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Clinical Assays in Sepsis: Prognosis, Diagnosis, Outcomes, and the Genetic Basis of Sepsis

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Abstract

Sepsis is the most widespread medical disorder of the intensive care unit (ICU) and the most common cause of death in hospitalized patients. Several endothelium-related molecules have been investigated as potential biomarkers for early diagnosis and/or prognosis of sepsis, providing different results depending on study designs. Therefore, it seems that we are still far from the right combination of sepsis markers to be used in clinical practice. It is more probable that a panel of diverse biomarkers will be more efficient in clinical practice. More recently, the potential use of genetic biomarkers for prognostic purposes started emerging for sepsis, in the form of genome-wide association studies. The successful use of modern molecular diagnostics could enable rapid identification of particularly susceptible or less susceptible individuals, leading to tailored therapeutic treatments.

Keywords: sepsis, biomarkers, polymorphisms

1. Introduction

Sepsis, as defined by the third consensus definitions for sepsis and septic shock, is a life-threatening organ dysfunction caused by a dysregulated host response to infection, while septic shock is a subset of sepsis with circulatory and cellular/metabolic dysfunction associated with a higher risk of mortality [1]. However, in the studies used to establish the sepsis-3 guidelines, patient populations were primarily characterized by the previous definitions of sepsis, severe sepsis, and septic shock [2].

Sepsis is the most common medical disorder of the intensive care unit (ICU) and the most frequent cause of death in hospitalized patients; it accounts for 1,000,000 cases and 200,000 deaths annually in the United States alone [3]. Unlike other major epidemic illnesses, treatment for sepsis is nonspecific. The new surviving sepsis guidelines [4], that provide an update to the older guidelines [5, 6], presented statements on early management and resuscitation, limited primarily to support organ function and administration of intravenous fluids, antibiotics, and oxygen. Sepsis is a syndrome, not a disease [7] and it occurs in patients with infection [8]. There are no approved drugs that specifically target sepsis. Drotrecogin alfa (activated protein C), the only approved drug specifically indicated for the treatment of severe sepsis, was withdrawn from the market in 2011 [5, 9].

Hence, in the last several years, the search for prognostic and diagnostic markers of sepsis for their use in clinical practice reached its peak. Indeed, the 2001 International Sepsis Definitions Conference [2] introduced C-reactive protein (CRP) and procalcitonin (PCT) as inflammatory markers in the diagnostic criteria for sepsis. However, the new sepsis-3 definitions [1] recognized that sepsis is a syndrome without as yet a validated standard diagnostic test. Sepsis is recognized to involve early activation of both pro- and anti-inflammatory responses [10] along with major modifications in nonimmunologic pathways such as cardiovascular, neuronal, autonomic, hormonal, bioenergetic, metabolic, and coagulation [11], all of which have prognostic significance. The use of biomarkers for the early diagnosis of sepsis may permit early intervention which may reduce the risk of death. Combinations of pro- and anti-inflammatory biomarkers in a multimarker testing kit may help identify patients who develop severe sepsis before organ dysfunction has advanced too far [12]. Biomarker-guided immunotherapy that is administered to patients at the proper immune phase of sepsis may potentially be a major advance in the treatment of sepsis.

In the first part of the chapter, the most commonly studied biomarkers of sepsis are reviewed for their current uses and diagnostic accuracies, including C-reactive protein, procalcitonin, various cytokines and chemokines, endothelial biomarkers, and lactate. The second part of the chapter will focus on the genetic markers of sepsis.

2. Sepsis biomarkers

2.1. Pro-inflammatory biomarkers (acute-phase)

2.1.1. C-reactive protein (CRP)

Proteins, such as C-reactive protein and procalcitonin, are synthesized in response to infection and inflammation. CRP, named after its ability to precipitate the somatic C-polysaccharide of *Streptococcus pneumoniae*, was the first acute-phase protein to be described and comprises a very sensitive systemic marker of inflammation and tissue damage [13]. Currently, CRP is used as a clinical marker to assess the presence of infection and can help discriminate bacterial and viral infections [14]. Various studies have shown CRP to be a valuable marker for the diagnosis of sepsis [15–19] and disease severity [15, 20]. Besides its use in the diagnosis of

sepsis, CRP has also been evaluated as a prognostic marker. More specifically, in ICU patients, elevated concentrations of serum CRP on admission have been associated with increased risk of organ failure and mortality [21, 22]. There have been studies, however, that have not been able to demonstrate that CRP levels are indicative of survival in septic patients [23, 24].

2.1.2. Procalcitonin (PCT)

PCT is a protein consisting of 116 amino acids with a molecular weight of 13 kDa and is a precursor of calcitonin produced by C-cells of the thyroid gland, which is intracellularly cleaved by proteolytic enzymes into the active hormone [25]. In 1993 when its elevated level was found in patients with bacterial infection, PCT became an important protein in the detection and differential diagnosis of inflammatory states [26]. The highest levels of PCT are achieved in acute bacterial infections and sepsis. Since then, it has been widely investigated for its prognostic value in sepsis, and has become the most widely used biomarker in the management of infection and sepsis in Europe [27]. The efficacy of serial PCT concentrations has been evaluated as a prognostic biomarker of outcome in sepsis [28, 29]. PCT clearance has also been extensively studied as a biomarker for monitoring sepsis outcomes; at this end various reports have demonstrated significant improvement in PCT clearance in survivors compared to nonsurvivors in both severe sepsis and septic shock patients [28, 30–32]. A large meta-analysis comprising 23 studies with 3944 patients concluded that PCT nonclearance was a prognostic factor of death in patients with sepsis [33]. Hence, it has been suggested that PCT clearance could be indicative of patient outcome and serial PCT concentration measurements throughout hospitalization could facilitate treatment planning to improve patient outcome.

Several meta-analyses have investigated the value of PCT as a diagnostic marker of sepsis. However, this vast number of studies and meta-analyses has produced conflicting results. Uzzan *et al.* found that PCT represents a good biological diagnostic marker for sepsis, severe sepsis, or septic shock and suggested that procalcitonin should be included in diagnostic guidelines for sepsis and in clinical practice in intensive care units [34]. The findings of Tang *et al.* on the other hand do not support the widespread use of the procalcitonin test in critical care settings [35]. Another large meta-analysis consisting of 3244 patients suggested that PCT is a helpful biomarker for early diagnosis of sepsis in critically ill patients [36]. As far as prognosis is concerned, a meta-analysis of 2353 patients proved that there is a significant difference between PCT levels as early as day 1 between survivors and nonsurvivors among septic patients [37].

The efficacy of procalcitonin-guided antibiotic treatment has also been studied. A meta-analysis of 1075 patients concluded that procalcitonin is a helpful method to guide antibiotic therapy and surgical interventions without, however, exhibiting a beneficial effect on mortality [38]. The major benefit was shorter antibiotic treatment duration.

In conclusion, PCT in some studies has been found to be a superior marker of infection than CRP in critically ill patients, and nonetheless is a useful marker of the severity of infection [15, 39–43].

2.2. Cytokine/chemokine biomarkers

Cytokines are immuno-regulators produced in response to an infection or injury. A more clear understanding of the pathophysiological basis of sepsis, including the pro- and anti-inflammatory response during the hyperinflammatory and immunosuppressive phase of the disease, respectively, can lead to an alternative treatment approach. In septic patients, secretion of pro-inflammatory cytokines at the systemic inflammatory response syndrome or SIRS and anti-inflammatory cytokines, at the compensatory anti-inflammatory response syndrome (CARS) [44], occurs in a simultaneous manner from the very first instant of infection [45]. Mean serum levels of cytokines are higher in septic compared to nonseptic patients. Cytokines have therefore been proposed to be sepsis biomarkers in cases of neonatal and adult sepsis [46, 47]. Interleukin-6 (IL-6), IL-8, and IL-10 are the most extensively studied cytokines in diagnosing sepsis, evaluating the intensity of the inflammatory response and determining the prognosis for the patient. IL-6 comprises a pro-inflammatory cytokine, IL-8 is a major chemokine, and IL-10 represents an anti-inflammatory cytokine.

2.2.1. Pro-inflammatory cytokines and chemokines

Tumor necrosis factor-alpha (TNF- α), IL-1 β , and IL-6 are the cytokines that mediate the initial response of the innate immune system to injury or infection. Neutrophils are the first and most important cellular host defense against invading pathogens. Neutrophils migrate rapidly from the blood to the site of infection and this recruitment is mediated by pro-inflammatory mediators, such as TNF- α , IL-1 β , and neutrophil-active chemoattractants, like IL-8. Therefore, these cytokines are essentially responsible for the features of SIRS and could be potentially useful as biomarkers of sepsis. IL-6 enhances the liver's production of the so-called acute phase reactants, including CRP, and also stimulates a shift in the production of cells in the bone marrow so that more polymorphonuclear cells (PMNs) are produced. However, it is also possible that the cells entering circulation could disseminate inflammation into other organs, eventually leading to damage [48]. Impairment of neutrophil migration has been described in sepsis, suggesting that in human sepsis, failure of neutrophil migration is associated with a poor prognosis. In human sepsis, lipopolysaccharide (LPS) is known to induce TNF- α production by activating various kinases, leading to NF κ B (nuclear factor kappa light chain enhancer of activated B cells) activation.

Levels of circulating cytokines are frequently increased in sepsis [49–57]. IL-6 levels are increased in patients with infectious complications and have been used to differentiate SIRS from sepsis [58]. Studies have shown that high concentrations of TNF- α and IL-6 are predictive of organ failure and increased mortality in septic patients [55, 57, 59]. IL-8 has been used to predict the severity of sepsis in pediatric patients, although the use of IL-8 has not been confirmed in adults [60, 61]. A very recent study showed that the interleukin-1 receptor 2 (IL1R2) might be a better biomarker not only for sepsis diagnosis but also for differentiation of sepsis infected with G-positive or G-negative bacteria compared to PCT, Acute Physiology and Chronic Health Evaluation II (APACHE II), and CRP [62].

In line with this, clinical trials with an anti-TNF- α monoclonal antibody in septic patients did not show any advantage [63]. Interestingly, it was demonstrated in subsequent studies that blocking IL-6 caused a complete inhibition of endotoxin-induced activation of coagulation [64]. Administration of an IL-1 receptor antagonist partly blocked the pro-coagulant response in experimental sepsis models and inhibited thrombin generation in patients [65]. Overall, anti-TNF- α and IL-1 β clinical trials undertaken in patients with sepsis have been unsuccessful [66].

2.2.2. IL-27

IL-27, a bioactive member of the IL-12 cytokine family, may serve as a useful biomarker in estimating risk of bacterial infection among critically ill pediatric and adult patients [67–70]. Moreover, when used in combination with PCT, IL-27 may improve classification of critically ill adults with sepsis [68, 71].

2.2.3. Anti-inflammatory cytokines

Just as described above how the pro-inflammatory syndrome is characterized by many different and sometimes redundant cytokines, the CARS response also seems to involve many cytokines. The most important, however, is IL-10 [72]. It now has been established that IL-10 has multiple immunosuppressive roles [73] with its most important being the downregulation of TNF- α . Poor patient outcome has been associated with increased blood levels of the anti-inflammatory cytokine IL-10 [74]. IL-10 has been shown to protect endotoxemic mice [75–77], whereas in models of polymicrobial sepsis it seems to be deleterious [78, 79]. These inconsistent results likely depend on the time of administration and the severity of infection. Indeed, in view of these contradicting results, studies have documented that administration of anti-IL-10 monoclonal antibodies beyond the initial pro-inflammatory state of polymicrobial sepsis improves survival of animals subjected to sepsis [80], and furthermore, it is the timing and scale of the anti-inflammatory response that predicts severity of infection in murine model of sepsis [81].

To summarize, pro- and anti-inflammatory cytokines and chemokines have some value in the evaluation of the inflammatory response; however, they lack discriminative power to differentiate between infectious and noninfectious systemic inflammation. Elevated levels of pro- and anti-inflammatory cytokines are found mostly in nonsurvivors, whereas reduced levels are found in survivors of sepsis [82]. Even though they play an important part in the pathogenesis of sepsis, the role of cytokines as sepsis biomarkers remains to be established.

2.3. Endothelial proteins as potential biomarkers

Since early widespread endothelial dysfunction and/or damage appear to be directly involved in sepsis [83], there is a strong biological rationale for targeting markers of endothelial activation and dysfunction as biomarkers of the septic syndrome.

2.3.1. Angiopoietins

Angiopoietin-1 (Ang-1) and angiopoietin-2 are antagonistic factors that trigger endothelial cell (EC) activation; the role of angiopoietin-1 is to maintain vessel integrity and block vascular leakage, while angiopoietin-2 (Ang-2) counteracts the protective effects of Ang-1-Tie2 signaling [84, 85]. Ang-2 has been proposed as a biomarker in sepsis, since its release directly reflects vascular barrier breakdown [86–88]. More specifically, Ang-2 levels have been found to be elevated in patients with severe sepsis compared to patients with sepsis or not [89–91], higher Ang-2 levels have been reported in septic patients with worse clinical outcome [92–94], and increased Ang-2 levels have been demonstrated in nonsurvivors compared to survivors [95, 96]. Fewer studies have examined the role of Ang-1 in sepsis; those reports have shown either decreased levels of Ang-1 in critically ill patients compared to healthy controls, or have associated decreased levels at ICU admission with higher mortality [94, 97].

