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Are circulating levels of CRP compared to IL-6 and PCT still relevant in intensive care unit patients?¹⁾

Abstract: C-reactive protein (CRP) currently constitutes one of the most widely used parameters for the diagnosis of infections and inflammatory processes, due to simple methods and low costs. However, in recent years, other parameters, such as interleukin 6 (IL-6) and procalcitonin (PCT), have gained in importance. Although these parameters are presently not established everywhere in clinical routine, they provide significant advantages in the diagnosis and monitoring of inflammatory diseases. For instance, in intensive care, the increase in IL-6 levels may indicate inflammatory complications 24 to 48 h prior to the increase in circulating CRP levels. In contrast to CRP, PCT shows a higher specificity for bacterial infections, which facilitates the diagnosis of bacterial infections and sepsis. PCT measurements further allow assessment of therapeutic success and indicate necessary changes in antibiotic therapy. These points raise the question whether CRP measurements should at least in part be replaced by PCT and/or IL-6. Thus, this review seeks to examine the value of CRP in relation to PCT and IL-6 for the diagnosis of bacterial infections, in therapeutic monitoring, and regarding prognosis in critical care patients.

Keywords: C-reactive protein (CRP); infection; inflammatory marker; intensive care; interleukin 6 (IL-6); procalcitonin (PCT); sepsis.

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Introduction

The ideal inflammatory marker should detect infections quickly and specifically, allow an evaluation of therapeutic success and indicate necessary changes in therapy. In addition, inflammatory markers should provide information on the patient's prognosis. This facilitates identifying high-risk patients and adapting therapeutic measures accordingly.

Moreover, the inflammatory marker has to be readily available and offer an acceptable cost-benefit ratio.

C-reactive protein (CRP) is currently one of the most widely used parameters for the diagnosis of infections and inflammatory processes. The protein consists of five identical, non-covalently associated monomers, which are symmetrically arranged around a central pore [1]. CRP was discovered through and named after its ability to bind and precipitate C-polysaccharide of *Streptococcus pneumoniae*. Apart from this classical ligand, CRP is involved in the opsonization of a number of other exogenous and endogenous ligands [1]. Further ligand-bound or aggregated CRP may activate the classical pathway of the complement system via interaction with complement factor C1q [2, 3].

In the day-to-day routine, measurement of CRP is mainly used for diagnosis and monitoring of infections as well as for risk stratification in cardiovascular diseases. The most notable advantages of CRP are good availability and low costs. However, the parameter's low specificity for bacterial infections must be taken into account. Elevated CRP levels may occur due to other infectious or chronic diseases, traumata, surgery or myocardial ischemia [4, 5].

Over the last few years, other parameters besides CRP, such as procalcitonin (PCT) and interleukin-6 (IL-6) have gained importance. PCT is the pro-hormone of calcitonin, which plays an important role in the regulation of the calcium homeostasis [6].

Contrary to calcitonin, PCT is not involved in regulating calcium levels. Whereas calcitonin is synthesized in the C-cells of the thyroid, a systemic microbial infection induces PCT synthesis and release by parenchymal

cells such as lung, liver, kidneys, muscle and adipose tissue [7, 8]. While only low concentrations of PCT are measurable in healthy subjects [9], PCT levels may rise up to several thousand times the norm in severe infections and sepsis [10, 11]. PCT levels increase approximately 4 h after contact to bacterial endotoxin and peak after 6 to 8 h [12, 13]. The increase in PCT correlates with both severity and prognosis of the disease [10, 11]. Experimental studies showed that synthesis of PCT may be induced by administration of bacterial toxins as well as IL-6 [12, 14, 15]. The pathophysiological role of PCT is not fully explained, however, animal studies demonstrated that injection of PCT increases severity and mortality of a pre-existing sepsis. In contrast, application of neutralizing antibodies against PCT ameliorated the condition of the animals [16–18]. Primary indications of measuring PCT levels include diagnosis of bacterial infections, severity assessment of sepsis and the evaluation of the course of disease, therapeutic success and, to some extent, the patient's prognosis [11, 19–23]. The high specificity of PCT for bacterial infections facilitates the differentiation of viral and bacterial infections [20, 24–29]. By means of risk stratification, PCT levels further allow a selective use of antibiotics, decreasing unnecessary treatment on the one hand and indicating beneficial effects of therapy in high-risk patients on the other hand [27, 30–33].

