

## Clinical biomarkers in sepsis

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### TABLE OF CONTENTS

1. Abstract
2. Introduction
3. The immunological response to sepsis
4. Clinical biomarkers
  - 4.1. C-reactive protein
  - 4.2. Procalcitonin
  - 4.3. Interleukin-6
  - 4.4. Lipopolysaccharide binding protein
5. Summary and Perspective
6. References

## 1. ABSTRACT

Sepsis is one of the leading causes of death in intensive care medicine in western countries. A strong body of evidence has been accumulated indicating that immediate resuscitation and restoration of tissue perfusion as well as early antibiotic treatment could significantly decrease the mortality in these patients. The clinical definitions of sepsis are basically nonspecific, often resulting in the delay of the diagnosis. Therefore, identification of specific clinical biomarkers may accelerate the diagnosis and thus improve sepsis treatment. During the last decade, a variety of different molecules have been proposed as clinical biomarkers in sepsis, most of which are still in the experimental stage. However, some have found their way into clinical practice and have evolved as valuable tools for diagnosis, therapy monitoring, and outcome prediction. This review will summarize the currently most important biomarkers and will discuss their clinical relevance.

## 2. INTRODUCTION

Despite fundamental medical progresses over the last decades, sepsis is still one of the leading causes of death in intensive care and its incidence is increasing (1-4). According to data published by the *Surviving Sepsis Campaign*, approximately 18 million of new sepsis cases occur each year worldwide (5). Severe sepsis and septic shock are associated with mortality rates ranging from 30 to 60% (6-8). Furthermore, sepsis has been estimated to generate costs of approximately 17 billion dollar annually only in the United States which represents a significant financial burden for the economy. There is now clear evidence, that early diagnosis of sepsis followed by immediate initiation of the adequate therapy is of vital importance for the patient's survival (9-11), as has been demonstrated for acute myocardial infarction (12), stroke (13), and polytrauma (14). A fundamental problem in the therapy of sepsis is that clinicians often miss or delay the diagnosis due to the fact that there is no final consensus on

## Clinical biomarkers in sepsis

**Table 1.** Clinical signs of sepsis

<b>General variables</b>
Body temperature > 38,3 °C or < 36 °C
Heart rate > 90 beats/min or > 2 SD above the normal value for age
Tachypnea
Altered mental status
Edema or positive fluid balance
Hyperglycemia in the absence of diabetes
<b>Inflammatory variables</b>
White blood cell count > 12,000/μl or < 4,000/μl or 10% immature forms
Plasma C-reactive protein > 2 SD above the normal value
Plasma procalcitonin > 2 SD above the normal value
<b>Hemodynamic variables</b>
Arterial hypotension (SBP < 90 mmHg, MAP < 70 mmHg, or an SBP decrease > 40 mmHg)
Mixed venous oxygen saturation > 70%
Cardiac index > 3.5 l/min/m <sup>2</sup>
<b>Organ dysfunction variables</b>
Arterial hypoxemia (PaO <sub>2</sub> /FiO <sub>2</sub> < 300)
Urine output < 0.5 ml/kg/h or creatinine increase > 0.5 mg/dl
INR > 1.5 or aPTT > 60 sec.
Paralytic ileus
Thrombocytopenia (platelet count < 100,000/μl)
Hyperbilirubinemia (plasma total bilirubin > 4 mg/dl)
<b>Tissue perfusion variables</b>
Hyperlactatemia > 1 mmol/l
Decreased capillary refill or mottling

Abbreviations: SD: standard deviation, SBP: systolic blood pressure, MAP: mean arterial pressure, INR: international normalized ratio, aPTT: activated partial thromboplastin time

the clinical definitions of sepsis, which are basically nonspecific (15). According to the 1992 statement of the Society of Critical Care Medicine (SCCM) and the American College of Chest Physicians (ACCP), sepsis is defined as the systemic inflammatory response to infection. In this regard, the concept of the ‘systemic inflammatory response syndrome’ (SIRS) was introduced which is considered to be present when patients present at least two of the following findings:

1. Body temperature > 38°C or < 36 °C
2. Heart rate > 90 beats/minute
3. Hyperventilation (respiratory rate > 20 breaths/minute or PaCO<sub>2</sub> < 32 mmHg)
4. White blood cell count > 12,000 cells/μl or < 4,000 cells/μl or > 10% immature forms

Severe sepsis is defined as sepsis plus sepsis-induced organ dysfunction or tissue hypoperfusion and septic shock is characterized as sepsis-induced hemodynamic instability despite adequate fluid administration (16).

The SIRS based concept was expanded in the 2001 International Sepsis Definition Conference, which stated that the diagnosis of sepsis should be considered in the presence of a documented or suspected infection concurrent with some clinical signs of general illness (Table 1) (17). The use of the word ‘some’ should reflect the clinical reality at the bedside, rather than an arbitrary list invented for the purpose of clinical entry criteria. The last update of the International Guidelines for Management of Severe Sepsis and Septic Shock published by the *Surviving Sepsis Campaign* in 2008 refers to this definition. It has to be stressed that none of the findings listed in Table

1 are specific for sepsis and could also be seen in other forms of diseases or aseptic inflammatory processes. In view of this, identification and implementation of reliable clinical biomarkers into the diagnostic process is essential and may provide a valuable tool for decision making in this striking disease. As shown in Table 1, C-reactive protein (CRP) and procalcitonin (PCT) have already been included in the current sepsis definition criteria. To date a lot of different molecules have been proposed as useful biological markers of sepsis (Table 2) (18). However, most of these molecules are still in the experimental stage and have not been validated in controlled clinical trials including a large number of patients.

