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Use of Procalcitonin for Optimizing Antimicrobial Therapy in Long Term ICU Patients

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ABSTRACT
Most of the studies are conducted to evaluate the role of procalcitonin in the diagnosis and management of sepsis at the time of admission or in a defined set of patients [Respiratory infection, surgical sepsis, neonatal sepsis, emergency department, burn patients etc]. The aim of the study was to determine the role of serial monitoring of PCT-serum level with the clinical assessment of the patients and guiding the antimicrobial therapy. The study was conducted for two months and all patients admitted to ICU with suspected sepsis, were included in the study. Patient's demography, SOFA score, APACHE II score and other laboratory parameters were recorded. The blood sample was collected on the day of admission and on alternate days till ten days of admission or discharge from ICU whichever comes earlier. The sera were separated and quantitative estimation of PCT was done by ELISA based technique. In total seven patients were included in the study. The median baseline level of PCT was 135.45 ng/ml higher than the other studies. The baseline level had no correlation with the severity of illness. Two of the patients admitted with septic shock succumbed to infection. There was 30% increase in PCT from baseline in these patients. All patients, who improved clinically and transfer out of the ICU and survived showed >10% decrease in PCT. The percent change in PCT started increasing a day before clinical deterioration in one of the patient. Hence percent change in PCT level may be used as a supportive marker while escalating/ de-escalating/ continuing same antimicrobial therapy.

Key-words: Procalcitonin, Sepsis, Serial monitoring, Intensive care unit (ICU), Antimicrobial Therapy

INTRODUCTION

Systemic inflammation is a common problem in Intensive care unit (ICU) and fever is one of the most common symptoms seen in such patients. The etiology of fever could be infectious or non-infectious [1]. The infectious causes require early diagnosis and immediate treatment with appropriate antibiotics, as failing to do so could result in significant morbidity and mortality associated with sepsis [2].

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In other cases where non-infectious insults are responsible for systemic inflammatory response syndrome (SIRS), the diagnosis remains difficult and results in over use of antibiotics [3]. Moreover, most of the patients in ICU with the slowly evolving disease are often colonized with bacteria at multiple sites and hence some degree of inflammation is always there [4]. Hence clinicians are often in dilemma to decide whether there is persisting inflammation or a new infection, whether to start a new course of antibiotics or wait and observe with the existing antibiotics.

The available diagnostic tools to differentiate between infectious and non-infectious SIRS are of little help. Microbiological examinations confirmed bacteremia in only about 30% of patients with sepsis [5] and the result takes several hours to days. Systemic inflammatory markers, such as C reactive protein (CRP) and

erythrocyte sedimentation rate (ESR), have poor sensitivity and specificity in diagnosing bacterial infections [6]. Hence, a biomarker to rapidly and accurately identify sepsis is warranted for use in the clinical setting.

Currently, procalcitonin (PCT) has emerged as a promising biomarker for bacterial infections. PCT is a precursor protein of calcitonin. Unlike calcitonin, which is only produced in the C-cells of the thyroid gland, PCT can be produced ubiquitously throughout the human body. The production of PCT is up-regulated by pro-inflammatory cytokines, bacterial endotoxins, and lipopolysaccharide. Interferon gamma, a cytokine associated with viral infections, reduces the up-regulation of PCT. It has been shown that PCT levels in non-infectious febrile conditions, such as autoimmune diseases or fever caused by malignant disorders stay low. Furthermore, an increase in PCT levels can be monitored within 4 to 6 h after the start of infection [7–11].

Many studies are conducted to evaluate the role of procalcitonin in diagnosis and management of sepsis at the time of admission in the emergency department [12]. Most of these patients often utilize emergency department as the first point of healthcare contact [12]. The clinical need to differentiate infectious from non-infectious SIRS is particularly important in such set up as diagnosing or excluding infection can alter treatment care of patient e.g. starting antibiotics, admit vs discharge. It has been found that the PCT may offer a more tailor made treatment to the individual patient with fever in the emergency department.

Other studies are conducted in a defined set of patients (Respiratory infection, surgical sepsis, neonatal sepsis, burn patients etc.). For patients with community acquired pneumonia, the serum PCT concentration is able to differentiate bacterial from viral causes. Postcardiotomy patients, who are at particularly high risk for postoperative infections and frequently develop postoperative SIRS and circulatory failure that can mimic severe bacterial infection, have been the focus of particular interest. However, the accuracy of PCT to distinguish infected from non-infected patients in this setting is poor [12].