The pro-inflammatory cytokine IL-6 is synthesized by macrophages, lymphocytes, endothelial and mesenchymal cells and plays a central role in the synthesis of acute phase proteins, such as CRP [34]. Hence, the increase in circulating IL-6 levels can be measured significantly earlier than the increase in CRP concentrations. This reduces the time to diagnosis and initiation of therapy as has been shown in neonates and in intensive care patients with incipient complications. The increase in IL-6 levels was evident 24 to 48 h before clinical symptoms and detectable changes in other established inflammatory markers [35, 36]. Apart from the parameter's high value as an early diagnostic marker, circulating IL-6 levels may also be used for assessment of the patient's prognosis. Data from various clinical studies show that elevated IL-6 levels are an indicator of both disease severity and mortality risk [23, 37–42].

In comparison to CRP, the newer inflammatory markers provide an earlier indication of inflammatory processes and offer better diagnostic value, as for example in the differentiation between viral and bacterial infection. In addition, they allow assessment of prognosis and risk stratification, whereby unnecessary use of antibiotics may be avoided, reducing the risk of the development of

multi-resistant bacteria. Furthermore, high-risk patients are more easily identified and will receive adequate therapy sooner [24–27, 30–33, 43–46].

Diagnostic value of CRP

CRP, a classical acute phase reactant, is synthesized in hepatocytes under the control of pro-inflammatory cytokines, such as IL-6 or IL-1 [2]. CRP-levels begin to increase approximately 4–6 h after an inflammatory stimulus and reach their maximum after about 36 h [47].

Indications for measurement of CRP include the diagnosis and monitoring of infections and sepsis, a number of chronic inflammatory diseases, suspected postoperative complications and differentiation between viral and bacterial meningitis or pneumonia. Moreover, minor elevations of CRP are used for risk stratification of cardiovascular diseases. These so-called high-sensitivity CRP measurements allow early identification of patients with high risk for future cardiovascular events. Elevated CRP levels may also be found in patients with traumata, metabolic syndrome, diabetes mellitus II, myocardial necrosis and malignant tumors [3–5].

The low specificity of CRP for bacterial infections limits the benefits of CRP measurements for several important indications, such as the differentiation between sepsis and SIRS. The value of CRP levels for the evaluation of prognosis and severity of infections and/or sepsis as well as mortality risk remains controversial. Several studies have come to the conclusion that elevated CRP levels are associated with a poor prognosis [48–51]. For instance, a prospective cohort study of 603 intensive care patients showed a higher mortality risk for patients who were discharged from intensive care with high CRP levels [51]. Increased CRP levels were further associated with a higher risk for organ failure and mortality [49]. Another study demonstrated that daily measurement of CRP was a good marker for identifying patients with an adverse prognosis. In contrast, a decrease in CRP levels within the first 5 days on an intensive care unit was associated with a good prognosis [48].

Recent studies have questioned the prognostic value of CRP, particularly concerning patients with infectious diseases. For instance, various studies showed that elevated CRP levels in patients with sepsis or pneumonia and in intensive care patients in general were not associated with an increased mortality risk [23, 52, 53]. In particular, early measurement of CRP levels was not found to be a good indicator of prognosis [54, 55].

Diagnostic value of IL-6

IL-6 belongs to the group of pro-inflammatory cytokines and is synthesized and released by immune-competent cells such as macrophages and lymphocytes as well as endothelial and mesenchymal cells. In combination with other cytokines such as TNF or IL-1, IL-6 induces the acute phase reaction and thus leads to the production of acute phase proteins including CRP [34].