This article summarizes the present knowledge about biomarkers in sepsis and their clinical relevance with regard to diagnosis, differentiation of bacterial, fungal, and viral infections, therapy monitoring, and outcome prediction.

### 3. THE IMMUNOLOGICAL RESPONSE TO SEPSIS

Severe infection leads to the appearance of immunogenic cell wall components of the infectious agent in the bloodstream, which triggers a complex immunological response in the host. Gram-positive and gram-negative bacteria, fungi, and viruses all have these unique cell-wall molecules that bind to specific receptors on the surface of immune cells.

Lipopolysaccharides are components of the outer membrane of gram-negative bacilli and bind to lipopolysaccharide binding protein (LBP), an acute phase protein mainly synthesized by hepatocytes under interleukin-1 (IL-1) and interleukin-6 (IL-6) stimulation (19). The lipopolysaccharide/LBP complex is then presented to CD14 receptors on neutrophils, endothelial cells, macrophages, and monocytes leading to activation of these cells (20). In addition, LBP could also associate with lipoteichoic acid and peptidoglycans of gram-positive bacteria. It is of interest that lipopeptides present in spirochetes, mycobacterium spp. and gram-positive bacteria as well as mycoplasma spp. are also recognized by LBP (21).

Peptidoglycans of gram-positive bacteria and the abovementioned lipopolysaccharide/LBP complex bind to toll-like receptor (TLR)-2 and TLR-4, respectively thereby initiating translocation of the transcription factor nuclear factor kappa-B (NF-kappaB) from the cytoplasm to the nucleus. This leads to the generation of proinflammatory cytokines like tumor necrosis factor (TNF)-alpha, IL-1, and IL-6. These cytokines activate the adaptive immune response but could also cause both direct and indirect tissue injury in the host (22). The activation of endothelial cells by cytokines results in upregulation of adhesion molecules causing neurophils, monocytes, macrophages, and platelets to bind to the endothelium. This leads to the release of different mediators resulting in increased vascular permeability, endothelial cell damage, and activation of the coagulation cascade. In addition, they stimulate endothelial nitric oxide synthetase leading to vasodilation and severe

**Table 2.** Potential biomarkers in sepsis (modified from reference 24)

Acute Phase Proteins	Apoptosis	Coagulation factors	Cytokines	Membrane cell markers	Soluble receptors	Miscellaneous
ET-1 (118)	Fas/Apo-1 (119)	aPTT waveform analysis (120)	IL-8 (121)	CD13-HLADR (122)	sCD14 (123)	Gc-globulin (124)
PTX3 (125)	Fas/FasL (126)	AT III (127)	IL-10 (128)	CD-64 (129)	sCD14-ST (130)	HDL (131)
	Gas6 (132)	PAI-1 (133)	IL-12 (134)	HLA-DR (135)	sCD163 (136)	IL-1ra (117)
	TNFR1 (126)	Protein C (117)	TNF-alpha (118)	HLA-G5 (137)	sTNF-RI (138)	ICAM-1 (139)
		Thrombopoietin (140)			sTNF-RII (138)	MBL (141)
		vWF (142)			sTNF-R p55 (143)	NGAL (117)
					sTREM-1 (144)	NT-proBNP (145)
						pro-ADM (146)
						Ang-2 (147)
						SAA (148)

Abbreviations: Ang-2: angiopoietin-2, aPTT: activated partial thromboplastin time, AT III: antithrombin III, CD13-HLADR: CD13-class II histocompatibility antigen DR, ET-1: endothelin-1, FasL: Fas ligand, Gas6: growth-arrest-specific protein 6, HDL: high-density lipoprotein, HLADR: class II histocompatibility antigen DR, HLA-G5: human leukocyte antigen-G5, ICAM-1: intercellular adhesion molecule-1, MBL: mannan-binding lectin, NT-proBNP: N-terminal pro-brain natriuretic peptide, PAI-1: plasminogen activator inhibitor type-1, pro-ADM: pro-adrenomedullin, PTX3: pentraxin3, SAA: serum amyloid-A, sIL-1ra: soluble interleukin-1 receptor antagonist, sTREM-1: soluble triggering receptor expressed on myeloid cells-1, sTNF-R: soluble tumor necrosis factor-alpha receptor, TNF-R p55: tumor necrosis factor-alpha receptor p55, TNFR1: tumor necrosis factor type-I receptor, vWF: von Willebrand factor

hypotension. These entire mechanisms could ultimately result in severe tissue injury, multiorgan dysfunction, and in the worst case in death.

