

Editorial

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Procalcitonin for diagnosing and monitoring bacterial infections: for or against?

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Procalcitonin (PCT), the 116-amino acid precursor of the hormone calcitonin, is normally synthesized and then released in the bloodstream, by the thyroid parafollicular C cells [1, 2]. This conventional pathway of PCT production may be abruptly altered as a consequence of specific inflammatory stimuli, principally mediated by increased concentrations of interleukin 6 (IL-6) or tumor necrosis factor alpha (TNF- α) in turn triggered by lipopolysaccharide, the major component of the external membrane of Gram-negative bacteria [3]. In this circumstance, a sustained transcription of the virtually ubiquitous calcitonin *CALC-1* gene occurs in many extra-thyroid tissues (e.g. liver, kidney, gut, lung and leukocytes), thus leading to a remarkable increase (up to 10,000-fold) of the measurable PCT concentration in blood [3].

The original discovery that PCT values may be considerably increased in blood of patients with sepsis and infections was made by Assicot et al. in 1993 [4]. Along these same lines, PCT has then been defined as a prototype of a “hormokine” mediator, which can follow either a traditional hormonal expression pathway or, alternatively, a cytokine-like expression pathway alongside bacterial infections [5]. This “paraphysiologic” pathway of PCT synthesis has since then garnered exceptional interest [6] and is now increasingly used as a surrogate marker for diagnosing many infectious diseases of bacterial origin and for guiding antimicrobial stewardship. The first evidence on the clinical usefulness of PCT for diagnosis, risk stratification and antimicrobial stewardship has emerged from studies in patients with lower respiratory tract infections, namely in those with community acquired pneumonia (CAP) [7]. These potential clinical applications were then supported by a respectable number of original studies and meta-analyses [8], which are now almost consistent to emphasize the cost-effectiveness of using this biomarker in patients with severe bacterial infections. Three official guidelines have been recently published by the Italian Society of Clinical Biochemistry and Clinical Molecular Biology/Academy of Emergency Medicine and Care [8], by the Society of Critical Care Medicine/European Society

of Intensive Care Medicine [9] and by the Infectious Diseases Society of America (IDSA) Sepsis Task Force [10], which substantially endorsed the use of PCT, not only for diagnosing severe bacterial infections but also for antimicrobial stewardship. The clinical significance of the latter clinical application is strengthened by factual evidence that antimicrobial resistance is now emerging as a public healthcare issue, which could only be counteracted by establishing worldwide policies deploying a more appropriate use of antimicrobial drugs [11]. A recent retrospective study, based on a large US research database and including over 130,000 intensive care unit (ICU) patients, has revealed that the measurement of PCT upon ICU admission was associated with many favorable clinical and economic outcomes [12], including 9% decreased hospital length of stay, 4% reduced ICU length of stay, 8% lower hospital costs and, even more importantly, 4% lower antimicrobial exposure. These results are not unexpected because a previous cost-effectiveness analysis, based on 18 separate studies, concluded that PCT-guided antimicrobial treatment has nearly 90% probability of being cost-effective across many different populations and healthcare settings [13]. The potential efficacy and efficiency of PCT has also been established in patients with localized bacterial infections, suffering from various medical or surgical conditions [14–17].

In this issue of *Clinical Chemistry and Laboratory Medicine*, we publish a series of articles aimed to dispel the doubts about the clinical effectiveness of measuring PCT in patients with bacterial infections.

In the first of these articles, Hey et al. [18] present the results of a meta-analysis of 11 studies evaluating the role of PCT-guided antimicrobial treatment in patients with lower respiratory tract infections. Overall, a statistically significant reduction in antimicrobial therapy could be estimated in PCT-guided cohorts compared to patients undergoing the standard of care, whereas no statistically significant difference could be found in hospital length of stay and all-cause mortality.

In the second article of this series, a group of 14 experts from different medical disciplines (including laboratory medicine) used a modified Delphi approach

for generating expert opinions about PCT-guided antimicrobial therapy [19]. A final consensus was reached that PCT may have clinical value when included within appropriate algorithms for antimicrobial stewardship, purporting that test results should be interpreted in the context of additional clinical and radiologic data, especially in patients with acute respiratory infections. The presentation of many clinical scenarios, in which the use of PCT may have specific features, is indeed the most straightforward aspect of this consensus document.

In an ensuing study, Horváth-Szalai et al. [20] measured PCT, C-reactive protein (CRP), Gc globulin and gelsolin in 46 ICU patients with sepsis, 28 ICU patients without sepsis and 35 outpatients. Notably, the diagnostic performance [area under the curve (AUC)] of PCT measured upon ICU admission was excellent for diagnosing sepsis (AUC, 0.98) and actually outperformed that of CRP (AUC, 0.80), gelsolin (AUC, 0.88) and Gc globulin (AUC, ns). Notably, the clinical usefulness of PCT measurement was also emphasized in the article of Aoki et al. [21], who found that the assessment of serum PCT within 2 days after liver resection efficiently predicted post-operative complications.

Beside the clinical usefulness of PCT in bacterial infections, interesting information also emerged from the article of Giovanella et al. [22], who published an interesting study showing that PCT may be an effective complementary biomarker in patients with medullary thyroid cancer (MTC) and contextually increased calcitonin values due to non-MTC conditions (i.e. heterophilic-antibody-induced hypercalcitoninemia).

Albeit the information published in the available scientific literature seems to ascribe to PCT a trustworthy clinical significance for both diagnosing and monitoring bacterial infections, the reasonable recommendations provided in the consensus document of Bartoletti et al. [19] do not obviate the need of using data of this biomarker in a broader perspective, thus taking into account other medical and radiologic findings, which should help ruling out non-bacterial causes of serum or plasma increase. Like other highly informative laboratory analyses, and cardiac troponins are a paradigmatic example, PCT test results shall not surrogate the clinical judgment but should be integrated within a multifaceted clinical reasoning for achieving better diagnostic performance. By some means, this entails fostering a more generalized process of “physician recalibration”, finalized to reach a better alignment between the information delivered by objective findings, such as PCT test results, and the ensuing clinical decision making (i.e. antibiotic stewardship) [23].

Nevertheless, the current lack of standardization of the many available techniques for measuring PCT remains an unmet target. The current armamentarium of PCT tests entails enzyme-linked, luminometric, chemiluminescent, electrochemiluminescent, fluorescent and turbidimetric immunoassays, the last of which can be adapted for use on a large number of clinical chemistry platforms, thus fostering widespread availability of PCT testing. However, the analytical performance of all these immunoassays is quite heterogeneous, especially regarding the limit of quantitation (LoQ) [24], which is defined as the lowest value at which the measurand can be reliably detected, meeting the predefined goals for bias and imprecision [25]. Although the LoD of the currently available techniques is predicted to have a less important impact for diagnosing sepsis, a high LoQ may actually jeopardize the clinical effectiveness of serial PCT monitoring for purposes of antimicrobial stewardship, especially in non-systemic bacterial infections, because there is a tangible risk that modest but clinically informative PCT changes over time could not be efficiently appreciated. Therefore, high-sensitive assays should be preferably used for obtaining more timely stewardship indications.

The use of molecular biology techniques is another far-reaching and pervasive issue. Although theoretically straightforward, the many molecular assays currently available in the market display different diagnostic performance, on occasion suboptimal not only for diagnosing sepsis and for identifying all the potential responsible bacteria [26], but also for antimicrobial stewardship [27]. Only time will tell us whether molecular biology, which is dubiously more practical than PCT, will become a basic tenet for accurate and timely management of patients with severe bacterial infections.

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