Brief Review

The role of Procalcitonin in the management of patients with sepsis and respiratory tract infections: from bench to bedside

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SUMMARY. Sepsis constitutes a clinical syndrome with complex pathophysiological mechanisms, and it is leading cause of mortality in intensive care units (ICUs) worldwide. Guidelines and recommendations published during the last decade have emphasized the need for early recognition and management of patients with sepsis, including timely antibiotic administration. The use of biomarkers such as procalcitonin (PCT), to help in the timely recognition and effective management of sepsis, employed either alone or as a part of a multi-dimensional model, represents one of the contemporary challenges of pulmonary and critical care medicine. Respiratory tract infections represent a significant burden in critical care settings, being a major reason for antibiotic consumption and a major cause of morbidity and mortality. Recent evidence derived from published studies, systematic reviews and meta-analyses supports the use of PCT as a marker for the selection of those patients with lower respiratory tract infections who need antibiotics, both in the ICU setting and in the ward, but with significant inconsistencies. This review aims to cover briefly the rationale for the use of PCT as a biomarker in patients with sepsis, especially those presenting with lower respiratory tract infections, and to provide insights into the possible use of this biomarker in everyday clinical practice. *Pneumon 2010, 23(4):369-375.*

INTRODUCTION

Despite the widespread use of guidelines and the progress made in supportive care of patients, sepsis continues to be a primary cause of mortality among critically ill patients and is associated with high morbidity rates[1]. For this reason, research efforts have been focused on the identification of parameters which might facilitate the early diagnosis of sepsis and provide information related to patient outcome. The initial phase of the care of

patients with sepsis (the so called "golden hours") is considered critical; timely haemodynamic support, along with administration of appropriate antibiotic treatment has been demonstrated to improve survival and significant clinical end points[2,3]. The identification of high-risk patients with sepsis and the early decision-making related to their management have until now been supported by clinical and laboratory findings with limited reliability[4,5]. In addition, European and other international surveys on treatment modalities in intensive care units (ICUs) have shown marked inconsistency regarding the duration and appropriateness of antibiotic use in critical care patients[6], which may account for an increase in side effects and development of multi-resistant bacteria[7].

Lower respiratory tract infections (LRTIs) represent a significant proportion of the patients currently admitted to critical care settings, and are a major cause of morbidity and mortality worldwide[8]. Ventilator-associated pneumonia (VAP) in ICU patients continues to be a common problem in the critical care environment and intensivists can base antibiotic treatment in these patients on subjective criteria only. Despite the availability of scoring systems to help clinicians to decide which patients with community-acquired pneumonia (CAP) and exacerbations of chronic obstructive pulmonary disease (ECOPD) can be managed at home, at present there is no model which can stratify high-risk hospitalized patients who need closer monitoring. For these reasons, one of the modern challenges of pulmonary and critical care medicine is the identification of biomarkers such as procalcitonin (PCT), which would facilitate the timely recognition and management of sepsis, either singly or as part of a multidimensional model. The aim of this review is to cover briefly the rationale for the use of PCT as a biomarker in patients with sepsis, especially in those presenting with LRTI, and to provide insights into the possible use of this biomarker in everyday clinical practice.

For this review, a search was performed in PubMed in July 2010, using the terms "Procalcitonin AND Sepsis", "Procalcitonin AND Septic Syndrome", "Procalcitonin and COPD", "Procalcitonin AND VAP", "Procalcitonin AND Respiratory infections". The search was limited to articles in English covering the period 2002-2010. References in the relevant articles were also identified and explored.

