

The Role of Procalcitonin in Septic Patients – A Brief Overview

Dominik Hentschel, Christoph B Olivier, Christoph Bode, and Philipp Diehl*

Heart Center Freiburg University, Dept. for Cardiology & Angiology I, Hugstetter Str. 55, 79100 Freiburg, Germany

Abstract

Bacterial infections with consecutive sepsis have a high incidence in intensive care patients and are often associated with lethal complications. As early diagnosis followed by antibiotic therapy is vital for these patients, sensitive biomarkers indicating sepsis are of fundamental importance for the survival of septic patients. Procalcitonin, which is a protein produced by thyroidal c-cells, has been shown over 20 years to be increased in patients with sepsis. Since then, multiple studies have investigated the role of procalcitonin in patients with sepsis and systemic inflammation. However, the value of procalcitonin in patients with sepsis is still discussed controversial. This review aims to briefly summarize the current literature of procalcitonin and sepsis.

Keywords: Procalcitonin; Sepsis; Intensive care medicine

Introduction

This review aims to summarize recent trials on procalcitonin (PCT) in septic patients. The discussed studies have been selected by the personal interest of the authors, with no claim of completeness. History of procalcitonin (PCT) begins with the discovery of the hormone calcitonin (CT) in the early 1960's by Copp et al. [1] being found in dogs as an adversary to parathormone. In 1975, Moya et al. [2] described a precursor protein of calcitonin which was named procalcitonin. The molecular structure of procalcitonin was first described in 1981, when it was shown that PCT is a glycoprotein consisting of 116 amino acids with a weight of 13 kDa that is processed from its own precursor preprocalcitonin [3,4]. Being transcribed from the CALC-1 gene located on chromosome 11, PCT is under physiological conditions only produced by thyroidal c-cells, and in small amounts in neuroendocrine cells of the lung and small intestine respectively, where it is processed into its effective hormone calcitonin and stored in cellular vesicles until released in conditions of high serum calcium levels. Hence, PCT is nearly not detectable in serum of normocalcaemic patients [5].

Clinical Implication

Assicot et al. [6] were one of the first describing increased PCT levels in the blood of patients with sepsis and systemic infection in 1993. Since then, several clinical studies have investigated the role of procalcitonin as biomarkers in patients with systemic infections and sepsis [7-9]. However, besides septic conditions, increased PCT levels have furthermore been described in several other pathological conditions, such as cardiogenic shock, severe systemic-inflammatory response syndrome (SIRS), surgery and trauma [10-13]. Anyway, procalcitonin levels > 10 ng/ml are rarely seen in these diseases and its relevance remains mainly unknown [14].

Becoming an additional marker for sepsis, the superiority of PCT against other surrogate markers (e.g. C-reactive protein, CRP) was shown in several studies. Simon et al. [15] performed a meta-analysis of studies that evaluated PCT and CRP for the diagnosis of bacterial infections. They found that procalcitonin is more sensitive and more specific than CRP in discriminating bacterial from non-infective causes of systemic inflammation. Even though procalcitonin has been found to be a promising diagnostic marker in sepsis, it does not play a major role in several international guidelines. Hence, as published in 2013, the American Society of Critical Care Medicine (SCCM, <http://www.sccm.org/Pages/default.aspx>) picks up PCT in a seemingly minor recommendation [16]. In a grade 2C recommendation it is suggested that low procalcitonin levels can aid stopping antibiotic therapy in patients with non-confirmed sepsis.

However, due to a lack of evidence the SCCM does not recommend PCT measurements to discriminate between sepsis and non-infective systemic inflammation. Guidelines of other societies such as the German Sepsis Society (DSG, <http://www.sepsis-gesellschaft.de/>) and German Interdisciplinary Association of Intensive Care and Emergency Medicine (DIVI, www.divi.de) recommend within limitations - early measurement of procalcitonin in order to rule out severe sepsis and to stop antibiotic treatment in case of non-confirmed sepsis [17]. For further studies that assessed the relevance of PCT for the guidance of antibiotic therapies, please see the already published work [18-20].

