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Original ARTICLE

Significance of Serum Procalcitonin in guiding antimicrobial therapy in patients with SIRS/Sepsis

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ABSTRACT
Background: Procalcitonin (PCT) is currently the most studied infection biomarker and its blood levels seem to mirror the severity of illness and outcome. **Material and methods**: Correlations of PCT values with infective etiologies and clinical diagnosis were compared in moderate SIRS, severe sepsis and septic shock.Serial PCT levels were monitored. Changes in PCT levels were analyzed. Antibiotic therapy was monitored according to PCT values and culture results and analysis was done accordingly. Fall/raise in the PCT levels was seen. **Results:** Out of total 200 cases, 182 (91%) had PCT value ≥0.5 ng/ml whereas 18 (9%) had PCT value of <0.5 ng/ml. Out of the 182 cases with first PCT values ≥0.5 ng/ml, serial PCT's were done for 91 patients.Amongst 99 patients with serial PCT's, 2nd PCT values ≥0.5 ng/ml were found in 90 patients.Relationship between antibiotic therapy and fall in PCT values was found to be statistically significant. **Conclusions:** PCT as a biological marker appears to have a significant value in identifying or ruling out an infection. It may be of value in modifying antibiotic therapy.PCT may assist in decisions about the escalation/de-escalation of antibiotic therapy.

Key words: Procalcitonin, Antibiotic Stewardship, Sepsis

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INTRODUCTION

Sepsis is a systemic immune response to infection by microbial organisms. Sepsis is defined as the presence (probable or documented) of infection together with systemic manifestations of infection. Sepsis and its complications are one of the leading causes of mortality. Timely diagnosis and treatment is highly important in reducing the morbidity and mortality. Serum biomarkers may aid in the early diagnosis of sepsis and therapeutic intervention.[1]Prompt diagnosis and administration of appropriate antimicrobial therapy are essential to reduce complicationsassociatedwithsepsis-relatedorganfailureand patient mortality.[2,3]Procalcitonin (PCT) is a prohormone of the calcium homeostasis hormone calcitonin encoded by the CALC 1 gene located on the short arm of the chromosome 11. In non-infectious conditions it is producedin the neuroendocrine medullary C-cells of the thyroid gland. During microbial infections, endotoxins (LPS) from bacterial cell wall and host responses to infection stimulate the production of cytokines (IL-1 b, TNF-α and IL-6) which increases the CALC-1 gene expression in various extra thyroid tissues and cells including kidneys, pancreas, liver, leucocytes, adipose tissue leading to concomitant release of PCT throughout the body.[4]

The normal physiological level of PCT in serum is less than 0.1ng/mL which can increase several folds in bacterial infections.[5] IFN Ɣ released in response to viral infections can cause a down regulation of PCT. This makes PCT more specific marker for bacterial infection.[6]Plasma levels of PCT in healthy individuals are quite low (<0.1 ng/mL). As a cut-off for the diagnosis of sepsis, plasma levels of ≥0.5 ng/mL are interpreted as abnormal and suggest sepsis. After reaching peak levels, the circulating PCT concentration declines with a 50% plasma-disappearance rate of roughly 1-1½ days. In patients with severe renal dysfunction, elimination rates may be prolonged (one third to one half), but accumulation of PCT does not occur.[7, 8]Thermo Fisher Scientific holds a patent for the use of PCT as a biomarker for sepsis. PCT is also a food and drug administration (FDA)-approved diagnostic marker.Up to 30%–50% of antibiotics given to hospitalized patients may be unnecessary.[9]Treatment courses

commonly exceed recommended durations or are targeted towards colonizing or contaminating microorganisms.[10]However, in the face of imperfect diagnostic tools, clinicians are reluctant to withhold antibiotics when infection is suspected. This pressure is compounded by national quality measures compelling clinicians to immediately start antibiotics in potentially septic patients, even when the diagnosis is uncertain.[11]Subsequent antibiotic de-escalation can be challenging because 40% or more of patients with sepsis never have a pathogen identified.[12]Several trials have reported significant reductions in antibiotic exposure, when PCT was used to guide decisions about initiation of antibiotics in low-risk patients (eg, patients with a clinical syndrome of bronchitis in the emergency department) and duration of treatment in high-risk patients (eg, in patients with pneumonia).[13]Mortality rate in sepsis remains high despite the current advances in medical science, technology and practice. Timely diagnosis and treatment is highly important in reducing the morbidity and mortality associated with sepsis. At-times the diagnostic uncertainty still remains high despite the available clinical information. Thus, a laboratory test with more specificity is essential.

