



Procalcitonin as a Diagnostic, Therapeutic, and Prognostic Tool: a Critical Review

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Abstract

Purpose of review The target of this review is to highlight the current evidence about the utility of procalcitonin (PCT) in different clinical conditions, such as sepsis, respiratory tract infections, urinary tract infections, and bacteremias. The authors aim to discuss the potential benefits and limitations of this biomarker and propose how to safely individualize antibiotic treatment in clinical practice.

Recent findings Many studies have demonstrated that PCT measurements increase within 6–12 h after bacterial invasion and correlate with disease severity and outcomes of patients with infection. Consequently, they can detect the presence and monitor the status of the bacterial infection, as an objectively and quickly available marker.

Summary PCT-guided algorithms have positive effects in reducing antimicrobial use and mortality, especially in sepsis and respiratory tract infections. However, the adherence to PCT-guided strategies is variable and more studies are needed to validate its regular clinical use on other frequent sites of infections (e.g., skin/soft tissues, bone, CNS) and on specific populations such as immunocompromised patients, since it can be truly recognized as a tool able to reduce antibiotic exposure and costs, improving quality of medical assistance safely.

Introduction

Early recognition and initiation of appropriate antibiotic treatment in the treatment of bacterial infections are knowingly associated with improved clinical outcomes in sepsis [1–3]. The current guidelines recommend empirical broad-spectrum therapy within 1 h of diagnosis for both sepsis and septic shock [4]. Although this recommendation encourages clinicians to adopt an aggressive strategy, recognition of such infections at bedside remains challenging. For instance, while missed diagnoses of sepsis culminate in tragic outcomes, less than 60% of patients admitted to intensive care units (ICUs) with a suspected diagnosis of sepsis have a definitive confirmation of it [5].

Inadequate diagnosis of infection and administration of antibiotics have actively contributed to increased emergence of multidrug-resistant bacteria, elevated healthcare costs, and drug-related adverse events, such as *Clostridium difficile* infection, hepatitis, acute kidney injury, and severe rashes [6–9]. Therefore, more effective efforts are needed to reduce unnecessary and prolonged use of antibiotics worldwide [10]. Given that clinical symptoms for monitoring patients with infection can be ambiguous and clinical signs such as the systemic inflammatory response syndrome (SIRS) criteria lack specificity [11], the use of additional blood biomarkers reflecting specific physiological pathways has been proposed [12–14].

While serum lactic acid is a biomarker commonly used to help guide resuscitation in severe infections [15], procalcitonin (PCT) has also been demonstrated to be useful in the antibiotic stewardship decision, being objectively and quickly available, as well as responsive to the clinical course [16, 17]. PCT is a polypeptide composed of 116 amino acids with the same sequence as the hormone calcitonin, produced by the C cells of the thyroid gland [18]. Calcitonin-related gene is expressed by human epithelial cells in response to bacterial infections via direct stimulation of cytokines, such as interleukins IL-1 β and IL-6 and tumor necrosis factor (TNF). Conversely, unlike

other inflammatory markers, PCT production is blocked by interferon gamma, a cytokine that characterizes the typical immune response to viral infections [19, 20].

Especially for emergency rooms, PCT has a favorable kinetic for employment as clinical marker. Its measurements increase within 6–12 h after bacterial invasion, are highest in patients who have bacteremia, and subsequently decrease once the infection is controlled by the immune system [21, 22] (Fig. 1). More impressive, by mirroring a slower bacterial clearance and a higher virulence of the microorganism, PCT levels also correlate with disease severity and clinical outcome of patients with infection [23]. As result, PCT has emerged as a sensitive biomarker that may be used when discriminating viral and bacterial infections, and therefore helping initiation of antibiotic therapy [24]. After treatment is initiated, rigorous monitoring is also of utmost importance to identify patients with a benign disease course who may consider the withdrawal of antibiotics [25]. PCT synthesis and secretion rapidly fall by about 50% each day during resolution of infection [26••] (Fig. 1), being dynamically able to support more precise discontinuation of antibiotics [26••].

International medical societies and authorities have come to diverse conclusions about PCT-guided antibiotic utilization in suspected infections, ranging from findings of moderate-strength evidence of benefit to recommendations against the routine use [27–30]. In this context, not all of the potential benefits and limitations of PCT have yet been recognized. Thus, this current review aims to highlight the recent evidence about the utility of PCT in clinical decision-making and discuss the potential benefits and limitations of this biomarker, trying to elucidate how to safely individualize antibiotic treatment in different, but frequent conditions, such as sepsis, respiratory tract infections, urinary tract infections (UTIs), and bacteremias.

