REVIEW

Are there new approaches for diagnosis, therapy guidance and outcome prediction of sepsis?

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Abstract

Beside many efforts to improve outcome, sepsis is still one of the most frequent causes of death in critically ill patients. It is the most common condition with high mortality in intensive care units. The complexity of the septic syndrome comprises immunological aspects - *i.e.*, sepsis induced immunosuppression - but is not restricted to this fact in modern concepts. So far, exact mechanisms and variables determining outcome and mortality stay unclear. Since there is no typical risk profile, early diagnosis and risk stratification remain difficult, which hinders rapid and effective treatment initiation. Due to the heterogeneous nature of sepsis, potential therapy options should be adapted to the individual. Biomarkers like C-reactive protein and procalcitonin are routinely used as complementary tools in clinical decision-making. Beyond the acute phase proteins, a wide bunch of promising substances and non-laboratory tools with potential diagnostic and prognostic value is under intensive investigation. So far, clinical decision just based on biomarker assessment is not yet feasible. However, biomarkers should be considered as a complementary approach.

Key words: Clinical decision-making; Biomarkers; Early prediction; Sepsis and mortality

Core tip: Sepsis is a complex continuum of disturbed systems. Despite the presence of clinical consensus criteria, the early diagnosis especially in the perioperative setting is challenging. A magnitude of potential new biomarkers is tested for this purpose, but evidence is mounting that due to the complex nature of the syndrome, biomarkers are rather complementary tools for clinical decision making than "magic bullets". Moreover, biomarkers are also evaluated for therapy guidance, linking diagnostic results to an individual therapeutic regime. This review summarizes the developments in the biomarker field, aiming to provide an overview about current targets and their limitations.

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INTRODUCTION

The incidence of sepsis is still unreasonable high in critically ill patients and represents a major challenge in treatment. It is a common reason for admission to the intensive care unit (ICU). In European ICUs, sepsis and severe sepsis occur in 30% and 37% of the patients[1]. Gaieski and colleagues designate severe sepsis as the third most common cause of death in the United States after heart disease and malignant tumors[2]. A reason for the elevated incidence of sepsis in developed countries may be the high proportion of the elderly population[3].

Sepsis is defined as a systemic inflammatory response syndrome (SIRS) with proven or probable infection of bacterial, fungal or viral origin[4]. Severe sepsis is characterized by additional existence of organ dysfunction, while septic shock is defined as sepsis together with the failure of the cardiovascular system to sustain adequate tissue perfusion[5] (Figure 1). Initially, the organism reacts with a proinflammatory immune response to the infectious stimulus. During the later course of disease, there is a co-existence between SIRS and compensatory mechanisms termed compensatory anti-inflammatory response syndrome (CARS, Figure 2). The resulting sepsis-induced immune suppression is characterized by a collapse of cellular immune response and an increased risk for opportunistic infections with high mortality[6]. Clinical signs of sepsis are unspecific and comprise general symptoms (*i.e.,* aberrances of body temperature, fluid balance, glucose metabolism or mental confusion), as well as laboratory indications of inflammation or signs of hemodynamic impairment and organ dysfunction[4]. Because of the high variability of symptoms and the pathophysiological complexity, clinical recognition and severity assessment remain difficult[7].

The therapy of septic patients represents a major challenge to physicians. To improve clinical management and outcome of critically ill patients, the Surviving Sepsis Campaign guidelines were published ten years ago and have been lastly revised in 2012[8]. However, despite modern resuscitating strategies and anti-infective therapy options morbidity and mortality remain notably high in septic disease.

The key to successful therapy remains the early detection of septic patients. Biomarkers may provide help for clinical decision-making and predicting sepsis-related outcome[9]. Therefore, beside commonly used substances like C-reactive protein (CRP) and procalcitonin (PCT), further biomarkers are needed. Additionally, in times with increasing prevalence of multidrug-resistant pathogens and a growing consumption of anti-infective drugs biomarker-guided strategies are of enormous importance[10]. The large involvement of organs and cell systems in the inflammatory response to an infection widens the number of putative biomarker candidates[11] (Figure 3).

BIOMARKERS OF INFLAMMATION

Cytokines and acute phase proteins

Triggered by inflammation, immune cells release a wide range of mediators, *i.e.,* interleukins or tumor necrosis factor (TNF-α), into circulation. These cytokines induce the production and secretion of acute phase proteins in the liver. Many of these substances have been investigated as potential sepsis-biomarkers. The following chapter reviews important markers of this group.

