Biomarkers of Infection: Are They Useful in the ICU?

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Abstract

Biomarkers are increasingly used in patients with serious infections in the critical care setting to complement clinical judgment and interpretation of other diagnostic and prognostic tests. The main purposes of such blood markers are (1) to improve infection diagnosis (i.e., differentiation between bacterial vs. viral vs. fungal vs. noninfectious), (2) to help in the early risk stratification and thus provide prognostic information regarding the risk for mortality and other adverse outcomes, and (3) to optimize antibiotic tailoring to individual needs of patients ("antibiotic stewardship").

Especially in critically ill patients, in whom sepsis is a major cause of morbidity and mortality, rapid diagnosis is desirable to start timely and specific treatment.

Besides some biomarkers, such as procalcitonin, which is well established and has shown positive effects in regard to utilization of antimicrobials and clinical outcomes, there is a growing number of novel markers from different pathophysiological pathways, where the final proof of an added value to clinical judgment and ultimately clinical benefit to patients is still lacking.

Without a doubt, the addition of blood biomarkers to clinical medicine has had a strong impact on the way we care for patients today. Recent trials show that as an adjunct to other clinical and laboratory parameters these markers provide important information about risks for bacterial infection and resolution of infection. Moreover, biomarkers can help to optimize management of patients with serious illness in the intensive care unit, thereby offering more individualized treatment courses with overall improvements in clinical outcomes.

Keywords

- biomarker
- ICU
- infection
- procalcitonin
- antibiotic stewardship

The term "biomarker" or "biological marker" refers to a medical state observed from outside the patient—which can be measured accurately, objectively, and reproducibly.[1] Thereby, it is any laboratory tool with the potential to better detect and characterize a disease, to simplify complex clinical algorithms, and to improve clinical problem solving.[2] From a clinical perspective, a biomarker must complement the clinical judgment and the interpretation of other diagnostic and prognostic tests and add information that eventually improves patient care. An ideal biomarker should have fast kinetics and high sensitivity and specificity. Further, it should be identifiable fully automatically, should have a short turnaround time, and at best be available as a point-of-care test with low production costs.[3]

In the setting of critically ill patients with severe infections, there are three main areas where biomarkers can improve clinical management (►**Fig. 1**): (1) to improve infection diagnosis (i.e., differentiation between bacterial vs. viral vs. fungal infection vs. noninfectious) which may translate into better empiric treatment of the patient, (2) to help in the early risk stratification and thus provide prognostic information that may improve site-of-care decisions (e.g., early discharge or escalation of care), and (3) to optimize therapeutic decisions (e.g., in regard to antibiotic

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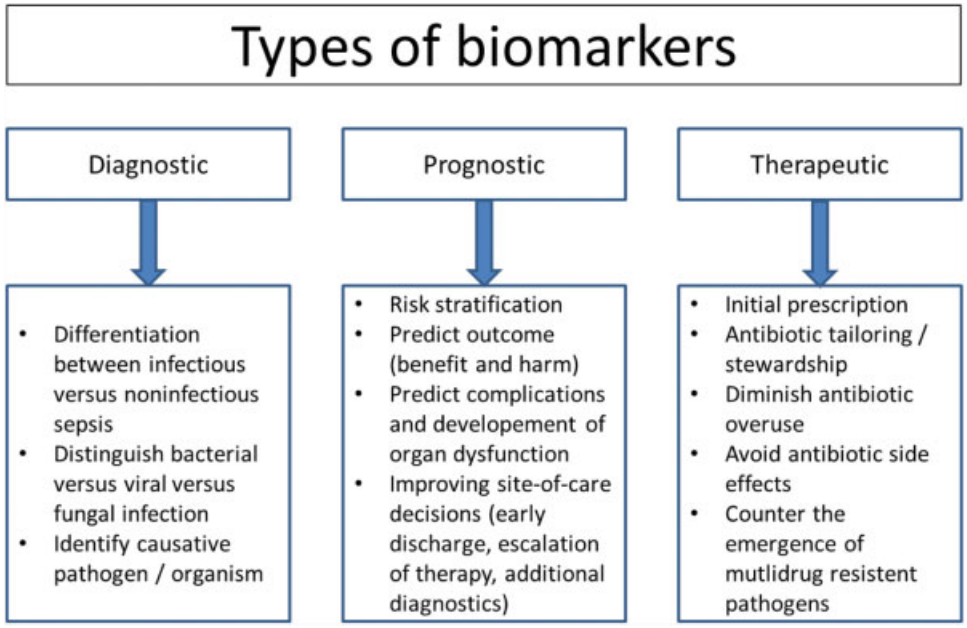

Fig. 1 Types of biomarkers and examples of their potential use.

tailoring to individual needs of patients, a term called "antibiotic stewardship").[4,5]

The aim of this narrative review is to summarize current concepts of biomarker use in the setting of serious infections in patients treated in the intensive care unit (ICU) regarding the diagnostic, prognostic, and therapeutic use.

