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Procalcitonin as an acute phase marker

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SUMMARY. Procalcitonin is a 14-kDa protein encoded by the *Calc-1* gene along with calcitonin and katacalcin. The function and regulation of this protein are quite different from those of the other gene products. Blood concentrations of procalcitonin are increased in systemic inflammation, especially when this is caused by bacterial infection. Studies of its behaviour in patients with bacterial sepsis have led to the proposal that it may be a useful marker of systemic bacterial infection, with greater specificity and sensitivity than acute phase proteins such as C-reactive protein.

INTRODUCTION

In clinical practice, two major diagnostic problems surround the management of patients with infection. The first is the distinction between infection *per se* and infection accompanied by inflammation with all its systemic effects, sepsis, or the systemic inflammatory response syndrome (SIRS). The systemic inflammatory response syndrome, sepsis and septic shock probably represent stages in the inflammatory response to infection, and in many infectious states it is the presence of SIRS and its severity which determines outcome. The pathophysiological effects of SIRS can be seen clinically and its presence determined with reasonable confidence (*see* Box 1) but its severity and prognosis are more difficult to assess.[1] The second challenge is the distinction between SIRS caused by infection and that caused by other causes such as trauma or immunological processes like rejection and immune complex disease.

Inflammation resulting from any form of tissue injury is accompanied by production of cytokines and acute phase proteins, the measurement of which may be used to indicate the presence of inflammation and its extent of severity. In some instances the differential response of certain acute phase proteins or

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BOX 1. *Definitions of the Consensus Conference of the American College of Chest Physicians*[1]

Systemic inflammatory response syndrome (SIRS)
Two or more of the following:
- Temperature $>38°C$ or $<36°C$
- Heart rate >90 beats/min
- Respiratory rate >20 breaths/min
- White blood cell count $>12{\cdot}0 \times 10^9$/L, $<4{\cdot}0 \times 10^9$/L, or $>0{\cdot}1$ immature forms (bands)

Sepsis
SIRS plus a documented infection (positive culture for organism)

Severe sepsis
Sepsis associated with organ dysfunction, hypoperfusion abnormalities or hypotension (Hypoperfusion abnormalities include, but are not limited to, lactic acidosis, oliguria or an acute alteration of mental status)

Septic shock
Sepsis-induced hypotension despite fluid resuscitation, plus hypoperfusion abnormalities

Culture-negative sepsis
SIRS plus empirical antibiotic treatment for a clinically suspected infection in which all cultures were negative

Culture-negative severe sepsis
SIRS associated with organ dysfunction, hypoperfusion abnormalities or hypotension

Culture-negative septic shock
SIRS associated with hypotension despite fluid resuscitation, plus hypoperfusion abnormalities. All cultures were negative, yet empirical antibiotic treatment for a clinically suspected infection has been prescribed

cytokines may give an indication of the nature of the inflammatory process or its complications; however, the response is generally very similar, regardless of cause.[2]

Since the early 1990s there has been mounting interest in the question of whether procalcitonin (PCT) is a specific marker of bacterial infection. Many studies have been carried out to address the key questions but, not surprisingly, they have often given conflicting results. The literature is now too large to list in its entirety, so we have extracted the essence of what we can conclude at this stage about the usefulness of PCT measurement in infection and sepsis.

MOLECULAR BIOLOGY OF PROCALCITONIN AND ITS SOURCE OF PRODUCTION

Procalcitonin was originally described in 1984 as a 116-amino acid protein with a molecular mass of 14·5 kDa.[3] The PCT gene, referred to as *Calc-1*, is located on chromosome 11p15.4 and was sequenced in 1989.[4] The promoter has sites for basal transcription factors but, more interestingly, also has sites for NF$\kappa\beta$ and AP-1, factors induced under inflammatory conditions. The *Calc-1* gene produces two different transcripts by tissue-specific alternative splicing (*see* Fig. 1).[5,6] The first, derived from exons 1–4 of the 6 exons, codes for prePCT, a 141-amino acid peptide which has a 25-amino acid hydrophobic signal peptide. In the C-cells of the thyroid this is proteolytically processed to produce an N-terminal fragment (57 amino acids), calcitonin (32 amino acids) and katacalcin (21 amino acids). This pathway is constitutively active and results only in the secretion of calcitonin. However, the presence of a signal peptide allows PCT to be secreted intact, after glycosylation, by other cells (see below). It is increasingly evident that PCT and calcitonin have very different functions. The second transcript is alternatively spliced to contain exons 1, 2, 3, 5 and 6 and codes for the calcitonin gene-related peptide, which is widely expressed in nerves in the brain, blood vessels and gut. It may have roles in immunomodulation, neurotransmission and vascular control.[7–9]

