Procalcitonin assay in systemic inflammation, infection, and sepsis: Clinical utility and limitations

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Objective: **The use of procalcitonin (ProCT) as a marker of several clinical conditions, in particular, systemic inflammation, infection, and sepsis, will be clarified, and its current limitations will be delineated. In particular, the need for a more sensitive assay will be emphasized. For these purposes, the medical literature comprising clinical studies pertaining to the measurement of serum ProCT in various clinical settings was examined.**

Data Source and Selection: **A PubMed search (1965 through November 2007) was conducted, including manual cross-referencing. Pertinent complete publications were obtained using the MeSH terms *procalcitonin*, *C-reactive protein*, *sepsis*, and *biological markers*. Textbook chapters were also read and extracted.**

Data Extraction and Synthesis: **Available clinical and other patient data from these sources were reviewed, including any data relating to precipitating factors, clinical findings, associated illnesses, and patient outcome. Published data concerning sensitivity, specificity, and reproducibility of ProCT assays were reviewed.**

Conclusions: **Based on available data, the measurement of serum ProCT has definite utility as a marker of severe systemic inflammation, infection, and sepsis. However, publications concerning its diagnostic and prognostic utility are contradictory. In addition, patient characteristics and clinical settings vary markedly, and the data have been difficult to interpret and often extrapolated inappropriately to clinical usage. Furthermore, attempts at meta-analyses are greatly compromised by the divergent circumstances of reported studies and by the sparsity and different timing of the ProCT assays. Although a high ProCT commonly occurs in infection, it is also elevated in some noninfectious conditions. Thus, the test is not a specific indicator of either infection or sepsis. Moreover, in any individual patient, the precipitating cause of an illness, the clinical milieu, and complicating conditions may render tenuous any reliable estimations of severity or prognosis. It also is apparent that even a febrile septic patient with documented bacteremia may not necessarily have a serum ProCT that is elevated above the limit of functional sensitivity of the assay. In this regard, the most commonly applied assay (i.e., LUMItest) is insufficiently sensitive to detect potentially important mild elevations or trends. Clinical studies with a more sensitive ProCT assay that is capable of rapid and practicable day-to-day monitoring are needed and shortly may be available. In addition, investigations showing that ProCT and its related peptides may have mediator relevance point to the need for evaluating therapeutic countermeasures and studying the pathophysiologic effect of hyperprocalcitonemia in serious infection and sepsis. (Crit Care Med 2008; 36:941–952)**

KEY WORDS: procalcitonin; inflammation; infection; sepsis

In the past decade, there have been a large number of publications concerning procalcitonin (ProCT) as a serum marker of systemic inflammation, infection, and sepsis. Results from these studies vary greatly according to the type of protocol, diverse characteristics of the patients, clinical milieu, and conclusions drawn from the data. Although most reports were promising, some were extrapolated inappropriately to clinical usage. Moreover, some have reported disappointing results or unenthusiastic conclusions (1–7). The objective of the authors is to review the measurement of serum ProCT in several clinical settings, to discuss its clinical utility and its limitations, and to elaborate on the need for a more sensitive and practicable test that would enable serial determinations. Furthermore, although its use in infections and sepsis will be discussed in detail, it will be emphasized that elevations of serum ProCT are not specific for these conditions.

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Hyperprocalcitonemia in Neuroendocrine Cell Disorders

Initially, it was determined that levels of the mature 32-amino acid hormone, calcitonin (CT), and its related peptides are increased in the serum of some patients harboring neuroendocrine tumors (8) (Table 1). This increase occurred in persons with cancer of the neuroendocrine C-cells of the thyroid (i.e., medullary thyroid cancer) (9), in those with small cell cancer of the lung (10), and in those with a carcinoid tumor. Consequently, CT was established as a serum marker to assist in the diagnosis or follow-up of many of these patients and to evaluate their response to therapy (9, 11). Subsequently, it was demonstrated that not only the CT hormone but also its larger molecular weight precursors, in particular, the 116-aminoacid prohormone, ProCT, are increased in these conditions (12). Indeed, it now has been shown that an assay for ProCT may be as useful a marker for medullary thyroid cancer as is the assay for CT (13).

Remarkably, in these neoplastic conditions, increased levels of serum CT and

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Table 1. Comparison of procalcitonin assays[a]

Assay[b]	Source	Type of Test	Status	Peptides Identified	Low Assay Standard pg/mL	Functional Sensitivity pg/mL	Healthy Control[c] pg/mL	Assay Time
LUMItest[2]	BRAHMS	ILMA	Commercial	ProCT and CT:CCP1	80	500	235	2 hrs 45 mins
ProCa-S	BRAHMS	ILMA	Research	ProCT and CT:CCP1	5	20	31	3 hrs
PCT sensitive	BRAHMS	ILMA	Research	ProCT and CT:CCP1	5	50	13	3 hrs
Kryptor	BRAHMS	TRACE	Commercial	ProCT and CT:CCP1	20	60	53	50, 25–45 mins[d]
QPCT	BRAHMS	Solid-phase	Commercial	ProCT and CT:CCP1	(500)	(500)	(500)	Bedside
NProCT	Becker	ELISA	Research	ProCT and NProCT	10	20	33[e]	16–18 hrs