Production of IL-6 is initiated by parts of bacterial membranes such as lipopolysaccharides (LPS), viral infection, tissue trauma along with the resulting oxygen deficit, and through other cytokines such as TNF, PDGF and IL-1 [56, 57]. In the course of sepsis, IL-6 concentrations may increase up to a thousand-fold [36]. Both IL-1 and TNF appear in the circulation shortly before the increase of IL-6 but have not been widely established due to their very short half-lives [58]. In contrast, IL-6 levels have a longer half life and thus allow the earliest possible detection of an inflammatory process with routine methods.

Early diagnostic marker

The elevation of IL-6 in response to an inflammatory stimulus is evident 24 to 48 h before presentation of clinical symptoms and measurable changes in other established inflammatory markers such as CRP [59–61]. In patients undergoing treatment with chemotherapy and consecutive neutropenia increased IL-6 concentrations were detected as early as 48 h prior to an increase of fever [59]. Further, IL-6 levels of intensive care patients at the time of admission were shown to be good predictors for subsequently established bacteraemia [58, 60]. In addition, IL-6 levels were described as an early diagnostic marker for bacterial infections in patients with liver cirrhosis [61]. In this early phase of the disease, the studies mentioned above found IL-6 to be superior to other inflammatory markers such as CRP, leukocyte count, fibrinogen and other acute phase proteins with regard to both sensitivity and specificity. For this reason, IL-6 concentrations play an important role as early diagnostic markers of incipient complications in intensive care patients.

In the diagnosis of neonatal sepsis, the time of diagnosis and an immediate commencement of therapy is crucial for the outcome of the disease. In this regard it has been demonstrated that IL-6 concentrations were elevated before the presentation of clinical symptoms and the increase of other routine parameters such as CRP [35]. In particular in premature infants, elevated IL-6 levels were detected 1–2 days prior to the clinical diagnosis of sepsis

and therefore may facilitate early diagnosis of neonatal sepsis [62–64].

Moreover, an increase in IL-6 levels may be used as an early indicator of postoperative infectious complications. In patients with postoperative infections, elevated IL-6 concentrations may be detected early on [65]. Whereas postoperative increases in IL-6 drop quickly in the absence of complications, particularly high postoperative concentrations or a delayed decrease in the consecutive days are associated with infectious complications [58, 65, 66]. Although CRP concentrations are also elevated after surgery, the decrease in CRP levels even without complications is significantly slower compared to IL-6 due to the longer half-life of CRP [5].

Apart from early diagnosis of infection, IL-6 levels may also be used to identify high risk patients and adapt therapeutic measures accordingly. This is possible because of the good correlation between IL-6 concentrations and disease severity. For instance, IL-6 levels above 1000 pg/mL at the time of an increase in temperature in intensive care patients may help to identify high risk patients. Also incipient complications may be diagnosed earlier than by means of other parameters [36, 42].

PCT levels rise approximately 4 h after stimulus with bacterial endotoxin and hence react slower than IL-6 but faster than CRP, which shows significant changes only 10 to 12 h after the onset of infection [5, 12, 13, 36]. Consequently, as an early diagnostic marker, IL-6 is superior to both CRP and PCT levels.

However, it should be noted, that elevated IL-6 concentrations may also stem from non-infectious causes. These include postoperative complications, such as insufficient sutures following extensive abdominal surgery, severe traumata, burns, transfusion reactions or fever of unknown origin in neutropenic patients [56, 66–70]. In spite of these restrictions, IL-6 levels allow for shorter time periods to diagnosis, risk assessment and initiation of therapy due to their earlier rise in comparison to CRP and PCT concentrations.

