Review Article:

Procalcitonin in sepsis and bacterial infections

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ABSTRACT

The differentiation of sepsis and systemic bacterial infections from other causes of systemic inflammatory response is crucial from the therapeutic point of view. The clinical signs and symptoms are non-specific and traditional biomarkers like white cell count, erythrocyte sedimentation rate and C-reactive protein are not sufficiently sensitive or specific to guide therapeutic decisions. Procalcitonin (PCT) is considered a reliable marker for the diagnosis and prognosis of moderate to severe bacterial infections, and it has also been evaluated to guide the clinicians in the rational usage of antibiotics. This review describes the diagnostic and prognostic role of PCT as a biomarker in various clinical settings along with the laboratory aspects and its usefulness in risk stratification and antibiotic stewardship.

Key words: Procalcitonin, Biomarker, Sepsis


INTRODUCTION

Sepsis is systemic inflammatory response syndrome (SIRS), due to bacterial infection and this condition requires prompt institution of antibiotic therapy. On the other hand, indiscriminate use of antibiotics in critically ill patients with SIRS due to other causes leads to overuse of antibiotic with risk of rise in antibiotic resistance. The search for a biomarker for sepsis which is highly specific and sensitive with the minimum turnaround time which can reliably distinguish between bacterial infection from other infections, such as, viral, fungal, or protozoal infections as well as non-infectious causes of SIRS have been ongoing. It has also been felt that the biomarker should also be able to determine the infection severity and response to treatment, thus acting as an effective prognostic indicator (Table 1).

Traditional markers of sepsis like C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and leucocyte count have been widely used worldwide but these lack specificity. Novel biomarkers which hold promise include procalcitonin (PCT), interleukins, low eosinophil count, adrenomedullin, interferon-γ (IFN-γ), resistin, natriuretic peptides, and copeptin; and the list is ever expanding. How-

Table 1: Features of an ideal sepsis biomarker

<table>
<thead>
<tr>
<th>Objective parameter</th>
<th>Easy to use and interpret</th>
<th>Reproducible</th>
<th>Readily available</th>
<th>High sensitivity and specificity</th>
<th>Should show rapid increase and decrease</th>
<th>Should show appropriate response with effective therapy</th>
<th>Should co-relate with disease severity</th>
<th>Should show sustained rise in any subsequent infection</th>
<th>Inexpensive</th>
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Procalcitonin: structure and synthesis

The first mention of PCT in sepsis appeared in a report of 1983 mentioning its elevated levels in toxic shock syndrome (TSS) caused by Staphylococcus aureus. However, it was Assicot et al who in 1993 first described PCT as a new marker for infection. PCT is a 116 amino acid long peptide having a molecular weight of 13 KDa. As the
name suggests, it is a precursor of calcitonin, produced by the C-cells of thyroid under the control of the calcitonin gene related peptide 1 (CALC-I) gene. Normally, the expression of the gene is found in the neuroendocrine cells of the thyroid and the lung. However, during microbial infections there is increased CALC-I gene expression in various extra-thyroid tissues and cells including kidneys, liver, pancreas, leucocytes, and adipose tissue with concomitant release of PCT throughout the body. The normal physiological level of PCT in serum is less than 0.1 ng/mL which can increase several folds in systemic bacterial infections.

The pathophysiological role of PCT in sepsis is imperfectly understood. It has been proposed that in inflammation, the release of PCT may be a two way process: direct and indirect. The toxins and lipopolysaccharides released by microbes can induce the release of PCT in a direct manner; or alternately the inflammatory cytokines like interleukin (IL) 1b, IL-6, tumour necrosis factor-α (TNF-α) etc may indirectly influence PCT production.

IFN-γ released in response to viral infection can cause a down-regulation of PCT. This makes PCT a more specific marker for bacterial infection. Thus, during severe bacterial infections, the level of PCT may rise several hundred-folds and may even reach a level of 1000 ng/mL without any change in serum calcitonin level. However, it is important to keep in mind the following situations while interpreting PCT reports: (i) Gram negative bacteraemias cause higher elevation of PCT than those caused by Gram positive pathogens; (ii) there is a low or negligible rise in PCT levels in localized infections, and in infections caused by viruses or intracellular bacteria; and (iii) in the neonatal period, particularly in the first 48-72 hours of life, serum PCT levels increase to a high level and then gradually fall during the first week. This is possibly due to initial establishment of gut flora.