ILMA, immunoluminometric assay; ProCT, procalcitonin; CT:CCPI, the conjoined peptide consisting of calcitonin + calcitonincarboxypeptide 1 (see Becker et al (8)); NProCT, aminoprocalcitonin; TRACE, time-resolved amplified cryptate emission; ELISA, enzyme-linked immunosorbent assay. As shown above, no currently available commercial assay measures procalcitonin exclusively. All detect at least one other constituent of this prohormone. High-power liquid chromatography studies of calcitonin gene peptides extracted from concentrated normal human serum reveal very low levels of ProCT (2.46 pg/mL) along with its component peptides (NProCT, CT, and CCP1) (18). In hyperprocalcitonemic states, procalcitonin and its constituent peptides all may be increased to varying extent from patient to patient. Unless the hyperprocalcitonemia is due to secretion from a neuroendocrine tumor, the amidated free CT remains low. CT is not measured in any of the above assays. Because ProCT is always increased whenever NProCT and/or CT:CCP1 is increased, for simplicity of expression, the assay is referred to by all investigators as a "procalcitonin" assay. [a]Based on the assay performance from the authors' laboratory; [b]only the LUMItest is currently available in the US (data obtained from the manufacturer's data sheet); [c]discrepancy between functional sensitivity and healthy control values (LUMItest, PCT sensitive, Kryptor) imply great uncertainty in actual values; [d]first number is time until results are obtained for first sample, and second range is time for second sample and dilution, if necessary; [e]this level is 90% aminoprocalcitonin; based on chromatography studies, the actual mean level of ProCT in healthy controls is <4 pg/mL. ProCT + CT:CCP1 <5 pg/mL.

Table 2. Principal causes of hyperprocalcitonemia

- A. Neuroendocrine tumors
  - Medullary thyroid cancer
  - Small cell lung cancer
  - Carcinoid syndrome
- B. Noninfectious systemic inflammation
  - Inhalational injury
  - Pulmonary aspiration
  - Pancreatitis
  - Heat stroke
  - Mesenteric infarction
- C. Severe infection
  - Bacterial
  - Viral
  - Parasitic
- D. Sepsis
- E. Trauma
  - Mechanical injury
  - Burns
  - Surgery

its precursors do not seem to be detrimental, nor are there any observable clinical effects. Thus, patients with medullary thyroid cancer, whose sera often contain enormous levels of this family of peptides, may live for many years without signs or symptoms other than the mechanical effects of the primary or metastatic lesions (14).

Current ProCT Assay

Although it would be highly desirable, there is no assay (research or otherwise) that detects the 116 kDa ProCT peptide exclusively. Depending on the type of assay, all tests detect various portions of several CT precursors (Table 2). Moreover, the determination of minimally elevated values of serum ProCT and the reproducible detection of small changes from day to day require an assay that is very sensitive (15, 16). In 1995, the authors developed such an assay for the aminoterminus of ProCT that also detects the intact ProCT prohormone (17). This research assay quantitates normal levels (0.033 ± 0.003 ng/mL, 90% of which is aminoprocalcitonin) (18); its utility in evaluating systemic inflammation and sepsis has been reported in several publications (18–21). However, the assay utilized in the vast majority of studies throughout the world is the immunoluminometric PCT assay (i.e., LUMItest, BRAHMS, Henningsdorf, Germany), which detects the ProCT prohormone and the conjoined segment of CT and calcitonin-carboxyl-peptide I. Although the sensitivity of this assay is purportedly 0.08 ng/mL (i.e., the low standard provided), the functional sensitivity is ~0.5 ng/mL (Table 1) (21). Thus, any reference in the literature for this assay that specifies a ProCT level of <0.5 ng/mL is uncertain and subject to great error. Appropriately, some authors chose to disregard values less than this level (2, 22–28). With this assay, values below this level are best referred to as *indeterminate*. Furthermore, because 0.5 ng/mL exceeds the average normal value by more than ten-fold, many mild increases in ProCT values are missed.

Pathophysiology of Hyperprocalcitonemia. Subsequent to the discovery of the secretion of ProCT by neuroendocrine neoplasms, it was demonstrated that the large molecular weight precursors of CT, including ProCT, were also markedly increased in the sera of patients with severe systemic inflammatory conditions, such as inhalational injury (29), pulmonary aspiration (30), severe burns (31, 32), pancreatitis (33, 34), heat stroke (35), mesenteric infarction (36), multitrauma (37, 38), and extensive surgery (24, 39), and in infections such as pneumonitis (30). In 1983, increased serum ProCT was reported (albeit at that time described as a high molecular weight form of CT) in the infectious illness associated with toxic shock syndrome (40), and later also in sepsis (41) (as discussed below). In contrast to the neuroendocrine cell origin of medullary thyroid cancer, small cell cancer of the lung, and the carcinoid tumor, in marked systemic inflammatory conditions such as infection and sepsis, the principal source of

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ProCT is nonneuroendocrine parenchymal cells throughout the body (e.g., lung, liver, kidney, fat, muscle, stomach) (42). Although these cells are stimulated to produce and secrete very large amounts of ProCT, they lack the posttranslational capability of the thyroidal and pulmonary neuroendocrine cells to biosynthesize the mature CT hormone. Hence, this mature hormone is seldom appreciably increased in the serum and even may be undetectable (18). The cause for this nearly ubiquitous constitutive secretion may be due to changes in the promotor for the ProCT gene, responding to intestinal translocation of lipopolysaccharide or other bacterial constituents, or by a secondary proinflammatory cytokine stimulus such as tumor necrosis factor-α (43).