The clear demonstration of a cellular origin for secreted PCT has proved elusive. PCT is

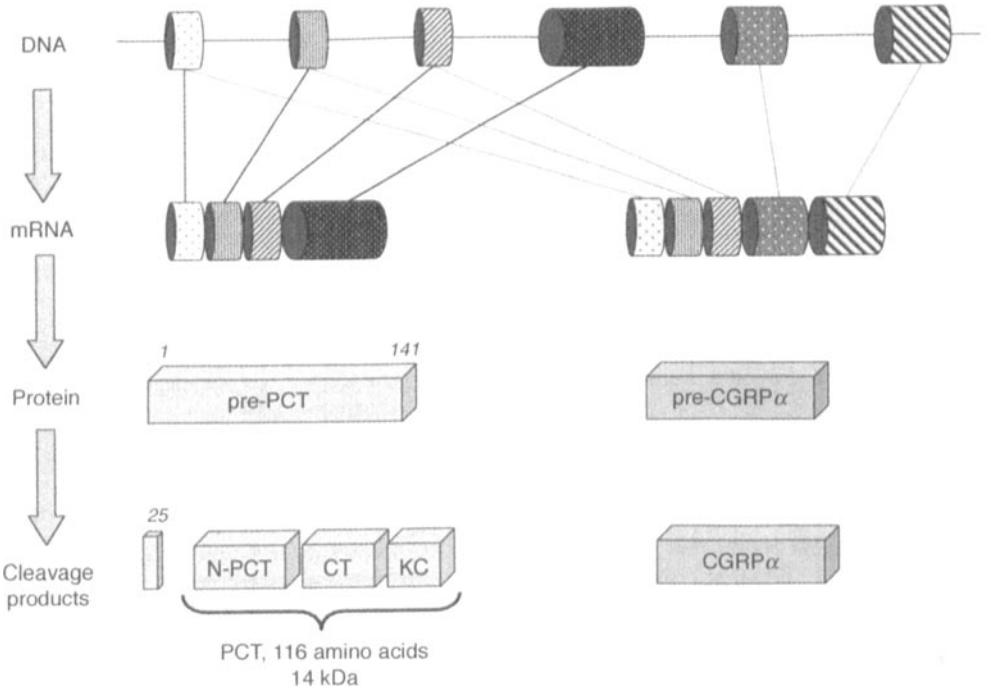

FIGURE 1. *Structure and alternative splicing of the* Calc-1 *gene (modified from ref 26 with permission). Stippled areas represent exons and numbers refer to amino acids. pre-PCT = preprocalcitonin; N-PCT = N-terminal procalcitonin; PCT = procalcitonin; CT = calcitonin; KC = katacalcin; pre-CGRP = pre-calcitonin gene-related peptide; CGRP = calcitonin gene-related peptide.*

present in the blood in sepsis and levels rise independently of calcitonin; in addition, PCT levels were elevated in a septic thyroidectomized patient,[10,11] which strongly suggests that thyroid C-cells are not the site of origin of PCT. PCT was first demonstrated from medullary thyroid carcinoma,[12–14] which secretes all the biosynthetic pathway products and has been detected in homogenates of human small-cell lung carcinoma cell lines.[15] Calcitonin and related peptides have been found in human neuroendocrine lung cells.[16,17] Procalcitonin mRNA is expressed in human peripheral blood mononuclear cells, and various pro-inflammatory cytokines and lipopolysaccharides (LPS) have a marked stimulatory effect. About one-third of unstimulated human lymphocytes and monocytes contain immunologically demonstrable PCT protein; this is only marginally induced by bacterial lipopolysaccharide,[18–20] but the monocytes from a patient with septic shock showed higher basal levels and increased PCT content upon stimulation with LPS.[19] In another study, peripheral blood mononuclear cells failed to release the protein in response to LPS;[21] the reasons for this discrepancy are unclear. Incubation of slices of human liver with interleukin-6 (IL-6) and tumour necrosis factor-α (TNF-α) results in more than twice as much PCT in the medium, whereas serum amyloid A protein (SAA) and C-reactive protein (CRP) concentrations increased only modestly and only in response to TNF-α.[22] Thus, at present, it is not clear where the considerable secretion of PCT in sepsis comes from, but monocytes and an 'acute phase' origin from the liver are candidates.