### Procalcitonin as a diagnostic marker of bacterial sepsis

A large number of studies have investigated the diagnostic role of PCT in bacterial infections, particularly in critically ill patients; and also to differentiate bacterial sepsis from SIRS. However, the results have been conflicting. To resolve this issue, a few systematic reviews and meta-analyses of representative studies have been attempted. One such meta-analysis compared 25 studies comprising of 2966 patients. This analysis found a global diagnostic accuracy odd ratio (OR) of 15.7 for PCT [95% confidence intervals (CI) 9.1-27.1] compared to 5.4 for CRP (95% CI, 3.2-9.2). The performance of PCT was significantly higher than CRP (Q-values 0.78 versus 0.71, p=0.02) In a similar systematic review of 18 studies, the mean sensitivity and specificity for PCT as a diagnostic marker for bacterial infections was found to be 71% (95% CI, 67-76) with a Q-value of 0.72. In another study in a series of 103 intensive care patients, it was found that PCT with an area under receiver operating curve (AUROC) of 0.81 and sequential organ failure assessment (SOFA) score with AUROC of 0.82 were the only independent predictors for infections; and not CRP. In a recent meta-analysis that assessed the usefulness of PCT as a diagnostic marker for sepsis, 30 reports out of a total search of 3487 reports fulfilled their inclusion criteria, accounting for 3244 patients. Bivariate analysis yielded a mean sensitivity of 0.77 (95% CI, 0.72-0.81) and a specificity of 0.79 (95% CI, 0.74-0.84), with an AUROC of 0.85 (95% CI, 0.81-0.88). The authors concluded that PCT was a helpful biomarker for early diagnosis of sepsis in critically ill patients, but cautioned that the results should be interpreted in the context of medical history, physical examination and microbiological assessments.

A number of formats are available for the detection and quantification of PCT in serum and plasma. These include semi-quantitative as well as sensi-
tive quantitative assays with variable detection limits. Table 2 gives the relevant information regarding the different platforms for PCT detection.

Knowledge of the various cut-off values for PCT and their interpretation is important for the clinicians and the laboratory may mention it when reporting PCT results (Table 3A). Moreover, like any other biomarker, false-positive and false-negative results (Table 3B) are also seen with PCT.

Published evidence suggests that PCT appears to have a distinct advantage over CRP in diagnosis of sepsis.\textsuperscript{17,20} However, clinicians regard it as a relatively non-specific marker of inflammation. This is reflected by the recommendations of American College of Critical Care Medicine (ACCM) and the Infectious Diseases Society of America (IDSA). The ACCM and IDSA have graded PCT as a level 2 evidence (reasonably justifiable by available scientific evidence and strongly supported by expert critical care opinion), and recommended that PCT can be used as an adjunctive diagnostic tool for discriminating infection as the cause for fever or sepsis presentation while evaluating new fever in critically ill patients.\textsuperscript{16} However, the Surviving Sepsis Campaign guidelines 2012\textsuperscript{23} mention that the utility of procalcitonin levels or other biomarkers (such as CRP) to discriminate the acute inflammatory pattern of sepsis from other causes of generalized inflammation (e.g. postoperative, other forms of shock) has not been demonstrated. These guidelines mention that no recommendation can be given for the use of these markers to distinguish between severe infection and other acute inflammatory states.\textsuperscript{23}

Procalcitonin for the diagnosis of bacterial infections in special settings

Apart from its usefulness in the diagnosis of bacterial sepsis in the critical care area, the utility of

<table>
<thead>
<tr>
<th>Table 2: Assay techniques for PCT detection and quantification</th>
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<tbody>
<tr>
<td><strong>Assay Technique</strong></td>
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<tr>
<td>--------------------</td>
</tr>
<tr>
<td>Semi-quantitative rapid assay (BRAHMS PCT-Q)</td>
</tr>
<tr>
<td>Quantitative manual assay (BRAHMS PCT-LIA)</td>
</tr>
<tr>
<td>Quantitative automated assay (BRAHMS PCT KRYPTOR)</td>
</tr>
<tr>
<td>Quantitative automated system (LIASION System)</td>
</tr>
<tr>
<td>VIDAS® BRAHMS PCT Test</td>
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</table>

