Importance of Procalcitonin and Presepsin for diagnosis of sepsis in the intensive care unit

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Abstract

Background: During the course of evolution, our immune system has eventually developed to deal with infectious pathogen invasions by various host defense mechanisms. Inflammatory response is one of the primary responses to a microbial invasion, which leads to the systemic illness which is referred to as sepsis. Its severity correlates with mortality. It may occur as a result of infections acquired from community, hospitals or other healthcare facilities. There is an alarming number of 18 million new sepsis cases reported each year worldwide with mortality rate ranging from 30–50% Early diagnosis and prompt antimicrobial therapy is crucial in the treatment of sepsis for saving lives. Sepsis is a systemic inflammatory response syndrome (SIRS) that affect all organs. Hence, host responses including cytokine, cell markers, receptor biomarkers, coagulations, vascular endothelial damage, vasodilation, organ failure and scientific advancement in the field of molecular biology can equip us to screen wide range of protein markers in acute phase of sepsis development that helps in identifying relevant biomarkers to diagnose sepsis. The actual mechanism of production of PCT during infection is not known, but it assumes that bacterial lipopolysaccharides and sepsis released cytokines modulate the liver and peripheral blood mononuclear cells to produce PCT. Microbial infection induces the elevated expression of CALC 1 gene followed by the release of PCT product which is correlated with severity of disease and mortality.

Keywords: Procalcitonin, sepsis

Introduction

Sepsis is a life-threatening condition that arises when the body's response to infection causes injury to its own tissues and organs. Previously, SIRS criteria had been used to define sepsis. If the SIRS criteria are negative, it is very unlikely the person has sepsis; if it is positive, there is just a moderate probability that the person has sepsis. According to SIRS, there were different levels of sepsis: sepsis, severe sepsis, and septic shock. The definition of SIRS is ***(1)****:*

In 2016 a new consensus was reached to replace screening by systemic inflammatory response syndrome (SIRS) with the sequential organ failure assessment (SOFA score) and the abbreviated version (qSOFA). The three criteria for the qSOFA score include a respiratory rate greater than or equal to 22 breaths per minute, systolic blood pressure 100 mmHg or less and altered mental status. Sepsis is suspected when 2 of the qSOFA criteria are met ***(2)***.

The SOFA score was intended to be used in the intensive care unit (ICU) where it is administered upon admission to the ICU and then repeated every 48 hours, whereas the qSOFA could be used outside the ICU. Some advantages of the qSOFA score are that it can be administered quickly and does not require labs. However, the American College of Chest Physicians (CHEST) raised concerns that qSOFA and SOFA criteria may lead to delayed diagnosis of serious infection, leading to delayed treatment. Although SIRS criteria can be too sensitive and not specific enough in identifying sepsis, SOFA also has its limitations and is not intended to replace the SIRS definition ***(3).***

qSOFA has also been found to be poorly sensitive though decently specific for the risk of death with SIRS possibly better for screening ***(4).***

Infections leading to sepsis are usually bacterial but may be fungal, parasitic or viral. Gram-positive bacteria were the primary cause of sepsis before the introduction of antibiotics in the 1950s. After the introduction of antibiotics, gram-negative bacteria became the predominant cause of sepsis from the 1960s to the 1980s ***(5).***
After the 1980s, gram-positive bacteria, most commonly staphylococci, are thought to cause more than 50% of cases of sepsis . Other commonly implicated bacteria include Streptococcus pyogenes, Escherichia coli, Pseudomonas aeruginosa, and Klebsiella species . Fungal sepsis accounts for approximately 5% of severe sepsis and septic shock cases; the most common cause of fungal sepsis is an infection by Candida species of yeast , a frequent hospital-acquired infection. The most common causes for parasitic sepsis are Plasmodium (which leads to malaria), Schistosoma and Echinococcus. The most common sites of infection resulting in severe sepsis are the lungs, the abdomen, and the urinary tract. Typically, 50% of all sepsis cases start as an infection in the lungs. In one-third to one-half of cases, the source of infection is unclear ***(5).***