It is clear that bacterial endotoxin releases PCT into the circulation. Healthy volunteers injected with *Escherichia coli* endotoxin[10] felt ill within 1 h of the injection, became febrile within 1–2 h and developed chills, rigors and myalgia in 1–3 h. PCT was not detectable in the plasma at 2 h but was consistently detected at 4 h, rising rapidly at 6 h and remaining elevated at 8 and 24 h. The half-life is estimated to be 25–30 h. Plasma TNF-α levels increased sharply at 1 h, peaked at 2 h, and declined to baseline by 6 h. Plasma IL-6 levels peaked at 3 h and returned to baseline by 8 h. The elevation of plasma PCT occurs shortly after the cytokine levels have peaked, which raises the question of whether these cytokines may be the mediators of PCT elevation. This question has been addressed in cancer patients treated with recombinant human (rh) TNF-α and melphalan by isolated limb perfusion (see below) or rhIL-6 intravenously and subcutaneously.[22] Plasma PCT rose after rhTNF-α perfusion within 3·5 h, peaking at 8 h, whereas plasma CRP and SAA reached half-maximal values only at 20 h. The response of PCT to IL-6 was much less dramatic and slower. Another study[23] of rhTNF-α and melphalan administration via isolated limb perfusion showed similar results and also showed that melphalan alone caused little response. Furthermore, levels of IL-6 and IL-8 were elevated after rhTNF-α perfusion and reached their peak several hours before PCT. We can conclude that elevation of serum levels of PCT is mediated, at least in part, directly or indirectly, by the cytokines rhTNF-α and rhIL-6. C-reactive protein and SAA respond to the same stimuli but more slowly. Thus, it is clear that PCT synthesis may be induced in the absence of bacterial products.

The functions, if any, of PCT in sepsis are equally elusive. PCT has been shown to inhibit prostaglandin and thromboxane synthesis in lymphocytes *in vitro* and to attenuate the LPS-related stimulation of TNF production in whole-blood cultures.[24] *In vivo*, Nylen *et al.*[25] have shown that administration of recombinant human PCT to septic hamsters resulted in an increased mortality which was reversed by administration of neutralizing antibodies. The possibility that PCT has a role to play in the physiology of sepsis is supported by the sequence homologies[26] between PCT and cytokines such as TNF, IL-6 and granulocyte colony-stimulating factor.

ASSAYS FOR PROCALCITONIN MEASUREMENT

Ghillani *et al.*[27] developed a specific assay with a monoclonal antibody directed against residues 96–106 of PCT as the capture antibody and another directed against residues 70–76 as the tracer which detected only intact PCT. The sequence 70–76 is part of the calcitonin molecule whereas 96–106 is part of the katacalcin molecule. To date, only one kit is commercially available (Lumitest PCT, Brahms Diagnostica, Berlin, Germany).[28] This test is an immunoluminometric assay using a capture antibody directed against residues 96–106 and a tracer antibody directed against the 70–76 sequence. While there are certainly disadvantages in this monopoly, it does have the advantage that the

majority of studies of the clinical usefulness of PCT use the same assay and reference material and are thus directly comparable. The assay has a small sample volume requirement of 20 μL serum or plasma.

Up to now, little work has been devoted to the practical aspects of PCT measurement using this kit. Meisner and colleagues[29] demonstrated that freezing and thawing cycles had no effect on PCT concentration. After storage of plasma for 24 h at room temperature there was a loss in PCT concentration of 12·4% and of 6·3% at 4°C. Arterial and venous samples did not differ in their concentrations of PCT. Of the anticoagulants only lithium heparin anticoagulation resulted in a difference from serum (7·6% higher value). The authors suggest using EDTA-plasma, storing samples at room temperature and measuring within 4 h of collection. In another study[30] good precision was found [inter-assay coefficient of variation (CV) varied between 7·2% at a serum PCT concentration of 1·2 μg/L and 3·2% at a concentration of 52 μg/L], no interference from haemoglobin, bilirubin or triglycerides was observed (except in the case of gross haemolysis) and the detection limit was calculated as 0·24 μg/L. Despite this, many authors of clinical studies quote a lower limit of detection, of 0·1 μg/L, which is in fact the limit of linearity of the standard curve. Analytical performance is satisfactory for a manual immunoluminometric assay but one of the major limitations for using this kit is the 2 h necessary for completing the assay. In the majority of cases, PCT is needed in critical clinical contexts where bacterial infection is suspected and constitutes an important mortality risk. In this respect, Brahms Diagnostica has recently proposed a bedside test for semi-quantitative measurement in intensive care units. Furthermore, an enzyme-linked immunosorbent assay kit will soon be available.

