RESEARCH PAPER

Serum Procalcitonin for Predicting Significant Infections and Mortality in Pediatric Oncology

VINOD GUNASEKARAN, NITA RADHAKRISHNAN, VERONIQUE DINAND AND ANUPAM SACHDEVA
From Pediatric Hematology Oncology and Bone Marrow Transplantation unit, Sir Ganga Ram Hospital, New Delhi, India.

Correspondence to:
Dr Anupam Sachdeva,
Head of Department,
Institute of Child Health,
Sir Ganga Ram Hospital,
Rajinder Nagar,
New Delhi - 110 060, India.
anupamace@yahoo.co.in
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***Objective*:** To evaluate the role of serum procalcitonin (PCT) level at admission in predicting significant infections and deaths among children on chemotherapy presenting with fever. ***Methods*:** Children with clinically significant (CSI) and microbiologically documented (MDI) infections were identified using standard definitions. Association of PCT with CSI, MDI and mortality was analyzed. ***Results*:** We evaluated 821 febrile episodes in 316 children. CSI, MDI and deaths were seen in 40.9%, 20.1% and 2.9%, respectively. PCT levels ranged from 0.05-560ng/mL. Median PCT was higher in episodes with CSI (0.80 *vs.* 0.28) and MDI (0.71 *vs.* 0.34) (*P*<0.001). PCT ≥0.7ng/mL optimally predicted CSI (AUC–0.740) and MDI (AUC–0.636). Relative risk of mortality for PCT ≥5ng/mL was 7.1. PCT ≥0.7ng/mL had poor sensitivity (45–55%) but good specificity and NPV (70–90%). PCT was elevated in nearly half of documented viral and fungal infections. ***Conclusion*:** PCT predicts significant infections and mortality in pediatric oncology but it has poor sensitivity to guide clinical decisions.

Keywords: *Cancer, Febrile neutropenia, Fever, Immunocompromised host.*

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Febrile neutropenia is a medical emergency necessitating early initiation of broad-spectrum parenteral antibiotics. The role of inflammatory markers needs to be delineated while managing febrile neutropenia. Procalcitonin (PCT) is a 116-amino acid peptide encoded by the *CALC-1* gene on chromosome 11 [1]. Recent systematic reviews have shown PCT to be more discriminatory than C-reactive peptide (CRP) while evaluating fever in oncology patients despite inconsistent results [1,2]. Guidelines for febrile neutropenia management highlight insufficient data in serum inflammatory markers' ability to guide treatment decisions [3].

Due to variability in the spectrum of infections observed and resources available in India, indigenous studies are needed to assess the clinical utility of newer diagnostic modalities. In this study, we evaluated the role of PCT in predicting significant infections and mortality in children on chemotherapy presenting with fever.

METHODS

Data from children receiving chemotherapy for cancer or undergoing hematopoietic stem cell transplantation (HSCT) and admitted with fever was prospectively recorded and retrospectively analyzed at Sir Ganga Ram hospital, a tertiary health care hospital in New Delhi, between June 2007 and February 2015. Demographic data, diagnosis, duration of fever, focus of infections and evidence of hemodynamic instability, blood counts, serum PCT level at admission (or at the onset of fever in admitted patients), blood culture, urine culture, serum galactomannan, culture from any other sites including broncho-alveolar lavage (BAL), serological and PCR-based tests for infections, imaging, etc. were recorded. PCT level was measured by time resolved amplified cryptate emission technique. Episodes without minimum evaluation (complete and differential blood counts, PCT and blood culture) were excluded.

Episodes with pneumonia (chest *X*-ray, CT scan or BAL positive), hemodynamic instability (requiring fluid resuscitation and/ or vasoactive support), identified focus of infection (*e.g.*, abscesses, neutropenic enterocolitis) or prolonged fever ≥72 hours with no identifiable non-infective causes were classified as CSI. Any organism identified (by culture, PCR, IgM serology or galactomannan) from sterile body fluids qualified for MDI. Documented bacterial infection was any bacterium identified from sterile body fluids, sputum, BAL or sinus aspirate samples. Documented fungal infection was defined as any fungus identified from above mentioned samples or serum galactomannan level ≥1. Febrile neutropenia was defined as single oral temperature

measurement of >101ºF or a temperature of >100.4ºF sustained over a 1 hour period with absolute neutrophil count (ANC) <1000/µL [3].