#### 4. CLINICAL BIOMARKERS

As mentioned above, many decisions in the management of septic patients are frequently based on clinical and laboratory signs with low sensitivity and specificity. This often results in a late diagnosis leading to a fatal delay of therapy and consecutively an increased mortality. Therefore, the discovery of clinical biomarkers may be a key step on the path to successful sepsis treatment since the outcome of sepsis is crucially dependent on an early diagnosis and initiation of resuscitation as fast as possible. A number of different potential biomarkers for sepsis have been proposed over the last years. As shown in Table 2, these include acute phase proteins, markers for apoptosis, coagulation factors, cytokines, membrane cell markers, soluble receptors, and others (23, 24). Most of these molecules are in the experimental stage at present but a handful have already found their way into clinical practice and can be routinely measured in the diagnostic laboratory. CRP, PCT, LBP, and IL-6 have recently emerged as valuable tools in the clinical routine. Their significance in the context of sepsis will be discussed in the following.

##### 4.1. C-reactive protein (CRP)

CRP was originally discovered by Tillet and Francis in 1930 as a substance in the serum of patients with acute inflammation that precipitated the C-polysaccharide of *Streptococcus pneumoniae* (25). It was the first acute phase protein to be described and is a sensitive but non-specific biochemical marker of inflammation and tissue damage. The circulating value of CRP reflects ongoing inflammation and/or organ injury in most, though not all, infectious and non-infectious diseases (Table 3) (26). Though extrahepatic synthesis has been reported in alveolar macrophages, neurons, atherosclerotic plaques, monocytes, and lymphocytes, CRP is principally generated by

hepatocytes as part of the acute phase response under the action of IL-1 and IL-6 (24, 26). Therefore, severe liver failure can impair CRP production (26). CRP binds with highest affinity to phosphocholine residues, but it also associate with ligands including other constituents of microorganisms, such as components of bacteria, fungi, and parasites. Ligand bound human CRP is recognized by complement C1q thereby activating the classical complement cascade. In addition to its pro-inflammatory action it has been recently reported that CRP could also exert anti-inflammatory effects (26, 27).

The use of CRP as a diagnostic tool in sepsis has been studied extensively over the last years. While CRP plasma levels in 99% of normal individuals are below 10 mg/L, they can rise as high as 500 mg/L in response to an acute infectious stimulus beginning at 4 – 6 hours and reaching a peak after 36 – 50 hours after the initial event (23). The half-life of CRP is short (approximately 19 hours) and is constant under all conditions of health and disease, so that the sole determinant of circulating CRP concentration is the synthesis rate (28). However, related to sepsis its kinetics may not be as favorable as those of PCT (29, 30). It should be noticed that CRP generation can be suppressed by corticosteroids (31, 32).

As shown in Table 3 and apart from non-infectious causes, CRP levels can be increased in bacterial, fungal, and viral infections, although the presence of bacterial infection could not be ruled out with low CRP plasma levels (33). It has been demonstrated that acute systemic bacterial and invasive fungal infections are generally associated with high CRP values, whereas the levels in chronic bacterial and in particular viral infections are usually rather low in adults. On the other hand, increased CRP levels could not accurately differentiate between bacterial and viral respiratory infections in children (34, 35).

In patients with sepsis compared to those with SIRS, higher CRP plasma levels had been described in a

## Clinical biomarkers in sepsis

number of studies (36, 37). Pova and colleagues reported that daily measurements and the designation of an appropriate cut-off value (CRP > 50 mg/L) may help to diagnose sepsis (37). Although normally increased in response to infection, accumulating evidence suggests that CRP is less accurate than PCT in differentiating SIRS from Sepsis and in particular to assess the degree of organ dysfunction (38). In addition, CRP concentrations are frequently induced near their maximum during less severe forms of sepsis and fail to further increase in response to severe sepsis or septic shock (36). As a consequence, different authors could show that CRP has no importance in distinguishing the severity of sepsis (39-41). CRP is also not useful for detection of septic complications after major trauma (42, 43).

Data presented by Lobo *et al.* indicate that high concentrations of plasma CRP at admission are correlated with an increased risk of organ failure and death (44). In sharp contrast, several authors could not find an association between CRP plasma levels and mortality. Neither a single determination at the day of sepsis diagnosis nor daily measurements correlated with the severity of the disease or mortality (39, 45-47). Hence, CRP is not an important prognostic marker.

However, CRP is at present the most commonly used clinical biomarker to evaluate inflammatory processes. According to the detection of sepsis, it is much more sensitive than parameters like body temperature or white blood cell count (37). Furthermore, the CRP assay is inexpensive and widely available. CRP is included into the diagnostic criteria of sepsis, which are based on the 2001 International Sepsis Definitions Conference (Table 1) (17). Therefore, and despite the abovementioned limitations, CRP has its use in the diagnosis of sepsis and could be used when PCT is not available as a laboratory marker.

### 4.2. Procalcitonin (PCT)

PCT is a precursor peptide of the hormone calcitonin, which is involved in calcium homeostasis. Under normal conditions, PCT is exclusively produced in the C-cells of the thyroid where it is cleaved into calcitonin, katacalcin and a protein residue. However in sepsis, PCT can be produced in nearly all extrathyroid tissues and its plasma concentration, which normally lies below 0.1 ng/mL can increase up to 10,000 fold under these conditions (48). Accumulating evidence suggests that PCT improves the clinical diagnosis of sepsis and antibiotic guidance in critically ill patients and is a promising candidate for the prediction of patient mortality (49). PCT can be upregulated in response to gram-negative and gram-positive bacterial as well as systemic fungal infections and in malaria. Of note and like all other clinical biomarkers in sepsis, infection-independent induction of PCT may occur. These situations include burns (50), trauma (51), cardiogenic shock (52), surgery (53), uremia (54), and others (Table 4) (55). In these cases, serum levels rarely exceed 5 ng/mL. PCT usually remains low in viral diseases, aseptic inflammatory processes and allergic reactions (56). It has an *in vivo* half-life of 20 - 24 hours and is highly stable in serum or plasma *ex vivo* where it is not converted

