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Rapid diagnosis of sepsis

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Abbreviations: CRP, C-reactive protein; ICU, intensive care unit; IL, interleukin; LBP, lipopolysaccharide binding protein; MD2, myeloid differentiation factor 2; PCR, polymerase chain reaction; PCT, procalcitonin; sTREM-1, soluble triggering receptor expressed on myeloid cells 1; suPAR, soluble urokinase plasminogen activator receptor; TNF, tumor necrosis factor

Fast and appropriate therapy is the cornerstone in the therapy of sepsis. However, the discrimination of sepsis from non-infectious causes of inflammation may be difficult. Biomarkers have been suggested to aid physicians in this decision. There is currently no biochemical technique available which alone allows a rapid and reliable discrimination between sepsis and non-infectious inflammation. Procalcitonin (PCT) is currently the most investigated biomarker for this purpose. C-reactive protein and interleukin 6 perform inferior to PCT in most studies and their value in diagnosing sepsis is not defined. All biomarkers including PCT are also released after various non-infectious inflammatory impacts. This shortcoming needs to be taken into account when biomarkers are used to aid the physician in the diagnosis of sepsis. Polymerase chain reaction (PCR) based pathogen detection may improve time to adequate therapy but cannot rule out the presence of infection when negative.

Sepsis is among the most common causes of death in hospitalized patients. Hospital mortality of patients with sepsis ranges from 28.3 to 41.1% in North America and Europe.[1] In the United States, Martin et al. reported a yearly increase of 8.7% in the occurrence of sepsis resulting in a sepsis incidence of 240.4 cases per 100 000 inhabitants in 2000.[2] Many patients with sepsis may remain unrecognized as occurrence of infection related organ dysfunction is poorly documented outside of the ICU.[3] Sepsis is especially common in the elderly and is likely to increase substantially as the population ages.[4]

Sepsis is defined as invasion of pathogens into the blood stream together with the host response to this invasion.[5] Thus, sepsis consists of the systemic inflammatory response syndrome (SIRS) caused by infection. Sepsis may be complicated by remote organ dysfunction (severe sepsis) or arterial hypotension (septic shock), which significantly worsens outcome of patients with infection.[6] Current guidelines recommend that anti-infectious therapy such as antimicrobial therapy and surgical source control should be initiated as soon as possible to optimize outcome.[7] Indeed, compliance to sepsis guidelines improves outcome and time to antimicrobial therapy is an independent predictor for death.[8-10] Conventional diagnosis relies on the recognition of SIRS caused by infection and the new onset of organ dysfunction.[6] However, this concept has been criticized after it has been published because SIRS lacks specificity to be clinically meaningful. The discrimination of SIRS with and without infection remains the main problem in the clinical setting.[11-13] Thus, confirming infection as cause of a severe inflammatory response is the main challenge in the diagnosis of sepsis. A group of experts revisited the original sepsis guidelines and developed the PIRO (**p**redisposition, **i**nfection, **r**esponse, **o**rgan dysfunction) concept for an improved characterization and staging of patients with sepsis.[14] Detection of microbial nucleic acids by polymerase chain reaction (PCR) and biomarkers were named as future tools to describe the conditions infection and response within the PIRO system. PCR-based pathogen detection as well as measurement of biomarkers should allow a more rapid diagnosis of sepsis as they are available within one working day. The aim of this review is to summarize the literature about the biomarkers (see **Table 1** for an overview) and PCR-based pathogen detection currently proposed for the diagnosis of sepsis. The publications for this review have been identified by systematic PubMed searches. Only studies comparing sepsis to non-infectious inflammation have been included for evaluation of the diagnostic value.

