Review Article

Utility of Biomarkers in Sepsis: Mirror Reflection of Inner Truculent Devil

Kota SK[1], Meher LK[2], Rao ES[3], Jammula S[4], Kota SK[5], Modi KD[6]

Abstract

There is a plethora of biomarkers proposed and being researched in the field of sepsis. The complex pathophysiology of sepsis involves many mediators of inflammation pertaining to coagulation, complement, contact system activation, inflammation, apoptosis, etc. Markers related to those processes can gauge the degree of sepsis. Compared with localized pathology, the systemic nature and involvement of multiple organs in sepsis gives scope for numerous potential biomarkers. There is no 'gold standard' for the diagnosis of sepsis. Currently available/in-research biomarkers are compared for their efficacy with methods used to diagnose and monitor sepsis such as combination of clinical signs and available laboratory variables. An arbitrary classification of these biomarkers is made and the literature surrounding these markers and their efficacy in diagnosis of sepsis is reviewed.

Keywords: Sepsis, Inflammation, Biomarkers

Introduction

A complex network of biological mediators underlies the clinical syndrome of sepsis. The non specific physiologic criteria of sepsis syndrome do not adequately identify patients who might benefit from either conventional anti-infective therapies or from novel therapies that target specific mediators of sepsis. The utility of a biomarker is a function of the degree to which it adds value to the available clinical information in the domains of screening, diagnosis, risk stratification and monitoring of the response to therapy. Validated biomarkers of sepsis may improve diagnosis and therapeutic decision making for these high risk patients, but will require an unprecedented degree of systemic investigation and collaboration. We hereby comprehensively review the utility of biomarkers in the diagnosis of sepsis, which would promise to transform sepsis from a physiologic syndrome to a group of distinct biochemical disorders. Table 1 grossly classifies the biomarkers.

Cytokine/chemoking Biomarkers

1. TNF (Tumor Necrosis Factor): TNF receptor signaling pathway (TNFR1 and TNFR2) plays a central role in the activation of innate immunity in response to pathogens. TNF is responsible for a decrease in CXCR2 expression which translates in to reduced neutrophil extravasation, migration to the infectious site and in neutrophil apoptosis. Absence of TNFR signaling leads to a decreased local and systemic inflammatory response with diminished organ injury. TNF levels are known to be significantly higher in septic shock than in sepsis without shock and are elevated in non-survivors than in survivors. Also TNF level negatively correlates with the platelet count in sepsis[1.]

1. Sunil Kumar Kota, Department of Endocrinology, Medwin Hospital, Hyderabad-500001, Andhra Pradesh, India
2. Lalit Kumar Meher, Department of Medicine, MKCG Medical College, Berhampur, Orissa, India
3. Epari Sanjeeva Rao, Department of Pathology, KIMS Research Foundation, Amalapuram, Andhra Pradesh, India
4. Sruti Jammula, Department of Pharmaceutics, Roland Institute of Pharmaceutical Sciences, Khodasingi, Ambapua, BERHAMPUR-760010, Orissa, India
5. Siva Krishna Kota, Department of Anaesthesia, Central Security Hospital, Riyadh- 11481, Saudi Arabia
6. Kirtikumar D Modi, Department of Endocrinology, Medwin Hospital, Hyderabad-500001, Andhra Pradesh, India

Corresponds to: Dr Sunil Kumar Kota, DNB Resident, Department of Endocrinology, Medwin Hospitals, Chiragh Ali Lane, Nampally, Hyderabad-500001, Andhra Pradesh, India. ***E-mail:*** hidocsunil@ibibo.com

2. High Mobility Group Box Protein-1 (HMGB1): HMGB1 is an important late mediator of endotoxin shock, intraabdominal sepsis, and acute lung injury, and a promising therapeutic target of severe sepsis. Significantly lower levels of HMGB1 are found in sepsis nonsurvivors compared with survivors. In animal models of sepsis treatment with anti-HMGB1 antibodies significantly increased survival [55% (anti-HMGB1) vs. 9% (controls)]. The serum HMGB1 concentrations at postoperative hours 20 and 32 of the anti-HMGB1 antibody-treated animals were significantly lower than those of the control. Treatment with anti-HMGB1 antibodies markedly diminished the pathological changes and the number of HMGB1-positive cells in the cecum and the lung[2.]

