

Procalcitonin and Other Biomarkers for the Assessment of Disease Severity and Guidance of Treatment in Bacterial Infections

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The ambiguities of clinical signs and the limitations of current microbial techniques for the diagnosis of bacterial infections – and to grade their severity – are well known. The use of biomarkers provides a novel, complementary approach to diagnose infection, and to estimate treatment response and the outcome of patients. In most infections, a true “gold standard” for diagnosis does not exist, thus the measurement of biomarkers, specifically the “hormokine” procalcitonin (PCT) in a clearly defined setting, has been shown to significantly improve the diagnostic certainty and also to reduce the utilization of antimicrobial therapy. For prognostic assessment, other promising biomarkers (e.g. adrenomedullin) have demonstrated high predictive potential to estimate the risk for mortality in the short and long term, and other adverse outcomes. A critical appraisal of the advantages and limitations of biomarkers in different clinical situations is mandatory. Herein, the present authors discuss the current data on the use of PCT and other biomarkers for the diagnosis, treatment guidance, and prognostic assessment of bacterial infections, and their potential role in the overall assessment of patients with sepsis. *Adv Sepsis* 2008;6(3):82–9.

The “gold standard” dilemma in bacterial infections

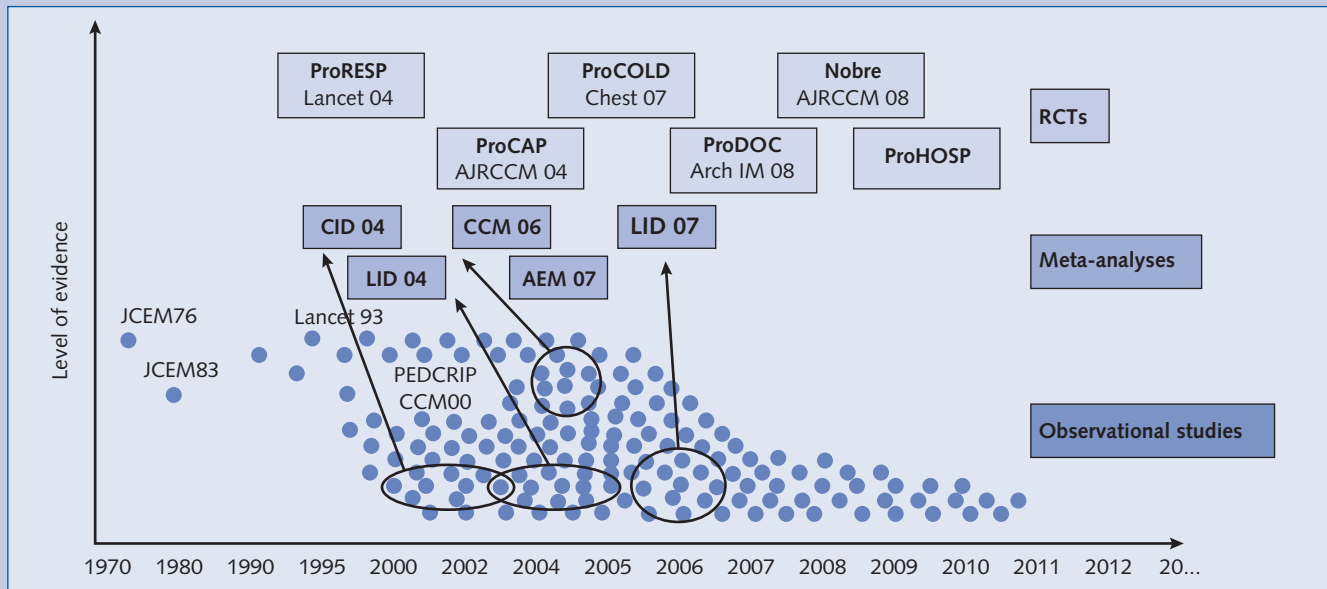
The presence of a diagnostic “gold standard” or reference standard represents the best available method for establishing the presence or absence of a disease [1,2]. Optimally, a morphological verification such as histopathology or, in the case of sepsis, growth of typical pathogens in blood cultures can be obtained to establish the “correct” diagnosis. In this context, repeated collection of blood cultures to identify causative microorganisms and to study resistance patterns is considered to be a cornerstone in the diagnostic work-up of patients with suspicion of bloodstream infection (BSI). Regrettably, the use of blood cultures as the assumed gold standard in sepsis lacks sensitivity or specificity, or both. For example, the causative microorganisms can not be detected in up to 80% of patients with suspected BSI [3,4], despite improved methods for identifying bacteremia including the lysis–centrifugation method of blood culture, immunofluorescence and enzyme-linked immunoabsorbent assays for antigen detection,