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Biomarkers

C-reactive protein

C-reactive (CRP) is an acute phase protein and is released from the liver after stimulation predominantly of IL-6 and other cytokines.[15] During infection, CRP has both pro-inflammatory and anti-inflammatory effects as it mediates elimination of pathogens but also inhibits interaction between endothelial cells and leukocytes. Secretion is started 4 to 6 h after stimulation and peaks at 36 h. CRP is frequently used for the diagnosis of infection. In primary care, addition of CRP to a set of diagnostic rules improved the recognition of pneumonia.[16] In surgical patients, CRP can aid to differentiate acute appendicitis from other noninfectious causes of lower abdominal pain[17] and may predict infectious complications after colorectal surgery.[18] However, data about the diagnostic accuracy of CRP to distinguish infection from noninfection are ambivalent. Prediction of infectious complication was insufficient after gastroesophageal cancer

Table 1. Diagnostic value and limitations of biomarkers to separate infectious from non-infectious causes of inflammation

Biomarker	Source	Sens.	Spec.	AUC	LR^+	LR^-	Limitations
C-reactive protein[21]	Metaanalysis (*n* = 1386)	0.75	0.67	–	2.43	0.42	Slow kinetic, independent of infection severity, increased in many inflammatory diseases
Procalcitonin[35]	Metaanalysis (*n* = 3244)	0.77	0.79	0.89	4.0	0.29	Increased in various non-infectious causes of SIRS (i.e., cardiac arrest, severe trauma)
Interleukin-6[57]	Cohort study (*n* = 327)	0.82	0.75	0.86	–	–	Limited data, conflicting results
sTREM-1[78]	Metaanalysis (*n* = 1795)	0.79	0.80	0.87	4.0	0.26	Present in inflammatory disease without infection
LBP[57]	Cohort study (*n* = 327)	0.57	0.85	0.73	–	–	Non-specific marker of inflammation
suPAR[98]	Cohort study (*n* = 273)	–	–	0.62	–	–	Limited data; low diagnostic value for sepsis

Data give sensitivity (sens.), specificity (spec.), area under the curve (AUC) from receiver operating characteristics, positive (LR^+) and negative (LR^-) likelihood ratios of a biomarker for differentiation of infectious vs. non-infectious causes of inflammation. LBP, lipopolysaccharide binding protein; suPAR, soluble urokinase plasminogen activator receptor; sTREM 1, soluble triggering receptor expressed on myeloid cells 1.

surgery and pancreatic surgery.[19,20] A metaanalysis showed only a sensitivity 0.75 and a specificity of 0.67 to differentiate bacterial from noninfectious causes of infection.[21]

In the ICU-setting, the performance of CRP to discriminate patients with and without sepsis is only moderate. In a recent study on critically ill patients with SIRS, elevated CRP-levels on ICU day 1 could differentiate between patients with and without sepsis. However, CRP was inferior to procalcitonin and sTREM-1 and could not predict prognosis or positivity of blood culture.[22] Similarly, CRP had some ability to correctly diagnose patients with severe sepsis in the emergency department but was significantly inferior to PCT and IL-6. No prospective randomized studies about the impact of CRP guided treatment algorithms on outcome are available. Reasons for the moderate discrimination of infectious from noninfectious patients may include (1) the slow kinetic of CRP levels after onset of infection, (2) CRP increases during minor infection and may not reflect severity of infection, and (3) CRP is elevated after noninfectious causes of inflammation such as trauma, surgery or rheumatic disorders.[23-25]

CRP levels decrease over the first 48 h when successful antimicrobial therapy is initiated.[26,27] The SACiUCI-study investigated patients with community acquired sepsis. The study demonstrated in 891 patients that CRP declined during the first 5 d after successful implementation of antimicrobial therapy.[28] However, CRP-levels are poor predictors of mortality.[29,30]

Procalcitonin

Procalcitonin (PCT) is the prohormone of calcitonin which is normally produced in the C-cells of the thyroid glands. In healthy humans, all PCT is cleaved to calcitonin and only < 0.1 ng/ml is measured in the blood. Regulation of PCT is changed during infection.[31] This results in a massive release of PCT into the bloodstream which depends on sepsis severity.[32] In 1993, Assicot and coworkers were the first to describe PCT as a potential biomarker for sepsis and infection.[33] PCT shows a more favorable kinetic profile than CRP and cytokines as its levels increase within 4 to 12 h after onset of infection.[34]

