

## Original Article

# Clinical utility of procalcitonin in bacterial infections in patients undergoing hematopoietic stem cell transplantation

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**Abstract:** Background: Infections are major contributor to morbidity and mortality in patients undergoing bone marrow transplant (BMT). Objective: To assess role of serum procalcitonin (PCT) as a useful biomarker for the infections and outcomes in these patients. Methods: Retrospective observational study. Results: Total 47 patients with febrile episodes were enrolled. Twenty patients underwent autologous BMT and 27 underwent allogeneic BMT. Bacterial infections were documented in 18/47 (38%) patients. Forty patients were neutropenic. The median fever duration was 10 days (range 3-30 days) in positive procalcitonin level group whereas it was 4 days (range 1-18) in negative group. This was statistically significant (P=0.000). Procalcitonin levels were high in 8/9 episodes of sepsis (P=0.029). Intensive care unit transfers and death were significantly higher in PCT positive group as compared to PCT negative group. Conclusion: Serum procalcitonin levels provide prognostic information of worse outcome in patients undergoing HSCT.

**Keywords:** Bone marrow transplant, infection, procalcitonin

## Introduction

Infectious complications remain a major concern for morbidity and mortality in patients with febrile neutropenic after hematopoietic stem cell transplant (HSCT) [1, 2]. Fever is, therefore, frequently treated with antimicrobial agents [3]. However, fever can occur with several transplant-related complications beside infectious diseases, such as drug infusion, acute graft versus host disease (GVHD) or engraftment syndrome [4, 5]. Conventionally blood and urine cultures have been employed to diagnose infections. However, yield of these cultures is not very high. We have earlier documented that exact cause of fever could be identified in only 50% of patients undergoing ASCT for multiple myeloma [6]. Turnaround time for culture reports to be available is also high given the clinical situation at hand. Unnecessary use of broad-spectrum antibiotic treatment harbors the risk of evolution of drug resistant bacteria and prolonged hospitalization [7]. Therefore, a

marker that could help us differentiate infective fever vs others will be useful.

Procalcitonin (PCT) is the propeptide of calcitonin devoid of hormonal activity and is normally produced during systemic infection in response to circulating microbial toxins and host inflammatory mediators in the C cells of the thyroid gland. Levels of PCT are undetectable (<0.1 ng/ml) in healthy individuals and small to modest increases (<1.5 ng/ml) are seen in viral infections and in non-infectious inflammatory responses. Procalcitonin has a long half-life of (25-30 hours) [8].

U.S. Food and Drug Administration (FDA) has approved PCT for use in conjunction with clinical assessment and other laboratory findings to assist in the risk assessment of critically sick people for progression to severe sepsis and septic shock [9].

High PCT levels at admission to the intensive care unit (ICU) were found to be a better predic-

tor of mortality. Many studies have demonstrated that serum PCT levels are increased in patients with sepsis, and the high levels of PCT correlate with the outcome of the disease [9, 10]. PCT can be used for differential diagnosis, prognosis, and follow-up of critically sick patients [11]. Serum PCT levels have been noted to increase with increasing severity of sepsis. In addition, a rising PCT level might be used as an indicator that an infectious process is not under control and that better source control is required [12].

However, there is limited data on usefulness of PCT in neutropenic population more so in patients who are undergoing HSCT. Only few studies are available regarding utility of procalcitonin in patients undergoing HSCT [1, 2, 13-16]. Majority of studies had small sample sizes and data were not sufficient for meaningful inclusion in clinical algorithms. In India, bone marrow transplant activity is increasing [17]. Therefore, its more relevant now that we have more studies on infections in HSCTs in India.

### Patients and methods

It is a retrospective observational study designed to ascertain role of serum procalcitonin as a useful biomarker for the infections and outcomes in patients who underwent hematopoietic stem cell transplantation. The study protocol (AB/MPH/2016/002; Version 1.1) was approved by the Institutional Review Board (IRB).

#### *Inclusion criteria*

Patients undergoing hematopoietic stem cell transplant with even a single febrile episode in our institute from April 2012 to September 2014 were included in the study. All episodes till patients were in pre-engraftment phase were included.

#### *Exclusion criteria*

Patients with no febrile episode were excluded from the study. Similarly patients with febrile episodes where procalcitonin levels were not assessed were excluded. Febrile episodes after engraftment were excluded.