PCT=procalcitonin
Source: http://www.procalcitonin.com
PCT in some other bacterial infection settings has also been evaluated. Respiratory tract infections

PCT has been extensively studied for the diagnosis of ventilator associated pneumonias (VAP) and community acquired pneumonia (CAP). A multinational study from 10 academic hospitals in Canada, The United States, and two European countries (Germany, Belgium) included 175 patients [57 with CAP, 61 with VAP, and 57 with hospital acquired pneumonia (HAP)]. Initial PCT levels were higher in CAP than VAP patients, but not significantly different from the levels seen in HAP patients. The initial and maximum PCT levels also showed agreement with the SOFA scores. On the basis of the various studies, it has been concluded that PCT remains the best validated biomarker, as compared to CRP and others, in differentiating viral and bacterial causes of pneumonia.25

**Neonatal and paediatric infections**

A systematic review26 which included studies on infections among the newborns (up to 59 days age) found that PCT was a useful diagnostic marker in early stages of bacterial infections (sensitivity=77%-93%, specificity=81%-84% at a cut off value of 8.92 ng/mL) compared to CRP (sensitivity=66%, specificity=86%, cut off value of 17 mg/L). However, it should be noted that there is a surge of PCT in the first 24-48 hours of life which returns to normal over the next 3-7 days.18 In older children with more invasive bacterial infections like sepsis and meningitis, levels of PCT were significantly higher compared to CRP; and moreover during the period of evolution of fever (<8 hours), PCT performed better than CRP with a more rapid rise in its level.27 Another study which involved children with bacterial and viral pneumonia revealed that on admission 100% of the children with bacterial pneumonia had high levels of PCT (0.94-6210 ng/mL), while only 34% of the children with viral pneumonia had PCT levels between 0.5-2.13 ng/mL.28 In this study, it was concluded that PCT concentration of greater than 2.0 ng/mL had 100% sensitivity, 98% specificity, and a positive predictive value of 93% for bacterial pneumonia. CRP levels were elevated in 100% and 88% cases of bacterial and viral pneumonia respectively, giving a specificity of 38% and positive predictive value of 42% for bacterial pneumonia. In a study29 of 359 children it was observed that PCT was superior to CRP and PCT levels increased significantly with the severity of illness (AUROC=0.91), but CRP could not mirror the change effectively (AUROC=0.75). In conclusion it may be said that

### Table 3A: Reference values of PCT

<table>
<thead>
<tr>
<th>Reference values (ng/mL)</th>
<th>Interpretation</th>
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<tr>
<td>&lt;0.05</td>
<td>Normal</td>
</tr>
<tr>
<td>&lt;0.5</td>
<td>Localized infection possible. Re-test after 6-24 hours</td>
</tr>
<tr>
<td>≥0.5-&lt;2</td>
<td>Systemic bacterial infection possible. Re-test after 6-24 hours</td>
</tr>
<tr>
<td>≥2-&lt;10</td>
<td>Systemic bacterial infection is likely. High risk for severe sepsis</td>
</tr>
<tr>
<td>≥10</td>
<td>Severe bacterial sepsis, septic shock</td>
</tr>
</tbody>
</table>

PCT=procalcitonin

**Source:** references 9,17

### Table 3B: Causes of false-positive and false-negative PCT results

**False positive Results**

Neonates <48 hrs age
First days after major surgery, trauma, burn
Treatment with OKT3 antibodies, interleukins, TNF-α
Invasive fungal infections, acute attack of falciparum malaria
Prolonged or severe cardiogenic shock
Malignancies: e.g., medullary C-cell carcinoma of thyroid, small cell cancer of lung, bronchial carcinoid

**False negative results**

Early course of infection
Localized infections
Sub acute bacterial endocarditis

PCT=procalcitonin; OKT3=orthoclone monoclonal antibody; TNF-α=tumor necrosis factor - alpha

PCT in some other bacterial infection settings has also been evaluated.

