ISSN Print: 2394-7500
ISSN Online: 2394-5869
Impact Factor: 8.4
IJAR 2022; 8(8): 336-339
www.allresearchjournal.com
Received: 11-05-2022
Accepted: 18-06-2022

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Biomarkers for diagnosis of sepsis and their role in sepsis management: A brief review

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Abstract
A marker of sepsis has been defined as "a measure that identifies a normal biologic state or that predicts the presence or severity of a pathologic process or disease."
Biomarkers can be useful for identifying or ruling out sepsis, identifying patients who may benefit from specific therapies or assessing the response to therapy.
Biomarkers can have an important place in this process because they can indicate the presence or absence or severity of sepsis and can differentiate bacterial from viral and fungal infection, and systemic sepsis from local infection. Other potential uses of biomarkers include roles in prognostication, guiding antibiotic therapy, evaluating the response to therapy and recovery from sepsis, differentiating Gram-positive from Gram-negative microorganisms as the cause of sepsis, predicting sepsis complications and the development of organ dysfunction (heart, kidneys, liver or multiple organ dysfunction). However, the exact role of biomarkers in the management of septic patients remains undefined. C-reactive protein (CRP) has been used for many years but its specificity has been challenged Procalcitonin (PCT) has been proposed as a more specific and better prognostic marker than CRP, although its value has also been challenged. It remains difficult to differentiate sepsis from other non-infectious causes of systemic inflammatory response syndrome, and there is a continuous search for better biomarkers of sepsis.

Keywords: Biomarkers, diagnosis of sepsis, sepsis management, pathologic process

Introduction
Sepsis is one of the most common causes of morbidity and mortality in the intensive care unit (ICU) Sepsis is generally characterized by clinical and laboratory parameters that are not specific and can mislead because these parameters often change in critically ill patients with systemic inflammatory response syndrome (SIRS) Sepsis and non infectious SIRS produce very similar clinical features. It is very important that clinicians have the tools to recognize and diagnose sepsis promptly because early diagnosis and treatment may lead to improvement in both mortality and morbidity an early diagnosis of sepsis before receiving the results of microbial culture would certainly facilitate the choice of antibiotic therapy and reduce the patient mortality. Unfortunately, the availability of a highly specific sensitive marker of infection is still not satisfied an ideal marker of infection would be highly specific, highly sensitive, easy to measure, rapid, inexpensive, and correlated with the severity and prognosis of infection. Recent studies have suggested an important role of procalcitonin plasma concentration monitoring and more recently the triggering receptor expressed on myeloid cells 1 in the clinical diagnosis of sepsis, because they differentiate sepsis from non infection causes of SIRS. The use of procalcitonin in developing countries such as Morocco, however, remains very expensive and hardly accessible in ICUs.

Table 1: Diagnostic Criteria for Sepsis

General Variables
Fever or hypothermia
Tachycardia
Tachypnea
Hyperglycemia (in the absence of diabetes)
Inflammatory Variables
Leukocytosis or leucopenia
Raised plasma CRP concentration
Raised PCT concentration
Hemodynamic Variables
Arterial hypotension
High cardiac index
Mixed venous oxygen saturation >70%
Organ Dysfunction Variables
Arterial hypoxemia
Acute oliguria
Altered mental status
Unexplained coagulation abnormalities
Unexplained ileus
Unexplained hyperbilirubinema
Tissue Perfusion Variables
Unexplained hyperlactatemia
Decreased capillary refill

CRP = C-reactive protein; PCT = pro-calcitonin.

The perfect biomarkers

- Must be easily and reliably measured, usually from a blood sample.
- Should have a good positive and negative predictive value.
- Should have a defined cut-off value for diagnosis.
- Would change or support the therapeutic decision making.
- Should monitor progress of disease and responses to therapy.
- Should improve hospital resource utilization.
- Should be able to distinguish between the inflammatory response and infection which allowing earlier identification of patients with a specific diseases process.