2.3.2. Selectins

Prior to the firm adhesion of leukocytes to the vascular endothelium and their transmigration to the sites of injury and inflammation, capture and rolling of leukocytes along the endothelium occurs. This is mediated by a family of cell adhesion molecules (or CAMs), called the selectin family [98]. Levels of soluble (s)E-selectin are very low in healthy individuals, whereas increased concentrations have been reported in various inflammatory pathologies [99–102]; other investigations have shown higher levels in nonsurvivors than survivors [103, 104]. Recently, it was demonstrated that sE-selectin levels may be used as predictor of fatal outcome in patients with SIRS [105]. Moreover, sE-selectin has also been proposed as a predictor of bacteremia in severe sepsis patients [106]. P-selectin has a similar function, but is constitutively expressed in lung ECs, and correlates with lung endothelial injury [107]. A recent study by Wang *et al.* [108] demonstrated in patients hospitalized for infections that higher baseline levels of interleukin-6, sE-selectin, and soluble intercellular adhesion molecule-1 (sICAM-1) may differentiate those patients who will develop a mild response to infection from those who will develop full-blown sepsis. A most recent study showed that high levels of the circulating endothelial adhesion molecules sE- and sP-selectin, measured at ICU admission, appear to be associated with sepsis development in time [109].

2.3.3. Soluble intercellular adhesion molecule-1 (sICAM-1)

Both the innate and adaptive immune responses depend on the migration of leukocytes across endothelial cells [110]. Specific adhesion glycoproteins are required for the binding of leukocytes to ECs. One such glycoprotein, intercellular adhesion molecule-1 (ICAM-1), controls the firm adhesion of neutrophils on endothelium and consequently their transmigration to the sites of infection. ICAM-1 has been studied as a biomarker of sepsis severity and outcome. These studies have produced inconsistent and conflicting results, possibly reflecting the time

point at which they were measured [105]. ICAM-1 production has been shown to be induced by endotoxins and has been associated with sepsis severity [102, 111] or mortality [111, 112], while sICAM-1 seems to be a reliable biomarker for distinguishing patients with sepsis from those with noninfectious SIRS [105].

2.3.4. Soluble platelet/endothelial cell adhesion molecule-1 (sPECAM-1)

Platelet/endothelial cell adhesion molecule-1 (PECAM-1, CD31) is a 130-kDa cell adhesion molecule that is expressed on the surfaces of leukocytes, such as monocytes, neutrophils, and some T-cell subsets, as well as on platelets and the intercellular junctions of endothelial cells [113]. Serum levels of sPECAM-1 have been demonstrated to be higher in septic patients compared with nonseptic patients at admission and are also higher compared to healthy controls [114, 115].

2.3.5. Endocan

Endocan is a proteoglycan expressed and secreted by the vascular endothelium in the lung and kidney, in response to pro-inflammatory cytokines and pro-angiogenic factors, which inhibits leukocyte migration [116]. The molecule is cleaved through the activity by cathepsin G generating a novel endocan peptide fragment of 14 kDa, named p14, which exhibits higher concentrations in septic patients compared to healthy volunteers [117]. Several studies have shown that this glycoprotein can be used as a strong and significant predictor of sepsis severity and outcome [118–122].

2.4. Receptor biomarkers

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

The soluble urokinase-type plasminogen activator receptor (suPAR) was first identified in 1985 as a cellular binding site for urokinase [123]. Since then suPAR has been investigated as a potential prognostic marker in the ICU. In critically ill patients, several studies have reported elevated suPAR in SIRS, bacteremia, sepsis, and septic shock, in which high circulating suPAR levels indicated a poor prognosis, including organ dysfunction and mortality [124–127].

Systematic reviews have concluded, however, that the diagnostic value of suPAR in sepsis is limited [128] and suPAR does not appear to be better in diagnosing sepsis compared to other biomarkers, like CRP and PCT [129, 130]. Plasma suPAR levels are, however, a sensitive and specific independent prognostic biomarker in patients with bacteremia. This plasma protein may be used to identify patients who are severely ill with pneumococcal bacteremia, and predict mortality [131–133].

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

Triggering receptor expressed on myeloid cells-1 (TREM-1) is an immunoglobulin whose signaling induces the production of cytokines, chemokines, and reactive oxygen species, all of which contribute to the inflammatory response. Furthermore, TREM-1 signaling leads to degranulation of neutrophils and increased phagocytosis. A soluble form of TREM-1 (sTREM-1) can be measured in body fluids and has potential as a diagnostic and prognostic biomarker of sepsis [134–139]. Other studies, however, have not been able to demonstrate sTREM-1 as a single marker sufficient for sepsis diagnosis and prognosis [140–142].

Systematic reviews of the literature have shown that elevated sTREM-1 concentrations have a moderate diagnostic performance in differentiating sepsis from SIRS and were not sufficient for sepsis diagnosis in systemic inflammatory patients [140]. Furthermore, it exhibits a moderate prognostic significance in assessing the mortality of infection in adult patients and sTREM-1 alone is insufficient to predict mortality as a biomarker [142]. However, sTREM-1 represents a reliable biological marker of bacterial infection [143].

2.4.3. Soluble endothelial protein C receptor (sEPCR)

The protein C (PC) anticoagulant system provides important control of both blood coagulation and inflammatory pathways [144]. This system also involves protein S (PS), and the endothelial receptors thrombomodulin (TM) and endothelial protein C receptor (EPCR). Conversion of PC to activated PC (APC) is generated by TM-bound thrombin and is drastically augmented by the presence of EPCR [145]. The presence of a soluble form of EPCR (sEPCR) that exists under normal conditions and which is elevated in conditions marked by enhanced inflammation [146], supports the notion of EPCR shedding. While the role of membrane EPCR is clearly antithrombotic and anti-inflammatory, the physiological significance of circulating sEPCR *in vivo* is as yet not fully understood and it is still unknown whether soluble EPCR levels may have a predictive value in the appearance of sepsis.

In previous studies, sEPCR levels in septic patients were found to be significantly higher [146, 147], unchanged [148], or even lower [149] than in healthy volunteers. A study by Kager *et al.* [150] showed that increased plasma sEPCR levels correlate with accelerated mortality in patients with melioidosis, while overexpression of EPCR in transgenic animals aggravates outcome during Gram-negative pneumonia-derived sepsis. In another recent report, early kinetics of sEPCR levels in severe sepsis was correlated with outcome [151], by a proposed mechanism of counteracting the anticoagulant action of membrane EPCR. The authors suggested that sEPCR could provide an early biological marker of outcome in severe sepsis. Vassiliou *et al.* [152] showed that levels of soluble EPCR at ICU admission are higher in originally nonseptic patients who subsequently become septic compared to those who will not.

2.4.4. Presepsin

Cluster of differentiation 14 (CD14) is a glycoprotein expressed on monocytes and macrophages, which serves as a receptor for lipopolysaccharides. As a pattern recognition molecule

it plays a role in the innate immune system by activating a pro-inflammatory signaling cascade upon contact with microorganisms [153]. During inflammation, protease activity releases soluble CD14 (sCD14) fragments, one of which has been identified as presepsin (sCD14-ST).

Presepsin was discovered as a new marker in Japan in 2002 [154], as a molecule whose levels were elevated specifically in the blood of patients with sepsis, and in the last few years has been extensively studied as a diagnostic and prognostic sepsis biomarker. In 2012, a multicenter prospective study investigated the clinical usefulness of presepsin for discriminating between bacterial and nonbacterial infections and compared it with PCT and IL-6 [155]. The study concluded that presepsin is useful for the diagnosis of sepsis and that it was superior to conventional markers and blood cultures. Ulla *et al.* [153] evaluated the diagnostic and prognostic value of presepsin in the emergency department and found that presepsin was useful in the early diagnosis of infection in a population of patients with SIRS, sepsis, severe sepsis, and septic shock. Moreover, presepsin exhibited a prognostic value, since its initial levels were correlated with mortality. In ICU patients, presepsin demonstrated diagnostic capacity in differentiating sepsis severity and prognostic value in mortality [156], while Masson *et al.* [157] found that presepsin measured on the first day in ICU in patients with severe sepsis or septic shock was higher in nonsurvivors compared to survivors, thus exhibiting useful prognostic importance. In 2015, three large meta-analyses concluded that presepsin has moderate diagnostic capacity for the detection of sepsis and it is an effective adjunct biomarker, but is insufficient to detect or rule out sepsis when used alone [158–160].

Since then, more studies have been performed, comparing presepsin to markers such as PCT and CRP. Results from these studies have shown that presepsin could differentiate between septic and nonseptic patients with comparable accuracy to CRP and PCT [161, 162], while presepsin and CRP showed similar performance for predicting 28-day mortality [161]. In patients with suspected sepsis, presepsin and PCT showed a good diagnostic accuracy in predicting bacteremia and bacterial DNAemia, superior to CRP [163]. In two very recent studies, presepsin seemed to be as valuable a biomarker as PCT or CRP in the evaluation of infectious complications in patients after heart transplantation [164], while another study concluded that the introduction of presepsin in clinical practice is not justified, since although it is a valuable biomarker for diagnosis of infection and sepsis, its diagnostic accuracy does not improve that of PCT [165].

Presepsin has been shown to be beneficial as a sepsis marker in adults. Nevertheless, very few data are available in neonates. Recent studies have shown that presepsin is significantly higher in preterm infants with early onset sepsis (EOS) compared with uninfected infants [166] and that it may be used as a reliable and accurate marker for both diagnosis and follow-up of EOS [167]. Pugni *et al.* [168] provided reference ranges for presepsin as an effective sepsis marker in neonates.

2.5. Lactate

Lactate is currently the most commonly used biomarker to identify sepsis. In the last years, several studies have emphasized the prognostic value of initial lactate levels or lactate

clearance [169, 170]. Lactate, apart from being the end product of anaerobic glycolysis reflecting tissue oxygen delivery-utilization, is also increased during stress and critical illness [171]. Elevated serum lactate levels are associated with poor outcomes in diverse populations of critically ill patients, such as multiple organ failure, morbidity, and mortality [172–175]. Clinically, serum lactate is a potentially useful biomarker to risk-stratify patients with severe sepsis presenting to the emergency department [170, 174, 175], so it has been hypothesized that early detection of elevated lactate levels may result in early identification of patients at risk of adverse outcomes [176]. In sepsis these elevated levels may be due to either impaired lactate clearance or excessive production [177, 178]. Two very recent studies [176, 179] utilized serum lactate levels at admission in order to diagnose sepsis in undifferentiated patients with suspected sepsis, emphasizing on the utility of early lactate measurement in such context, while Vassiliou *et al.* demonstrated that combining sE- and sP-selectin with serum lactate offers better prognostic value for sepsis development in initially nonseptic ICU patients [180].

Lactate kinetics has proved a valuable marker for response to resuscitative handlings in septic patients, associated with clinical outcome and mortality. Thus, according to the new sepsis-3 guidelines “patients with septic shock can be clinically identified by a vasopressor requirement to maintain a mean arterial pressure of 65 mmHg or greater and serum lactate level greater than 2 mmol/L (>18 mg/dL) in the absence of hypovolemia. This combination is associated with hospital mortality rates greater than 40%” [1].

2.6. Biomarker panels

Since as yet no single accepted biomarker or combination of biomarkers can be clinically used to diagnose patients with suspected sepsis, the multi-marker or panel approach has been suggested to improve clinical utility. Many groups have studied such biomarker panels. Kofoed *et al.* [181] showed that combining data from several markers improves diagnostic accuracy in detecting bacterial versus nonbacterial causes of inflammation. Another study identified a panel of three different biomarkers that could assess risk of organ dysfunction, shock, and death in emergency department patients with suspected sepsis [182].

Another panel including both pro-inflammatory and anti-inflammatory markers, comprising IL-6, IL-8, and the anti-inflammatory cytokine IL-10 was associated with a worse outcome for patients with sepsis [183]. As mentioned earlier, high concentrations of TNF- α and IL-6 are predictive of organ failure and increased mortality [55, 57], but poor patient outcome is also associated with increased levels of the anti-inflammatory cytokine IL-10 [74]. This apparent paradox is explained by the proposal that infection induces an initial stage of systemic inflammation (SIRS), with elevated blood levels of pro-inflammatory cytokines (e.g., TNF- α and IL-1 β), that is followed by a compensatory anti-inflammatory response (CARS) defined by high circulating levels of anti-inflammatory cytokines (e.g., IL-10 and IL-13), and it is indeed the sustained overproduction of the anti-inflammatory cytokine IL-10 that is the main predictor of severity and fatal outcome [184].

Figure 1 summarizes all major biomarkers involved in the inflammatory response in sepsis.

