Special reviews

Procalcitonin in Critical Illness

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ABSTRACT

Objective: *To detail the biology and diagnostic usefulness of serum procalcitonin in critical illness.*

Data sources: *A review of articles published in peer reviewed journals from 1990 to 2001 and identified through a MEDLINE search on procalcitonin.*

Summary of review: *Procalcitonin (PCT) is a prohormone of calcitonin. Serum levels are elevated during sepsis and have been identified as a potential marker of infection in critical illness. However, its function and precise source of origin during sepsis remain unclear. The value of estimating serum PCT appears to be in the differentiation of infectious from non-infectious forms of systemic inflammatory response syndrome. A number of studies also point to its usefulness in distinguishing between bacterial and viral meningitis. However, there are a number of non-infectious conditions, where elevations in serum PCT occur, reducing its specificity. Its superiority as a marker of sepsis compared with other acute phase reactants continues to be debated.*

Conclusions: *The utility of serum procalcitonin as a diagnostic test of sepsis is still under evaluation. Moreover, a number of unanswered questions remain regarding the biological role of PCT during sepsis, its target receptors and its protective value to the patient.* (**Critical Care and Resuscitation 2001; 3: 236-243**)

Key words: Procalcitonin, physiology, critical illness, sepsis, SIRS, bacterial, viral, meningitis

The diagnosis of bacterial infection in the critically ill patient remains notoriously difficult, particularly in the presence of other non-infectious conditions that can generate an inflammatory response (e.g. trauma, major surgery and burns). Conventional clinical and laboratory parameters for the diagnosis of infection lack sensitivity and specificity. During the past few years, several variables have been examined as suitable markers of infection and sepsis, but none have become a well-established standard.

In 1993, Assicot *et al* described elevations in serum procalcitonin as a marker of bacterial sepsis. This was followed by a spate of publications testifying to its status as a reliable marker of sepsis. Since then, there has also been a growing list of non-infectious conditions in critical illness associated with elevations in serum procalcitonin concentration. In this review, we outline the biology of procalcitonin, critically examine its diagnostic value in critical illness, and discuss the potential role of procalcitonin assay in critical care practice.

Biology of procalcitonin

Procalcitonin (PCT) was first identified from a medullary thyroid carcinoma cell line. It is a 116 amino acid, 13 kDa protein, encoded by the CALC-1 gene on the short arm of chromosome 11, and is produced in the C-cells of the thyroid gland as a prohormone of calcitonin. Normally, all of the PCT is cleaved in the thyroid to calcitonin. Consequently, the serum concen-

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trations of PCT are very low in healthy humans (e.g. < 0.1 ng/mL). Release of PCT into the circulation in large concentrations in various disease states is not accompanied by significant elevations in calcitonin levels. Structurally, the PCT peptide is comprised of 3 parts. Situated in the centre of the peptide is calcitonin; at the aminoterminal end is aminoprocalcitonin and at the carboxyterminal end is calcitonin carboxyterminal peptide-1 (CCP-1 or katacalcin).

The half-life of PCT is 25 - 35 hr,[1,2] which is not altered significantly by renal failure or by continuous veno-venous haemo-diafiltration,[3] therefore serum concentrations can be used for diagnostic purposes in patients with impaired renal function. The tissue of origin of PCT has not been elucidated although there are data to suggest that activated macrophages and hepatocytes might be possible sites of origin.[4]

In sepsis, elevations in serum levels of PCT are in part mediated by the cytokines, TNF-alpha and IL-6.[5,6] However, the precise biological role of PCT during sepsis remains a mystery. It has been suggested that PCT may reduce calcium availability to the cell, thus reducing cell death.[7] Other possible roles include bone remodeling during sepsis.[4] There are also data to suggest that this protein might modulate the inflammatory response during bacterial sepsis. In support of this is the work of Nylen *et al*,[8] who showed that the mortality of hamsters with induced peritoneal sepsis was significantly higher with the co-administration of PCT and was reduced if the effects of PCT were immunoneutralised. A further study by Whang *et al* showed that PCT affected mortality only when administered to septic animals and had no effect on healthy animals,[9] suggesting that PCT may play a secondary mediator role in the inflammatory cascade acting in a host already "primed" by activation of proximal mediators.