Hyperprocalcitonemia in marked systemic inflammation or in infection occurs within 2–4 hrs, often reaches high values in 8–24 hrs (see below), and then persists as long as the inflammatory process continues (i.e., days to weeks). With recovery, these levels normalize. This has led to the hypothesis that ProCT might exert a harmful effect in these conditions, influencing morbidity and mortality. Experiments revealed that when a large quantity of ProCT is administered to normal hamsters, there are minor changes in glucose, calcium, and phosphate but otherwise no noticeable deleterious symptoms and no mortality. In contrast, if hamsters that are rendered hyperprocalcitonemic by infection are given additional ProCT, the mortality approaches 100% (44). Hence, it seems that to exert its toxic effect, ProCT requires the presence of other factors that are present during systemic inflammation or infection. Importantly, immunoneutralization by an antiserum that is reactive to ProCT ameliorates the symptomatology and also markedly improves survival of severely infected animals (i.e., hamsters and pigs) (44–46). This occurs whether such therapy commences early or later in the course of the illness. Thus, the marked improvement of physiologic and metabolic variables and much improved survival after neutralization of this prohormone may offer new therapeutic possibilities in the septic human (47).

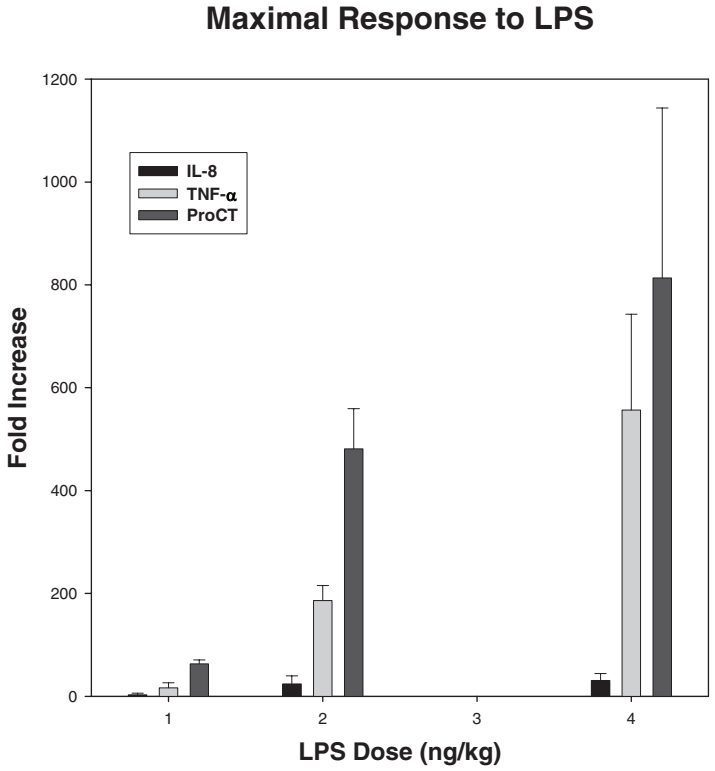

Figure 1. Peak (*fold*) increase of interleukin (*IL*)-8, tumor necrosis factor (*TNF*)-α, and procalcitonin (*ProCT*) in four healthy volunteers after increasing doses of endotoxin (lipopolysaccharide [*LPS*]; 1, 2, and 4 ng/kg). IL-8 reached peak levels at 4 hrs; TNF-α peaked at 1.5 hrs, and ProCT peaked at 24 hrs (unpublished data from Suffredini et al (164)).

Sick Patient with Increased ProCT

Systemic Inflammation Without Infection. Both in the literature and at the bedside, there may be confusion concerning the evaluation of a sick patient with hyperprocalcitonemia. As aforementioned, serum ProCT levels may be very high in patients with inhalational injury, burn injury, pancreatitis (particularly if it is obstructive in etiology), mechanical trauma, extensive surgery, or heatstroke. Although bacterial infection may be absent in these conditions, the ProCT levels attained may not differ very much from many of the levels seen in sepsis. Presumably, these conditions often are accompanied by translocation of lipopolysaccharide or other bacterial products from the gut to the systemic circulation (19, 48, 49). Here, it is pertinent that the experimental administration of lipopolysaccharide to healthy human volunteers induces a marked and prolonged elevation of serum ProCT to very high levels (50, 51). Thus, as shown in Figure 1, the peak levels of ProCT are multifold higher than both tumor necrosis factor and interleukin-8 after human exposure to lipopolysaccharide.

Mechanical trauma, involving the head, trunk, abdomen, or limbs, is one of the most common causes of elevated ProCT in the noninfected patient (52–55). In this condition, serum levels rapidly increase within 2–4 hrs, usually peak in the first or second day after the occurrence, and subsequently diminish (52). Typical values are in the range of 2–3 ng/mL, although they may be in the 10–20 ng/mL range when the injury is severe (37, 52). A persistence or a subsequent marked increase of serum ProCT often indicates the advent of infection or sepsis. In this respect, even early on, ProCT levels tend to be significantly higher in those who subsequently develop these complications or eventually die (52–54). High levels occurring early in trauma statistically predict multiple organ failure, but not necessarily sepsis (54).

Similarly, increased ProCT levels are seen frequently after extensive surgery (e.g., aortic, cardiac, colonic) (24, 39, 56). The postsurgical ProCT results tend to correlate with the extent of the procedure (24, 57, 58), and the early hyperprocalcitonemia often seen in these occurrences may be independent of any infection or sepsis. Nonetheless, as with mechanical trauma, very high initial levels, their persistence, or a secondary increase at a later time may herald the onset of these latter occurrences (39, 58, 59).