polymerase chain reaction (PCR), and detection of microbial heat production (calorimetry) [5]. In addition, false-positive results often pose a diagnostic “headache”, as growth of coagulase-negative staphylococci (the most common skin commensals) represents both the most frequent cause of nosocomial BSI and of blood culture contamination [6–8].

In this diagnostic uncertainty in sepsis, surrogate biomarkers to estimate the likelihood for the presence of a bacterial infection and to grade disease severity are of great interest. In past years, countless observational studies have analyzed a plethora of novel biomarkers. In conventional diagnostic accuracy studies, the usefulness of a novel test is determined by comparing the results with the definitive diagnosis ascertained by the gold standard. Sepsis is merely a clinical syndrome, not a final diagnosis, and encompasses highly heterogeneous groups of disorders that vary with respect to the site involved, bacteriology, and even presence of infection; thus, a true gold standard is lacking [9]. In such a circumstance, two fundamentally different concepts are employed [2]. One concept tends to ignore potential dilemmas in the accuracy of the alleged gold standard but assumes a well-defined illness, which is represented by the assumption drawn following a diagnostic test or a clinical diagnosis [2]. In this context, many observational studies

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Figure 1. Diagnostic accuracy of PCT to diagnose bacterial infections. Starting in the early 1970s, many observational studies have investigated the diagnostic accuracy of PCT in different clinical settings. The majority of observational studies used the clinical evaluation as the alleged gold standard to establish the diagnosis of sepsis and, unsurprisingly, reported somewhat confusing and conflicting results. As a consequence, several published meta-analyses of data from observational studies only, drew different and even opposing conclusions depending on the underlying studies included. Only RCTs in which antimicrobial therapy is guided by PCT and in which the primary measure of efficacy is the medical outcome of patients, have the potential to resolve this dilemma and evaluate the clinical usefulness of PCT-guided antibiotic stewardship.



PCT: procalcitonin; RCT: randomized controlled trial.
 Observational studies [81–84], meta-analyses [14,31,32,85,86], and RCTs [35–40] are referenced.

have been published investigating the diagnostic accuracy of a diversity of “promising” biomarkers for the diagnosis of sepsis (Fig. 1). The majority of these studies used the clinical evaluation of the patient and the presence of the “septic syndrome” as the reference standard. Accordingly, these observational studies and subsequent meta-analyses of these observational studies reported somewhat conflicting and confusing results as they were biased by inclusion criteria of the meta-analysis and the interpretation of the investigators [10–12]. Importantly, all meta-analyses of research involving the biomarker procalcitonin (PCT) performed to date include only observational studies, thus, they should be interpreted with caution [13,14]. Undoubtedly, there is an unmet need for meta-analyses based on randomized controlled trials (RCTs).

The second concept discards alleged gold standards and focuses on the outcomes of patients. In the case of sepsis, the clinical benefit of a diagnostic biomarker can be measured by clinical outcomes of randomized intervention studies, assuming that if the patient recovered without antibiotics then there was no relevant bacterial illness. In our opinion, only RCTs, in which antimicrobial therapy is guided by a specific biomarker and in which the primary measure of efficacy is

medical outcome, have the potential to evaluate the ultimate clinical usefulness of a diagnostic biomarker (Fig. 1).

