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# The role of procalcitonin outside of the Intensive Care Unit (ICU): a multidisciplinary approach

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**Abstract. – OBJECTIVE: Biochemical markers are commonly used in medicine to guide diagnostic investigation or therapy duration and/or monitor treatment efficacy. Due to the emergence and spread of antimicrobial resistance, markers able to prompt a more rational use of antimicrobial therapy are regarded with the greatest attention. Procalcitonin (PCT) certainly stands out among others, yet its role must be better established especially outside of the critical care area. Data about PCT utilization in non-critical patients, optimal negativity cut-offs as well as a protocol for measurement timing are all lacking.**

**MATERIALS AND METHODS: To address these issues, a focus group was set up to propose and endorse shared statements regarding the most beneficial use of PCT in real life as infection marker for non-critical patients, based on the authors' experience and a review of recent literature.**

**RESULTS: A group of nine experts in the fields of Infectious Diseases, Internal Medicine, Microbiology, Clinical Chemistry, Surgery and Medical Economics participated in the discussion of nine pre-specified statements.**

**CONCLUSIONS: The potential role for PCT in differentiating infectious and non-infectious clinical syndromes and guiding antimicrobial therapy discontinuation was acknowledged. Moreover, a shared measurement protocol and desirable cut-offs for the non-critical area were proposed. Finally, observations were made about a reasonable selection of the patient population to be tested.**

*Key Words:*
Procalcitonin, Biomarkers, Antibiotic therapy, Antimicrobial stewardship, Sepsis.

### Abbreviations

ABSSSI: Acute Bacterial Skin and Skin Structure Infection; AS: Antimicrobial Stewardship; BSI: Bloodstream Infection; (c) IAI: (complicated) Intra-Abdominal Infections; CRP: C-Reactive Protein; ED: Emergency Department; IAP: Intra-Abdominal Pressure; ICU: Intensive Care Unit; PCT: Procalcitonin; SIRS: Systemic Inflammatory Response Syndrome; UTI: Urinary Tract Infections.

## Introduction

Procalcitonin (PCT) is a human protein with a well-studied production process inducible in most human cells by some cytokines, which in turn are produced during inflammation with or without infection. Highest PCT levels have been reported in the case of bacterial infections. The role of PCT in diagnosis, prognosis and treatment of infections was investigated by seminal studies, sometimes reporting conflicting results[1-3]. PCT is also abnormally elevated in sepsis, thus being usually considered a good diagnostic marker of sepsis in critically ill patients. As a diagnostic tool, PCT proved useful in differentiating sepsis from Systemic Inflammatory Response Syndrome (SIRS)[4,5] or infectious from cardiogenic pulmonary syndromes[6-9].

The well-established role of PCT in supporting discontinuation of antibiotic therapy and as a prognostic marker of infection, mostly comes from studies conducted in the critical-care



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field[10-15]. Evidence was also generated in primary care settings[16,17], in Hospital Medicine and in the Emergency Department (ED)[18-22].

Whether the mainstay of PCT utilization, an indication toward antibiotic withdrawal in case of negativity, is applicable outside of the Intensive Care Unit (ICU) remains to be established. Moreover, there is no commonly accepted algorithm for PCT-guided antibiotic therapy outside the ICU. This prompts some considerations on the optimal way to introduce a new clinical paradigm, most of all in high-specialty contexts.

## Materials and Methods

A panel of nine experts in the fields of Infectious Diseases, Internal Medicine, Microbiology, Clinical Chemistry, Surgery and Medical Economics met to discuss nine pre-specified statements. The achieved conclusions are summarized below, and an agreed version of the discussed statements is provided.

### The Clinical Chemist's View

Procalcitonin, as a biomarker, shares the potential of defining health and disease. Since technology became widely available, a range of tests made it easier to stratify patients and analyze their characteristics through multivariate analysis. A risk of so-called "over-parametrization" exists, therefore clinicians should order a test only when they believe it will modify or confirm a clinical decision. On the other hand, clinicians need to receive "meaningful" responses from the laboratory. The laboratory should be involved in the management of complicated clinical cases and data integration should be performed.