3. Monocyte chemoattractant protein (MCP)-1: MCP-1, a prototype of CC chemokines, is a potent chemoattractant and a regulatory mediator involved in a variety of inflammatory diseases. Anti-MCP-1 strategies have shown promise in the treatment of sepsis and endotoxemia. In a study MCP-1 blockade, is shown to be significantly protective against sepsis and endotoxemia (attenuation in lung and liver myeloperoxidase (MPO) activity, reduced lung and liver injury as indicated by decreased thickening of alveolar and neutrophil infiltration in sepsis and LPS-induced endotoxemia)[3.]

4. Growth-related oncogene-alpha (GRO alpha): GRO-alpha, a member of the CXC chemokine family, induces endothelial dysfunction through oxidative stress and downregulation of eNOS. Studies have shown high levels of GRO-alpha in meningococcal sepsis/ septic shock and endotoxin induced shock[4.]

5. Interleukins: Interleukins play a major role in the initiation/propagation of sepsis. Various studies have established the roles of each interleukin. IL1 receptor antagonist correlates with SOFA score in sepsis[5] while IL1-beta is increased in septic compared to non septic patients6. IL-2 rise parallels the severity of sepsis[7] where as IL-4 is associated with development of sepsis8. Soluble interleukin-2 receptor levels facilitate the diagnosis of sepsis in premature infants with negative blood culture results. IL-6 and IL10 help distinguish survivors vs. non-survivors of sepsis at 28 days (IL10 and IL-13 are higher in septic shock than in sepsis)[9, 10.] IL-8 predicts development of multiorgan dysfunction and DIC (Disseminated Intravascular Coagulation)[11] and IL-12 helps predict lethal outcome after post-operative sepsis[12.]

6. Others: Macrophage inflammatory proteins (MIP-1 and MIP-2), Macrophage migration inhibitory factor (MIF), Osteopontin and RANTES have all showed association with sepsis.

Cell Marker Biomarkers

1. CD14: CD14, present in macrophage, monocyte, and granulocyte cells and their cell membranes, is responsible for intracellular transduction of endotoxin signals. The soluble CD14-subtype (sCD14-ST), also called presepsin, is produced in association with infections and is specifically expressed in sepsis. A study showed that presepsin values were significantly higher in patients with local infection, sepsis, and severe sepsis (compared to procalcitonin, CRP or IL-6) than in patients who did not have infection as a complication. It also significantly correlated with the APACHE II scores[13.]

2. Neutrophil CD64 index (CD64in): Activated neutrophilic granulocytes express Fc-gamma receptor [cluster of differentiation 64 (CD64) antigen. Neutrophil CD64 is known to be superior to C-reactive protein and hematological determinations for detecting systemic infection or sepsis with high sensitivity (?90%) and specificity (90%-100%) in both adults and children. It also helps us in distinguishing infection from flares in autoimmune inflammatory diseases and some utility in differentiating bacterial from viral infection. A study showed that CD64in is the best individual marker for bacterial sepsis in children, while in neonates the highest diagnostic accuracy at the time of suspected sepsis was achieved by LBP (lipopolysaccharide-binding protein) and 24 h later by CD64in[14.]

3. Soluble CD163: CD163 is expressed predominantly on macrophages with an anti-inflammatory phenotype (alternatively activated

macrophages). It may function as a scavenger receptor for haptoglobin-haemoglobin complexes. Soluble CD163 (sCD163), a part of the membrane-bound CD163 receptor, is shed by monocytes and macrophages upon inflammatory stimuli. sCD163 shows promise as an early indicator for the susceptibility to sepsis. A study showed that patients with high SOFA scores, sepsis and/or MODS/MOF during the time of hospitalization show high levels of sCD163[15].