Prognosis

IL-6 not only constitutes a useful tool for the early diagnosis of systemic infections but also for the evaluation of the patient's prognosis [38, 42, 59, 61, 70]. For instance, this has been shown in patients suffering from sepsis or septic shock, in patients with fever and in patients with peritonitis [39, 40, 59, 70]. In septic patients, IL-6 levels were demonstrated to correlate with mortality, severity of sepsis, organ dysfunction and occurrence of septic shock

[42]. In intensive care patients the early rise of IL-6 allows a prognostic assessment already at the onset of fever, which makes it possible to identify high risk patients and adapt therapeutic measures accordingly [36]. In this early phase, IL-6 levels provide a better assessment of the patient's prognosis than PCT concentrations. A prospective study of 253 septic patients found that elevated IL-6 levels had a better correlation with mortality risk than PCT. In contrast, high CRP concentrations were not associated with mortality rates. IL-6 concentrations remained significant throughout the course of the disease (day 7, day 28, discharge, 6 months and 1 year after discharge). IL-6 levels were strongly associated with severity of sepsis [23]. In patients with burn injuries IL-6 concentrations of patients who did not survive were significantly higher than in survivors. Moreover, while IL-6 concentrations were shown to rise in the pre-final stage, patients who survived exhibited a drop of IL-6 levels in the course of the disease [41].

A prospective cohort study, in which the mortality of pneumonia 1 year after discharge was evaluated, demonstrated that elevated IL-6 levels at the time of discharge were associated with a higher mortality risk. In particular, high IL-6 concentrations were associated with death by cardiovascular diseases, malignant tumours, infections and renal failure [37]. In surgical ward patients, IL-6 concentrations may indicate the severity and extent of tissue trauma. In case of herniotomy, which is associated with significant tissue trauma, higher IL-6 levels were detected than in laparoscopic surgery with little tissue trauma [71]. Another study was able to assess the severity of soft tissue and fracture trauma by means of IL-6 levels [72].

Although numerous studies support the prognostic value of IL-6, especially in the early stages of disease, several studies suggest that repeated measurement of PCT may be better suited for assessment of prognosis than IL-6 measurements [73–75]. However, both PCT and the earlier increasing IL-6 appear to be superior to CRP regarding the evaluation of prognosis, particularly in the early stages of disease.

Diagnostic value of PCT

Bacterial infections

The differential diagnosis of bacterial infections may present difficulties, since Gram-negative, Gram-positive, viral or fungal infections as well as non-infectious processes such as pancreatitis or vasculitis, often cause similar symptoms of inflammation [76–79]. In this regard,

numerous studies have confirmed that PCT levels have a higher specificity for bacterial infections than CRP concentrations [11, 27, 28, 80–87].

In intensive care wards, PCT's high specificity for bacterial infections facilitates the diagnosis of sepsis [11, 28, 80–83, 88–90]. As early as 1993 Assicot et al. [10] found elevated PCT levels in septic patients. Since then, numerous studies have shown PCT to be superior to CRP as a diagnostic marker for sepsis [11, 28, 80–83, 88–90]. For instance, Becker et al. [6] stated that PCT had a sensitivity of 89% and a specificity of 94% for the diagnosis of sepsis. Furthermore, PCT was found to exhibit better diagnostic value than IL-6 or CRP for the differentiation between sepsis and SIRS in intensive care patients with prolonged stay [81]. Another typical challenge on intensive care wards is the modulation of inflammatory markers by steroids. However, in contrast to CRP and IL-6, the elevation of PCT appears not to be influenced by the administration of corticosteroids [21, 91, 92]. In addition, numerous studies support the high utility of PCT with regard to the diagnosis of other infections such as meningitis, pancreatitis and acute infectious endocarditis [10, 20, 27, 84–87, 93–98]. For instance, PCT has been demonstrated to be better suited for the differentiation between bacterial and viral meningitis in both children and adults [27, 84, 85].