CRP and PCT

The most used biomarkers in clinical settings are the acute phase proteins CRP and PCT[4,10,12]. The synthesis of CRP in the liver is triggered by interleukin-6 (IL-6) in response to tissue damages, inflammatory and/or infectious stimuli[13]. There is a notable increase of CRP level 4-6 h after stimulation. These levels double every 8 h and peak 36 to 50 h after an infection/inflammation stimulus[14]. CRP measurement is cheap and rapidly available, but increases of CRP levels are unspecific, since they can be observed, *i.e.,* after surgery or trauma[15]. However, CRP is commonly used to screen early onset of sepsis in neonates[16]. High CRP levels correlate with disease severity and are discussed to represent the effectiveness of an antimicrobial therapy[17-19]. Although CRP assessment does not sufficiently allow to discriminate between infectious and non-infectious stimuli, a secondary rise in CRP level after 3 to 4 d after infection, surgery or trauma could be helpful for diagnosing septic complications.

PCT is a prohormone of calcitonin. The peptide precursor is released by parenchymal cells including liver, kidney and muscles cells as well as adipocytes in response to bacterial toxins. After exposition to those toxins, serum levels of PCT increase within 2 to 4 h[20] and a peak of PCT in serum can be detected after approximately 14 h[21,22]. PCT is seen as a specific biomarker for bacterial infection[23], although elevations of PCT in serum can also be observed under non-infectious conditions, such as trauma[24], major surgical procedures, pancreatitis and renal impairment[25-28]. Thus, the use of PCT as a diagnostic biomarker of sepsis is discussed in a couple of meta-analyses with conflicting results[29,30]. However, other trials investigated the potential use of PCT to guide antimicrobial therapies[31], *i.e.,* in patients with community-acquired pneumonia (CAP), acute exacerbation of chronic bronchitis and sepsis. A recent multicentre study demonstrated, that serum PCT levels are not an accurate indicator for ventilator-associated
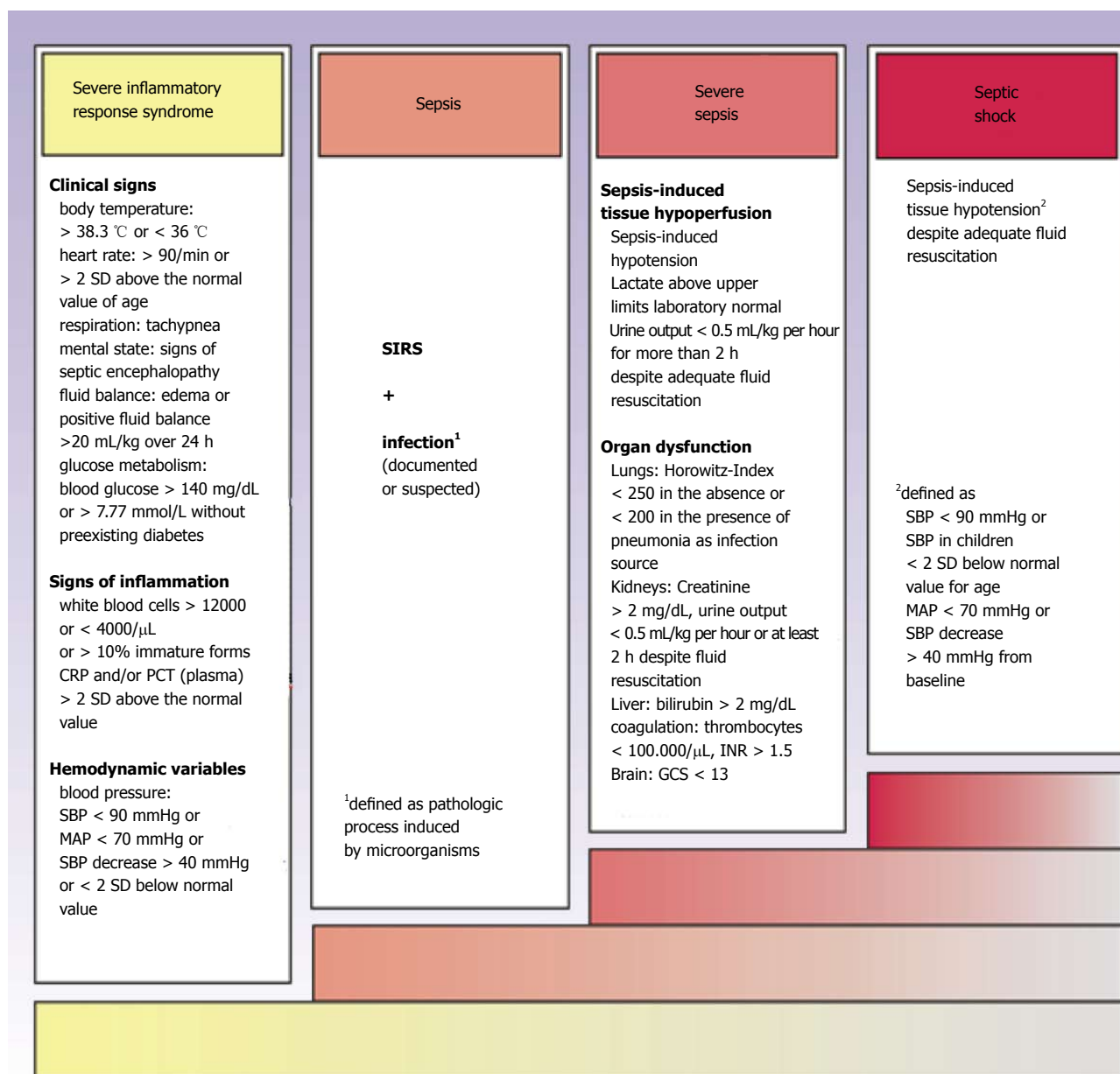
Figure 1 Diagnostic criteria of systemic inflammatory response syndrome, sepsis, severe sepsis and septic shock (modified from[5]). CRP: C-reactive protein; PCT: Procalcitonin; SIRS: Systemic inflammatory response syndrome.

