



The Role of Procalcitonin as a Biomarker in Sepsis

Bethel Shiferaw^{1*}, Ebisa Bekele¹, Krishan Kumar², Anthony Boutin² and Marianne Frieri^{1,3}

¹Department of Medicine, Nassau University Medical Center, USA

²Department of Emergency Medicine, Nassau University Medical Center, USA

³Division of Allergy and Immunology, Department of Medicine, Nassau University Medical Center, USA

*Corresponding author: Bethel Shiferaw, Nassau University Medical Center, An affiliation of North Shore Long Island Jewish Health Care System, East Meadow, New York, USA, E-mail: bshifera@numc.edu

Abstract

Sepsis and its complications are one of the leading causes of mortality. Timely diagnosis and treatment is highly important in reducing the morbidity and mortality. Serum biomarkers may aid in the early diagnosis of sepsis and therapeutic intervention. Procalcitonin (PCT) is a peptide precursor of the hormone calcitonin and its primary trigger is infection. PCT is identified as part of the complex pro-inflammatory response of the innate immune system. PCT is widely reported as a useful biochemical marker to differentiate sepsis from other non-infectious causes. Serum PCT levels are elevated in patients with bacterial infections. The diagnosis of infection in critically sick patients is challenging as the current biomarkers are non specific. Our review showed that PCT is a more accurate diagnostic parameter for sepsis and a better predictor of mortality. PCT is a more reliable marker than other biomarkers including C-reactive protein, Interleukins and lactate levels. PCT has been proved to be superior biomarker, however its use still has to be interpreted in the context of clinical presentation. Further study on the role of PCT is needed for more effective and targeted approach in sepsis.

Keywords

Procalcitonin, Biomarker, Sepsis

Introduction

Sepsis

Sepsis is a systemic immune response to infection by microbial organisms. Sepsis is defined as the presence (probable or documented) of infection together with systemic manifestations of infection. The most common primary source of infection resulting in sepsis is the lungs, accounting for about half of all cases, followed by the abdomen, and the urinary tract. No definitive source is found in one third of cases [1]. Sepsis encompasses a spectrum of illness that ranges from minor signs and symptoms through to organ dysfunction (severe sepsis) and shock. Increasing severity correlates with increasing mortality, which rises from 25-30% for severe sepsis up to 40-70% for septic shock [2].

Sepsis and its complications have a significant and increasing impact on health sector, and are one of the leading causes of mortality. The incidence of sepsis is increasing in all areas of the world. In

general, sepsis occurs in approximately 2% of all hospitalizations in developed countries [3]. Severe sepsis is a common, frequently fatal, and expensive condition. Epidemiological studies indicate an incidence of severe sepsis approximately 751,000 sepsis cases per year in the United States (3.0 cases per 1,000 population and 2.26 cases per 100 hospital discharges) [4].

Mortality rate in sepsis remains high despite the current advances in medical science, technology and practice. Timely diagnosis and treatment is highly important in reducing the morbidity and mortality associated with sepsis. At-times the diagnostic uncertainty still remains high despite the available clinical information. Thus, a laboratory test with more specificity is essential. Serum biomarkers like procalcitonin may aid in the early diagnosis of sepsis and therapeutic intervention.

Procalcitonin

Procalcitonin (PCT) is a peptide precursor of the hormone calcitonin, the latter being involved with calcium homeostasis. This 116-amino acid prohormone is comprised of three constituent peptides: a 57-amino acid sequence at the amino terminus (NProCT); the centrally positioned immature CT that contains a terminal glycine; and a 21-amino acid CT carboxyterminus peptide I (CCP-I) [5]. All these peptides are found in the serum of normal persons. In contrast to the short half-life of calcitonin (10 minutes), procalcitonin has a long half-life of (25-30 hours) [6].

PCT is produced by parafollicular cells (C cells) of the thyroid and by the neuroendocrine cells of the lung and the intestine. PCT originate from the calcitonin I (CALC-1) gene on chromosome 11. Expression of the PCT-producing calcitonin 1 (CALC-1) gene is increasing in multiple extrathyroid tissues throughout the body in the bacterial infections. In the absence of infection, the extrathyroidal transcription of CALC1 gene is suppressed [7,8]. Therefore PCT detectable in the plasma during infection is not produced by C-cells of the thyroid rather by the neuroendocrine cells in the lungs or intestine. PCT becomes detectable within 2 to 4 hours after a triggering event and peaks by 12 to 24 hours. After reaching peak levels, the circulating procalcitonin concentration declines with a 50% plasma-disappearance rate of roughly 1-1½ days [9].

PCT belongs to a different class of molecules, called "hormokines," given the hormonal origin of the mature protein

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and the inflammation-related functions of its propeptides [10]. It may follow either a classical hormonal expression or, alternatively, a cytokine-like expression pathway. The production of hormokines is mediated by as yet unknown factors and may be induced either directly via microbial toxins or indirectly via a humoral or cell-mediated host response [11].