During the course of evolution, our immune system has eventually developed to deal with infectious pathogen invasions by various host defense mechanisms. Inflammatory response is one of the primary responses to a microbial invasion, which leads to the systemic illness which is referred to as sepsis. Its severity correlates with mortality. It may occur as a result of infections acquired from community, hospitals or other healthcare facilities. There is an alarming number of 18 million new sepsis cases reported each year worldwide with mortality rate ranging from 30–50% **(6).**
All types of microbes like bacteria, virus, fungi and parasites can cause sepsis, but bacteria cause the most common pathogenic invasion. During sepsis, the microorganisms invade to the blood stream and directly proliferate locally and release various virulent factors into the bloodstream. These products can stimulate the release of endogenous mediators of sepsis from endothelial cells, monocytes, macrophages neutrophils and plasma cell precursors **(7).**
Sepsis-related inflammatory response arise when the body attempts to neutralize pathogenic infection which in turn leads to the activation of various mechanism with the immune cells to secrete inflammatory protein which in turn damage tissues and organs of the host. Clinical symptoms of sepsis include tachycardia, tachypnea, fever, leukocytosis, etc. Usually severe sepsis is accompanied with hypo perfusion or dysfunction of at least one organ. Sepsis associated with multiple organ dysfunction syndrome (MODS) or hypotension is known as septic shock **(7).**
Early diagnosis and prompt antimicrobial therapy is crucial in the treatment of sepsis for saving lives. Sepsis is a systemic inflammatory response syndrome (SIRS) that affect all organs. Hence, host responses including cytokine, cell markers, receptor biomarkers, coagulations, vascular endothelial damage, vasodilation, organ failure and scientific advancement in the field of molecular biology can equip us to screen wide range of protein markers in acute phase of sepsis development that helps in identifying relevant biomarkers to diagnose sepsis **(8).**
WBC, C-reactive protein (CRP) and interleukin-1 (IL-1) are the conventional markers used for diagnosis of sepsis. Compared to CRP, PCT has better diagnostic and prognostic value and will clearly distinguish viral and bacterial meningitis. Cytokines like TNF-α, IL-1 and IL-6 are elevated during sepsis, but they do not possess sufficient sensitivity or specificity for the development of clinical markers (**9).**
Blood culture is considered as the gold standard for the confirmation of bacteremia which can isolate and identify the causative agent and subsequently test the antimicrobial sensitivity, but the delayed process of bacterial culture emphasizes the early diagnosis of sepsis. Several studies mentioned the advantages of the precursor molecule of calcitonin, namely Procalcitonin as a biomarker for sepsis. The serum PCT level rises rapidly than CRP levels and peaks within very short time; moreover, if the patient responds appropriately to the treatment, the level of PCT returns to normal range faster than CRP which makes it a better biomarker for sepsis. In general, PCT alone or in combination with other biomarkers would serve as a promising tool for understanding the prediction, cause, diagnosis, progression, regression and outcome of the treatment regimens (**6).**

History of Procalcitonin

It Was suggested that the existence of a precursor for calcitonin in chicken. The large biosynthetic molecule splits intracellular to generate the hormone, and they named it as Procalcitonin. Allison's study (1981) in RNA isolated from human medullary carcinoma demonstrated the synthesis of calcitonin as a precursor protein molecule in human. Later studies show that calcitonin is secreted after a sequential Co and post translational modification like glycosylation protiolytic cleavage, etc. In healthy individuals, PCT is produced in thyroid C cells, from a CALC-1 gene located on chromosome 11 (**10).**

The mRNA product is known as preprocalcitonin. It is further modified to 116 amino acid Procalcitonin. Finally, it is cleaved into 3 distinct molecules; active calcitonin (32 amino acid), kata calcitonin (21 amino acid) and N-terminal Procalcitonin (57 amino acid). Calcitonin hormone is involved in the homeostasis of calcium and phosphorous. Normally, CALC-1 gene in thyroid C cells are induced by elevated calcium level, glucocorticoid, calcitonin gene-related peptide (CGRP), glucagon, gastrin or β-adregenic stimulations. Practically, all the PCT formed in thyroid C cells are converted to calcitonin so that no PCT is released into the circulation **(8).**

Hence, the PCT level in healthy subjects is very low (0.05 ng/mL) but the inflammatory release of PCT is independent of the above regulations. During inflammation, PCT is produced mainly by two alternative mechanisms; direct pathway induced by lipopolysaccharide (LPS) or other toxic metabolite from microbes and indirect pathway induced by various inflammatory mediators like IL-6, TNF-α (**11).**