Although PCT does not initiate the septic response, it might augment and amplify the process, and therefore may have an impact on the outcome. In the clinical setting, high levels of PCT have been correlated with poor outcome,[10-12] but it is unclear whether this is a causal relationship or an association.

Recently, data from physiological studies suggest that PCT release may be beneficial. Hoffman *et al* showed that PCT significantly reduced the iNOS-inducing effects of the pro-inflammatory mediators, TNF-alpha and interferon gamma in an in vitro cell line.[13] Taken in isolation, these findings would suggest that PCT may decrease NO production, thus ameliorating the circulatory failure of sepsis. The significance of these findings in light of data that suggest a detrimental effect of PCT in sepsis remains unclear.

In summary, the role of PCT in the host inflammatory response has yet to be clarified. It seems to exert an anti-inflammatory influence by inhibition of proximal mediators and of iNOS but its administration is associated with increasing mortality in animal models of sepsis.

Procalcitonin serum assay

PCT is measured in the serum using an immunolumimetric assay.[14,15] The assay employs two antigen specific monoclonal antibodies, one directed at the calcitonin region (which carries the luminescence label) and the other at the katacalcin region. The detection limit for the assay is 0.1 ng/mL and the coefficient of variation, between 1 - 1000 ng/mL, is 5 - 10%. The assay is also free of interference from the antibiotics, sedatives and vasoactive agents that are commonly used in the intensive care unit.

Elevated levels of PCT in the absence of an infection are observed in severe trauma, post cardio-pulmonary bypass and following the administration of OKT3.[16] PCT levels may also be elevated during the first 24 hr of life.[17] Patients with C-cell carcinoma of the thyroid and small cell lung cancer have also been reported to have elevated serum PCT concentrations.

PCT in critical illness

As a marker of infection

Much of the original prospective work on PCT as a diagnostic marker for infection was performed on paediatric populations. Assicot *et al* published data in 1993 demonstrating high levels of PCT in children with severe bacterial infections in contrast with those who had absent, localized or viral infections.[18] Levels were shown to decrease with antibiotic therapy. Gendrel *et al* subsequently showed that in neonates, PCT was a more accurate marker of bacterial infection than C-reactive protein.[19]

Following the initial work by Assicot's group, other published data supported the notion that serum PCT levels were dramatically elevated in patients with bacterial[18,20-22] and malarial infections.[12,23,24] The data in fungal sepsis are less convincing. Two clinical trials demonstrated a predictive role for procalcitonin as a marker of fungal sepsis in transplant recipients.[25,26] However, there are other reports documenting either little or no increase in procalcitonin in patients with disseminated fungal sepsis.[27,28] In contrast to bacterial and parasitic infections, only modest elevations of PCT are seen in viral infections. Consequently, serum PCT levels have been proposed as a marker to distinguish between viral and bacterial sepsis, particularly in

patients with meningitis.[21,29,30] However, it's utility in distinguishing between bacterial and viral pneumonias is less convincing.[31] The serum levels of PCT observed in various infections[18,20-22,24] are illustrated in Figure 1.

From these published data, it is evident that both bacterial infections and infections accompanied by serious systemic inflammation are associated with higher levels of PCT compared with viral and localised bacterial infections. Nevertheless, patients who have a localised infection without a general systemic response do not appear to have high levels of serum PCT.[18 20] As an extrapolation, patients who do not develop a marked systemic inflammatory response syndrome such as the elderly or the malnourished patient may not generate a significant PCT response, although this has not been tested. There are also data to show that greater elevations in PCT are observed in Gram-positive than Gram-negative meningitis.[32] This might be of relevance in the neurosurgical critical care unit, where patients are at risk of nosocomial meningitis. Importantly, the threshold value of PCT indicative of infection varies from one study to another. In children, a value of 5 ng/mL has been reported to identify bacterial sepsis with positive and negative predictive values of 100% and 82% respectively, compared with C-reactive protein where the corresponding values were 90% and 36%, respectively.