Diagnostic Biomarkers for Infections in the ICU

Several reports indicate that sepsis is a leading cause of mortality and critical illness worldwide,[6] particularly if the initial diagnosis is missed. Early and accurate diagnosis of sepsis and differentiation from noninfectious causes are crucial for rapidly starting fluid resuscitation and antibiotic treatment.

Sepsis has been characterized as a dysregulated reaction of the host to an infecting pathogen. Affected patients show heterogeneous symptoms, response to treatment, and outcomes.[3,6,7] Currently, no gold standard exists for detecting sepsis due to blood stream infection, which would be a key factor for targeted therapy and may improve survival. There are important limitations to the use of conventional diagnostic modalities such as blood cultures and inflammatory blood markers (i.e., C-reactive protein, white blood cells) in patients with clinical suspicion of infection and sepsis in the ICU setting.[8]

Physicians are thus often ambiguous regarding the necessity and timing of antimicrobial treatment, which can delay the appropriate treatment with negative clinical consequences.

Blood cultures, currently the most reliable diagnostic method for identification of pathogens, give important information about type of microorganism and susceptibility toward antibiotic treatment. However, only a small proportion of cultures turn positive and in 40 to 90% of patients with a suspected systematic infection, the culture does not grow any pathogens.[9,10]

For example, a large retrospective study from China found that of 2,829 blood cultures taken upon hospital admission, only 440 (15.5%) came back positive.[11] Further limitations of blood cultures include a long time to result, which in turn limits initial treatment decision making and contamination resulting in suboptimal specificity of results. These limitations call for additional tests to improve the diagnostic work-up of patients.

There are high hopes in novel technologies that may help to improve identification of pathogens including matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) and nucleic acid aptamers.[12] These technologies are all pathogen directed aiming to identify the causative organism and potentially give some information about expected resistance. Typically, such novel approaches need lower amounts of pathogen DNA, which increases their sensitivity, but may limit specificity because false-positive results—particularly pathogens that are present in the blood stream but are not causing the disease—may occur more frequently.

Another approach to improve diagnostic work-up of patients is to look at host-response markers, which indirectly provide information about severity of infection and possibly type of pathogen. Compared with healthy individuals, peripheral blood cells in septic patients exhibit modified RNA transcripts in response to infection.[3] Therefore, an emerging technology is gene expression profiling of peripheral blood cells, which simultaneously measures the expression of a large number of genes to generate a snapshot of host immune cell function.[13,14] Pattern-recognition receptors on immune cells are activated by different pathogen-derived ligands, which results in the initiation of distinct sets of transcriptional programs. The resultant pattern of gene expression represents a transcriptional signature of a specific pathogen. Several studies have looked at gene expression profiling of peripheral blood cells as a means to improve diagnosis in patients with infection in the ICU. Early results are promising,[15] but larger

and more definite trials are needed to understand whether this technology will add to the clinical assessment of patients.

Not only gene expression profiling, but also the so-called proteomics and metabolomics profiling are subjects of current research.[16] The objective of this technology is to identify protein and metabolic biomarkers being capable of differentiation infectious from noninfectious sepsis.[3] Despite promising first results the use of these technologies is currently still limited by technical challenges, high costs, and lack of reproducibility.

The most widely studied host-directed marker is procalcitonin (PCT), a hormokine that is released in different tissues in the body in response to sepsis caused by bacterial infections via stimulation through cytokines (e.g., interleukin [IL]-1β, tumor necrosis factor [TNF]-α, and IL-6).[17] Interestingly, interferon-gamma (INF-γ), a cytokine released in response to viral infections, reduces the upregulation of PCT. This results in a higher specificity of PCT for distinguishing bacterial from viral infection.