From the many studies cited below we can conclude that the 'normal' plasma/serum levels of PCT in healthy adults, measured using this kit, are $<0{\cdot}5$ μg/L. It is clear that the published studies have sometimes employed plasma and sometimes serum, both frozen and fresh. Some studies do not specify which has been used, and in that case we will use the term 'blood PCT'. Levels below the calculated detection limit of Monneret *et al.*,[30] i.e. 0·24 μg/L, are frequently quoted, but whether much confidence can be placed in these low levels is debatable.

SERUM AND PLASMA PROCALCITONIN IN INFECTION AND INFLAMMATION

The first seeds of interest in the relationship between PCT and infection came from early studies using assays for 'calcitonin-like activity'.[31] However, it was Assicot *et al.*[11] using a specific assay[27] together with an assay able to detect calcitonin and N-proCT$_{1-57}$, who first investigated PCT in infection. Procalcitonin measurements in the serum of 79 children with suspected infections showed that PCT alone was raised during septic conditions and burns and that the serum levels related to the severity of microbial invasion. In 21 uninfected children the serum PCT was $<0{\cdot}1$ μg/L, whereas in 19 patients with severe bacterial infections it was 6–53 μg/L, decreasing rapidly during antibiotic therapy. In local infection and in 18/21 patients with viral infection, serum PCT was low – between 0·1 and 1·5 μg/L. Among nine severely burned patients the time course of PCT concentration was closely related to the onset of infectious complications and acute septic episodes. Concentrations of calcitonin were normal in all subjects. This thorough prospective study led to the proposal that serum PCT could be a new marker for severe generalized infections or sepsis.[28] However, it is clear even in this first study that an increase in serum PCT does not of itself indicate sepsis; levels were raised in two patients with uncomplicated burns, to 2 μg/L and 3 μg/L. The key question is therefore whether levels can be adopted for different clinical situations which allow the reliable diagnosis of infection and whether the levels relate to the severity of SIRS and have prognostic value.

Markedly raised serum PCT, even as high as 1000 μg/L, can occasionally be found in patients without evidence of sepsis.[32] One of the problems is the difficulty of defining the absence of sepsis. However, it is clear that SIRS, for whatever cause, is associated with elevated levels of PCT which relate to the severity of the systemic response. In most situations the highest levels are associated with sepsis, and this has given rise to a plethora of suggested levels or cut-off values to be used in detecting it. Such cut-off values are essential if PCT measurement is to be used for this purpose but the values must be context-specific, as the non-infectious complications of each clinical scenario vary.

PROCALCITONIN AS A MARKER OF INFECTION FOLLOWING SURGERY

Surgery often forms a good model for the identification of laboratory markers of infection, as values prior to the onset of surgical inflammation and infection can be obtained. Reith *et al.*[33] showed a marked increase in blood PCT, from 0·19 to 1·2 μg/L, after uncomplicated surgery, whereas with complications the increase was from 0·36 to 6·9 μg/L. Meisner *et al.*[34] showed that patients undergoing minor aseptic operations had increased plasma PCT in about one-third of cases, but seldom to levels above 1 μg/L. Cardiac and thoracic surgery gave rise to levels above 2 μg/L in 8% of patients, while after abdominal surgery with intestinal anastamosis such levels were seen in 25%. PCT concentrations above 10 μg/L were very unusual in patients with an uncomplicated post-operative course, while 92% of patients with an abnormal post-operative course had an increased plasma PCT.