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In burns, serum ProCT frequently is elevated (29, 31, 32, 60). In one study, values within 24 hrs varied from indeterminate to approximately 350 ng/mL, and levels tended to be higher in those who were severely burned (32). In another study, if sepsis did not later complicate their course, the surviving burn patients had a mean ProCT of 1.4 ng/mL at admission; later, these levels peaked at 2.3 ng/mL (60). The mean admission ProCT of the burn patients who eventually became septic and survived was 4.6 ng/mL, and their values peaked at 12.8 ng/mL. Among nonsurviving patients, mean admission ProCT was 4.6 ng/mL, and the peak was 86.8 ng/mL. For all of these determinations, the standard deviations were extremely large, indicating a great range and overlap of values.

Infection

Localized Bacterial Infections. In addition to the several noninfectious conditions in which serum ProCT may be increased, high levels may occur in localized infections with negative blood cultures and an absence of the classic symptomatology of sepsis, such as in pneumonitis (27, 30, 61, 62). Thus, in a study of 35 patients with bacterial pneumonitis, the mean ProCT value was 19.5 ng/mL (61); in another, the highest level attained was 63.2 ng/mL (62). Although occasional nonbacteremic pneumonitis patients can have levels exceeding 60 ng/mL (63), those with bacteremia tend to have levels that are higher than those with negative blood cultures (62, 63). Moreover, increased serum ProCT levels often occur in urinary tract infections, attaining levels as high as 10 ng/mL (64). In pyelonephritis, the serum ProCT is roughly proportional to the extent of renal involvement (65). Among patients with acute bacterial arthritis, it is uncertain whether serum ProCT levels are increased in the absence of systemic infection (66, 67).

Sepsis

In Search of a Definition. Sepsis, a term lacking biochemical specificity, had previously been defined as the presence of known infection in a patient with at least two of four clinical findings (fever or hypothermia, tachycardia, tachypnea, leukocytosis, or leukopenia), which may be accompanied or followed by hypotension and multiple organ failure (68). Not all investigators agree with this definition; some state that the infection need not be documented, but only suspected (so-called culture-positive and culture-negative sepsis) (68, 69). In this regard, up to half of patients with an illness termed *sepsis* have no definitive proof of infection (69, 70). Notably, the mortality of these two groups is similar, irrespective of the documented presence or apparent absence of infection (69). Some authors have proposed that if infection is not demonstrated or not suspected, the term systemic inflammatory response syndrome (SIRS) be used. Still others decry the nonspecificity of SIRS (71). More recently, a definition of sepsis (that includes known or suspected infection) was amplified to include optional factors that commonly coexist, such as hemodynamic organ dysfunction, tissue perfusion abnormalities, and increased serum C-reactive protein (CRP) and ProCT levels (72).

Undoubtedly, in some patients with suspected sepsis, an apparent absence of infection may be due to factors such as technical problems with culture of the blood, urine, or sputum or to a bacteremia that is undiagnosed because it is transient or intermittent. Nevertheless, the high frequency of a culture-negative "sepsis-like" syndrome among numerous ill patients with multitrauma, burns, or other inflammatory conditions cannot be clinically ignored and often may be just as ominous as the classic septic patient with proven infection (69, 73). Furthermore, the question must be posed as to whether a documented bacteremia, per se, in a patient with only minimal symptomatology should, in itself, be considered as being synonymous with sepsis (see below).

In studies of patients with severe infection or sepsis, serum ProCT levels have varied over an enormous range (41, 55, 74–77) (Table 3). Some authors have stated that threshold values of >2 ng/mL ProCT in the LUMItest assay are strongly indicative of sepsis or severe bacterial infection, that values below this level render the diagnosis less likely, and that values below approximately 0.4 or 0.5 ng/mL render these conditions unlikely (27, 74). However, although serum ProCT may increase by hundreds to thousands of fold above the detectable level in sepsis, many patients diagnosed with severe bacterial infection or sepsis have been reported to have serum levels of <2 ng/mL, and some have levels of <0.5 ng/mL (i.e., indeterminate by the LUMItest) (2, 78–84). Indeed, some of these latter patients die (77, 85). Furthermore, even the presence of documented bacteremia does not obligate the presence of increased serum levels of ProCT (1, 2, 4, 6, 79, 86, 87). Although there is much overlap of values, patients with diagnosed sepsis often have statistically higher serum ProCT levels than do those with SIRS only, and patients with severe sepsis or with septic shock often tend to have the highest levels (54, 76, 88–92). However, because these studies are based on statistical analysis of groups of patients, for an individual patient, such a diagnostic discrimination is invalid.

Sepsis and ProCT: The Clinical Setting. High initial ProCT levels in sepsis may have ominous prognostic implications (26, 77, 85). However, it is hazardous to draw definitive prognostic conclusions based only on such early ProCT levels because sepsis has many etiological precipitants, and the variable characteristics and severity of the initial causative insult (e.g., surgery, burns, trauma, pancreatitis) may in themselves markedly raise ProCT levels. Similarly, although relatively low initial levels early in the course of a sepsis may indicate a good prognosis, this illness may be followed later by several possible complications: heart failure (93), hypotension (94), respiratory failure (95), renal failure (96), hyperglycemia (97), disseminated intravascular coagulation (98), and coma, among others. Such occurrences may be severe or fatal but are not necessarily causative of further systemic inflammation or of an augmentation of ProCT.