In spite of the predominantly positive results concerning the use of PCT for the diagnosis of systemic infections, several studies question the value of PCT [48, 99–102]. For example, a meta-analysis by Tang et al. concluded that PCT does not allow an unequivocal differentiation between sepsis and SIRS through non infectious causes [99]. These differing results are explained by varying inclusion criteria and different measuring methods [103, 104]. As is the case with CRP measurements, several restrictions need to be considered with PCT levels. First, PCT levels may also be increased without the presence of bacterial infection, for instance following severe traumata, surgery or burn injuries [93, 105–107]. Second, “false” low PCT concentrations in spite of the presence of bacterial infection are possible in the early stages of infection, in sub-acute infectious endocarditis and in localized infections [30, 93–95]. Since PCT is released by parenchymal cells of, e.g., the lung or the liver in the context of severe systemic infections, it is to be expected that localized infections without systemic reactions generally show low or only slightly elevated PCT levels [93]. In view of these restrictions, a single PCT measurement may be misleading. However, in the absence of bacterial infection, PCT concentrations generally drop under 1ng/mL within 48 h [27, 108]. This is particularly relevant for serial measurements and evaluation of elevated levels following surgery.

Summarizing, various studies have concluded that PCT measurements, in comparison to CRP levels, have a higher specificity and sensitivity for the diagnosis of bacterial infections [81, 109].

Therapeutic guidance

On the basis of the microbiological report, the patient's therapy will be changed from prophylactic to targeted antibiotic treatment. Limitations in correctly differentiating between viral and bacterial aetiology of, e.g., respiratory tract infections result in increased use of antibiotics. Reduction of antibiotic use may decrease both the danger of the development of multi-resistant micro-organisms and the risk of allergic reactions [43–46, 110].

Numerous studies have shown that elevated PCT levels are associated with infections. Specificity and sensitivity are superior to other inflammatory markers such as CRP. Conversely, PCT offers a high negative predictive value, i.e., low PCT concentrations exclude an infection with high probability [22, 28]. At a cut-off of 0.2 ng/mL, PCT has a negative predictive value of 99% for the exclusion of sepsis [111]. In comparison, using a cut-off of 15.4 mg/dL, CRP levels only reached a negative predictive value of 63.5% for the exclusion of severe sepsis or septic shock [112]. Various studies illustrate that PCT-guidance of antibiotic treatment could significantly reduce use of antibiotics in lower respiratory tract infections, community acquired pneumonia, meningitis and severe sepsis without negative effects on outcome or duration of hospital stay [27, 30–33, 113–115]. For instance, in patients with acute respiratory infections PCT guidance allowed for a reduction in the use of antibiotics by more than 40% [116]. In addition, PCT may indicate an ineffective antibiotic treatment in advance of microbiological results. Charles et al. [117] illustrated that antibiotic therapy, which is effective against the causal micro-organism leads to a drop in PCT levels within 2 days. Conversely, antibiotic treatment that was not directed against the causal pathogen was associated with a further increase in PCT concentrations. Thus, persistent PCT elevations under empiric antibiotic therapy may indicate therapy failure and the necessity of a change in antibiotics [117].

To what extent such a therapeutic guidance may also be possible with CRP is not clear because no studies were conducted in this regard. Although an increase in CRP concentrations of at least 2.2 mg/dL in septic patients may indicate an ineffective antibiotic treatment, sensitivity was reported to be only at 77% and specificity as low as 67% for this indication [118]. Several other studies suggest that

CRP and PCT offer comparable benefits in assessing therapeutic success or risk of therapy failure. For example, in patients with community acquired pneumonia, both elevated CRP and PCT levels on day 1 and day 3, respectively were associated with a higher risk of therapy failure. Conversely, low CRP or PCT levels on day 1 had a high negative predictive value for early therapy failure [119].

In view of all available data, PCT appears to be better suited for the guidance of antibiotic therapy due to its higher specificity for bacterial infections compared to CRP levels.

Prognosis

The value of PCT for assessing the prognosis of different infections is subject to controversial debate. In a study on 472 critically ill intensive care patients, Jensen et al. [53] demonstrated a correlation between PCT levels and all-cause mortality within 90 days of admission whereas CRP levels were not associated with mortality [53]. Moreover, in patients with community acquired pneumonia PCT was better suited for the evaluation of the patients' prognosis than CRP [52]. Furthermore, persistent PCT elevations are associated with an unfavorable outcome, whereas declining PCT levels indicate a good prognosis [29, 108, 120]. However, several studies found no unequivocal association between PCT levels and mortality rates [120]. In assessing the prognostic value of PCT, the reservation must be made, that as in CRP levels, false negative and false positive values, for instance following surgery or traumata, may occur.