Table 2: The grouping of serum inflammatory markers

Group	Serum inflammatory markers
Acute-phase reactants	LBP, CRP, Procalcitonin
Mediator activity	TNF, IL-1, IL-6, IL-10, IL-18
Cellular activity	TNF-RI; TNF-R11; IL-1R-1; IL-1R-II; sIL-6-R, mIL-6-R; ICAM-1; Eselectin; CD11b; Elastase; HLA-DR; class II antigenes DNA

Procalcitonin

PCT, a 14.5-kDa 116 amino acid polypeptide precursor of calcitonin, is normally produced in the C-cells of the thyroid gland. PCT levels were increased in patients with sepsis and bacterial infection but not those with viral infections, and the origin of PCT in these patients is thought to be extrathyroidal.

Procalcitonin is fast and highly specific increase in bacterial infection and sepsis and distinguishing bacterial and viral infections.

Procalcitonin has been recognized as a marker of choice, assisting clinicians in the early detection and therapeutic follow-up of bacterial infections. This marker helps clinicians distinguishing between bacterial and viral infections as in case of viral infections PCT levels are very low. In fact, the initial clinical signs of bacterial infection are non-specific, sometimes leading to diagnostic and therapeutic delays that compromise the prognosis. As the progression of severe bacterial infections is affected by how early the patient receives treatment, measuring procalcitonin levels is valuable, not only in emergency rooms to enable a quick medical decision, but also in intensive care units where sepsis represents a major problem.

One major advantage of Procalcitonin (PCT) compared to other parameters is its early and highly specific increase in response to severe systemic bacterial infections and sepsis. Thus, in septic conditions increased PCT levels can be observed 3-6 hours after infectious challenge.

PCT levels are usually low in viral infections, chronic inflammatory disorders or autoimmune processes. PCT levels in sepsis are generally greater than 1-2 ng/mL and often reach values between 10 and 100 ng/mL, or considerably higher in individual cases, thus enabling the diagnostic differentiation between these various clinical conditions and a severe bacterial infection (sepsis).

C-reactive protein (CRP) and procalcitonin (PCT): CRP, named for its capacity to precipitate the somatic C-polysaccharide of Streptococcus pneumoniae, is an acute phase protein and a sensitive systemic marker of inflammation and tissue damage. CRP is 115-kDa cyclic pentameric protein of five protomers, each consisting of 206 amino acid residues.

Diagnostic capacity of CRP and PCT in sepsis and in SIRS

CRP and PCT are released both in sepsis and in SIRS. CRP and PCT are equally effective, although not perfect, in differentiating between sepsis and SIRS. However, CRP and PCT have different kinetics and profiles. The kinetics of CRP is slower than that of PCT, and CRP levels may not further increase during more severe stages of sepsis. On the contrary, PCT rises in proportion to the severity of sepsis and reaches its highest levels in septic shock. PCT tends to be higher in non-survivor than in survivor. Therefore, the diagnostic capacity of PCT is superior to that of CRP due to the close correlation between PCT levels and the severity of sepsis and outcome.

A recent meta-analysis reported that PCT was more sensitive and specific than CRP for differentiating bacterial from non infective causes of inflammation. In addition, PCT is produced and cleared more rapidly than CRP, making it potentially more useful for identifying infection early and for following the progress of disease.

Neopterin: Neopterin, a pteridine derivative produced by activated monocytes/macrophages, is a marker of immune activation. Neopterin is increased in viral infection as well as bacterial infection, and neopterin is also a useful indicator of sepsis.

Endotoxin: Endotoxin is lipopolysaccharides (LPS) which is the cell wall component of the Gram-negative bacterium. Endotoxin is a potent trigger of the mediator cascade and sepsis. Limulus amebocyte lysate (LAL) test is the sensitive clinically available test for endotoxin, and the detection of endotoxin with LAL test is used as a reliable marker of

Gram-negative infection. There are two types of LAL assay, namely gelatin LAL assay and chromogenic LAL assay, and there was no difference between the 2 types of LAL assays. Recently, a novel chemiluminescent assay, the endotoxin activity assay (EAA) was approved by the FDA in the US. Endotoxemia (EAA level >50 pg/ml) was significantly associated with Gram-negative infection and EEA was superior to LAL method to detect endotoxemia. Combination of two or three of these markers may help as a diagnostic tool for sepsis.