THE HISTORY AND RATIONALE FOR THE USE OF PROCALCITONIN IN SEPSIS

In the early 1960s, a novel hormone, calcitonin (CT), was observed to show an increase in serum level in response to excessive hypercalcaemia, and it was demonstrated to be secreted by the thyroid gland and specifically by its parafollicular neuroendocrine C-cells[9]. A few years later, in the late 1960s, CT was detected in high levels in the serum of patients with medullary thyroid cancer originating in the thyroid C-cells, and it remains the classical biomarker for this malignancy as its levels correlate well with the mass of tumour cells[10]. It has been known since the mid 1970s that CT is biosynthesized as part of the larger pre-hormone, PCT. In the early 1990s, the first systematic study was reported of patients with severe bacterial infections and high serum PCT concentrations[11]. Subsequently this pre-hormone was used for the differentiation of the aetiology of systemic inflammation[12] and for the identification of severe sepsis[13].

PCT is a 116 amino-acid peptide which represents three smaller peptides; the central 33 amino-acid immature CT is then converted into the 32 amino-acid mature form of PCT[14]. In addition to the systemic inflammatory response syndrome (SIRS) where an overexpression of the PCT gene on chromosome 11 has been identified[15], the precursor of CT molecules is increased in several other clinical conditions (Table 1).

PCT is characterized by certain kinetic qualities which can be considered substantial for a good biomarker: PCT is a peptide of high stability in blood samples; secretion of PCT begins four hours after a trigger incident, and finally reaches its peak level eight hours after the onset[16], thus being detectable relatively early in the initial phase of infection and sepsis; its levels remain high for several days and return to normal when the stimulus is over[17]; the most frequently used commercial assays are relatively

TABLE 1. Causes of increase in serum levels of procalcitonin

- Neuroendocrine tumours
- Mechanical trauma
- Burns
- Major operations
- Septic shock
- Cardiogenic shock
- Other systemic inflammatory diseases:
  - Heat stroke
  - Acute pancreatitis
  - Mesenteric embolism
  - Acute appendicitis
- Other infections:
  - Pneumonitis
  - Urinary tract infections

simple to perform and the relevant results are obtained within 30 minutes to approximately three hours[18,19]. Are these pharmacokinetic characteristics of PCT sufficiently satisfactory for it to be considered the 'gold-standard' indicator of sepsis? Apparently not, since there is also a need for high quality evidence to illustrate a good correlation between the hormone and patient outcome, an issue that will be further analyzed in the following chapters.

CLINICAL TRIALS OF PROCALCITONIN IN SEPSIS

Findings regarding the use of PCT in the identification and/or monitoring of patients with sepsis have been inconsistent. Two reviews on this subject[20,21] demonstrated greater sensitivity and specificity of C-reactive protein (CRP) than PCT for the recognition of bacterial infection as the main contributor in patients with sepsis, while two reviews[22,23] concluded that PCT cannot be used to distinguish effectively between bacterial sepsis and the non-bacterial SIRS.

Studies published during the last few years, however, support the suitability of PCT for monitoring sepsis[24-28]. Castelli and colleagues, in the context of a recent prospective trial conducted on 94 ICU patients with trauma[24], reported an early and statistically significant rise in serum levels of PCT during the onset of septic complications. These complications, and particularly multi-organ failure, could be predicted better by PCT levels than by CRP levels ($p<0.001$). A randomized double-blind study with 79 patients with sepsis demonstrated that the use of PCT levels had helped in reduction of the duration of antibiotic use by four days ($p<0.003$), without affecting the percentage of patients who eventually recovered from the infection[25].

A similar significant reduction in the administration of antibiotics was reported by two German studies on 110[26] and 27[27] surgical patients, respectively. A 2009 study showed that PCT kinetics may confirm the appropriate use of empirical antibiotic treatment during the initial phase of sepsis, since patients receiving the appropriate antibiotics presented a greater decline in PCT levels in the first 3 days of admission in the ICU[28].