Procalcitonin and Pathogenesis of Sepsis

Cytokines have been implicated in the pathogenesis of sepsis. Macrophages phagocytose bacteria and produce a range of proinflammatory cytokines, which initiate the innate immune system's response to the bacterial pathogen. This results in the production of interleukin (IL)-1 β , tumor necrosis factor (TNF), and IL-6. The surge of proinflammatory cytokines during the innate immune response is a clinically visible and widely studied aspect of the pathophysiology of sepsis [12].

As the paradigm of sepsis pathogenesis has evolved over time and as different therapeutic approaches to sepsis have been tried, different biomarkers have been used for diagnosis of sepsis and monitoring of treatment [13]. TNF, IL-1 β and IL-6, as well as C-reactive protein (CRP), were all investigated as potential biomarkers. In the 1990s, investigators discovered that the levels of PCT were elevated in patients with bacterial infection, and it emerged as another potential biomarker [6]. Increased plasma PCT was suggested to be added to the updated definition of sepsis in 2003, as one of the diagnostic criteria for sepsis [14].

The primary pathophysiological trigger for elevated level of PCT is infection. Investigations identified PCT as part of the complex pro-inflammatory response of the innate immune system [15]. A marked increase in serum PCT often indicates an exacerbation of the disease, and a decreasing level is a sign of improvement.

During Sepsis, there is an increase in CALC-1 gene expression which causes a release of PCT and, more importantly, their levels persist for relatively long periods of time and correlate with sepsis severity and mortality. However, researchers have not determined the exact role that PCT plays in the pathogenesis of sepsis, further pathophysiological studies recommended regarding the biological role of calcitonin precursors during sepsis [16].

A recent experiment showed that PCT is a potent amplifier of the inflammatory cascade. It has shown that it induces pro-inflammatory like effects on leukocytes (increased the expression of surface markers on neutrophils and lymphocytes), increases leukocyte-derived cytokines and also augments nitric oxide (increases level correlates with severity of inflammation) [17]. Advance researches that are designed in clarifying the role of PCT in sepsis would aid in better understanding the pathogenesis of sepsis. The PCT test is relatively new, but its utilization is increasing. Multiple studies have shown that it has promise in helping to evaluate the risk of developing sepsis.

Procalcitonin as a Diagnosis Marker for Sepsis

A number of the inflammatory markers, such as leukocyte cell count, CRP, and cytokines (TNF- α , IL-1 β , or IL-6), have been applied in the diagnosis of inflammation and infection, but their lack of specificity has generated a continued interest to develop more specific clinical laboratory tests [2]. PCT is widely reported as a useful biochemical marker to differentiate sepsis from other non-infectious causes. The PCT test has been approved by the U.S. Food and Drug Administration (FDA) for use in conjunction with other laboratory findings and clinical assessments to assist in the risk assessment of critically sick people for progression to severe sepsis and septic shock.

Serum PCT levels are elevated in patients with bacterial infections, but are below the detection limit in healthy individuals and in patients with viral infections. This indicates that PCT level is useful for the diagnosis of systemic bacterial infections [18]. PCT secretion reflects the severity of the inflammatory insult, with higher levels associated with more severe disease and declining levels with

resolution of illness. Normal reference value is $< \text{or} = 0.15 \text{ ng/mL}$. PCT level between 0.15 and 2.0 ng/mL do not exclude an infection, because localized infections (without systemic signs) may be associated with such low levels. Levels $> 2.0 \text{ ng/mL}$ are highly suggestive of systemic bacterial infection/sepsis or severe localized bacterial infection. Although increased PCT levels may not always be related to systemic bacterial infection [19].

The diagnosis of infection in critically sick patients is challenging because traditional markers of infection are often non-specific and misleading. PCT was found to be a more accurate diagnostic parameter for sepsis, and therefore daily determinations of PCT may be helpful in the follow up of critically sick patients [20,21]. A systemic review and meta-analysis done on 30 studies (2013) revealed that PCT has a mean sensitivity of 0.77 (95% CI 0.72-0.81) and specificity of 0.79 (95% CI 0.74-0.84) [22]. The authors concluded that PCT is a helpful marker for diagnosis of sepsis in critically sick patients. However, it cannot be recommended as the single definitive test for sepsis diagnosis but rather it must be interpreted in context with information from clinical data.

The application of procalcitonin has to be considered along with clinical diagnosis of sepsis and septic shock. A description of the specific clinical diagnostic criteria is used. Systemic inflammatory response syndrome (SIRS) can be readily diagnosed at the bedside by the presence of at least two of the following four signs: body temperature variations (hyperthermia or hypothermia), tachycardia, tachypnea, and variations in white blood cell count (leukocytosis or leukopenia). The clinical diagnosis of sepsis requires the presence of SIRS resulting from presumed or known site of infection. Septic shock, a subset of sepsis, can be clinically diagnosed as a persistently low blood pressure despite adequate fluid resuscitation.