into calcitonin (56, 57). Increases in plasma concentrations are detectable 2 - 4 hours upon infection. Hence, it shows an earlier increase and has its maximum prior to CRP but later than the cytokines, e.g. IL-6 (see below). PCT values start to decline after a decrease in IL-6, but noticeably before the decline in CRP-values (29, 36, 56). Interestingly and in contrast to IL-6 and CRP concentrations, steroids do not influence the induction of PCT (31, 49, 58). PCT measurements must be used with caution in patients with renal failure, because uremia per se could elevate PCT levels and data from Dahaba *et al.* suggest that PCT may be dialyzed (54, 59).

There is now considerable evidence that elevated PCT values indicate systemic bacterial infection with high sensitivity and specificity (60). Therefore, a plasma PCT concentration above two standard deviations of the normal value is considered as one criterion of sepsis (17, 61). Data from Harbarth *et al.* show that addition of PCT measurements to standard indicators significantly improved the predictive power of detecting sepsis (41). Luzzani and colleagues reported that PCT is a better marker of sepsis than CRP. They could show a closer correlation of PCT than that of CRP with the severity of infection and organ dysfunction (38). According to the *German Sepsis Society*, plasma levels below 0.5 ng/mL nearly exclude severe sepsis whereas values above 2.0 ng/mL can identify individuals with high risk. In particular, PCT plasma concentrations higher than 10 ng/mL indicate patients with severe sepsis or septic shock in all probability (Figure 1) (40, 46, 62, 63). Furthermore, Meisner *et al.* found higher sepsis-related organ failure assessment (SOFA) scores in patients with significantly higher PCT plasma concentrations, whereas CRP was elevated irrespective of the scores observed (47).

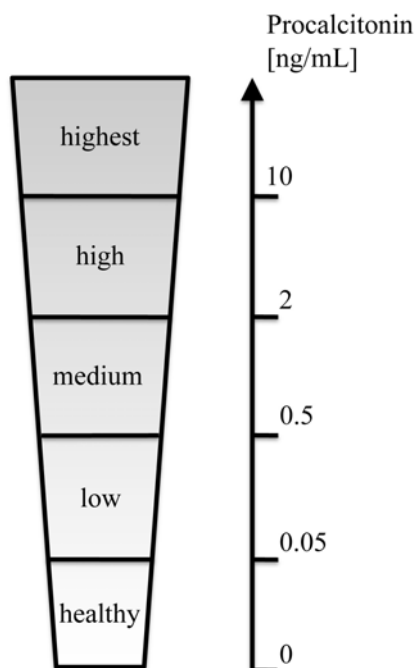
Although PCT appears to be the most promising biomarker of sepsis at present, one has to keep in mind, that other causes than infection could lead to transient moderate increases in PCT plasma levels (Table 4). Typically, these changes rapidly decline in follow up measurements if infection is not emerging (64). Therefore, serial measurements using a highly sensitive PCT immunoassay with functional assay sensitivity of 0.06 ng/mL rather than single determinations are preferable to detect the onset of infection. In a recently published study by Castelli *et al.* and in contrast to CRP, PCT plasma re-induction was associated with the occurrence of septic complications after major trauma. In addition, high PCT values at admission after trauma in ICU patients indicated an increased risk of septic complications (43). Similar data have been obtained in a study by Wanner *et al.* (51). It has also been demonstrated that PCT determinations could be useful in identifying septic complications after major surgery (65).

Lower respiratory tract infections and community-acquired pneumonia are the leading causes of sepsis in industrial countries (66, 67). In two clinical trials by Christ-Crain *et al.*, antibiotic treatment in these diseases was based on serum PCT concentrations and strongly discouraged when PCT levels were < 0.1 ng/mL, discouraged < 0.25 ng/mL, encouraged > 0.25 ng/mL and strongly encouraged at concentrations > 0.5 ng/mL. It

## Clinical biomarkers in sepsis

**Table 3.** Principle causes of increased circulating values of C-reactive protein

<b>Infections</b>
Bacterial
Systemic/Severe Fungal
Viral
Mycobacterial
<b>Allergic complications of infection</b>
Rheumatic fever
Erythema nodosum
<b>Noninfectious inflammatory disease</b>
Rheumatoid arthritis
Juvenile chronic arthritis
Ankylosing spondylitis
Psoriatic arthritis
Systemic vasculitis
Polymyalgia rheumatica
Crohn disease
<b>Necrosis</b>
Myocardial infarction
Acute pancreatitis
Tumor embolization
<b>Trauma</b>
Surgery
Burns
Fractures
<b>Malignancy</b>
Lymphoma
Carcinoma
Sarcoma