Clearly, the age, nature, and extent of the etiological precipitant, coexistent illnesses, extent of organ dysfunction, rapidity and adequacy of therapeutic intervention, complications, and genetically influenced phenotypic polymorphisms in

Table 3. Range of serum procalcitonin levels in several studies of patients with severe systemic infection/sepsis

Range, ng/mL	Reference
6–53	41
1.48–15.26	55
Indeterminate[a] to 353	74
1–722	75
2.1–607.7	76
Indeterminate to 767	77

[a]Indeterminate indicates below the functional sensitivity of the assay.

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cell signaling (99, 100) all affect the course and eventual outcome of the sepsis.

Serum ProCT is only one of many variables to gauge the severity of illness, and as is the case for most clinical or biological determinations, it certainly is not flawless. Nevertheless, although there are many exceptions, as a group, ill patients with extremely high serum ProCT levels do tend to be sicker and have a worse prognosis, regardless of whether infection is present (21, 27, 36, 37, 55, 58, 77, 83, 92, 101–103). However, some patients with serum ProCT levels in the range of hundreds of nanograms per milliliter have survived and others with comparatively low values have died (3, 21, 73, 85). Importantly, whether they are high, moderately elevated, or in the indeterminate range, single or occasional values can be misleading (104). Furthermore, very early determinations after admission may not have prognostic value; later in the course, they may become more meaningful (105). Consequently, serial measurements should be performed whenever possible (85, 106). Such repetitive serum ProCT values during the course of sepsis are particularly useful if a clear trend is demonstrable (i.e., decreasing or increasing, or an unchanging plateau) (76, 83, 91, 107–109). Although a persistence of high levels commonly is ominous and decreasing levels are associated with a higher probability of survival (108, 110), in some nonsurvivors, ProCT levels may actually decrease as the disease worsens (104, 111).

In most studies, septic patients with known bacteremia commonly tend to have higher ProCT levels than do septic patients without bloodstream involvement (3, 6, 7, 77, 91). Some studies report that Gram-negative systemic infections result in higher ProCT levels than do Gram-positive infections (4, 112–114), but others find no significant difference (2, 3, 78).

A very high serum ProCT may aid in the differential diagnosis in a patient with shock, distinguishing septic shock from the lower levels encountered in a shock that is cardiogenic (115) or due to adrenal insufficiency (116).

Nonbacterial Infections: Viruses, Fungi, Parasites. In a febrile patient, a serum ProCT that is undetectable or low may offer particularly useful confirmatory information of a possible viral etiology. Of 236 cases of viral infections, only three had a serum ProCT of >2 ng/mL, the highest level being 5.2 ng/mL (117). In such infections, including viral meningitis, the level is frequently <1 ng/mL and often in the indeterminate range (118), whereas levels are markedly increased in bacterial meningitis (119). Nevertheless, values as high as 17 ng/mL occur in viral infections that are systemic, and there may be an overlap with systemic bacterial infection or sepsis (41). For example, in a study of 45 febrile children without localizing signs (28), the median serum ProCT level for viral infection (i.e., virus isolated or uneventful recovery without antibiotics) was 0.43 ng/mL (i.e., indeterminate), although values ranged from indeterminate to 8.3 ng/mL; for bacterial infection, the median was 3.09 ng/mL, with a range of indeterminate to 25.4 ng/mL. At a cutoff of 2 ng/mL, the marker sensitivity was found to be only 50% and specificity 85.9%. Therefore, these authors concluded that a low serum ProCT cannot be used to exclude bacterial from viral infections but that a combination of ProCT, CRP, white blood cell count, and clinical illness scoring might be more useful (32).

In patients with fungal infections, the results have been variable. Among five reported patients with pulmonary candidiasis who had elevated CRP levels, the serum ProCT levels were not increased (120). The studies of patients with fungus infections that are systemic reveal levels that tend to be lower than many patients with bacterial infections (121, 122). In an evaluation of a large number of infected patients with systemic fungal involvement and fever (23 who had systemic aspergillosis and 21 with candidiasis), the ProCT on the day of diagnosis was 0.69 ng/mL and 1.03 ng/mL on the next day; in comparison, for 47 bacterial-induced sepsis patients, the values were 7.10 ng/mL on the day of diagnosis and 5.22 ng/mL on the following day (121) (although these differences were significant, the ranges and extent of overlap of levels were not specified). A study of 15 patients with candidemia revealed only minimal overlapping, with higher mean levels being found in bacteremic patients, and ProCT levels of >5.5 ng/mL excluded candida (122). Serum ProCT levels were reportedly higher in severe fungal infections (123). A study of infants with clinical signs of infection revealed that among ten patients with candidiasis, the mean ProCT was 6.7 ng/mL as compared with a somewhat higher mean of 10.8 ng/mL for patients with bacterial infection (124). As is the case with viral infections, it is not known to what extent the high levels occurring in some patients with systemic fungal infection may be due to translocation of microbial constituents from the gut or to secondary bacterial infection (125).

Infection with the malaria parasite often leads to very high levels of serum ProCT. Although the range is wide, values as high as 662 ng/mL have been reported (126). Although some authors note a significant positive correlation with severity (126, 127), others find no correlation (128). Levels decrease with therapy (127, 129). Insufficient studies have been performed to detect differences among the varieties of malaria parasite.

Sepsis and ProCT: The Pediatric Experience. Among the very young, who are more susceptible to severe infections and to sepsis, the mortality is high. Moreover, the symptoms and signs may be meager and difficult to detect. Consequently, particular attention has been directed toward the efficacy of serum ProCT determinations in these groups. In the neonate, a further difficulty is posed by a normal rise in serum ProCT levels after birth that probably is related to normal peripartum proinflammatory changes (130). Although the sensitivity of the assay was relatively poor, ProCT levels in healthy newborns reportedly began rising at 6 hrs postbirth, increasing further until 24–36 hrs (peak geometric mean of approximately 2.5 ng/mL), after which they progressively decreased to normal levels at about 3 days after birth (131).

