conclusive. Our data is suggestive of PCT being more sensitive than C-reactive protein. In our prospective study it is very evident that C-reactive protein has low sensitivity, which doesn't qualify CRP as a good marker for detection of inflammations due to infections. In our centre CRP, was commonly used for distinguishing bacterial infection from other causes of fever, but our present study shows PCT as more sensitive marker than bacterial culture and CRP. A statistically significant P value was not obtained for PCT and CRP ROC curve. The values obtained for the PCT were widely variable and did not follow a Gaussian distribution and evaluating a cutoff point with optimum sensitivity and specificity was difficult.

Conclusion

We observed PCT to be very sensitive in our pediatric oncology patients, but the specificity was low. In case of CRP, the sensitivity was questionable, but the specificity was relatively very high at the mentioned cut-offs. The other evaluated parameters like absolute neutrophil counts and platelets did not correlate with PCT and Blood cultures. The other advantage is that the test can be performed within 30 minutes and provided information, long before the blood culture results were available. The PCT value is certainly helpful in guiding the physicians in clinical decisions and thus the better approach towards the management of pediatric oncology patients with FN. Our data suggests the inclusion of PCT testing as a routine investigation for evaluation of febrile neutropenic episodes in children undergoing chemotherapy. PCT may emerge as a useful biomarker to identify bacterial /viral and fungal infections. It is also proposed that PCT value may help in titrating the duration of antimicrobial therapy in such patients.

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