**Figure 1.** Probability of severe sepsis and septic shock depending on procalcitonin serum levels.

could be shown that PCT guidance by following this protocol allows reducing the use of antibiotics in these patients without compromising outcome (68, 69). In a recently published randomized clinical trial, Nobre *et al.* demonstrated that a protocol based on serial PCT measurements allows reducing antibiotic treatment duration in patients with severe sepsis and septic shock without

apparent harm (70). In patients assigned to the intervention group, antibiotics were stopped when PCT levels had decreased 90% or more from the initial value but not before day 3 (if baseline PCT levels were  $< 1$  ng/mL) or day 5 (if baseline PCT levels were  $\geq 1$  ng/mL). In control patients, clinicians decided on the duration of antibiotic therapy based on empirical rules. The authors could find a 4-day reduction in the duration of antibiotic therapy and a smaller overall antibiotic exposure in patients in whom a decision could be taken from serial PCT measurements. A similar mortality and a 2-day shorter intensive care unit stay were also observed in patients assigned to the PCT group. Since antibiotic overuse is a serious problem in septic patients and leads to high costs, increased toxicity and to the development of bacterial resistance, therapy monitoring by serial PCT measurements could evolve as valuable tool in clinical decision making on treatment of septic patients.

The prognostic value of PCT in sepsis is not finally evaluated. Plasma levels obtained early after admission might have less prognostic value becoming more important in the course of the disease (29, 47, 67, 71). The questionable relevance of initial PCT levels is a clear disadvantage since the decision in favor or against the administration of antibiotics in septic patients has to be made as early as possible. On the other hand, it has been repeatedly shown that persistent elevation of PCT can be associated with poor outcome, distinguishing survivors from nonsurvivors (24, 41, 72). In contrast to CRP or leukocyte count, Jensen and colleagues recently demonstrated that the prognostic accuracy of PCT in the ICU could be profoundly improved by serial measurements. The authors identified the absolute PCT level, but especially the PCT increase for one day, as an independent predictor of 90-day all-cause mortality. Mortality increased for every day that PCT increased (72).

Although at present, PCT seems to be the most promising biomarker in sepsis confirmed by various clinical studies and two recent metaanalyses (60, 73), there is still a controversy about its definite impact (74-77).

### 4.3. Interleukin-6

IL-6 is not only a mediator of sepsis but also a clinical biomarker. IL-6 is principally synthesized by endothelial cells, fibroblasts and monocytes/macrophages during systemic inflammatory reactions associated with infection but also with stress, tissue injury, trauma, brain death and other situations (78). Its production can be triggered by a large number of different stimulators comprising bacterial endotoxins, viruses, fungi, cytokines and others. It has to be stressed that IL-6 gene expression is regulated by steroid hormones. Data obtained by Woloski *et al.* show that dexamethasone could down-regulate IL-6 production *in vitro* and recently published results from Weis *et al.* demonstrated that stress doses of hydrocortisone suppresses IL-6 levels in patients (58, 79).

In humans, the liver seems to be the major target organ for IL-6 where it strongly induces acute phase proteins like CRP and LBP. Therefore, IL-6 elevations in the plasma are seen earlier than the increases of the

## Clinical biomarkers in sepsis

**Table 4.** Principle causes of increased circulating values of procalcitonin

<b>Severe Infections</b>
Bacterial
Systemic/Severe Fungal
Parasitic (Malaria)
Viral (only minor PCT increases)
<b>Noninfectious systemic inflammation</b>
Inhalational injury
Pulmonary aspiration
Pancreatitis
Heat stroke
Mesenteric infarction
<b>Trauma</b>
Surgery
Burns
Mechanical Injury
<b>Malignancy</b>
Neuroendocrine tumors
Medullary thyroid cancer
Small cell lung cancer
Carcinoid syndrome
<b>Newborns</b>

forementioned acute phase proteins (80). Fong *et al.* showed a substantial increase of IL-6 in the serum of healthy volunteers after intravenous administration of a small amount of endotoxin, peaking as fast as 2 hours post injection (81). In comparison, peak values of PCT are seen after 6 - 8 hours and of CRP after 36 – 50 hours. Therefore, IL-6 is of considerable interest to evaluate the initial phase of sepsis. The biological half-life of IL-6 is approximately 20 - 30 minutes.

In healthy adults, IL-6 concentrations in the plasma are below 10 pg/mL. However, in sepsis IL-6 levels could rise above 10,000 pg/mL, in individual cases even higher than 100,000 pg/mL. Due to the enormous range and the heterogeneity of IL-6 plasma levels found intra- and inter-individually, a cut-off value for patients at risk is hard to find. Fraunberger *et al.* reported recently, that IL-6 levels above 1,000 pg/mL at the onset of fever may identify high-risk patients in the intensive care unit (82). In the MONARCS-trial, Panacek *et al.* defined 1,000 pg/mL as inclusion criterion for the therapy with a monoclonal TNF-alpha antibody in patients with severe sepsis. The initial IL-6 plasma level in the placebo group correlated with both organ dysfunction and mortality (28,6%: IL-6 < 1,000 pg/mL versus 47,6%: IL-6 > 1,000 pg/mL) (83). Data from other clinical studies have also shown that the majority of septic patients have increased IL-6 plasma levels, and that these levels are associated with the severity of the disease and with outcome (23, 84-88). Permanently elevated IL-6 levels are accompanied with multiple organ dysfunction and death (89, 90). On the other hand, Wunder *et al.* found no correlation of IL-6 plasma levels and outcome in a small cohort of patients with severe sepsis (91).