A large study was undertaken of neonates with suspected sepsis of nosocomial origin who were admitted to 13 acute care teaching hospitals (4). The diagnosis of sepsis was ultimately confirmed by blood culture in 61 patients. The controls were neonates with initially suspected but never confirmed sepsis. Among the proven septic neonates, ProCT levels were highest during the first 2 days of onset of symptoms. At a cutoff of 0.59 ng/mL, the sensitivity was 81.4% and the specificity was 80.6%. No statistical comparison was made with CRP or leukocyte count. The authors concluded that the reliability of serum ProCT determinations was modest and not sufficiently dependable as a unique marker of sepsis but that it could be a useful component of follow-up.

In an extensive review of several studies of ProCT testing in neonatal infection, there were extraordinarily large differences in sensitivity (ranging from 30% to

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100%) and in specificity (ranging from 50% to 99%) (132). Such disparate findings are explicable on the basis of the diverse clinical settings of the groups, different study designs, differing ages of the neonates, the types of infection, coexistent illnesses, varying definitions of sepsis, differing cutoff points, and insufficient sensitivity of the ProCT assay.

In a prospective study of 46 hospitalized neonates with bacterial infection (nine of whom had positive blood cultures), a comparison was made of ProCT, CRP, and leukocyte count (80). The median ProCT for the entire group was 0.8 ng/mL, as compared with a median ProCT level of 4.68 ng/mL for those with positive blood cultures. At a cutoff point of 0.5 ng/mL (i.e., indeterminate), the diagnostic sensitivity for the initial ProCT determination of the entire group was 57% and the specificity was 66%. The authors concluded that these disappointing findings were not better than those obtained for CRP or the blood immature-to-total neutrophil ratios. Indeed, the positive predictive values were considered to be poor for all these tests. Because of the more complicated nature of the ProCT measurement and its expense in comparison with CRP, the authors recommended against the use of ProCT in the routine diagnosis of bacterial sepsis in neonates.

Among sick infants and children, the evaluation of ProCT studies has also been a topic of interest (28, 124, 133). In a study of 80 children (ranging in age from 1 month to 16 yrs) who were admitted to a pediatric intensive care unit for the suspicion of sepsis (133), there was a wide range of the admission serum ProCT levels (ranging from 1 to 722 ng/mL). In comparison with CRP, ProCT levels had a greater prognostic value; they were higher in those with shock or multiple organ failure and correlated positively with the pediatric risk of mortality severity score and with the mortality *per se*.

In febrile neutropenic children with cancer, serum ProCT assays performed on three successive days were evaluated as a marker for bacteremia (134). There was a moderately better accuracy on the initial day of determination than on succeeding days. Using a cutoff of 0.55 ng/mL, the sensitivity was high (93.8%), but the specificity was disappointing (70.6%).

A study of febrile infants and children that attempted to identify those having bacterial infection as opposed to those with no infection or with viral infection determined that at a ProCT cut-off of 0.5 ng/mL (i.e., indeterminate), the assay sensitivity was 87.5% and the specificity only 50% (32). The diagnostic utility was similar to that for CRP, for increased leukocyte count, or for the McCarthy score of severity of pediatric illness. Although the combination of these tests increased the sensitivity of ProCT, it lowered the specificity markedly. The authors concluded that the utility of ProCT as a marker of severe infection was much less than in previous reports (several other studies in this review also deal with the pediatric population).

However, as previously mentioned, the above results may have been affected by the poor assay performance at the cutoff near or at 0.5 ng/mL. Indeed, using a very sensitive research assay (Table 1), a cutoff at $>$0.5 ng/mL resulted in a sensitivity and specificity $>$90% for bacterial sepsis in febrile neutropenic children (135).

ProCT and Severity of Illness Scoring. Several groups have examined the relationship between serum ProCT and severity of illness scores, showing a moderate to fairly strong statistical correlation (21, 54, 88, 89, 104, 109, 110, 133, 136). In a study of 33 patients with severe sepsis, of whom 14 died, ProCT, Acute Physiology and Chronic Health Evaluation (APACHE III) scores, and Simplified Acute Physiology Score (SAPS II) were determined on the first 3 days after admission. ProCT correlated with APACHE III on all days and with SAPS II on day one (109). In children with severe infections, serum ProCT correlated with Pediatric Risk of Mortality scores (133), and a correlation was noted between ProCT and severity of illness scoring in trauma patients (137). In another study of sepsis, although there was a correlation between serum ProCT and APACHE II, this latter score was a better overall predictor of mortality than was serum ProCT (21). An evaluation of 95 patients with SIRS admitted to a surgical intensive care unit revealed a correlation between serum ProCT at the admission day and a fatal outcome, but the APACHE II and the Multiple Organ Dysfunction Score (MODS) correlated better with a fatal outcome (136). In a surgical intensive care unit, patients with SIRS or sepsis demonstrated a good correlation with Sequential Organ Failure Assessment (SOFA) scores (110). In burns, a positive correlation was noted between serum ProCT and the Baltimore Sepsis Scale (BSS) score of selected organ function (60), and in another study, there was a positive correlation with the unit burn standard (UBS) score (32). In contrast, among patients with sepsis, there was no correlation between serum ProCT and APACHE II (88). It is apparent that in these and other studies that have compared severity of illness scoring and serum ProCT levels, the correlations are only approximate (35, 55). Furthermore, although useful, scoring systems should not be regarded as unerring criteria for the determination of severity of illness (72, 138).