pneumonia (VAP). Higher PCT levels were shown in CAP than in VAP[32]. Although PCT-guided antibiotic therapy is associated with a reduction in antibiotic usage and may reduce overall costs of care, an increase in hospital mortality of 7% under PCT guided conditions could not be ruled out by a meta analysis of Heyland *et al*[33]. Despite the association of high PCT and CRP levels in the onset of sepsis with poor outcome[34,35], the prognostic value of PCT is limited[10].

IL-6

IL-6 is secreted by macrophages and T cells to stimulate immune response which occurs during infection and after trauma, especially burns or other tissue damage leading to inflammation[36,37]. Compared to CRP or PCT, IL-6 levels peak 2 h after initiation of the inflammatory cascade. Based on this rapid increase, IL-6 was introduced as a biomarker of early sepsis in emergency units[38,39]. A multicenter study showed that IL-6 can predict survival on the 28th day after sepsis onset[40]. The value of IL-6 to distinguish between SIRS and sepsis is controversially discussed[41,42], since high levels can also be detected after trauma, surgery or in patients with autoimmune diseases[43-45]. Nevertheless, the IL-6 expression correlates with sepsis severity[10]. Further prospective and multicenter studies are required to elucidate the benefit of IL-6 and acute-phase proteins like CRP and PCT in diagnosis and risk-stratification of septic patients.

Pentraxin 3

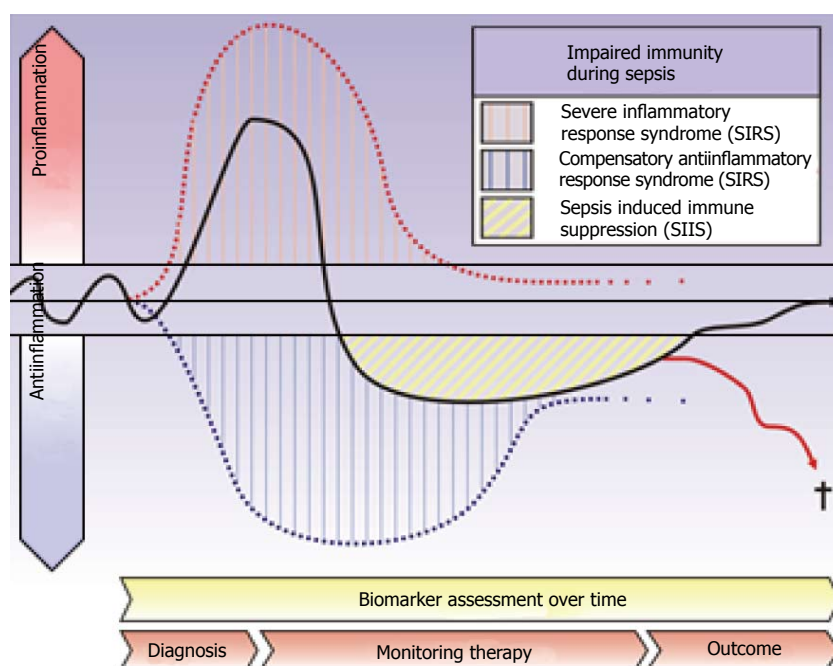The pentraxin superfamily comprises a wide range of

Figure 2 Simplified scheme of the impaired immunity during sepsis and the potential use of biomarkers: Initially, the body reacts to infectious stimuli with a proinflammatory immune response. Simultaneously, compensatory mechanisms are initiated to counteract the inflammatory process. The resulting net immune suppression is characterised by an increased risk of opportunistic infections. Beside C-reactive protein and procalcitonin, further biomarkers may be used in diagnosis, therapy-guidance and outcome prediction of sepsis.