Procalcitonin to diagnose bacterial infections and sepsis

In sepsis, microbes and their antigens stimulate numerous pro- and anti-inflammatory mediators that characterize the host-defense response with leukocyte recruitment to the site of infection. Precursors, mature forms, and degradation products of these mediators penetrate from the site of action into the circulation where, theoretically, they can be measured. As surrogate biomarkers, these substances mirror the extent and severity of an infection. Significant attempts have been undertaken to correlate the levels of different mediators with the presence of sepsis [12,15–17]. PCT has been demonstrated to be most clinically useful, and superior to commonly used clinical variables and laboratory tests in the diagnosis of sepsis; moreover, it has been shown to correlate with the extent and severity of microbial invasion [4,8,12,18–21]. The dual function of PCT as a precursor peptide of the hormone calcitonin and as a mediator that is elevated upon systemic bacterial infections, along with other cytokines, has resulted in the term “hormokine” being coined [22]. Importantly, administration of

PCT to septic hamsters with peritonitis doubled their death rate [23]. Conversely, treatment with PCT-reactive antiserum increased the survival rate of septic hamsters and pigs with mono- and polymicrobial sepsis, respectively [23–26]. A 1-h intravenous infusion of an immuno-neutralizing agent against porcine PCT improved all vital parameters in septic pigs: it increased short-term survival rate from 0% to 80% and was effective even when administered after the animals were moribund [24]. These features are not shared by any other known molecule. From a teleological perspective, it is interesting to learn that PCT belongs to the family of calcitonin peptides, and, together with the calcitonin gene-related peptides – adrenomedullin and amylin – forms a functional entity during infection and inflammation [27].

Clearly, the septic syndrome is far too heterogeneous and complex to be reduced to a single cut-off of any surrogate marker. Different microbes might induce distinct responses, resulting in a variable upregulation of circulating biomarkers and mediators. Nevertheless, the likelihood for a bacterial infection increases gradually with increasing serum levels of PCT. Knowledge of PCT assay characteristics, particularly the functional sensitivity of the available PCT assay, and strengths, pitfalls, and optimal cut-off ranges in predefined clinical settings, are prerequisites for the optimal use of PCT in routine clinical practice.

As a diagnostic marker, PCT has several advantages over other inflammatory markers, including C-reactive protein (CRP). It shows an increase at an earlier stage in infection, and a more rapid decrease when the infection is controlled by the immune system supported by antibiotic therapy. PCT correlates with the extent and severity of infection and has prognostic implications, namely predicting the course of disease and the risk for mortality in critically ill patients with infections and in those with ventilator-associated pneumonia [28–30]. Furthermore, unlike CRP, its production is not attenuated by nonsteroidal and steroidal anti-inflammatory drugs [29,30]. Findings from many clinical studies have established the superior diagnostic accuracy of PCT in severe infections, relative to other markers [31,32].