Sepsis and Infection: How Does ProCT Compare with CRP? CRP is a popular marker of inflammation that also has been employed in patients with infections and sepsis. The majority of several studies comparing ProCT with CRP have demonstrated that serum ProCT is a more useful monitor. For example, one study found that in contrast to CRP, ProCT was significantly higher in patients with bacteremia and septic shock than in other infected patients (139). In septic infants and children, ProCT was noted to increase earlier than CRP and had a greater sensitivity and negative predictive value (140). Similarly, other studies found ProCT to be an earlier marker of infection or sepsis (104, 124). In bacterial endocarditis, in addition to ProCT being more accurate diagnostically than CRP, ProCT levels fell more rapidly with recovery (114). In sick children, ProCT performed better than CRP in discriminating between viral and bacterial infections (117). Postoperatively, the persistence of a high ProCT level better indicated the presence of complicating infection than did CRP (57). ProCT has also been reported to better correlate with the overall course of the septic patient (89), and others have noted a better correlation with the outcome than for CRP (77, 92, 110). As discussed below, the authors of two meta-analyses concluded that ProCT was a superior marker than CRP in infections and sepsis (22, 140). However, one of these (140) has been criticized because of issues related to data extraction and classification of the patients studied (141).

On the other hand, in a study comparing the two markers, CRP was reported to have a higher sensitivity in detecting infection, although ProCT was better correlated with the presence of bacteremia (7). However, in this study, the cutoff used for ProCT was 0.6 ng/mL, too close to the indeterminate level of the assay. Several studies concluded that a combination of ProCT and CRP would provide

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the most useful information (28, 55, 91). In this respect, there is recent interest in combining multiple markers to more effectively diagnose infection (142, 143).

Sepsis and ProCT: How Helpful Is Meta-analysis? The lack of a gold standard for the diagnosis of sepsis hinders a meaningful meta-analysis of ProCT levels in this illness. Furthermore, the controls in the publications that might be analyzed for the purpose of performing a meta-analysis differ markedly (e.g., noninfected patients with fever, noninfected patients meeting the criteria of SIRS, postoperative patients who are critically ill, trauma patients, patients with local infections but no apparent systemic symptomatology). Also, many articles do not describe the clinical context of the illness of the patients being studied. For example, does the patient have infection, bacteremia, or diagnosed sepsis? Is the patient postoperative? Is the admission to the hospital or the intensive care unit for infection, burn, or trauma? Is there renal failure, respiratory failure, or intravascular coagulation? Were antibiotics previously or concomitantly administered? Was the ProCT assay very early in the course or later; was it single or serial?

The meta-analyses evaluating serum ProCT values in sepsis included only studies using the LUMItest assay (22, 140, 144). The main finding of the first such analysis (140), which examined 12 previous studies of infected patients with either bacterial or viral sepsis, was that serum ProCT differentiated bacterial from noninfected cases of systemic inflammation and bacterial from viral infection with greater accuracy than did CRP (i.e., greater sensitivity and specificity). The authors concluded that serum ProCT determinations should be used widely for these clinical purposes. Another meta-analysis that evaluated studies of patients with sepsis focused on 15 publications in which both ProCT and CRP were measured (22). Frequently, proof of infection had not been documented, and often, the timing and frequency of the testing had not been specified. Most importantly, this analysis revealed a great variation for the performance of the markers in the diagnosis of infection. Both sensitivity and specificity differed greatly: ProCT sensitivity ranged from 42% to 100%, and ProCT specificity ranged from 54% to 100%. CRP sensitivity ranged from 35% to 100% and specificity from 18% to 82%. The cutoff points that had been chosen in these studies also differed greatly, ranging from 0.6 to 2.97 ng/mL. For the studies that assessed both ProCT and CRP, data obtained from the plotting of the receiver operator characteristics (ROC) curve revealed a global diagnostic odds ratio of 14.7 for ProCT and 5.4 for CRP (indicating that for infected patients, there was a 14.7-fold higher risk of a positive ProCT test and a 5.4-fold higher risk of a positive CRP test). Both of these odds ratios were statistically significant. To further compare the ProCT and CRP performance, the authors utilized the summary receiver operator characteristics curve to determine the Q* values (intersection with the diagonal line where sensitivity equals specificity). The Q* values for ProCT and CRP were 0.8 and 0.64, respectively (both being statistically significant for discriminating tests). The authors of the meta-analysis concluded that serum ProCT was not a gold standard for the presence of an infection. Nevertheless, it was deemed to be a useful screening test for infection and a good biological marker for sepsis that should be included as a diagnostic and prognostic tool in intensive care units. The most recent meta-analysis reported a low diagnostic performance of ProCT in diagnosing sepsis in adult patients (144). However, the marked disparity of the studies that were examined compromised the validity of the analysis markedly.