Biochemistry

PCT is a member of the calcitonin (CT) superfamily of peptides. It is a peptide of 116 amino acid with an approximate molecular weight of 14.5 kDa, and its structure can be divided into three sections : amino terminus , immature calcitonin, and calcitonin carboxyl-terminus peptide 1. Under normal physiological conditions, active CT is produced and secreted in the C-cells of the thyroid gland after proteolytic cleavage of PCT, meaning, in a healthy individual, that PCT levels in circulation are very low (<.05 ng/mL) (**12).**

The pathway for production of PCT under normal and inflammatory conditions. During inflammation, LPS, microbial toxin, and inflammatory mediators, such as IL-6 or TNF-α, induce the CALC-1 gene in adipocytes, but PCT never gets cleaved to produce CT. In a healthy individual, PCT in endocrine cells is produced by CALC-1 by elevated calcium levels, glucocorticoids, CGRP, glucagon, or gastrin, and is cleaved to form CT, which is released to the blood. PCT is located on the CALC-1 gene on chromosome (**13).**

Bacterial infections induce a universal increase in the CALC-1 gene expression and a release of PCT (>1 μg/mL). Expression of this hormone occurs in a site specific manner. In healthy and non-infected individuals, transcription of PCT only occurs in neuroendocrine tissue, except for the C cells in the thyroid. The formed PCT then undergoes post-translational modifications, resulting in the production small peptides and mature CT by removal of the C-terminal glycine from the immature CT by peptidylglycine α-amidating monooxygenase (PAM) **(8).**

In a microbial infected individual, non-neuroendocrine tissue also secretes PCT by expression of CALC-1. A microbial infection induces a substantial increase in the expression of CALC-1, leading to the production of PCT in all differentiated cell types. The function of PCT synthesized in no neuroendocrine tissue due to a microbial infection is currently unknown, but, its detection aids in the differentiation of inflammatory processes **(8).**

Procalcitonin as diagnostic tool

An ideal biomarker should possess high diagnostic accuracy, for an early and rapid diagnosis. PCT is a recently re-discovered biomarker that fulfills many of these requirements especially in comparison to conventional and widely used other biomarkers that have demonstrated superior diagnostic accuracy for a variety of infections, including sepsis. PCT is helpful for early detection of sepsis as well as to monitor the antimicrobial treatment regimen (**14).**

In fact, PCT can be a useful tool for antimicrobial stewardship and its utilization may safely lead to significant reduction of unnecessary administration of antimicrobial therapy. Laboratories and clinicians must comprehend the precincts of the present microbiological methods and the need for highly sensitive

biomarker assays to facilitate accurate diagnosis and goal directed therapy in patients suspected of sepsis (**15).**

During sepsis conditions, microbes and their antigens stimulate numerous anti-inflammatory mediators, which will trigger the host immune response. Precursors, mature forms and degradation products of these mediators penetrate from the site of action into the circulation, where which can be measured theoretically. These substances can be measured as surrogate markers for the diagnosis and the severity of infection. The actual mechanism of production of PCT during infection is not known, but it assumes that bacterial lipopolysaccharides and sepsis released cytokines modulate the liver and peripheral blood mononuclear cells to produce PCT. Microbial infection induces the elevated expression of CALC 1 gene followed by the release of PCT product which is correlated with severity of disease and mortality. The PCT as a biomarker proved successfully its clinical usefulness in determining the presence of sepsis. Moreover, it has been shown to correlate the extent and the severity of microbial invasion. It clearly showed the significance of early diagnosis of bacterial infected sepsis. PCT can be used for early detection of sepsis and prediction of outcome after major trauma (**16).**

Medical uses

Sepsis

Measurement of procalcitonin can be used as a marker of severe sepsis caused by bacteria and generally grades well with the degree of sepsis, although levels of procalcitonin in the blood are very low. PCT has the greatest sensitivity (90%) and specificity (91%) for differentiating patients with systemic inflammatory response syndrome (SIRS) from those with sepsis, when compared with IL-2, IL-6, IL-8, CRP and TNF-alpha. Evidence is emerging that procalcitonin levels can reduce unnecessary antibiotic prescribing to people with lower respiratory tract infections. Currently, procalcitonin assays are widely used in the clinical environment. A systematic review comparing PCT and C-reactive protein (CRP) found PCT to have a sensitivity of 80% and a specificity of 77% in identifying septic patients. In the study, PCT outperformed CRP in diagnostic accuracy of predicting sepsis ***(17).***