A recent metaanalysis including 3244 patients from 30 studies calculated a sensitivity of 0.77 and a specificity of 0.79 to discriminate sepsis from non-infectious causes of sepsis.[35] It was concluded that PCT is a helpful marker for early diagnosis in sepsis both in medical as well as in surgical patients. This confirms a former metaanalysis on patients after surgery or trauma where PCT identified sepsis better than CRP.[36] A third metaanalysis did not find a sufficient diagnostic accuracy for the diagnosis of sepsis.[37] However, the latter analysis was biased by the choice of selection criteria.[35,38] PCT levels between 0.1 and 0.5 ng/ml suggest presence of bacterial infection such as lower respiratory tract infections requiring antimicrobial therapy.[39] For critically ill patients, cut-offs for sepsis diagnosis differ considerably and a median cut-off of 1.1 (interquartile range 0.5–2.0) ng/ml across the studies was reported.[35] Patients with septic shock have the highest PCT levels averaging between 4 and 45 ng/ml.[38]

A metaanalysis reported that moderately increased PCT values around 1 ng/ml in critically ill patients are suspicious for invasive fungal rather than bacterial infections.[40] However, the number of studies included into the metaanalysis was low and the statistical heterogeneity considerable. The authors concluded that further studies are necessary to decide on empirical antifungal therapy based on PCT levels.[40]

Circulating PCT levels decrease with a half-time of about 24 h when the infection is sufficiently treated. Dropping PCT levels are therefore associated with improved survival rates while increasing or persistent elevated PCT levels are predictive for an unfavorable outcome.[41-43] The sufficient discrimination between infectious and noninfectious conditions by PCT and the drop of PCT-levels in appropriately treated patients raised the hypothesis that PCT levels can aid the physician in determining duration of antimicrobial therapy. Several prospective randomized studies have been undertaken comparing a PCT-guided antimicrobial therapy with a control group without a PCT algorithm. In patients presenting with lower respiratory tract infections in the primary care or emergency department setting, a PCT-guided therapy resulted in a significant reduction in duration of antimicrobial

therapy without jeopardizing the treatment result.[39,44-46] In the critical care setting, a structured review including 5 studies suggested that PCT guided antimicrobial therapy may be safe and cost efficient.[47] However, only one study systematically included patients with severe sepsis and septic shock.[48] It is currently unclear whether a PCT algorithm can be safely and efficiently applied in this patient population; this hypothesis is currently tested in a prospective randomized multicenter study (SISPCT study; Clinical Trials ID: NCT00832039). Applying a PCT algorithm as an alert system to escalate antibiotic use for all ICU patients at risk for infection did not improve outcome and significantly increased the length of stay.[49]

PCT has a number of limitations as it can be elevated also in noninfectious diseases. PCT levels can be elevated in absence of bacterial infections in conditions such as severe trauma, surgery,[50] or after cardiac arrest.[51] Some authors therefore described a better PCT-based sepsis diagnosis in medical than in surgical patients.[52] Elevated PCT levels have also been reported in patients with medullary thyroid carcinoma.[53] Other conditions with increased serum concentrations of PCT include heat shock, birth stress, different types of immunotherapies, and some autoimmune diseases.[38] Thus, PCT may guide the physician in the diagnosis of sepsis and management of antimicrobial therapy. However, as any other biomarker, PCT levels have to be assessed within the clinical context of the patient's history.

Interleukin-6

Interleukin (IL)-6 is directly induced by the primary cytokines of sepsis tumor necrosis factor (TNF) and IL-1. IL6 appears rapidly, reaches peak levels within 2 h after the infectious stimulus and persists much longer in the bloodstream than TNF and IL-1.[54] The very fast response of IL-6 to infection is a compelling feature of this biomarker. However, convincing data from large prospective studies are missing and data from available studies are showing ambivalent results. In severely traumatized patients, IL-6 levels are higher in patients with infectious complications than in patients without infection.[55] In one study, Il-6 with a cutoff >500 pg/ml had similar discriminating power as PCT to differentiate between sepsis and noninfectious SIRS in ICU patients.[56] These findings were confirmed in a cohort study comparing different biomarkers including IL-6.[57] Another study found only a moderate diagnostic accuracy of IL-6.[58] Among PCT and CRP, IL-6 had the lowest discriminative value to diagnose sepsis in patients with suspected sepsis in the emergency department.[59] In a similar study, PCT and IL-6 were both significant independent predictors of severe sepsis and were superior to CRP.[60] More studies have been published in pediatric patients with suspected sepsis which concluded that IL-6 levels might be helpful for the diagnosis of sepsis.[61-65] However, a conclusive study with large sample size is also missing for this patient population.

