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ORIGINAL ARTICLE

IMPORTANCE OF SERUM PROCALCITONIN IN FEBRILE NEUTROPENIA

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ABSTRACT: Febrile neutropenia is defined as a fever >101°F for 1 hour, with an absolute neutrophil count of ≤500 cells/microliter, or an ANC of ≤1000 cells/microliter with a projected nadir of ≤500 cells/microliter. In haematological malignancies it is the common complication and requires broad-spectrum antibacterial therapy. Clinical examination and cultures fail to detect a pathogen or an infectious focus in 25–50%, which are classified as pyrexia of unknown origin (PUO). Patient with pyrexia of unknown origin may receive long duration of antibiotic treatment as the cause is unclear of being infective or not. Febrile neutropenia is a common complication of many chemotherapeutic regimens for all types of cancers. Mortality and Morbidity is high particularly in elderly, immuno-compromised. Approximately 20- 40 % of patients with severe sepsis and 45-60% patients with septic shock die within 15-20 days. This study was done to know the sources of infection and to assess the diagnostic value of serum Procalcitonin and its relation with mortality in various stages of sepsis. Sepsis incidence was more in patient age more than 55yrs. the most common source of sepsis was respiratory tract infection. Serum PCT proved to be an indicator of sepsis in ill patients, with sensitivity of 91%. Presence of both persistent and profound neutropenia was associated with a much higher mortality. The occurrence of infection is directly proportional to the degree of neutropenia, at the onset of fever the PCT levels will not be helpful for the decision to start or stop the antibacterial therapy, and a PCT value higher than 0.5ng/ml in pyrexia of unknown origin might suggest a possibility of occult infection, i.e. with lacking microbiological and clinical documentation. A delayed PCT peak higher than0.5ng/ml contributes to the early diagnosis of fungal disease.

KEYWORDS: Sepsis, Septicemic shock, Severe sepsis, Neutropenia, Procalcitonin, Haematological malignancy, Febrile, PUO, BRAHMS, Elecsys AND COBASE IMMUNOASSAY analyses.

INTRODUCTION: Febrile neutropenia is defined as a fever >101°F for 1 hour, with an absolute neutrophil count of ≤500 cells/microliter, or an ANC of ≤1000 cells/microliter with a projected nadir of ≤500 cells/microliter. In hematological malignancies it is the common complication and requires broad-spectrum antibacterial therapy. Clinical examination and cultures fail to detect a pathogen or an infectious focus in 25–50%, which are classified as pyrexia of unknown origin (PUO). Patient with pyrexia of unknown origin may receive long duration of antibiotic treatment as the cause is unclear of being infective or not. Febrile neutropenia is a common complication of many chemotherapeutic regimens for all types of cancers.

Mortality and Morbidity is high particularly in elderly, immune-compromised. Approximately 20- 40 % of patients with severe sepsis and 45-60% patients with septic shock die within 15-20 days.

This study was done to know the sources of infection and to assess the diagnostic value of serum Procalcitonin and its relation with mortality in various stages of sepsis.

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METHODS: For the study we had selected 292 patients who were diagnosed with cancer and were on the treatment of the cancer. Those patients who developed neutropenia during induction of chemotherapy or maintenance dose of chemotherapy were enrolled. During the study we have grouped the patients into three groups,

- Sepsis
- Severe sepsis
- Septicemic shock

Exclusion Criteria:

- Mild neutropenia
- Moderate neutropenia
- Afebrile neutropenia
- Patients without cancer

All Selected Patient in Study underwent these Investigation:

1. Within 24 hrs of admission in ICU the Blood samples were collected for the Complete blood count and ESR
2. Prothrombin time, APTT
3. Liver Function Test
4. Renal Function Test(blood urea, serum creatinine)
5. Two sets of blood culture are drawn one from peripheral line and one from central line.
6. Urine culture
7. Chest X-ray
8. Serum PCT
9. Complete Urine Examination
10. U/S Abdomen were done for all patients.
11. Ig M Leptospira antibodies
12. Smear for malaria parasite.
13. Specific investigations (e.g.: PCR for HSV on oro-pharyngeal swabs in patients with severe mucositis) was done only in selected cases or suspected cases.
14. Fungal cultures was done in patients with the absence of defervescence in 3 to 5 days of empiric antibiotics (because both neutropenia and antibiotic exposure are independent risk factors for fungemia)
15. If Mycobacterium infections is suspected at initial presentation based on history, sputum for AFB was sent
16. Lumbar puncture: If patients are having symptoms of CNS like headache, neck stiffness, photophobia, altered mental status, or lethargy, lumbar puncture should be performed.
17. CT scans of the chest; abdomen and pelvis should be done on presentation if there are signs or symptoms suggestive.
18. Echocardiogram: An echocardiogram should be taken for all patients, to rule out any cardiac involvement.