Vascular catheter-related bloodstream infection

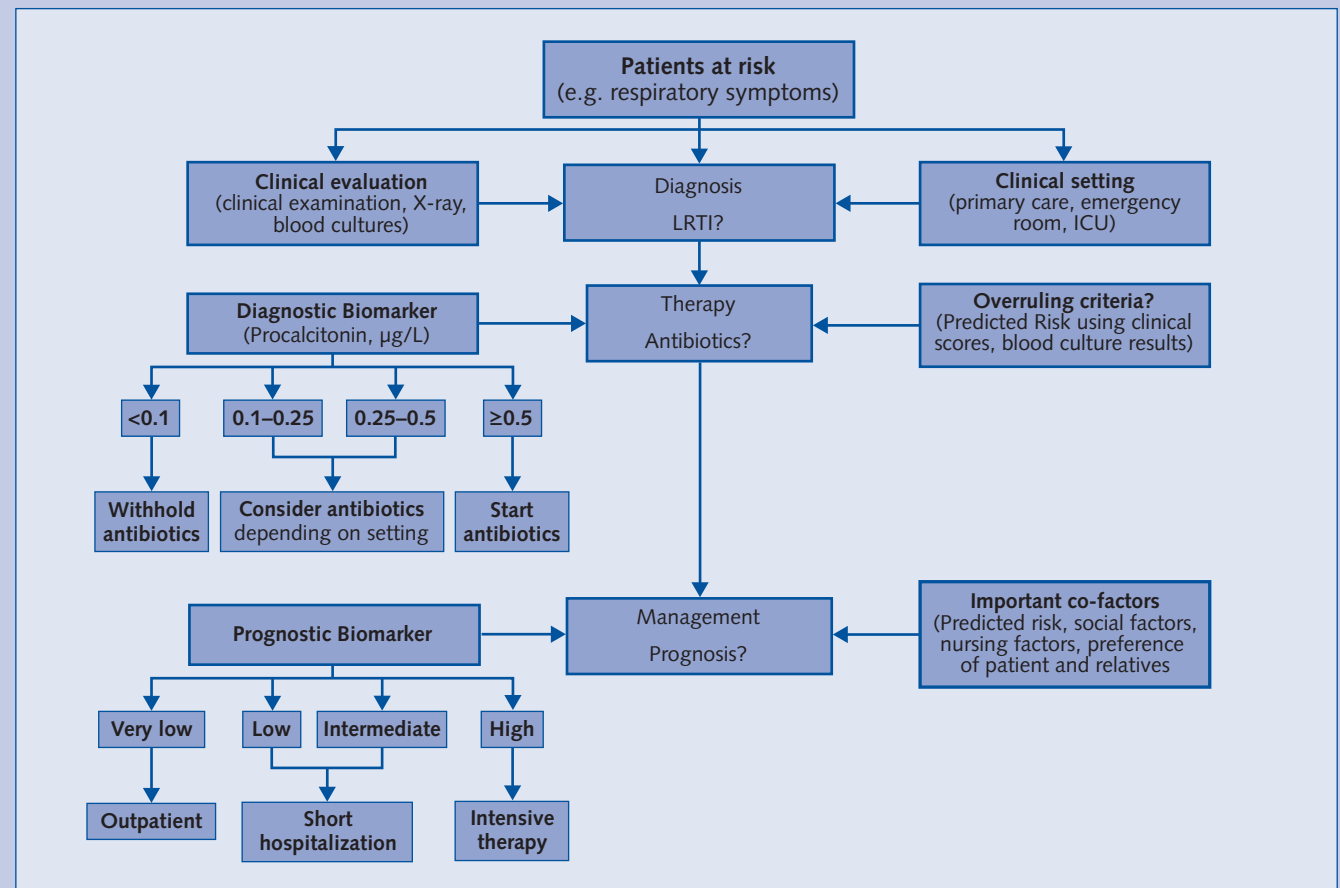
Commensals from the human skin flora, mainly coagulase-negative *Staphylococcus*, play a major role in catheter colonization. The distinction of blood contamination from BSI is important to promptly initiate an adequate therapy in true infection and, in the case of contamination, to avoid unnecessary antimicrobial usage. Conventional methods of diagnosing catheter-related infection generally require catheter removal and culture with quantitative or semiquantitative methods. However, the majority of catheters are withdrawn unnecessarily and the removal of a

central venous catheter may be undesirable because of limited vascular access and the potential complications associated with re-insertion. Thus, reliable and more cost-effective diagnostic approaches that do not require catheter removal would be desirable. In this context, the diagnostic value of serum PCT measurement to distinguish blood contamination from BSI due to coagulase-negative staphylococci has been evaluated in a pilot study [8]. Therein, PCT demonstrated a better discriminatory ability compared with white blood cell count and serum CRP levels. In that study, increased PCT concentrations were found even prior to the clinical manifestation of BSI (i.e. fever) illustrating the high sensitivity of PCT to detect colonization of the catheter with only subclinical infection, ultimately leading to BSI [33]. Importantly, the optimal cut-off to achieve 100% sensitivity in the pilot study was at a low PCT level of 0.1 µg/L [8], illustrating the need for a highly sensitive PCT assay in most clinical settings.