4. mHLA-DR: HLA-DR molecules play a central role in the specific immune response to infection. The reduced HLA-DR expression on monocytes is considered to correlate with infectious complications and the development of sepsis. mHLA-DR is an independent predictor of mortality in septic shock patients and low mHLA-DR may provide a rationale for initiating therapy to reverse immunosuppression. In a study on 93 consecutive patients with septic shock at days 3-4 survivors had significantly increased mHLA-DR values, compared to non-survivors (43% vs. 18%). Low mHLA-DR (< 30%) at days 3-4 remained independently associated with mortality after adjustment for usual clinical confounders. mHLA-DR values may help to stratify patients when designing a mediator-directed therapy in a time-dependent manner[16].

5. Others: Other cluster designation markers like CD10, CD11b, CD11c, CD14 (cellular and soluble, CD18, CD25, CD28, CD40, CD48, CD64, CD69 and CD80 have shown documented associations with sepsis.

Receptor Biomarkers

1. Th2 response: Septic shock induces the shift of T lymphocytes toward a Th2 profile. The CRTH2 (chemoattractant receptor-homologous molecule expressed on Th2 cells) or CCR3 (eotaxin receptor, type 2 chemokine) expression which mirrors the Th2 response is severely decreased during septic shock. A study concluded the same and also found that in non-survivors of sepsis, there is persistence over time of low levels of CRTH2 or CCR3 expression[17].

2. FLT-1/VEGF: Vascular endothelial growth factor (VEGF), mediated by the gene FLT-1, contributes to endothelial cell activation and severity of illness in sepsis. Circulating levels of soluble VEGF receptor 1 (sFLT) levels were found to increase as part of the early response to sepsis. A study showed that the mean VEGF and sFLT levels were high among infected patients (higher among septic shock patients). While initial and 24-h VEGF levels had a significant correlation with the presence of septic shock at 24 h, the initial and 24-h sFLT levels correlated with Acute Physiology Age Chronic Health Evaluation II and Sepsis-related Organ Failure Assessment scores initially and at 24 h. They also correlated with inflammatory cascade activation[18].

3. Soluble uPAR: Urokinase plasminogen activator (uPAR) is a receptor mainly expressed on peripheral blood mononuclear cells and neutrophils. suPAR is a reliable marker of the severity of sepsis and a strong independent predictor of unfavorable outcome in VAP and sepsis. In a study suPAR in supernatants of neutrophils of patients with sepsis were greater compared to controls. Levels greater than 10.5Â ng/ml had 80% specificity and 77.6% positive predictive value to discriminate between severe sepsis and sepsis. It was also found to be an independent factor related with unfavorable outcome[19].

4. Soluble TREM-I (triggering receptor expressed on myeloid cells-I): Soluble TREM-I (soluble triggering receptor expressed on myeloid cells-I) is proven to get upregulated in the presence of infection. It is a sensitive and specific marker for early differentiation of infection from SIRS in trauma patients. In a study a highly significant increase in the level of sTREM-I was noted in patients with sepsis than in SIRS (which in turn was higher than the control group). The sensitivity and specificity of sTREM-I were significantly higher than those of procalcitonin (94.7% and 91.8% for sTREM-I and 84.2% and 75.4% for procalcitonin)[20].

5. Others: Transient receptor potential vanilloid (TRPV)1, RAGE (soluble Receptor for advanced glycation end products), Group II phospholipase A2 (PLA2-II) (soluble), GP130, Fc-gamma RIII, Fas receptor (soluble), C5a anaphylatoxin chemotactic receptor (C5L2) are

a few other receptor biomarkers researched for use in diagnosing sepsis.