The systematic use of PCT measurement in patients with sepsis is hampered by a variety of drawbacks which have been extensively discussed in the literature. One important consideration that has already been pointed out is the elevation of PCT in conditions other than sepsis (Table 1). In these conditions, the stimulus causes an inflammatory reaction and PCT levels are increased despite the absence of bacteria[29]. In a prospective study on 276 surgical patients, the differential interpretation of PCT levels according to the patients' renal function resulted in higher accuracy of PCT in the diagnosis of sepsis[30]. Specifically, when threshold PCT levels were adjusted for serum creatinine (Cr) clearance, the diagnostic accuracy of PCT was significantly increased (0.74 vs. 0.70, $p < 0.05$). This finding indicates a need for further studies that will determine the pharmacokinetic behaviour of PCT in the subgroup of patients with impaired renal function, which is common in the ICU population.

The great inconsistencies between studies regarding threshold values of PCT need to be addressed. While most researchers maintain that a PCT value of 0.1 ng/mL represents a clinically important threshold for distinguishing patients with sepsis[31,32], others propose a higher limit (i.e., 0.4 ng/mL)[33]. Muller and colleagues have proposed an algorithm for treatment management in febrile patients, with PCT values ranging from <0.1 ng/mL to >0.5 ng/mL (Figure 1)[34]. Finally, the availability of various methods of measurement with different sensitivities for PCT puts in doubt the reliability of the results and makes the comparison of published trials difficult. Studies comparing the results of different methods for the measurement of PCT in clinical settings are urgently needed[18,19].

PROCALCITONIN AND RESPIRATORY TRACT INFECTIONS

LRTIs are a major indication for antibiotic use, as well as being an important cause of morbidity and mortality worldwide[35,36]. Researchers have recently focussed their interest on methods which can limit the days of antibiotic therapy and duration of hospitalization of patients with pneumonia, in order to reduce the uncontrolled use of antibiotics and the emergence of complications, such as antibiotic resistance. Three major studies have highlighted a possible role for PCT in this particular area[37-39]. The use of algorithms based on different cut-off levels of PCT led to a significant decrease in the duration of administration of antibiotics by 5 days at least. In addition, antibiotic prescription was reduced by 14% - 72%, without compromising patient outcome[37,39], even in the primary care setting[39]. Furthermore, the use of PCT monitoring may result in lowered cost, since it can effectively identify in the emergency department those patients who are likely to have positive blood cultures, with a high degree of