Figure 1. Major biomarkers in sepsis. During the inflammatory response a large number of cytokines, chemokines, and soluble molecules are secreted, affecting coagulation, endothelial activation and dysfunction, and vascular barrier permeability. The result is immune dysregulation and persistent immune suppression. The host immune response to sepsis includes activation of both pro- and anti-inflammatory stages and excessive activation of immune cells. Proteins, such as CRP and PCT are synthesized in the acute phase in response to infection and inflammation. The cells of the innate immune system release large amounts of pro- and anti-inflammatory cytokines, such as IL-1 β , IL-6, IL-8, TNF- α , and IL-10, during the hyper-inflammatory and immunosuppressive phase of the disease, respectively, from the very first instant of infection. The high levels of circulating cytokines can potentiate organ damage by endothelial injury and other routes. Ang-2 disrupts the protective effects of Ang-1-Tie2 signaling that maintains vessel integrity and inhibits vascular leakage. In critically ill patients, the release of Ang-2 directly reflects vascular barrier breakdown. Endothelial damage is associated with activation of neutrophils and expression of neutrophil and endothelial adhesion molecules. These molecules help localize leukocytes to the area of injury; however, before leaving the blood vessel, inflammatory molecules released by activated neutrophils can produce additional endothelial injury. Both the innate and adaptive immune responses depend on the migration of leukocytes across endothelial cells. The selectin family, including E-selectin and P-selectin, is an early mediator of the adhesion of activated neutrophils to endothelia in inflammatory states, before their firm adhesion and diapedesis at sites of tissue injury and inflammation. ICAM-1 controls the firm adhesion of neutrophils on endothelium and consequently transendothelial neutrophil migration response to sites of infection. PECAM-1 is a phosphoprotein highly expressed on endothelial cells and leukocytes, and comprises an important component in the regulation of neutrophil transendothelial migration. Endocan is a proteoglycan expressed and secreted by the vascular endothelium in response to pro-inflammatory cytokines and pro-angiogenic factors, and inhibits leukocyte migration. The soluble forms of these proteins have been found increased in the sera of septic patients. uPAR is a part of the plasminogen activation system, which is involved in tissue reorganization events. The soluble form of uPAR, suPAR, forms when UPA binds to uPAR, and its levels are increased in sepsis. TREM-1 is an inflammatory immunoglobulin superfamily member, which is expressed in neutrophils, monocytes, and macrophages. TREM-1 triggers and expands the inflammatory response, with promoted production of inflammatory mediators, inhibited expression of anti-inflammatory mediators, and activated and amplified inflammatory cascade. sTREM-1 is a subtype of secreted TREM-1, which has been shown to be released into the blood during infection. The protein C anticoagulant system also involves protein S, and the endothelial receptors TM and EPCR. Conversion of protein C to the anticoagulant APC is generated by TM-bound thrombin and is drastically augmented by the presence of EPCR. The presence of a soluble form of EPCR (sEPCR) is elevated in conditions marked by enhanced inflammation, of unknown physiological significance. CD14 is yet another glycoprotein expressed on monocytes and macrophages, and serves as a receptor for lipopolysaccharides. As a pattern recognition molecule it plays a role in the innate immune system by activating a pro-inflammatory signaling cascade upon contact with microorganisms. During inflammation, protease activity releases soluble CD14 (sCD14) fragments, one of which has been identified as presepsin. Other pattern recognition receptors involved in immunity are TLRs. Stimulation of TLRs by microbial components triggers expression of several genes that are involved in immune responses. Finally, lactate is also increased due to production by various tissues through aerobic and anaerobic glycolysis, and from a decreased lactate clearance. Ang-1, angiopoietin-1; Ang-2, angiopoietin-2; APC, activated protein C; CD14, cluster of differentiation 14; CRP, C-reactive protein; IL, interleukin; PCT, procalcitonin; sEPCR, soluble endothelial protein C receptor; sICAM-1, soluble intercellular adhesion molecule-1; sPECAM-1, soluble platelet/endothelial cell adhesion molecule-1; sTREM-1, soluble triggering receptor expressed on myeloid cells-1; suPAR, soluble urokinase-type plasminogen activator receptor; TM, thrombomodulin; TNF- α , tumor necrosis factor-alpha; TLR, Toll-like receptors; UPA, urokinase-type plasminogen activator.

3. Genetic polymorphisms in sepsis

The prospective of genetic biomarkers for prognostic use is well-known for mostly uncommon/rare inherited disorders, but is also emerging for sepsis [185, 186]. Most genes carry single-nucleotide polymorphisms (SNPs) at specific exonic or intronic regions.

In order to identify potential markers of susceptibility, severity, and clinical outcome, potential markers for survivors and nonsurvivors, and ultimately to identify targets for therapeutic intervention, gene polymorphisms have become the most widely used form of experimental study. In an attempt to deal with the limitations of these studies, such as small sample size and bias in selecting candidate polymorphisms and genes, genome-wide association studies (GWAS) are now emerging. GWAS concern large, well-conducted, multicenter studies that do not involve a prior hypothesis of candidate genes to test for association with disease.

3.1. Cell signaling pathways of the innate immune system

3.1.1. Pattern recognition receptors (PRR)

3.1.1.1. Toll-like receptors (TLRs)

Functional characterization of Toll-like receptors (TLRs) has established that innate immunity is an adept system that detects invasion of microbial pathogens. Stimulation of TLRs by microbial components triggers expression of several genes that are involved in immune responses [187]. TLR4 is an essential receptor for Gram-negative enteric LPS recognition [188, 189]. The Asp299Gly mutation in human TLR4 impairs LPS signaling in homozygous and heterozygous individuals [190], while Smirnova *et al.* [191] observed that rare heterozygous missense mutations of TLR4 contribute to the development of systemic meningococcal disease. The D299G allele of the *TLR4* gene has also been associated with increased susceptibility to severe bacterial infections and Gram-negative sepsis [192, 193].

3.1.2. Cellular innate immune response

3.1.2.1. IL-8

The 251A/T allele (rs4073) of the *IL-8* gene has been studied for its implication in sepsis and outcomes. Results until now have shown association of the allele with higher plasma IL-8 levels, as well as with survival [194]. The A allele has been suggested to be associated with protection against sepsis [195], and also with increased risk of sepsis [196]. The heterozygote AT genotype has been associated with increased risk of developing severe sepsis [197]. In a more recent study, the male population carrying the homozygote TT genotype was found to be more susceptible to sepsis, while no association was determined between the 251A/T allele and IL-8 serum levels in septic patients [198].

3.2. Adaptive immune response

3.2.1. Cytokines

3.2.1.1. Tumor necrosis factor- α promoter polymorphisms

Initially, the G-to-A polymorphism at position 308nt in the promoter region of the *TNF- α* gene was found to be associated with adverse outcome in patients with severe sepsis and septic shock [199, 200]. A large meta-analysis [201] concluded that the polymorphism is associated with sepsis, but is not associated with sepsis mortality. However, several studies later were not able to show association of *TNF- α* -308 SNP and development of sepsis [202, 203].

3.2.1.2. *IL-6* polymorphisms

A key inflammatory cytokine that has been examined in genetic association studies in infectious diseases is , producing also conflicting results. First of all, studies on the C allele of the G/C polymorphism at position 174nt of the *IL-6* gene have shown its association with both high and low plasma *IL-6* levels [204, 205], or even no association at all [206]. One study in critically ill patients did not find association between the 174 G/C polymorphism and sepsis appearance, but associated the polymorphism with improved survival rates in patients with sepsis [207]. A different study reported that the same polymorphism was not associated with survival [208]. A meta-analysis on the position 174nt polymorphism and the risk of sepsis in very low birth weight infants concluded that the available data are not consistent with more than a modest association between the *IL-6* polymorphism and neonatal sepsis [209].

3.3. Systemic effectors of inflammation and coagulation

3.3.1. Angiotensin-converting enzyme (ACE)

Studies have compared the effects of the angiotensin-converting enzyme (ACE) insertion/deletion (I/D) polymorphisms on the incidence and outcome of sepsis and acute respiratory distress syndrome (ARDS). In ventilated low birth weight infants the ACE insertion/deletion (I/D) polymorphism does not have a significant effect on the incidence or outcome of sepsis [210, 211]. Studies and meta-analyses showed that carriers of I allele (D/I genotype and I/I genotype) were at increased sepsis risk [212–214], but the polymorphism is not associated with outcome in critically ill septic patients [214, 215]. With regard to ARDS, the data of Villar *et al.* [216] do not support an association of the ACE gene I/D polymorphism with susceptibility or mortality in severe sepsis or with sepsis-induced ARDS in Spanish patients, but Cardinal-Fernandez *et al.* demonstrated that the presence of the allele D of the ACE gene is associated with ARDS in patients with severe sepsis [217].

3.3.2. Endothelial protein C receptor (EPCR)

A few studies have compared the effects of the *EPCR* haplotypes on the incidence and outcome of sepsis. Two studies have shown that *EPCR* mutations and polymorphisms influence the risk of severe sepsis in children and adults [218, 219]. More specifically, the rare 23-bp insertion is significantly more common among patients with severe sepsis [218], while simultaneous carriers of minor alleles belonging to both the H1 and H3 haplotypes may be at reduced risk of developing severe sepsis and/or septic shock among critically ill patients [219].

Table 1 lists the role of major circulating biomarkers and genetic polymorphisms in the prognosis and diagnosis of sepsis.

Biomarker	Diagnostic significance	Prognostic significance
C-reactive protein (CRP)	<ul style="list-style-type: none"> - Discriminates bacterial and viral infections [14] - Measurement of CRP is an indicator of sepsis [15–19] 	<ul style="list-style-type: none"> - CRP is a valuable marker for the disease severity [15, 20] - Elevated concentrations of serum CRP on admission have been associated with increased risk of organ failure and mortality [21, 22]
Procalcitonin (PCT)	<ul style="list-style-type: none"> - PCT is important in the detection and differential diagnosis of inflammatory states [26]. The highest levels of PCT are achieved in acute bacterial infections and sepsis - PCT is a good biological diagnostic marker for sepsis, severe sepsis, or septic shock [34] - PCT is a helpful biomarker for early diagnosis of sepsis in critically ill patients [36] - Serial PCT concentrations may have value in monitoring sepsis outcomes [28, 29] 	<ul style="list-style-type: none"> - PCT nonclearance is a prognostic factor of death in patients with sepsis [33] - Significant difference between PCT levels as early as day 1 between survivors and nonsurvivors among septic patients [37]
Tumor necrosis factor- α (TNF- α)	<ul style="list-style-type: none"> - Levels of TNF-α are frequently increased in sepsis [49, 56] 	<ul style="list-style-type: none"> - High concentrations of TNF-α are predictive of organ failure and increased mortality in septic patients [55]
Interleukin-1 β (IL-1 β)	<ul style="list-style-type: none"> - Levels of IL-1β are frequently increased in sepsis [56] 	
Interleukin-6 (IL-6)	<ul style="list-style-type: none"> - Levels of IL-6 are frequently increased in sepsis [50, 54, 56] - IL-6 levels are increased in patients with infectious complications and have been used to differentiate systemic inflammatory response syndrome (SIRS) from sepsis [58] 	<ul style="list-style-type: none"> - High concentrations of IL-6 are predictive of organ failure and increased mortality in septic patients [57, 59]

Biomarker	Diagnostic significance	Prognostic significance
Interleukin-8 (IL-8)	- Levels of IL-8 are frequently increased in sepsis [50, 56]	- IL-8 has been used to predict the severity of sepsis in pediatric patients, although the use of IL-8 has not been confirmed in adults [60, 61]
Interleukin-27 (IL-27)	- Useful biomarker in estimating risk of bacterial infection among critically ill pediatric and adult patients [67–70] - In combination with PCT, IL-27 may improve classification of critically ill adults with sepsis [68, 71]	
Interleukin-10 (IL-10)		- Poor patient outcome has been associated with increased blood levels of the anti-inflammatory cytokine IL-10 [74]
Angiopietin-1 (Ang-1)	- Decreased levels in critically ill septic or nonseptic patients compared to healthy controls [94]	- Decreased levels of Ang-1 at ICU admission are correlated with higher mortality [97]
Angiopietin-2 (Ang-2)	- Ang-2 levels are higher in patients with severe sepsis compared to patients with or without SIRS or sepsis [89–91]	- Increased Ang-2 plasma levels have been associated with worst clinical outcome in patients with major trauma and severe sepsis or shock [92–94] - Increased Ang-2 plasma in nonsurvivors compared to survivors [95, 96]
Selectins	- Soluble E-selectin concentration increases in various inflammatory pathologies [99–102]	- Higher sE-selectin levels in nonsurvivors than survivors [103, 104] - sE-selectin levels may be used as predictor of fatal outcome in patients with SIRS [105] - sE-selectin has also been proposed as a predictor of bacteremia in severe sepsis patients [106] High levels of sE- and sP-selectin at ICU admission, are associated with sepsis development in time [109]
Soluble intercellular adhesion molecule-1 (sICAM-1)	- sICAM-1 production has been shown to be related to increased sepsis severity [102, 111] - sICAM-1 appears to be a reliable biomarker for classifying patients with infectious SIRS, i.e., sepsis, from those with noninfectious SIRS [105]	- sICAM-1 concentration has been shown to be related to increased mortality [111, 112]
Soluble platelet/endothelial cell adhesion molecule-1 (sPECAM-1)	- sPECAM-1 is higher at admission in septic patients compared with nonseptic patients and healthy controls [114, 115]	
Endocan	- Exhibits higher concentrations in septic patients compared to healthy volunteers [117]	- A strong and significant predictor of sepsis severity and outcome [118–122]