#### *Supportive care during transplant*

Patients were nursed in HEPA filtered air-conditioned single bone marrow transplant (BMT)

rooms with reverse barrier nursing. All persons entering the room used shoe covers, put on a face mask and cap, and washed their hands thoroughly or used antiseptic hand wash antimicrobial prophylaxis. All patients received oral ciprofloxacin, fluconazole and valacyclovir as antibacterial, antifungal and antiviral prophylaxis, respectively. Fluconazole and valacyclovir were stopped on day 28. Cotrimoxazole prophylaxis was not used after HSC infusion.

#### *Febrile neutropenia protocol*

Fever was defined as a single temperature of  $\geq 101$  F or  $>100.4$  F lasting for more than 1 hour. Any febrile episode was treated with broad-spectrum antibiotics. When febrile episodes occurred, blood and urine cultures or clinical sample as indicated like pus culture or swab were sent. First-line antibiotic cover during conditioning consisted of piperacillin-tazobactam or cefoperazone-sulbactam and amikacin. This was modified later depending on microbiological information or clinical evolution. If fever persisted for 5 days or more empirical antifungal treatment with amphotericin B was started. For each episode of fever, we took measurement of PCT within 24 hour from the onset of fever. Any value  $>0.5$  ng/ml was taken as positive. Patients were divided in two 2 groups depending on procalcitonin values: patients with even a single positive PCT report and patients with all negative PCT reports.

#### *Statistical analysis*

Baseline characteristics like age, sex, diagnosis, conditioning regimen and type of transplant were compared between the two groups. Outcome measures like sepsis, mortality, intensive care unit (ICU) transfer, fever duration was compared between the 2 groups. Incidence of proven gram-negative bacilli (GNB) and gram-positive cocci (GPC) sepsis, intracellular viral infections and non-infectious causes of fever were compared between the 2 groups. Associations between procalcitonin and outcomes was done with Spearman's correlation coefficient. Data was analysed with SPSS v 23 software.  $P$  value  $\leq 0.05$  was considered significant in all statistical evaluations.

### Results

A total of 47 patients with febrile episodes were enrolled. Twenty-eight patients had positive PCT and 19 patients had negative PCT.

## Procalcitonin in HSCT

**Table 1.** Demographic and clinical characteristics of study population

	Positive PCT N=28	Negative PCT N=19	Total N=47	P value
Gender				0.458
Male	20	12	32	
Female	8	7	15	
Age (years)				0.085
Median	16	31	22	
Range	2.4-64	1.3-68	1.3-68	
Diagnosis				0.153
Acute lymphoblastic leukemia	2	0	2	
Aplastic anemia	4	0	4	
Hodgkin lymphoma	1	2	3	
Non-hodgkin lymphoma	1	2	3	
Multiple myeloma	6	7	13	
Thalassemia	8	3	11	
Acute myeloid leukemia	1	1	2	
Chronic myeloid leukemia	0	2	2	
Others	5	2	7	
Conditioning regimens				0.022
Melphalan	6	7	13	
Busulfan cyclophosphamide	9	6	15	
BEAM	2	4	6	
Fludarabine/cyclophosphamide/ATG	4	0	4	
Fludarabine/melphalan	1	0	1	
Others	6	2	8	
Transplant types				0.019
Autologous	9	11	20	
Allogeneic	19	8	27	

PCT-Procalcitonin; BEAM-Carmustine, Etoposide, Cytarabine, Melphalan; ATG-Anti-Thymocyte Globulin.

### Demography

**Table 1** depicts the demographic profile and general characteristics of bone marrow transplant. There were 32 males and 15 females. Twenty patients underwent autologous BMT and 27 underwent allogeneic BMT. Baseline characteristics were comparable between the 2 groups except for conditioning regimen and type of transplant.

### Infections

Febrile episodes were classified as follows: systemic bacterial infections, intracellular infections and non-infectious febrile episodes. The detailed etiology of each episode in different group described in below **Table 2**. There was no difference in the incidence of GPC, GNB and non-infectious fever between the 2 groups.

Bacterial infections were documented in 18/47 (38%) patients. Forty patients were neutropenic. The median fever duration in the positive PCT level group was 10 days (range 3-30 days) as compared to 4 days (range 1-18) in negative PCT level group. This was statistically significant ( $P=0.000$ ). Procalcitonin levels were high in 8/9 episodes of sepsis ( $P=0.029$ ).

