Review Article

The Use of Biomarkers in the Diagnosis and Management of Sepsis

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Rapid diagnosis of patients with sepsis or septic shock is critical to improve care and reduce morbidity and mortality. Traditional diagnostic methods such as blood cultures and complete blood count analyses are non-specific and do not always correlate with the patient condition. In addition, blood cultures may not be positive even in confirmed cases of sepsis and may take 48 hours or longer for confirmation. Alternative diagnostic methods such as biomarkers, have been investigated for their possible value in prediction, diagnosis, and management of patients with sepsis. Biomarkers are compounds associated with a particular condition, organ, or disease state. An ideal biomarker should confirm or predict that a patient has sepsis or is at high risk for sepsis. To be effective, these biomarkers must provide high sensitivity and specificity as well as allow testing by methods that are readily available and allow rapid turn-around of results. This study reviews the potential of several biomarkers that are part of the inflammatory reaction during infection and sepsis and those involved in the patients' immunologic response to infection. Many of the biomarkers associated with the inflammatory response are non-specific for diagnosis of sepsis but may have a role in monitoring the patients' response to therapy. Immune response related biomarkers may help rule-in or rule-out sepsis in patients diagnosed with systemic inflammatory response syndrome. Each of these biomarkers has advantages and disadvantages. The majority of studies have shown that a combination of inflammatory biomarkers and immune response related biomarkers may provide the best diagnostic advantage for rapid confirmation of sepsis.

Key words: sepsis, inflammatory biomarkers, immune regulatory biomarkers, lactate, procalcitonin

Introduction

The importance of developing rapid and accurate methods is critical for identifying patients with sepsis to improve care and reduce mortality. Laboratory tests such as a complete blood count and white cell differential can provide useful information to clinicians but are not conclusive, nor are they specific for sepsis. The limitations associated with culture-based and specific organism identification methods have created increased interest in alternative laboratory testing to identify patients with sepsis or at risk for sepsis. A number of biomarkers have been shown to correlate with a diagnosis of sepsis or provide useful information in the management of patients with sepsis or septic shock. The National Institutes of Health Biomarkers Definitions Working Group defines biological marker (biomarker) as a compound having a "characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention."[1]

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Biomarkers are typically associated with a particular organ physiology or disease state. Changes in detectable blood levels of biomarkers correlate with existence or progression of the disease or increased risk. Biomarkers can be used as diagnostic tools when for example an elevated level is indicative of a specific disease or condition (prostate-specific antigen or PSA). Carcinoembryonic antigen 125 is an example of a biomarker that is used to indicate the presence of disease and to help stage the severity of disease (e.g. spread of tumor or recurrence).

Biomarkers can also be used to indicate the prognosis or potential patient outcome or provide guidance for the best therapeutic approach. Another use for biomarkers is to indicate whether the patient's disease is responding to therapy if the blood levels decrease after treatment.

For a biomarker to be useful it should be an "accurate reflection of a physiologic or pathophysiologic state or process; appropriately high sensitivity and specificity; high positive predictive value and negative predictive value; and diagnostic accuracy as assessed by calculation of positive and negative likelihood ratios."[2] Although several biomarkers may correlate with sepsis, not all of them have sufficient sensitivity or specificity to allow direct diagnosis or appropriate clinical management of patients. The clinical utility of some biomarkers is limited if the method does not allow rapid turn-around or when it may not be available to smaller facilities, such as flow cytometry that requires expensive instrumentation, highly complex technical expertise, and is cost prohibitive.

Actual experimental research involving biomarkers and sepsis patients is not always appropriate, researchers must often rely on retrospective meta-analyses to evaluate clinical efficacy.

Pierrakos and Vincent's literature review revealed over 3,000 articles and 178 different biomarkers. The majority of these biomarkers were assessed in clinical studies while only 40% were evaluated through actual experimental studies.[3] Of those reviewed, only 34 biomarkers were specifically investigated for their diagnostic value related to sepsis and only five had sensitivity and specificity greater than 90%.[3] The majority of these biomarkers were investigated for their ability to identify patients at risk for death or to distinguish patients exhibiting systemic inflammation from those with true sepsis.[3] At the time of the review, no individual biomarkers were identified as having sufficient clinical utility to diagnose or manage patients with sepsis.