The systemic inflammatory response syndrome commonly follows coronary artery bypass grafting (CABG) and may be associated with pulmonary damage or infection. Boeken *et al.*[35] found no significant elevation of blood PCT in patients with uncomplicated CABG, whereas in patients who developed SIRS the levels rose to values not exceeding 0·9 μg/L. In a group developing severe sepsis, blood PCT rose to 18·6 ± 6·3 μg/L. In another study,[36] uncomplicated CABG patients had serum PCT of 0·9 ± 1·0 μg/L; SIRS developed in 42% of patients who had values of 0·9 ± 0·7 μg/L. Half of these patients developed acute lung injury associated with serum PCT ranging from 5·1 to 14·3 μg/L. Rothenburger[37] found seven systemic infections in a group of 563 patients undergoing CABG. Their median serum PCT was 10·86 μg/L with an interquartile range of 3·28–15·13 μg/L. Using receiver operating curve analysis (ROC) with a threshold value for PCT of 4 μg/L, they found a positive predictive value for sepsis of 0·86 and a negative prediction of 0·98. At a threshold of 180 mg/L, CRP gave values of 0·35 and 1·00, respectively. Unfortunately, lung injury did not feature in this study, which highlights the problems of inherent dissimilarity between case groups.

Thus, systemic infection and lung injury each result in high serum PCT following surgery and it would be difficult to separate them on the basis of the PCT level. High levels are also seen in inhalation injuries following burns.[38–40] Despite this, it would seem that PCT levels above 5 μg/L should be an indication for further investigation of a post-operative patient.

PROCALCITONIN AS A MARKER OF INFECTION IN THE INTENSIVE CARE UNIT

Several studies have addressed the issue of which markers best indicate severity of SIRS and the onset of sepsis in the patient in the intensive care unit following major trauma or surgery. It is important to examine the findings in some detail as they differ in case mix and selection.

A small study of 15 patients with septic shock, seven patients with cardiogenic shock and seven patients with bacterial pneumonia[41] showed that plasma PCT levels increased to 72–135 μg/L in septic shock, compared with means of 1·4 and 2·4 μg/L in cardiogenic shock and bacterial pneumonia, respectively. At a threshold of 1·5 μg/L plasma PCT had a positive predictive value of 86% and a negative predictive value of 92% for septic shock. However, plasma PCT was not evaluated prospectively and the numbers are small.

Mimoz *et al.*[32] studied patients admitted to the surgical intensive care unit in the first 3 h after trauma. The majority developed SIRS and one-third developed multiple organ dysfunction syndrome (MODS). Following trauma, MODS is a bimodal phenomenon. In the first 3 days after trauma, organ dysfunction is influenced by the systemic response to tissue damage and shock, without evidence of infection. Less severe trauma can create an environment where a subsequent secondary inflammatory insult (which in other circumstances may be innocuous) may precipitate severe SIRS or MODS. For that reason this study only examined serum PCT during the first 3 days and found that a significant relationship existed between the early peak of serum PCT and injury score and amount of fluid replacement. In 3/21 patients, PCT levels were grossly elevated to 162, 925 and 1097 μg/L in the absence of any evidence of infection.

Oberhoffer *et al.*[42] studied 242 patients admitted to the intensive care unit and categorized for infection. They found that the ability of infection markers to predict survival was best for serum PCT (sensitivity 88%, positive predictive value 57%), good for serum CRP (sensitivity 66%, positive predictive value 51%) and poor

TABLE 1. *Mean procalcitonin (PCT) values of the maxima from day 0 and 1 in patients with systemic inflammatory response syndrome (SIRS) and sepsis*

Group	Mean PCT (μg/L)	SD (μg/L)	*n*
SIRS only	0·6	2·2	215
SIRS + infection	6·6	22·5	53
SIRS + septicaemia	8·5	19·0	49
SIRS + septic shock	34·7	68·4	20

SD = standard deviation. Modified with permission.[44]

for leukocyte count and body temperature. Schröder *et al.*[43] examined the relationship of serum levels of TNF, IL-6, CRP and PCT to survival in patients with septic shock and found that only PCT and IL-6 showed a difference between survivors and non-survivors; of these, serum PCT was the most reliable because patients who died demonstrated significantly higher levels than did survivors at any time point.