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Based on the:

1. Procalcitonin results
2. Radiological finding
3. Clinical finding
4. Microbiological findings

The fever was classified as follows:

* **Culture Positive for Infection** (both site of infection and pathogen identified)[1,7]
* **Clinically Documented Infection** (site of infection identified but no pathogen isolated)[1,7]
* **Pyrexia of unexplained Origin** (new fever without identifiable pathogen and site of infection)[1]

Patients with signs and symptoms of infection were initially started on broad spectrum antibiotics like third generation cephalosporins. Despite on antibiotics if the patients are not responding, the antibiotics were changed depending on cultures reports. On admission If patient presents in septicemic shock state, those patients were started on board spectrum antibiotics (i.e. for gram negative and gram positive cover).[2] If a patient remained febrile for more than 3 days despite on appropriate antibacterial therapy and/or presented signs of invasive fungal disease, antifungal drugs were added as recommended.[2-4]

Serum Procalcitonin Measurement: Serum Procalcitonin was measured by Elecsys BRAHMS. In early detection of the infection (bacterial) the estimation of procalcitonin assay is used. The electro chemiluminescence immunoassay "ECLIA" is intended for use on Elecsys AND COBASE IMMUNOASSAY analyses.

Procalcitonin: it is a prohormone with 116 AA and molecular weight is 12.7Kd, it is expressed by neuroendocrine cells i.e. C cells of thyroid, pulmonary and pancreatic tissues and it is enzymatically cleaved into (immature) katacalcin, calcitonin, and N-terminal region.

In healthy persons the PCT level is low. Various studies have shown that PCT level increases in bacterial infection. Procalcitonin circulating in septic patients consists of only 114 amino acids lacking the N-terminal dipeptide Ala- Pro. Procalcitonin levels increases in patients with bacterial sepsis (severe sepsis and septic shock).

Test Principle: Sandwich principle;
Limitation- Interference: The assay is not affected by

- Icterus (bilirubin <428µmol/L or < 25mg/dl)
- Hemolysis (HB<0.559mmol/L or < 0.900g/dl),
- Lipemia (intralipid <1500mg/dl),
- Biotin <123nmol/L or <30ng/ml.

Criterion: recovery within $\pm$15% of initial valve.

Patients on biotin doses (i.e. >5 mg/day), blood sample for PCT should be taken after 8 hrs of the last biotin dose taken.

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Expected Values:

i) <0.5ng/ml : Minor or no significant systemic inflammatory response.
ii) 0.5 - <2.0ng/ml : Positive for sepsis.
iii) 2 and < 10ng/ml : High risk for developing organ dysfunction.
iv) >10ng/ml : Severe organ dysfunction.

RESULT: 292 patients were included in the study from BIACI and RC. The age wise and gender wise distribution of the study subjects is given in Figure 2. The mean age of the study population was 53.5 years. The various sites of the primary source of infection are given in Table 1. Serum pct was positive in 91.09% of the study subjects. Table 1 shows the number of cases with various sites involved in sepsis, severe sepsis, and septicemic shock. Table 2 shows Serum Procalcitonin in sepsis, severe sepsis, and septic shock patients.

IV DISCUSSION: Procalcitonin (PCT) is a prohormone of calcitonin. It is produced during in response to circulating microbial toxins and host inflammatory mediators.[8,9] PCT concentrations helps in distinguishing systemic from localized infections and as well as infections from virulent and nonvirulent pathogens.

Christ-Crain et al have shown that algorithm for management of infections based on PCT levels, reduces usage of antibiotic in lower respiratory tract infections. Less data is available on PCT in neutropenic fever and suspected fungal infection.[5,9]

The most common cause reported is Sepsis. Risk is also increased with:

- Prior history of neutropenic fever.
- Prolonged duration of neutropenia.
- Magnitude of neutropenia.
- Chemotherapy intensity.
- Age.
- Low performance status.
- Pre-existing organ dysfunction.
- Associated anemia.
- Bone marrow involvement.