PCT as a marker of infection in oncology, transplantation and immunodeficient states

Serum PCT levels are useful in patients with solid tumours (as a marker of bacteraemia),[33] in liver transplantation (to distinguish between infection and rejection),[34] in haemodialysis (to identify infective complications)[35] and in burns patients (to diagnose superinfection).[36] One category of patients in whom infection is notoriously difficult to diagnose is the post chemotherapy neutropaenic group. Giamarellos-Bourboulis *et al*,[37] examined the sensitivity of PCT as a marker of infection in 115 post-chemotherapy neutropaenic patients presenting with fever. The value of PCT as a marker of infection was strongest on the first day of febrile neutropaenia. Median values for bacteraemic patients and those with localised bacterial infections were 8.23 ng/mL and 0.86 ng/mL respectively ($p = 0.017$). At a cut-off of 2 ng/mL, PCT had a sensitivity of 91%, specificity of 87% and a negative predictive value of 77% for the diagnosis of severe sepsis. In addition, 60% of patients with a pyrexia of unknown origin who responded clinically to empirical antibiotic therapy had PCT levels > 0.5 ng/mL, compared with 6.7% of those with a pyrexia of unknown origin who did not respond to antibiotics. In all cases, clinical resolution of infection was accompan-ied by a rapid fall in PCT levels to values similar to control

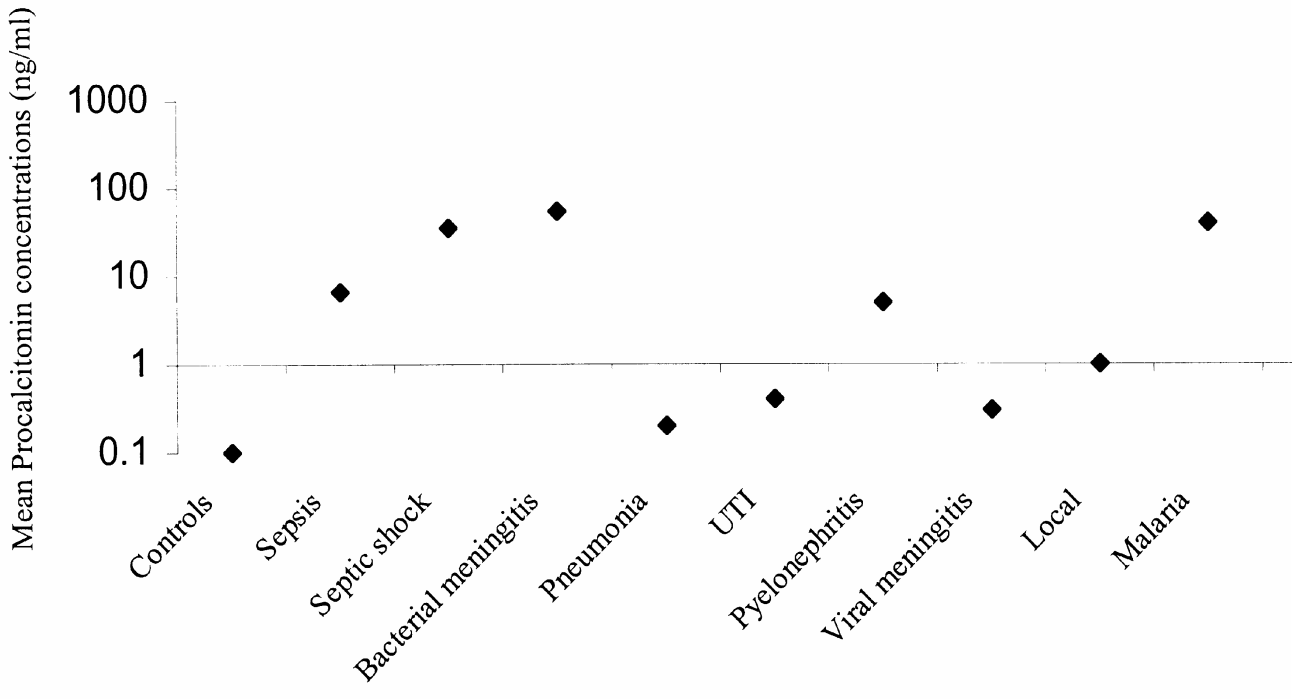

Figure 1. Serum procalcitonin levels reported in various disorders

values by the second day of treatment. Conversely, persistence of infection was associated with a higher PCT level