The present study was conducted in ICU (Medical surgical) of a large public sector tertiary care hospital. The patients admitted here are often referred from other private or small healthcare facilities. Majority of the patients suspected to have sepsis have already been receiving antibiotics. This makes the clinical decision even more difficult e.g. whether to continue the same antibiotic or escalates/ de-escalates the antibiotics. As this set up is usually not the first point of healthcare contact of patients, the baseline level of procalcitonin will not reflect the level in the initial days of illness or before starting the antibiotic. Hence single point measurement of PCT has limited role here. Therefore the aim was to address the role of serial PCT-serum monitoring in ICU patients to predict mortality and treatment failure in sepsis and guiding antimicrobial therapy.

MATERIALS AND METHODS

The ethical approval of this study was taken from the Institute Ethics Committee before starting the study. Written informed consent was obtained from all patients or their relatives before enrollment.

Study design- Prospective observational study.

Study site- The study was conducted at Intensive Care Unit [Medical and Surgical] of a tertiary care Hospital, Delhi, India. The hospital is a 1531 bedded, tertiary care, government hospital. The daily average out-patient department visits were 9538 and in-patient admission were 434. The ICU (Medical and Surgical) is eight bedded and admits patients with medical or surgical complications and hence caters mixed population.

The hospital provides diagnostic laboratory support for multiple disciplines like hematology, pathology, histopathology, biochemistry etc. The hospital has also clinical microbiology laboratory that performs microscopy, serology, culture, identification, and sensitivity of various micro-organism by conventional and/or molecular techniques as per standard microbiological protocol [13]. The laboratory participates in internal and external quality assurance program.

Study Duration- The study was conducted for 2 months in August to September, 2017.

Inclusion criteria- All patients staying for more than 24 hours in the ICU suspected to have sepsis were consecutively enrolled in the study. The study subjects were grouped into severe sepsis and septic shock based on American College of Chest Physicians/Society of

Critical Care Medicine (ACCP/SCCM) Consensus guidelines [14,15].

Exclusion criteria- Patients were excluded from the study if anticipated duration of stay was under 24 hours, severe immuno-compromised, autoimmune disease, on chemotherapy or on chronic steroid therapy.

Follow up period- All patients included in the study were contacted telephonically within 28 days of ICU admission to find out 28 days mortality, if any.

Data collection- At admission, the patient's age, sex, height, and weight was recorded. Daily record of the clinical status of the patients was maintained. These data included the following: clinical status (severe sepsis or septic shock); Acute Physiology and Chronic Health Evaluation (APACHE)-II score; SOFA score, temperature; heart rate; respiratory rate; blood pressure; central venous pressure; laboratory analysis and arterial blood gas analysis. The daily course of the treatment and antimicrobials therapy was also recorded. The final determination of the patient's status was done retrospectively, on the basis of the complete patient charts, results of microbiological cultures and other investigations requested by attending physician.

Estimation of Human procalcitonin- Quantitative estimation of serum PCT was measured by using QAYEE-BIO manufactured by Qayee Biotechnology Co., Ltd. Shanghai [Lot No. 08/2016 (96T), Cat No QY-E02848] as per manufacturer instruction. The blood sample was collected from eligible patients on alternate days till 10 days of admission in ICU. Blood samples were centrifuged at 3000 g for 10 min and serum was collected in sterile tubes and stored at –20°C until assayed to avoid loss of bioactivity and contamination.

Statistical Analysis- All data was entered in a Microsoft Excel 2010 sheet. The percentage increase or decrease of procalcitonin was calculated as follows-

$$\frac{\text{Baseline PCT value - PCT value on subsequent days}}{\text{Baseline PCT value and multiply}} \times 100$$

RESULTS

During the study period, there were total ten patients that were admitted to ICU with suspected sepsis. Three of the patients were excluded from the study as one patient was shifted out of the ICU within 24hours of stay, one was on chronic steroid therapy and one expired on day one of admission. In total seven patients were included in the study.

To maintain confidentiality each patient included in the study has been given ID no from 1 to 7 and the results are described accordingly. Table 1 shows the characteristics of patients admitted, specific diagnosis on ICU admission, length of stay in ICU, predicted mortality as per APACHE-II and SOFA scoring system and 28 day mortality.

It was observed that the predicted mortality by APACHE-II and SOFA score system, of two patients were 71% and 95% respectively. Both of these patients admitted with septic shock and expired in the hospital. Blood culture did not show any growth in any of these patients.