PCT and sepsis diagnosis

Sepsis remains as one important healthcare problem [31] and it is well known that delays in starting adequate treatment can drastically increase mortality rates [1]. Recently, the diagnosis criteria for sepsis were adapted to increase specificity on recognizing the clinical scenario [31]. However, sepsis diagnosis criteria are still unspecific, and the culture-based methods are insensitive and usually take several hours to provide a preliminary result. Several studies have been

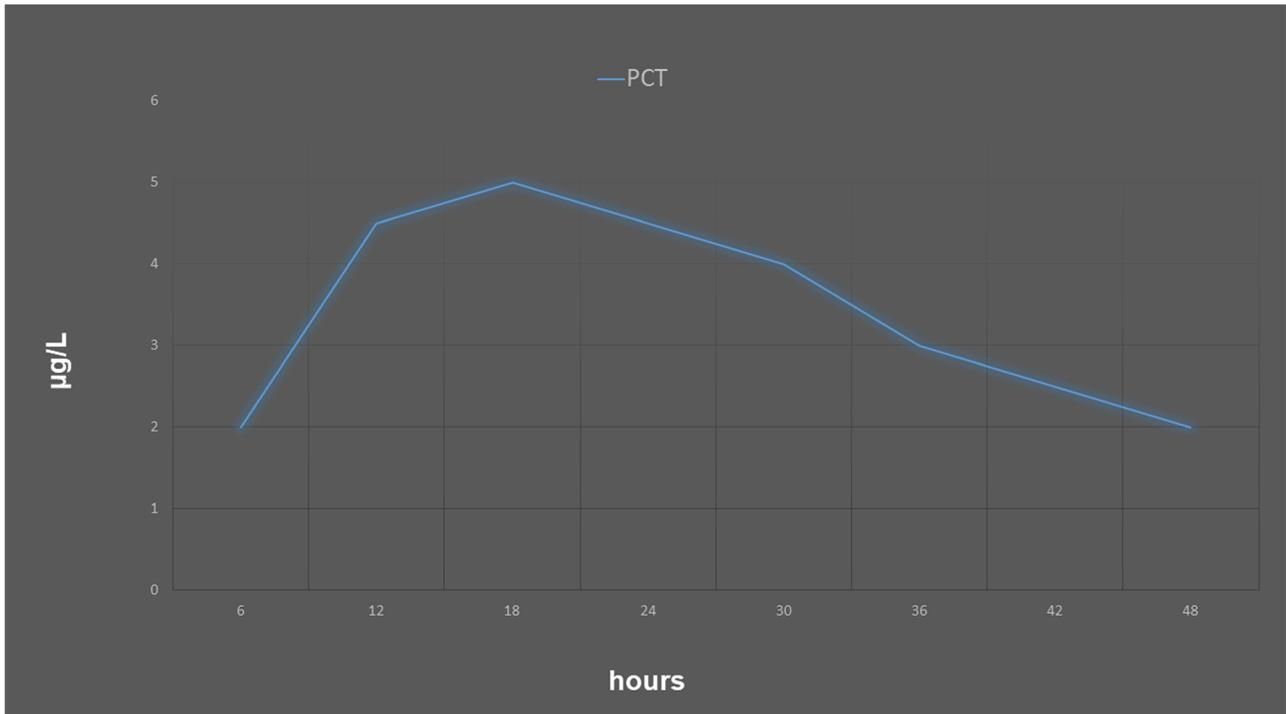


Fig. 1. Kinetics of procalcitonin after bacterial insult and appropriate antibiotic treatment [21, 22, 26••].

published on how PCT can contribute to the diagnosis of sepsis [14, 16, 19, 22, 32, 34], as a fast and relatively low-cost test.

In 2013, a meta-analysis found that PCT could be helpful in differentiating sepsis from SIRS [32]. The review included 30 studies with a total of 3244 patients and showed that PCT could discriminate sepsis from SIRS with an area under the receiver operating characteristic curve of 0.85 (95% CI 0.81–0.88), having similar performance between surgical and clinical patients. Moreover, the mean sensitivity in this bivariate analysis was 0.77 (95% CI 0.72–0.81) and mean specificity 0.79 (95% CI 0.74–0.84) [32].