Trends in procalcitonin levels

Serial increase in PCT levels suggests an increasing severity of the inflammatory response to infection. In a study of septic patients, procalcitonin levels decreased during the course of the illness in survivors compared with non-survivors.[18] High levels of PCT or a progressive increase in PCT concentrations portend a poor prognosis, whilst successful resolution of infection is accompanied by a fall in serum procalcitonin.[10,12]

Marker of systemic inflammatory response syndrome

The systemic inflammatory response syndrome (SIRS) is a frequently encountered clinical entity in the medical and surgical intensive care unit, and is a feature of a wide variety of infectious and non-infectious insults.[10,38,39] Twenty five to forty nine percent of patients with SIRS have a clinical infection. Of those patients with sepsis, only 10 - 40% have a bacteraemia.[10,38,39] Sepsis is a common cause of morbidity and mortality in the intensive care unit. It is important to differentiate non-infectious SIRS from infectious SIRS for two reasons: a) early diagnosis and appropriate treatment of sepsis has been shown to reduce mortality, and b) inappropriate use of antibiotics (which carries with it problems of cost and emerging antibiotic resistance) may be minimised.

The ability of PCT to distinguish between infectious and non-infectious SIRS has been examined in a number of studies. It has been shown repeatedly to have a high sensitivity and specificity in discriminating between infectious and non-infectious SIRS and has been correlated with disease severity and patient outcome. The sensitivity and specificity of various cut-off values of PCT for differentiating infectious from non-infectious SIRS is shown in Figure 2.[21,40-43] The important point to note, however, is that the threshold value which predicts a high likelihood of infection appears to vary between studies.

In acute pancreatitis, serum PCT levels seem to distinguish between infected and sterile pancreatic necrosis (a common diagnostic problem in critical illness) with a high degree of specificity and sensitivity.[40] Other uses include a marker of infective SIRS[44,45] in post cardiac surgical patients and to distinguish between bacterial and non-bacterial causes of acute respiratory distress syndrome.[46]

Procalcitonin compared with other markers of inflammation

Not surprisingly, the diagnostic sensitivity and specificity of PCT has been compared with other acute phase reactants in their ability to diagnose sepsis.[38,39] Whilst some studies suggest that PCT is more sensitive and specific for the diagnosis of infection compared with C-reactive protein,[38,39,47] IL-6,[48] and IL-8[40,48] in a variety of clinical situations, other data dispute this