MATERIAL AND METHODS

This was a prospective observational clinical study done in a tertiary care hospital of North India. A total number of 200 cases admitted in medical ICU's, satisfying two or more criteria's of SIRS/sepsis i.e. Temperature more than 38˚C or less than 36˚C, heart rate more than 90 beats/ minute, respiratory rate more than 20 times/ minute or PaCO2 less than 32mm Hg, WBC more than 12,000 cells/µL or less than 4,000 cells/µL (1992 ACCP/SCCM Sepsis definitions) were included.[14] Patients below the age of 18 years; with any malignancy or cardiogenic illness were excluded from the study.

Procalcitonin Assay

The PCT levels were measured using an automated system based on electrochemiluminescence (ECL) technique (Roche diagnostics Cobas e 411 analyzer).Interpretation of PCT concentrations for diagnosis of sepsis was: -0.05 - < 0.5ng/ml - no bacterial infection; ≥0.5 - < 2 ng/ml - local infection, moderate SIRS, severe trauma, surgery, cardiogenic shock ;≥ 2.0 - <10 ng/ml - severe SIRS (sepsis and organ dysfunction ; ≥ 10 ng/ml - severe bacterial sepsis/ septic shock(sepsis and hypotension).[15]

Blood and body fluid culture:

Blood and body fluids samples were collected taking all aseptic precautions andwere inoculated into blood culture bottles. The bottles were incubated in the BacT/Alert or BACTEC blood culture system till they were flagged positive or maximum for a period of 7 days. Gram's stained smears from the positive culture bottles were prepared. Simultaneously subcultures from positive bottles were done on blood agar and MacConkey's agar plates. The plates were incubated at 37°C for 18-24 hours. Growth was identified and antimicrobial sensitivity testing was done in VITEK 2 system. For each patient, only one bloodstream infection episode and, for each episode, only the first samples were considered. Coagulase- negative staphylococci and other skin commensals were considered contaminants when isolated from only one blood culture.

Other specimens (apart from blood and body fluids samples) were inoculated on blood agar and MacConkey's agar and incubated for 24-48 hours. The organisms were identified as per the standard protocols.[4]

Data analysis:

Patients with SIRS/Sepsis were included in the study. Infectious etiologies were correlated with PCT levels. Infections were characterized into bacterial/fungal/viral etiologies & correlated with PCT levels. Serial PCT levels were monitored. Consecutive PCT levels were correlated with antibiotic therapy. Changes in PCT levels were analyzed. Antibiotic therapy was monitored according to PCT values and culture results and analysis was done accordingly. Fall/raise in the PCT levels was seen. The software used was SPSS version 21. Data analysis was done by using chi-square test, ANOVA test & t-test.

RESULTS

Out of 200 cases of SIRS/Sepsis, 182 (91%) had PCT values ≥0.5 ng/ml. Among these patients, 63 patients had PCT ≥10 ng/ml;73 patients had values between ≥2-<10 ng/ml; whereas 46 patients had PCT values between ≥0.5-<2 ng/ml. Only 18 patients (9%) had PCT values of <0.5 ng/ml.