Procalcitonin for guidance of antibiotic therapy in lower respiratory tract infection and sepsis

As the PCT level increases upon bacterial infection and decreases upon recovery, it can be used to guide antibiotic therapy in individual patients. Using a highly sensitive PCT immunoassay that has a functional assay sensitivity of 0.06 µg/L (Kryptor PCT, Brahms, Henningsdorf, Germany), antibiotic stewardship based on PCT cut-off ranges has been successfully implemented in patients with lower respiratory tract infections (LRTI) in different clinical settings [34]. For this purpose, specific PCT cut-off ranges, reflecting the setting-specific likelihood of relevant bacterial infections, have been proposed using multi-level likelihood ratios and have been translated into an easy-to-use and pragmatic clinical algorithm (Fig. 2). Based on the specific cut-off ranges, initiation or continuation of antibiotics was discouraged to a greater or lesser extent (<0.1 µg/L or <0.25 µg/L), or encouraged (>0.5 µg/L or >0.25 µg/L), respectively. In cases in which antibiotics were withheld, clinical re-evaluation and a repeated measurement of PCT were recommended after 6–24 h. If PCT values were increased and antibiotic therapy was initiated, repeated PCT measurements were recommended and antibiotics were discontinued using the same cut-off ranges. In patients with very high PCT values on admission (e.g. >10 µg/L), discontinuation of antibiotic therapy was encouraged if levels decreased to below 80–90% of the initial value. To ensure the safety of patients, the present authors have instituted predefined specific “overruling” criteria, where this algorithm could be bypassed (e.g. immediate life-threatening disease or need for intensive care unit [ICU] admission). Physicians were advised that persistently

Figure 2. Diagnostic and prognostic biomarkers in the management of patients with LRTIs. Embedded in a predefined clinical algorithm, after history taking and a profound clinical examination, diagnostic and prognostic biomarkers improve the management of patients with LRTI. For establishing the correct diagnosis, clinical signs and symptoms including a chest X-ray and collection of blood cultures are most helpful. PCT as a diagnostic biomarker correlates with the likelihood of bacterial infection and PCT guidance safely reduces antibiotic exposure in patients with LRTI and in critically ill septic patients. The further management of patients relies on different factors including social and nursing factors, preferences of patients and relatives, and, importantly, on the predicted risk for patients. As different prognostic biomarkers (e.g. proADM, copeptin, proET-1) independently predict clinical outcomes of patients, namely mortality and the need for ICU admission, these biomarkers have the potential to improve the management of patients and shorten unnecessary hospital stays.



ICU: intensive care unit; LRTI: lower respiratory tract infection; proADM: pro-adrenomedullin; PCT: procalcitonin; proET-1: pro-endothelin-1.

elevated PCT levels may indicate a complicated course, while PCT levels may remain relatively low in localized infections (e.g. empyema or abscess). This clinical algorithm was prospectively tested in four intervention trials in the emergency department [35–37] and ICU [38] settings at different University Hospitals in Switzerland, and in the primary care setting by >50 primary care physicians [39]. It is currently being externally validated in the nationwide, multicenter ProHOSP (Procalcitonin Guided Antibiotic Therapy and Hospitalization in Patients With Lower Respiratory Tract Infections) study in Switzerland [40]. The validity of this algorithm was measured by clinical outcomes. PCT-guided antibiotic stewardship reduced antibiotic