CD64

CD64 expression on the neutrophil membrane is upregulated in response to pro-inflammatory cytokines, and neutrophil CD64 expression has been reported to have good sensitivity and specificity for a diagnosis of sepsis in several studies.

Soluble Triggering Receptor Expressed on Myeloid Cells

Expression of soluble triggering receptor expressed on myeloid cells (sTREM)-1 is up regulated in the presence of bacteria or fungi, but not in non-infectious inflammatory diseases [21], and levels of sTREM-1 are elevated in patients with sepsis. Gibot *et al*. [22] showed that sTREM-1 was more sensitive and specific for infection than other markers, including CRP, PCT, TNF, and IL-1β. In addition, a decrease in sTREM-1 levels over time was associated with a favorable outcome [24], suggesting a potential place in tracking response to therapy.

Macrophage Migration Inhibitory Factor

Macrophage migration inhibitory factor (MIF) is a mediator of sepsis, which induces the production of various pro-inflammatory mediators by modulating the expression of toll-like receptor 4 (TLR4) [25]. MIF levels are raised in patients with sepsis and correlate with outcome [26], and higher levels have been associated with development of sepsis after cardiac surgery [27]. However, MIF levels are also raised in non-septic, critically ill patients, 28 and in non-infectious inflammatory diseases [29].

Microarrays and Multiplex Panels

It is increasingly recognized that, given the complexities of the sepsis response, the likelihood of finding a single 'magic bullet' marker of sepsis is remote. However, sampling of multiple individual markers is time-consuming and requires considerable amounts of blood from the patient. An alternative approach to the combination of individual diagnostic markers and measures is, therefore, the use of microarrays and multiplexes. Genomic and proteomic techniques have advanced hugely in the last few years, enabling microarrays for multiple proteins, DNA probes, and antibodies to be multiplexed onto miniaturized diagnostic assays. Using small samples of blood, the individual patient profiles produced can be translated using bioinformatics into a diagnostic index for that patient [30]. Repeated sampling could assess changes in the profile over time, theoretically allowing treatments to be adapted accordingly [31]. Such systems are already being applied to many disease processes [32-34]. In addition to continuing to improve the necessary biochemical and bioinformatic technology, challenges for the future will be to determine which specific combinations of biomarkers should be included in multiplexes, and whether adjusting treatment according to multiplex-derived profiles will indeed improve outcomes.

Scoring and Staging

Diagnosis in many, if not all, disease states relies on multiple factors including clinical assessment, imaging, and biochemical tests. For example, a diagnosis of acute myocardial infarction will be based on clinical symptoms of chest pain, electrocardiographic evidence of ischaemia, and raised levels of several cardiac isoenzymes, for example CK-MB, troponin T, aldolase, and lactate dehydrogenase. In sepsis, also, attempts have been made to create diagnostic 'collections' that can be used to identify patients with, or at risk of, the disease. Peres Bota *et al*. [35] devised a so-called infection probability score using statistical logistic regression techniques. The score incorporates five variables routinely associated with the presence of infection (temperature, heart rate, respiratory rate, white blood cell count, and SOFA score) and assigned each a weighted score ranging from 0 to 26 (see Table 2). Using a cut off value of 14 points, the infection probability score had a positive predictive value for infection of 53.6% and a negative predictive value of 89.5%. With a score less than 14, patients had only a 10% chance of having an infection. As new biomarkers and even microarray systems are developed, such scores could be adapted to provide a more accurate probability of infection.

Table 2: The Infection Probability Score

Variable	0	1	2	3	6	8	10
Temperature,	<37.5	>37.5					
°C							
C-reactive	<6				>6		
protein, mg/dl							
WBC,	5–12	>12		<5			
cells/mm3							
Heart rate,	<80					81–140	>140
beats/min							
Respiratory	<25	>25					
rate, breaths/min							
SOFA	<5		>5				

SOFA = sequential organ failure assessment; WBC = white blood cells.