In 1996 Al-Nawas *et al.*[44] conducted a prospective study of 337 hospitalized adult patients fulfilling the SIRS criteria. Patients with microbiologically documented infection showed peak values of plasma PCT as high as 30 μg/L at day 3, which rapidly decreased to normal on resolution of infection, and there was a strong relationship of peak plasma PCT with severity. Patients with SIRS in the absence of proven infection showed much lower levels but a few patients had high values, in one case nearly 30 μg/L. The results on days 0 and 1 (the most clinically useful) are summarized in Table 1. Predictive values at different levels of plasma PCT on day 0 and 1 are shown in Table 2.

In a study of 205 consecutive patients admitted to the intensive care unit (111 infected and 79 non-infected), Ugarte *et al.*[45] set out to determine the value of PCT as a marker of infection. Sepsis was defined using the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference definition of sepsis. Blood for CRP and PCT was taken every day and measurements made after storage of samples frozen for 2 weeks. The best cut-off values were 0·6 μg/L for PCT and 79 mg/L for CRP at day 0. The predictive values are shown in Table 2 and it can be seen that PCT is less sensitive and specific than CRP. Blood PCT levels are however much higher in shock than are CRP levels and relate to severity and outcome. The authors recommend that if the CRP level is >79 mg/L the diagnosis of infection can be further confirmed by PCT >0·6 μg/L. In contrast, another study of 101 critically ill patients, 58 of whom were infected, found that PCT had a better predictive value for sepsis than did CRP and showed a relationship to survival.[46]

In a consecutive series of 405 trauma patients, Wanner and colleagues[47] measured serial plasma PCT values over 3 weeks and documented the incidence of SIRS, sepsis and MODS. The study benefits from a large sample size and range of trauma severity but suffers from being retrospective. Mechanical trauma led to increased plasma PCT dependent on the severity of injury, with peak values on days 1 and 3 and a continuous decrease within 21 days after

TABLE 2. *Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for infection, from various studies*

Ref	Marker cut-off		Time	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
44	PCT	0·1 μg/L	Days 0 and 1	91	25	39	86
		0·3 μg/L		69	67	48	79
		0·4 μg/L		63	74	52	79
		0·5 μg/L		60	79	61	78
45	PCT	0·6 μg/L	Day 0	67·6	61·3	71·0	57·5
	CRP	79 mg/L		71·8	66·6	75·2	62·6
	PCT + CRP			60·0	82·3	82·5	59·6
	PCT and/or CRP			81·8	48·1	68·7	65·5
47	PCT	0·5 μg/L	Days 1 and 3	97·8	17·0	37·6	93·8
		1·5 μg/L		75·6	77·3	63·0	86·1
		3·0 μg/L		53·3	86·4	66·7	78·4

Ref = reference.

trauma. Patients who developed SIRS showed a significant increase of peak plasma PCT compared with patients without SIRS. The highest values early after injury were observed in patients with sepsis ($6{\cdot}9 \pm 2{\cdot}5\,\mu g/L$; day 1) or severe MODS ($5{\cdot}7 \pm 2{\cdot}2\,\mu g/L$; day 1) with a sustained increase for 14 days, compared with patients with an uneventful post-traumatic course ($1{\cdot}1 \pm 0{\cdot}2\,\mu g/L$). Moreover, increased plasma PCT during the first 3 days after trauma predicted severe SIRS, sepsis, and MODS. Predictive values for several cut-off points of maximum serum PCT level on day 1 and 3 are shown in Table 2.

What lessons can be drawn from these studies? Every study is different in its design, patient groups and cut-off values, and Table 2 shows that the predictive values differ considerably between studies. Nonetheless, it would be reasonable to conclude that PCT, possibly combined with CRP, provides a marker for sepsis. Serum or plasma PCT rarely rise above $12\,\mu g/L$ after trauma alone and rarely rise above $1\,\mu g/L$ in other non-infective conditions,[48] so levels above $10\,\mu g/L$ would be a strong indication for further investigation after trauma, and levels above $1{\cdot}5\,\mu g/L$ provide useful predictive values for sepsis. Most of the studies we have reviewed found that the relationship of the peak PCT level to prognosis may be useful in assessing the severity of SIRS and septic shock (*see* Table 1). In patients with multiple trauma, PCT always increases in the first few days after admission; this is due to cytokine production and the release of bacterial products from the gut. In this patient group, monitoring is helpful as PCT levels normalize rapidly in non-infectious conditions.