Table 1: Characteristics of the patients admitted to ICU with suspected sepsis

	1	2	3	4	5	6	7
Age (Years)	20	45	40	38	69	28	55
Gender	F	M	M	M	M	F	M
Diagnosis	Perforation peritonitis	Acute pancreatitis	Necrotizing soft tissue infection with Fournier's gangrene	Necrotizing Pancreatitis	Left Parotid carcinoma with radical parotidecto-my with aspiration & right lung consolidation	Uterine perforation with colon perforation	Ruptured liver abscess with exploratory laparotomy
Sepsis	Septic	Septic	Septic shock	Severe	Severe	Severe	Severe

classification	shock	shock		Sepsis	Sepsis	Sepsis	Sepsis
Length of stay in ICU, days	3	10	10	7	14	3	3
APACHE II predicted mortality	71%	71%	51%	15%	40%	12%	15%
SOFA predicted mortality	95%	95%	40–50%	33%	33%	33%	33%
28 day mortality	Yes	Yes	No	No	No	No	Not traceable

Patient No.= 1,2,3,4,5,6,7

Table 2 describes the fall or rise of serum level of PCT since admission of the patient in ICU till discharge. The longest stay of the patient admitted with suspected sepsis in ICU was ten days. Hence monitoring of serum level of PCT was done till day 9 of admission. The median level of PCT at the time of admission was 135.45 ng/ml.

Table 2: Serum Procalcitonin level[#] on serial monitoring of patients suspected with sepsis

	1	**2**	**3***	**4**	**5**	**6**	**7**
Baseline level	135.45	105.85	152	108.45	176.3	254.40	125.35
Day 3	179.5	106.65	152.55	126.2	164.15	182.1	119.1
Day 5	Exp	107.0	137.75	113.35	158.4	Tf	Tf
Day 7		111.2	126.3	109 Tf	151.25		
Day 9		134.6	126.1		151		

 # Serum PCT values expressed in ng/ml, Exp- Expired, Tf= Transferred out of the ICU, *The patient was transferred out on Day 10

Table 3 describes the percentage change of serum level of PCT from the baseline level. Percent increase of serum PCT was observed in three patients, two of them expired having percent increase of 30%. The patient who survived, there was 16% PCT increased on day 3 but the level started falling on subsequent days and percent increase on day 7 was only 1% when patient was transferred out based on clinical assessment.

Table 3: Percentage change of Serum procalcitonin level from baseline level on serial monitoring

	1	**2**	**3**	**4**	**5**	**6**	**7**
Day 3	+31	+1	0	+16	-7	-30	-5
Day 5		+1	-9	+5	-10		
Day 7		+5	-17	+1	-14		
Day 9		+31	-17		-14		

+ Percentage increase, – Percentage decrease, Patient No.= 1,2,3,4,5,6,7

Table 4 describes the antibiotic regimen prescribed to the patients during their stay in ICU. All patients were given injectable broad spectrum and combination of antibiotics (except patient 3 on day 1 & 2). The regimen covered both gram negative and gram positive organism. Three patients were also given metronidazole (Patient 1, 6 & 7) due to suspicion of sepsis caused by abdominal flora that has proportionately more number of anaerobic bacteria.

Table 4: Antibiotic treatment of patient admitted in ICU with suspected sepsis

	1	2	3	4	5*	6	7
Day 1	Ip+Mz+Te	Te+Mp	Mp	Te+Mp	Te+Mp+Co	Ip+Mz+PT	Ip+Mz+PT
Day 2	Ip+Mz+Te	Te+Mp	Mp	Te+Mp	Te+Mp+Co	Ip+Mz+PT	Ip+Mz+PT
Day 3	Ip+Mz+Te	Lz+Tg+PT+Co	Te+Mp	Te+Mp	Te+Mp+Co	Ip+Mz+PT	Ip+Mz+PT
Day 4		Lz+Tg+PT+Co	Te+Mp	Te+Mp	Te+Mp+Co		
Day 5		Tg+PT+Co	Te+Mp	Te+Mp	Te+Mp+Co		
Day 6		Tg+PT+Co	Te+Mp	Te+Mp	Te+Mp+Co		
Day 7		Tg+PT+Co	Te+Mp	Te+Mp	Te+Mp+Co		
Day 8		Tg+PT+Co+Va+Casp	Te+Mp		Te+Mp+Co		
Day 9		Tg+PT+Co+Va+Casp	Te+Mp		Te+Mp+Co		
Day 10		Tg+PT+Co+Va+Casp	Te+Mp		Te+Mp+Co		