proteins involved in the initial phase of the inflammatory response[46]. Prototypic long pentraxin 3 (PTX 3) is rapidly produced and released by various cells like mononuclear phagocytes, dendritic cells (DC), fibroblasts and endothelial cells[47-49]. It binds to specific patterns of fungi, bacteria and viruses[46,50,51] and induces the complement pathway[52]. A prospective study by Mauri and colleagues showed significantly elevated PTX3 levels in non-survivors compared to survivors over the first five days. In addition, PTX3 plasma levels were higher in the septic shock group than in patients with severe sepsis[53]. Concordantly, Bastrup-Birk and colleagues describe an association between disease severity and PTX3 levels. Furthermore, using ROC-analyses, moderate statistic values for PTX3 could be found to distinguish between patients with SIRS and healthy individuals[54]. Thus, PTX3 should be considered as a potential tool to monitor disease severity.

CELL-SURFACE RECEPTORS AND THEIR SOLUBLE FORMS

The expression of various proteins, *i.e.,* cell surface receptors, is up-regulated in activated immune cells. These receptors as well as their soluble forms occur as potential biomarkers in septic patients.

Soluble receptor for advanced glycation end products
The transmembrane receptor of advanced glycation end products (RAGE) belongs to the immunoglobulin superfamily. During inflammation, the receptor induces cell activation by initiating intracellular signalling cascades[10,55] resulting in rapid gene transcription[56]. RAGE is upregulated in various inflammatory diseases, such as rheumatoid arthritis[57,58], inflammatory kidney disease[59,60], arteriosclerosis[61] and inflammatory

bowel disease[62]. The truncated form of the receptor, soluble RAGE (sRAGE), was demonstrated to be elevated in septic ICU patients at early onset of sepsis. There were also higher levels in nonsurvivors than survivors at day 28[63]. A multivariate analysis showed an association between sRAGE levels and mortality in acute respiratory distress syndrome (ARDS) patients, but not with severity of illness[64]. There is a relation between sRAGE and outcome of septic patients. To prove suitability of sRAGE as a prognostic marker, further clinical studies are needed.

Soluble triggering receptor expresses on myeloid cells-1
As a member of the immunoglobulin superfamily, the triggering receptor expressed on myeloid cells-1 (TREM-1) is strongly expressed on activated phagocytes[65,66]. A soluble form is released during bacterial or fungal infections and can be detected as biomarker in distinct body fluids[67]. After an induction period of less than 2 h, plasma levels of soluble triggering receptor expresses on myeloid cells-1 (sTREM-1) peak within 24 h[68]. However, a meta-analysis of 11 studies showed only moderate diagnostic performance in differentiating sepsis from SIRS[67]. Accordingly, Bopp and colleagues could not detect significantly different plasma concentrations between healthy controls and patients with SIRS, sepsis, severe sepsis or septic shock in the early phase of disease[63]. Since some trials report elevated sTREM-1 plasma levels during non-infectious states[69,70], the role of sTREM-1 as diagnostic biomarker remains uncertain.