Organ rejection

Immune responses to both organ rejection and severe bacterial infection can lead to similar symptoms such as swelling and fever that can make initial diagnosis difficult. To differentiate between acute rejection of an organ transplant and bacterial infections, plasma procalcitonin levels have been proposed as a potential diagnostic tool. Typically, the levels of procalcitonin in the blood remain below 0.5 ng/mL in cases of acute organ rejection, which has been stated previously to be well below the 1 μg/mL typically seen in bacterial infection ***(18).***

Respiratory illnesses

Given procalcitonin is a blood marker for bacterial infections, evidence shows that it is a useful tool in guiding the initiation and duration of antibiotics in patients with bacterial pneumonia and other acute respiratory infections. The use of procalcitonin guided antibiotic therapy leads to lower mortality, less antibiotic usage, decreased side effects due to antibiotics and promotes good antibiotic stewardship **(19).**

The value in these protocols are evident since a high PCT level correlates with increased mortality in critically ill pneumonia patients especially those with a low CURB-65 pneumonia risk factor score. In adults with acute respiratory infections, a systematic review found that PCT-guided therapy reduced mortality, reduced antibiotic use (2.4 less days of antibiotics) and led to decreased adverse drug effects across a variety of clinical settings (ED, ICU, primary care clinic) ***(20).***

Procalcitonin-guided treatment limits antibiotic exposure with no increased mortality in patients with acute exacerbation of chronic obstructive pulmonary disease. Using procalcitonin to guide protocol in acute asthma exacerbation led to reduction in prescriptions of antibiotics in primary care clinics, emergency departments and during hospital admission. This was apparent without an increase in ventilator days or risk of intubation. Be that acute asthma exacerbation is one condition that leads to overuse of antibiotics worldwide, researchers concluded that PCT could help curb over-prescribing ***(20).***

Cardiovascular disease

PCT serves a marker to help differentiate acute respiratory illness such as infection from an acute cardiovascular concern. It also has value as a prognostic lab value in patients with atherosclerosis or coronary heart disease as its levels correlate with the severity of the illness. The European Society of Cardiology recently released a PCT-guided algorithm for administering antibiotics in patients with dyspnea and suspected acute heart failure. The guidelines use a cutoff point of .2 ng/mL and above as the point at which to give antibiotics. This coincides with a 2017 review of literature which concluded that PCT can help reduce antibiotic overuse in patients presenting with acute heart failure. In regards to mortality, a meta-analysis of over 5000 patients with heart failure concluded that elevated PCT was reliable in predicting short term mortality ***(21).***

Meningitis

Blood procalcitonin levels can help confirm bacterial meningitis and. if negative, can effectively rule out bacterial meningitis. This was shown in a review of over 2000 patients in which PCT had a sensitivity of 86% and a specificity of 80% for cerebrospinal fluid PCT. Blood PCT measurements proved superior to cerebrospinal fluid PCT with a sensitivity of 95% and a specificity of 97% as a marker for bacterial meningitis. In acute meningitis, serum PCT is useful as a biomarker for sepsis. It can also be of use in determining viral meningitis versus bacterial meningitis. These findings are the result of a 2018 literature review. This followed a meta-analysis that showed that PCT had a sensitivity of 90% and a specificity of 98% in judging viral versus bacterial meningitis. PCT also outperformed other biomarkers such as C-reactive protein **(*22).***

Gastrointestinal disease

Evidence shows that an elevated PCT above .5 ng/mL could help diagnose infectious complications of inflammatory bowel disease such as abdominal abscesses, bacterial entercolitis etc. PCT can be effective in early recognition of infections in IBD patients and decisions on whether to prescribe antibiotics **(*23).***

Hepatitis

PCT, possibly together with CRP, is used to corroborate the MELD (Model for End-Stage Liver Disease) score **(*24).***

Cancer

PCT has good value in diagnosing infections in oncologic patients. It is especially effective in diagnosing major life threatening episodes in cancer patient such as bacteremia and sepsis. Procalcitonin is reliable to monitor recurrence of medullary thyroid carcinoma. In detecting cancer recurrence, PCT had a sensitivity and specificity of 96% and 96% respectively **(*25).***

Pediatrics

In children presenting with fever without an apparent source, a PCT level of .5ng/mL had a sensitivity of 82% and specificity of 86%. At a 5 ng/mL value, the sensitivity and specificity were 61% and 94%. PCT can help the clinical decision making while identifying invasive bacterial infection in children with unexplained fever.PCT levels correlate with the degree of illness in pediatric patients with sepsis or urinary tract infections making it effective as a prognostic lab value in these patients **(26).**