Biomarker	Diagnostic significance	Prognostic significance
Soluble urokinase-type plasminogen activator receptor (suPAR)	<ul style="list-style-type: none"> - Elevated suPAR in conditions of SIRS, bacteremia, sepsis, and septic shock [124–127] - Diagnostic value of suPAR for identifying sepsis is limited [128] 	<ul style="list-style-type: none"> - High circulating suPAR levels indicate an unfavorable prognosis, including organ dysfunction and mortality [124–127] - In patients with bacteremia, suPAR may be used to identify severely ill patients and predict mortality [131, 133]
Soluble triggering receptor expressed on myeloid cells-1 (sTREM-1)	<ul style="list-style-type: none"> - Moderate diagnostic performance in differentiating sepsis from SIRS [140] - sTREM-1 represents a reliable biological marker of bacterial infection [143] 	<ul style="list-style-type: none"> - Moderate prognostic significance in assessing the mortality of infection in adult patients and sTREM-1 alone is insufficient to predict mortality as a biomarker [142]
Soluble endothelial protein C receptor (sEPCR)	<ul style="list-style-type: none"> - sEPCR levels in septic patients have been found to be significantly higher [146, 147], unchanged [148], or lower [149] than in healthy volunteers 	<ul style="list-style-type: none"> - sEPCR levels correlated with worst outcomes; has been suggested that it may act as a biological marker of outcome in severe sepsis [150–152] - Levels of sEPCR at ICU admission are higher in originally nonseptic patients who subsequently become septic compared to those who will not [152]
Presepsin	<ul style="list-style-type: none"> - Discriminates between bacterial and nonbacterial infections [155] - Early diagnosis of infection in a population of patients with SIRS, sepsis, severe sepsis, and septic shock [153] - In patients with suspected severe sepsis and septic shock, presepsin reveals valuable diagnostic capacity to differentiate sepsis severity [156] - Presepsin can differentiate between septic and nonseptic patients with comparable accuracy to CRP and PCT [161, 162] 	<ul style="list-style-type: none"> - Initial values significantly correlated with in-hospital mortality of patients affected by sepsis, severe sepsis, or septic shock [156] - Presepsin reveals prognostic value with respect to 30 days and 6 months all-cause mortality throughout the first week of ICU treatment [153] - Presepsin measured on the first day in ICU in patients with severe sepsis or septic shock was higher in nonsurvivors compared to survivors [157]
Lactate	<ul style="list-style-type: none"> - Elevated serum lactate levels in sepsis [177, 178] - Early serum lactate levels can diagnose sepsis in undifferentiated patients with suspected sepsis [176, 179] 	<ul style="list-style-type: none"> - Elevated serum lactate levels are associated with poor outcomes in diverse populations of critically ill patients, such as multiple organ failure, morbidity, and mortality [172–175] - Serum lactate is a potentially useful biomarker to risk-stratify patients with severe sepsis presenting to the emergency department [170, 174, 175]

Biomarker	Diagnostic significance	Prognostic significance
		- Combining sE- and sP-selectin with serum lactate offers better prognostic value for sepsis development in initially nonseptic ICU patients [180]
Genetic polymorphisms	- Distinguish patients with sepsis from patients with sterile inflammation	- Predict long-term outcomes and identify patients who will be at risk for developing adverse clinical outcomes
Toll-like receptors (TLRs)		- D299G allele of <i>TLR4</i> gene associated with increased susceptibility to severe bacterial infections and Gram-negative sepsis [192, 193]
<i>IL-8</i>		- The 251A/T allele has been associated with survival [194], protection against sepsis [195], and also increased risk of sepsis [196]
		- The heterozygote AT genotype has been associated with increased risk of developing sepsis [197]
		- Male T allele carriers are more susceptible to sepsis [198]
<i>TNF-α</i>	- G-to-A polymorphism associated with sepsis [201]	- G-to-A polymorphism associated with adverse outcomes in patients with severe sepsis and septic shock [199, 200]
	- No association of G-to-A polymorphism and development of sepsis [202, 203]	- G-to-A polymorphism not associated with sepsis mortality [201]
<i>IL-6</i>	- 174 G/C polymorphism showed modest association with neonatal sepsis [209]	- 174 G/C polymorphism was associated with improved survival rates in patients with sepsis [207]
		- 174 G/C polymorphism was not associated with a difference in survival [208]
Angiotensin-converting enzyme (<i>ACE</i>)		- Insertion/deletion (I/D) polymorphism does not have an effect on the incidence or outcome of sepsis in ventilated low birth infants [210, 211]
		- Carriers of the I allele at increased sepsis risk [212–214]
		- I polymorphism not associated with outcome in critically ill septic patients [214–216]
		- The presence of the D allele is associated with ARDS in patients with severe sepsis [217]

Biomarker	Diagnostic significance	Prognostic significance
Endothelial protein C receptor (<i>EPCR</i>)	- The rare 23-bp insertion is significantly more common among patients with severe sepsis [218]	- Influences the risk of severe sepsis in children and adults [218, 219] - Simultaneous carriers of minor alleles belonging to both the H1 and H3 haplotypes may be at reduced risk of developing severe sepsis and/or septic shock among critically ill patients [219]

Table 1. Role of major circulating biomarkers and genetic polymorphisms in sepsis. Please note that the protein names are capitalized, whereas gene names are capitalized and italicized.

4. Conclusion

Unfortunately, a lot of work remains to find the right combination of markers to be used in clinical practice. Some have been effective in reducing mortality, but their use in diagnosis and prognosis of sepsis has been limited. It seems that a panel of diverse biomarkers rather than a group of two or three related biomarkers will be more efficient in clinical practice.

Genome-wide association studies may help confirm current findings and make them clinically applicable. Hence, developing high-throughput approaches for the analysis of alternative mechanisms by which SNPs can cause disease will be one of the remaining challenges for genomic research. Hopefully, the findings that will be generated will facilitate the successful use of modern molecular diagnostics and could enable rapid identification of particularly susceptible or less susceptible individuals, leading to tailored therapeutic approaches.

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References

- [1] Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *The Journal of the American Medical Association*. 2016 Feb 23;315(8):801-10.
- [2] Levy MM, Fink MP, Marshall JC, Abraham E, Angus D, Cook D, et al. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. *Intensive Care Medicine*. 2003 Apr;29(4):530-8.
- [3] Angus DC, van der Poll T. Severe sepsis and septic shock. *The New England Journal of Medicine*. 2013 Aug 29;369(9):840-51.
- [4] Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, et al. Surviving Sepsis Campaign: International guidelines for management of sepsis and septic shock: 2016. *Critical Care Medicine*. 2017 Mar;45(3):486-552.
- [5] Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, et al. Surviving Sepsis Campaign: International guidelines for management of severe sepsis and septic shock, 2012. *Intensive Care Medicine*. 2013 Feb;39(2):165-228.
- [6] Levy MM, Dellinger RP, Townsend SR, Linde-Zwirble WT, Marshall JC, Bion J, et al. The surviving sepsis campaign: Results of an international guideline-based performance improvement program targeting severe sepsis. *Intensive Care Medicine*. 2010 Feb;36(2):222-31.
- [7] Vincent JL, Opal SM, Marshall JC, Tracey KJ. Sepsis definitions: Time for change. *Lancet*. 2013 Mar 2;381(9868):774-5.
- [8] Deutschman CS, Tracey KJ. Sepsis: Current dogma and new perspectives. *Immunity*. 2014 Apr 17;40(4):463-75.
- [9] Angus DC. Drotrecogin alfa (activated)...a sad final fizzler to a roller-coaster party. *Critical Care*. 2012 Feb 06;16(1):107.
- [10] Hotchkiss RS, Monneret G, Payen D. Sepsis-induced immunosuppression: From cellular dysfunctions to immunotherapy. *Nature Reviews Immunology*. 2013 Dec;13(12):862-74.
- [11] Singer M, De Santis V, Vitale D, Jeffcoate W. Multiorgan failure is an adaptive, endocrine-mediated, metabolic response to overwhelming systemic inflammation. *Lancet*. 2004 Aug 7-13;364(9433):545-8.
- [12] Vincent JL, Beumier M. Diagnostic and prognostic markers in sepsis: Expert review of anti-infective therapy. 2013 Mar;11(3):265-75.
- [13] Pepys MB, Hirschfield GM. C-reactive protein: A critical update. *Journal of Clinical Investigation*. 2003 Jun;111(12):1805-12.
- [14] Shaw AC. Serum C-reactive protein and neopterin concentrations in patients with viral or bacterial infection. *Journal of Clinical Pathology*. 1991 Jul;44(7):596-9.

- [15] Ugarte H, Silva E, Mercan D, De Mendonca A, Vincent JL. Procalcitonin used as a marker of infection in the intensive care unit. *Critical Care Medicine*. 1999 Mar;27(3):498-504.
- [16] Huntley JS, Kelly MB. C-reactive protein: A valuable acute investigation: A case of pneumococcal meningitis presenting as ankle pain. *Emergency Medicine Journal*. 2005 Aug;22(8):602-3.
- [17] Kawczynski P, Piotrowski A. Procalcitonin and C-reactive protein as a markers of neonatal sepsis. *Ginekologia Polska*. 2004 Jun;75(6):439-44.
- [18] Povoia P. C-reactive protein: A valuable marker of sepsis. *Intensive Care Medicine*. 2002 Mar;28(3):235-43.
- [19] Povoia P, Teixeira-Pinto AM, Carneiro AH. C-reactive protein, an early marker of community-acquired sepsis resolution: A multi-center prospective observational study. *Critical Care*. 2011 Jul 15;15(4):R169.
- [20] Suprin E, Camus C, Gacouin A, Le Tulzo Y, Lavoue S, Feuillu A, et al. Procalcitonin: A valuable indicator of infection in a medical ICU? *Intensive Care Medicine*. 2000 Sep;26(9):1232-8.
- [21] Devran O, Karakurt Z, Adiguzel N, Gungor G, Mocin OY, Balci MK, et al. C-reactive protein as a predictor of mortality in patients affected with severe sepsis in intensive care unit. *Multidisciplinary Respiratory Medicine*. 2012 Nov 21;7(1):47.
- [22] Lobo SM, Lobo FR, Bota DP, Lopes-Ferreira F, Soliman HM, Melot C, et al. C-reactive protein levels correlate with mortality and organ failure in critically ill patients. *Chest*. 2003 Jun;123(6):2043-9.
- [23] Miguel-Bayarri V, Casanoves-Laparra EB, Pallas-Beneyto L, Sancho-Chinesta S, Martin-Osorio LF, Tormo-Calandin C, et al. Prognostic value of the biomarkers procalcitonin, interleukin-6 and C-reactive protein in severe sepsis. *Medicina Intensiva*. 2012 Nov;36(8):556-62.
- [24] Tschaikowsky K, Hedwig-Geissing M, Braun GG, Radespiel-Troeger M. Predictive value of procalcitonin, interleukin-6, and C-reactive protein for survival in postoperative patients with severe sepsis. *Journal of Critical Care*. 2011 Feb;26(1):54-64.
- [25] Maruna P, Nedelnikova K, Gurlich R. Physiology and genetics of procalcitonin. *Physiological Research*. 2000;49(Suppl. 1):S57-61.
- [26] Assicot M, Gendrel D, Carsin H, Raymond J, Guilbaud J, Bohuon C. High serum procalcitonin concentrations in patients with sepsis and infection. *Lancet*. 1993 Feb 27;341(8844):515-8.
- [27] Reinhart K, Bauer M, Riedemann NC, Hartog CS. New approaches to sepsis: Molecular diagnostics and biomarkers. *Clinical Microbiology Reviews*. 2012 Oct;25(4):609-34. PubMed PMID: 23034322. Pubmed Central PMCID: PMC3485751. Epub 2012/10/05. Eng.