Another important finding was the PCT cutoff levels [32], suggesting that a value from 1.0 to 2.0 ng/mL could be helpful to segregate patients with sepsis from others with different inflammatory conditions [32]. However, some important limitations of this study should also be mentioned such as the following: (1) the heterogeneity among the observational studies (e.g., methodological quality, clinical spectrum, PCT assays); (2) the fact that all patients included in the final analysis had a microbiologically proven infection, although it was not clear which method was used to confirm it; and (3) PCT cutoff levels used for the final decision were not homogenous among all studies [32].

PCT and sepsis treatment

Early recognition and adequate antibiotic treatment remain the cornerstone of sepsis management [4]. Once antibiotic therapy is initiated, close monitoring

and daily assessments are required, both for prescribed medications and for patient's clinical status. Biomarkers such as PCT can be helpful in those circumstances, evaluating and even guiding an adequate therapy, as showed by previous large clinical trials [33–35]. The largest and more recent study was performed in 15 different hospitals in the Netherlands, enrolling 1475 patients. The authors demonstrated that a PCT-guided therapy was able to reduce 28-day mortality from 25 to 20%, when compared with the standard treatment (95% CI 1.2–9.5, $p = 0.0122$), as well as 1-year mortality from 43 to 36% (95% CI 1.3–13.8, $p = 0.0188$) [35].

Recently, an individual patient data meta-analysis from 11 randomized controlled trials (RCTs) was conducted to assess the safety of using PCT to guide antibiotic decisions on patients with sepsis in the ICU [36••]. The outcomes were mortality, antibiotic use, and length of stay (LOS) [36••]. For mortality, the death rates were 21.1% for the PCT group versus 23.7% for the control group, resulting in a significantly lower mortality in the PCT group (adjusted OR 0.89, 95% CI 0.80 to 0.99; $p = 0.03$) [36••]. The effects in mortality were consistent in patients meeting the Sepsis-3 criteria, and also among different types of infection such as UTI, respiratory, abdominal, skin/soft tissues, and central nervous system [36••]. A reduction in treatment duration for the PCT group was also reported (mean 10.4 ± 9.7 vs 9.3 ± 9.2 days; adjusted regression coefficient -1.19 days, 95% CI -1.73 to -0.66 ; $p < 0.001$), with the exception of patients with abdominal infections [36••]. Finally, there was no reduction in LOS (either hospital or ICU LOS) in the PCT group.

PCT and clinical outcomes in patients with sepsis

Severity of illness assessment in the ICU is a common and necessary practice. For sepsis, some clinical scores allow this type of evaluation, such as the Acute Physiology Age and Chronic Health Evaluation (APACHE), the Simplified Acute Physiology Score (SAPS), and the Sepsis-related Organ Failure Assessment (SOFA) [37–39]. Considering that PCT is fast and objectively measurable, it can also be useful for these assessments [21, 22] and was already studied as a tool for both severity of illness and risk stratification in septic patients.

The majority of the studies regarding this subject already demonstrated that changes in PCT levels during sepsis treatment can be used to monitor efficacy of therapy [40–42] and that its kinetics correlate with outcomes: decreasing values associated with good prognosis and increasing or static values associated with adverse outcomes and increased mortality [43, 44]. Also, it was shown that high PCT levels or its increase over more than 1 day was independent predictors of all-cause mortality in ICU patients [43]. Similarly, a retrospective analysis of data derived from American ICUs showed that PCT change over the first 72 h was a predictor for ICU and in-hospital mortality in septic patients [45].

Recently, a large prospective multicenter observational study that enrolled 858 patients in 13 American ICUs and emergency departments was published [46•]. The authors demonstrated that PCT kinetics over the first 4 days was predictive for survival in patients with sepsis or septic shock [46•]. Mortality rate was almost twice higher for those who did not have a decrease in their PCT level by more than 80% from baseline to day 4, when compared with those who did (20% vs 10%; $p = 0.001$). The prognostic measures of this cutoff showed a

sensitivity of 77% (95% CI, 69–85%) and a negative predictive value of 90% (86–94%) [46•].

PCT and respiratory tract infections

Acute respiratory tract infections are one of the most frequent causes of adult hospitalizations and death worldwide [47] and more than 40% of them are caused by virus. Consequently, they are the most studied clinical situation for the use of PCT as a biomarker, helping differentiate bacterial and viral infections [47–51]. So far, many studies on that population have already demonstrated positive effects of PCT on the reduction of antimicrobial use when compared with antibiotic prescription guideline [48–52]. Based on these findings, the FDA (US Food and Drug Administration) recently approved PCT to guide antibiotic use in acute respiratory infections and sepsis [53].