Faix compared the use of biomarkers based on their function as pro-inflammatory cytokines or chemokines, acute phase reactants, and markers of white cell activation in concert with physiologic staging of sepsis patients. Again no individual marker provided exclusive diagnostic or patient management insight. However, the author's summary suggested that a combination of both pro-inflammatory and anti-inflammatory markers would provide the best diagnostic information as well as information to determine severity and risk for death.[4] Other reviews provided similar evidence concluding that each marker provided contributing information but, again no individual marker distinguished itself as the essential biomarker for diagnosis or management of sepsis.[5,6]

The following sections will discuss a number of inflammatory or immune response regulated biomarkers that are associated with infection, sepsis, and septic shock and their analytical and clinical utility. (Table 1)

Table 1 Sepsis Biomarkers

Inflammatory Biomarkers	
Lactate	Metabolite of glucose; increased when there is inadequate oxygen access for utilization e.g. decreased tissue or organ perfusion rates, or decreased blood flow or oxygen transport; non-specific inflammation; predicted response to therapy
C-Reactive Protein (CRP or hsCRP)	Acute phase reactant produced in the liver; pattern recognition receptor; binds to phosphocholine residues on microbes and damaged cells; opsonization improves phagocytosis; non-specific for inflammation; decreases in response to therapy
Procalcitonin (PCT)	Precursor of calcitonin hormone produced by parafollicular (C cells) cells of the thyroid gland and K cells of the lungs. Normal levels undetectable due to rapid conversion. Acute phase reactant but non-specific indicator of inflammation; increased in infected vs non-infected patients; indicator of effective antibiotic therapy
Heparin Binding Protein (HBP)	Found in the azurophilic granules of neutrophils; released with neutrophil activation; non-specific inflammation
Immune Response Related Biomarkers	
Interleukin 6 (IL6)	Produced by a variety of cell types including macrophages and monocytes; stimulates the production of acute phase reactants
Interleukin 8 (IL8)	Produced by macrophages, monocytes; also known as neutrophilic chemotactic factor; high levels predict risk for disseminated intravascular coagulation or multiple organ failure
Interleukin 10 (IL10)	Produced by monocytes and some lymphocytes; mixed role - downregulating T helper cells - positive role in B cell survival and maturation; Higher in septic shock than sepsis, distinguished between
Presepsin (sCD14)	Found on surface of macrophages and soluble; early marker of sepsis; differentiates bacterial sepsis vs SIRS; distinguished between sepsis survivors and non-survivors at 28 days
Monocyte chemoattractant protein (MCP)	Found on monocytes and vascular endothelial cells; chemotactic factor for monocytes; distinguished between sepsis survivors and non-survivors at 28 days
High affinity immunoglobulin receptor (CD64)	High affinity receptor for IgG; found on monocytes and macrophages; role in antigen capture
Soluble-urokinase-type-plasminogen-activator-receptor (suPAR/CD87)	Expressed on immune activated white cells; also tumor cells; distinguished between sepsis survivors and non-survivors at 28 days
Soluble triggering receptor expressed on myeloid cells 1 (sTREM-1)	Member of the immunoglobulin superfamily; found on surface of neutrophils and monocytes; upregulated during systemic infections; not elevated in non-infectious inflammation

Inflammatory Biomarkers

Lactate

Lactate is a metabolite of glucose produced by a variety of tissues in the body (muscle, brain, skin, and erythrocytes) and is consumed by cells for energy, especially during times of stress. Lactate is cleared by the liver and the kidneys such that normal blood levels for lactate are 0.3-1.5 mmol/L. Blood levels of lactate depend on the rate of production and the rate of metabolism or clearance. A high lactate level indicates that a disease or condition is allowing lactate to build up in the blood; e.g. inadequate oxygen access for utilization; decreased tissue or organ perfusion rates, or decreased blood flow or oxygen transport. See Figure 1 for an overview of inflammatory reactions and biomarker production.[6] An elevated lactate level is not diagnostic for sepsis and must be evaluated in conjunction with the clinical presentation of the patient and other parameters. In patients with confirmed sepsis however, the higher the lactate level the more severe the patient's condition. Patients with lactate levels greater than 4 mmol/L have a higher mortality rate (25-30%). Decreasing lactate levels can indicate a patient's positive response to treatment.[7]

