Opinion Paper

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Procalcitonin-guided antibiotic therapy: an expert consensus

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Abstract

Background: Procalcitonin (PCT) is a useful biomarker of bacterial infection and its use is associated to reduced duration of antibiotic therapy in the setting of intensive care medicine. To address the need of practical guidance for the use of PCT in various clinical settings, a group of experts was invited to participate at a consensus process with the aims of defining the rationale for appropriate use of PCT and for improving the management of critically ill patients with sepsis.

Methods: A group of 14 experts from anesthesiology and critical care, infectious diseases, internal medicine, pulmonology, clinical microbiology, laboratory medicine, clinical pharmacology and methodology provided expert opinion through a modified Delphi process, after a comprehensive literature review.

Results: The appropriateness of use of PCT in terms of diagnosis, prognosis and antimicrobial stewardship was assessed for different scenarios or settings such us management of infection in the emergency department, regular wards, surgical wards or in the intensive care unit. Similarly, appropriateness and timing of PCT measurement were evaluated. All the process consisted in three Delphi rounds.

Conclusions: PCT use is appropriate in algorithms for antibiotic de-escalation and discontinuation. In this case, reproducible, high sensitive assays should be used. However, initiation or escalation of antibiotic therapy in specific scenarios, including acute respiratory infections, should not be based solely on PCT serum levels. Clinical and radiological findings, evaluation of severity of illness

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and of patient's characteristics should be taken into proper account in order to correctly interpret PCT results.

Keywords: antibiotic therapy; antimicrobial stewardship; expert consensus; procalcitonin.

Introduction

The growing prevalence of antibiotic resistance is a global emergence. It is estimated that, by 2050, 10 million people will die every year due to antimicrobial resistance [1]. The reason of antibiotic crisis relies on several factors, including the antibiotic misuse or overuse. In fact, it is reported that treatment indication, doses or duration of treatment are incorrect in up to 30%–50% of antibiotic prescriptions [2–4]. The over prescription of antibiotic, in turn, may be associated to increased costs, adverse events and prolonged length of hospitalization. On the other hand, early antibiotic prescription may be necessary in patients with sepsis or septic shock [5]. In several studies on critically ill patients, any delay of adequate antibiotic treatment was associated to an increased risk for mortality [6, 7].

Procalcitonin (PCT) is a calcitonin precursor ubiquitously distributed in the human organs and tissues [8]. Several characteristics have conferred to PCT a key role as a biomarker of bacterial sepsis. First, during the acute phase of sepsis, PCT production is commonly upregulated [9]. Second, peak levels of PCT after a bacterial insult are usually achieved very rapidly with values that are correlated with the intensity of the stimulation [10]. Third, PCT has a short half-life, and therefore levels usually drop rapidly after the end of the insult. According with these characteristics, previous studies indicate that PCT is a marker of bacterial infection with good sensitivity and specificity [9, 11, 12]. In addition, use of PCT was associated to lower antibiotic use, being able to rule out bacterial infectious processes or to identify patients eligible to early antibiotic de-escalation or discontinuation [13, 14].

Despite the aforementioned encouraging results, the proper use of PCT should be further addressed in several specific clinical situations. More specifically, the effect of implementation of PCT algorithms in different clinical scenarios to improve antibiotic use and outcomes and to limit cost remains unknown [15]. To address the need of practical guidance for the use of PCT in various clinical settings, a group of experts was invited to participate at a consensus process with the aims of defining the rationale for appropriate use of PCT and for improving the management of critically ill patients with sepsis.

Materials and methods

The consensus was managed by a multidisciplinary team, including experts in anesthesiology and critical care, infectious diseases, internal medicine, pulmonology, clinical microbiology, laboratory medicine, clinical pharmacology and methodology (Table 1). Expert opinion from the board was obtained through a modified Delphi process [16].

Consensus process

The process was conducted on January 2017. The opinion of experts about the appropriateness of use of PCT was assessed in different clinical settings. In addition, the judgment of experts about the role of PCT as a diagnostic test, prognostic marker or as an antimicrobial stewardship tool was assessed as well. It consisted in a series of rounds as follows. During the first round, the experts were invited to share their opinion based on their knowledge and experiences. Thereafter, a free discussion and a comprehensive review of the literature was promoted. During the literature review process, only studies using high sensitive assays (B·R·A·H·M·S· PCT antibodies assays) were included. These assays have shown reproducibility of results and great reliability.