Statistical methods: Descriptive data were expressed in percentages or median (inter-quartile range (IQR)). The optimum PCT cut-off level was calculated using receiver operating characteristic (ROC) curve method. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated using 2 by 2 contingency tables. The prevalence of CSI, MDI, documented bacterial infection and deaths was compared among four groups of PCT ranges using Chi Square test. Statistical analyses were performed using SPSS Statistics for Windows Version 17.0 (SPSS Inc., Chicago, USA).

RESULTS

There were 1127 febrile episodes. Among these, 306 episodes were excluded due to incomplete data and alternate diagnosis. Finally, 821 febrile episodes (63.5% being neutropenic) from 316 children were evaluated. Patient characteristics are summarized in ***Table* I**.

Median PCT (IQR) was higher in episodes of CSI [0.80(0.34–3.17) *vs.* 0.28 (0.16–0.50), *P*<0.001] and in episodes of MDI [0.71 (0.28–3.63) *vs.* 0.34 (0.19–0.76), *P*<0.001]. Median PCT (interquartile range) was higher in episodes leading to mortality [1.98 (0.46–15.9) *vs.* 0.38 (0.19–0.94), *P*<0.001]. ROC curve showed that PCT cut-off level ≥0.7 ng/mL better discriminated episodes with CSI from those without CSI (AUC=0.740). PCT ≥0.7 ng/mL was also optimum to discriminate episodes with MDI (AUC=0.636). PCT ≥5.0 ng/mL had better discrimination for episodes resulting in death (AUC=0.751).

The diagnostic accuracy of PCT at a cut-off of ≥0.7 ng/mL is tabulated in ***Table* II**. PCT had a poor sensitivity but a good specificity and NPV. PCT ≥0.7 ng/mL adequately predicted CSI (PPV around 70%), but not

TABLE I CLINICAL AND LABORATORY CHARACTERISTICS OF FEBRILE EPISODES (*N*=821)

Characteristics	*No. (%)*
Underlying diagnosis	
Leukemias	540 (65.7)
Lymphomas	28 (3.4)
Solid tumours	123 (14.9)
HSCT	59 (7.1)
Aplastic anemia	25 (3)
Others	46 (5.6)
Episodes with CSI	334 (40.7)
Characteristics of CSI	
Pneumonia	62 (7.6)
Hemodynamic instability	46 (5.6)
Ventilation	26 (3.2)
Identifiable infective focus	76 (9.3)
Prolonged fever ≥72 hours	307 (37.4)
Episodes with MDI	165 (20.1)
Characteristics of MDI	
Documented bacterial infection	105 (12.8)
Documented fungal infection	47 (5.7)
Documented viral infection	28 (3.4)
Others	2 (0.2)
Episodes resulting in death	24 (2.9%)
Investigations, median (range)	
Total leucocyte count (per µL)	1600 (0-481000)
Absolute neutrophil count (per µL)	361 (0-63210)
Procalcitonin level (ng/mL)	0.38 (0.05-560)

HSCT – hematopoietic stem cell transplantation; CSI – clinically significant infection; MDI – microbiologically documented infection.

TABLE II DIAGNOSTIC ACCURACY OF PCT ≥0.7 ng/mL IN DETECTING SIGNIFICANT INFECTIONS

Patient characteristics	*Sensitivity (%)*	*Specificity (%)*	*PPV (%)*	*NPV (%)*
All febrile episodes (n=821)				
In clinically significant infection	54.9	83.4	69.3	72.9
In microbiologically documented infection	50.3	72.9	31.4	85.3
In documented bacterial infection	47.6	70.1	18.9	90.1
Febrile neutropenia episodes (n=521				
In clinically significant infection	52.1	85.2	71.5	71.4
In microbiologically documented infection	46.6	73.7	30	84.9
In documented bacterial infection	44.4	71.7	20.8	89.6

PPV – positive predictive value, NPV – negative predictive value.

WHAT THIS STUDY ADDS?