C-Reactive Protein (CRP)

CRP is a pentameric ring compound synthesized in the liver in response to inflammatory cytokine production (e.g. Interleukin-6 and others). It is part of the pentraxin group of proteins that act as pattern recognition receptors. Serum levels are elevated in response to microbial infections as well as response to tissue damage from autoimmune diseases, malignancies, traumatic tissue injury or necrosis. CRP is part of the innate immune defense system and binds to phosphocholine residues found on the surfaces of injured or dying cells as well as on the surfaces of polysaccharides present on many bacteria, fungi, and protozoa. This binding (opsonization) activates the complement system, enhancing phagocytosis, as well as clearance and antigen presentation by macrophages (Figure 1). CRP levels begin to rise about 12 hours after the start of an infection and may not reach peak levels for 2-3 days. Moderately elevated levels may be seen with chronic inflammatory processes such as autoimmune disease or chronic cardiovascular disease. Wang et.al. examined the use of the highly sensitive test for CRP (hsCRP) and found similar results; high levels of hsCRP indicate patients at risk for sepsis.[8]

The lack of specificity limits the overall clinical utility of CRP, but because it is a quick and easy test to perform it remains a key indicator of inflammation and possible sepsis.[6]

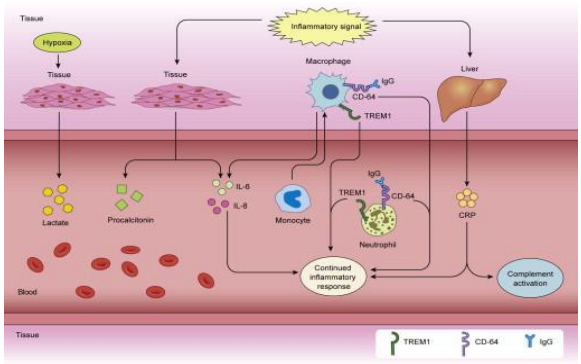

Figure 1: A simplified depiction of biomarker production in inflammation. An inflammatory signal stimulates the production of procalcitonin (PCT) as well as IL-6 and IL-8 from various immune system cells, including macrophages as well as many other cell types. Triggering receptor expressed on myeloid cells 1 (TREM-1) is expressed on neutrophils and macrophages as is CD64, which binds certain subclasses of immunoglobulin G (IgG). Downstream effects are numerous and further modulate the immune response. C-reactive protein (CRP), primarily produced by the liver in response to inflammation, participates in complement activation as well as other functions. Lactate is a product of anaerobic metabolism in the presence of tissue hypoxia. Together, these biomarkers are just a few of the molecules that collectively function to further the inflammatory response. Reprinted from Clinical Pediatric Emergency Medicine. Vol.15, No.2. Alqahtani MF, Marsillio LE, Rozenfeld RA. A Review of Biomarkers and Physiomarkers in Pediatric Sepsis. Pages No. 177-184. Copyright (2010), with permission from Elsevier.

Procalcitonin

Procalcitonin (PCT) is the precursor molecule of calcitonin, a hormone that plays a crucial role in calcium metabolism and homeostasis. In healthy individuals procalcitonin is produced by the parafollicular (C cells) cells of the thyroid gland and K cells of the lungs and is essentially undetectable in the blood. This is in part because it is converted as needed to calcitonin. PCT is considered an acute

phase reactant and during infection blood levels rise quickly with inflammation. Proinflammatory cytokines such as interleukin 6 (IL-6), tumor necrosis factor (TNF) and interleukin 1 (IL-1) are thought to induce other cells to produce PCT Bacterial lipopolysaccharide can also induce the production and release of PCT. However, PCT is not specific for any one condition. Although PCT can be increased in bacterial infections it can also be increased in cases of trauma, burns and other forms of tissue injury.