prescription rates by 40–50% in patients with LRTIs presenting to the emergency department, including in patients with acute exacerbation of chronic bronchitis (chronic obstructive pulmonary disease [COPD]), without an increased relapse rate over a 6-month follow-up period [36]. In patients with community-acquired pneumonia (CAP), PCT guidance reduced the initial antibiotic prescription rate by approximately 10%, but importantly shortened the duration of such therapy by 65% with a similar outcome in patients with all severities of CAP [35]. In the PARTI (Procalcitonin Guided Antibiotic Use in Acute Respiratory Tract Infections) study, the safety and feasibility of the PCT-guided algorithm was proven in the primary care setting,

which enrolled >450 patients with acute upper and lower RTI [39]. In a low antibiotic prescription setting in Switzerland, PCT guidance safely reduced antibiotic exposure by >75%, thus significantly reducing antibiotic-related side effects, especially diarrhea. Using a similar PCT algorithm, a recently published trial including critically ill septic patients from a medical ICU reported a 4-day shorter duration of antibiotic therapy in PCT-guided cases (6 days compared with 10 days in the control group) with similar mortality and recurrence rates [38]. Importantly, a 2-day shorter ICU stay was observed in patients assigned to the PCT-guided group. Of note, in >70% of patients with radiologically proven CAP, the causative microbe was not identified in our studies. Conversely, in patients with acute exacerbations of COPD, significant numbers of bacteria were isolated from sputum in up to 50%, representing colonization in many cases.

Biomarker for prognostic assessment

LRTI, specifically CAP, is the leading cause of death from infectious diseases in Western countries and health expenditures are substantial, particularly for inpatient management [41,42]. Accurate assessment of disease severity, risk stratification, and prediction of outcome are prerequisites for safe decision-making regarding the need for hospitalization and for identifying patients who are at a low risk of complications (and are thus suitable for outpatient management). Despite their widespread use in clinical practice, traditional markers such as fever, white blood cell numbers, and CRP levels are not reliable for assessing disease severity and mortality risk [12]. Several organizations have developed prediction rules and disseminated guidelines to stratify the management of patients based on predicted mortalities in order to optimize hospital referral and reduce hospital admission rates [43,44]. The pneumonia severity index (PSI) is a widely propagated North American scoring system that assesses the risk of death in a two-step algorithm [45]. However, its complexity jeopardizes its dissemination and implementation in everyday practice. Therefore, the CURB-65 (Confusion, Urea nitrogen, Respiratory rate, Blood pressure, 65 years of age and older) and the CRB-65 (Confusion, Respiratory rate, Blood pressure, 65 years of age and older) scores – modified versions of the British Thoracic Society assessment tool – which are based on only five and four predictors, respectively, have been proposed as simpler but somewhat less reliable alternatives [46,47]. These scores are only evaluated for CAP and not for all LTRIs, and have a considerable risk of miscalibration – and therefore misclassification of patients, depending on the clinical setting [48]. In this context, new and measurable biomarkers mirroring distinct pathogenetic mechanisms to predict severity and

outcome may improve the prognostication of patients. Importantly, the utility of a biomarker in this context is defined by the degree to which it improves clinical decision-making and adds timely information beyond that which is readily available from clinical examination [17].

Does PCT have prognostic implications?

A recent study suggested that very low PCT values on admission (optimal PCT cut-off at 0.23 µg/L) in patients with CAP have a moderate negative prognostic value and thereby improve the CRB-65 score [49]. However, it is more helpful to consider the dynamics of PCT levels in LRTI, as persistently elevated levels are associated with adverse outcome and decreasing PCT levels suggest a favorable outcome, usually showing a log-linear drop-off and a half-life of 20–24 h [18,49,50]. In the ICU setting, elevated PCT levels, in particular an increase in PCT for 1 day, were independent predictors for 90-day, all-cause mortality in septic patients [28], while increasing levels of CRP and white blood cells did not predict mortality. Similarly in our studies, PCT showed a better prognostic accuracy compared with CRP and white blood cell count, but there was a wide overlap in PCT levels between different severities of CAP and only a small difference in PCT levels between survivors and non-survivors. Moreover, PCT did not improve clinical prognostic assessment scores (e.g. Acute Physiology and Chronic Health Evaluation II [APACHE II] or Simplified Acute Physiology Score II [SAPS II]) [12,19,51,52]. Based on these data, PCT seems to be a reliable diagnostic marker able to guide decisions on antibiotic therapy, rather than an ideal prognostic tool [12,19,52,53]. In addition, future studies must demonstrate whether an improved prognostic assessment using PCT or any other biomarker translates into better clinical outcomes and a higher quality of patient care.