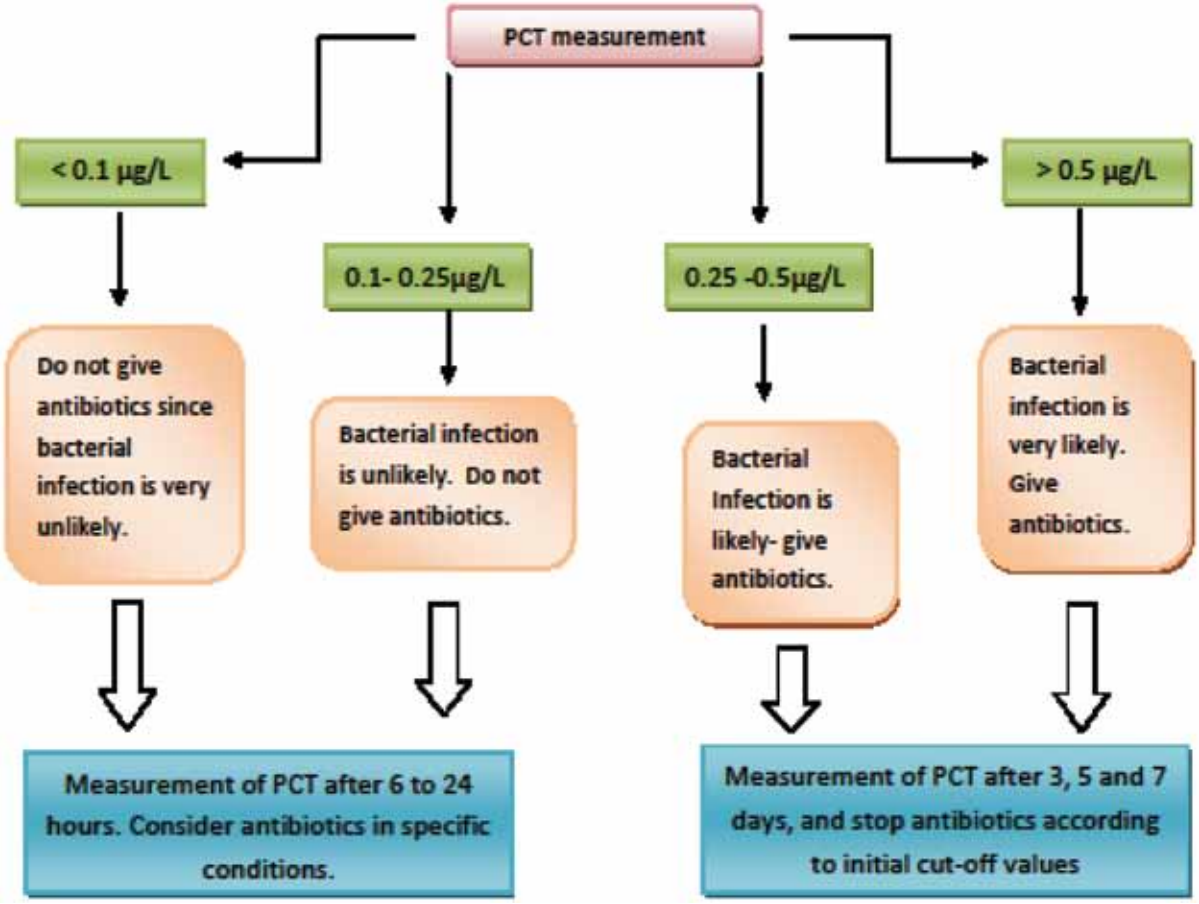

FIGURE 1. Proposed algorithm for antibiotic treatment of patients with fever, based on initial serum level and sequential measurements of procalcitonin (PCT) (modified after permission from Muller[34]).

sensitivity, and thus reduce the need for blood culture sampling, especially in settings with limited healthcare resources[40].

A large multicentre prospective study involving 1,651 patients with CAP investigated the value of the information that could be provided by adding PCT to the most commonly used systems for the assessment of patients with pneumonia[41]. The Pneumonia Severity Index (PSI)[42] and CURB-65[43] are two systems that classify patients with CAP according to severity and predict their outcome. In this population, PCT serum levels <0.1 ng/mL were found associated with low 30-day mortality, independent of clinical risk factors. In additionally, low levels of PCT in patients at high-risk according to PSI identified patients with a lower burden of adverse outcomes[41].

The use of PCT levels has been evaluated in VAP, but the data regarding the accuracy of PCT for VAP diagnosis involve only a small number of patients and the results are inconsistent[44-46]. Specifically, while Ramirez et al report that PCT might be useful as a diagnostic tool for VAP[46], two other observational studies found poor diagnostic accuracy of PCT[44,45]. Selligman and colleagues[47] suggested that measurements of PCT and CRP on the 1st and 4th days can predict survival of patients with VAP. A recent multicentre randomized trial[48] reported a statistically significant reduction in the duration of antibiotic administration by 27% ($p = 0.038$), in patients with VAP who received treatment guided by PCT. In contrast, a recent study involving 45 patients with VAP, found that neither initial PCT or CRP levels nor their kinetics predict survival of patients with VAP or the development of septic shock[49]. Based on the currently available data, it would be highly risky to rely on a single biomarker for the prediction of the outcome of critically ill patients with pneumonia, rather than using the widely accepted clinical models such as the APACHE and the SOFA scores. PCT studies have

provided promising data but further trials are needed prior to the systematic application of its measurement in clinical practice.