Attempts have also been made to characterize patients with a diagnosis of sepsis, such that treatment can be applied appropriate to the severity of disease. Alberti *et al.* [36] developed a score of risk for worsening sepsis (the Risk of Infection to Severe Sepsis and Shock Score, or RISSC), including 12 variables, six of which were physiological parameters (temperature, heart rate, systolic blood pressure, platelet count, serum sodium, and bilirubin), as well as mechanical ventilation (used in place of respiratory rate in patients on a ventilator), three infection sites (pneumonia, peritonitis, and primary bacteremia), and two micro-organism groups (Gram-positive cocci and aerobic Gram-negative bacilli). Using statistical modeling, these variables were weighted resulting in a score from 0 to 49. The scores were then summarized into four classes: low (score 0-8), moderate (8.5-16), high (16.5-24), and very high (>24) risk of the sepsis worsening.

Conclusion

Early and accurate diagnosis of sepsis is essential to provide adequate early therapy. An ideal marker of sepsis should be able to differentiate a patient with sepsis from one without sepsis, assess the severity of the sepsis if present, vary with the course of sepsis over time and with treatment, and predict outcome. Many such markers have been proposed, and as our understanding of sepsis improves, new mediators and potential markers will be identified. At present, diagnosis relies on combining various parameters known to be of diagnostic value, including: clinical examination; 'traditional' signs of sepsis, such as white blood cell count, fever, and tachycardia; and currently available 'markers' of sepsis, such as CRP and PCT.

With continuing advances in proteomic, genomic, and microarray techniques, we will be able to obtain an infectious or septic profile on each patient almost instantaneously from one small blood sample. Bioinformatics will help interpret that profile into a clinically relevant index that can be used to determine and adapt treatments, and may be incorporated into staging systems such as the IRO to provide a more complete characterization of patients with sepsis, with the ultimate aim of reducing the high mortality rates associated with this common disease process.

Suggested reading

1. Gattas, Cook. Procalcitonin as a diagnostic test for sepsis: health technology assessment in the ICU, 2003 Mar 1;18(1):52-8.
2. Kremmer, *et al*. A new strategy for the development of monoclonal antibodies for the determination of human procalcitonin in serum sample, 2012 Jan;402(2):989-95.
3. Vatcheva-Dobrevsky R, *et al*. Application of procalcitonin-Q test for early detection of bacteremia and sepsis, 2004 Jan 1;18(2):177-84.
4. Meisner *et al*. Comparison of PCT and C - reactive protein plasma concentrations at different SOFA scores during the course of sepsis and MODS; c1999.
5. Guven *et al*. Diagnostic value of PCT levels as an early indicator of sepsis, 2002 May 1;20(3):202-6.
6. Beat muller *et al*. How a hormone become marker and mediator of sepsis; c2001.
7. Charalampos piierrakos *et al*. Sepsis biomarkers: a review; c2010.
8. Wallis C, *et al*. Rapid isolation of bacteria from septicemic patients by use of an antimicrobial removal device. J Clin. Microbiol. 1980 May;11(5):462-4.
9. Applebaum PC, *et al*. Enhanced detection of bacteremia with a new BD BACTEC resin blood culture medium. J. Clin Microbiol. 1983 Jan;17(1):48-51.
10. Clinical and Laboratory Standards Institute. Approved Guideline M29-A3. Protection of laboratory workers from occupationally acquired infections. 3rd ed. CLSI, Wayne, Pa; c2005.
11. Clinical and Laboratory Standards Institute. Approved Standard M22-A3.Quality control for commercially prepared microbiological culture media, 3rd ed., CLSI, Wayne, Pa; c2004.
12. Murray PR, Baron EJ, Jorgensen JH, Landry ML, Pfaller MA. Manual of clinical microbiology, 9th ed., American Society for Microbiology. Washington, D.C; c2007.