Procalcitonin and Pneumonia: Is it a Useful Marker?

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An ideal biomarker for pneumonia should allow an early diagnosis and differential diagnosis from noninfectious conditions and should inform about the course and prognosis of the disease. Procalcitonin (PCT) covers these features better as compared to more commonly used biomarkers like C-reactive protein or leukocyte count. PCT complements and improves the assessment of pneumonia based on careful patient history, dedicated physical examination, and appropriate cultures. Importantly, a PCT-based therapeutic strategy can safely and markedly reduce antibiotic courses in community-acquired pneumonia. However, as is the cast with all diagnostic surrogate markers, PCT can be increased in noninfectious conditions and may remain low in bacterial infections, especially localized infections. This stresses the importance of follow-up measurements, because PCT levels in these patients often show a gradual increase during follow-up. Although PCT is better than more common biomarkers for the prognosis of pneumonia and to predict survival and outcome, novel biomarkers show an even better prognostic accuracy.

Introduction

Procalcitonin (PCT) is a precursor peptide of the hormone calcitonin (CT) [1]. After translation from CT messenger RNA (mRNA), PCT is cleaved enzymatically into smaller peptides, finally yielding the 32 amino acid mature CT [2]. Most CT precursor peptides including PCT are found in the serum of healthy persons.

Originally, mature CT was thought to be a hormone exclusively of thyroidal C-cell origin that played an important role in skeletal homeostasis [1]. However, provided that thyroid hormone is replaced, thyroidectomy in humans has no important pathologic consequences: calcium homeostasis remains intact, and bone density is not decreased [3,4]. The presence of the parathyroid gland and other evolutionary changes in tetrapods suggest that the function of the mature CT hormone in humans is no longer essential [5].

Conversely, a cytokine-like role in the host defense is likely. Accordingly, in microbial infections and various forms of inflammation, circulating levels of several CT precursors, including PCT but not mature CT, increase up to several-thousand–fold. This increase and especially the course correlate with mortality and the severity of the condition [6–9].

In the absence of infection, the extrathyroidal transcription of the CALC-I gene is suppressed and restricted to a selective expression in neuroendocrine cells found mainly in the thyroid and lung. In these neuroendocrine cells, the mature hormone is processed and stored in secretory granules (Fig. 1) [10,11].

A microbial infection induces an ubiquitous increase of CALC-I gene expression and a constitutive release of PCT from all parenchymal tissues and differentiated cell types throughout the body [12]. The transcriptional expression of CT-mRNA is more uniformly upregulated in sepsis than are the mRNAs of the classical cytokines (eg, tumor necrosis factor–α and interleukin [IL]-6) [12]. Parenchymal cells (including liver, kidney, adipocytes, and muscle) provide the largest tissue mass and principal source of circulating PCT in sepsis and infections [11]. Thus, CALC gene products are a prototype of hormokine mediators and can follow either a classical hormonal expression in neuroendocrine cells or a cytokine-like ubiquitous expression pathway in various cell types [12]. The inflammatory release of hormokines can be induced either directly via microbial toxins (eg, endotoxin) or indirectly via a humoral or cell-mediated host response (eg, IL-1β, tumor necrosis factor–α, IL-6). The induction can be attenuated by cytokines also released during a viral infection (eg, interferon-γ), which may be the reason for the less pronounced increase of PCT in viral infections.

For the diagnosis of infections, the diagnostic accuracy of PCT and its optimum cut-offs are completely dependent on the use of a sensitive assay in a predefined clinical setting. Ideally, an ultrasensitive assay should reliably measure circulating concentrations of PCT in all