sCD14-ST
Bacterial infections lead to complex formation of lipopolysaccharides (LPS), LPS binding protein (LPB) and the surface receptor cluster of differentiation 14 (CD14), which is located on the cell-surface membrane
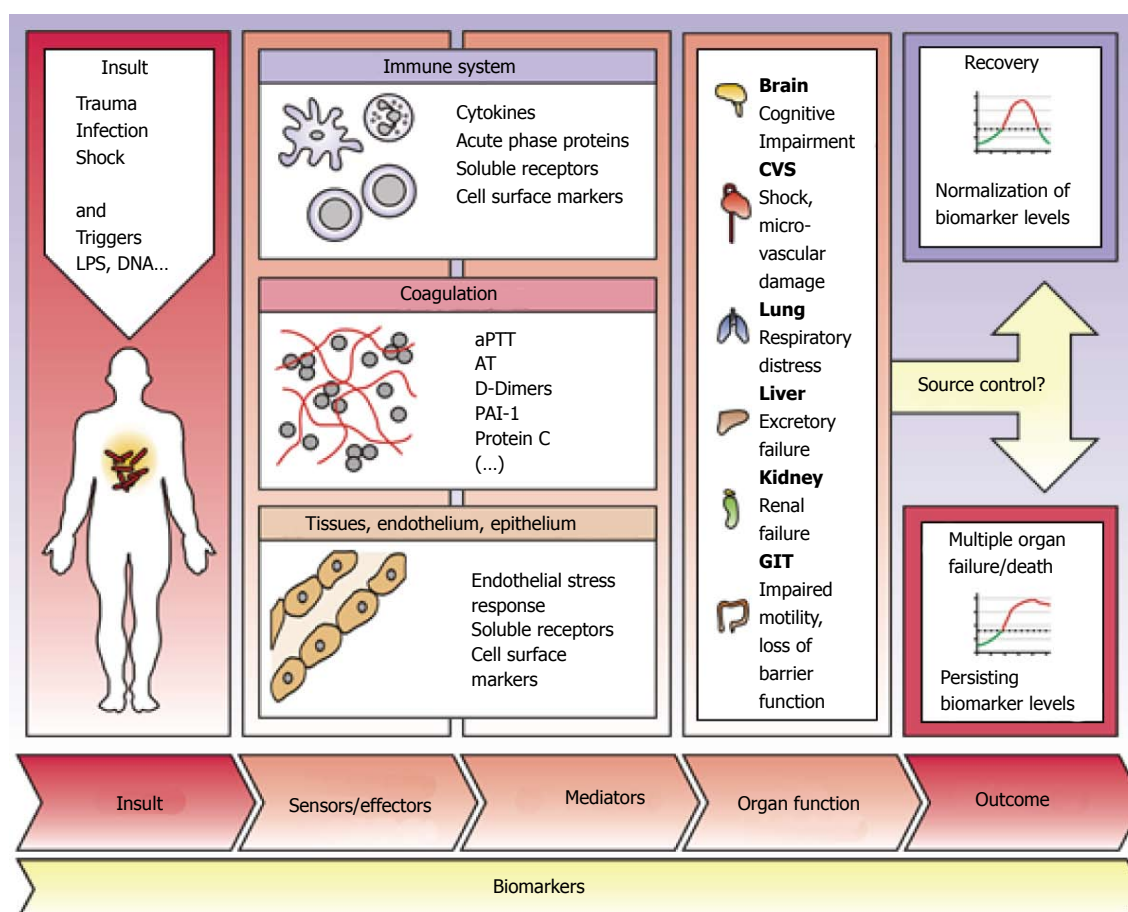
Figure 3 Use of biomarkers in sepsis: A wide range of biomarkers has been under intensive investigation to assist the clinician in diagnosis, outcome prediction and therapy guidance. LPS: Lipopolysaccharide; aPTT: Activated partial thromboplastin time; AT: Antithrombin; PAI-1: Plasminogen activator inhibitor-1; CVS: Cardio vascular system; GIT: Gastrointenstinal.

of phagocytes. During inflammation, a soluble form of this complex is further cleaved and termed soluble CD14 subtype (sCD14-ST = presepsin)[71,72]. Presepsin is a promising biomarker for diagnosing sepsis, severe sepsis and septic shock compared to other biomarkers such as PCT[73-76] and seems specific for infectious diseases[71]. High plasma levels in septic patients can be detected 6 h after early onset[72]. A recent study demonstrated that measurements of presepsin levels revealed diagnostic and prognostic value in patients with severe sepsis and septic shock within the first week of ICU treatment. Presepsin showed diagnostic value for sepsis, severe sepsis and septic shock at days 1, 3 and 8 after ICU admission in comparison to PCT, IL-6, CRP, white blood cells (WBC). It also revealed prognostic effort to prospect short- and long-term mortality[77]. These findings suggest that it may be used as a prognostic marker in early risk stratification.

Soluble urokinase-type plasminogen activator receptor
The urokinase-type plasminogen activator receptor (uPAR) is expressed on various cell types such as macrophages, endothelial and tumor cells. It participates in cellular immunity including migration, adhesion, angiogenesis, fibrinolysis and cell proliferation. After inflammatory stimulation, the receptor is cleaved from the cell surface by proteases and can be detected as soluble uPAR (suPAR) in urine, cerebrospinal fluid and blood[78].

Recent studies showed that high levels of suPAR are able to predict mortality in patients with diseases that are associated with inflammatory response. Additionally, the time course of suPAR seems to correlate with disease severity and the degree of organ dysfunction[79,80]. suPAR has gained growing interest because of its role as a predictor of disease severity in patients with bacteraemia[81]. In contrast to the prognostic value, the diagnostic performance of suPAR is limited[82].

Human leukocyte antigen-DR on circulating monocytes
Human leukocyte antigen-DR on circulating monocytes (mHLA-DR) is a major histocompatibility complex (MHC) class Ⅱ cell surface receptor and was originally defined as cell surface antigen. HLA-DR molecules are upregulated in response to inflammation[83]. Monocytes with low HLA-DR expression are unable to generate a proinflammatory response to microbial challenge or properly present antigens to T cells[84,85]. Decreased mHLA-DR levels could predict poor outcome and septic

complications after trauma, surgery, burn, pancreatitis and septic shock[86-89] but there is few knowledge about the underlying mechanisms[90].