The reports comparing IL-6 with PCT in regard to diagnosis of sepsis are conflicting. Mokart and colleagues identified both, PCT and IL-6 as early markers of postoperative sepsis after major surgery. An IL-6 cut-off point set at 310 pg/mL yielded a sensitivity of 90% and a specificity of 58% to differentiate septic from non-septic patients. A PCT cut-off point set at 1.1 ng/mL yielded a sensitivity of 81% and a specificity of 72% (65). Recently

published data from Gaini *et al.* demonstrate that IL-6 appears to be superior to PCT as diagnostic marker for infection and sepsis (80). In sharp contrast to these findings, the majority of reports identified PCT as more reliable biomarker of sepsis compared to IL-6 (41, 62, 92). IL-6 determinations are very sensitive indicating the general inflammatory response of the host. However, compared to PCT it has a lower specificity for detecting infection.

### 4.4. Lipopolysaccharide binding protein

In 1986 Tobias *et al.* identified for the first time a new acute phase reactant from rabbit serum now known as lipopolysaccharide binding protein (LBP) (93). LBP is mainly synthesized by hepatocytes and is induced as acute phase protein by IL-6 and IL-1. In addition, LBP can be synthesized in the lung, intestine, and by gingival tissue of the mouth (94). Schumann and Zweigner could demonstrate that changes in LBP serum concentrations might influence the host reactivity to endotoxins (95). There are further indications that low levels of LBP enhance lipopolysaccharide triggered cell-activation and promote inflammation at sites of infection, whereas high serum-concentrations of LBP may inhibit lipopolysaccharide dependent systemic inflammation (96). Interestingly, LBP has been recently suggested as a new clinical biomarker of sepsis (97). LBP serum levels could rise dramatically in patients with SIRS (98), pancreatitis (99), trauma (100), and in response to gram-negative and gram-positive as well as fungal infections (101). Maximum peak levels can typically be detected at day 2 – 3 after the initial insult. This time frame appears to be comparable to that of CRP (95). Normal serum levels of LBP are usually between 5 - 15 µg/mL and increase up to 200 µg/mL during an acute-phase reaction (95, 102). Although Oude Nijhuis *et al.* reported higher LBP concentrations in patients with gram-negative infections (103), the majority of studies showed that serum LBP levels in patients with gram-negative infections did not differ from those with gram-positive or fungal infections (101, 104-106).

In a recent investigation by Sakr *et al.* on 327 patients admitted to a surgical intensive care unit, LBP measurements moderately discriminated patients without infection from patients with severe sepsis but not from patients with sepsis without organ dysfunction. These authors concluded that LBP serum levels are clearly inferior to IL-6 and PCT in differentiating between SIRS and sepsis and correlated to a lesser degree with the severity of sepsis and organ dysfunction (104). In agreement with these results, Prucha and colleagues found no difference in LBP levels of patients with SIRS and those with sepsis. However, the authors could show higher concentrations in patients with septic shock compared to those with SIRS (105). In contrast to these data, a prospective study by Gaini *et al.* including 194 patients with suspected community-acquired infections and sepsis found LBP to be

## Clinical biomarkers in sepsis

superior to PCT as diagnostic marker for infection and sepsis (80). These authors reported a cut-off level of 20 µg/mL for diagnosing infection (sensitivity: 81%; specificity: 68%). In a preliminary study with only 12 patients following open heart surgery, Sablotzki *et al.* found significantly elevated LBP levels in those patients with documented infections (97). Reports from Oude Nijhuis *et al.* also suggest the suitability of LPB serum levels as a biomarker for infection with a cut-off value of 46.3 µg/mL (sensitivity: 100%; specificity: 92%) (103). In addition, Albillos *et al.* documented in cirrhotic patients with ascites that those showing higher LBP serum levels were significantly at risk for a severe infection (107).

At present, there is no clear association between LBP serum concentrations and patient outcome. While data by Opal *et al.* show a correlation of low LBP serum concentrations and worse outcome (108), the studies by Sakr *et al.* as well as Prucha and colleagues found higher LBP levels in non-survivors compared to survivors (104, 105).

The impact of LBP measurements as a diagnostic and prognostic tool in sepsis differs between adults, children and neonates. Due to the abovementioned contradictory findings regarding the low potential to differentiate between SIRS and sepsis as well as its weak prognostic value, LBP could at present not be recommended as first line sepsis biomarker in adults. In contrast, LBP proved to be more sensitive than other markers such as CRP, IL-6 and PCT in neonatal sepsis (109). Pavcnik-Arnol and colleagues reported the superiority of LBP as a biomarker for infection over IL-6 and CRP in critically ill children and neonates aged over 48h, being as powerful as PCT. In critically ill neonates under 48h LBP on the first day of suspected infection was a better marker of sepsis than IL-6 and PCT, and was similar to CRP (110). Recently published data by the same group supported the earlier findings (111). Data collected in 39 children with invasive bacterial infection caused by *Haemophilus influenzae* supported the usability of LBP as a biomarker of infection (109). On the other hand Orlikowsky *et al.* found LPB not sufficiently sensitive in the prediction of early-onset bacterial infection in newborns (112). The results in children and neonates are promising but also not completely consistent. More controlled studies in a larger number of patients are required to make final recommendations.