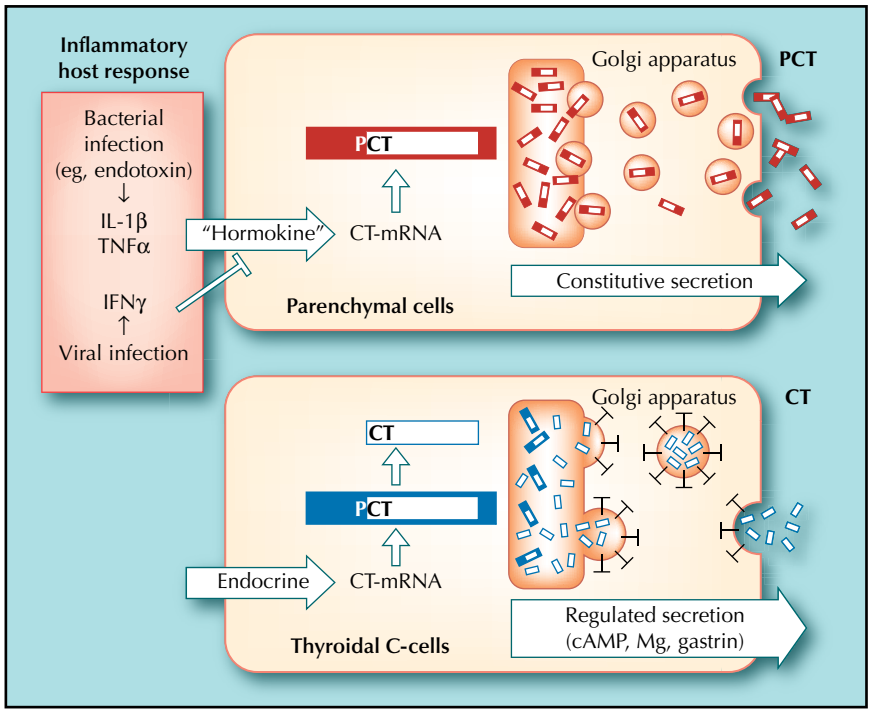

Figure 1. Schematic diagram of CALC I expression in adipocytes and thyroidal C-cells. In the classic neuroendocrine paradigm, the expression of CT-mRNA is restricted to neuroendocrine cells, mainly C cells of the thyroid. Initially, the 116-amino acid prohormone PCT is synthesized and subsequently processed to the considerably smaller mature CT. In sepsis and inflammation, proinflammatory mediators induce CT-mRNA. In contrast to thyroidal cells, parenchymal cells (eg, liver, kidney, adipocytes, and muscle) lack secretory granules. Hence, unprocessed ProCT is released in a nonregulated, constitutive manner. In the serum of septic patients, it is a peptide of only 114 amino acids, instead of 116 amino acids, lacking the N-terminal dipeptide alanine-proline. cAMP—cyclic adenoside monophosphate; CT—calcitonin; IFN—interferon; IL—interleukin; Mg—magnesium; mRNA—messenger RNA; PCT—procalcitonin; TNF—tumor necrosis factor; (*Adapted from* Muller et al. [12]).

healthy individuals. Such assays are currently available for research purposes (PCT-sensitive LIA® [BRAHMS, Hennigsdorf, Germany] and N-ProCT^{KLB}) and should be widely available for clinicians in the near future. A rapid assay assures that results can be timely enough to be incorporated into clinical decision making.

The commercially available Kryptor® PCT assay (BRAHMS) takes advantage of a time-resolved amplified cryptate emission (TRACE) technology. It is based on a sheep polyclonal anti-CT antibody and a monoclonal antikatacalcin antibody, which bind to the CT and katacalcin sequence of CT precursor molecules. The assay has a functional assay sensitivity of 0.06 µg/L (ie, three- to 10-fold above normal mean values) [13]. Assay time is 19 minutes, and in clinical routine, results can be obtained within 1 hour using 20 to 50 µL of plasma or serum. Another commercially available two-site assay (LUMItest® PCT, BRAHMS), measures both PCT and the conjoined CT:calcitonin-carboxypeptide I (CCP I) by means of a luminometer. This assay is useful to detect markedly elevated PCT levels in severe, systemic bacterial infections (ie, sepsis). However, this manual assay has the disadvantage of a relative insensitivity, with an accurate detection limit of approximately 0.3 to 0.5 µg/L [7,13]. Thus, the LUMItest® assay is not sensitive enough to detect mildly or moderately elevated PCT levels, which limits its diagnostic use in conditions other than overt sepsis. A colorimetric, "quick" bedside test, PCT®-Q (BRAHMS), has the advantage of rapid determination of circulating CT precursor levels in 30 minutes. Unfortunately, the assay is only semiquantitative and is not sensitive enough to detect moderately elevated ProCT levels.