- Procalcitonin level at admission need not be measured in every child with febrile neutropenia as it does not guide in making clinical decisions and discriminating types of infections. However, in selected cases, it may be used as a tool to predict the severity of the underlying infection.

MDI and DBI (PPV 20-30%). We compared the prevalence of significant infections among different ranges of PCT (normal PCT range <0.7 ng/mL); mild (0.7-1.4 ng/mL), moderate (1.5-4.9 ng/mL) and significant elevation of PCT (≥5 ng/mL). The prevalence of CSI, MDI, documented bacterial infection and deaths increased significantly with the degree of elevation of PCT level (P<0.001).

Among 27 episodes with documented viral infections, 15 (55.5%) had PCT ≥0.7 ng/mL (one had co-existent Documented bacterial infection). Viral etiology included cytomegalovirus, Epstein-Barr virus, herpes simplex, dengue and hepatitis viruses. Among 47 episodes with documented fungal infections, 23 (49%) had PCT ≥0.7ng/mL (6 had co-existent documented bacterial infection). Isolated fungi included Aspergillus, Candida and Trichosporon asahii.

Among 24 deaths, 16 (66.7%) had neutropenia at admission, 7 (29.2%) had documented bacterial infection (6 were gram negative) and 3 (12.5%) had documented fungal infection. Mortality was higher in episodes with PCT ≥5 ng/mL (12.4% *vs*.1.8%, P<0.001, relative risk of mortality 7.1 (95% CI=3.2–15.1)).

DISCUSSION

Our single-center study evaluated the role of PCT in children on chemotherapy presenting with fever. The incidence of documented infections in our population is comparable to available literature [3]. We found significantly increased PCT levels in children with CSI and MDI, indicating that PCT levels increase upon infective stimulus despite immunosuppression.

The optimum cut-off of PCT identified in our study (³0.7ng/ml) falls within the range identified in previous studies (0.5-0.8ng/mL) [1]. At this level, we found that PCT at admission is poorly sensitive (45-55%), both in neutropenic and non-neutropenic febrile episodes. Thus, a normal PCT level at admission does not exclude the possibility of an underlying significant infection. The good PPV for CSI (69-71%) as against that for MDI (30-31%) highlights the limited capability of currently available investigations to isolate the microorganisms, and elevated PCT at admission warns the clinician early about the likelihood of an underlying clinically significant infection. PCT ≥5ng/mL at admission increased the risk of mortality by 7 fold. This warns the clinician to aggressively manage these episodes. Elevated PCT in viral and fungal infections (despite no bacterial co-infections) suggests that PCT is unable to discriminate bacterial infections from others. Our findings suggest that PCT correlates with the severity of infection rather than the type of infection.

The limitation of our study is that PCT measured only at the onset of fever was analyzed. Serial PCT monitoring was available only in a few patients and hence not analyzed. Serial PCT monitoring might improve its diagnostic and prognostic accuracy.

A review of 30 studies including both adults and children done in 2008 reported that PCT discriminates systemic infections from non-infectious etiologies in febrile neutropenia patients [4]. In 2012, a systematic review of 9 studies (total 1498 episodes) testing the role of PCT in febrile neutropenia among adult oncology patients estimated the sensitivity, specificity, PPV and NPV to be 42-72%, 64-89%, 28-87% and 19-95% respectively (PCT cut-off range 0.5-0.8 ng/mL) and also found the superiority of PCT over CRP [1]. Our study shows similar findings.

Another prospective study of 230 febrile episodes in children receiving chemotherapy found a sensitivity of 93% at PCT ≥0.4 ng/mL, but the specificity decreased to 45% at this cut-off [5]. We found PCT ≥0.7 ng/mL as the optimum cut-off, which has reasonable sensitivity and specificity.

To conclude, a cut-off PCT levels of ≥0.7 ng/mL and ≥5.0 ng/mL at admission were optimum to predict significant infections and mortality in pediatric oncology patients, respectively. PCT at admission identifies febrile pediatric oncology patients with high risk for significant clinical course and death. However, it does not select a low risk group in whom hospitalization and parenteral antibiotics can be avoided. PCT correlates with the severity of infection and not the type of infection.

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