### The Microbiologist's view

If laboratory results must be given not as simple numbers but as a real, meaningful response, a clinician's request to the laboratory must be guided by a rationale. In microbiology, rapid tests, which are available for ten years, acted like a real "game changer" and modified the bed-bench relationship. In the last few years, time to diagnosis has become significantly shorter as well as the duration of empirical therapy and the exposure to antibiotics, with a positive impact on health and economic benefit. However, expensive diagnostic techniques require a team approach for virtuous utilization and correct interpretation. The pre-test probability aspect is crucial: the tested population influences the results as much as other aspects related to test execution. These considerations that are relevant to all biomarkers, apply to PCT as well. The implementation of laboratory/diagnostic stewardship to avoid indiscriminate testing is desirable. An important issue for the correct use of PCT is patient selection before testing.

### The Medical Economist's View

When technology is evaluated, especially in public healthcare, three aspects are considered: 1) does it have a market? 2) Is financing with public funds feasible for it? 3) How does it integrate into the current system, and what could be the consequences of such introduction? As to diagnostic tests, efficacy and innovation are specifically considered, measuring for example how the test will improve cure rate, ensure resource sparing (hospital days or treatment costs) and reduce adverse effects resulting from treatment. Economic analysis of these aspects is usually based on cost-benefit (based on the same investment, the most beneficial choice is made) or cost-efficacy models (based on a pre-specified efficacy target, the less expensive choice is made). Further evaluations include how the potential efficacy of new technology will be influenced by other dynamics in the system that could neutralize it. For example, in the case of PCT, a reduction of hospital length-of-stay could be obtained, but if results come out systematically late, or are ignored, the effective length of stay will not change. In order to prevent systematic failure of innovation it is important to assess in advance how a test will become part of a specific setting.

### The Internal Medicine Specialist's View

Modern Internal Medicine is ever more dealing with geriatric patients, with their burden of comorbidities, polytherapy, frailty and a tendency to atypical presentations of clinical conditions, including sepsis. In the clinical management of an elderly patient we suggest considering PCT as an aid to discriminate between infective causes of dyspnea or other common symptoms. Given the possible absence of fever during infections in the elderly, the measurement of PCT, as well as other selected biomarkers, may be justified even in the absence of clear signs of sepsis or SIRS.

### The Infectious Diseases Specialist's View

Several controlled studies showed that integrating the use of the infection biomarker PCT into diagnostic and therapeutic algorithms may not only allow better management of patients

with clinically relevant bacterial infections but also contribute to more effective antimicrobial therapy. The efficacy of this biomarker has been well demonstrated especially for lower respiratory tract infections and critically ill sepsis patients. Furthermore, the monitoring of PCT kinetics during treatment has also proved to be very important in allowing to customize the type and duration of antibiotic therapy with a view to proper implementation of AS, as well as to have an additional prognostic criterion correlating with disease severity. However, PCT is far from being considered an optimal and definitive marker of infection. Its use should be placed in the context of a careful clinical and microbiological assessment of each selected patient. PCT values can be correctly evaluated by the clinician only by considering the likelihood of a bacterial infection, the probable site of infection, the severity of illness and any other pertinent clinical data that should be kept in mind to evaluate the clinical presentation and re-asses it over time.

### The Surgeon's View

PCT dosing proved to be useful in surgery, with a focus on complicated Intra-Abdominal Infections (cIAI) and Acute Bacterial Skin and Skin Structure Infections (ABSSSI) that usually require urgent evaluation and intervention. Clinical evaluation of the surgical site is still key in patient management and surgical revision usually remains the most important intervention. However, since antibiotic therapy plays a relevant role in controlling surgical infections, PCT can conveniently guide it. Seminal published works underlined source control contribution to shorten antibiotic therapy in cIAIs, acute pancreatitis and ABSSSI. Due to its rapid kinetics, PCT is more adequate than CRP. PCT cut-offs still need to be defined in surgery and will probably differ between different anatomic districts. Besides, PCT absolute values, a PCT ratio (t0/t24h ratio) seems to be useful to immediately define the size of PCT increase. A correlation between PCT rise and anastomotic dehiscence was observed, and PCT plus intra-abdominal pressure (IAP) elevation correlate to mortality in cIAIs.