Procalcitonin as Diagnostic Marker for Bacterial Pneumonia

A variety of studies and reviews have shown the superior diagnostic accuracy of PCT as compared to other parameters for the diagnosis of sepsis, independent of the origin of infection [9,14••,15]. Although the increase of other inflammatory markers such as C-reactive protein (CRP) is attenuated by immunosuppressive medication (namely steroids), the diagnostic accuracy of PCT remains unaffected [16]. In addition, PCT seems to have an advantage over CRP because of its earlier increase when infection occurs and better negative predictive value, which has been shown in children with fever of unknown origin [17] or adults in the intensive care unit (ICU) with sepsis [14••].

The most frequent source of systemic infections is the lung [9]. Lower respiratory tract infections (LRTIs) (ie, acute bronchitis, acute exacerbations of chronic obstructive lung disease or asthma, and pneumonia) account for almost 10% of the worldwide burden of morbidity and mortality [18]. As much as 75% of all antibiotic doses are prescribed for acute respiratory tract infections, in spite of their predominantly viral etiology [18]. This excessive use of antibiotics is the main cause of the spread of antibiotic-resistant bacteria [19]. Thus, decreasing the excess use of antibiotics is essential to combat the increase of antibiotic-resistant microorganisms [20]. A reduction of antibiotic use results in fewer side effects, lower costs, and in the long-term, decreased drug resistance [21].

In this context, we conceived and validated a PCT-guided diagnosis and antibiotic stewardship using cut-off ranges in the continuum of LRTIs. In four intervention trials enrolling more than 1200 patients, the success of the intervention was measured by clinical outcomes, assuming

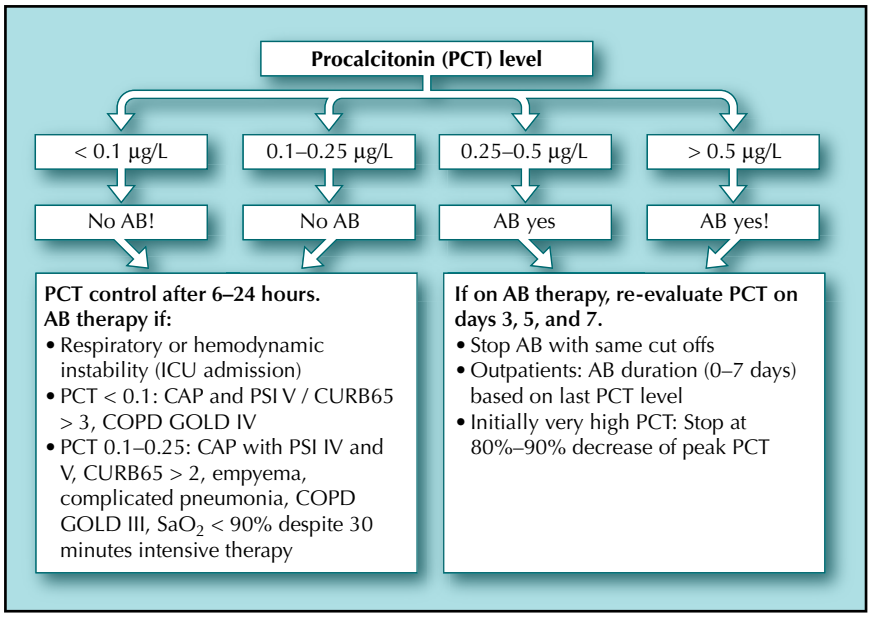

Figure 2. Procalcitonin-guided antibiotic stewardship. Procalcitonin-guided antibiotic therapy was successfully validated in more than 1200 patients with lower respiratory tract infections in the emergency department, primary care, and hospital settings. The following cut-off ranges are proposed for antibiotic stewardship. AB—antibiotics; CAP—community-acquired pneumonia; COPD—chronic obstructive pulmonary disease; CURB65—confusion, urea nitrogen, respiratory rate, blood pressure, 65 years of age and older; GOLD—global initiative for chronic obstructive lung disease; ICU—intensive care unit; PCT—procalcitonin; PSI—pneumonia severity index; SaO_2—oxygen saturation of arterial blood.