By means of PCT measurement, a specific pathogen cannot be detected, but the level of PCT may help estimate the probability of severe bacterial infections and thus the clinical relevance of a positive blood culture result.[18]

Yet, observational studies investigating the diagnostic accuracy of PCT for sepsis diagnosis yielded diverging results, which is mainly explained by differences in study populations and reference standard for infection used in the studies.

In 2007, a meta-analysis including 18 studies with 2,097 critically ill patients assessing PCT showed a median sensitivity and specificity of 71% as well as an area under the summary receiver operating characteristic curve (ROC) of 0.78 (95% confidence interval [CI]: 0.73–0.83) and led to the conclusion that PCT could not distinguish infectious from noninfectious systemic inflammatory response syndrome (SIRS) with high certainty.[19] A more recent meta-analysis including 30 high-quality studies and a total of 3,244 patients found that PCT in fact can differentiate effectively between sepsis and SIRS of noninfectious origin with an ROC curve of 0.85 (95% CI: 0.81–0.88).[20] The later study used blood cultures as the reference standard.

Recently, an international expert consensus was published, recommending PCT cutoff levels in critically ill patients to estimate the probability of bacterial infection and therefore improving initial clinical assessment (►**Fig. 2**).[21] Instead of one cutoff, these guidelines recommended cutoff ranges with higher and lower positive and negative predictive values for sepsis.