### Outcomes

ICU transfers and death were significantly higher in PCT positive group as compared to PCT negative group (**Table 3**). Incidentally, all deaths occurred in positive procalcitonin group.

### Discussion

Several studies have attempted at assessing utility of procalcitonin in infections. There are

## Procalcitonin in HSCT

**Table 2.** Etiology of febrile episodes

	Positive PCT N=28	Negative PCT N=19	Total N=47	P value
Systemic bacterial infection	13	5	18	0.390
Gram positive	4	3	7	
Gram negative	9	2	11	
Intracellular infection	1	0	1	0.134
CMV	1	0	1	
Non-infectious febrile episode	15	13	28	
GVHD	2	0	2	0.134
PUO	4	7	11	
Other	9	6	15	

PCT-Procalcitonin; CMV-Cytomegalovirus; GVHD-Graft versus Host Disease; PUO-Pyrexia of Unknown Origin.

**Table 3.** Outcomes and events of patients in relation to procalcitonin levels

	Positive PCT N=28	Negative PCT N=19	Total N=47	P value	Spearman correlation coefficient
Outcomes					
Fever duration	28	19	47		0.203
Median (days)	10	4	9.5	0.000	
range	(3-30)	(1-18)	(1-30)		
Fever episode				0.451	
Neutropenic	24	16	40		
Non-neutropenic	4	3	7		
Sepsis	8	1	9	0.029	0.485
Event					0.648
ICU transfer	6	2	8	0.003	
Death	4	0	4	0.031	0.536
Alive	24	19	43		

PCT-Procalcitonin; ICU-intensive care unit.

only few studies in bone marrow transplant situations. This is first such Indian study. Since there was only 1 patient with CMV infection and none with proven fungal infection, it is difficult to comment on these etiologies and role of procalcitonin in these situations. Despite some heterogeneity in our data in terms of mix of autologous and allogeneic transplants, our data suggest that procalcitonin levels correlate with worse outcomes in terms of fever duration, incidence of sepsis, ICU transfer and even mortality. Stoma et al identified a 62% sensitivity was 62% and 88% specificity 88% at a PCT threshold of 1.5 ng/ml. Specificity increased to 100% if a higher cutoff of 26.7 ng/mL was used [15]. On the other hand, Knoll et al used a PCT cutoff of <2 ng/mL to identify patients with non-infectious fever after autologous BMT in patients with multiple myeloma

[14]. PCT was able to differentiate bacterial pneumonia from other pneumonia in a cohort of 58 patients with lung transplant [18]. However, procalcitonin was not useful in smaller cohort of 11 patients undergoing heart transplant even though authors felt that a trend of procalcitonin is more important [19]. Guidance for duration of antibiotics with PCT has been studied. Haddad et al identified a specific subgroup of patient with low baseline PCT levels where duration of antibiotic therapy could be restricted to 7 days [8].

There are algorithms available based on procalcitonin values to modify antimicrobial regimen [7, 10, 14]. These algorithms discourage stopping antibiotics if PCT was <0.1 ng/mL and suggest starting antibiotics if PCT was >0.5 ng/mL. However, if one is not starting antibiot-

ics, then serial PCT measurements are recommended. It is tempting to stop or de-escalate antibiotics based on procalcitonin values alone. However, HSCT is a high mortality procedure with infection being major contributor [1, 2]. We will be ill-advised to not use antibiotics in cases of fever based on PCT values only. It has been shown in other studies that PCT did not help much in differentiating infections and other transplant related complications [20, 21]. Procalcitonin levels are expected to reduce misuse of broad-spectrum antibiotics and therefore antibiotic-associated adverse effects and the emergence of drug-resistant bacteria [9]. However, in the field of hematological malignancy, such as neutropenic fever during chemotherapy and transplantation-related complications, it is premature to change the practice of antibiotic usage in febrile neutropenic patients only on grounds of PCT. Limitations of our studies include a small sample size despite this being larger than previous published studies on HSCT, retrospective nature of illness, no proven fungal infection in this cohort and a single patient with CMV infection. We measured procalcitonin levels only during febrile episodes and no serial monitoring was performed. These limitations notwithstanding, we are able to demonstrate worse outcomes in patients with high PCT level during HSCT.

### Conclusions

Serum procalcitonin levels correlate with worse outcome in patients undergoing hematopoietic stem cell transplant.

### Disclosure of conflict of interest

None.

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