After the FDA approval, a patient-level meta-analysis considering data from 26 RCTs aiming to assess the safety of PCT-based treatment in patients with acute respiratory infections was published [26••]. In total, 6708 individual patients from 12 countries were included in the study [26••]. Findings included significant reduction in mortality rate within 30 days for the PCT group (9%) compared with the control group (10%) (adjusted OR 0.83 [95% CI 0.70–0.99], $p = 0.037$) [26••]. This effect on mortality was consistent across both clinical settings (ICU and ward), and between types of respiratory infection [26••]. Also, PCT guidance was associated with a 2.4-day reduction in antibiotic exposure (5.7 vs 8.1 days [95% CI – 2.71 to – 2.15], $p < 0.0001$) and a reduction in antibiotic-related side effects (16% vs 22%, adjusted OR 0.68 [95% CI 0.57 to 0.82], $p < 0.0001$) [26••].

Different from these previous results, a recent large multicenter RCT was designed to assess whether a PCT antibiotic prescribing guideline implemented for suspected lower respiratory tract infections would be able to reduce exposure to antibiotics compared with usual care, without increasing the risk of adverse effects [54]. A total of 1656 patients from 14 different hospitals in the USA were enrolled and no significant difference was found between the PCT group and the usual-care group in antibiotic days (mean, 4.2 and 4.3 days, respectively; difference, – 0.05 day [95% CI – 0.6 to 0.5], $p = 0.87$) or the proportion of patients with adverse outcomes (11.7% [96 patients] and 13.1% [109 patients]; difference, – 1.5 percentage points [95% CI – 4.6 to 1.7], $p < 0.001$ for noninferiority) [54]. The authors concluded that the use of an antibiotic prescription guideline did not result in less exposure to antibiotics than the usual care among patients with suspected lower respiratory tract infection [54]. They argue that these findings may be attributed to differences in design, case mix, and setting [54]. For instance, in this trial, the control group had less antibiotics prescribed than usual, probably because of good practice by clinicians after adoption quality-improvement principles, such as extensive education, prompts, and stewardship feedbacks [54].

PCT and urinary tract infections

Urinary tract infections (UTIs) are a common cause of antibiotic prescription and hospitalization [55]. Also, because of its high frequency, unspecific

symptoms, and imprecise rapid diagnostic methods, UTIs can lead to misdiagnosis and unnecessary antimicrobial use [55]. Current guidelines, mostly based on expert opinions, usually recommend long antibiotic courses with no objective endpoint for the treatment of febrile UTIs and pyelonephritis [56, 57].

In a subgroup analysis of the PRORATA trial, it was demonstrated that a PCT-guided strategy can safely reduce antibiotic use in patients with sepsis due to UTIs [33]. In 2015, a Swiss group conducted a factorial randomized controlled open-label trial, enrolling immunocompetent adults with non-catheter-related UTIs into two groups: a PCT-pyuria-based group and usual-care group based on guidelines [58]. The investigators found that overall antibiotic exposure within 30 days was shorter in the PCT-pyuria compared with the control group (median 7.0 [IQR, 5.0–14.0] vs 10.0 [IQR, 7.0–16.0] days, $p = 0.011$) [58]. Although the difference in the antibiotic exposure was significant between the groups, mortality rates of persistent infections, recurrences, and rehospitalizations were similar [57]. Despite the small sample size (125 patients) and the large heterogeneity, this trial still suggests that a PCT-pyuria-guided treatment can decrease antibiotic exposure without increasing risks of recurrence of infection, rehospitalization, and, specially, death [58].

An individual patient data meta-analysis evaluating the effect of PCT-guided antibiotic treatment in patients with positive blood cultures from different primary sites was recently published [59]. The authors described a decreased antibiotic exposure and shorter LOS in the PCT-guided arm for the subgroup of patients with UTIs as primary site of infections, without increased mortality [59]. These findings also corroborate the usefulness of PCT-guided algorithms to manage therapy in patients with UTIs.