A prospective randomised placebo-controlled trial used mHLA-DR to stratify the administration of granulocyte-macrophage colony-stimulating factor (GM-CSF) in a small group of septic patients. After administration, there was an increase of monocyte release of tumor necrosis factor α (TNF-α). This biomarker-guided therapy appeared reliable and successful in reestablishing monocyte immunocompetence and shortening hospital and ICU stay[91,92]. The expression of mHLA-DR represents a valid indicator for monocyte function and should be tested in more clinical trials as it could be a reliable future marker for immunosuppression.

BIOMARKERS OF TISSUE DYSFUNCTION AND ORGAN FAILURE

The multiple organ failure (MOF) is the fatal end feature in the pathophysiology of sepsis. During severe sepsis or septic shock, development of organ dysfunction dramatically increases morbidity and mortality[93]. During the acute phase of sepsis or septic shock, circulatory failure is discussed as the predominant cause of death[94,95]. However, underlying mechanisms leading to organ failure are not fully understood yet. Since the breakdown of endothelial barrier functions is estimated to play an important role in this context[96], biomarkers of endothelial integrity as well as markers of cardiac injury are reviewed in the following.

Heart type fatty acid binding protein

Cellular as well as metabolic alterations during organ failure result in rapidly elevated blood levels of the heart type fatty acid binding protein (hFABP)[97]. The low molecular weight protein is predominantly detectable in myocardial cytoplasm and lung tissue. It participates in the uptake and transport of long chain fatty acids and is suggested as a promising biomarker of cardiac impairment[98-100]. Recent studies indicate, that hFABP can independently predict 28-d mortality and organ failure in patients with sepsis, severe sepsis or septic shock. Additionally, a correlation between plasma concentration and sepsis-induced myocardial dysfunction has been described and elevation of hFABP is associated with an increasing mortality rate[101-103]. hFABP may thus be a promising marker to identify high risk patients in the emergency department.

Troponin

Troponin T (TNT), a regulatory protein, is a highly specific marker for myocardial infarction or heart muscle cell death. Several trials accounted significantly increased TNT levels in patients with septic disease[104,105]. Contradictory, myocardial wall abnormalities, diagnosed by echocardiography, proved to be more specific in septic patients than increased troponin levels[10].

Natriuretic peptides

Many vasoactive hormones rise in sepsis[10]. Natriuretic peptides like atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP) and C-type natriuretic peptide (CNP) influence diuresis, natriuresis and vaso-relaxants[106]. ANP and BNP are predictors for cardiac dysfunction and are able to predict congestive heart failure[10]. Several trials demonstrated a correlation between high BNP levels and worse morbidity and mortality in septic patients combined with low ejection fraction[107,108]. High CNP levels have been detected in sepsis. Koch *et al*[80] showed significantly higher N-terminal pro-CNP levels in septic than in non-septic patients.

Cytokeratin 18

Apoptosis represents a major mechanism of cell death in patients with sepsis and multi-organ-failure[109]. Cytokeratins are proteins of keratin-containing intermediate filaments in epithelial tissue. It is cleaved by activated caspases (caspase-cleaved cytokeratin 18, cCK-18) and can be detected with the help of the monoclonal antibody M30[110,111]. The measurement of cCK-18 concentration conduce the dimension of apoptosis in critically ill patients[112-114]. There is a correlation between persisting high concentrations of cCK-18 in the early treatment of sepsis and 28 d mortality[115]. Several trials showed higher concentration of cCK-18 in septic patients than in trauma patients or healthy individuals[116,117]. Measurements of cCK-18 could be of valuable use in detecting risk of multi-organ-failure.

Angiopoetin-1 und -2

Microvascular disorders contribute to the development of MOF. The integrity and function of the endothelial barrier depends on the stability of distinct receptors and their ligands, *i.e.,* the Angiopoietin/Tie2 system. Regarding their antagonistic roles, especially the balance between Angiopoietin-1 and -2 (Ang-1 and -2) is of particular importance[118]. In a multicenter cohort study, low plasma levels of Ang-1 at admission as well as serially measured Ang-1 and -2 were associated with higher 28-d mortality in critically ill patients with severe sepsis[119]. Additionally, in patients with suspected infection, elevated Ang-2 plasma levels were detected during the first hour after admission and correlated with the development of severe sepsis and a higher mortality[120]. A number of trials investigate the value of an Ang-1/-2 ratio in predicting outcome of septic patients. This ratio was significantly elevated in children with severe sepsis and septic shock compared to control patients with or without SIRS or sepsis during the first 3 d on pediatric ICU[121]. Similarly, using Canonical Correlation Analysis, Wang *et al*[122] identified a strong correlation between the combination of Ang-1, Ang-2,

bicarbonate and disease severity or outcome of sepsis in children. Thus, the components of the Angiopoietin/Tie2-System are promising targets of further studies to improve outcome prediction in septic patients.