Toward a More Sensitive Assay for ProCT

As has been discussed, in nearly all the literature to date, the ProCT assay is the insensitive LUMItest. A more sensitive, second generation assay for ProCT using time-resolved amplified cryptate emission (Kryptor assay, BRAHMS) has recently been developed and used in several studies (Table 1) (145). Once the instrumentation has been properly prepared and calibrated (including running of controls), a newly introduced sample can be determined in 20 mins. The intra-assay precision is 10% at <0.1 ng/mL, 6% at 0.15 ng/mL, and 3% at 0.4 ng/mL. The interassay precision is 20% at <0.1 ng/mL, 8% at 0.15 ng/mL, and 3% at 0.4 ng/mL (unpublished data). Although this assay has a lower functional sensitivity of 0.06 ng/mL, it still is moderately above the normal levels (i.e., 0.033 ± 0.003 ng/mL) that have been determined by the more sensitive research assay (Table 1) (13, 18). Although further confirmatory studies are needed, the Kryptor assay shows promise of being able to quantitate mild elevations and, when used in a serial manner, of detecting relatively small day-to-day variations during a patient's clinical course. Multiple specimens can be performed at a comparatively low cost.

Potential Applicability of a More Sensitive Assay. As discussed, using the LUMItest assay for ProCT, many patients with sepsis, including many with bacteremia, have levels in the indeterminate range. It is likely that some of these patients may indeed have true elevations that would only be determined by a more sensitive assay. Moreover, in patients with intravascular catheters, daily monitoring with a sensitive assay might predict the onset of bacteremia. Another use might be to establish more appropriate guidelines to aid in distinguishing viral from bacterial infections and therefore avoid unnecessary antibiotic therapy (146). The Kryptor assay has been used to determine the need for antibiotic therapy in lower respiratory infections and also is being evaluated in upper respiratory infections and chronic obstructive pulmonary disease (146–148). If such studies prove to be dependable, this might minimize the use of such therapy and perhaps diminish the emergence and spread of resistant bacteria. Furthermore, if a bacterial infection is indeed present, the elucidation of bona fide trends by this assay might aid in the ongoing determination of the efficacy of a chosen antibiotic (148).

Moreover, previous studies with the approximately eight-fold less-sensitive LUMItest assay had suggested that pneumonias due to tuberculosis, *Pneumocystis*, *Legionella*, and SARS are associated with serum ProCT levels that are lower than those caused by other bacteria. Hence, a sensitive assay might prove more helpful in achieving a better diagnostic discrimination (63, 149, 150). Another use of a sensitive assay is the diagnostic challenge of the febrile infant. Indeed, the use of the Kryptor seems promising in this setting (151). Improved sensitivity would be useful in evaluating young children with diarrhea to better separate the rather low values encountered in those with retroviral infection or inflammatory bowel disease from the slightly higher levels of those with bacterial enterocolitis (152, 153). Serum ProCT previously has been shown to be high in severe appendicitis (154), and a more sensitive assay may discern cases at

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an earlier stage. Another use might be to evaluate surgical patients with an early postoperative fever of unknown origin, a usage that has already commenced in neurosurgical patients (155). In allogenic hematopoietic stem cell recipients, a further mild increase of serum ProCT may aid in differentiating an episode of infection from acute graft-vs.-host disease (156).

There are several conditions characterized by low-grade inflammation in which the currently available ProCT assay demonstrates serum values that seem to be slightly elevated but are difficult to quantitate; here, a sensitive assay might prove helpful. These low-grade inflammatory conditions include the obesity-associated insulin-resistant syndrome that often occurs with polycystic ovaries (157) and also the acute coronary syndrome due to atherosclerosis (158). Lastly, as discussed, newborns manifest a moderate increase of serum ProCT, probably due in part to the acquisition of an intestinal bacterial flora (159), and a sensitive serum ProCT assay (such as Kryptor) might facilitate a more accurate establishment of normal baseline levels during this period and afterward and perhaps permit an earlier identification of systemic infection in the neonate (160).

Summary

The measurement of serum ProCT in severe systemic inflammation, infection, and sepsis has considerable utility. However, the results must be interpreted cautiously, taking into consideration the clinical setting and the technical limitations of the currently available LUMItest. Increased serum ProCT levels often indicate systemic infection or sepsis, but similar levels can be encountered in several noninfectious inflammatory conditions. In general, in trauma, burns, infection, or sepsis, there is a reported statistically positive correlation between serum ProCT levels and severity of illness and prognosis. Also, in most studies, there is a statistical correlation between the clinical course and a further increase of serum ProCT, a persistence of high values, or a progressive diminution. Similarly, an approximate correlation between serum ProCT levels and various formal severity-of-illness scores has often been noted. Importantly, it should be emphasized that some of the reported ProCT correlations, and the resultant clinical conclusions, were based on statistics using indeterminate levels of ProCT. To elicit subtle trends in the course of systemic inflammation or infection, to determine whether a localized infection is worsening, to evaluate the response to antibiotic therapy: all might benefit from a reproducible assay that could be used on a daily basis to evaluate the course of an illness by measuring minimally increased values and their subsequent changes. Thus, the improved second generation assay of ProCT, with enhanced functional sensitivity and practicality (e.g., Kryptor), may possibly reduce some of the current uncertainties. However, whatever the sensitivity of the assay that is eventually employed, determination of serum ProCT is only one of several procedures to help diagnose these conditions or evaluate their severity.

Hyperprocalcitonemia as a marker of inflammation, infection, and sepsis can be an important clinical variable and contribute important insights into the pathophysiology of these illnesses. In this respect, the intact ProCT hormone and the constituent aminoprocalcitonin peptide are bioactive (161–163). In the future, the various circulating precursors (including ProCT itself) should be detected individually, and the concentrations documented in health and disease. Moreover, in view of the effectiveness of immunoneutralization of ProCT in septic animals, this might ultimately offer new therapeutic strategies for these serious conditions [(164)].

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