Coagulation Biomarkers

1. Activated partial thromboplastin time (aPTT): aPTT waveform analysis may be a rapid and highly specific means to identify patients with sepsis. A study measured the degree of change causing a biphasic waveform aPTT transmittance (within the first hour of admission). Direct correlation was observed between the likelihood for sepsis and in-patient mortality with increasing waveform abnormalities. These were comparable with APACHE II scores and superior to those estimated by CRP for mortality/sepsis prediction. Biphasic waveforms also show a comparable specificity for the diagnosis of overt disseminated intravascular coagulation in sepsis[21.]

2. D-Dimers, TAT, Prothrombin factor (F1+2),PT, Fibrin: Elevated plasma tissue factor in patients with trauma and sepsis gives rise to thrombin generation, followed by intravascular coagulation. Development of DIC doubles the risk of mortality in sepsis. In a study on patients with sepsis, plasma tissue factor antigen concentration (tissue factor-markedly elevated in DIC) on days 0 through 4 showed markedly higher values than those in the control patients. Likewise significant correlations between tissue factor and prothrombin fragment F1+2, thrombin antithrombin complex (TAT), fibrinopeptide A (FPA), and D-dimer were observed in the DIC patients[22.]

3. Protein C and S, Thrombomodulin: The activation of coagulation seems to be amplified by impaired function of the protein C-protein S inhibitory pathway. An imbalance between coagulation and fibrinolysis, ultimately leading to plasminogen activator inhibitor type 1-mediated inhibition of fibrinolysis, may further promote the procoagulant state. A study showed that the expression of endothelial thrombomodulin and of the endothelial protein C receptor was lower in the patients with meningococcal sepsis than in the controls. Plasma thrombomodulin levels in the children with meningococcal sepsis (6.4 ng per liter) were higher than those in the controls (3.6 ng). Plasma levels of protein C antigen, protein S antigen, and antithrombin antigen were lower than those in the controls[23.]

4. Others: Antithrombin, PF-4 and Plasminogen activator are other coagulation biomarkers that can help diagnose the severity/presence of sepsis.

Endothelial Damage Biomarkers

1. Heparin-binding protein (HBP): HBP is released from activated neutrophils and is a potent inducer of vascular leakage. High plasma levels of HBP in febrile patients help to identify patients with an imminent risk of developing sepsis with circulatory failure. A study proved that plasma HBP level >= 15 ng/mL was a better indicator of severe sepsis (with or without septic shock) than procalcitonin, interleukin-6, lactate, C-reactive protein, and the number of white blood cells (sensitivity, 87.1%; specificity, 95.1%; positive predictive value, 88.4%; negative predictive value, 94.5%)[24.]

2. Neopterin (NT): Neopterin (NT) a pteridine compound is secreted by macrophages as a response to the stimulation of cytokines such as interferon-?, interferon-1?, tumor necrosis factor ? or bacterial components such as lipopolysaccharides. NT is known to predict the prognosis in patients with sepsis. In a study serum NT levels have been found to be increased in nonsurvivors (15 ng/mL) compared to survivors (5ng/ml) of sepsis[25.]

3. E-Selectin, L-Selectin: E-selectin is an early mediator of leukocyte-endothelial adhesion and is expressed on activated endothelium. Soluble E-selectin is present in the supernatant of cytokine-activated endothelial cells and elevated serum levels are found in a variety of inflammatory conditions. A study showed that patients with culture-positive sepsis had higher E-selectin levels (15.39 ng/ml) than those with culture-negative sepsis (4.87 ng/ml). Microbiological and hemodynamic status are independent variables related to E-selectin levels which are strongly related to the degree of hemodynamic compromise. Day 1 E-selectin levels correlated positively with peak organ failure score over the course of ICU hospitalization

and were higher for nonsurvivors than survivors26. L-selectin acts as a low-affinity signalling LPS receptor at higher concentrations of LPS. L-Selectin is also integral to leukocyte-rolling, the initial step in leukocyte recruitment to an inflammatory site. Soluble L-selectin (shed from leukocytes in sepsis) is known to diminish leukocyte rolling dose dependently at levels present in sepsis (2.33 ?g/mL). Increase in soluble L-selectin levels is one of the mechanisms for decreased leukocyte delivery and exudation to remote sites in septic patients[27].