On the first round, two experts, one of infectious disease and the other of clinical pharmacology, developed a list of questions and of possible predefined answers, which had to be submitted to the panel. The questions were directed to assess the appropriateness of use of PCT in different settings, including emergency department (ED), intensive care unit (ICU) and internal medicine ward counting of pulmonology and infectious disease department. The preestablished answers included at first step a dichotomous choice (i.e. yes or no) with a secondary choice that motivated the answer based on expert opinion, relevant clinical trials or both of them. During the second round, the panel of expert answered the questions anonymously without any influence of group's opinions. After a free discussion and reading the answers, a third round was conducted in which the experts reviewed their answers and had the opportunity to change it according with the view of the board's response.

Consensus was defined with a cutoff of agreement ≥80%. According with the agreement reached on indication and level of evidence, the recommendation for use or not use of PCT in different scenarios was classified with three levels of certainty following the National Institute for Health and Clinical Excellence guidelines: (i) "must" and "must not", (ii) "should" and "should not" and (iii) "could" [17].

Table 1: List of all members of the expert board.

Name	Affiliation	Role	Field of expertise
Massimo Antonelli	UOC Anestesia, Rianimazione, Terapia Intensiva e Tossicologia Clinica (UOC) Fondazione Policlicnico Universitario A. Gemelli-Università Cattolica del Sacro Cuore	Expert	Intensive care medicine
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Arturo Chieregato	Neurorianimazione, Ospedale Niguarda Ca' Granda, Milano	Expert	Neurological intensive care medicine
Roberto Fumagalli	Anestesia e rianimazione I, Ospedale Niguarda Ca' Granda, Milano	Expert	Intensive care medicine
Massimo Girardis	Anestesia e Rianimazione I, Dipartimento chirurgia generale e specialità chirurgiche, Azienda Ospedaliero-Universitaria di Modena – Policlinico, Modena	Expert	Intensive care medicine
Federico Pea	Institute of Clinical Pharmacology, Santa Maria della Misericordia University Hospital of Udine, ASUIUD, Udine, Italy; Department of Medicine, University of Udine, Udine, Italy	Facilitator	Clinical pharmacology
Filippo Pieralli	Subintensiva di Medicina, – Azienda Ospedaliero Universitaria Careggi – Firenze	Expert	Internal medicine
Mario Plebani	UO Medicina di Laboratorio, Azienda Ospedale-Università di Padova, Padova	Expert	Laboratory medicine
Gian Maria Rossolini	Dipartimento di Medicina Sperimentale e Clinica, Università di Firenze e SOD Microbiologia e Virologia- Azienda Ospedaliero Universitaria Careggi – Firenze	Expert	Clinical microbiology
Massimo Sartelli	UO Chirurgia Generale, Dipartimento Chirurgia maggiore oncologica, Ospedale di Macerata, Macerata	Expert	Abdominal surgery
Bruno Viaggi	NeuroAnestesia e Rianimazione, Dipartimento di Anestesia, Azienda Ospedaliero Universitaria Careggi – Firenze	Expert	Intensive care medicine Neurological intensive care medicine
Pierluigi Viale	UO Malattie Infettive, Policlinico S.Orsola Malpighi, Bologna	Facilitator	Infectious disease
Claudio Viscoli	Clinica Malattie Infettive, Università di Genova e Ospedale Policlinico San Martino, IRCCS per l'Oncologia	Expert	Infectious disease

Results

The opinion of experts about the appropriateness of use of PCT was assessed in different clinical settings. In addition, the judgment of experts about the role of PCT as a diagnostic test, prognostic marker or an antimicrobial stewardship tool was assessed.

General considerations

- Careful evaluation of clinical and radiological findings, evaluation of severity of illness and of patient's characteristics should be taken into proper account in order to correctly interpret PCT results.
- In patients with diagnosis of infection, PCT should be used to identify patients with poor prognosis. In this case, the trend of serum concentrations over time is more accurate than a single measurement. The usual cutoff for diagnosis of sepsis (>0.5 ng/mL) is inaccurate and should be tailored for specific setting, site of infection and severity of underlying disease.

Emergency department [18–24]

- According with experts' opinion, in the setting of ED and/or emergency room, PCT should be used to differentiate bacterial infections from non-bacterial ones or from non-infectious processes. Thus, PCT should be included among the available biochemical laboratory tests that may be required in the urgency/emergency settings.