- [28] de Azevedo JR, Torres OJ, Beraldi RA, Ribas CA, Malafaia O. Prognostic evaluation of severe sepsis and septic shock: Procalcitonin clearance vs delta sequential organ failure assessment. *Journal of Critical Care*. 2015 Feb;30(1):219 e9-12.
- [29] Sridharan P, Chamberlain RS. The efficacy of procalcitonin as a biomarker in the management of sepsis: Slaying dragons or tilting at windmills? *Surgical Infections*. 2013 Dec;14(6):489-511.
- [30] Huang MY, Chen CY, Chien JH, Wu KH, Chang YJ, Wu KH, et al. Serum procalcitonin and procalcitonin clearance as a prognostic biomarker in patients with severe sepsis and septic shock. *Biomed Research International*. 2016;2016:1758501.
- [31] Mat Nor MB, Md Ralib A. Procalcitonin clearance for early prediction of survival in critically ill patients with severe sepsis. *Critical Care Research and Practice*. 2014;2014:819034. PubMed PMID: 24719759.
- [32] Shi Y, Peng JM, Hu XY, Wang Y. The utility of initial procalcitonin and procalcitonin clearance for prediction of bacterial infection and outcome in critically ill patients with autoimmune diseases: A prospective observational study. *BMC Anesthesiology*. 2015 Oct 07;15:137.
- [33] Liu D, Su L, Han G, Yan P, Xie L. Prognostic value of procalcitonin in adult patients with sepsis: A systematic review and meta-analysis. *PLoS One*. 2015;10(6):e0129450. PubMed PMID: 26076027.
- [34] Uzzan B, Cohen R, Nicolas P, Cucherat M, Perret GY. Procalcitonin as a diagnostic test for sepsis in critically ill adults and after surgery or trauma: A systematic review and meta-analysis. *Critical Care Medicine*. 2006 Jul;34(7):1996-2003.
- [35] Tang BM, Eslick GD, Craig JC, McLean AS. Accuracy of procalcitonin for sepsis diagnosis in critically ill patients: Systematic review and meta-analysis. *The Lancet Infectious Diseases*. 2007 Mar;7(3):210-7.
- [36] Wacker C, Prkno A, Brunkhorst FM, Schlattmann P. Procalcitonin as a diagnostic marker for sepsis: A systematic review and meta-analysis. *The Lancet Infectious Diseases*. 2013 May;13(5):426-35.
- [37] Arora S, Singh P, Singh PM, Trikha A. Procalcitonin levels in survivors and nonsurvivors of sepsis: Systematic review and meta-analysis. *Shock*. 2015 Mar;43(3):212-21.
- [38] Prkno A, Wacker C, Brunkhorst FM, Schlattmann P. Procalcitonin-guided therapy in intensive care unit patients with severe sepsis and septic shock: A systematic review and meta-analysis. *Critical Care*. 2013;17(6):R291.
- [39] Oberhoffer M, Vogelsang H, Russwurm S, Hartung T, Reinhart K. Outcome prediction by traditional and new markers of inflammation in patients with sepsis. *Clinical Chemistry and Laboratory Medicine*. 1999 Mar;37(3):363-8.
- [40] Schroder J, Staubach KH, Zabel P, Stuber F, Kremer B. Procalcitonin as a marker of severity in septic shock. *Langenbeck's Archives of Surgery*. 1999 Feb;384(1):33-8.

- [41] Nargis W, Ibrahim M, Ahamed BU. Procalcitonin versus C-reactive protein: Usefulness as biomarker of sepsis in ICU patient. *International Journal of Critical Illness and Injury Science*. 2014 Jul;4(3):195-9.
- [42] Selberg O, Hecker H, Martin M, Klos A, Bautsch W, Kohl J. Discrimination of sepsis and systemic inflammatory response syndrome by determination of circulating plasma concentrations of procalcitonin, protein complement 3a, and interleukin-6. *Critical Care Medicine*. 2000 Aug;28(8):2793-8.
- [43] Simon L, Gauvin F, Amre D, Saint-Louis P, Lacroix J. Serum procalcitonin and C-reactive protein levels as markers of bacterial infection: A systematic review and meta-analysis. *Clinical Infectious Diseases*. 2004;39(2):206-17.
- [44] Bone RC. Sir Isaac Newton, sepsis, SIRS, and CARS. *Critical Care Medicine*. 1996;24(7):1125-8.
- [45] Tamayo E, Fernández A, Almansa R, Carrasco E, Heredia M, Lajo C, et al. Pro- and anti-inflammatory responses are regulated simultaneously from the first moments of septic shock. *European Cytokine Network*. 2011;22:82-7.
- [46] Sherwin C, Broadbent R, Young S, Worth J, McCaffrey F, Medlicott NJ, et al. Utility of interleukin-12 and interleukin-10 in comparison with other cytokines and acute-phase reactants in the diagnosis of neonatal sepsis. *The American Journal of Perinatology*. 2008;25:629-36.
- [47] Engel A, Mack E, Kern P, Kern W. An analysis of interleukin-8, interleukin-6 and C-reactive protein serum concentrations to predict fever, gram-negative bacteremia and complicated infection in neutropenic cancer patients. *Infection*. 1998;26:213-21.
- [48] Kolaczkowska E, Kubes P. Neutrophil recruitment and function in health and inflammation. *Nature Reviews Immunology*. 2013 Mar;13(3):159-75.
- [49] Lewis SM, Treacher DF, Bergmeier L, Brain SD, Chambers DJ, Pearson JD, et al. Plasma from patients with sepsis up-regulates the expression of CD49d and CD64 on blood neutrophils. *The American Journal of Respiratory Cell and Molecular Biology*. 2009 Jun;40(6):724-32.
- [50] Harbarth S, Holeckova K, Froidevaux C, Pittet D, Ricou B, Grau GE, et al. Diagnostic value of procalcitonin, interleukin-6, and interleukin-8 in critically ill patients admitted with suspected sepsis. *The American Journal of Respiratory and Critical Care Medicine*. 2001 Aug 1;164(3):396-402.
- [51] Bosmann M, Ward PA. Therapeutic potential of targeting IL-17 and IL-23 in sepsis. *Clinical and Translational Medicine*. 2012;1(1):4.
- [52] Tschoeke SK, Oberholzer A, Moldawer LL. Interleukin-18: A novel prognostic cytokine in bacteria-induced sepsis. *Critical Care Medicine*. 2006 Apr;34(4):1225-33.
- [53] Bingold TM, Ziesche E, Scheller B, Sadik CD, Franck K, Just L, et al. Interleukin-22 detected in patients with abdominal sepsis. *Shock*. 2010 Oct;34(4):337-40.

- [54] Calandra T, Gerain J, Heumann D, Baumgartner JD, Glauser MP. High circulating levels of interleukin-6 in patients with septic shock: Evolution during sepsis, prognostic value, and interplay with other cytokines. The Swiss-Dutch J5 Immunoglobulin Study Group. *The American Journal of Medicine*. 1991 Jul;91(1):23-9.
- [55] Damas P, Reuter A, Gysen P, Demonty J, Lamy M, Franchimont P. Tumor necrosis factor and interleukin-1 serum levels during severe sepsis in humans. *Critical Care Medicine*. 1989 Oct;17(10):975-8.
- [56] Kurt AN, Aygun AD, Godekmerdan A, Kurt A, Dogan Y, Yilmaz E. Serum IL-1beta, IL-6, IL-8, and TNF-alpha levels in early diagnosis and management of neonatal sepsis. *Mediators of Inflammation*. 2007;2007:31397.
- [57] Pettila V, Hynninen M, Takkunen O, Kuusela P, Valtonen M. Predictive value of procalcitonin and interleukin 6 in critically ill patients with suspected sepsis. *Intensive Care Medicine*. 2002 Sep;28(9):1220-5.
- [58] Du B, Pan J, Chen D, Li Y. Serum procalcitonin and interleukin-6 levels may help to differentiate systemic inflammatory response of infectious and non-infectious origin. *Chinese Medical Journal*. 2003 Apr;116(4):538-42.
- [59] Kellum JA, Kong L, Fink MP, Weissfeld LA, Yealy DM, Pinsky MR, et al. Understanding the inflammatory cytokine response in pneumonia and sepsis: Results of the genetic and inflammatory markers of sepsis (GenIMS) study. *Archives of Internal Medicine*. 2007 Aug 13-27;167(15):1655-63.
- [60] Calfee CS, Thompson BT, Parsons PE, Ware LB, Matthay MA, Wong HR. Plasma interleukin-8 is not an effective risk stratification tool for adults with vasopressor-dependent septic shock. *Critical Care Medicine*. 2010 Jun;38(6):1436-41.
- [61] Wong HR, Cvijanovich N, Wheeler DS, Bigham MT, Monaco M, Odoms K, et al. Interleukin-8 as a stratification tool for interventional trials involving pediatric septic shock. *The American Journal of Respiratory and Critical Care Medicine*. 2008 Aug 1;178(3):276-82.
- [62] Lang Y, Jiang Y, Gao M, Wang W, Wang N, Wang K, et al. Interleukin-1 Receptor 2: A new biomarker for sepsis diagnosis and gram-negative/gram-positive bacterial differentiation. *Shock*. 2017 Jan;47(1):119-24.
- [63] Abraham E, Anzueto A, Gutierrez G, Tessler S, San Pedro G, Wunderink R, et al. Double-blind randomised controlled trial of monoclonal antibody to human tumour necrosis factor in treatment of septic shock. NORASEPT II Study Group. *Lancet*. 1998 Mar 28;351(9107):929-33.
- [64] van der Poll T, Levi M, Hack CE, ten Cate H, van Deventer SJ, Eerenberg AJ, et al. wElimination of interleukin 6 attenuates coagulation activation in experimental endotoxemia in chimpanzees. *Journal of Experimental Medicine*. 1994 Apr 1;179(4):1253-9.

- [65] Boermeester MA, van Leeuwen PA, Coyle SM, Wolbink GJ, Hack CE, Lowry SF. Interleukin-1 blockade attenuates mediator release and dysregulation of the hemostatic mechanism during human sepsis. *Archives of Surgery (Chicago, IL: 1960)*. 1995 Jul;130(7):739-48.
- [66] Brown KA, Brown GA, Lewis SM, Beale R, Treacher DF. Targeting cytokines as a treatment for patients with sepsis: A lost cause or a strategy still worthy of pursuit? *International Immunopharmacology*. 2016 Jul;36:291-9.
- [67] Wong HR, Cvijanovich NZ, Hall M, Allen GL, Thomas NJ, Freishtat RJ, et al. Interleukin-27 is a novel candidate diagnostic biomarker for bacterial infection in critically ill children. *Critical Care*. 2012 Oct 29;16(5):R213.
- [68] Wong HR, Lindsell CJ, Lahni P, Hart KW, Gibot S. Interleukin 27 as a sepsis diagnostic biomarker in critically ill adults. *Shock*. 2013 Nov;40(5):382-6.
- [69] Wong HR, Liu KD, Kangelaris KN, Lahni P, Calfee CS. Performance of interleukin-27 as a sepsis diagnostic biomarker in critically ill adults. *Journal of Critical Care*. 2014 Oct;29(5):718-22.
- [70] Hanna WJ, Berrens Z, Langner T, Lahni P, Wong HR. Interleukin-27: A novel biomarker in predicting bacterial infection among the critically ill. *Critical Care*. 2015 Oct 30;19:378.
- [71] Fu J, Wang Y, Zeng P, Niu S. Value of interleukin-27 as a diagnostic biomarker of sepsis in critically ill adults. *Zhonghua wei zhong bing ji jiu yi xue*. 2015 Jun;27(6):460-4.
- [72] Ward N, Casserly B, Ayala A. The compensatory anti-inflammatory response syndrome (CARS) in critically ill patients. *Clinics in Chest Medicine*. 2008;29(4):617-25.
- [73] Oberholzer A, Oberholzer C, Moldawer L. Interleukin-10: A complex role in the pathogenesis of sepsis syndromes and its potential as an anti-inflammatory drug. *Critical Care Medicine*. 2002;30(1 Suppl.):S58-63.
- [74] Monneret G, Finck ME, Venet F, Debard AL, Bohe J, Bienvenu J, et al. The anti-inflammatory response dominates after septic shock: Association of low monocyte HLA-DR expression and high interleukin-10 concentration. *Immunology Letters*. 2004 Sep;95(2):193-8.
- [75] Berg D, Kühn R, Rajewsky K, Müller W, Menon S, Davidson N, et al. Interleukin-10 is a central regulator of the response to LPS in murine models of endotoxic shock and the Shwartzman reaction but not endotoxin tolerance. *The Journal of Clinical Investigation*. 1995;96(5):2339-47.
- [76] Howard M, Muchamuel T, Andrade S, Menon S. Interleukin 10 protects mice from lethal endotoxemia. *Journal of Experimental Medicine*. 1993;177(4):1205-8.
- [77] van der Poll T, Jansen P, Montegut W, Braxton C, Calvano S, Stackpole S, et al. Effects of IL-10 on systemic inflammatory responses during sublethal primate endotoxemia. *Journal of Immunology*. 1997;158(4):1971-5.