4. ICAM-1, VCAM-1: Soluble ICAM-1 levels were independently related to group of sepsis, (initial cut off 274 ?g/L;higher values suggest hemoculture positive sepsis). The highest sICAM-1 levels were positively correlated with Score for Neonatal Acute Physiology (SNAP-II) scores28. In a study, plasma concentrations of VCAM-1(also E-selectin, ICAM-1) were increased in children with sepsis vs. control on day 1. Plasma VCAM-1 was increased in children with more than three organ failures vs. children with less than three organ failures. Plasma VCAM-1(and ICAM-1) predicted mortality and development of sequential (pulmonary/hepatic/renal) MOF[29].

5. Others: ADAMTS-13, Angiopoietin (1 and 2), Endocan, Endothelial leukocyte adhesion molecule (ELAM)-1 (cellular and soluble), Endothelial progenitor cells (cEPC), Laminin, Platelet-derived growth factor (PDGF)-BB, Vascular endothelial growth factor(VEGF), von Willebrand factor and antigen are other markers of endothelial damage in sepsis.

Vasodilation Biomarkers:

1. C-terminal pro-arginine vasopressin: Arginine vasopressin (AVP) levels are increased in hemorrhagic and septic shock. Since AVP has short half-life and its measurement is cumbersome, its precursor Copeptin can be measured. Copeptin is proved to be an independent significant predictor of outcome in sepsis. In a study Copeptin values increased significantly with the severity of the disease (27.6 pM in those without sepsis, 50.0 pM in sepsis, 73.6 pM in severe sepsis, and 171.5 pM in septic shock compared with 4.1 pM in healthy controls). They were also higher in nunsurvivors of sepsis30. In another study Mid-regional pro-atrial natriuretic peptide (MR-proANP) and C-terminal ProAVP (CT-proAVP) increased with increasing severity of CAP (according to the CURB-65 score), and were significantly lower in CAP survivors[31].

2. Substance-P: Substance P (SP), a preprotachykinin-A (PPTA) gene product, is an immunoregulatory neuropeptide implicated in various inflammatory diseases. Substance-P induces TNF-alpha mRNA expression and TNF-alpha secretion in a dose-dependent manner. In post-operative sepsis high substance P levels were identified as late predictive indicators of lethal outcome[32]. Substance-P also contributes to lung inflammation and lung injury in sepsis mainly via activation of the neurokinin-1 receptor[33].

3. cGRP: Calcitonin gene-related peptide (CGRP), a potent vasodilatory peptide, is upregulated after endotoxic shock. Upregulation of CGRP occurs transiently during the progression of sepsis (at the late phase of the hyperdynamic sepsis), and the gut appears to be a major source of such an increase in circulating levels of this peptide. In experimental models plasma levels of CGRP, 10 hours after induced early, hyperdynamic sepsis, increased by 177% and intestines are proposed to be the major source for sepsis[34]. CGRP is also known to be elevated in patients with acute bacterial meningitis and sepsis35. In sepsis it helps distinguish between survivors and non-survivors at 28 days and correlates with APACHE II score.

4. Others: Adrenomedullin, Proadrenomedullin, Anandamide, Angiotensin converting enzyme (ACE) (activity and serum), 2-arachidonoylglycerol, C-type natriuretic peptide, Cycling nucleotides and elastin, high-molecular weight kininogen, Neuropeptide Y, Nitric oxide (NO), nitrate, nitrite, Tetrahydrobiopterin, Vasoactive intestinal peptide (VIP) are some of the markers elevated in response ot vasodilation in sepsis.