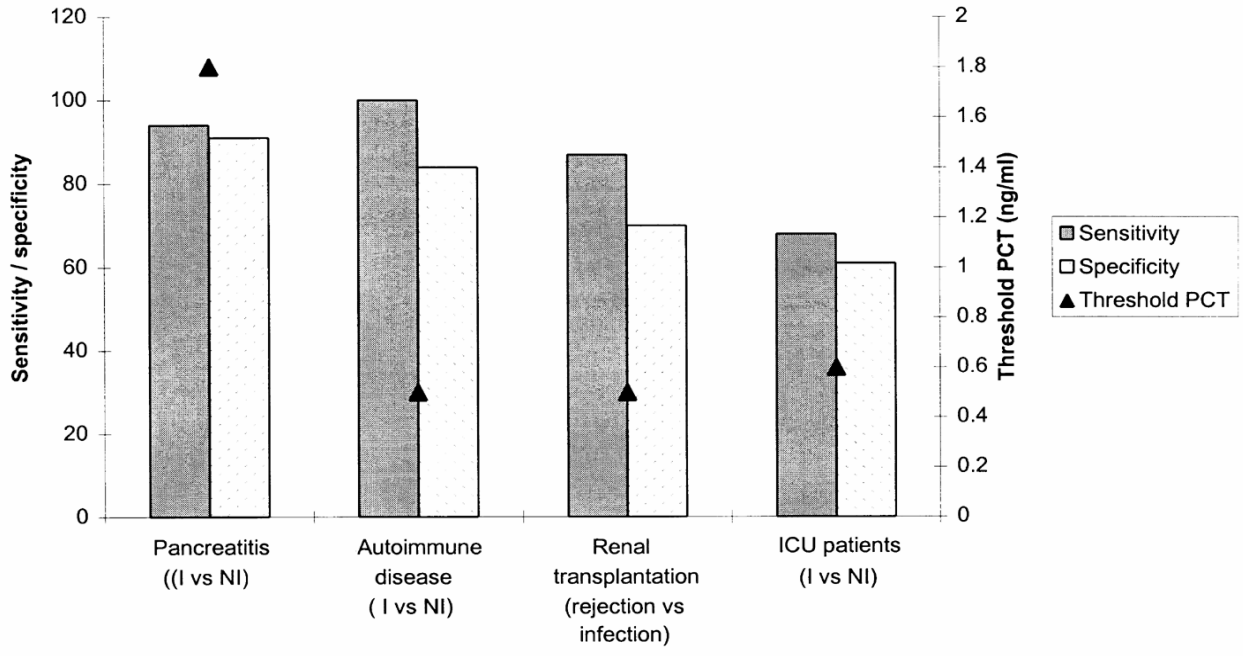

Figure 2. Specificity and sensitivity of serum procalcitonin levels reported in controls and various disorders (I = infectious, NI = non-infectious).

claim. Muller *et al*,[38] enrolled 101 consecutive adult patients admitted to a medical intensive care unit with a predicted length of stay greater than 24 hr and divided them according to diagnoses: no SIRS and no infection, SIRS and no infection, sepsis, severe sepsis and septic shock. At a cut-off of 1.0 ng/mL, PCT levels were significantly elevated in patients with sepsis, severe sepsis and septic shock compared with those without SIRS or infection. PCT was the most accurate laboratory test variable for the diagnosis of infection with a sensitivity of 89%, specificity 94%, negative predictive value 90% and positive predictive value 94%, and was superior to CRP, IL-6 and serum lactate levels. PCT levels were also significantly higher in non-survivors.

In a recent well-conducted prospective blinded trial by Harbarth *et al*,[49] the investigators measured PCT, IL-6, IL-8 and CRP levels in 78 consecutive patients admitted to a joint medical and surgical intensive care unit with SIRS. Sixty patients (77%) had clinically suspected infection of which 44 had microbial infection and 23 had bacteraemia. Median PCT concentrations were 0.6 (range 0 - 5.3) ng/mL in SIRS, 3.5 (range 0.4 - 6.7) ng/mL in sepsis, 6.2 (range 2.2 - 85) ng/mL in severe sepsis and 21.3 (range 1.2 - 654) ng/mL in septic shock. At a cut-off value of 1.1 ng/mL, PCT was shown to yield a sensitivity of 97%, specificity of 78% and area under the receiver operating curve 0.92 (CI 0.85 - 1.0) to differentiate patients with SIRS from those with sepsis, severe sepsis and septic shock. The serum level of PCT was a stronger predictive marker than IL-6 and IL-8. The authors also noted that a slow decrease or no decrease in PCT levels 48 hr after admission was correlated with a poor outcome. In those who died, the serum PCT level never fell below 1.1 ng/mL except for one time point in one patient. Four patients had a recurrent sepsis which were associated with further spikes in PCT levels.

There is no agreement, however, regarding the benefit of PCT compared with C-reactive protein for investigation of SIRS. In a study of 101 patients, Suprin *et al*,[50] concluded that although C-reactive protein and PCT levels were both significantly elevated in patients with sepsis, C-reactive protein, at a cut-off of 100 mg/L had a greater sensitivity and specificity than PCT (cut-off 2 ng/mL) for discriminating between sepsis and non-septic SIRS: 70% vs 65% and 74% vs 70%. A prospect-ive observational study by Ugarte *et al*,[41] showed that as a marker of infection and compared with C-reactive protein, PCT had a lower sensitivity (67.6% vs 71.8%) and specificity (61.3% vs 66.6%).