that if the patient recovered without antibiotics, then there was no serious bacterial illness. This circumvented the problem of the nonexistent diagnostic gold standard based on traditional criteria (eg, clinical signs, CRP, leukocytosis, culture result). We compared the routine use of antimicrobial therapy versus PCT-guided antimicrobial treatment for LRTI. In the PCT group, the physician was advised to follow the antibiotic treatment algorithm based on the PCT value and the likelihood for bacterial disease (Fig. 2) [9,22–24].

Thereby, a PCT level less than 0.1 µg/L suggests the absence of bacterial infection, and the initiation or continuation of antibiotics should be strongly discouraged. Antibiotic therapy can be considered in critically ill patients; that is, in community-acquired pneumonia (CAP) patients, those with pneumonia severity index (PSI) class V or those with a CURB-65 (ie, confusion, urea nitrogen, respiratory rate, blood pressure, 65 years of age and older) score greater than three points, chronic obstructive pulmonary disease (COPD) patients, and those with a GOLD (ie, global initiative for chronic obstructive lung disease) IV. If antibiotics are given, an early discontinuation of antibiotic therapy after 1 to 3 days should be endorsed if PCT levels checked daily remain less than 0.1 µg/L.

A PCT level between 0.1 and 0.25 µg/L indicates that bacterial infection is unlikely, and the initiation or continuation of antibiotics should be discouraged. Antibiotic therapy can be considered in high-risk patients (ie, PSI IV or CURB-65 > 2 in CAP patients; GOLD III or an arterial oxygen saturation [SaO_2] < 90% after 30 minutes therapy on the emergency unit in COPD patients), necrotizing CAP (*Staphylococcus aureus*, *Klebsiella pneumoniae*, anaerobics), critically ill patients suffering from *Mycoplasma pneumoniae*, empyema, and abscesses.

A PCT level between 0.26 and 0.5 µg/L indicates a possible bacterial infection, and the initiation or continuation of antibiotic therapy should be encouraged.

A PCT level greater than 0.5 µg/L strongly suggests the presence of bacterial infection and antibiotic treatment, and continuation should be strongly encouraged.

The same cut-offs can be used for patients pretreated with antibiotics (ie, treated with one or more doses of antibiotics prior to admission to the emergency department).

In hospitalized patients, PCT levels should be reassessed on days 3, 5, and 7 in patients with ongoing antibiotic therapy and in cases of worsening or delayed recovery of signs and symptoms. Antibiotics should be discontinued using the PCT cut-offs defined above. In all patients with a high-peak PCT value (eg, > 1 µg/L), discontinuation of antibiotics can already be encouraged if levels decrease below 80% to 90% of the initial value (eg, stop at 1 µg/L, instead of 0.25 µg/L if peak was 10 µg/L).

Persistently elevated PCT levels may indicate a complicated course, but the possibility of falsely high PCT levels should be considered [25•]. Conversely, it should also be considered that PCT levels may remain relatively low in localized infections (eg, empyema, abscess) [25•]. Consequently, the PCT algorithm can be overruled in patients with immediately life-threatening disease (eg, severest comorbidity, emerging ICU need during the initial follow-up, hemodynamic or respiratory instability, and positive antigen test for legionellosis). If the algorithm is overruled and antibiotics are given, an early discontinuation of antibiotic therapy after 3, 5, or 7 days can be more or less endorsed, if PCT levels, checked on day 3, 5, and 7 remain less than 0.1 µg/L or less than 0.25 µg/L, respectively.

Procalcitonin and Antibiotic Stewardship: What is the Evidence?

In the first PCT in Respiratory Tract Infections (ProRESP) Study, we assessed the capability of the sensitive PCT assay (Kryptor® PCT) to identify bacterial LRTIs requiring antimicrobial treatment [26••]. The clinical and laboratory outcome after a mean of 13 ± 5.4 days was similar in both groups. In the PCT group, the percentage of patients with LRTI who received antibiotic therapy was reduced by 46.6%, compared with the standard group ($P < 0.001$). Antibiotic use could be significantly reduced in all diagnostic subgroups, but most strikingly in acute bronchitis and acute exacerbations of COPD.