Pro-adrenomedullin to assess outcome and prognosis of septic patients

A more promising prognostic biomarker is adrenomedullin (ADM), which is also a product of the calcitonin gene family. It is a very potent vasodilating agent and has additional immunomodulating and metabolic properties [54–57]. Measurement of ADM is challenging as it is rapidly cleared from the circulation [54,55]. A new sandwich immunoassay has been developed that measures the more stable, mid-regional fragment of pro-adrenomedullin (proADM) directly, reflecting levels of the rapidly degraded active peptide [58]. In patients with CAP, proADM levels measured on admission showed a comparable correlation with disease severity and outcome of CAP, relative to the PSI. Importantly, proADM improved the prognostic accuracy of the PSI alone, providing an additional margin of safety [52].

Do stress hormones correlate with medical outcomes?

During severe illness, a series of important hormonal changes occur, mirroring the patients' individual stress level [59–61]. For this reason, hormones are promising candidate biomarkers for the prognostic assessment of patients with systemic infections. The classical stress response of the body includes stimulation of the hypothalamic–pituitary–adrenal axis with an increased production of cortisol and vasopressin and a functional deficit of anabolic hormones [59,60]. As plasma cortisol levels mirror the individual stress level associated with the underlying illness, we evaluated the prognostic value of cortisol in patients with CAP [62]. Cortisol concentrations measured on presentation accurately predicted the severity and outcome of CAP similarly to the PSI, and to a greater extent than commonly measured laboratory parameters, namely CRP, white blood cells, and PCT. The higher level of pro-inflammatory cytokines in patients who subsequently died may additionally explain the pronounced increase of cortisol as the strongest known natural inhibitor of inflammation in non-surviving patients. An additional, less well known stress hormone is anti-diuretic hormone, also known as vasopressin, which has hemodynamic and osmoregulatory effects and reflects the individual stress response. This hormone co-regulates the secretion of adrenocorticotrophic hormone together with corticotrophin-releasing hormone. Copeptin, which is stoichiometrically co-secreted with vasopressin and directly mirrors vasopressin production, has a longer half-life in the circulation and is thus easier to measure [63]. We evaluated the prognostic value of copeptin and found significantly higher concentrations in patients with LRTI compared with control subjects, with highest levels found in patients with CAP [64]. Copeptin levels increased with increasing severity of CAP, and in patients who died, copeptin levels on admission were significantly higher compared with those in surviving subjects [64]. Recently, in patients with acute exacerbations of COPD, copeptin was shown to be predictive for long-term clinical failure independent of age, co-morbidity, hypoxemia, and lung functional impairment in a multivariate analysis [65]. The combination of copeptin and previous hospitalization for COPD increased the risk of a poor outcome.

Endothelial biomarkers in the prognostic assessment

Another interesting endothelium-derived biomarker is endothelin-1 (ET-1) and its precursor peptide proET-1 [66]. In humans, elevated plasma levels of mature ET-1 are found during systemic infections and correlate with mortality risk [67–69]. Preliminary studies in animals demonstrated beneficial effects of ET-1 antagonism by using a selective ET-1 receptor antagonist during septic shock [70–73]. Using a new sandwich immunoassay, we recently evaluated proET-1 levels in patients with CAP and found proET-1 levels on

admission to be independent predictors of short-term mortality and the need for ICU admission. In this setting, proET-1 levels improved the prognostic accuracy of the commonly used CURB-65 score to predict adverse outcome [74]. Interestingly, in critically ill and septic patients from a medical ICU, the ratio of the endothelium-derived and counteracting substances proADM and proET-1 showed the highest predictive accuracy [75].