All the results are depicted in the tables and graphs that follow:

PCT values were found to be statistically significant in bacterial infections. In 147 cases with infections, 11 cases had PCT <0.5 ng/ml and 136 patients had PCT values ≥0.5 ng/ml. Serial PCT's were done in 99 patients out of 200 cases of SIRS/ Sepsis. Out of the 182 cases with first PCT values ≥0.5 ng/ml, serial PCT's were done for 91 patients. Amongst 99 patients with serial PCT's, 2nd PCT values ≥0.5 ng/ml were found in 90 patients. In 76 patients out of 99 patients, antibiotic therapy was escalated/ de-escalated according to PCT levels and culture results. Amongst the 91 patients with 1st PCT ≥0.5 ng/ml and in whom serial PCT's were requested, antibiotic escalation/de-escalation according to PCT values and culture results were done in 72 patients. Figure 1 shows that PCT-2 decreased in 5 patients, increased in 7 patients. Out of the 7 patients, antibiotics were escalated in 5 patients. Amongst the 7 patients, 2 patients were discharged in satisfactory condition and 5 patients died. Figure 2 shows that PCT-2 decreased in 29 patients, increased in 12 patients. Out of the 12 patients, antibiotics were escalated in 11 patients. Amongst the 12 patients, 5 patients were discharged in satisfactory condition and 7 patients died. Figure 3 shows that out of total 38 patients, PCT-2 decreased in 27 patients, increased in 9 patients. No changes in PCT-2 levels were seen in 2 patients. Out of the 9 patients, antibiotics were escalated in 7 patients. Amongst the 9 patients, 3 patients were discharged and 6 patients died.In the 72 patients, in whom antibiotic therapy was given according to PCT values and culture results, relation between antibiotic therapy and fall in PCT values was found to be statistically significant (p value <0.05).

Table 1: Correlation of PCT values with bacterial, fungal and viral infections (n=147)

ETIOLOGY	PCT values (ng/ml)				Total		
	<0.5	≥0.5-<2	≥2-<10	≥10		Chi-square value	p-value
Bacterial	4 (22.2%)	13 (28.3%)	36 (49.3%)	34 (54.0%)	87	3.644	0.046
Fungal	2 (11.1%)	10 (21.7%)	13 (17.8%)	8 (12.7%)	33	0.417	0.401
Viral	4 (22.2%)	2 (4.3%)	1 (1.4%)	0 (0.0%)	7	20.528	0.001
Mixed	1 (5.6%)	3 (6.5%)	10 (13.7%)	6 (9.5%)	20	0.434	0.44

Table 2: Serial PCT'S

PCT values (ng/ml)	Serial PCT (Yes/No)		Total
	Yes	No	
<0.5	8	10	18
≥0.5-<2	12	34	46
≥2-<10	41	32	73
≥10	38	25	63
Total	99	101	200

Table 3: - Evaluation of 2nd PCT levels (n=

PCT (ng/ml)	Total No. of Patients	Serial PCT No. of Patients	PCT- 2 (ng/ml) < 0.5	≥0.5-<2	≥2-<10	≥10
<0.5	18	8	6	1	1	0
≥0.5-<2	46	12	0	8	3	1
≥2-<10	73	41	2	17	18	4
≥10	63	38	1	4	11	22
Total	200	99	9	30	33	27

Table 4: Evaluation of antibiotic therapy (n=99)

		Antibiotic therapy according to PCT				Total
		No		Yes		
PCT (ng/ml)	<0.5	4	17.4%	4	5.3%	8
	≥0.5-<2	3	13.0%	9	11.8%	12
	≥2-<10	8	34.8%	33	43.4%	41
	≥10	8	34.8%	30	39.5%	38
	Total	23	100.0%	76	100.0%	99

Figure 1: Evaluation of escalation/de-escalation of antibiotic therapy in patients with serial PCT's (1st PCT- ≥0.5-<2 ng/ml)