In patients with CAP, PCT levels were almost always high. Pneumonia is defined as inflammation of the pulmonary parenchyma, which is often caused by a bacterial agent, mirrored in markedly elevated PCT levels. In CAP, antimicrobial therapy must be promptly initiated, because a delay in treatment is associated with increased mortality. Thus, the primary value of PCT in CAP was not to reduce antibiotics, but to facilitate the differential diagnosis of new or progressing infiltrates. Accordingly, PCT guidance could markedly lower the number of antibiotic courses in patients with infiltrates on chest x-ray unrelated to pneumonia.

Importantly, the optimal duration of antimicrobial therapy in CAP is largely unknown [27]. Most likely, it varies from patient to patient and is dependent on, among other things, the severity of the disease, the fitness of the host response, and the underlying microorganism. Current guidelines recommend antibiotic courses of 7 to 14 days, depending on illness severity and type of pathogen [28]. However, adherence to guidelines is variable [29], and physicians tend to treat longer, especially in elderly patients with comorbidities and patients with severe CAP [26••]. Duration of antibiotic therapy can be guided by clinical signs such as defervescence, decrease of sputum production and coughing, or improvement of general condition. However, the interpretation of the clinical response lacks standardization and validation and is prone to interobserver variability [30].

The dynamics of PCT levels have prognostic implications, as persistently elevated levels are associated with adverse outcomes [31]. Conversely, decreasing PCT levels suggest a favorable outcome, usually showing a log-linear drop-off and a half-life of 20 to 24 hours [1]. Therefore, in the randomized intervention trial, PCT in CAP (ProCAP), we assessed the capability of PCT-guidance to shorten antibiotic duration in patients with all severity levels of CAP admitted to the emergency department. We demonstrated in more than 300 patients with CAP that PCT guidance allows a safe and marked reduction in the duration of antibiotic treatment from a median of 12 to 5 days with a similar outcome after a clinical follow-up of disease status after 6 weeks. Importantly, measures of clinical and laboratory outcome were similar in both groups [32••]. Thus, PCT appears to be a more reliable measure for individual tailoring and early discontinuation of antibiotic therapy compared to routinely used clinical and laboratory parameters. Only in the PCT group was duration of antibiotic courses adapted to the severity of CAP. The presence of fever is an important clinical sign indicating infection. However, defervescence is of limited value to stop antibiotic therapy in view of the up to 40% of patients with CAP who present without fever. Similarly, in over 70% of patients with CAP of presumed bacterial origin, the causative microbe cannot be identified [26••,33]. Therefore, culture results are not considered central to the clinical care of this infection. This wide ambiguity of clinical symptoms and the high rate of negative culture results could explain the reluctance to stop antibiotic therapy early in the control group. Conversely, especially if bacteremic, CAP is associated with adverse outcomes, and thus, longer antibiotic courses are recommended [34,35]. Accordingly, in the PCT group antibiotic therapy was longer in bacteremic patients with a median duration of more than 10 days.

In bacterial CAP, delayed initiation of antibiotic therapy can be associated with increased mortality. Therefore, in the emergency management of suspected CAP, antibiotic therapy is rapidly initiated in all patients. The presence of nonbacterial diseases is suspected usually only after failure of antibiotic therapy, with the ensuing risks related to untreated, potentially life-threatening nonbacterial disease [36]. In self-limiting viral infections, cure of CAP under antibiotic therapy may be falsely considered as proof of bacterial etiology. In the PCT group, antibiotics were withheld from 15% of the patients with suspected CAP based on low PCT levels, confirming previous findings [26••]. The uneventful course strongly argues against the presence of a clinically relevant bacterial infection in these patients. If a patient shows an infiltrate on chest radiograph in the presence of acute respiratory symptoms and repetitively low PCT levels, clinicians should consider watchful waiting or early discontinuation of antibiotic therapy and actively seek an alternative diagnosis to bacterial pneumonia, including viral pneumonia, pulmonary embolism, malignancy, cryptogenic organizing pneumonia, and congestive heart failure, among others [37]. Conversely, in patients with diagnostic ambiguities, PCT levels greater than 0.25 μg/L to greater than 0.5 μg/L support the clinician in the diagnosis of CAP. In summary, in this study including patients with CAP, PCT was a useful marker for the diagnosis and differential diagnosis from noninfectious infiltrates and viral infections and to guide the duration of antibiotics.