Serum levels of IL-6 are closely related to the severity and outcome of sepsis in patients.[66-68] IL-6 levels decrease in patients where the infection is controlled and is predictive for survival.[30] As true for other biomarkers of sepsis, several noninfectious stimuli can also induce IL-6 release such as major surgery and major trauma,[69,70] acute exacerbations of autoimmune disorders,[71] and transplant rejection.[72] Although IL-6 plays an important role in the pathophysiology of sepsis, the role of this cytokine as sepsis biomarker remains to be established.[73]

sTREM-1

The triggering receptor expressed on myeloid cells-1 (TREM-1) is a member of the immunoglobulin superfamily which is upregulated on phagocytes after exposure to bacteria and fungi.[74] During sepsis, activated phagocytes release a soluble form of TREM-1 (*s*TREM-1) which among other body fluids can be found in the plasma.[75] Non-survivors of sepsis have higher *s*TREM-1 levels than non-survivors.[76] Several studies have examined the usefulness of serum *s*TREM-1 levels as a biomarker for the diagnosis of sepsis suggesting *s*TREM-1 as a reliable biomarker for bacterial infections.[77] However, a recent metaanalysis included 11 studies with 1795 patients to calculate sensitivity and specificity for differentiating sepsis from noninfectious SIRS.[78] Sensitivity was calculated to 0.79 and specificity to 0.8. The authors concluded that *s*TREM-1 has only a moderate diagnostic accuracy for differentiating sepsis from SIRS although sensitivity and specificity were comparable to the values found for PCT. As many other biomarkers, *s*TREM-1 was found to be present in other inflammatory disease without infection. *s*TREM-1 levels were elevated in patients with mild acute pancreatitis and did not differ to *s*TREM-1 levels in patients with complicated acute pancreatitis.[79] The role of *s*TREM-1 in diagnosis of sepsis remains undefined and larger studies are necessary to clarify this issue.

Lipopolysaccharide-binding protein

Lipopolysaccharide (LPS)-binding protein (LBP) is an acute-phase reactant that forms a complex with LPS. The LPS-LBP complex binds to CD14 and to the Toll-like receptor 4/MD2-complex resulting in transcription of cytokines and other pro-inflammatory mediators.[80,81] In human serum, LBP is constitutively present at a concentration of 5 to 10 μg/ml. During sepsis, LBP levels increase to median peak levels of 30–40 μg/ml within 24 h.[57,82,83] These properties made LBP promising for the diagnosis of sepsis. Indeed, a good discrimination between SIRS and sepsis was reported.[84] However, further studies did not confirm these findings showing that LBP is a rather non-specific marker of the inflammatory response.[57,82] It was also found that LBP does not detect resolution of sepsis or is predictive of outcome.[29,57] Currently, LBP does not appear to have a role in the diagnosis of sepsis.

suPAR

The urokinase plasminogen activator receptor (uPAR) is a membrane based protein mainly expressed on various immune cells. Soluble uPAR (suPAR) is released by cleavage from the membrane and appears in various body fluids including the blood.[85] Increased levels of suPAR are found in cancer as well as in various infectious and inflammatory diseases.[86] Several observational studies have been performed to elucidate the usefulness of this molecule for the diagnosis of sepsis. A structured review summarizing these studies confirmed that suPAR is a general marker of inflammation and therefore has a low diagnostic value for sepsis. However, higher suPAR levels are associated with increased mortality.[86] Two large studies confirmed the prognostic value of suPAR. In a study on 454 critically patients receiving

ventilatory support showed that suPAR levels were slightly higher in patients that died or developed acute kidney failure.[87] In another large study with 1914 patients with sepsis, suPAR levels >12 ng/ml were associated with an unfavorable outcome, especially in patients with an APACHE II score >17.[88] suPAR does not, as yet, have a role as a biomarker for sepsis diagnosis.