- [78] Remick D, Garg S, Newcomb D, Wollenberg G, Huie T, Bolgos G. Exogenous interleukin-10 fails to decrease the mortality or morbidity of sepsis. *Critical Care Medicine*. 1998;26(5):985-04.
- [79] Steinhäuser M, Hogaboam C, Kunkel S, Lukacs N, Strieter R, Standiford T. IL-10 is a major mediator of sepsis-induced impairment in lung antibacterial host defense. *Journal of Immunology*. 1999;162(1):392-9.
- [80] Song G, Chung C, Chaudry I, Ayala A. What is the role of interleukin 10 in polymicrobial sepsis: Anti-inflammatory agent or immunosuppressant? *Surgery*. 1999;126(2):378-83.
- [81] Ashare A, Powers L, Butler N, Doerschug K, Monick M, Hunninghake G. Anti-inflammatory response is associated with mortality and severity of infection in sepsis. *The American Journal of Physiology – Lung Cellular and Molecular Physiology*. 2005;288(4):L633-40.
- [82] Panacek E, Marshall J, Albertson T, Johnson D, Johnson S, MacArthur R, et al. Efficacy and safety of the monoclonal anti-tumor necrosis factor antibody F(ab')₂ fragment afe-limomab in patients with severe sepsis and elevated interleukin-6 levels. *Critical Care Medicine*. 2004;32:2173-218.
- [83] Maniatis NA, Kotanidou A, Catravas JD, Orfanos SE. Endothelial pathomechanisms in acute lung injury. *Vascular Pharmacology*. 2008 Oct–Dec;49(4-6):119-33.
- [84] Maisonpierre PC, Suri C, Jones PF, Bartunkova S, Wiegand SJ, Radziejewski C, et al. Angiopoietin-2, a natural antagonist for Tie2 that disrupts in vivo angiogenesis. *Science*. 1997 Jul 4;277(5322):55-60.
- [85] Thurston G, Rudge JS, Ioffe E, Zhou H, Ross L, Croll SD, et al. Angiopoietin-1 protects the adult vasculature against plasma leakage. *Nature Medicine*. 2000 Apr;6(4):460-3.
- [86] Fiedler U, Augustin HG. Angiopoietins: A link between angiogenesis and inflammation. *Trends Immunology*. 2006 Dec;27(12):552-8.
- [87] Roviezzo F, Tsigkos S, Kotanidou A, Bucci M, Brancalone V, Cirino G, et al. Angiopoietin-2 causes inflammation in vivo by promoting vascular leakage. *Journal of Pharmacology and Experimental Therapeutics*. 2005 Aug;314(2):738-44.
- [88] Xing K, Murthy S, Liles WC, Singh JM. Clinical utility of biomarkers of endothelial activation in sepsis – A systematic review. *Critical Care*. 2012;16(1):R7.
- [89] Davis JS, Yeo TW, Piera KA, Woodberry T, Celermajer DS, Stephens DP, et al. Angiopoietin-2 is increased in sepsis and inversely associated with nitric oxide-dependent microvascular reactivity. *Critical Care*. 2010;14(3):R89.
- [90] Orfanos SE, Kotanidou A, Glynos C, Athanasiou C, Tsigkos S, Dimopoulou I, et al. Angiopoietin-2 is increased in severe sepsis: Correlation with inflammatory mediators. *Critical Care Medicine*. 2007 Jan;35(1):199-206.

- [91] Parikh SM, Mammoto T, Schultz A, Yuan HT, Christiani D, Karumanchi SA, et al. Excess circulating angiopoietin-2 may contribute to pulmonary vascular leak in sepsis in humans. *PLoS Medicine*. 2006 Mar;3(3):e46.
- [92] Calfee CS, Gallagher D, Abbott J, Thompson BT, Matthay MA. Plasma angiopoietin-2 in clinical acute lung injury: Prognostic and pathogenetic significance. *Critical Care Medicine*. 2012 Jun;40(6):1731-7.
- [93] Ganter MT, Cohen MJ, Brohi K, Chesebro BB, Staudenmayer KL, Rahn P, et al. Angiopoietin-2, marker and mediator of endothelial activation with prognostic significance early after trauma? *Annals of Surgery*. 2008 Feb;247(2):320-6.
- [94] Ricciuto DR, dos Santos CC, Hawkes M, Toltl LJ, Conroy AL, Rajwans N, et al. Angiopoietin-1 and angiopoietin-2 as clinically informative prognostic biomarkers of morbidity and mortality in severe sepsis. *Critical Care Medicine*. 2011 Apr;39(4):702-10.
- [95] Kranidioti H, Orfanos SE, Vaki I, Kotanidou A, Raftogiannis M, Dimopoulou I, et al. Angiopoietin-2 is increased in septic shock: Evidence for the existence of a circulating factor stimulating its release from human monocytes. *Immunology Letters*. 2009 Jun 30;125(1):65-71.
- [96] Kumpers P, Lukasz A, David S, Horn R, Hafer C, Faulhaber-Walter R, et al. Excess circulating angiopoietin-2 is a strong predictor of mortality in critically ill medical patients. *Critical Care*. 2008;12(6):R147.
- [97] Kumpers P, van Meurs M, David S, Molema G, Bijzet J, Lukasz A, et al. Time course of angiopoietin-2 release during experimental human endotoxemia and sepsis. *Critical Care*. 2009;13(3):R64.
- [98] Tedder TF, Steeber DA, Chen A, Engel P. The selectins: Vascular adhesion molecules. *FASEB Journal*. 1995 Jul;9(10):866-73.
- [99] Boldt J, Wollbruck M, Kuhn D, Linke LC, Hempelmann G. Do plasma levels of circulating soluble adhesion molecules differ between surviving and nonsurviving critically ill patients? *Chest*. 1995 Mar;107(3):787-92.
- [100] Cowley HC, Heney D, Gearing AJ, Hemingway I, Webster NR. Increased circulating adhesion molecule concentrations in patients with the systemic inflammatory response syndrome: A prospective cohort study. *Critical Care Medicine*. 1994 Apr;22(4):651-7.
- [101] Knapp S, Thalhammer F, Locker GJ, Laczika K, Hollenstein U, Frass M, et al. Prognostic value of MIP-1 alpha, TGF-beta 2, sELAM-1, and sVCAM-1 in patients with gram-positive sepsis. *Clinical Immunology and Immunopathology*. 1998 May;87(2):139-44.
- [102] Sessler CN, Windsor AC, Schwartz M, Watson L, Fisher BJ, Sugerman HJ, et al. Circulating ICAM-1 is increased in septic shock. *The American Journal of Respiratory and Critical Care Medicine*. 1995 May;151(5):1420-7.
- [103] Cummings CJ, Sessler CN, Beall LD, Fisher BJ, Best AM, Fowler AA, 3rd. Soluble E-selectin levels in sepsis and critical illness. Correlation with infection and

- hemodynamic dysfunction. *The American Journal of Respiratory and Critical Care Medicine*. 1997 Aug;156(2 Pt 1):431-7.
- [104] Simons RK, Hoyt DB, Winchell RJ, Rose RM, Holbrook T. Elevated selectin levels after severe trauma: A marker for sepsis and organ failure and a potential target for immunomodulatory therapy. *Journal of Trauma*. 1996 Oct;41(4):653-62.
 - [105] de Pablo R, Monserrat J, Reyes E, Diaz D, Rodriguez-Zapata M, de la Hera A, et al. Circulating sICAM-1 and sE-Selectin as biomarker of infection and prognosis in patients with systemic inflammatory response syndrome. *European Journal of Internal Medicine*. 2013 Mar; 24(2):132-8.
 - [106] Kung CT, Hsiao SY, Su CM, Tsai TC, Cheng HH, Tsai NW, et al. Serum adhesion molecules as predictors of bacteremia in adult severe sepsis patients at the emergency department. *Clinica Chimica Acta*. 2013 Feb 28;421:116-20.
 - [107] Sakamaki F, Ishizaka A, Handa M, Fujishima S, Urano T, Sayama K, et al. Soluble form of P-selectin in plasma is elevated in acute lung injury. *The American Journal of Respiratory and Critical Care Medicine*. 1995 Jun;151(6):1821-6.
 - [108] Wang HE, Shapiro NI, Griffin R, Safford MM, Judd S, Howard G. Inflammatory and endothelial activation biomarkers and risk of sepsis: A nested case-control study. *Journal of Critical Care*. 2013 Feb 12;28(5):549-55.
 - [109] Vassiliou AG, Mastora Z, Orfanos SE, Jahaj E, Maniatis NA, Koutsoukou A, et al. Elevated biomarkers of endothelial dysfunction/activation at ICU admission are associated with sepsis development. *Cytokine*. 2014 Jul 9;69(2):240-7.
 - [110] Muller WA. Leukocyte-endothelial-cell interactions in leukocyte transmigration and the inflammatory response. *Trends in Immunology*. 2003 Jun;24(6):327-34.
 - [111] Shapiro NI, Schuetz P, Yano K, Sorasaki M, Parikh SM, Jones AE, et al. The association of endothelial cell signaling, severity of illness, and organ dysfunction in sepsis. *Critical Care*. 2010;14(5):R182.
 - [112] Kayal S, Jais JP, Aguin N, Chaudiere J, Labrousse J. Elevated circulating E-selectin, intercellular adhesion molecule 1, and von Willebrand factor in patients with severe infection. *The American Journal of Respiratory and Critical Care Medicine*. 1998 Mar;157(3 Pt 1):776-84.
 - [113] Berman ME, Muller WA. Ligation of platelet/endothelial cell adhesion molecule 1 (PECAM-1/CD31) on monocytes and neutrophils increases binding capacity of leukocyte CR3 (CD11b/CD18). *Journal of Immunology*. 1995 Jan 01;154(1):299-307.
 - [114] Kjaergaard AG, Dige A, Nielsen JS, Tonnesen E, Krog J. The use of the soluble adhesion molecules sE-selectin, sICAM-1, sVCAM-1, sPECAM-1 and their ligands CD11a and CD49d as diagnostic and prognostic biomarkers in septic and critically ill non-septic ICU patients. *Acta Pathologica, Microbiologica, et Immunologica Scandinavica*. 2016 Oct;124(10):846-55.

- [115] Sun W, Li FS, Zhang YH, Wang XP, Wang CR. Association of susceptibility to septic shock with platelet endothelial cell adhesion molecule-1 gene Leu125Val polymorphism and serum sPECAM-1 levels in sepsis patients. *International Journal of Clinical and Experimental Medicine*. 2015;8(11):20490-8.
- [116] Bechard D, Gentina T, Delehedde M, Scherpereel A, Lyon M, Aumercier M, et al. Endocan is a novel chondroitin sulfate/dermatan sulfate proteoglycan that promotes hepatocyte growth factor/scatter factor mitogenic activity. *Journal of Biological Chemistry*. 2001 Dec 21;276(51):48341-9.
- [117] De Freitas Caires N, Legendre B, Parmentier E, Scherpereel A, Tsicopoulos A, Mathieu D, et al. Identification of a 14 kDa endocan fragment generated by cathepsin G, a novel circulating biomarker in patients with sepsis. *Journal of Pharmaceutical and Biomedical Analysis*. 2013 May 5;78-79:45-51.
- [118] Kao SJ, Chuang CY, Tang CH, Lin CH, Bien MY, Yu MC, et al. Plasma endothelial cell-specific molecule-1 (ESM-1) in management of community-acquired pneumonia. *Clinical Chemistry and Laboratory Medicine*. 2014 Mar;52(3):445-51.
- [119] Mihajlovic DM, Lendak DF, Brkic SV, Draskovic BG, Mitic GP, Novakov Mikic AS, et al. Endocan is useful biomarker of survival and severity in sepsis. *Microvascular Research*. 2014 May;93:92-7.
- [120] Mikkelsen ME, Shah CV, Scherpereel A, Lanken PN, Lassalle P, Bellamy SL, et al. Lower serum endocan levels are associated with the development of acute lung injury after major trauma. *Journal of Critical Care*. 2012 Oct;27(5):522 e11-7.
- [121] Palud A, Parmentier-Decrucq E, Pastre J, De Freitas Caires N, Lassalle P, Mathieu D. Evaluation of endothelial biomarkers as predictors of organ failures in septic shock patients. *Cytokine*. 2015 Jun;73(2):213-8.
- [122] Pauly D, Hamed S, Behnes M, Lepiorz D, Lang S, Akin I, et al. Endothelial cell-specific molecule-1/endocan: Diagnostic and prognostic value in patients suffering from severe sepsis and septic shock. *Journal of Critical Care*. 2016 Feb;31(1):68-75.
- [123] Roldan AL, Cubellis MV, Masucci MT, Behrendt N, Lund LR, Dano K, et al. Cloning and expression of the receptor for human urokinase plasminogen activator, a central molecule in cell surface, plasmin dependent proteolysis. *The EMBO Journal*. 1990 Feb;9(2):467-74.
- [124] Donadello K, Scolletta S, Taccone FS, Covajes C, Santonocito C, Cortes DO, et al. Soluble urokinase-type plasminogen activator receptor as a prognostic biomarker in critically ill patients. *Journal of Critical Care*. 2014 Feb;29(1):144-9.
- [125] Hoenigl M, Raggam RB, Wagner J, Valentin T, Leitner E, Seeber K, et al. Diagnostic accuracy of soluble urokinase plasminogen activator receptor (suPAR) for prediction of bacteremia in patients with systemic inflammatory response syndrome. *Clinical Biochemistry*. 2013 Feb;46(3):225-9.