Ip= Imipenem; Mz= Metronidazole; Te= Teicoplanin; Mp= Meropenem; Lz= Linezolid; Tg= Tigecycline; PT= Piperacillin-Tazobactum; Co= Colistin; Va= Vancomycin; Casp = Caspofungin; *The patient transferred out on day 14 of ICU admission on Te+Mp, Patient No.= 1,2,3,4,5,6,7

The monitoring of PCT may offer a more tailor-made treatment to the individual patients with fever admitted in ICU. A prospective cost analysis can reveal the economic consequences of implementing PCT guided therapy in long term ICU patients. This may contribute to an optimized antibiotic regimen with beneficial effects on microbial resistance.

DISCUSSION

Many patients admitted in ICU and treated intensively, bacterial colonization at multiple sites and some degree of inflammation is nearly unavoidable [4]. In such patients, the daily dilemma of deciding whether there is a new infection versus persisting inflammation and whether to start a new course of antimicrobials versus waiting and observing is well known to clinicians. Appropriate and timely treatment with antimicrobials could save lives, whereas excessive and prolonged treatment favours the emergence of multi-resistant strains [4]. The available diagnostic tools are of little help. Clinical signs and laboratory parameters are even less specific than in the initial phase, infection always has to be suspected, and microbiology, seldom specific, requires time to give results. Measurements of these inflammatory markers at ICU admission or even in the emergency room are thought to distinguish between inflammations without infection and to delineate the various degrees of inflammatory response to infection [4]. Treatment decisions are adapted daily to the changing clinical severity of the patient, and objective criteria for doing this are often lacking.

PCT has been evaluated in multiple clinical settings as a tool to distinguish bacterial infection from other inflammatory states and infectious processes [12]. In addition, PCT has demonstrated diagnostic, prognostic, and management utility. Of particular relevance to this study, four meta-analyses have reported on PCT performance in the diagnosis of sepsis and/ or bacteremia. Two suggested that PCT is superior to other markers such as CRP and should be used in sepsis diagnosis [16,17] whereas the others found either a moderate or poor ability for PCT to identify sepsis in critically ill patients [5,18]. As evidenced by these divergent results, it remains unclear what role PCT can and should play in the management of septic patients.

In the present study, the baseline serum PCT level ranged from 105-254 ng/ml and is not correlating with severity of the disease (Table 1). The median level of PCT at the time of admission was 135.45 ng/ml. The level observed in the study is much higher when compared to other studies. For a prospective cohort of 78 patients with SIRS, symptoms admitted to the ICU, including 60 with subsequently confirmed bacterial infection, a PCT threshold of 1.1 ng/mL predicted bacterial infection with 97% sensitivity but only 78% specificity [19]. PCT concentrations of another cohort of 101 unselected patients with SIRS symptoms were associated with infection severity, and 1 ng/mL predicted bacterial infection with 89% sensitivity and 94% specificity [20]. The three meta-analyses conducted on this subject have yielded conflicting results [5,16,21]. One of it analyzed 3244 patients included in 30 studies. Heterogeneity of the

results among studies was very high (I2=96%). The overall optimal PCT threshold of 1.1 ng/mL to detect bacterial sepsis gave a mean sensitivity of 77% [95% confidence interval (CI) 72–81%] and a mean specificity of 79% (95% CI 74–84%) [5].

Thus, although PCT is associated with bacterial infections in ICU patients, its diagnostic accuracy as a biomarker remains inadequate. Several factors may explain this poor performance. First, PCT increases with a 24-48 h time lag after infection onset, which reduces the effectiveness of crude PCT measured when an infection was suspected. Second, PCT remains elevated for up to several weeks after infection onset. Because ICU patients may be subjected to several bacterial insults during their ICU stay, PCT might still be elevated due to previous episodes, thereby lowering its specificity to detect a new infection. Third, PCT does not rise during localized infections, even severe, such as mediastinitis or abscesses. Lastly, many conditions associated with ICU care (profound circulatory failure, major surgery, trauma, pancreatitis etc) trigger the systemic release of inflammatory mediators responsible for non-specific PCT increase [12].

To better quantify the fall in procalcitonin levels, the percentage change in the PCT value from the baseline value as a prognostic marker was calculated (Table 3). It was observed that there was 30% increase in percent change of PCT in two patients. These patients were admitted to ICU with septic shock and succumbed to infection. One patient admitted with severe sepsis also showed rise in PCT level and percent increased up to 16%. This patient improved by day 7 of admission and shifted out of ICU. All other patients who survived, there was fall in the level and percent change of PCT. The percent decreased varied from 5 to 30%. The level of percent decrease in survivors and percent increase in non survivors are not as high as observed in other studies.