PROCALCITONIN IN NEONATES

In a prospective study of 177 newborn infants, Gendrel *et al.*[49] measured plasma PCT in uninfected patients and neonates with bacterial sepsis, bacterial colonization and acute viral infection. In the control group, the plasma PCT concentrations were $<0{\cdot}71\,\mu g/L$. Of 50 infants with neonatal distress, 48 had plasma PCT $<0{\cdot}40\,\mu g/L$ on admission and two had increased values of 2·70 and $2{\cdot}80\,\mu g/L$, respectively. Mean plasma PCT was slightly higher in the eight virus-infected infants and in the 15 infants with bacterial colonization – upper values were 1·5 and $1{\cdot}8\,\mu g/L$, respectively. All 18 infants with proven or suspected bacterial sepsis had high plasma PCT levels. Though the values are not given in the paper, it can be inferred from the figure that they are between 3 and $100\,\mu g/L$. The plasma PCT in the 13 infants with culture-positive sepsis did not differ significantly from values in the five infants with obvious clinical signs of infection but negative results on blood or cerebrospinal fluid culture. The PCT and CRP levels distinguished infants with bacterial sepsis from those in the other groups, but 4/18 neonates with sepsis had only slightly elevated CRP levels, overlapping the other groups, whereas PCT values showed no overlap.

This work has been extended by studies from our laboratory. We and others have shown a considerable physiological increase in plasma or serum PCT on day 1 of life in normal neonates.[50–52] Levels were: at birth, $0{\cdot}12$–$1{\cdot}1\,\mu g/L$; day 1, $0{\cdot}45$–$15{\cdot}2\,\mu g/L$; day 3, $0{\cdot}18$–$2{\cdot}2$.[50] Neonates suffering from respiratory distress syndrome showed a peak serum PCT in the first 2 days of life, steadily declining to normal thereafter, much like an exaggerated physiological response.[53] However, the PCT increase was to levels usually indicative of bacterial infection (up to $172\,\mu g/L$). In neonates with bacterial infection,[50] high serum PCT (up to $400\,\mu g/L$) correlated with bacterial invasion, as did CRP levels, but returned to normal more quickly on resolution. Unfortunately, two patients with septic shock had no elevation of PCT or CRP. In premature infants,[54] serum PCT was much higher in the infected group than in the non-infected (median $42{\cdot}0\,\mu g/L$ versus $4{\cdot}5\,\mu g/L$), but the values varied greatly in both groups. Taking a threshold value of $5\,\mu g/L$, sensitivity for the diagnosis of bacterial infection was 84% whereas specificity was only 50%, probably because of the high serum PCT we measured in neonates with respiratory distress syndrome or haemodynamic failure. Despite these findings, the very much higher levels of PCT seen in infections compared with the physiological peak are claimed to be useful[52] for the diagnosis of early- and late-onset sepsis in neonates at risk from bacterial infection. In a group of neonates with clinical signs of infection treated with antibiotics but with negative blood cultures, we found a median serum PCT of $60\,\mu g/L$ at 24 h and 6·5 at 72 h, which decreased on the third day of life.[55] These values were lower than our previously reported serum PCT concentrations in proven materno-foetal infection[50] but higher than the physiological peak.[52] The failure of levels to fall on the third day may be used to indicate

inappropriate antibiotic therapy, as even in respiratory distress syndrome a significant fall has occurred by this time. The relationship of neonatal to maternal serum PCT has been investigated by Assuma *et al.*[56] Serum PCT levels in babies at birth were significantly higher than in their mothers, with even larger differences at 24 and 48 h of age. The only clinical factor that significantly increased neonatal serum PCT at both 24 and 48 h of age was rupture of the membranes.

Procalcitonin may also be used to make a distinction between bacterial and viral meningitis. Gendrel *et al.*[57] found that neonates and children with acute bacterial meningitis had elevated plasma PCT (mean level, 54·5 μg/L; range, 4·8–110 μg/L), while levels in children with viral meningitis were low (mean level, 0·32 μg/L; range 0–1·7 μg/L).

Further studies are required to substantiate these conclusions but the use of PCT for the diagnosis and monitoring of infection in term infants is becoming established despite the fact that false negatives do occur.[50] However, at present there is insufficient evidence to justify withholding antibiotic treatment in the absence of a rise in serum or plasma PCT concentration. In addition, in premature neonates we must sound a note of caution as respiratory distress syndrome and haemodynamic failure may cause substantial elevations of PCT in the first 10 days of life, independent of any bacterial infection. This underlines the importance of sequential measurements.