One advantage for PCT is that it is more specific for bacterial infection than other types of infection (fungi, viral or parasitic) or inflammatory conditions. PCT is down-regulated in viral infection through the production of interferon-γ (IFN-γ) which assists in determining the cause of infection. PCT is an early indicator of inflammation rising to detectable levels within 3-4 hours and peaking in 6-24 hours after the beginning of an infection. In comparison, CRP is elevated in a wider variety of inflammatory conditions such as autoimmune disease and begins to rise later during an infectious process.[2,9,10]

One of PCT's advantages is its role in helping determine appropriate use of antibiotics and length of treatment. PCT levels are low in patients with viral bronchitis or pneumonia while they are elevated in patients with bacterial pneumonia or sepsis. PCT can be used to rapidly identify patients who do not need antibiotic therapy and therefore limit the empirical use of broad-spectrum antibiotics for these patients. Low PCT levels in patients with positive blood cultures are more likely to indicate bacterial contamination rather sepsis. This is especially helpful when a common skin contaminant such as a coagulase-negative staphylococci are identified in the culture. PCT can be used as an indicator of effective antibiotic therapy as PCT levels should decrease rapidly and perhaps shortening the length of treatment as well.[11,12]

Heparin Binding Protein

Heparin-binding protein (HBP) also known as azurocidin, is found in the azurophilic granules of neutrophils and is released when activated by inflammatory cytokines. HBP induces vascular leakage (vasodilation) when it interacts with endothelial cells that enhance chemotaxis of white cells that are transmigrating to the site of tissue injury during inflammation. High levels of HBP are an indicator of neutrophil activation and therefore an inflammatory reaction; but not specifically sepsis or a bacterial infection. Linder et al. compared the HBP levels of patients with infection and those at risk for severe sepsis. Their studies showed that high levels of HBP were related to vascular failure. In some cases, the patients developed neutropenia which would further compromise the patient's condition and increase the likelihood for the development of sepsis.[13]

Immune Response Related Biomarkers

Interleukins

IL-6 is produced by a variety of cell types including macrophages and monocytes, adipocytes, fibroblasts, and smooth muscle cells. It is produced at the site of the local lesion or infection and enters the bloodstream. Along with TNF and IL-1, IL-6 plays a key role in stimulating the production of acute phase reactants by hepatocytes, including CRP. IL-6 also plays a role in the differentiation of CD4+ T lymphocytes and the activation of B cells into plasma cells. It is thought that increased levels of CRP in obese individuals can be attributed to production of IL-6 by adipocytes. Although IL-6 levels rise quickly in response to infection or inflammation, blood levels also drop rapidly to within normal levels in 24 hours.[10,14]

An additional cytokine, interleukin 8 (IL-8), is a chemokine produced by macrophages, monocytes, some lymphocytes and granulocytes as well as non-immune cells; e.g. epithelial and endothelial cells. IL-8 is also known as a neutrophilic chemotactic factor. IL-8 is the primary chemokine responsible for attracting and recruiting granulocytes to the site of inflammation thereby increasing phagocytosis and neutrophil degranulation. IL-8 has been found to be a good indicator of survival for pediatric patients. However, testing for this interleukin is specialized and therefore not always available in routine clinical laboratories.[6]

Interleukin 10 (IL-10) is produced by monocytes and some lymphocytes during the inflammatory response. It has a mixed role in the inflammatory response by inhibiting or downregulating production of cytokines by T helper 1 (Th1) and T helper 2 (Th2) lymphocytes and expression of co-stimulatory receptors on macrophages. IL-10 also plays a positive role in B lymphocyte survival and maturation. Potjoa et. al. found that sepsis patients also expressed anti- inflammatory cytokines and that

IL-10 was able to distinguish patients with systemic inflammatory response syndrome (SIRS) from those with sepsis.[15]

Presepsin (sCD14)