Evidence from Other Studies?

In children admitted with pneumonia, PCT levels had a higher sensitivity and specificity to differentiate bacterial from viral causes of pneumonia than CRP, IL-6, or leuko-

cyte count [38]. Ventilator-associated pneumonia (VAP) is the most frequent nosocomially acquired infection in patients on mechanical ventilation [39]. Bacteriologic cultures including endotracheal aspirates are helpful in the diagnosis of VAP; however, complete results often are not available within 24 to 48 hours after the sample has been taken. Recently, PCT has been used as a complementary diagnostic marker for VAP [40]. It is also a useful marker for diagnosing VAP in patients with an already triggered acute-phase response after successful cardiopulmonary resuscitation, where PCT levels were elevated a median of 2 days earlier than the clinical diagnosis of VAP [41]. However, other studies reported a poor sensitivity for PCT in VAP [42,43••]. The problem is that any observational study investigating the diagnostic accuracy of a given marker is biased by the choice of gold standard. This gold standard does not exist in infections, and thus, all studies are prone to a potential bias.

For example, soluble triggering receptor expressed on myeloid cells (sTREM-1) has been put forward for diagnosis and outcome prediction in patients with sepsis, namely due to CAP and VAP [44]. Analyzing circulating levels of sTREM-1 in our asserved samples from the ProCAP study revealed unexpected inaccuracies of this marker for the routine use of CAP [45]. Circulating sTREM-1 levels were not helpful for the assessment of etiology and severity in patients with CAP or in predicting outcome of the disease. We found no significant correlation between sTREM-1 levels, independent if assessed with the use of immunoblot technique or enzyme-linked immunosorbent assay using several antibodies (from R&D Systems, Minneapolis, MN, and others), before and after ultracentrifugation, in plasma or serum, respectively. Similarly, sTREM-1 concentrations did not correlate with other markers of infection: CRP (r = 0.03, P = not significant), PCT (r = -0.03, P = not significant) and leukocyte count (r = 0.03, P = not significant). Conversely, measurement of the local production of sTREM-1 in bronchoalveolar fluid might provide more reliable results [46]. This, however, is not a cost-efficient approach in the routine care of patients with CAP.

Interventional studies, in which the antimicrobial therapy is guided by PCT and in which the gold standard is the outcome, have the potential to resolve this dilemma. No marker other than PCT has been rigorously assessed in intervention studies for its capability to be used safely for antibiotic stewardship, the ultimate proof for its diagnostic accuracy. In the context of VAP, intervention studies are still lacking, including for PCT [47]. The time has arrived to move beyond the observational reporting of "promising" biomarkers [48]. Specific cutoff ranges must be proposed and intervention studies conducted. Only this will open our eyes and reveal if biomarkers can really help us in the routine care of patients with pneumonia, LRTIs, and ultimately sites of infection other than the lung.

Procalcitonin as Prognostic Marker in CAP?

Another pivotal aspect in CAP is to be able to predict its prognosis and estimate its severity for guiding therapeutic options such as the need for hospital or intensive care admission, suitability for discharge, and choice and route of antimicrobial agents. PSI is a widely accepted and validated severity scoring system that assesses the risk of mortality for pneumonia patients in a two-step algorithm [49]. However, its complexity is high, jeopardizing its dissemination and implementation, especially in everyday practice. Therefore, the CURB-65 score has been proposed as a simpler alternative [50]. Additionally, various easy-to-determine surrogate biomarkers have been proposed to predict disease severity in CAP patients, thereby aiming to complement PSI [51–53]. The prognostic value of PCT in CAP and VAP patients has therefore been investigated in several studies.