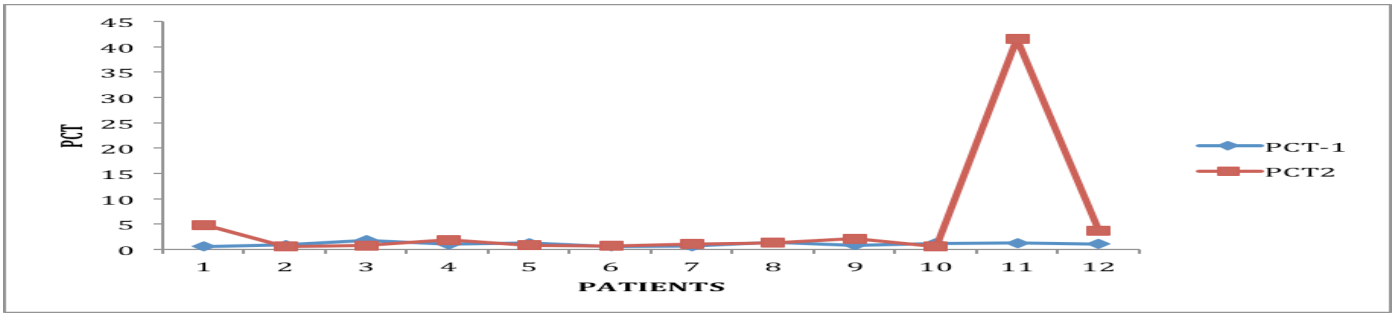


Figure 2: Evaluation of escalation/de-escalation of antibiotic therapy in patients with serial PCT's (1st PCT ≥2- <10 ng/ml)

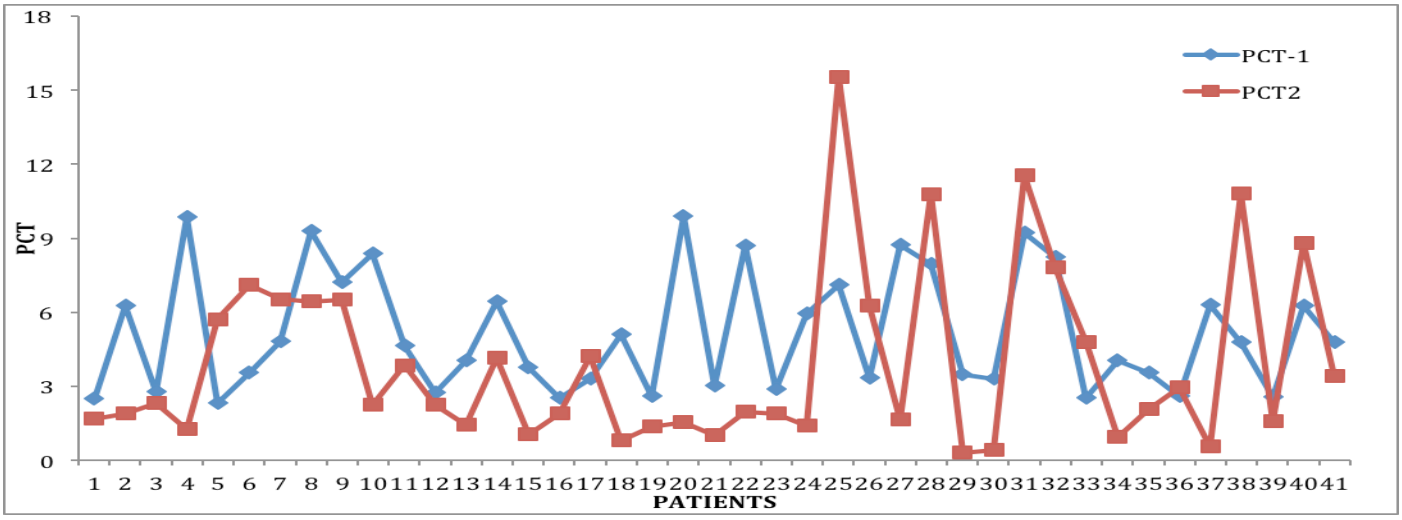


Figure 3: Evaluation of escalation/de-escalation of antibiotic therapy in patients with serial PCT's (1st PCT ≥10 ng/ml)