Midregional-pro-adrenomedullin

Posttranslational processing of the precursor peptide preproadrenomedullin results in the generation of the vasoactive, antimicrobial and anti-inflammatory peptide adrenomedullin (ADM)[123]. Systemic inflammation and sepsis leads to an increased release of ADM into circulation[124,125], but a short half-life and other difficulties in the measurement impede the clinical use[126]. However, another fragment termed midregional-pro-adrenomedullin (MR-proADM) seems to be a promising sepsis-biomarker. When blood samples are stored at 20 ℃, MR-proADM is stable up to 24 h. Thus, it seems more suitable for daily routine in the primary care setting[127]. The release of MR-proADM is increased during viral and bacterial infections. So far, the potential utility of MR-proADM to predict outcome of sepsis is controversially discussed in a number of trials. At admission to the ICU, single MR-proADM assessment may be useful to predict in-hospital mortality, although the statistic performance is not outstanding[128]. In patients with CAP, Suberviola *et al*[129] showed a correlation between severity of illness, outcome and the plasma levels of MR-proADM. However, this correlation could not be confirmed by another recent single-center study[130]. Further investigations are necessary to clarify this gap.

Endocan

Endothelial function, *i.e.,* the expression of surface proteins and the release of cyto- and chemokines, is crucial for migration of immune cells from circulation into tissues[131]. The proteoglycan Endocan, originally named endothelial cell-specific molecule 1, is expressed on the surface of pulmonal and renal endothelial cells. Proinflammatory cytokines like TNF-α and IL-β induce the expression and release into the bloodstream *in vitro*[132]. Various studies report altered levels of the proteoglycan in neoplastic diseases, since tumor-derived factors also regulate Endocan expression[133-136]. In septic patients however, elevated plasma levels are correlated with sepsis severity. Furthermore, significantly higher Endocan values can be detected in non-survivors at admission to ICU[137]. In addition, a recent study by Mihajlovic *et al*[138] determined a correlation between initially elevated Endocan levels and the development of sepsis induced organ failure over time[139]. Accordingly, in patients with ARDS, Endocan levels seem useful to predict mortality and multiple-organ dysfunction. Thus, Endocan may be a promising biomarker to predict disease severity and outcome of critically ill patients.

NON-LABORATORY BIOMARKERS

Besides numerous markers derived from plasma or other body fluids, a variety of non-laboratory tools like the assessment of body temperature, heart rate variability, blood coagulation or sidestream darkfield videomicroscopy can assist the clinician in diagnosis, outcome prediction and monitoring of septic patients. However, putative findings - although promising - are challenged by a variable user-dependency.

Body temperature patterns

A non-invasive technique to identify critically ill patients is recognition of body temperature patterns. Fever as a classic symptom of septic patients has minor sensitivity and specificity in relation to diagnostic expressiveness[140,141]. Drewry *et al*[142] showed that abnormal body temperature curves were predictive of the diagnosis of sepsis in afebrile critically ill patients. Analysis of temperature patterns may relieve the decision to antimicrobial therapy rather than absolute temperature values.

Heart rate variability

Besides its role in the regulation of various body functions, *i.e.,* heart rate, the autonomic nervous system participates in the complex host response to a systemic inflammation[143]. This link has been under intensive investigation. Measurement of the "heart rate variability" (HRV) is a promising technique to evaluate the autonomic cardiac regulation in patients with suspected sepsis. Although underlying mechanisms are still unclear, changes in HRV are associated with the appearance of systemic infections[144] and correlate with disease severity[145,146]. The measurement of HRV may be a promising tool to improve an early diagnosis of sepsis. In adult bone marrow transplant patients, alterations in HRV could be detected prior to the clinical diagnosis of sepsis[147]. Furthermore, in a prospective, observational study, initial detection of HRV changes in septic patients via electrocardiogram in the emergency department showed to be valuable in predicting in-hospital mortality[148]. However, since changes in cardiac function also depend on various cofactors, further research is needed to elucidate the role of HRV assessment in diagnosis and outcome prediction in patients with suspected sepsis.

Sidestream darkfield videomicroscopy

Impairment of the microcirculatory blood flow (MBF) is common in patients with sepsis and designated as an important step in the development of organ failure[149]. Sidestream darkfield videomicroscopy can be used to identify alterations of microvascular parameters, *i.e.,* the microvascular flow index, the perfused (small) vessel density or the proportion of perfused (small) vessels. Clinical studies using this technique in critically ill patients with cardiogenic or septic shock, but also in patients before and after cardiac bypass surgery, support the idea, that changes in MBF occur independent from macrocirculatory hemodynamic parameters[149-151]. In patients with sepsis, abnormalities in the sublingual MBF can be detected early in the septic

progress and correlate with disease severity[152,153]. Several trials investigated beneficial effects of various interventions to optimize sublingual MBF. However, these results should be interpreted carefully due to methodological limitations[154]. Further studies about the use of sidestream darkfield videomicroscopy in the clinical setting are necessary, but should consider potential observer bias, as reported by Sallisalmi *et al*[155].

