REVIEW ARTICLE

Procalcitonin, a Reliable Biomarker in Management of Sepsis

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Procalcitonin is widely used as a biomarker for diagnosis and prognosis for sepsis and infection as well as monitoring the response to antibiotic therapy. In this study we systematically reviewed the value of procalcitonin in diagnosis, treatment, and prognosis in patients with sepsis or infection.
keywords: procalcitonin; sepsis; infection; prognosis

Sepsis and its consequences are a common cause of admission and mortality and morbidity in ICU patients.

Although it is defined as a systemic inflammatory response caused by infection, no gold standard exists for its diagnosis. On the other hand, bacteremia is found in only about 30% of patients with sepsis, depending on previous antibiotic treatment. Furthermore, early clinical signs of sepsis, such as fever, tachycardia, and leukocytosis are non-specific. Other signs, such as arterial hypotension, thrombocytopenia, or increased lactate concentrations are too late for both diagnosis and life-saving treatment. These emphasize the need for development of early and reliable diagnostic biomarkers for diagnosis of sepsis [1].

Since using prolonged courses of broad-spectrum antimicrobial agents for treatment of severe septic patients is associated with emergence of antimicrobial resistance, using biomarkers for clinical decision-making seems prudent [2].

Procalcitonin is a small molecular peptide that has been used frequently as a useful diagnostic marker of infection in the adult population; Procalcitonin (PCT) is a 116-amino acid prohormone of calcitonin but lacks hormonal activity. Under normal conditions, the C-cells of the thyroid and K-cells of the lung are responsible for PCT gene expression. The prohormone is expressed in response to elevated serum calcium concentrations and undergoes an intracellular proteolytic cleave to the active calcitonin hormone. Calcitonin then acts to lower blood calcium levels through three separate mechanisms including inhibition of intestinal absorption, renal tubular cell reabsorption, and osteoclast activity [3].

Hyperprocalcitonemia appears within 2 to 4 h in patients with infection, often reaches peak values in 8 to 24 h, and then persists as long as the inflammatory process continues. With recovery, PCT levels return to normal [4]. The normal range of PCT in adult human serum is 0.033–0.003 ng/ml [5]. The release of PCT may be a two way process during inflammation: direct and indirect. The toxins and lipopolysaccharides released by microbes can induce the release of PCT in a direct manner; or alternately the inflammatory cytokines like interleukin (IL) 1b, IL-6, tumor necrosis factor-alfa (TNF-alfa) may indirectly influence PCT production. IFN-gama released in response to viral infection can cause a down-regulation of PCT [6].

Gram negative bacteraemias cause higher elevation of PCT than those caused by Gram positive pathogens; there is a low or negligible rise in PCT levels in localized infections, and in infections caused by viruses or intracellular bacteria. In the neonatal period, particularly in the first 48-72 hours of life, serum PCT levels increase to a high level and then gradually fall during the first week [6]. PCT is measured as semi-quantitative as well as sensitive quantitative assays with variable detection limits. Knowledge of the various cut-off values for PCT and their interpretation is important for the clinicians and the laboratory may mention it when reporting PCT results [6].

The variation in cut-offs suggests that PCT should not be utilized alone but rather considered as a supplement to help guide appropriate clinical judgment [3]. There are false positive results with PCT measurement including: Neonates <48 hrs age; first days after major surgery, trauma, burn; treatment with OKT3 antibodies, interleukins, TNF-alfa; invasive fungal infections, acute attack of falciparum malaria; prolonged or severe cardiogenic shock; and malignancies: e.g., medullary C-cell carcinoma of thyroid, small cell cancer of lung, bronchial carcinoid. It may also be falsely reported negative in early course of infection, localized infections, and sub-acute bacterial endocarditis [6].

Diagnostic value of procalcitonin

Levels of PCT are elevated in parasite, fungal, and bacterial infection with slight (levels below 0.1 ng/mL) or no elevation in viral infections and in severe inflammation without an infectious etiology and in patients without Infection [4].

The addition of PCT levels to bacterial culture and viral detection results can assist with the separation of colonization and invasion by pathogenic bacteria [7].

The ACCM and IDSA have recommended that PCT can be used as an adjunctive diagnostic tool for discriminating infection as the cause for fever or sepsis presentation while evaluating new fever in critically ill patients [6]. Procalcitonin has been proposed as a promising diagnostic

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marker for evaluating bacteremia and establishing a diagnosis of sepsis [8-12], ventilator associated pneumonia (VAP) [13], skin infection [14], respiratory tract infection in asthmatic patients [15], and bacterial meningitis [16-17].

Nevertheless, it cannot be recommended as the single definitive test for sepsis diagnosis [1].