### The Antimicrobial Stewardship Team View

AS is defined as the coordinated interventions designed to optimize the selection of antibiotics, their dosing, duration and route of administration, while limiting the unintended consequences, such as the emergence of bacterial resistance, adverse effects and costs. PCT is a valuable biomarker and its use is included in many AS programs. PCT-guided antibiotic use in patients with sepsis or bacterial infections can allow optimizing treatment duration. In fact, in our clinical practice PCT dosing is more commonly used to shorten antibiotic therapy than as a diagnostic marker of infection. We, also observed the trend towards an association between PCT levels and Gram-negative etiology. If PCT levels are high and blood cultures are positive for fungi, a polymicrobial etiology of bloodstream infection (BSI) cannot be excluded. PCT role in shortening antimicrobial therapy is more valuable for BSI and sepsis compared to pneumonia, since in the latter case antimicrobial therapy is already relatively short (5-7 days). We believe that more studies are needed to guide the interpretation of elevated PCT values in the absence of clinical signs of sepsis. Finally, on the basis of the available evidence and personal experience, we propose a higher cut-off (1 ng/ml rather than 0.5) and acknowledge that the grey area in between the two values is worth further studies.

## Results

The panel agreed on the following statements:

1) PCT dosing is recommended only if sepsis, BSI or pneumonia is suspected. If PCT turns out negative (<1 ng/ml) but clinical suspicion is still high, repeating measurement after a 24-hour interval is recommended in order to identify later elevation (Figure 1).
2) In case of PCT positivity (>1 ng/ml), it is recommended to repeat measurement after a 72-hour interval, to substantiate decision on the duration of antibiotic therapy. In case of PCT negativity (<1 ng/ml) at onset and at 24 hours, a new measurement of PCT is not recommended unless a new suspicion of sepsis, BSI or pneumonia arises during follow-up.
3) Therapy escalation based on increasing PCT values during follow-up without clinical worsening or microbiological data is not recommended.
4) The choice of PCT cut-offs should be based on care setting: we suggest adopting a 1-ng/ml cut-off in middle-intensity settings, such as Hospital Medicine and ED triage.
5) If respiratory signs and symptoms appear at presentation, PCT can help to discriminate

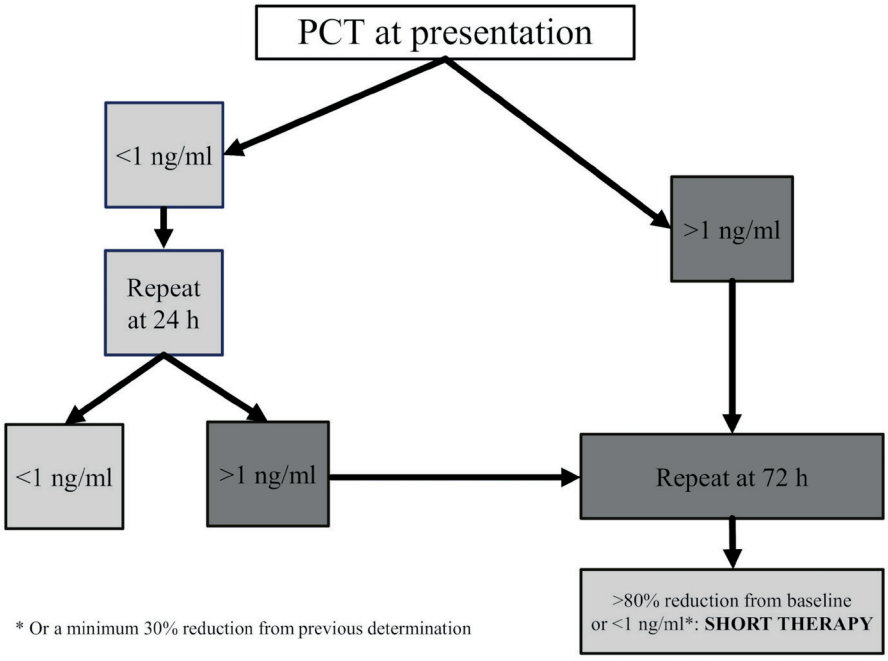


**Figure 1.** Proposed PCT-dosing algorithm for suspected sepsis/BSI/pneumonia outside of the ICU.

between pneumonia, non-infectious lung disease and heart disease.