Clot-Lysis-Index

Thrombelastometry is a proper tool for monitoring and therapy guidance of haemostatic dysfunction[156]. The Clot-Lysis-Index (CLI) measures the mechanical properties of forming a clot in whole-blood samples in a time-dependent modality. The clot firmness is measured at 30, 45 or 60 min. Recent trails have demonstrated significantly higher CLI in septic patients than non-septic patients and control groups. These changes have been detected in patients even before sepsis was diagnosed[157,158]. The CLI could be useful as a future tool for early diagnosis of critically ill patients.

CONCLUSION

In hospitalized patients, sepsis still belongs to the most frequent causes of death[1,94,159]. Unspecific predictive signs complicate an early diagnosis, and - when sepsis is successfully diagnosed - treatment strategies are rare. So far, therapeutic approaches are limited to fluid administration, antibiotics and the attempt to sustain or restore organ function[160]. Originally, sepsis was designated as a distinct inflammatory response to an infectious stimulus[161]. Modern concepts define sepsis as a syndrome and focus on the problem, that also non-infectious stimuli result in defence mechanisms and clinical signs, which in the end do not allow a discrimination between infectious or non-infectious origin[36].

Although sepsis is a major problem for the critically ill, it is not exclusively restricted to these individuals. The exact mechanisms and variables determining outcome and mortality are not yet fully understood. As a consequence, since there is no typical risk profile, it remains hard to define patients at risk, which hinders rapid and effective treatment initiation. Nevertheless, recent studies report a reduction of acute mortality of patients with sepsis, severe sepsis or septic shock[162]. However, survivors of the acute phase are confronted with a chronic dysfunction of organ systems with high mortality, recently termed as "persistent critical illness" (PCI)[96]. Thus, early diagnosis and a rapid treatment initiation are even more of crucial importance for the prognosis. Since the role of scoring systems in initial evaluation, monitoring and outcome prediction of septic patients is controversially discussed, biomarkers should be considered as complementary tools[163]. During the last decades, a variety of promising sepsis related biomarkers has been under intensive investigation. Some, *i.e.*, acute phase proteins, are already widely-used in clinical practice. So far, the Surviving Sepsis Campaign guidelines only recommend PCT evaluation over time to deescalate antibiotic therapies[5]. Although many efforts to find more specific biomarkers seem promising, evaluation and comparison of the results is limited by unstandardized development- and evaluation strategies.

The pathophysiology of sepsis is characterized by an impairment of various systems on cellular, tissue-specific or functional level. In contrast to the original idea of an explicit immunological dysfunction, sepsis is now seen as a more complex syndrome that is characterized by an "impaired homeostasis". This concept combines immunological aspects with a neuroendocrine dysregulation and barrier failures[96]. The complex nature of sepsis complicates the search for new treatment targets. Furthermore, physicians are confronted with various individual comorbidities and other influencing factors[164].

Lately, Brenner *et al*[165] showed the involvement of alternative mediators of cellular stress in the pathophysiology of sepsis. Methylglyoxal (MG), which is one of these highly reactive carbonyl species, is produced endogenously from the spontaneous degradation of triosephosphates (glyceraldehyde-3-phosphate and dihydroxyacetone phosphate) during glycolysis. The study identified MG as a better marker for the identification of patients with sepsis in comparison to routine diagnostic markers and furthermore, MG was shown to be an early predictor for survival in patients with septic shock. Hopefully, these findings will help to improve early recognition of sepsis.

Recent research approaches try to enlighten the (epi)genetic regulation of sepsis. Hopefully, new findings in this field may once help to improve early risk stratification. In this context, it seems obvious that no single biomarker can yet feature a high diagnostic value together with an outstanding sensitivity and specificity to predict outcome and to guide (antiinfective) treatment. Thus, the combination of markers can be beneficial. However, despite some interesting trials, a promising combination is still missing.

When discussing the use of sepsis-related biomarkers, the question remains which marker should be preferred in clinical use. Due to the complexity of sepsis, adequate interpretation of laboratory results is the basis for a reasonable biomarker assessment. Here, we reviewed the state of knowledge about some key biomarkers. Although many substances and methods seem promising, most of them are not yet established in the intensive care unit. In the daily routine, the assessment of biomarkers can be a complementary tool in clinical decision making. However, it should be restricted to accurately defined problems and pursue the objective to achieve direct benefits for the critically ill patient. Together with new findings in the epigenetic field, the concept of directly linking diagnostic

results to an individual therapeutic regime - also termed theragnostics[166] - may be the next step to improve the outcome of patients with sepsis. Thus, beside the need to find valuable diagnostic substances, biomarker-guided therapy approaches should gain further attention.

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