Organ Dysfunction Biomarkers: 1. Visfatin: Visfatin, a Pre-B cell colony-enhancing factor (PBEF) is an adipocytokine affecting insulin

resistance by binding to the insulin receptor. It is upregulated in neutrophils by IL-1beta and functions as a novel inhibitor of apoptosis in response to a variety of inflammatory stimuli. Recombinant visfatin activates human leukocytes and induces cytokine production. In CD14+ monocytes, visfatin induces the production of IL-1, TNF-?,IL-6 and NF-?B activation36. There are several reports demonstrating enhanced tissue expression of visfatin in inflammatory conditions including acute lung injury and clinical sepsis.

2. Highly sensitive cardiac troponin T: Patients with severe sepsis and septic shock sport. Circulating hs-cTnT and it is known to associate with disease severity and survival. A study documented that levels of hs-cTnT were higher in patients with septic shock and non-survivors had higher levels than survivors (0.054 versus 0.035)[37.]

3. Heart-type fatty acid-binding protein (H-FABP): H-FABP is known to alter during infection-evoked organ dysfunction. Serum H-FABP and leptin are known to increase simultaneously and significantly in patients with pulmonary infection-induced multiple organ dysfunction[38.] Leptin may alleviate pulmonary and intestinal injuries by restraining tissue H-FABP secretions in sepsis.

4. Urinary L-type fatty acid-binding protein (L-FABP): In animal models sepsis is documented to induce significant increases of urinary L-type fatty acid-binding protein levels. It predicted severity more accurately than blood urea nitrogen, serum creatinine, and urinary N-acetyl-d-glucosaminidase levels. In clinical evaluation, urinary L-FABP measured at admission was significantly higher in the nonsurvivors of septic shock with established acute kidney injury than in the survivors[39.]

5. Gc-globulin: Gc-globulin has an important role in the clearance of procoagulant actin from the circulation after its release during cell necrosis and tissue injury. Gc-globulin has other potential roles in responses to acute tissue injury through conversion to a macrophage-activating factor, neutrophil chemotactic activity, and enhancement of C5a-mediated signaling. Admission levels of circulating Gc-globulin are associated with survival in sepsis. In a study plasma concentrations of Gc-globulin remained significantly lower in trauma patients who developed sepsis related severe multiorgan dysfunction, compared with those without these complications (127mg/dl vs 184mg/dl)[40.]

6. Hepatocyte growth factor (HGF): High plasma HGF levels may indicate the occurrence or necessity for tissue protection and regeneration after acute systemic insults in sepsis and significantly correlate with the presence of infection and with serum total bilirubin (TB) level. In a study plasma HGF levels in infection and SIRS were significantly higher than those groups without infection[41.]

7. Others: Brain natriuretic peptide (BNP), Carbomyl phosphate synthase, Endothelin-1 and pro-endothelin-1, Filterable cardiodepressant substance (FCS), Glial fibrillary acidic protein (GFAP), monoethylglycinexylidide, Myocardial angiotensin II, NSE, Pancreatitis-associated protein-I, Surfactant protein (A, B, C, D) have shown efficacy in quantifying the organ dysfunction in sepsis.

Acute Phase Protein Biomarkers

1. Procalcitonin (ProCT): ProCT is a potent partial agonist (50-60% of the CGRP efficacy) of the CGRP1 receptor (and inhibited CGRP-dependent cAMP responses) and a weak partial agonist activity at the AMY1 receptor. Procalcitonin is a useful marker to rule out sepsis and systemic inflammation. A study showed that with a calculated threshold of 0.1475 ng/mL, the sensitivity and specificity of procalcitonin assay for blood stream infections were 75% and 79%, respectively and the negative predictive value was 98% compared with blood cultures[42.] Another study documented that the reduction in unnecessary antibiotic usage (and consequent cost reduction implications) in patients with low PCT values, resulted in no adverse effects (neither progression of bacterial infection requiring antibiotics, nor complications or infection-related mortality)[43.]