Other biomarkers

It is advisable to base the difficult task of prognostic assessment and treatment decisions on several rather than one parameter. Thus, we have studied other hormonal and metabolic mediators and biomarkers in CAP and in LRTI, including brain natriuretic peptide [76], *N*-terminal pro-atrial natriuretic peptide [77,78], and plasma lipid levels [79], each mirroring different pathophysiological aspects and showing promising results in predicting disease severity and outcome [11,12].

There is good evidence that different biomarkers have the potential to complement existing clinical severity scores and thus improve the risk stratification of patients with LRTI. Nevertheless, specific cut-off ranges and clinical algorithms with single or repeated biomarker measurements need to be proposed, and prospective intervention studies conducted, to determine whether these biomarkers really do improve the daily clinical management of patients with sepsis.

Limitations of biomarkers

Importantly, biomarker levels must always be evaluated in the context of a careful clinical and microbiological assessment. As the kinetics of biomarkers is of particular diagnostic and prognostic interest, repeated measurements should always be performed, especially if antibiotics are withheld, and/or in persistently sick patients. Limitations of every biomarker include false-positive and false-negative results. Non-specific elevations of PCT levels in the absence of a bacterial infection can typically be seen in situations of massive stress, for example, after severe trauma or surgery [30,31]. In these situations, PCT values are usually only moderately elevated and show a rapid decline at follow-up measurements. Conversely, falsely low PCT levels, typically seen during the early course or localized state of an infection, are often increased in follow-up assessments. In these situations, highly sensitive PCT assays are required, as subtle changes of PCT (at very low concentrations) can be monitored, increasing the sensitivity of the test and ultimately the safety of patients.

Summary

The ambiguities of clinical signs and the limitations of current microbial techniques for the diagnosis of bacterial infections

and to grade its severity are well known. The use of biomarkers provides a novel, complementary approach to diagnose infection, and to estimate treatment response and the outcome of patients. A critical appraisal of the advantages and limitations of biomarkers in different clinical situations is mandatory. Interpretation of a biomarker level must always comprise the clinical setting and the assay characteristics, particularly the defining of specific cut-off ranges and functional assay sensitivities. In most infections, a true gold standard for diagnosis does not exist, thus physicians must remain skeptical regarding data from observational studies on diagnostic biomarkers. The higher the absolute risk of a patient, the more cautious physicians must be and empirical antibiotic therapies should be considered in spite of low biomarker levels. Nonetheless, measurement of biomarkers, particularly highly sensitive PCT measurements, embedded in a clearly defined setting and prospectively validated with clinical algorithms can significantly improve the diagnostic certainty and reduce the utilization of antimicrobial therapy. Today, this concept has been proven for lower respiratory tract infection, and in a pilot study in meningitis [80]. For almost all other infections, only observational studies have been conducted. In these clinical situations, disease- and setting-specific cut-off ranges must be proposed and validated, and intervention studies conducted to tackle the existing vicious cycle of diagnostic uncertainty, antibiotic overuse, and emerging multi-drug resistance. For the prognostic assessment, distinct promising biomarkers have demonstrated high predictive potential to estimate the risk for mortality in the short and long term, and other adverse outcomes. Future intervention studies must prove whether these biomarkers improve clinical decision-making and thus improve medical care of patients in the long-term.

Disclosures

Philipp Schuetz, Mirjam Christ-Crain, and Beat Müller have served as consultants and received payments from Brahms to attend scientific meetings and for travel expenses, speaking engagements, and research.

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