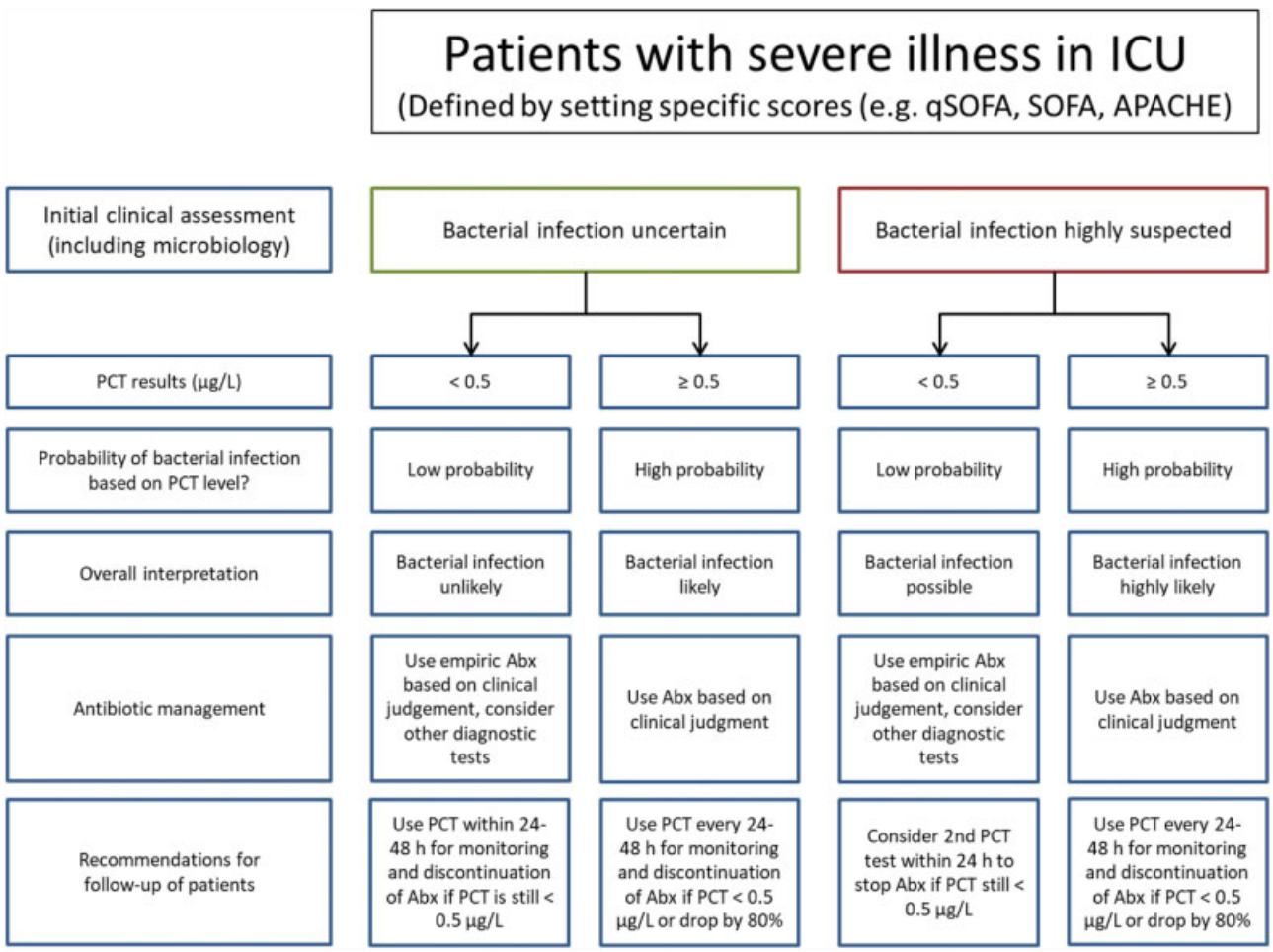

Fig. 2 PCT use in patients with severe illness in the ICU. Note: caution in patients with immunosuppression (including HIV), cystic fibrosis, pancreatitis, trauma, pregnancy, high volume transfusion, malaria; PCT-guided stewardship should not be applied to patients with chronic infections (e.g., abscess, osteomyelitis, endocarditis). ICU, intensive care unit; PCT, procalcitonin. (Adapted from Schuetz et al.[21])

In this context it is important to emphasize that any diagnosis should not only be based on a specific biomarker but rather in conjunction with the pretest probability based on the clinical assessment and other laboratory results.

Prognostic Biomarkers Assessing Risk in Infected Patients in the ICU

The second main purpose of biological markers in the setting of severe infection in the ICU is to assess a patient's individual risk profile and therefore to predict outcome. Accurate disease severity assessment and clinical course prediction assist patients, families as well as caregivers in setting realistic expectations regarding the illness. Risk stratification and prognostication are also important prerequisites for appropriately applying health care resources and therapeutic options. It may help to identify patients who would likely benefit the most from targeted and extensive therapy without causing unnecessary harm.

The recently updated criteria for the definition of sepsis based on the Sequential Organ Failure Assessment (SOFA) score ≥ 2 in the presence of infection showed a high prognostic accuracy for in-hospital mortality in the ICU.[6,22] Still, SOFA is a complex tool composed of 11 different clinical and laboratory markers which limit its use especially outside the ICU.

Using clinical risk scores, such as APACHE or SAPS II, for the purpose of prognostication, is partly also limited by practicality issues and these scores are only validated when admission values are used.[23,24]

Thus, there is interest in predictive use of newly available biomarkers that are objectively and rapidly measurable, respond to clinical recovery, and add relevant, reliable, and real-time information.[25] Interestingly, a recent retrospective analysis using data from 63,858 patients in three observational cohorts suggests that patients with sepsis can be further phenotyped based on biomarkers of host response, which has consequences for future treatment approaches.[26] The authors proposed four novel sepsis phenotypes (α, β, γ, and δ) with different demographics, laboratory values, and patterns of organ dysfunction, which correlated with biomarkers and mortality. In a simulation, patient outcomes related to the treatments were sensitive to changes in the distribution of these phenotypes.

Several biomarkers have been proposed to improve prognostic work-up of sepsis patients. These include markers based on the complex pathophysiology of sepsis, characterized by activating pro- and anti-inflammatory responses combined with reactions and modification in nonimmunological pathways (e.g., cardiovascular, neuronal, renal, coagulation, and metabolism). Hence, numerous biomarkers have been identified and examined in regard to their prognostic value (►**Fig. 3**).[6,27]

►**Table 1** shows an overview of some prognostic markers, which may help in the risk assessment of septic patients.

One of the commonly used biomarkers is serum lactate, a surrogate of tissue hypoperfusion and metabolic stress in septic patients. Higher lactate levels are not only associated with increased mortality,[28] but mortality rates can also significantly be reduced by lactate-guided resuscitation.[29,30] Lactate kinetics are thus of prognostic significance[31] and repeated measurements within 2 to 4 hours are recommended by the Surviving Sepsis Campaign if initial lactate is elevated (> 2 mmol/L).