Presepsin: A Promising Biomarker for Sepsis

Sepsis triggers a systemic host response releasing several mediators that have the potential to be used as biomarkers for diagnosing sepsis and can also be of prognostic utility. In this issue, Abdelshafey et al. have evaluated presepsin as a biomarker for sepsis and compared it with SIRS and qSOFA. Biomarkers play a role in decision tools for managing sepsis and also play a vital role in antibiotic stewardship which is extremely essential in this era of increasing antibiotic resistance. Literature review on biomarkers in sepsis suggests that nearly 258 biomarkers have been evaluated in different clinical settings of sepsis (**27).**

Amongst these biomarkers, some of them have established themselves over a period of time while some biomarkers continue to be in various stages of evolution. Procalcitonin (PCT) and C-reactive protein (CRP) are acute-phase proteins that are being most commonly utilized to diagnose bacterial sepsis and also to guide antibiotic therapy. Limitations associated with them include that their levels can get elevated in a

variety of inflammatory conditions. Hence, the search is still on for a novel biomarker that holds promise as a tool for evaluating sepsis either as an individual or in combination with other biomarkers to improve the overall sensitivity and specificity for diagnosing and prognosticating bacterial infections **(28).**

System has the unique characteristic of providing an immediate protective response to invasive pathogens. CD14 is a co-receptor present on the surface of the monocyte/ macrophage. It is a member of the Toll-like receptors (TLRs), with an ability to identify groups of ligands of both gram-positive and gram-negative pathogens. Lipopolysaccharide (LPS) which is competent of the gram-negative bacterial cell wall is one of the best-studied ligands. CD14 presents LPS to TLR and then contributes to intracellular signals promoting the expression of genes responsible for the immune response. CD14 exists in two forms namely membrane-bound (mCD14) and a soluble form (sCD14). The sCD14 has different subtypes that get released in circulation and acted upon by proteases and cathepsin D. The N-terminal fragment of the sCD14-ST subtype is called presepsin. Of late presepsin has aroused interest among the researchers but its utility is still under investigation **(29).**

Presepsin for Sepsis Diagnosis and Prognosis:

Presepsin levels are not only helpful in differentiating between sepsis and systemic inflammatory response syndrome (SIRS) but also act as a prognostic tool in bacterial sepsis. SCD14-ST was first studied in 2005 to differentiate patients with sepsis from healthy controls and patients in SIRS. The level of sCD14-ST in subjects with sepsis was much higher than the levels in subjects with SIRS and healthy controls. They reported a receiver operating characteristic (ROC) curve of 0.817 for diagnosing sepsis (**22).**

A meta-analysis on presepsin has shown that it has a higher sensitivity and specificity when used as a biomarker for diagnosing sepsis. Although another systematic review suggested that it should not be studied in isolation for diagnosis of bacterial infections and expressed a word of caution. Using it in combination with other biomarkers would be more useful to differentiate sepsis from the systemic inflammatory response **(26).**

This study is an observational exploratory study because the sample size was not calculated. Though it is limited by its inadequate randomization, it does highlight the role of presepsin as a biomarker for sepsis patients **(28).**

Several multicentric and prospective trials have shown that presepsin levels are significantly higher in patients with bacterial infections. Sensitivity has ranged from 70 to 87% and specificity from 63 to 81% when cutoff values have ranged from 600 to 864 ng/L. A cutoff value of 600 ng/L failed to differentiate between gram-positive and gram-negative infections. However, levels above 946 ng/L correlated well with gram-negative bacterial infections **(26).**

Single elevated values of presepsin levels at ICU admission have correlated with acute kidney injury, need for renal replacement therapy, longer ICU stay, longer days of mechanical ventilation, and more days on vasopressor. Serial monitoring of presepsin levels would prove more useful for clinicians at the bedside to monitor the appropriateness of antibiotic therapy and thereby influencing the overall outcome. Studies suggest that reduction in presepsin levels on Day 7 strongly correlates with the efficacy of antibiotic therapy (**30).**

The different performance efficiency values in the literature may be due to the heterogeneity in the included studies, variations in sepsis criteria, and even the type of sample used (plasma, serum, or whole blood) for measurement of presepsin. Further prospective studies with larger and more diverse populations are required to establish the cutoff values for presepsin for the diagnosis and prognosis of bacterial infections **(26).**

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