## 5. SUMMARY AND PERSPECTIVE

Sepsis is one of the major causes of morbidity and mortality in intensive care units in industrial countries. Effective management of this striking disease requires urgent initiation of hemodynamic support and antimicrobial therapy. Therefore, early diagnosis of infection is the ultimate goal to a successful treatment. Unfortunately, the

clinical signs of sepsis can be misleading due to their low sensitivity and specificity. This often leads to a delay of the diagnosis and therapy with a subsequent rise of mortality in these patients. Due to this unresolved problem, it is of major importance to identify adequate biomarkers with the quality to differentiate infectious from non-infectious causes of SIRS with an optimal specificity and sensitivity and specific cut-off values. Unfortunately, this 'gold standard biomarker' does not exist at present. Many different potential biomarkers have been investigated during the last years. However, most of them are still in the experimental stage and only some have found a way into the clinical routine. Currently, the most relevant clinical biomarkers in sepsis are CRP, PCT, IL-6, and LBP. Regarding these markers, an overview of cut-off levels together with sensitivity and specificity from the most recent clinical trials is presented in Table 5. Importantly, one has to keep in mind that all of these markers could also be upregulated in response to non-infectious stimuli. Although CRP and IL-6 are highly sensitive for detection of inflammatory processes, they are too non-specific which limit their use in diagnosing sepsis. At present, PCT is the most promising clinical biomarker in this regard. It has been shown that determination of PCT is a valuable tool to diagnose and assess the severity of sepsis as well as guide antimicrobial therapy and predict patient outcome. Therefore, serial rather than single measurements provide more useful information in critically ill patients. LBP can currently not be recommended for routine use as a biomarker in sepsis in adults based on the present data. In contrast, the results in children and neonates are promising but also not completely consistent. Data obtained in adults and children suggest that the combination of different biomarkers could possibly improve the diagnosis of sepsis and bacteremia and may serve as an advanced prognostic tool in septic patients by further increasing sensitivity and specificity (113, 114). In this regard, Bell and colleagues demonstrated that simultaneous measurement of PCT and CRP plasma levels resulted in a more sensitive screen than either one alone (114). In addition, Kofoed *et al.* could show an improved accuracy in detecting sepsis by combined measurement of CRP, PCT, and neutrophil count (115). Phua *et al.* provided evidence that the combined use of lactate and PCT could independently predict 28-day mortality in patients with septic shock (116). This "multi-marker approach" including panels of different biomarkers, cytokines, coagulation factors, and others is under active investigation at present and may be integrated into future concepts of sepsis management (117).

As already stated by Schuetz *et al.*, a gold standard to differentiate infectious from non-infectious causes, especially in critically ill patients with SIRS, is currently lacking. As a consequence, biomarker levels must always be evaluated and reevaluated during follow-up, and interpreted in the context of a careful clinical and microbiological