Kinetics of PCT over time has also been shown to improve monitoring of the critically ill patient with sepsis and respiratory infection.[32–38] Indeed, PCT kinetics have shown prognostic implications, as decreasing values correlate with good outcomes, while increasing values correlate with adverse outcomes including mortality.[39–41] A Finnish investigation found PCT concentrations to be higher in more severe cases of advanced sepsis, but a substantial decrease in concentration was a more important survival predictor than were absolute values.[40]

A derivation-validation study using retrospective data from two independent U.S. critical care institutions revealed a high prognostic value when considering the 72-hour PCT kinetics for sepsis mortality.[42]

In the derivation and validation cohorts, a PCT decrease over 72 hours of >80% had a negative predictive value of 90 and 91% to exclude ICU mortality, probably helping to identify individuals at reduced risk, who thus are good candidates for therapy de-escalation or early ICU discharge. Conversely, a nondecrease or increase of PCT within this timeframe had a positive predictive value of around 35 to 50%, potentially flagging patients who are at high mortality risk and thus are likely to require treatment escalation. These results were also confirmed in an U.S. Food and Drug Administration (FDA) study among different United States based hospitals (MOSES study).[43]

However, it has been challenging to understand whether prognostic information also results in improved clinical outcomes of patients. Herein, a large interventional trial did not show a mortality benefit when PCT was used to escalate the diagnostic and therapeutic management.[39]

Yet, patients in the intervention arm had more complications (e.g., renal impairment, ventilation days) due to prolonged antibiotic therapy and more diagnostic studies.

Compared with other medical fields such as oncology or cardiovascular medicine, the clinical use of prognostic biomarkers in critically ill patients with sepsis is still ill defined. Besides markers of infection and inflammation, there is a wide range of markers for organ dysfunction that could be used for monitoring specific pathways and inform about the physiopathology, thereby improving risk stratification and prognostication. Regarding the complex pathophysiology of sepsis, it is questionable if one optimal biomarker for prognosis will ever be found. Combination of different markers from distinct pathways with clinical parameters may have more potential to accurately predict outcomes.[44]

Further research is warranted to identify sets of biomarkers reflecting changes in patient's physiology with sepsis that can be obtained reliably, simply, and cost-efficiently, leading to an even more personalized medicine.

