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REVIEW ARTICLE

PROCALCITONIN: A BIOMARKER OF SEPSIS

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ABSTRACT

Sepsis and severe sepsis are one of the leading causes of significant morbidity and mortality among the critical patients despite the use of broad spectrum antibiotics and fluid resuscitation therapies. Microbiological cultures which are considered the gold standard to diagnose sepsis require time. The rapid diagnosis of sepsis still remains a challenge for the clinicians thus requiring the role of a biomarker for early and rapid detection and also the prognosis in septicemia. Procalcitonin has been proposed as sepsis biomarker as it rises early in sepsis and has also been found to have a significant role in antibiotic stewardship and monitoring the efficacy of the treatment. The level of procalcitonin along with the clinical and other laboratory parameters can help in early detection and management of sepsis. This short review intends to provide an overview of the procalcitonin and its importance.

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INTRODUCTION

Sepsis is defined as the presence of an infection (documented or probable) along with the systemic manifestation of infection –the systemic inflammatory response syndrome (SIRS). It is known as severe sepsis when the sepsis is associated with sepsis-induced organ dysfunction or tissue hypo perfusion (Dellinger *et al*., 2013). Septic shock refers to a systolic blood pressure (SBP) < 90mmHg or mean arterial pressure (MAP) < 70mmHg or a SBP decrease > 40mmHg or less than two standard deviations below normal for age in the absence of other causes of hypotension other than sepsis (Dellinger *et al*., 2013). This inflammatory response is developed by the body's immune system to microbes in the blood, urine, lungs, skin, or other tissues**.** The diagnosis of sepsis has always remained difficult, particularly in the presence of other noninfectious conditions that can generate a similar inflammatory response, for example trauma, burn, and major surgery. It has been established that starting effective antibiotic therapy early in the course of an infection decreases morbidity and mortality of the patients (Kumar *et al*., 2006). Equally balanced against this is the need for antibiotic stewardship as the widespread administration of antibiotics increases the risk of antibiotic resistance, drug toxicity and also increased medical cost. The classical clinical signs of infection and the routine laboratory tests of sepsis are nonspecific and at many times misleading, thus there is a need for a specific and sensitive marker of sepsis which would help in early and proper management of patients with sepsis. Several chemicals have been examined as suitable bio- markers of infection and sepsis. These include procalcitonin (PCT) (Harbarth *et al*., 2001), resistin (Koch *et al*., 2009), various interleukins (Harbarth *et al*., 2001), adrenomedullin (ADM) and pro-ADM (Guignant *et al*., 2009), pro vasopressin (Guignant *et al*., 2009), eosinophil count (Ho and Towler, 2009) and c-reactive protein (Ho and Towler, 2009). Among these PCT has been most extensively studied and is now being increasingly used in clinical practice and guidelines of sepsis diagnosis and treatment (O'Grady *et al*., 2008). The elevations in serum procalcitonin (PCT) as a marker of bacterial sepsis was described as early as 1993 (Assicot *et al*., 1993).

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What is procalcitonin?

The PCT is a precursor of the hormone calcitonin and is physiologically synthesized by thyroid C cells. It was first identified in 1984 from a medullary thyroid carcinoma cell line (Birnbaum *et al*., 1984). In normal physiological conditions, PCT levels in the serum are low (<0.1 ng/mL) or undetectable as the PCT is cleaved by a protease enzyme to specific protease cleaves all PCT to calcitonin, katacalcin and an N-