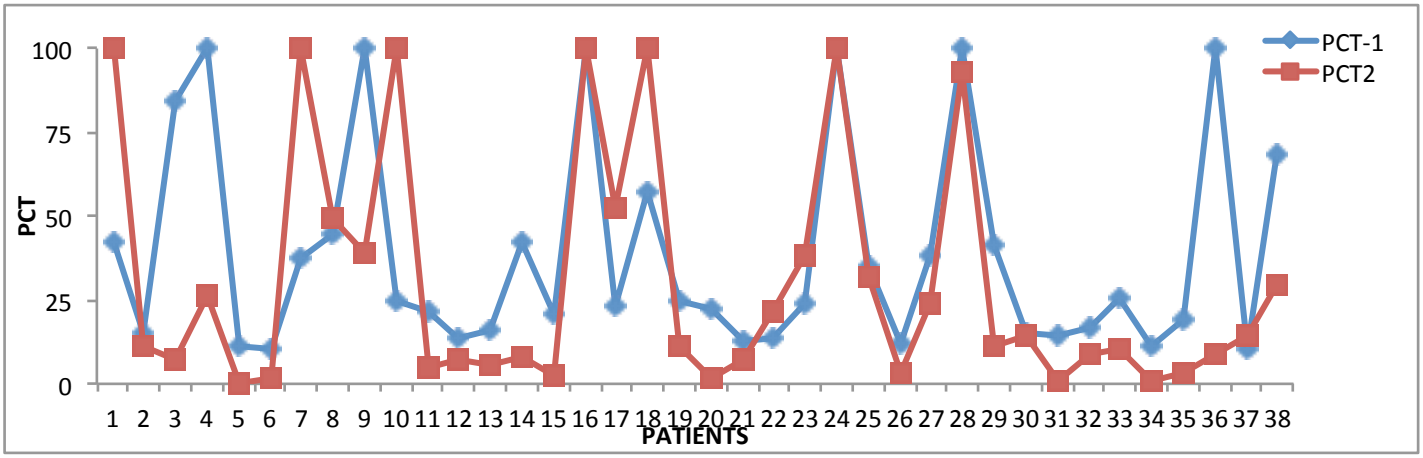
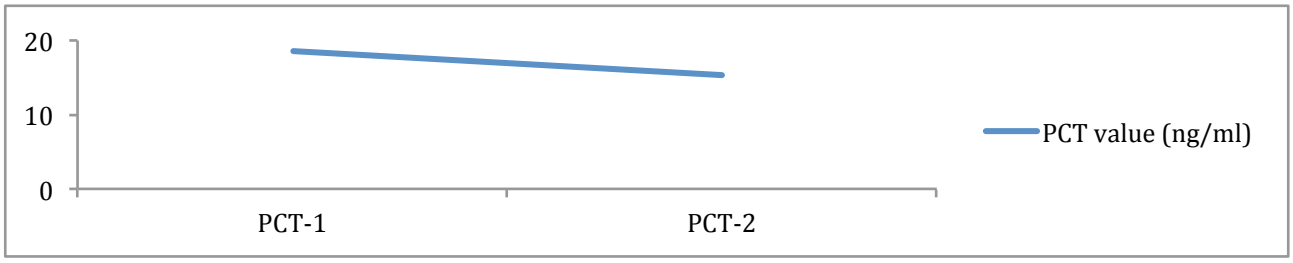


Figure 4: Correlation between antibiotic therapy and fall in PCT levels (n=72)