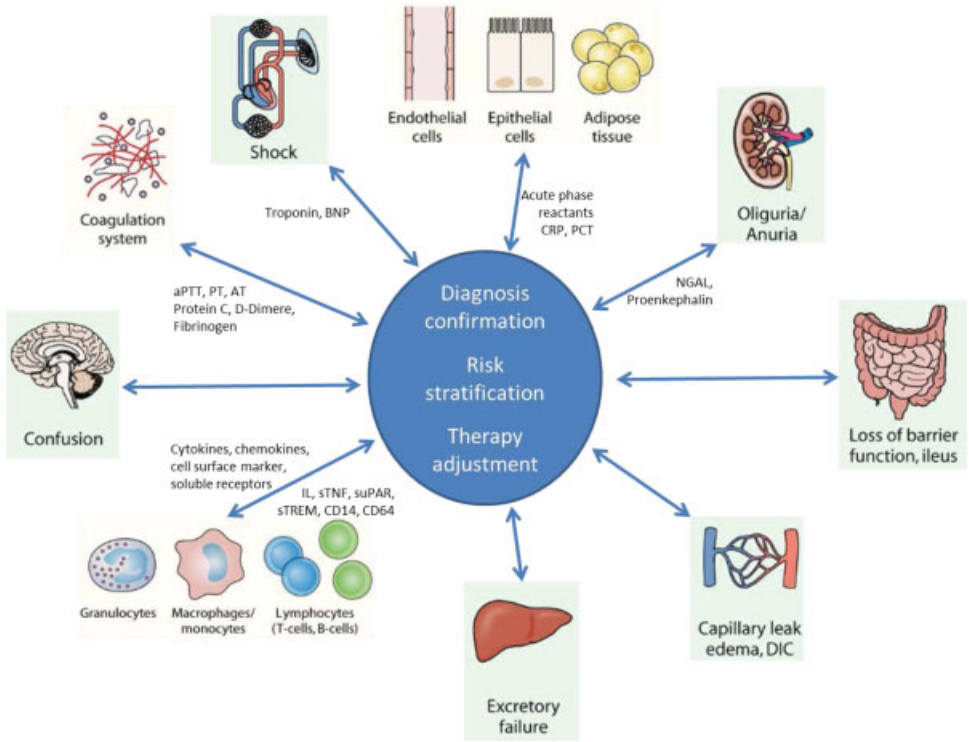

Fig. 3 Immunological and nonimmunological response through biomarkers and mediators to a bacterial pathogen and the resulting multiorgan dysfunction. Biomarkers and their impact on organ function can help confirm a diagnosis, to assess the patients risk for mortality and morbidity as well as to tailor individual treatment. Once the source of infection is controlled due to adequate treatment, organ function can recover and biomarker abnormalities normalize. Otherwise biomarker abnormalities persist and leading to progredient organ failure and maybe death. aPTT, activated partial thromboplastin time; AT, antithrombin; BNP, B-type natriuretic peptide; CD14 and CD64, integral membrane glycoproteins; CRP, C-reactive protein; DIC, disseminated intravascular coagulation; IL, interleukin; NGAL, neutrophil gelatinase-associated lipocalin; PCT, procalcitonin; PT, prothrombin time; sTNF, soluble tumor necrosis factor; sTREM, soluble triggered receptor expressed on myeloid cells; suPAR, soluble urokinase type plasminogen activator receptor. (Adapted from Reinhart K. et al. New approaches to sepsis: molecular diagnostics and biomarkers. Clin Microbiol Rev 2012;25(4):609–634.)

Therapeutic Biomarkers for Antibiotic Stewardship in the ICU

Appropriate empirical antibiotic therapy is a cornerstone of therapy and highly effective for reducing mortality and morbidity in community-acquired pneumonia and sepsis.[45,46]

Still, antibiotic overuse, mainly due to long treatment durations and use of antibiotics in viral infections, puts individual patients to the risk of adverse drug reactions with no therapeutic benefit. Antibiotic overuse is also strongly associated with the emergence of bacterial resistance.[47,48]

Clinical signs and symptoms have low sensitivity and specificity to differentiate self-limited and mild viral infections from more severe bacterial disease. Due to this uncertainty, physicians are often reluctant to abstain from or limit the duration of antibiotic therapy based only on clinical grounds. Using blood biomarkers that can accurately indicate the risk for bacterial infection and can be measured in a short time after admission of the patient can help fill this gap. Such a strategy not only leads to a lower antibiotic overuse, but also potentially lowers antibiotics-associated side effects and mortality, and treatment failure.[49,50]

In this context, PCT has gained much attention lately. Its advantages as well as its limitations are well known and its use to guide antibiotic treatment recently has been approved by FDA,[21] based on a series of randomized trials showing efficacy and safety.

The efficacy and safety of PCT-guided decision-marking regarding antibiotics has been demonstrated in several randomized controlled trials including infections of varying severity in different clinical settings from primary care to the ICU.[50–52] Particularly in the ICU, the issue of safety is of outmost importance because patients' baseline risk is high.

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One of the first randomized "proof of concept" trials studying the effect and safety of PCT-guided therapy in patients with sepsis requiring intensive care showed a reduced exposure to antibiotics without causing any harm or negative outcome.[36] Subsequent several large, multicenter trials, including the PRORATA trial[53] and the Stop Antibiotics on Procalcitonin Guidance Study (SAPS),[49] validated the use of PCT-guided therapy and found PCT to be helpful in reducing antibiotic exposure by reducing the duration of treatment. Importantly, in any clinical scenario where the probability for bacterial infection is a priori high and time to appropriate treatment is crucial, such as sepsis patients in the ICU, initial antibiotics should be used and PCT is mainly used for treatment cessation based on its kinetics.

Table 1 Overview of some biomarkers and their prognostic value regarding risk assessment of critically ill septic patients