Boussekey et al. [54] showed that the kinetics of PCT when increasing from day 1 to day 3 in severe CAP indicated a poor prognosis. Conversely, a PCT level less than 0.95 μg/L on day 3 in intubated patients was associated with a favorable outcome [54]. Similarly, higher PCT concentrations were associated with the development of complications and with death [52]. The kinetics of PCT proved also to be a useful prognostic marker in patients with VAP [43••,55].

In our study, PCT showed better prognostic accuracy compared to routinely measured parameters like CRP or leukocyte count and has therefore been proposed as a marker of disease severity [32••,52,56]. However, a wide overlap existed in PCT levels between different severities of CAP and only a small difference in PCT levels between survivors and nonsurvivors of CAP. Based on these data, PCT seems to be rather a reliable diagnostic marker to guide decisions on antibiotic therapy and not an ideal prognostic tool [25•,32••]. However, the prognostic accuracy of PCT can be markedly improved considering the course of PCT [57]. Jensen et al. [57] analyzed 3642 PCT measurements in 472 critically ill patients. PCT and especially the PCT increase within 1 day was an independent predictor of 90-day all-cause mortality in a multivariate Cox regression analysis model. The adjusted hazard ratio for the PCT increase for 1 day was 1.8 (95% CI, 1.3–2.7) and the relative risk for mortality in the ICU for patients with an increasing PCT was, after 1 day increase, 1.8 (95% CI, 1.4–2.4), after 2 days increase, 2.2 (95% CI, 1.6–3), and after 3 days increase, 2.8 (95% CI, 2–3.8). Thus, a PCT increase during the course of disease was an independent predictor of all-cause mortality in a 90-day follow-up period after ICU admission. Levels or increases in CRP and leukocyte count did not seem to predict mortality. Interestingly, other recently evaluated hormone levels show better prognostic accuracy to predict survival and outcome in patients with CAP as compared to PCT [58–60].

Procalcitonin and Pneumonia: Some Words of Caution

The likelihood for bacterial infections increases with increasing PCT levels. Therefore, we propagate the use of cut-off ranges for the diagnosis of bacterial infections and antibiotic stewardship in several intervention trials. It cannot be overemphasized that the diagnostic accuracy of PCT and its optimal cut-offs are completely dependent on the use of a sensitive assay in an appropriate clinical setting with a pretest probability for the presence of a specific infection. PCT is never a substitute for a careful history and physical examination. A clinician should resist the temptation to rely solely on the result of a laboratory test rather than a demanding clinical examination.

As is the case for all diagnostic tests, a PCT level must always be evaluated and re-evaluated during follow-up, with proper regard to the clinical context. Importantly, circulating PCT levels can be increased in noninfectious conditions, such as severe mechanical or surgical trauma, chemical pneumonitis, severe burns, or heat strokes [25•] and may remain relatively low even in sepsis induced by bacterial infections [22,24,61]. Falsely low PCT levels are typically seen during the early course or localized state of an infection and must be considered in patients with suspected complications of CAP (ie, empyema). PCT levels in these patients often show a gradual increase during follow-up measurements after 6 to 24 hours and thereby point to an underlying bacterial disease. Again, this stresses the importance of follow-up measurements.

Conclusions

An ideal marker for pneumonia should allow an early diagnosis and a differential diagnosis from noninfectious or viral conditions, and it should inform about the course and prognosis of the disease. PCT covers these features better than other markers, namely CRP, leukocyte count, and proinflammatory cytokines [14••]. PCT has emerged as a reliable diagnostic marker of pneumonia. A PCT-based therapeutic strategy can reduce antibiotic usage, mainly by reducing the duration of antibiotic courses, by using a new rapid and sensitive assay. However, PCT should not be used uncontrolled as a substitute for a careful clinical assessment. Especially, falsely low PCT levels must be considered in patients with localized infections and in the context of pneumonia especially in patients with empyema.

The prognostic accuracy of PCT proved to be better than routinely available parameters. However, other biomarkers, namely proadrenomedullin and natriuretic peptides, are even more promising in this respect. Therefore, PCT should be considered a diagnostic parameter able to reduce and guide antibiotic use, whereas novel biomarkers might guide prognostic decision making, improve the allocation of healthcare resources, and reduce hospitalization costs.

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