## Clinical biomarkers in sepsis

**Table 5.** Characteristics of clinical biomarkers in diagnosing SIRS versus sepsis

Reference	Year	n	Biomarker	Best cut-off value	Sensitivity	Specificity
Aikawa N <i>et al.</i> (92)	2005	245	CRP PCT IL-6	5 mg/L 0.5 ng/mL 100 pg/mL	83% 64% 71%	69% 86% 66%
Al-Nawas B <i>et al.</i> (149)	1996	337	PCT	0.5 ng/mL	60%	79%
Arkader R <i>et al.</i> (150)	2006	28	CRP PCT	79 mg/L 2 ng/mL	30% 88%	97% 100%
Aouifi A <i>et al.</i> (151)	2000	97	CRP PCT	50 mg/L 1 ng/mL	84% 85%	40% 95%
Balci C <i>et al.</i> (152)	2003	33	CRP PCT IL-6	145 mg/L 2.4 ng/mL 68.5 pg/mL	58% 85% 51%	58% 91% 53%
Bell K <i>et al.</i> (114)	2003	123	CRP PCT	185 mg/L 3.03 ng/mL	83% 83%	48% 76%
Bossink A <i>et al.</i> (153)	1999	300	PCT	0.5 ng/mL	65%	58%
Brunkhorst FM <i>et al.</i> (40) (sepsis vs. severe sepsis)	2000	185	PCT	2.0 ng/mL	96%	86%
Castelli GP <i>et al.</i> (36)	2004	150	CRP PCT	90 mg/L 1.2 ng/mL	74% 63%	85% 87%
Castelli GP <i>et al.</i> (154)	2006	(254 clinical events)	CRP PCT	128 mg/L 0.47 ng/mL	61% 83%	87% 81%
Chan YL <i>et al.</i> (155)	2004	120	CRP PCT	60 mg/L 0.6 ng/mL	67% 71%	94% 63%
Cheval C <i>et al.</i> (156)	2000	60	CRP PCT	100 mg/L 5 ng/mL	93% 88%	40% 67%
Clec'h C <i>et al.</i> (46)	2004	75	PCT	1 ng/mL	95%	54%
Dorge H <i>et al.</i> (157)	2003	80	PCT	5 ng/mL	63%	62%
Du B <i>et al.</i> (158)	2003	51	CRP PCT IL-6	75 mg/L 1.6 ng/mL 290 pg/mL	80% 80% 85%	29% 74% 74%
Endo S <i>et al.</i> (159)	2008	82	PCT	2.0 ng/mL	95%	78%
Enguix A <i>et al.</i> (160)	2001	116	CRP PCT CRP PCT	23 mg/L (neonates) 6.1 ng/mL (neonates) 22 mg/L (children) 8.1 ng/mL (children)	96% 99% 89% 100%	84% 89% 81% 100%
Gaini S <i>et al.</i> (80)	2006	194	CRP PCT IL-6 LBP	38 mg/L 0.25 ng/mL 25 pg/mL 20 µg/mL	80% 55% 81% 81%	58% 90% 79% 68%
Geppert A <i>et al.</i> (161)	2003	55	CRP PCT	91.5 mg/L 2 ng/mL	100% 87%	65% 75%
Giamarellos-Bourboulis EJ <i>et al.</i> (162)	2002	119	PCT	1 ng/mL	95%	65%
Gibot S <i>et al.</i> (144)	2004	76	CRP PCT	70 mg/L 0.6 ng/mL	76% 84%	67% 70%
Harbarth S <i>et al.</i> (41)	2001	78	CRP PCT IL-6	150 mg/L 1.1 ng/mL 200 pg/mL	68% 97% 67%	73% 78% 72%
Hausfater P <i>et al.</i> (163)	2002	195	PCT	0.2 ng/mL	62%	88%
Luzzani A <i>et al.</i> (38)	2003	70	CRP PCT	50 mg/L 2 ng/mL	90% 76%	75% 84%
Meisner M <i>et al.</i> (164)	2002	208	PCT	2 ng/mL	87%	78%
Mokart D <i>et al.</i> (65)	2005	50	CRP PCT IL-6	93 mg/L 1.1 ng/mL 310 pg/mL	63% 81% 90%	72% 72% 58%
Muller B <i>et al.</i> (62)	2000	101	CRP PCT IL-6	100 mg/L 1 ng/mL 50 pg/mL	71% 89% 65%	78% 94% 79%
Oude-Nijhuis CSM <i>et al.</i> (103)	2003	57	CRP LBP	19.5 mg/L 46.3 mg/L	100% 100%	19% 92%
Povoa P <i>et al.</i> (37)	1998	23	CRP	50 mg/L	99%	75%
Prucha M <i>et al.</i> (105)	2003	68	LBP	29.8 µg/mL	74%	50%
Resch B <i>et al.</i> (165)	2003	68	CRP PCT IL-6	2.5 mg/L (neonates) 6 ng/mL (neonates) 60 pg/mL (neonates)	69% 77% 54%	96% 91% 100%
Ruokonen E <i>et al.</i> (166)	2002	208	CRP PCT	154 mg/L 0.8 ng/mL	50% 68%	74% 48%
Sakr Y <i>et al.</i> (104) (SIRS vs. sepsis)	2008	327	CRP PCT LBP	200 mg/L 2 ng/mL 32 µg/mL	46% 69% 60%	84% 56% 62%
Sakr Y <i>et al.</i> (104) (SIRS versus severe sepsis)	2008	327	CRP PCT LBP	200 mg/L 6 ng/mL 47 µg/mL	56% 76% 51%	79% 78% 82%
Sakr Y <i>et al.</i> (104) (Sepsis versus severe sepsis)	2008	327	CRP PCT LBP	200 mg/L 6.5 ng/mL 47 µg/mL	56% 76% 51%	84% 81% 85%
Selberg O <i>et al.</i> (167)	2000	33	CRP	60 mg/L	86%	18%



## Clinical biomarkers in sepsis

			PCT	3.3 ng/mL	86%	54%
			IL-6	110 pg/mL	86%	54%
Stryjewski G <i>et al.</i> (168)	2005	56	PCT	0.5 ng/mL (children)	94%	90%
Suprin E <i>et al.</i> (169)	2000	101	CRP	100 mg/L	74%	74%
			PCT	2 ng/mL	65%	70%
Tugrul S <i>et al.</i> (170)	2002	85	CRP	139 mg/L	35%	42%
			PCT	1.3 ng/mL	73%	83%
Ugarte H <i>et al.</i> (171)	1999	205	CRP	79 mg/L	72%	67%
			PCT	0.6 ng/mL	68%	61%
Wanner GA <i>et al.</i> (51)	2000	405	PCT	1.5 ng/mL	76%	77%
Whang KT <i>et al.</i> (172)	1998	29	PCT	0.68 ng/mL	67%	80%

Abbreviations: CRP: C-reactive protein, IL-6: interleukin-6, LBP: lipopolysaccharide binding protein, PCT: procalcitonin

assessment (49). Furthermore, the definition of specific cut-off ranges for each proposed biomarker would be essential for therapeutic decision making in intensive care. There is still much need for standardized multicenter clinical trials in further evaluating additional makers for their introduction in intensive care medicine.

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## Clinical biomarkers in sepsis

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**Abbreviations:** CRP: C-reactive protein, IL-1: interleukin-1, IL-6: interleukin-6, LBP: lipopolysaccharide-binding protein, NF-kappaB: nuclear factor kappa-B, PCT: procalcitonin, TNF: tumor necrosis factor

**Key Words:** Sepsis, SIRS, Biomarkers, Systemic Inflammation, Procalcitonin, C-reactive Protein, Interleukin-6, Lipopolysaccharide Binding Protein, Multi Organ Failure, Review

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