2. Pentraxin 3 (PTX3): PTX3 is an inflammatory mediator produced by neutrophils, macrophages, myeloid dendritic and endothelial cells and is believed to be early marker of severity and outcome in sepsis. PTX3 correlates with severity of sepsis, with sepsis-associated coagulation/fibrinolysis dysfunction and mortality especially over the first few days. In a study PTX3 remained significantly higher in non-survivors than in survivors over the first 5 days. On day 1, PTX3 levels were higher in septic shock than in severely septic patients and significantly correlated with platelet count, PAI-1 activity and concentration, SAPS II score and SOFA score[44.]

3. Serum calprotectin: Serum Calprotectin (aka MRP8/14, calgranulin, cystic fibrosis-associated antigen), a complex of S100A8 and S100A9 is actively secreted via autocrine and paracrine mechanisms in phagocytes, endothelium, and other cells during stress response and it augments the inflammatory response in infections. It is an endogenous activator of TLR4 and promotes lethal, endotoxin-induced shock and a potent amplifier of inflammation in autoimmunity as well as in cancer development and tumor spread. Calprotectin protects cells against invasive microorganisms and regulates adhesion of leukocytes to the endothelium and extracellular matrix during the inflammatory process. A multicenter study involving newborns with a birth weight < 1500?g and a postnatal age > 72 hours of life compared and established the diagnostic accuracy of serum calprotectin (sensitivity 89%, specificity 96%) over most commonly used markers of neonatal sepsis (white blood cell count, immature-to-total-neutrophil ratio, platelet count, and C-reactive protein). Calprotectin is an early, accurate, and easy-to-use marker of neonatal sepsis[45.]

4. C-Reactive Protein: CRP is useful in the detection of sepsis and it is more sensitive than WBC although is now superceded by other better markers. A study showed that the median CRP values for Negative (without systemic inflammatory response syndrome (SIRS), Unlikely (SIRS with improbable sepsis), Probable (one criteria or more as SIRS with probable sepsis)and Definite groups(SIRS and a positive culture) were [24.5, 34, 143,] and 148 mg/l. The plasma CRP levels were significantly related to the infectious status (Negative, Unlikely, Probable or Definite). Concentrations of CRP in the Negative and Unlikely groups were significantly lower than in the Probable and Definite ones. A plasma CRP of 50 mg/l or more was highly suggestive of sepsis (sensitivity 98.5 %, specificity 75 %)[46.]

5. LBP: LBP is a type I acute phase response protein that is produced by hepatocytes, respiratory epithelial cells and a myriad of other cell types and enhances the recognition of endotoxin and pathogens by the immune system. LBP binds to Gram-negative bacteria via the lipid A part of the lipopolysaccharide (LPS) which mediates its binding to the CD14 cellular receptor molecule presented by monocytes and macrophages activating them inturn via Toll like receptors. Lipopolysaccharide binding protein (LBP) is a useful marker for diagnosis and prognosis of patients with bacterial infections. In a study LBP serum levels at 48 hours and at 7 days were significantly higher in nonsurvivors compared to survivors of severe sepsis (77.2 vs. 121.2 and 64.7 vs. 89.7 µg/ml respectively. These higher values correlated with ARDS and higher mortality as well[47.]

6. Others: Serum amyloid A (SAA), Ceruloplasmin, Ferritin, Alpha1-acid glycoprotein, Hepcidin are other acute phase proteins that can gauge the presence/severity of sepsis.

Other Markers

1. Neutrophil distribution width (NDW): NDW is a promising parameter to aid in the diagnosis of acute infection in adults (after ruling out the possibility of haematological disorders). In a study comparing NDW with C-reactive protein (CRP) and procalcitonin (PCT), a cut-off of 21.9 resulted in 90% sensitivity, 92% specificity, 90% positive predictive value, and 92% negative predictive value. Unlike the others, only NDW was able to differentiate an acute inflammatory process from early infection in postoperative patients. NDW had the highest diagnostic accuracy and is available with the complete

blood count with differential (CBC)[48].