Conclusions

In the diagnosis of systemic infections and sepsis, IL-6 and PCT have gained progressively more importance alongside the classical CRP measurement. As accurate and fast diagnosis in connection with immediate initiation of therapy may have a substantial influence on the patient's outcome, high demands are placed on inflammatory markers. These include high diagnostic sensitivity and specificity, a high negative predictive value and precise statements on the severity of the disease as well as individual mortality risk. These requirements are better met by IL-6 and/or PCT than by CRP concentrations.

Due to its early rise, measurement of IL-6 is of particularly high diagnostic value in the early stages of an infection. Elevated IL-6 levels may be measurable up to 48 h

prior to presentation of clinical symptoms such as fever and the rise of CRP levels. This early increase allows not only a quicker orientation regarding the danger of infection or sepsis but also an early risk stratification, because elevated IL-6 levels correlate with disease severity and mortality. In the challenging diagnosis of neonatal sepsis, IL-6 measurements are of major importance. Since IL-6 levels are elevated prior to the development of clinical symptoms and other routine parameters, such as CRP, IL-6 measurements significantly facilitate the early diagnosis of neonatal sepsis and allow for an earlier initiation of therapy. Moreover numerous studies have come to the conclusion that PCT levels in comparison to CRP measurements offer both better specificity and better sensitivity for bacterial infections. Owing to their high negative predictive value, PCT levels further permit a more precise guidance of antibiotic therapy. In contrast to CRP, PCT concentrations additionally have a good correlation with severity of sepsis.

In comparison to PCT and IL-6, the lower specificity of CRP and its slower kinetics restrict the utility of CRP measurements. For instance, the delayed increase of CRP in relation to IL-6 significantly reduces the value of CRP as an early diagnostic marker. The prognostic value of CRP has been the subject of controversial debate. Although several studies postulate that CRP and PCT have a comparable prognostic value, numerous other studies conclude that PCT is better suited than CRP for both monitoring and assessment of prognosis. In the very early stages of disease, IL-6 appears to be best qualified for the evaluation of the patient's prognosis due to its early increase.

However, newer inflammatory markers, such as PCT and IL-6, may also show "false" positive or "false" negative results. As a consequence it is necessary to be aware of both strengths and weaknesses of every parameter. For instance, elevated PCT concentrations in the absence of a bacterial infection may be found following traumata, burn injuries or major surgery. Moreover, in monitoring a patient, it should be noted that PCT levels may drop significantly before death. This decrease might be caused by a general exhaustion of the immune system [121].

Table 1 Suitability of PCT, IL-6 and CRP for different indications in diagnosis and the course of infection and sepsis.

	IL-6	PCT	CRP
Early diagnostic marker	+++	+(+)	–
Differential diagnosis bacterial/viral	+	+++	+
Prognosis	+++	+	(+)
Therapeutic success	++	+++	+

However, in comparison to PCT, CRP levels are, in part, connected with more constraints owing to the low specificity of CRP measurements. Elevated CRP concentrations may be detected in numerous diseases such as myocardial infarction, malignant tumours, traumata and rheumatic-degenerative diseases. This underlines the importance of evaluating a patient not only based on inflammatory markers but in conjunction with the clinical picture and other medical results. It should also be noted that a single measurement may be misleading. Thus, inflammatory markers should be evaluated by means of serial measurements.

CRP levels, particularly in an ambulatory setting, remain useful for diagnosis of infections and therapeutic monitoring due to their good availability and low costs. However, on intensive care wards, measurement of IL-6 and PCT, compared to CRP, provide better diagnostic value for early diagnosis of sepsis and presence of bacterial infection. Table 1 summarizes the suitability of PCT, IL-6 and CRP for diagnosis and monitoring of infections and sepsis.

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