Organ	Biomarker	Clinical value	Physiology	Recent studies	Comment/limitations
Metabolic	Procalcitonin (PCT)	Diagnostic Prognostic	• PCT expression is upregulated in response to bacterial infection • PCT expression is reduced in response to viral infection	21,39,40,42,43	• Adjunct to clinical judgment to assess risk for bacterial infection • Kinetics over time have prognostic implications • PCT-guided antibiotic stewardship reduces antibiotic exposure and shows evidence for improved survival • Limited data in immunosuppressed patients • Increased PCT also in noninfectious conditions (trauma, surgery, C-cell carcinoma)
	Adrenomedullin (ADM), pro-adrenomedullin (Pro-ADM)	Prognostic	• ADM/Pro-ADM is upregulated in different tissues in several conditions (SIRS, shock, cellular hypoxia, oxidative stress, myocardial injury; remarkably high levels in sepsis)	60–63	• Strict association between high levels of biological ADM/Pro-ADM and disease severity, organ failure and mortality • Pro-ADM kinetics may be helpful for risk assessment of treatment failure
	C-reactive protein (CRP)	Diagnostic Prognostic	• Stimulated by cytokines • Liver cells synthesize CRP after onset of inflammation or damage (within 6–8 h, peak 36–50 h)	64–66	• Established marker of infection and inflammation • Low specificity
	Lactate	Prognostic	• Increased levels in hypoxia, stress, and critical illness as a product of anaerobic glycolysis	29,31,67	• Prognostic predictor of mortality
Cardial	Highly sensitive troponin	Prognostic	• Released by damaged myocytes • Sensitive and specific marker of myocardial injury	68,69	• Elevated troponin level in septic patients is a predictor of mortality
	B-type natriuretic peptide (BNP)	Prognostic	• Released from cardiomyocytessecondary to volume or pressure overload, ischemia, necrosis, remodeling	70–72	• Controversial data • Limited prognostic value for mortality
Renal	Neutrophil gelatinase-associated lipocalin (NGAL)	Diagnostic Prognostic	• Released by neutrophils in response to bacterial components • Secreted by injured renal tubules	73–76	• Data inconsistent • Controversial specific value because of its extra-renal production (confounder)
	Proenkephalin (PENK)	Diagnostic Prognostic	• Negatively correlated with glomerular filtration rate • In case of acute kidney dysfunction proenkephalin increases more quickly than creatinine	77–80	• Association with acute kidney injury in septic patients • Predictive of short-term mortality

Table 1 (*Continued*)

Organ	Biomarker	Clinical value	Physiology	Recent studies	Comment/limitations
Coagulation	Disseminated intravascular coagulation (DIC)	Prognostic	• DIC is an hemorrhagic-thrombotic state triggered by proinflammatory cytokines in response to several diseases (sepsis, trauma, cancer)	81–83	• DIC is associated with poor prognosis • Coagulation dysregulation is best interpreted through repeated measurements
Cell marker	Presepsin (soluble CD14)	Diagnostic Prognostic	• Expressed on monocytes and macrophages in response to lipopolysaccharide stimulation (within 2–3 h)	84–87	• Conflicting data, its clinical utility needs to be further evaluated
	CD 64	Diagnostic Prognostic	• During systemic inflammation circulating monocytes and polymorphic cells increase expression of CD64 (within 2–6 h) • Levels decrease within 48 h after removal of the initial stimulus	7,88–90	• Reviews consistently demonstrated good diagnostic performance, but included studies were heterogeneous and defined sepsis differently → further evaluation is warranted • Lower CD64 expression levels are an indicator of better prognosis
Receptor	Urokinase type plasminogen activator receptor (soluble) (suPAR)	Prognostic	• Upregulated and released from monocytes and T-lymphocytes in response to bacterial components and inflammatory cytokines	7,91–93	• Prognostic value for mortality in critically ill patients, including septic patients
	Triggering receptor expressed on myeloid cells TREM-1 (soluble)	Prognostic	• Upregulated in the presence of bacteria or fungi; but also in inflammatory bowel disease, cancer, and atherosclerosis	7,94,95	• Poor diagnostic marker • Predictive biomarker for the 28-day mortality in septic patients

While much work has been done for patients with respiratory infections,[38,50] a recent meta-analysis, including 11 trials and 4,482 patients, investigating the effects of PCT use in patients with sepsis treated in the ICU demonstrated a significant reduction in mean treatment duration (from 10.4 to 9.3 days, $p = 0.001$). Interestingly, the mortality rate in PCT-guided patients was also significantly lower compared with the control group (21.1 vs. 23.7%, $p = 0.03$).[54] Similar effects were also noted in subgroup analyses stratified by Sepsis-3 definition, severity of sepsis, presence of renal shock, renal failure and type of infection. These positive effects may be explained by a lower risk for antibiotic side effects with PCT-guided care. Also, the prognostic information derived from PCT kinetics may influence therapeutic decisions and prompt additional diagnostic assessment.[55]

Consistent with the results mentioned above, another meta-analysis studying PCT use in septic patients with positive blood cultures found a significantly shorter duration of antibiotic therapy for PCT-guided patients (−2.86 days). Additionally, a trend toward a lower mortality in the intervention group was observed (16.6 vs. 20.0%, $p = 0.263$).[56]