6) Decision on the collection of blood cultures and on starting an empiric antimicrobial therapy should be based on clinical judgment and not on PCT values.
7) BSI sustained by *Candida* spp. or Gram-positive bacteria are often associated by negative (<1 ng/ml) or moderately positive PCT values compared to Gram-negative etiology. A negative PCT accompanied by a beta-D-glucan >80 pg/ml is predictive of fungal etiology.
8) It is recommended to implement PCT measurement in the context of AS programs to support reducing the duration of antibiotic treatments.
9) Among elderly patients, co-morbidities and anergy can modify clinical presentation. PCT measurement may be valuable as an early marker of BSI, sepsis or pneumonia in this population, although evidence is still scarce.

## Discussion

In this focus group, we collected expert opinions about the role of PCT as a diagnostic and prognostic test, and as a tool for AS.

PCT role has not been well established for all infectious syndromes, pneumonia being well studied in all settings[23]. An agreement about PCT usefulness for shortening antibiotic therapy for pneumonia was generally reached[24-26], despite some conflicting evidence[27,28]. Infections other than pneumonia have been considered, such as urinary tract infections (UTI) [29], infective endocarditis[30], bacterial meningitis[31], febrile neutropenia[32], as well as infections in surgical patients, with intra-abdominal infections (IAI) being well studied[33,34]. Since PCT measurement in other infectious conditions is supported by weaker evidence, or not supported, it should be recommended to limit PCT use to pre-defined, highly suspicious scenarios. The use of PCT in supporting antibiotic discontinuation, without a negative impact on patient outcome, has been mostly demonstrated in ICU settings. Generally established negativity and positivity cut-offs that result from ICU studies seem not to fit all clinical situations. Neither protocols nor cut-offs have been widely accepted and the most frequently quoted protocol derives from the seminal PRORATA trial, thus from ICU field[11]. Differently from the classical cut-off of 0.5 ng/ml, in the author's experience[35] a cut-off of 1 ng/ml can be used to increase test specificity: on such thresholds are based statements 2 and 4. Statement 3 is supported by negative evidence that emerged when testing PCT as guidance to start[36] or escalate[37] antibiotic

therapy, rather than withdraw it. One ongoing European trial[38] will possibly provide more conclusive results. The role of PCT in clinical decisions other than antibiotic discontinuation remains controversial. Evidence is poor, for example, to recommend toward or against blood culture collection based on PCT values[39-45]. Moreover, even if higher levels of PCT are usually detected in Gram-negative infections compared to Gram-positive and fungal infections[35,46,47], data are insufficient to encourage empirical therapy modification based on PCT levels. Combining PCT with other markers, such as beta-D-glucan[48] or specific risk factors seems to be of use to suspect fungaemia[49]. The use of PCT has been investigated as a tool for cost-effective optimization of antimicrobial therapy in hospitals[50]. In line with several international guidelines, which include PCT dosing in protocols of infection management[51-53], or AS programs[54] AS expert are encouraged to promote PCT measurement in their facilities. Trials including elderly patients are missing, and smaller studies produced conflicting results[55,56]. Based on adult population data and the authors' experience, PCT elevation could still be considered as an early marker of bacterial infection.

## Conclusions

Optimal use of PCT in the context of non-ICU wards could improve patient management and save resources. Early diagnosis, early discrimination of etiology in BSI, early discontinuation of antimicrobial treatment are all valuable issues to be taken into account when considering the implementation of PCT use in clinical practice, in the perspective of an AS approach.

### Conflict of Interest

The Authors declare that they have no conflict of interest.

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