Besides its role as a diagnostic marker in bacterial infections, only few studies have investigated whether PCT itself triggers inflammation and sepsis progression. Promising results obtained in septic hamsters, in which PCT increased and anti-PCT antibodies reduced mortality, underline the role of procalcitonin as a mediator in sepsis [21,22]. However, these data have not been transferred on humans yet.

Recently Published Data

Since the second Surviving Sepsis Campaign was published in 2013, several studies have shown the value of PCT as a diagnostic marker in septic patients [16]. However, there was no convincing evidence showing that PCT discriminates between bacterial sepsis and non-infective SIRS until Anand et al. [23] recently published a prospective observational single-centre trial in which they investigated whether procalcitonin and interleukin-6 (IL-6) can be used to distinguish between sepsis (cultural positive and negative) and non-infective SIRS.

They found in 208 patients with either non-infectious SIRS, culture-negative or culture-positive sepsis that PCT was significantly elevated in patients with culture-negative and culture-positive groups compared to patients with SIRS. If these findings can be confirmed in larger multicentre trials, they will likely change the role of PCT in future sepsis guidelines. Current guidelines do not consider PCT as a marker predicting the clinical prognosis of septic patients. De Azevedo et al. [24] investigated whether PCT levels may

***Corresponding author:** Philipp Diehl, Heart Center Freiburg University, Department for Cardiology & Angiology, Hugstetter Str. 55, 79100 Freiburg, Germany, Tel: 49 761 270 35600; E-mail: philipp.diehl@universitaets-herzzentrum.de

Received: November 20, 2014; **Accepted:** December 18, 2014; **Published:** December 25, 2014

Citation: Hentschel D, Olivier CB, Bode C, Diehl P (2014) The Role of Procalcitonin in Septic Patients – A Brief Overview. Transl Med 4: 144. doi: 10.4172/2161-1025.1000144

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predict the outcome of sepsis patients. They used the so-called procalcitonin clearance (PCT-c), which was implemented by two Spanish studies in 2012 and is calculated by the initial PCT value and those after 24 h and 48 h [25,26]. By correlating the PCT-c with the survival of 130 patients suffering from sepsis, De Azevedo et al. [24] found in patients with severe sepsis and septic shock that the PCT-c after 24 h/48 h was 10%/35.5% among survivors and -100%/-170% in non-survivors respectively. These data suggest that the PCT-c of 24 h and 48 h might be useful markers to assess the prognosis of patients with severe sepsis and are therefore in line with the aforementioned studies.

Multi organ failure with impaired hepatic or renal function is common in patients with severe sepsis. As it has been described that C reactive protein is increased during renal insufficiency, the question arose whether a reduced glomerular filtration rate might be associated with increased procalcitonin levels, too. In 2002, Sitter et al. [27] investigated whether PCT allows to differ between chronic inflammation in kidney disease and bacterial invasion. They found that renal insufficiency is not associated with increased procalcitonin levels, or at least almost always below a cut-off <1,5 ng/dl, and thus can be used as a parameter for early diagnosis of acute bacterial infection. These data are in line with recently published studies [28]. Besides impaired renal function, liver dysfunction has a high co incidence in septic patients. Hypothesizing that patients with decreased liver functions might have altered PCT levels, Rahimkhani et al. [29] assessed PCT levels in 64 patients with cirrhotic liver diseases and compared the data to 32 control subjects. They found that PCT levels are increased in patients with liver cirrhosis and particularly in those with a bacterial infection suggesting that an impaired hepatic function is related to increased PCT levels. This data was partly confirmed by Elefsiniotis, who found that patients with liver cirrhosis develop increased PCT levels under bacterial infection [30]. However, since studies in which PCT levels were assessed in cirrhotic patients show controversial results, procalcitonin levels of these patients might need to be interpreted with caution.

In summary, as indicated in recently published studies PCT might have a higher diagnostic and prognostic value than reflected in current guidelines. Nevertheless, data from the above mentioned studies base on comparably small patient numbers and need to be confirmed in multicenter trials.

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