Multiplex PCR-Based Pathogen Detection

Another option to proof the infectious origin of SIRS is to verify the underlying pathogen. Microbiological sampling including blood cultures and samples from the presumed site of infection belongs to the basic workup in the primary care of patients with sepsis. However, results of microbiological specimen may not be available up to 72 h after sampling and receipt of early empirical antimicrobial therapy can render blood cultures negative. Thus, results of microbiological samples do not play a role in the immediate treatment decisions of patients with suspected sepsis. Furthermore, blood culture are only positive in 30% of the patients with sepsis.[89] As appropriateness and timing of the empirical antimicrobial therapy is crucial for the survival of patients with sepsis,[10] a faster pathogen detection would be desirable. This gap may be filled by application of pathogen detection based on polymerase chain reaction (PCR) which detects specific sequences of bacterial and fungal rRNA.[90] Results of a PCR may theoretically be available within 6 to 8 h.

Several studies have addressed the performance of PCR in various settings. A recent metaanalysis to compare multiplex PCR with blood culture included 34 studies.[91] Most of the included studies addressed patients with suspected sepsis on the ICU. The pooled sensitivity for combined bacteremia and fungemia was 0.75 and specificity was 0.92. It was concluded that a positive PCR is good to rule in infection but the sensitivity is too low to rule out infection. In general, multiplex PCR has twice as many positive results than a single set of blood cultures which still leaves more than half of the septic patients with a negative PCR.[92,93] Furthermore, time to positivity was about 24 h in the clinical setting instead of the suggested 6–8 h.[93] Faster availability of the results would need a 24 h a day and seven days a week coverage of technicians and equipment. It was suggested that PCR might still be cost effective[94,95] but data for robust cost effectiveness calculations are missing.

PCR-based pathogen detection may be especially helpful to detect invasive fungal infections. A metaanalysis reported a good sensitivity (0.95) and specificity (0.92) for the PCR-based diagnosis of invasive fungal detection.[96] Indeed, time to prescription of antifungals was shorter when PCR was available compared with blood culture alone.[95] A prospective randomized trial demonstrated an improved survival rate when PCR-based fungal detection was added to clinical decision for the prescription of amphotericin B in patients after bone marrow transplantation.[97]

Multiplex PCR can only detect those pathogens covered by the target list of the assay. Likewise, only specific resistances such as methicillin resistance or vancomycin resistance are available, depending on the applied assay. Together with the still high rate of negative rate of the PCR in sepsis patients with sepsis, PCR-based pathogen detection can only be recommended as an add-on to the conventional culture-based methods but cannot replace blood cultures.[90]

Conclusion

There is currently no biomarker or biomolecular technique available which alone allows a rapid and reliable discrimination between sepsis and SIRS without infection. Furthermore, the currently available biomarkers seem to mainly identify invasive bacterial infections but viruses, fungi, and parasites may also evoke sepsis. Studies about biomarkers and other tools of sepsis diagnosis are also hampered by a poor gold standard as differentiation between colonization and infection is often challenging. Thus, diagnosis and initiation of therapy remains a clinical decision by assessing the patient's history, possible symptoms of infection, and development of acute organ dysfunction. However, biomarkers can aid and shorten this decision process when taking into account the shortcomings of biomarkers. PCT is currently the most investigated biomarker for this purpose and the only biomarker which has been integrated into treatment algorithms. CRP and IL-6 are inferior to PCT for the diagnosis of sepsis in most of the studies. Likewise, PCR-based pathogen detection may shorten the time to prescription of an appropriate antimicrobial therapy but cannot out-rule the presence of infection when negative. It may be too ambitious to assume that one single measurement of a biomarker can differentiate the complex response to infection from a non-infectious stimulus. Some promising studies showed a better performance when using a panel of biomarkers but data are too patchy to choose an optimal set of biomarkers. Future studies should also focus on incorporating biomarkers into clinical algorithms to investigate their usefulness in affecting the clinical course of the patient.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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