CD14 is a protein found on the surface of macrophages and is involved in the innate immune system response. CD14 comes in two forms. The membrane form (mCD14) is typically found on the surface of macrophages but can also be found on other white blood cell membranes including neutrophils and dendritic cells. The soluble form (sCD14), also known as presepsin (P-SEP), is secreted by macrophages or may be found in the circulation as a result of cellular membrane shedding. Elevated presepsin levels have been considered an early marker of sepsis that assists in the differentiation of bacterial infections or other systemic inflammatory conditions. Low levels of presepsin may help to rule out sepsis in patients that present clinically with SIRS.[16,17]

Monocyte chemoattractant protein- (MCP-) 1

Monocyte chemoattractant protein 1 (MCP-1), also known as CCL2, is a member of the C-C chemokine group of compounds that are involved in inflammatory and immune responses. MCP-1 is produced by a variety of cells including monocytes and vascular endothelial cells. It acts as a recruiter (chemotactic factor) for monocytes and other white blood cells from the bloodstream into the area of inflammation or infection to engage in the innate immune response to infection. Receptors for CCL2 (CCL2R) are predominately found on monocytes and vascular smooth muscle. A study by Holub found that patient blood levels of MCP-1/CCL2 and cortisol correlated with the patient's Sequential Organ Failure Assessment, or SOFA score, indicating that it may be an important factor for patient outcomes.[18,19]

High affinity immunoglobulin receptor - CD64

CD64 is a membrane-bound, high-affinity receptor that binds to the Fc portion of Immunoglobulin G (IgG1, IgG3 and IgG4) molecules, also known as Fc-gamma receptor 1 (FcγRI). This receptor is naturally found on the surface of monocytes and macrophages. Neutrophils will also express CD64 when stimulated by cytokines (i.e. IFN-γ). When an IgG molecule binds CD64 it stimulates activation of the monocytes, macrophages, dendritic cells, or neutrophils, initiating phagocytosis or receptor-mediated endocytosis of the IgG molecule and its corresponding antigen. It also plays a role in antigen capture for eventual presentation to T cells as part of the immune response.[20] Cells that express CD64 are identified and quantified using flow cytometry and is therefore cost prohibitive for some health care facilities.[21] CD64 detection has the potential to serve as an indicator for the differentiation of infections caused by bacteria versus other microbes.

Soluble-urokinase-type-plasminogen-activator-receptor (suPAR)

Urokinase type plasminogen activator receptor (CD87/uPAR) is expressed on immune activated neutrophils, lymphocytes, monocytes and macrophages. It is also increased in tumor cells and has been used as a target for chemotherapeutic treatments. CD87 expression is increased in the presence of bacterial lipopolysaccharide, IFN-γ, TNF, and other inflammatory cytokines resulting in a parallel increase in the soluble form (suPAR). Increased blood levels of suPAR parallel several other sepsis biomarkers. However, suPAR levels greater than 8 ng/ml are a significant predictor of mortality.[22,23]

Soluble triggering receptor expressed on myeloid cells 1 (sTREM-1)

Triggering receptor expressed on myeloid cell-1 (TREM-1) is a member of the immunoglobulin superfamily on the surface of neutrophils and monocytes. Like CRP and PCT expression, TREM-1 is upregulated during systemic infections. A soluble form of the marker (sTREM-1) can be detected in a number of body fluids including serum, pleural effusions, sputum, and urine. Unlike CRP and PCT, however sTREM-1 is not increased in other forms of inflammation such as autoimmune disease. A prospective study showed that sTREM-1 in combination with PCT and IL-6 are accurate prognostic indicators for survival of sepsis when applied along with the patient's SOFA score. The advantage of sTREM-1 is that it is not elevated in the presence inflammation not associated with infectious disease and can differentiate patients with sepsis from SIRS.[6,10,24,25]

Application of Biomarkers for Diagnosis of Sepsis

Multiple studies have examined the data for different biomarkers and their combined ability to act as sentinel markers, confirm a sepsis diagnosis, indicate severity of the patient's condition, or differentiate between types of infections. Most studies have evaluated the use of inflammatory biomarkers such as lactate, CRP, PCT and a combination of immune biomarkers. A 2010 review found that although CRP and PCT are the most widely used biomarkers for sepsis, they both have limited abilities to identify patients with sepsis in contrast to other conditions and they do not provide any indications related to the patient outcome.[3]