### Respiratory tract infections

PCT has been extensively studied for the diagnosis of ventilator associated pneumonias (VAP) and community acquired pneumonia (CAP). A multinational study from 10 academic hospitals in Canada, The United States, and two European countries (Germany, Belgium) included 175 patients [57 with CAP, 61 with VAP, and 57 with hospital acquired pneumonia (HAP)].24 Initial PCT levels were higher in CAP than VAP patients, but not significantly different from the levels seen in HAP patients. The initial and maximum PCT levels also showed agreement with the SOFA scores. On the basis of the various studies, it has been concluded that PCT remains the best validated biomarker, as compared to CRP and others, in differentiating viral and bacterial causes of pneumonia.25
serum PCT levels appears to be a significant improvement over CRP.30

Neutropenic and/or immunosuppressed patients

Early diagnosis of bacterial infection, particularly in febrile neutropenic patients is difficult because the typical clinical features and routine laboratory tests used to diagnose such infections lack diagnostic accuracy.31,32 In studies in children with haematological malignancies, using a cut-off level of 2.0 ng/mL, PCT was found to have a sensitivity and specificity of 94% and 96.5% respectively for predicting bacteraemia.17 In a study33 of 286 episodes of febrile neutropenia, PCT was considered to be an useful early diagnostic marker for the detection of bacteraemia and was found to have a better profile than CRP. A systematic review34 evaluated 30 studies and found that PCT was a valuable diagnostic tool in febrile neutropenic patients.34 One attractive aspect of PCT is that its level is not influenced by corticosteroid use.35 In a study36 with 102 critically ill patients with systemic bacterial infections receiving parenteral prednisolone 20-1500 mg/day, while appropriately high PCT levels were observed, significantly lower levels of CRP and IL-6 were observed.36

Dialysis patients

In a recent study,37 the usefulness of PCT, CRP, IL-6, and white cell count for detecting bacterial infection in patients on haemodialysis was investigated. The AUROC for PCT was 0.921, which was significantly higher than the AUROC for CRP (0.853, p<0.01), IL-6 (0.739, p<0.01), and white cell count (0.692, p<0.01). Among continuous ambulatory peritoneal dialysis (CAPD) patients presenting with peritonitis, conflicting reports are available. In a report from Turkey,38 among 50 patients on CAPD related peritonitis, increased levels of PCT was found in 42% patients while bacterial culture was positive in 74% cases.38 In a study39 of 35 patients on CAPD with peritonitis although serum PCT was elevated in some patients at the time of peritonitis, its value in making a diagnosis and predicting long term prognosis was observed to be doubtful.

Procalcitonin as a prognostic marker of bacterial infections

PCT level have been observed to be definitely increased with increasing severity of sepsis and organ dysfunction.40 PCT was also found to be a predictor of mortality in a study involving 472 critical care patients.41 PCT measurement was done daily in these patients and both high PCT levels and the increase in the levels following the first reading of greater then 1.0 ng/mL were independent predictors of 90 day mortality. White cell count and CRP were not found to be predictors of mortality in this study.41 On the other hand, in another study42 there was a significant difference in PCT values between survivors and non-survivors, but only the Acute Physiology and Chronic Health Evaluation (APACHE II) score and male gender were found to be independent predictors for death. In another recent study, CRP, SOFA score, age, and gender could predict mortality, but not PCT.21

APACHE II and SOFA scores have been well validated for mortality risk stratification, but they are more commonly used for audit and research purposes rather than for clinical decision making. Thus a point-of-care rapid test which can provide prognostic information can be very useful for the clinician in decision making regarding early intervention. PCT may be helpful to assess the severity of the infection.38 The favourable kinetic profile of PCT makes it a useful clinical marker. PCT promptly increases within 6-12 hours after an infection trigger and the levels halve daily when the infection is controlled.43 A decrease in PCT level by more than 30% after the first 24 hrs from the onset of antimicrobial therapy is indication of appropriate treatment and control of infection.44

Role of procalcitonin in antibiotic stewardship

Antibiotic stewardship has been defined as the optimal selection, dosage, and duration of antimicrobial treatment that results in the best clinical outcome for the treatment or prevention of infec-
tion, with minimal toxicity to the patients and minimal impact on subsequent resistance. Thus the 4Ds of optimal antimicrobial therapy are: right drug, right dosage, de-escalation to pathogen-directed therapy, and right duration of therapy.