- [126] Koch A, Voigt S, Kruschinski C, Sanson E, Duckers H, Horn A, et al. Circulating soluble urokinase plasminogen activator receptor is stably elevated during the first week of treatment in the intensive care unit and predicts mortality in critically ill patients. *Critical Care*. 2011;15(1):R63.
- [127] Suberviola B, Castellanos-Ortega A, Ruiz Ruiz A, Lopez-Hoyos M, Santibanez M. Hospital mortality prognostication in sepsis using the new biomarkers suPAR and proADM in a single determination on ICU admission. *Intensive Care Medicine*. 2013 Nov;39(11):1945-52.
- [128] Backes Y, van der Sluijs KF, Mackie DP, Tacke F, Koch A, Tenhunen JJ, et al. Usefulness of suPAR as a biological marker in patients with systemic inflammation or infection: A systematic review. *Intensive Care Medicine*. 2012 Sep;38(9):1418-28.
- [129] Donadello K, Scolletta S, Covajes C, Vincent JL. suPAR as a prognostic biomarker in sepsis. *BMC Medicine*. 2012 Jan 05;10:2.
- [130] Eugen-Olsen J, Giamarellos-Bourboulis EJ. suPAR: The unspecific marker for disease presence, severity and prognosis. *International Journal of Antimicrobial Agents*. 2015 Dec;46(Suppl. 1):S33-4.
- [131] Huttunen R, Syrjanen J, Vuento R, Hurme M, Huhtala H, Laine J, et al. Plasma level of soluble urokinase-type plasminogen activator receptor as a predictor of disease severity and case fatality in patients with bacteraemia: A prospective cohort study. *Journal of Internal Medicine*. 2011 Jul;270(1):32-40.
- [132] Molkanen T, Ruotsalainen E, Thorball CW, Jarvinen A. Elevated soluble urokinase plasminogen activator receptor (suPAR) predicts mortality in *Staphylococcus aureus* bacteremia. *European Journal of Clinical Microbiology and Infectious Diseases*. 2011 Nov;30(11):1417-24.
- [133] Wittenhagen P, Kronborg G, Weis N, Nielsen H, Obel N, Pedersen SS, et al. The plasma level of soluble urokinase receptor is elevated in patients with *Streptococcus pneumoniae* bacteraemia and predicts mortality. *Clinical Microbiology and Infection*. 2004 May;10(5):409-15.
- [134] Brenner T, Uhle F, Fleming T, Wieland M, Schmoch T, Schmitt F, et al. Soluble TREM-1 as a diagnostic and prognostic biomarker in patients with septic shock: An observational clinical study. *Biomarkers*. 2017 Feb; 22(1):63-69.
- [135] Charles PE, Noel R, Massin F, Guy J, Bollaert PE, Quenot JP, et al. Significance of soluble triggering receptor expressed on myeloid cells-1 elevation in patients admitted to the intensive care unit with sepsis. *BMC Infectious Diseases*. 2016 Oct 12;16(1):559.
- [136] Li Z, Zhang E, Hu Y, Liu Y, Chen B. High serum sTREM-1 correlates with myocardial dysfunction and predicts prognosis in septic patients. *The American Journal of the Medical Sciences*. 2016 Jun;351(6):555-62.

- [137] Su L, Feng L, Song Q, Kang H, Zhang X, Liang Z, et al. Diagnostic value of dynamics serum sCD163, sTREM-1, PCT, and CRP in differentiating sepsis, severity assessment, and prognostic prediction. *Mediators of Inflammation*. 2013;2013:969875.
- [138] Arizaga-Ballesteros V, Alcorta-Garcia MR, Lazaro-Martinez LC, Amezcuita-Gomez JM, Alanis-Cajero JM, Villela L, et al. Can sTREM-1 predict septic shock & death in late-onset neonatal sepsis? A pilot study. *International Journal of Infectious Diseases*. 2015 Jan;30:27-32.
- [139] Adly AA, Ismail EA, Andrawes NG, El-Saadany MA. Circulating soluble triggering receptor expressed on myeloid cells-1 (sTREM-1) as diagnostic and prognostic marker in neonatal sepsis. *Cytokine*. 2014 Feb;65(2):184-91.
- [140] Wu Y, Wang F, Fan X, Bao R, Bo L, Li J, et al. Accuracy of plasma sTREM-1 for sepsis diagnosis in systemic inflammatory patients: A systematic review and meta-analysis. *Critical Care*. 2012 Nov 29;16(6):R229.
- [141] Velasquez S, Matute JD, Gamez LY, Enriquez LE, Gomez ID, Toro F, et al. Characterization of nCD64 expression in neutrophils and levels of s-TREM-1 and HMGB-1 in patients with suspected infection admitted in an emergency department. *Biomedica: Revista del Instituto Nacional de Salud*. 2013 Oct-Dec;33(4):643-52.
- [142] Su L, Liu D, Chai W, Liu D, Long Y. Role of sTREM-1 in predicting mortality of infection: A systematic review and meta-analysis. *BMJ Open*. 2016 May 13;6(5):e010314.
- [143] Jiyong J, Tiancha H, Wei C, Huahao S. Diagnostic value of the soluble triggering receptor expressed on myeloid cells-1 in bacterial infection: A meta-analysis. *Intensive Care Medicine*. 2009 Apr;35(4):587-95.
- [144] Orfanos SE, Maniatis NA, Kotanidou A. The effects of Activated Protein C on the Septic Syndrome. In: Vincent J-L, editor. *Yearbook of Intensive Care and Emergency Medicine*. Berlin, Heidelberg, New York: Springer-Verlag; 2008. pp. 721-9.
- [145] Stearns-Kurosawa DJ, Kurosawa S, Mollica JS, Ferrell GL, Esmon CT. The endothelial cell protein C receptor augments protein C activation by the thrombin-thrombomodulin complex. *Proceedings of the National Academy of Sciences of the United States of America*. 1996 Sep 17;93(19):10212-6.
- [146] Kurosawa S, Stearns-Kurosawa DJ, Carson CW, D'Angelo A, Della Valle P, Esmon CT. Plasma levels of endothelial cell protein C receptor are elevated in patients with sepsis and systemic lupus erythematosus: Lack of correlation with thrombomodulin suggests involvement of different pathological processes. *Blood*. 1998 Jan 15;91(2):725-7.
- [147] Liaw PC, Esmon CT, Kahnamoui K, Schmidt S, Kahnamoui S, Ferrell G, et al. Patients with severe sepsis vary markedly in their ability to generate activated protein C. *Blood*. 2004 Dec 15;104(13):3958-64.

- [148] Faust SN, Levin M, Harrison OB, Goldin RD, Lockhart MS, Kondaveeti S, et al. Dysfunction of endothelial protein C activation in severe meningococcal sepsis. *The New England Journal of Medicine*. 2001 Aug 9;345(6):408-16.
- [149] Borgel D, Bornstain C, Reitsma PH, Lerolle N, Gandrille S, Dali-Ali F, et al. A comparative study of the protein C pathway in septic and nonseptic patients with organ failure. *The American Journal of Respiratory and Critical Care Medicine*. 2007 Nov 1; 176(9):878-85.
- [150] Kager LM, Schouten M, Wiersinga WJ, de Boer JD, Lattenist LC, Roelofs JJ, et al. Overexpression of the Endothelial Protein C Receptor Is Detrimental during Pneumonia-Derived Gram-negative Sepsis (Meliodosis). *PLoS Neglected Tropical Diseases*. 2013 Jul;7(7):e2306.
- [151] Guitton C, Gerard N, Sebillle V, Bretonniere C, Zambon O, Villers D, et al. Early rise in circulating endothelial protein C receptor correlates with poor outcome in severe sepsis. *Intensive Care Medicine*. 2011 Jun;37(6):950-6.
- [152] Vassiliou AG, Kotanidou A, Mastora Z, Maniatis NA, Albani P, Jahaj E, et al. Elevated soluble endothelial protein C receptor levels at ICU admission are associated with sepsis development. *Minerva Anestesiologica*. 2015 Feb;81(2):125-34.
- [153] Ulla M, Pizzolato E, Lucchiari M, Loiacono M, Soardo F, Forno D, et al. Diagnostic and prognostic value of presepsin in the management of sepsis in the emergency department: A multicenter prospective study. *Critical Care*. 2013 Jul 30;17(4):R168.
- [154] Okamura Y. Usefulness of presepsin measurement: A new biomarker for sepsis. *Rinsho Byori*. 2015 Jan;63(1):62-71.
- [155] Endo S, Suzuki Y, Takahashi G, Shozushima T, Ishikura H, Murai A, et al. Usefulness of presepsin in the diagnosis of sepsis in a multicenter prospective study. *Journal of Infection and Chemotherapy*. 2012 Dec;18(6):891-7.
- [156] Behnes M, Bertsch T, Lepiorz D, Lang S, Trinkmann F, Brueckmann M, et al. Diagnostic and prognostic utility of soluble CD 14 subtype (presepsin) for severe sepsis and septic shock during the first week of intensive care treatment. *Critical Care*. 2014 Sep 05;18(5):507.
- [157] Masson S, Caironi P, Spanuth E, Thomae R, Panigada M, Sangiorgi G, et al. Presepsin (soluble CD14 subtype) and procalcitonin levels for mortality prediction in sepsis: Data from the Albumin Italian Outcome Sepsis trial. *Critical Care*. 2014 Jan 07;18(1):R6.
- [158] Zhang J, Hu ZD, Song J, Shao J. Diagnostic value of presepsin for sepsis: A systematic review and meta-analysis. *Medicine*. 2015 Nov;94(47):e2158.
- [159] Zheng Z, Jiang L, Ye L, Gao Y, Tang L, Zhang M. The accuracy of presepsin for the diagnosis of sepsis from SIRS: A systematic review and meta-analysis. *Annals of Intensive Care*. 2015 Dec;5(1):48.

- [160] Wu J, Hu L, Zhang G, Wu F, He T. Accuracy of Presepsin in Sepsis Diagnosis: A systematic review and meta-analysis. *PLoS One*. 2015;10(7):e0133057.
- [161] Ali FT, Ali MA, Elnakeeb MM, Bendary HN. Presepsin is an early monitoring biomarker for predicting clinical outcome in patients with sepsis. *Clinica Chimica Acta*. 2016 Sep 01;460:93-101.
- [162] Klouche K, Cristol JP, Devin J, Gilles V, Kuster N, Larcher R, et al. Diagnostic and prognostic value of soluble CD14 subtype (Presepsin) for sepsis and community-acquired pneumonia in ICU patients. *Annals of Intensive Care*. 2016 Dec;6(1):59.
- [163] Leli C, Ferranti M, Marrano U, Al Dhahab ZS, Bozza S, Cenci E, et al. Diagnostic accuracy of presepsin (sCD14-ST) and procalcitonin for prediction of bacteraemia and bacterial DNAemia in patients with suspected sepsis. *Journal of Medical Microbiology*. 2016 Aug;65(8):713-9.
- [164] Franekova J, Secnik P, Jr., Lavrikova P, Kubicek Z, Hoskova L, Kieslichova E, et al. Serial measurement of presepsin, procalcitonin, and C-reactive protein in the early postoperative period and the response to antithymocyte globulin administration after heart transplantation. *Clinical Transplantation*. 2017 Jan;31(1): e12870.
- [165] de Guadiana Romualdo LG, Torrella PE, Acebes SR, Oton MD, Sanchez RJ, Holgado AH, et al. Diagnostic accuracy of presepsin (sCD14-ST) as a biomarker of infection and sepsis in the emergency department. *Clinica Chimica Acta*. 2017 Jan;464:6-11.
- [166] Montaldo P, Rosso R, Santantonio A, Chello G, Giliberti P. Presepsin for the detection of early-onset sepsis in preterm newborns. *Pediatric Research*. 2017 Feb;81(2):329-334.
- [167] Ozdemir AA, Elgormus Y. Diagnostic Value of Presepsin in Detection of Early-Onset Neonatal Sepsis. *The American Journal of Perinatology*. 2016 Nov 08. DOI: 10.1055/s-0036-1593851.
- [168] Pugni L, Pietrasanta C, Milani S, Vener C, Ronchi A, Falbo M, et al. Presepsin (Soluble CD14 Subtype): Reference ranges of a new sepsis marker in term and preterm neonates. *PLoS One*. 2015;10(12):e0146020.
- [169] Arnold RC, Shapiro NI, Jones AE, Schorr C, Pope J, Casner E, et al. Multicenter study of early lactate clearance as a determinant of survival in patients with presumed sepsis. *Shock*. 2009 Jul;32(1):35-9.
- [170] Nguyen HB, Rivers EP, Knoblich BP, Jacobsen G, Muzzin A, Ressler JA, et al. Early lactate clearance is associated with improved outcome in severe sepsis and septic shock. *Critical Care Medicine*. 2004 Aug;32(8):1637-42.
- [171] Singer AJ, Taylor M, Domingo A, Ghazipura S, Khorasonchi A, Thode HC, Jr., et al. Diagnostic characteristics of a clinical screening tool in combination with measuring bedside lactate level in emergency department patients with suspected sepsis. *Academic Emergency Medicine*. 2014 Aug;21(8):853-7.