PCT and infections with positive blood cultures

Clinicians are still very concerned about prescribing short courses of antibiotics on complicated infections, such as those with bacteremia. This is attributed to the fact that there are limited options of objective treatment endpoints, besides clinical improvement. Trying to tackle this problem, an individual patient-level meta-analysis of 13 trials (including 523 patients with positive blood cultures from different primary site infections) was recently published and compared a PCT-guided antibiotic treatment with a standard antibiotic treatment [59]. The authors found that antibiotic exposure on the PCT-guided group was shorter than that on the control group (12.7 ± 10.9 days vs 15.6 ± 12.8 , adjusted difference -2.86 days [95% CI -4.88 to -0.84], $p = 0.006$), although there was no difference on hospital LOS (mean 22.5 ± 21.9 vs 21.2 ± 24.0 days, adjusted difference -1.48 days [95% CI -5.27 to 2.30], $p = 0.443$) and on ICU LOS (mean 13.3 ± 14.6 vs 13.6 ± 16.4 days, adjusted difference 0.55 days [95% CI -2.48 to 3.57], $p = 0.723$) [59]. More importantly, the meta-analysis showed that a PCT-based antibiotic algorithm does not increase mortality in such infections (16.6% of deaths in the PCT arm vs 20% in the control arm, with an adjusted OR of 0.82 [95% CI 0.57 to 1.16, $p = 0.263$]) [59]. The authors concluded that PCT-

guided antibiotic management in patients with positive bloodstream infections can safely decrease the antibiotic exposure with no evident increase in mortality.

PCT limitations

Although PCT is very useful to identify and monitor the treatment of bacterial infections, it has several limitations [60]. First, false positives can occur, especially in situations of major systemic inflammatory stress, such as severe trauma, surgery, burns, acute pancreatitis, intracranial hemorrhage, and circulatory shock [12, 18, 60]. Also, other situations may modify the PCT kinetics, such as renal failure and use of immunomodulatory agents (T cell antibodies, immunobiological drugs, thyroid and neuroendocrine neoplasms) [60].

Second, the absence of standard PCT cutoff points is still subject of concerns. Usually, the majority of the studies differ on the cutoffs used, the populations studied (e.g., high-risk or low-risk patients; emergency room or ICU; systemic or localized situations), and the objectives (e.g., to start or to discontinue antibiotics) [61]. For example, studies with ED and hospitalized patients are more focused on recommendations of when to start antibiotics, since they usually approach low-risk patients; the cutoff used in these cases is < 0.25 mcg/L to discourage antibiotic prescription and < 0.1 mcg/L to strongly discourage antibiotic usage. On the other hand, studies with ICU patients are more focused on when to stop antibiotics after empirical therapy, and the cutoff used in high-risk patients is < 0.5 mcg/L to recommend discontinuation of antibiotics, and < 0.25 mcg/dL to strongly recommend antibiotic discontinuation.

Third, adherence of PCT algorithms protocols is also an obstacle, as the most important trials so far demonstrated it was inconstant and ranged from 44 to 100% [59]. This variation was found to be closely related to the severity of the infection, with higher adherence in less severe cases, and lower in the more severe ones [59]. Fourth, another important issue is the validation of PCT in specific populations such as in immunocompromised hosts. The majority of the studies were performed in immunocompetent patients, which does not allow generalization for such population [36••]. Lastly, there is still a lack of cost-effectiveness analyses in the literature. It is still unknown if PCT-based protocols may decrease the monetary expenses for specific clinical scenarios [36••].

Conclusions

PCT is already approved by the FDA to be used as guide in the treatment of sepsis and respiratory infections [53]. However, more evidence is needed to corroborate its regular clinical use on other frequent infections (e.g., skin/soft tissues, bone, CNS) and on populations other than immunocompetent patients (e.g., neutropenic, HIV, recipients of solid organ and bone marrow transplants), since it can be truly recognized as a tool able to reduce antibiotic exposure, improving quality of medical assistance and with a possible reduction in costs.

Nowadays, we are facing an era of rapidly emerging bacterial resistance to antibiotics and extremely elevated costs regarding healthcare. This scenario yearns for measures aiming to reduce prolonged, unnecessary, and expensive

antibiotic treatments, for both hospitalized and non-hospitalized patients. In order to develop such politics, efforts from healthcare professionals (specially physicians), patients, and the pharmaceutical industry are needed. Here, we reviewed some evidence showing that although PCT is still not validated to a considerable number of clinical circumstances, it can play an important role at this scenario.

Compliance with Ethical Standards

Conflict of Interest

Fabrício Torres de Carvalho declares that he has no conflict of interest. Roberto Rabello Filho declares that he has no conflict of interest. Lucas Bulgarelli declares that he has no conflict of interest. Ary Serpa Neto declares that he has no conflict of interest. Rodrigo Octavio Deliberato declares that he has no conflict of interest.

Human and Animal Rights and Informed Consent

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