A literature review on the usefulness of PCT test among patients with chronic renal insufficiency found that PCT can be a useful test in identifying systemic infections among patients with renal dysfunction [23]. It is often challenging to distinguish between bacterial infections and disease-flares in patients with systemic autoimmune diseases, because of similar clinical presentation. A high PCT level is an excellent marker of bacterial infection in patients with systemic autoimmune diseases, even when they are being treated with corticosteroids and immunosuppressive agents [24].

Procalcitonin as a Prognosis Marker for Sepsis

A comprehensive knowledge of the biology, advantages and limitations of biomarkers is essential before applying them as a routine clinical tool for prognostic value. Elevated level of PCT at admission to the ICU was found to be a better predictor of mortality that helps in the stratification of patients and to identify patients at higher risk of adverse outcomes [25].

Many studies have demonstrated that serum PCT levels are increased in patients with sepsis, and the high levels of PCT correlate with the outcome of the disease. PCT can be used for differential diagnosis, prognosis, and follow-up of critically sick patients [26]. Serum PCT levels have been noted to increase with increasing severity of sepsis. In addition, a rising PCT level might be used as an indicator that an infectious process is not under control and that better source control is required [27].

A large cohort study (2006) done among critical care patients with daily PCT measurements showed that a high maximum PCT level and a PCT increase for 1 day are both independent predictors of 90 day mortality [28]. The study also revealed that the relative risk for mortality increased with every day rise of the PCT value. PCT levels should be determined serially, it is used for monitoring the host response to the infection and the antibiotic treatment. Few studies suggest that if PCT levels decrease more than 30% of the initial value after the first 24 hours of antibacterial treatment, the infection can be considered under control and the treatment is favorable [29].

A systemic review of these trials revealed that measurement of

PCT levels for antibiotic decisions in patients with sepsis appears to reduce antibiotic exposure without worsening the mortality rate [30].

Procalcitonin and other Bio-Markers of Sepsis

Biomarkers should provide a more reliable tool in ascertaining the presence of a relevant bacterial infection, its severity and treatment response. An ideal biomarker should allow, with high diagnostic accuracy, for an early and rapid recognition of sepsis. PCT is a biomarker that fulfills many of these requirements, especially in comparison to other commonly used biomarkers, and that has demonstrated superior diagnostic accuracy for sepsis [31].

PCT is found to be superior to CRP in terms of accuracy at identifying sepsis and assessing the severity of sepsis [32-35]. PCT was a more reliable marker in the diagnosis of sepsis than other biomarkers including TNF- α , IL-2, IL-6 and IL-8 [20]. Serum PCT concentration is more sensitive and specific marker of sepsis as compared with serum IL-6 and lactate levels [21].

There is still a need for new sepsis biomarkers that can aid in therapeutic decision making and add information about screening, diagnosis, risk stratification, and monitoring of the response to therapy. Novel approaches to sepsis promise to transform sepsis from a physiologic syndrome into a group of distinct biochemical disorders and help in the development of better diagnostic tools and effective adjunctive sepsis therapies [36].

Procalcitonin, Sepsis and Emergency Room

Biomarkers may play an important role in the management of patients with sepsis in emergency rooms. PCT is considered a relatively innovative and highly specific biomarker for the diagnosis of clinically relevant bacterial infections and sepsis; therefore it is increasingly recognized as an important diagnostic tool in clinical practice of emergency room. [37]. In addition, a multimarker panel approach performed by rapid and accurate assays (PCT being one of the important biomarkers) is useful for emergency physicians to promptly identify sepsis thus managing through better diagnosis, treatment and risk stratification. [37,38]. Therefore PCT could be a safe and effective tool to guide clinical and therapeutic decisions in emergency rooms.

An observational study conducted in Europe and Asia involving 340 patients who were enrolled from the emergency department investigated the diagnostic and prognostic utilities of PCT [39]. The study evidently showed that PCT concentration-based sepsis diagnosis is more reliable than the clinical diagnosis. Therefore assessment of patients with sepsis in emergency room should include appropriate use of PCT for improved diagnosis and management of patients.

Procalcitonin and Sepsis Treatment

PCT provides important information in early stages of sepsis as well as during antimicrobial treatment. In fact, PCT can be useful for antimicrobial stewardship and its utilization may safely lead to significant reduction of unnecessary antimicrobial therapy [31].

A systemic review and meta-analysis (2013) on PCT-guided antibiotic therapy indicated that PCT guidance can safely reduce antibiotic usage when used to discontinue antibiotic therapy in critically sick patients [40]. PCT-protocols to guide antibiotic treatment in severe infections are known to be effective. These protocols are based on daily measurement of PCT and clinical signs & symptoms of infection. Implementation of a PCT-protocol in a real-life clinical setting was also associated with a reduced duration of antibiotic therapy in septic patients without compromising clinical or economical outcomes [41].

Conclusion

PCT has been proved to be superior biomarker, however its use still has to be interpreted in the context of clinical presentation. This short review identified the association of PCT and sepsis. Additional

knowledge on the role of PCT might be valuable for more effective and targeted treatment in sepsis. More research is needed to further explore PCT as a possible gold standard biomarker in sepsis.

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