- [172] Bakker J, Gris P, Coffernils M, Kahn RJ, Vincent JL. Serial blood lactate levels can predict the development of multiple organ failure following septic shock. *The American Journal of Surgery*. 1996 Feb;171(2):221-6.
- [173] Mikkelsen ME, Miltiades AN, Gaieski DF, Goyal M, Fuchs BD, Shah CV, et al. Serum lactate is associated with mortality in severe sepsis independent of organ failure and shock. *Critical Care Medicine*. 2009 May;37(5):1670-7.
- [174] Shapiro NI, Howell MD, Talmor D, Nathanson LA, Lisbon A, Wolfe RE, et al. Serum lactate as a predictor of mortality in emergency department patients with infection. *Annals of Emergency Medicine*. 2005 May;45(5):524-8.
- [175] Trzeciak S, Dellinger RP, Chansky ME, Arnold RC, Schorr C, Milcarek B, et al. Serum lactate as a predictor of mortality in patients with infection. *Intensive Care Medicine*. 2007 Jun;33(6):970-7.
- [176] Singer AJ, Taylor M, LeBlanc D, Williams J, Thode HC, Jr. ED bedside point-of-care lactate in patients with suspected sepsis is associated with reduced time to iv fluids and mortality. *The American Journal of Emergency Medicine*. 2014 Sep;32(9):1120-4.
- [177] Levraut J, Ciebiera JP, Chave S, Rabary O, Jambou P, Carles M, et al. Mild hyperlactatemia in stable septic patients is due to impaired lactate clearance rather than overproduction. *The American Journal of Respiratory and Critical Care Medicine*. 1998 Apr;157(4 Pt 1):1021-6.
- [178] Revelly JP, Tappy L, Martinez A, Bollmann M, Cayeux MC, Berger MM, et al. Lactate and glucose metabolism in severe sepsis and cardiogenic shock. *Critical Care Medicine*. 2005 Oct;33(10):2235-40.
- [179] Scott HF, Donoghue AJ, Gaieski DF, Marchese RF, Mistry RD. The utility of early lactate testing in undifferentiated pediatric systemic inflammatory response syndrome. *Academic Emergency Medicine*. 2012 Nov;19(11):1276-80.
- [180] Vassiliou AG, Mastora Z, Jahaj E, Koutsoukou A, Orfanos SE, Kotanidou A. Does serum lactate combined with soluble endothelial selectins at ICU admission predict sepsis development? *In Vivo*. 2015 Mar-Apr;29(2):305-8.
- [181] Kofoed K, Andersen O, Kronborg G, Tvede M, Petersen J, Eugen-Olsen J, et al. Use of plasma C-reactive protein, procalcitonin, neutrophils, macrophage migration inhibitory factor, soluble urokinase-type plasminogen activator receptor, and soluble triggering receptor expressed on myeloid cells-1 in combination to diagnose infections: A prospective study. *Critical Care*. 2007;11(2):R38.
- [182] Shapiro NI, Trzeciak S, Hollander JE, Birkhahn R, Otero R, Osborn TM, et al. A prospective, multicenter derivation of a biomarker panel to assess risk of organ dysfunction, shock, and death in emergency department patients with suspected sepsis. *Critical Care Medicine*. 2009 Jan;37(1):96-104.
- [183] Andaluz-Ojeda D, Bobillo F, Iglesias V, Almansa R, Rico L, Gandía F, et al. A combined score of pro- and anti-inflammatory interleukins improves mortality prediction in severe sepsis. *Cytokine*. 2012;57:332-6.

- [184] Gogos CA, Drosou E, Bassaris HP, Skoutelis A. Pro- versus anti-inflammatory cytokine profile in patients with severe sepsis: A marker for prognosis and future therapeutic options. *Journal of Infectious Diseases*. 2000 Jan;181(1):176-80. PubMed PMID: 10608764. Epub 1999/12/23. Eng.
- [185] Sutherland AM, Walley KR. Bench-to-bedside review: Association of genetic variation with sepsis. *Critical Care*. 2009;13(2):210.
- [186] Villar J, Maca-Meyer N, Perez-Mendez L, Flores C. Bench-to-bedside review: Understanding genetic predisposition to sepsis. *Critical Care*. 2004 Jun;8(3):180-9.
- [187] Takeda K, Akira S. Toll-like receptors in innate immunity. *International Immunology*. 2005 Jan;17(1):1-14. PubMed PMID: 15585605. Epub 2004/12/09. Eng.
- [188] Poltorak A, He X, Smirnova I, Liu MY, Van Huffel C, Du X, et al. Defective LPS signaling in C3H/HeJ and C57BL/10ScCr mice: Mutations in Tlr4 gene. *Science*. 1998 Dec 11;282(5396):2085-8.
- [189] Hoshino K, Takeuchi O, Kawai T, Sanjo H, Ogawa T, Takeda Y, et al. Pillars article: Cutting edge: Toll-like receptor 4 (TLR4)-deficient mice are hyporesponsive to lipopolysaccharide: Evidence for TLR4 as the Lps gene product. *Journal of Immunology*. 1999;162:3749-52. *Journal of Immunology*. 2016 Oct 1;197(7):2563-6.
- [190] Feterowski C, Emmanuilidis K, Miethke T, Gerauer K, Rump M, Ulm K, et al. Effects of functional Toll-like receptor-4 mutations on the immune response to human and experimental sepsis. *Immunology*. 2003 Jul;109(3):426-31.
- [191] Smirnova I, Mann N, Dols A, Derkx HH, Hibberd ML, Levin M, et al. Assay of locus-specific genetic load implicates rare Toll-like receptor 4 mutations in meningococcal susceptibility. *Proceedings of the National Academy of Sciences of the United States of America*. 2003 May 13;100(10):6075-80.
- [192] Lorenz E, Mira JP, Frees KL, Schwartz DA. Relevance of mutations in the TLR4 receptor in patients with gram-negative septic shock. *Archives of Internal Medicine*. 2002 May 13;162(9):1028-32.
- [193] Kiechl S, Lorenz E, Reindl M, Wiedermann CJ, Oberhollenzer F, Bonora E, et al. Toll-like receptor 4 polymorphisms and atherogenesis. *The New England Journal of Medicine*. 2002 Jul 18;347(3):185-92.
- [194] Yousef AA, Suliman GA, Mabrouk MM. The value of admission serum IL-8 monitoring and the correlation with IL-8 (-251A/T) polymorphism in critically ill patients. *ISRN Inflammation*. 2014 Mar;6:494985.
- [195] Belopolskaya OB, Smelaya TV, Moroz VV, Golubev AM, Salnikova LE. Clinical associations of host genetic variations in the genes of cytokines in critically ill patients. *Clinical & Experimental Immunology*. 2015 Jun;180(3):531-41.
- [196] Abu-Maziad A, Schaa K, Bell EF, Dagle JM, Cooper M, Marazita ML, et al. Role of polymorphic variants as genetic modulators of infection in neonatal sepsis. *Pediatric Research*. 2010 Oct;68(4):323-9.

- [197] Esposito S, Zampiero A, Pugni L, Tabano S, Pelucchi C, Ghirardi B, et al. Genetic polymorphisms and sepsis in premature neonates. *PLoS One*. 2014;9(7):e101248.
- [198] Hu D, Wang H, Huang X, Jiang Y, Qin Y, Xiong B, et al. Investigation of association between IL-8 serum levels and IL8 polymorphisms in Chinese patients with sepsis. *Gene*. 2016 Dec 5;594(1):165-70.
- [199] Mira JP, Cariou A, Grall F, Delclaux C, Losser MR, Heshmati F, et al. Association of TNF-2, a TNF-alpha promoter polymorphism, with septic shock susceptibility and mortality: A multicenter study. *The Journal of the American Medical Association*. 1999 Aug 11;282(6):561-8.
- [200] Stuber F, Petersen M, Bokelmann F, Schade U. A genomic polymorphism within the tumor necrosis factor locus influences plasma tumor necrosis factor-alpha concentrations and outcome of patients with severe sepsis. *Critical Care Medicine*. 1996 Mar;24(3):381-4.
- [201] Teuffel O, Ethier MC, Beyene J, Sung L. Association between tumor necrosis factor-alpha promoter -308 A/G polymorphism and susceptibility to sepsis and sepsis mortality: A systematic review and meta-analysis. *Critical Care Medicine*. 2010 Jan;38(1):276-82.
- [202] Gordon AC, Lagan AL, Aganna E, Cheung L, Peters CJ, McDermott MF, et al. TNF and TNF-R polymorphisms in severe sepsis and septic shock: A prospective multicentre study. *Genes and Immunity*. 2004 Dec;5(8):631-40.
- [203] Carvalho JK, Moore DB, Luz RA, Xavier-Elsas PP, Gaspar-Elsas MI. Prediction of sepsis-related outcomes in neonates through systematic genotyping of polymorphisms in genes for innate immunity and inflammation: A narrative review and critical perspective. *Sao Paulo Medical Journal = Revista paulista de medicina*. 2013;131(5):338-50.
- [204] Fishman D, Faulds G, Jeffery R, Mohamed-Ali V, Yudkin JS, Humphries S, et al. The effect of novel polymorphisms in the interleukin-6 (IL-6) gene on IL-6 transcription and plasma IL-6 levels, and an association with systemic-onset juvenile chronic arthritis. *Journal of Clinical Investigation*. 1998 Oct 1;102(7):1369-76.
- [205] Gaudino M, Andreotti F, Zamparelli R, Di Castelnuovo A, Nasso G, Burzotta F, et al. The -174G/C interleukin-6 polymorphism influences postoperative interleukin-6 levels and postoperative atrial fibrillation. Is atrial fibrillation an inflammatory complication? *Circulation*. 2003 Sep 9;108(Suppl. 1):II195-9.
- [206] Roth-Isigkeit A, Hasselbach L, Ocklitz E, Bruckner S, Ros A, Gehring H, et al. Inter-individual differences in cytokine release in patients undergoing cardiac surgery with cardiopulmonary bypass. *Clinical & Experimental Immunology*. 2001 Jul;125(1):80-8.
- [207] Schluter B, Raufhake C, Erren M, Schotte H, Kipp F, Rust S, et al. Effect of the interleukin-6 promoter polymorphism (-174 G/C) on the incidence and outcome of sepsis. *Critical Care Medicine*. 2002 Jan;30(1):32-7.
- [208] Sutherland AM, Walley KR, Manocha S, Russell JA. The association of interleukin 6 haplotype clades with mortality in critically ill adults. *Archives of Internal Medicine*. 2005 Jan 10;165(1):75-82.

- [209] Chauhan M, McGuire W. Interleukin-6 (-174C) polymorphism and the risk of sepsis in very low birth weight infants: Meta-analysis. *Archives of Disease in Childhood Fetal and Neonatal Edition*. 2008 Nov;93(6):F427-9.
- [210] John Baier R, Loggins J, Yanamandra K. Angiotensin converting enzyme insertion/deletion polymorphism does not alter sepsis outcome in ventilated very low birth weight infants. *Journal of Perinatology*. 2005 Mar;25(3):205-9.
- [211] Spiegler J, Gilhaus A, Konig IR, Kattner E, Vochem M, Kuster H, et al. Polymorphisms in the Renin-Angiotensin system and outcome of very-low-birthweight infants. *Neonatology*. 2010;97(1):10-4.
- [212] Cogulu O, Onay H, Uzunkaya D, Gunduz C, Pehlivan S, Vardar F, et al. Role of angiotensin-converting enzyme gene polymorphisms in children with sepsis and septic shock. *Pediatrics International*. 2008 Aug;50(4):477-80.
- [213] Yang H, Wang Y, Liu L, Hu Q. Increased susceptibility of sepsis associated with CD143 deletion/insertion polymorphism in Caucasians: A meta analysis. *International Journal of Clinical and Experimental Pathology*. 2014;7(10):6551-8.
- [214] Hou X, Zhang P, Nie W, Tang S, Wang J, Zhang Q, et al. Association between angiotensin-converting enzyme I/D polymorphism and sepsis: A meta-analysis. *Journal of the Renin-Angiotensin-Aldosterone System*. 2015 Jun;16(2):415-21.
- [215] Tsantes A, Tsangaris I, Kopterides P, Nikolopoulos G, Kalamara E, Antonakos G, et al. Angiotensin converting enzyme (ACE) insertion/deletion (I/D) polymorphism and circulating ACE levels are not associated with outcome in critically ill septic patients. *Clinical Chemistry and Laboratory Medicine*. 2011 Oct 21;50(2):293-9.
- [216] Villar J, Flores C, Perez-Mendez L, Maca-Meyer N, Espinosa E, Blanco J, et al. Angiotensin-converting enzyme insertion/deletion polymorphism is not associated with susceptibility and outcome in sepsis and acute respiratory distress syndrome. *Intensive Care Medicine*. 2008 Mar;34(3):488-95.
- [217] Cardinal-Fernandez P, Ferruelo A, El-Assar M, Santiago C, Gomez-Gallego F, Martin-Pellicer A, et al. Genetic predisposition to acute respiratory distress syndrome in patients with severe sepsis. *Shock*. 2013 Mar;39(3):255-60.
- [218] Sipahi T, Pocan H, Akar N. Effect of various genetic polymorphisms on the incidence and outcome of severe sepsis. *Clinical and Applied Thrombosis/Hemostasis*. 2006 Jan;12(1):47-54.
- [219] Vassiliou AG, Maniatis NA, Kotanidou A, Kallergi M, Karystinaki FS, Letsiou E, et al. Endothelial protein C receptor polymorphisms and risk of severe sepsis in critically ill patients. *Intensive Care Medicine*. 2013 Oct;39(10):1752-9.