PCT IN TRANSPLANT MONITORING

It is not surprising that PCT measurement has been used in an attempt to discriminate the SIRS of acute graft rejection from that of invasive bacterial infection. In patients with renal allograft rejection,[58] serum PCT concentrations did not differ significantly from those of healthy transplant recipients. However, PCT was clearly elevated with invasive bacterial infection and partial graft necrosis and very high levels were seen after treatment with the monoclonal anti-T cell antibody OKT3. The specificity for distinguishing invasive bacterial infection or partial graft necrosis from rejection was 0·7 for PCT (cut-off 0·5 μg/L) and 0·43 for CRP (cut-off 6 μg/L). Sensitivity was 0·87 for PCT and 1·0 for CRP. In cardiac transplant recipients suffering from bacterial, fungal, or protozoal infection,[59] plasma PCT concentrations were significantly higher than in healthy persons, but were not elevated in patients without evidence of infection. Levels higher than 10 μg/L indicated systemic infection and a decline in plasma PCT reflected successful antibiotic therapy. Procalcitonin was not elevated during acute rejection and was not affected by immunosuppressive drugs. Another study of cardiac transplant recipients[60] made similar observations and concluded that a plasma PCT of $<0{\cdot}8$ μg/L had a sensitivity for rejection of 100%, specificity 82% and predictive value 89%. At a cut-off of $>0{\cdot}5$ μg/L for systemic infections, all three criteria reached 89%. Surprisingly, after liver transplantation serum PCT was elevated in all patients (up to 40 μg/L) without any signs of systemic infection.[61] Serum PCT rapidly decreased to normal in cases with an uncomplicated course but persistence of raised levels or a repeated increase indicated severe systemic inflammatory complications, though it is not clear whether these were due to infection or other causes. These observations are interesting in view of the suggestion that the liver might be a source of PCT.[22]

CONCLUSIONS

The publications that we have discussed, in our view, reflect the most relevant areas for the use of serum or plasma PCT measurements in the immediate future. There are however many other studies on the use of PCT to diagnose bacterial infection in such conditions as acute pancreatitis, peritoneal dialysis, autoimmune disease and human immunodeficiency virus infection, amongst others.[62] Unfortunately, space does not allow us to review this literature. Our conclusions on the material that we have covered are:

- Serum or plasma PCT is modestly elevated in SIRS.
- Higher PCT levels occur in SIRS due to sepsis.
- PCT levels reflect systemic response to infection, not infection *per se*.
- Specificity for infection increases with higher PCT values. The best cut-off to be used should depend on the clinical situation.
- PCT levels relate to the severity of SIRS caused by sepsis and provide prognostic information.

- Lung damage due to inhalation injury or respiratory distress syndrome raises PCT levels.
- Sequential measurements are more useful than single values.
- PCT in general provides better sensitivity and specificity than CRP for diagnosis of infection and is a better prognostic indicator than CRP.
- PCT has a shorter half-life than CRP and better reflects outcome and response to antibiotics.
- After bacterial challenge plasma PCT rises more rapidly than CRP, which probably explains the higher sensitivity of PCT.
- PCT plus CRP may be more useful than either alone.

RECOMMENDATIONS FOR CLINICAL BIOCHEMISTS

At the present time we are lacking fundamental data about PCT, such as its site of synthesis, mechanism of induction and function in sepsis. Published studies are not comparable in their designs; this makes it difficult to define cut-off levels, and well designed multi-centre studies are urgently required. PCT is a fashionable marker but it will not remain so without more robust information. From a practical point of view, we can make the following recommendations:

- Cut-off values for clinical decision-making are essential and must be context-specific.
- 'Normal' values are in general $<0{\cdot}5\,\mu g/L$.
- Following surgery, transplantation and trauma:
  - In the first 4 days after trauma or surgery, levels may rise to $<10\,\mu g/L$. Levels higher than this suggest infection.
  - During the subsequent days, values should fall to $<1\,\mu g/L$. A PCT increase during this period strongly suggests bacterial infection.
- Neonates:
  - In the first 10 days of life, in the absence of infection or respiratory distress, levels are $<10\,\mu g/L$.
  - Subsequently, values are $<1\,\mu g/L$.

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