The role of serum Procalcitonin was studied in febrile neutropenic patients with hematological malignancies and solid tumors which are at high risk for Bacterial and Fungal infections,[2,7,11] A serum Procalcitonin rise was observed in Microbiological proven Infection and clinical documentation of Infection after the onset of fever. Repeated Procalcitonin estimations were not possible in all the patients due their financial constraints. [7, 10, 11]

In few cases Procalcitonin values higher than the threshold were observed in pyrexia of unknown origin, [10,11] suggesting that these Febrile Episodes may have been due to deep-seated bacterial infections with absence of clinical and microbiological documentation. In this present study we found that there is slightly higher percentage of males affected with sepsis compared to females.

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1. Respiratory tract infection (32.53%) was more common source of sepsis in our study (table 1). These cases had Lobar Pneumonia and Bronchopneumonia, Bilateral Pneumonia, ARDS.
2. In 28.08% of patient, the primary source could not be identified (table 1).
3. UTI: second most common focus, partly due to more number of elderly patients with risk factors like diabetes (table 1).
4. Invasive fungal infection in 7.19% of cases (table 1).
5. Grade 4 mucositis in 6.50% of cases (table 1).

The most frequently isolated pathogens were the Gram-positive cocci, gram-negative bacilli, most of which were Klebsiella, P. aeruginosa, and E. coli. Gram-positive cocci isolates consisted of S. aureus isolated from the wound and blood, S. epidermidis isolated from the blood of a patient with indwelling vascular catheter, and S. saprophyticus from the urine. Candidiasis was documented in patient; oral candidiasis was seen in the patients.

Most of these patients were previously exposed to cancer chemotherapeutic agents, which could have caused the myelosuppression. In 60-70 percent of the febrile neutropenic patients, documented infection was observed; and in 30-40 percent of them, fever was unexplained. According to various studies common infection sites in the causation of sepsis (pneumonia, blood stream infection including infective endocarditis, intravascular catheter related sepsis, intra-abdominal infection, urosepsis, surgical wound infections, fungal infection, superficial and deep seated infection).

In present study the Mortality was 105 patients (35.95%). Mortality could be attributed to various risk factors like diabetes and age.

* 70% of the cases in these 105 patient were having septicemic shock (61.9% were elderly {mean age 70years} and diabetic, remaining 38.1% were having mean age of 41yrs).
* 21.5 % of patients were severe sepsis (44% were elderly, 52% diabetic).
* 8.5% of patients were having sepsis (31.6% elderly and diabetic).

PCT is a prognostic marker for sepsis and to predict of outcome in sepsis patient. Serum PCT level increased during bacterial, parasitic, or fungal infections. In severe viral infection, serum PCT level does not increase or only show moderate increase. In some life-threatening Invasive fungal diseases there was no increase of PCT concentrations, while others associated with elevated PCT values had poor outcome in Invasive fungal diseases.

In conclusion, sepsis incidence was more in patient age more than 55yrs. the most common source of sepsis was respiratory tract infection. Serum PCT proved to be an indicator of sepsis in ill patients, with sensitivity of 91%. Presence of both persistent and profound neutropenia was associated with a much higher mortality.

The occurrence of infection is directly proportional to the degree of neutropenia, at the onset of fever the PCT levels cannot be used for the decision to start or withhold immediate antibacterial therapy, a PCT value higher than 0.5ng/ml in pyrexia of unknown origin might suggest an occult bacterial infection, i.e. with lacking microbiological and clinical documentation. A delayed PCT peak higher than 0.5ng/ml contributes to the early diagnosis of fungal disease.

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SOURCES OF INFECTION		SEPSIS	SEVERE SEPSIS	SEPTICEMIC SHOCK	TOTAL
Respiratory Tract Infection		45	17	33	95
Urinary Tract Infection		22	09	15	46
G.I.T.		16	3	5	24
Cellulitis		2	1	1	4
Leptospirosis		1	-	-	1
Source unknown		26	19	37	82
Invasive Fungal Infection	Possible	3	6	4	13
	Proven	5	2	1	8
Grade IV Mucositis		12	5	2	19
TOTAL		**132**	**32**	**44**	**292**

Table 1

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Diagnosis	Serum PCT (ng/ml)				
	<0.5	>0.5 - <2	> 2- < 10	10	**Total**
Sepsis	12 (8.16)	43 (29.25)	55 (37.41)	37 (25.17)	147 (50.34)
Severe Sepsis	3 (4.2)	10 (14.28)	25 (35.7)	32 (45.7)	70 (23.97)
Septic shock	4 (5.33)	12 (16)	23 (30.67)	36 (51.4)	75 (25.68)
TOTAL	**19 (6.5)**	**65 (22.26)**	**103 (35.27)**	**105 (35.96)**	**292**

Table 2

Serum Procalcitonin in Sepsis, Severe sepsis, and Septic shock patients

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