PROCALCITONIN AND EXACERBATIONS OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

COPD is the leading cause of hospitalization in people suffering from chronic respiratory problems, and it is predicted that in the coming years an increase in the numbers of exacerbations of the disease worldwide will be observed[50]. The recognition of the primary cause of these exacerbations is a diagnostic challenge for respiratory physicians, as the colonization of the bronchial tree of these patients with common pathogens makes the differential diagnosis from 'true' bacterial infections difficult[51]. The usual practice of antibiotic administration in ECOPD appears not to be effective in all cases, leading not only to increased side effects due to uncontrolled antibiotic use, but also to a significant economic burden for health systems[52,53]. The use of PCT measurement has been investigated in order to determine those patients with ECOPD who will benefit the most by the administration of antibiotic therapy.

A double-blind randomized trial involving 208 patients[54] suggested that measurements of PCT in ECOPD might be a valuable tool for guiding antibiotic treatment. Specifically, the measurement of PCT in patients with ECOPD led to a 30% reduction in antibiotic prescription ($p < 0.0001$) compared to the usual practice. The clinical outcome, exacerbation and hospitalization rates did not differ between the two strategies, further supporting a potential role for PCT for determining a more rational approach in the use of antibiotics for ECOPD[54].

A significant advantage of PCT over other biomarkers in the setting of ECOPD is the fact that its molecule remains stable in patients receiving corticosteroids[55]. This may be of particular importance for hospitalized patients with ECOPD, in whom the use of systemic corticosteroids is standard practice, according to the current guidelines[56].

Schuetz and colleagues have recently reported the findings of the large ProHOSP Randomized Controlled Trial[57], a multicentre prospective study involving 1,359 patients. The study patients suffered from respiratory tract infections (ECOPD, CAP, acute bronchitis) and the decision for the administration of antibiotics was based either on standard practice or on an algorithm taking into account PCT measurements. Application of the algorithm led to a significant reduction in the duration of antibiotic therapy (5.7 days) compared to standard practice (8.7 days). Adverse effects of antibiotics were significantly higher among patients receiving empirical treatment (28.1%) than in the PCT algorithm group (19%). Mortality and the combined adverse outcomes within 30 days of ICU admission were similar in both groups. These results support the earlier conclusions derived from the studies of Stolz, Christ-Crain and Briel[37-39,54]. As pointed out in the accompanying editorial, however, this study involved only Swiss hospitals and did not take into account the financial parameters regarding the use of PCT[58].

CONCLUSIONS

In 2008, the American College of Critical Care accepted the use of PCT as a tool for differentiating between bacterial and non-bacterial origin of fever in ICU patients[33]. During the same year, the Surviving Sepsis Campaign Guidelines declared the need for proof of infection prior to antibiotic treatment[59], recognizing the benefits resulting from early administration of antibiotics to patients with sepsis[26]. These guidelines are in line with the pharmacokinetic characteristics of PCT, which provide a significant advantage compared with the other biomarkers that have been used in the monitoring of sepsis. Additional evidence, derived from recently published studies, reviews, and meta-analyses[60-63], may constitute grounds for the beginning of the systematic use of PCU measurement in the ICU. There is a need, however for large trials in ICUs in order to determine the most appropriate PCT threshold values for use in different group of patients. The absence of a 'gold-standard' technique for the identification of the sepsis syndrome, has led to serious drawbacks in many observational studies and meta-analyses[63]. To this end, clinicians should be cautious when interpreting the results of trials comparing PCT levels with other markers of sepsis.

The diagnosis and management of bacterial infections continues to require a thorough history of the patient, comprehensive clinical examination and a series of tests. It is essential for parameters such as PCT to be developed through research for use as biomarkers in order to help physicians to make faster and better informed decisions. The current data are insufficient to justify the use of PCT as a single biomarker for the management of patients with lower respiratory tract infections and/or sepsis, and therefore at present this biomarker can only have a role in multi-parameter staging systems[64]. Further standardiza-

tion of the various methods for PCT measurement and the performance of multinational trials in well-defined populations, both in the acute care setting and in the ward or ICU, are essential for confirmation of the value of wider application of PCT in the identification of patients with sepsis in need for antibiotics or at high risk for adverse outcomes.

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