In contrast to the available evidence regarding PCT-guided antibiotic de-escalation, therapy escalation based on PCT concentrations cannot be recommended. A large interventional trial testing the hypothesis that therapy escalation in septic patients in whom PCT did not decrease appropriately would improve outcomes did not reveal a benefit for PCT-guided patients.[39]

Despite the current body of evidence for PCT-guided antibiotic discontinuation, a commonly accepted clinical algorithm in critically ill patients was long lacking, which in turn limited a more widespread use of PCT.[21] Still, PCT protocols used in the different trials were all somewhat similar and based on a similar intuitive concept: in patients with suspicion of sepsis, initial antibiotics were recommended based on clinical grounds, and PCT kinetics over time were used for recommendations regarding early discontinuation of antibiotic therapy.[51] Thereby, PCT cutoffs of <0.5 ng/mL or a decrease of 80 to 90% from the peak level were used to indicate resolution of illness and stopping of treatment in case the clinical course was also favorable. An international expert group recently also published a consensus algorithm for PCT use in patients with suspected bacterial infection and came to similar conclusions (►**Fig. 2**).[21] Importantly, this algorithm has been tested in different interventional trials, which all documented significantly reduced antibiotic exposure and no excess mortality or

increase in adverse event rates. However, adherence rates to PCT protocols were variable, particularly for ICU trials.[36,37]

Practical Considerations When Implementing Procalcitonin Testing

Decisions regarding antibiotic use in an individual patient are complex and should be based on several considerations including the pretest probability for bacterial infection. The pretest probability can be assessed by means of clinical examinations and the results from microbiological tests.

►**Fig. 2** provides practical guides for a rational use of PCT in high-risk settings in conjunction with the clinical assessment including interpretation of PCT and recommendations for antibiotic use.[21,57]

To optimize antibiotic stewardship, implementation of supplemental educational programs would be useful. In the interventional noninferiority proACT trial, no reduction of antibiotic prescription or treatment duration among patients with suspected lower respiratory tract infection in the emergency department could be observed.[58] Indeed, the adherence rate to the PCT protocol was low, illustrating lack of experience with PCT use and its interpretation in the clinical context as well as uncertainty regarding efficacy and safety of this approach. Therefore, frequent education in the context of an antibiotic stewardship may help physicians to gain more confidence in dealing with PCT measurements and improve patient care.[21] This hypothesis is supported by the results of the retrospective cohort study by Broyles and colleagues. By means of education-based antibiotic stewardship, including the use of PCT measurements, lower rates of antibiotic prescriptions as well as reduced resistance rates were found. Additionally, this was associated with an improved outcome (e.g., lower readmission rates, shorter length of stay, less *Clostridium difficile* infections).[59]

Limitations of Procalcitonin

Most PCT studies were done in patients with respiratory infections or sepsis and there are only limited data in immunosuppressed patients including those with human immunodeficiency virus (HIV) and patients with cystic fibrosis, pancreatitis, trauma, pregnancy, and high volume transfusion. Moreover, some noninfectious conditions such as C-cell carcinoma or trauma cause systemic inflammation and also affect PCT levels. Furthermore, it is not recommended to apply PCT-guided stewardship in patients with chronic infections such as osteomyelitis or endocarditis as observational studies have not shown positive results and interventional research is largely lacking.[31]

Conclusions and Outlook

Biomarkers from distinct pathophysiological pathways are increasingly being used in patients with serious infections in the critical care setting to improve patient care, particularly for improved infection diagnosis, for early risk stratification, and to optimize antibiotic tailoring to individual needs of patients. In the critical care setting, rapid diagnosis is important to start the right medication for the right patient in a timely fashion, thereby reducing mortality and morbidity. Several biomarkers hold great promise to further improve patient management by providing diagnostic, prognostic, and therapeutic information. While some markers, such as PCT, are well established and showed positive effects in regard to utilization of antimicrobials and clinical outcomes in interventional trials, many other markers have not been well studied except for observational studies. Thus, the final proof of an added value to clinical judgment and ultimately clinical benefit to patients is still lacking. Biomarkers had a strong impact on clinical medicine and have changed the way we care for patients today. Still, further research is needed to explore the optimal use of biomarkers in combination with pathogen-directed tests.

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