Karlsson *et al*.[22] found that a substantial decrease in the procalcitonin level at 72 h (>50% decrease) was associated with lower hospital mortality (12.2%) as compared to those with <50% decrease (29.8%, P= 0.007); however, this was not an independent predictor of mortality. Suberviola *et al*. [23] found that a decreasing value of procalcitonin (over 72 h) among 88 patients with septic shock was an independent predictor of survival (odds ratio 0.1); procalcitonin clearance of 70% differentiated survivors from non-survivor with a sensitivity of 94.7% and a specificity of 53%. Among 64 postoperative ICU patients with severe sepsis/septic shock, Tschaikowsky *et al*. [24] showed that a fall in procalcitonin level to ≤50% of the baseline was an independent predictor of survival; the sensitivity was good (97%), but the specificity was only 35%. Li *et al*. [25] in a recent study on 102 septic patients from an ICU in China, showed that the level of PCT decreased in survivors from D1 to D3 and D5 while there was no change in the level in NS (P<0.05).

As shown in Table 4, the percent change of PCT in patient 2 was stable till day 5 but started rising from day 7. As per clinical assessment, the antibiotics were escalated on day 8. But the PCT kept rising and maybe infection and patient succumbed to his illness on day 10 of admission. Hence the escalation of antibiotic could have been done a day earlier based on serum PCT result.

A strategy based on PCT concentration kinetics was proposed to detect unfavorable infection evolution under antibiotics and to guide treatment escalation in the large, randomized, multicenter, Procalcitonin and Survival Study (PASS) [12]. In total, 1200 ICU patients were randomized to receive standard antibiotic guidance or PCT-guided antimicrobial-spectrum escalation. Serum PCT was measured daily after infection onset. 'Alert PCT', defined as PCT ≥ 1 ng/mL and <10% decrease from the previous day, served as a signal indicating that the infection might be uncontrolled. On 'alert PCT' days, physicians collected culture samples from possible infection sites and were encouraged to obtain diagnostic imaging, and then had to follow an algorithm to guide antibiotic escalation. Adequate antibiotic treatment was initiated slightly earlier for PCT group patients with bloodstream infections (-0.1 days vs. 0.8 days; P= 0.02), but the timing remained comparable for other infections. 28-Day mortality was comparable (31.5% vs. 32%; relative risk= 0.98, 95% CI 0.83 - 1.16; P= 0.83), but the PCT group consumed more antibiotics (6 days vs. 4 days; P= 0.001) and had longer ICU stays (6 days vs. 5 days; P= 0.004) and times on mechanical ventilation (+4.9%), dialysis and vasopressors [12].

This study has some limitations. First, all patients presented late to the ICU, after being managed in other healthcare facilities and hence the time of the first procalcitonin estimation was not the day one of severe sepsis or septic shock. Second, the number of patients

enrolled in the study were too less to do any statistical analysis or extrapolate the results to other patients admitted in ICU. Third, there was no growth in blood culture of any of the patient. Hence the causative agent of sepsis, its antimicrobial susceptibility pattern, its relation with prescribed antibiotic and its relation with the level of PCT could not be analyzed. Fourth, the kit used to detect serum level of PCT is based on ELISA. Expertise is required to perform the test. The time taken to perform the test is approximately 2 hour. With every test, at least six standard controls are required to put into plot standard curve. As the test is not simple and rapid, limits its use for a single sample.

CONCLUSIONS

There is a paucity of data, substantiation and inclination of physicians to initiate or deescalate the antibiotic treatment based on PCT-guided algorithms for severely ill patients. This may be attributed to inaccuracy and less reliability of biomarkers to determine bacterial infections in these patients. Considering the possible adverse outcomes of delaying antibiotics for critically ill patients, crude PCT concentration may not be adapted as a reliable tool sought to guide antibiotic escalation/ de-escalation in the ICU. However the present study shows that delta PCT or percent change in PCT level might prove to be a valuable tool and can be used as a supportive marker while deciding antimicrobial therapy. Further studies using larger sample size will be vital to establish PCT and delta PCT as the reliable markers for rationalizing antibiotic therapy amongst the ICU patients for improved outcomes.

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CONTRIBUTION OF AUTHORS

All authors equally contributed to this research article.

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