DISCUSSION

Sepsis and its complications have a significant and increasing impact on health sector, and are one of the leading causes of mortality. The incidence of sepsis is increasing in all areas of the world.[16,17]Biomarkers to diagnose sepsis may allow early intervention which, although primarily supportive, can reduce the risk of death.[18]In our study, 200 patients satisfying the criteria of SIRS/sepsis (ACCP) were included and 182 (91%) patients had PCT value of ≥0.5 ng/ml. Infective foci were seen in 74.7% (136/182) of patients with PCT levels of ≥0.5ng/ml as demonstrated by positive cultures (bacterial and fungal) or serological evidence. Sinhaet al studied a group of 40 patients and found a statistically significant correlation between the presence of sepsis and a PCT levels. The study concluded that PCT levels above 2 ng/ml are effective markers of sepsis.[19] In another study, PCT proved to be an excellent indicator of sepsis with sensitivity of 94 %.[20] Serial measurement of biomarkers may be helpful because of the large variability of biomarker secretion at different times during the progression of critical illness. A single value of PCT, done at the time of admission, cannot predict the prognosis of the critically ill septic patient. This has been substantiated in several studies. [21, 22, 23]Table 2 depicts serial PCT's done in our study. PCT has an elimination half-life of approximately 24 hours. Thus, following the initiation of appropriate antibiotic therapy, one should expect PCT to reduce by approximately 50% in daily intervals.[24]Lack of daily PCT reduction suggests that the bacterial source is not controlled, affording an opportunity to reassess therapy choices.[25] The PCT level is *expected* to fall with therapy; hence many studies looked at the value of PCT at the end of 48–72 h. In the study by Karlsson *et al,* the value after 72 hours did not differ among survivors and non survivors.[26] In 28 patients with severe sepsis/septic shock from Brazil, found that the PCT level after 24–48 hours was significantly different among survivors and non survivors.[27] Similar findings were obtained by Suberviola *et al*, with significantly different levels of PCT 72 hours after admission ($P < 0.01$). This difference was, however, not significant on multivariate analysis. [28] PCT values of 420 consecutive patients during hospitalization were observed. Of the 420 patients, 91 patients died. In patients who died, PCT values were higher on last day as compared to other patients.[29] Figure 1,2,3 depicts the Evaluation of escalation/de-escalation of antibiotic therapy in patients with serial PCT's. it is reported that treatment indication, doses or duration of treatment are incorrect in up to 30%–50% of antibiotic prescriptions.[30,31,32] The over prescription of antibiotic, in turn, may be associated to increased costs, adverse events and prolonged length of hospitalization. On the other hand, early antibiotic prescription may be necessary in

patients with sepsis or septic shock.[33]In several studies on critically ill patients, any delay of adequate antibiotic treatment was associated to an increased risk for mortality.[34, 35] Antimicrobial stewardship approach has largely demonstrated that the greatest utility of PCT is in guiding antibiotic de-escalation, based on PCT reduction. PCT dosing helps to reduce antibiotic therapy duration for serious infections – with no harm in terms of mortality.[36, 37] It is not surprising that PCT potential to reduce length of therapy was also studied in terms of health economics, showing expenditure reduction.[38]PCT, as a biomarkeris a useful in combating antimicrobial resistance and should not be wasted. A multicenter trial in France revealed that patients in which PCT monitoring was done had more antibiotic free days as compared to the other group, whereas no difference in 30 day mortality and rate of relapse was seen. Intervention studies favors the use of PCT for de-escalation of antibiotic therapy, the same may not be true for escalation of antibiotics when PCT increases.[36]

Bouadmaet al encouraged the use of antibiotics at PCT values ≥0.5 ng/ml. They encouraged the use of same antibiotics if the subsequent PCT levels declined 80% than the initial value and change in antibiotics strongly encouraged if there is an increase in the PCT level than before.[37] If the clinical impression indicates a possible diagnosis of sepsis, but PCT levels are not elevated, patients should still be treated for sepsis initially, regardless of the high negative predictive value of normal PCT. Monitoring patients during the next one to two days will indicate whether the initial diagnosis is correct and antibiotics can be discontinued early if sepsis is excluded and PCT remains low. This approach is also supported by the society of critical care medicine (SCCM) sepsis guidelines.[39] In the present study, 72 patients, in whom antibiotic therapy was given according to PCT values and culture results, relation between antibiotic therapy and fall in PCT values was found to be statistically significant.

CONCLUSIONS

Serum biomarkers like PCT may aid in the early diagnosis of sepsis and therapeutic intervention.[39]PCT is a widely used biomarker in the management of sepsis around the world. PCT has a high sensitivity and specificity for predicting systemic bacterial inflammation. High PCT concentrations have a positive predictive value for severe sepsis and septic shock and distinguish between viral and bacterial infections. The levels of PCT correlate with the severity of bacterial infection and bacterial load. PCT may assist in decisions about the escalation/de-escalation of antibiotic therapy. PCT has a role as a mortality or prognostic indicator.

PCT measurement, when applied to the appropriate patient population can prove useful in reducing inappropriate antimicrobial therapies. PCT provides the opportunity for clinicians to engage with infectious disease physicians, pharmacologists, microbiologists for a multidisciplinary approach towards stewardship.

LIMITATIONS

Serial PCT's were not obtained for all the patients. Variability in the antibiotic decisions according to PCT was there due to difference in opinions of the clinicians.

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