2. Peroxiredoxin 4 (Prx4): Prx4 is a hydrogen peroxide degrading peroxidase found elevated in sepsis and reflects a perturbed antioxidant system. It plays a regulatory role in the activation of the transcription factor NF-kappaB. Prx 4 is a new biomarker for diagnosing, monitoring, and risk assessing patients in sepsis. In a study on 79 sick patients the diagnostic and prognostic performance of Prx4 was compared with other biomarkers (Procalcitonin, C-reactive protein and interleukin 6, total bilirubin and albumin), the APACHE II score and the SOFA score and a positive correlation was found with the severity score, poor prognosis, in hospital mortality. Median Prx4 serum levels gradually increased with disease severity (SIRS-2.32, sepsis -5.02, severe sepsis -11.7, or septic shock -11.4 arbitrary U/L). Prx 4 distinguished noninfectious from infectious inflammatory response syndrome[49].

3. RNA levels: Tie2 mRNA in peripheral blood is known to rise in conditions associated with the damage of endothelial cells. In rat sepsis models, Tie2 mRNA is found to be markedly raised and measurement of Tie2 mRNA using quantitative real-time PCR may thus be a simple and relatively sensitive method to evaluate the degree of endothelial damage50. Serum miR-146a and miR-223 were significantly reduced in septic patients compared with SIRS patients and healthy controls. They might serve as new biomarkers for sepsis with high specificity and sensitivity51. miR-150 levels in both leukocytes and plasma correlate with the aggressiveness of sepsis and can be used as a marker of early sepsis[52].

4. Eosinopenia: Eosinopenia is a very sensitive yet not specific serological marker of sepsis in the intensive care unit and can be utilized to guide physicians in the diagnosis of sepsis. In a study the eosinophil cell count (cutoff of 50 cells/mm3) produced a sensitivity of 81%, specificity of 65%, a PPV of 66%, and a NPV of 80%. The comparison of the eosinophil cell count (<50 cells/mm3) and procalcitonin levels among the non-infected and infected groups showed a significant statistical difference[53].

5. Glutathione S-transferase: Urinary pi-GST(glutathione S-transferase) is elevated early in all patients with sepsis syndrome. Testing for it may also indicate sensitive detection of an earlier phase of kidney injury, and suggests that sepsis-related renal injury affects the distal tubules. In a study median urinary pi-GST level (microg/L) in patients with sepsis at ICU admission was 10.8 in the non-AKI group, 19.3 in those who developed Stage 1 AKI, and 27.4 in those who developed Stage 3 AKI and was higher in all groups than in healthy control subjects[54].

6. YKL-40: YKL-40, also called human cartilage glycoprotein-39 (HC gp-39), is a member of family 18 glycosyl hydrolases/ mammalian chitinase-like proteins. It is a matrix protein of specific granules in human neutrophils. It is also secreted by chondrocytes, synovial cells, and macrophages and may be an autoantigen in rheumatoid arthritis. Serum YKL-40 levels are known to be significantly higher in sepsis. The higher sYKL-40 levels correlated with blood IL-6 level, positive blood culture, with septic shock, and those requiring continuous hemodiafiltration or hydrocortisone replacement therapy during subsequent treatment[55].

There is a myriad of other markers such as Apolipoprotein CI, cholesterol, HDL cholesterol, HLA-G5 protein (soluble), Inter-alpha inhibitor proteins (IalphaIp),Interferon gamma-induced protein 10(IP-10),lactate, lactoferrin, Nucleosomes, Plasmin alpha2-antiplasmin complex, Resistin, Selenium, Uric acid,Urinary 8-hydroxy-2'-deoxyguanosine, Xanthine oxidase (activity), Diiodotyrosine (DIT), Elastase-a1-antitrypsin complex, Heat shock proteins (HSP)70, 72, 73, 90 and 32, etc have been evaluated for diagnostic accuracy in sepsis with promising results.

Conclusion

In most scenarios this array of biomarkers can only adjuvant the over-all clinical picture that spans findings of history-examination and the laboratory values in navigating towards the diagnosis and severity of sepsis. Nevertheless the quest for the ideal biomarker goes on and clinicians need to be abreast of such relentless developments.

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