In contrast to C-reactive protein, however, PCT was significantly elevat-ed in bacteraemic patients and in non-survivors leading the authors to conclude that although PCT was inferior as a marker for infection, it was a useful prognostic indicator. The authors also suggested that combining PCT and C-reactive protein measurements might improve the diagnostic specificity of PCT.

PCT in surgery, trauma and other conditions

PCT levels are modestly elevated in a variety of non-infectious conditions including non-infectious SIRS,[49] burns (especially electrical and inhalation burns),[36] cardiopulmonary bypass,[44,45] heat stroke[51] and in cardiogenic shock.[52] Trauma and elective surgery have also been shown to induce elevated levels of PCT.[53,54] Increases in PCT are also significant after bowel surgery suggesting that bowel manipulation and endotoxaemia might play a crucial role in the genesis of elevated PCT. Meisner *et al*,[53] in a follow up of 113 patients, who underwent both minor and major procedures reported that in patients undergoing cardio-thoracic and bowel surgery, serum levels in excess of 2 ng/mL were seen in 8% and 25% of patients, respect-ively with the highest seen after bowel anastamosis (5.76 ng/mL). The peak values in PCT after cardiac surgery are on the first post-operative day and are in the order of 1.08 ± 1.36 ng/mL[45] and 0.9 ± 0.7 ng/mL.[55] PCT has been shown to be a useful marker of post-operative infection, and to discriminate between bacterial infection and transplant rejection or viral infection.[26,45]

Wanner *et al*,[54] studied 405 patients to ascertain the usefulness of PCT in the posttraumatic period to diagnose sepsis and the multiple organ dysfunction syndrome. They confirmed that PCT correlated with injury severity according to the ISS but determined that in low-ISS (> 25) and high-ISS (≤ 25) groups, PCT values at days 1 and 3 were significantly elevated in those who developed sepsis compared with those who did not. They concluded that at a cut-off of 1.5 ng/mL (peak values day 1 or day 3), PCT could be used to discriminate sepsis from non-infectious SIRS with 3 or 4 criteria with a sensitivity 76% and a specificity of 77%.

Whilst the above data support the usefulness of PCT in trauma and in post operative states as a marker of sepsis, appropriate consideration will need to be given to baseline increments in PCT concentrations in these conditions, even in the absence of sepsis.

Procalcitonin in neurosurgical critical care

We are currently undertaking a study looking at serum PCT concentrations in neurosurgical critically ill patients (e.g. patients with isolated head injury and subarachnoid haemorrhage). The preliminary data ($n = 22$) reveal that procalcitonin is elevated in $> 50\%$ of patients (0.51 - 71 ng/mL). Two thirds of these patients have an elevated PCT concentration within the first 24 hr of admission. The significance of this is unclear.

CONCLUSION

The advent of serum PCT as a marker of infection represents a new strategy in the diagnosis of sepsis. The usefulness of serum PCT measurements as a marker may be summarised as, 1) to distinguish between infectious and non infectious causes of SIRS, 2) to differentiate between bacterial and viral sepsis, and 3) to assess the severity of infection and judge the response to therapy. However, there are caveats. Firstly, a number of non-infectious conditions can give rise to elevations in PCT levels and should not necessarily be used as an indication to commence antimicrobial therapy. Secondly, the cut off value of PCT giving the optimum sensitivity and specificity for the diagnosis of infection varies with different conditions. Thirdly, localised infections may cause no increase in PCT levels. Finally, a falling PCT level in response to antibiotic therapy does not necessarily imply eradication of infection, but merely that the systemic response is under control.

Concerning the function of PCT, a number of unanswered questions remain. For example, what is the biological role of PCT? What are its target receptors? Does it have any protective value? Answers to these questions might enhance the value of assaying this peptide.

Received: 19 November 2001
Accepted: 28 November 2001

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