terminal residue. However, in the presence of bacterial infection PCT is synthesized in various extrathyroidal neuroendocrine tissues, thus increasing its concentration in blood and making it detectable. It was described by Muller *et al* in 2001that PCT synthesis can be induced by inflammatory cytokines like IL-1 β, TNF-alpha and lipopolysaccharides (Muller *et al*., 2001). Systemic secretion of PCT has been described as a component of the inflammatory response that appears to be relatively specific to systemic bacterial infections. Bacterial sepsis appears to cause the highest increase in PCT with lower or negligible increase in localized, viral and intracellular bacterial (e.g. Mycoplasma pneumoniae) infections (Dahaba and Metzler, 2009 and Shehabi and Seppelt, 2008). Evidence also suggests that Gram-negative bacteraemias cause higher PCT rises as compared to Gram positive bacteraemia's (Charles *et al*., 2008). Interestingly, PCT levels in response to septicemia do not appear to be significantly affected by the use of corticosteroids (Perren *et al*., 2008). In bacterial sepsis, serum PCT levels increases within 2-6 hours after the onset of systemic infection (response to endotoxin), and peak at between 6 and 12 hours (Dandona *et al*., 1994). PCT has a half-life of 24 hours (Shehabi and Seppelt, 2008). The PCT can be elevated in renal impairment in the absence of infection as there is a role of kidneys in excretion of PCT (Meisner *et al*., 2000 and Meisner *et al*., 1999). In the absence of infection PCT can increase transiently for 12-24 hours, after trauma or surgery (particularly major abdominal surgery) and also in pancreatitis (Lindberg *et al*., 2002).

Importance of PCT

A) Diagnostic importance

Various studies have shown PCT to have diagnostic value which may be beneficial in early diagnosis of infection in critically patients thus aiding in management and prevent further complications (Harbarth *et al*., 2001; Dahaba and Metzler, 2009; Shehabi and Seppelt, 2008; Charles *et al*., 2008 and Gendrel and Bohuon, 2000). It shows an early increase in sepsis and a rapid decrease when the sepsis is controlled and thus can be used as a tool to guide antibiotic therapy. The concentration of PCT has been shown to correlate with the severity of sepsis and organ dysfunction in various studies (Zeni *et al*., 1994 and Giamarellos-Bourboulis *et al*., 2002). The PCT value should be used in conjunction with clinical findings and other laboratory values by the clinician in order to reach a diagnosis and accordingly manage the patient. Table 1 shows the reference range of PCT and its interpretation.

Table 1. Reference range of PCT and its interpretation

PCT < 0.5 ng/mL	Systemic infection is not likely. Local bacterial infection possible. If done very early should be reassessed 6-24 hours later.
PCT > 0.5 and < 2ng/mL	Systemic infection is possible. Monitor the patient both clinically and by reassessing the PCT level within 6-24 hours.
PCT > 2 and < 10ng/mL	Systemic infection is likely. Carries high risk for progression to severe systemic infection.
PCT > 10 ng/mL	Systemic inflammatory response, almost exclusively due to severe bacterial sepsis or septic shock.

B) Prognostic importance

PCT level is reflective of the extent of systemic inflammation (SIRS) secondary to infection. An initial high level of PCT does not necessarily reflect poor prognosis. Increasing or decreasing levels of PCT is more crucial in determining the not only the diagnosis of sepsis, but also the response of the patient to the therapeutic interventions. Study by Das *et al.* 2007 demonstrated a significant decline in PCT levels in patients who responded well to the treatment and also showed that the change in treatment instituted subsequent to persistently high PCT levels improved patients clinical response (Das *et al*., 2007). Thus the prognostic evaluation of the patient must be based on changes in PCT levels and can be used as a guiding tool for the therapeutic interventions for the sepsis, as the increasing or persistently high PCT values indicate poor prognosis with ongoing sepsis whereas declining values indicate a reducing inflammatory reaction and hence a favorable outcome for the patient.

C) Antibiotic stewardship

In the current situation of increasing antibiotic resistance with a spread of multi drug resistant microbes, the use of PCT has a really important role as a tool in the antibiotic stewardship. The use of PCT in the avoidance of antibiotic initiation and in reducing antibiotic course length and de-escalation of antibiotics has been studied extensively (Sridharan and Chamberlain, 2013 and Riedel, 2012).

Conclusion

The rapid diagnosis of sepsis still remains a challenge for the clinicians thus requiring the role of a biomarker for early and rapid detection and also the prognosis in septicemia. The serial estimation of PCT in patients with sepsis along with clinical correlation can help in assessing the severity of infection, the prognosis of disease and response to therapeutic measures which would eventually lead to better management of sepsis.

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