In a meta-analysis of 14 randomized controlled trials comprising 4211 patients that studied the role of PCT in guiding antibiotic therapy in acute respiratory infections, it was seen that PCT guided antibiotic therapy reduced treatment failures but not mortality, compared with usual care. The PCT guided group had less antibiotic exposure than the usual care group (median 4 days Vs 8 days). Similar observations were noted for respiratory tract infections, and critically ill patients. In a large randomized trial conducted in eight French intensive care units patients with elevated PCT had significantly more days without antibiotic exposure than control patients and received significantly fewer days of antibiotics. To date, the most comprehensive analysis which examined 18 randomized controlled trials focusing on PCT-guided antibiotic therapy among 5 patient populations was published in 2012. The salient findings were as follows: (i) PCT guidance reduces antibiotic use when used to discontinue antibiotics in adult intensive care patients; (ii) PCT reduces antibiotic use when used to initiate or discontinue antibiotics without increasing morbidity and mortality; (iii) PCT guidance reduces antibiotic use (moderate evidence), without sufficient evidence on morbidity and mortality outcomes in early neonatal sepsis; and (iv) regarding utility of PCT in fever of unknown origin in children 1-36 months age and in post-surgical patients evidence was insufficient to draw any meaningful conclusions.

Apart from these, it has been opined that in certain units where antibiotics are used for 10-14 days or more, PCT may be a highly cost-effective strategy to give the confidence to clinicians to stop antibiotics earlier. Similarly, the Surviving Sepsis Campaign Group recommends the use of low PCT levels to help clinicians in the discontinuation of empiric antibiotics in patients who appeared to have sepsis, but do not have final evidence of infection.

**Other novel biomarkers for sepsis on the horizon**

A number of molecules are in the evaluation stage as biomarkers in the diagnosis and prognosis of sepsis and bacterial infections. Some of these are described below. Pro-adrenomedullin (p-ADM) is the precursor protein of adrenomedullin first discovered in 1993. In a study of 99 septic shock patients, both p-ADM and pro-vasopressin (copeptin) were significantly elevated in the first week in those who died and were found to be significantly associated with mortality on bivariate analysis. Interestingly, these two molecules have competing biological properties but when used as a combination improved the predictive ability. It is felt that there is need for further evaluation to find out whether they reflect an adaptive response to shock since both the molecules partly reflect the level of stress in an individual.

In an analysis of 12 studies using brain natriuretic peptide (BNP) and N-terminal pro-B type natriuretic peptide (NT-pro BNP) comprising of 1865 sepsis patients, both were found to be significantly associated with increased risk of mortality (OR 8.65, 95% CI 4.94-15.13, p<0.00001). The pooled sensitivity was 79% and specificity was 60%. It was concluded that these may prove to be a powerful predictor of mortality. A review of ten papers revealed that soluble urokinase-type plasminogen activator receptor (suPAR) had little diagnostic value in critically ill patients with sepsis, SIRS, or bacteraemia. But mortality prediction by other biological markers, or severity of disease classification system scores improved when combined with suPAR.

Levels of both matrix metalloproteinase (MMP) and tissue inhibitor of MMP (TIMP) were significantly elevated in a series of 37 patients with severe sepsis compared to similar number of healthy controls, and TIMP was found to be at higher lev-
els in those who died, compared to the survivors.56 Other markers like IL-6, IL-8, IL-18, transforming growth factor β-1, interferon-γ, resistin, cluster of differentiation 64 (CD-64), serum lactate etc., have also been evaluated in various studies30,57-59 to find out their diagnostic and prognostic potentials in sepsis with variable results.

PCT thus, appears to be promising as a biomarker for diagnosis and prognosis of moderate to severe bacterial infections and as a guide for antibiotic therapy. Further studies in field-conditions from tropical countries may help in establishing PCT as a point-of-care diagnostic test.

The other potential biomarkers need additional studies using larger number of patients before their use can be validated. The scenario which is emerging seems to suggest that any single biomarker is unlikely to identify and stratify all patients adequately,30 and a combination of such markers may reveal a clearer picture.

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