However, Serum PCT failed to distinguish bacterial aspiration from pneumonia from aspiration pneumonitis [18]. Serum PCT may provide some useful clinical information for differentiation between invasive fungal disease and bacterial infection. It is important to realize that PCT is of little to moderate diagnostic value for differentiating fungal infection from other noninfectious conditions [19].

In burn patients, the determination of PCT levels has not been a useful tool for decision making when infection is suspected [20]. However, it is indicated that serum PCT in addition to other clinical and paraclinical parameters could be a useful sepsis biomarker in burned patients [21]. Furthermore, it has been shown that the semi-quantitative PCT-Q1-test is a practicable and useful marker in routine autopsy investigations for classifying death due to sepsis [22-23]. At PCT levels <2 ng/ml, bacterial sepsis or septic shock can almost certainly be excluded as cause of death. [22].

Comparison to Other Biomarkers

Several studies have shown that measurement of PCT in comparison to CRP and leukocytes was a better predictor for mortality in patients with different kinds of infection [24-28]. Although PCT appears to be better than CRP and WCC in the diagnosis and prognosis of infection in some scenarios, this is not universal and it seems clear that PCT cannot be used as a stand-alone diagnostic and/or prognostic tool [29]. In contrast, in one study CRP has been a better marker than PCT in early diagnosis of sepsis following colorectal surgery. In this study both PCT and CRP increased following surgery irrespective of presence of infection [30].

Combining CRP and PCT levels with temperature has been suggested to increase specificity for diagnosing nosocomial infection [31]. Gibot S et al developed a bioscore combining the PMNCD64 index together with PCT and sTREM-1 serum levels to increase the chance of early detection of sepsis in the critically ill patient with good performance [32]. Schrage et al suggested that both serum and vitreous PCT in comparison to other biomarkers including C-reactive protein, procalcitonin, tumor necrosis factor alpha, interleukin-6, and interleukin-8 might be useful for the postmortem diagnosis of sepsis [33]. One attractive aspect of PCT is that its level is not influenced by corticosteroid use in comparison to CRP and IL-6 [6].

Procalcitonin as a Prognostic Biomarker in Sepsis

Studies in patients with severe sepsis and septic shock revealed that measurement of procalcitonin was a good prognostic marker of mortality and decision making over degree of given care and discharge form ICU [34-38]. Azededo et al revealed that the clearance of 24- and 48-hour PCT is as useful as the 48-hour Δ SOFA score to determine prognosis in patients with severe sepsis and septic shock [39].

Combining of mortality in patients with ventilator-associated pneumonia, Cleophas m. Rumende, et al found that by combining procalcitonin and lipopolysaccharide-binding protein as prognostic markers for mortality and morbidity, the sensitivity increased to 88.5% and 96.3%, the specificity increased to 53.2% and 66.7% after three days and seven days treatment, respectively [40].

Duration of Antibiotic Therapy

PCT has been reported to be effective in deciding to stop antibiotic use in different groups of patients including those with acute respiratory tract infection [41,4], sepsis and septic shock [6,42-43], secondary peritonitis [44], ICU patients suspected to have infection [45-47], in the critically ill burn patient [48], and in exacerbation of idiopathic pulmonary fibrosis [49].

It has been found that procalcitonin guidance can reduce duration of antibiotic use by 50% [50].

A decrease in PCT level by more than 30% after the first 24 hours from the onset of antimicrobial therapy is indication of appropriate treatment and control of infection [6]. A biomarker-guided approach as a treatment algorithm using procalcitonin levels may be helpful to guide antimicrobial treatment with respect to escalation and de-escalation of therapeutic interventions in severe sepsis patients, treated in ICUs and reduces the duration of antimicrobial therapy without an obvious increase in mortality [5]. Decreasing level of PCT along with a negative culture for ICU patients treated for infection might convince clinicians that antimicrobials may be stopped safely. However, this might not be always as straightforward in inflammatory conditions with high levels of PCT such as pancreatitis, trauma, or major surgery [5].

It has been proposed that in certain units where antibiotics are used for 10-14 days or more, PCT may be a highly cost-effective strategy to give the confidence to clinicians to stop antibiotics earlier [6]. In contrast, Zielinska-Borkowska U et al suggested that PCT is of low utility in predicting survival and the development of septic shock in VAP. In addition, PCT concentration does not indicate the adequacy of antibiotic treatment or the Gram etiology of VAP [51].

Conclusion

PCT together with other clinical manifestations can be used as a reliable biomarker in diagnosis of sepsis and decision making toward initiation and stopping antibiotic therapy as well as predicting the outcome of infection.

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