Another study suggests that a combination of procalcitonin, presepsin, CD64, suPAR, and sTREM-1 provide sufficient information for diagnosis of sepsis as well as predict patient outcome.[5] Additional studies combined a variety of biomarkers in the reviews however none were exhaustive in the biomarker list they examined.[10,18,26] When examined together, this information has little value as it is difficult to compare the studies because of differences in patient populations and the diversity in the patients' underlying conditions. For example, in some studies the patients with underlying immunosuppressive disorders were excluded. Another factor that complicates using all of the biomarkers together, is that the testing methodology may not be appropriate for rapid turnaround, and may be cost or expertise prohibitive for many facilities; e.g. by flow cytometry. Commercial testing methods are widely available for the inflammatory biomarkers (Lactate, CRP, and PCT) but access to many immune mediated biomarkers may be limited for smaller or rural facilities. It is also critical to understand that use of alternate biomarkers is not meant to substitute nor eliminate the need for traditional microbiological testing for the diagnosis of sepsis. Suffice it to say that the need for rapid testing that is readily available is a crucial concern for the management of sepsis and SIRS.

Biomarker Utility in the Management of Antibiotic Therapy

Procalcitonin is one of the most commonly studied biomarkers to determine when to prescribe antibiotics, when antibiotics are working effectively, and when antibiotic treatment can be discontinued. Because PCT can help distinguish patients who are at risk for bacterial sepsis and others with SIRS, it can be used to prevent overuse of antibiotics and improve antibiotic stewardship.[27] PCT can also be used to indicate successful treatment of sepsis and therefore reduce or discontinue the use of antibiotic treatment. Clinical trials demonstrate that when using PCT as the indicator for removal of antibiotic treatment 1) no adverse outcomes were evident and 2) it reduced the cost of the hospital stay.[12] PCT levels <0.25 μg/L in non-critically ill patients is an indicator to withhold or withdraw antibiotic treatment. For critically ill patients, i.e. those with sepsis, the minimum level for PCT is <0.5 μg/L or an ≥56-80% decrease in peak levels before the clinician should consider discontinuing antibiotic therapy. However, these levels must be interpreted in conjunction with the clinical presentation of the patient.

An additional review of eight randomized trials using PCT as an indicator for antibiotic usage supports the results of the previous study. Four of the trials involved patients with respiratory infection and four involved sepsis patients. In each trial, PCT levels prevented initiation of antibiotic treatment or indicated early withdraw of antibiotic treatment without any adverse effects.[11,28]

Based on the available information the following summary and suggestions for the application of PCT levels and the use of antibiotics has been developed according to the Oxford Centre for Evidence-Based Medicine.[28]

1. In septic ICU patients, with a clinically recovered physiological status and a serum procalcitonin level less than 0.5 ng/mL appear to be an acceptable and safe time to discontinue antibiotics. (Level 1b evidence)
2. The use of procalcitonin to decide when to stop antibiotics based upon a level less than 0.5 ng/mL in patients with pulmonary infection and/or sepsis has been shown to reduce total antibiotic use and decrease the duration of antibiotics. (Level 1b evidence)
3. An appropriate clinical situation and a procalcitonin level above 2 ng/mL are diagnostic of sepsis with a high sensitivity and specificity, and antibiotic therapy should be started immediately. (Level 2a evidence)
4. A patient with a systemic inflammatory response

and a procalcitonin level less than 0.5 ng/mL is very unlikely to have an infectious etiology of the SIRS response, and antibiotics can be withheld, although the procalcitonin level should be trended (Level 2a evidence).[28]

Summary

Biomarkers have shown significant promise in providing critical diagnostic relevance for patients with sepsis or at risk for sepsis. In addition to identifying biomarkers with high sensitivity and specificity, the testing method must be readily available for medical facilities and provide rapid turn-around time of the results. However, more research is still needed to determine which biomarkers or combination of biomarkers provides the most effective support and utility for patient management.

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