Internal medicine, pulmonology and infectious disease departments [14, 21, 25–31]

- In non-critically ill patients admitted in general wards, such us internal medicine department or

infectious disease department, PCT should be used in the diagnosis of bacterial infections that may need prompt antibiotic treatment.
- In patients with community-acquired pneumonia, not fulfilling criteria for sepsis or septic shock PCT could be used to support starting of antibiotic treatment.
- In patients with acute exacerbation of chronic obstructive pulmonary disease (COPD), PCT could be useful in the diagnosis of bacterial superinfection.
- In patients with community-acquired pneumonia, not fulfilling criteria for sepsis or septic shock PCT could be used as a prognostic marker of worse outcome.
- In non-critically ill patients, a PCT increase after 48 h of antibiotic therapy must not justify treatment escalation.
- In this setting, PCT level should be monitored over time to guide treatment discontinuation.

ICU or critically ill patients [11–13, 29, 32, 33]

- In critical care medicine, PCT should be used to identify patients who need prompt antibiotic treatment.
- In addition, PCT should be used to identify patients with poor prognosis. In this latter case, PCT serum level trend must be analyzed over time. However, the time frame between two consecutive samples should be tailored on different clinical scenarios.
- In critically ill patients, a PCT increase after 48 h of antibiotic therapy must not be used to support treatment escalation.
- In ICU, PCT must be included as a tool in an algorithm for antimicrobial stewardship. Monitoring PCT levels over time must guide the discontinuation and its timing.
- In ICU, PCT must be used also in patients undergoing renal replacement therapy. However, PCT results should be interpreted cautiously and in accordance with clinical, radiological, microbiological and biohumoral findings.

Surgical patients and patients with intra-abdominal infections [34–38]

- In patients undergoing surgical intervention for intra-abdominal infections, PCT should be used to guide the duration of antibiotic treatment even in presence of suspicion of postoperative peritonitis.
- Conversely, in postsurgical patients with intra-abdominal infections, a worsening trend of PCT over time should be used for supporting the need of reintervention.
- In patients with acute necrotizing pancreatitis, monitoring of PCT levels over time should be used to support the need of antibiotic escalation or discontinuation. However, in this setting, the most accurate cutoff level of PCT for supporting antibiotic escalation is still to be defined.

Discussion

In this expert consensus, we evaluated the usefulness and appropriateness of PCT measurement in different clinical scenarios. We also assessed the expert opinions about the role of PCT as a diagnostic and/or prognostic test, and as a tool for antimicrobial stewardship.

PCT is considered a helpful biomarker of bacterial infection and an early marker of sepsis in different settings, including ED, regular wards, surgical wards and ICU [11, 39]. In a previous meta-analysis including 30 reports and 3244 patients, the overall sensitivity, specificity and area under the receiver operating characteristics (ROC) curve of PCT in the diagnosis of sepsis were 0.79, 0.77 and 0.85, respectively [12]. Despite the level of evidence suggested by the literature, the panel did not reach an agreement about the role of PCT in supporting the diagnosis of pneumonia or of bacterial superinfection in patients with acute exacerbation of COPD. In this setting, it was believed that clinical criteria, patient's medical history and radiological findings should be preferred over the results of biomarkers. As stated before, this result may contribute to generate controversy in the role of PCT in the diagnosis of lower respiratory tract infections. In a previous multicenter study, patients with lower respiratory tract infections were randomized to start and discontinue antibiotics according with a PCT predefined algorithm or with clinical decision. The overall antibiotic exposure was significantly lower in patients included in the PCT group, whereas the rate of adverse outcome was similar in the two groups [14]. The results of our consensus are in the line with current Infectious Disease Society of America guidelines on hospital-acquired pneumonia or ventilator associated pneumonia, which do not consider PCT as relevant in the decision process to start antibiotic treatment in this setting [40].

An important setting of PCT use may be for antimicrobial stewardship purposes in critically ill patients in order to reduce the length of antibiotic treatment [33]. In

a randomized trial including 621 critically ill non-surgical patients, PCT guidance was useful to reduce the duration of antibiotic treatment with no adverse events [13]. Moreover, in a recent trial, 1575 ICU patients were randomized to receive a PCT-based algorithm to guide antibiotic prescription. In this group, a non-mandatory advice to discontinue antibiotics was given to all patients showing a PCT decrease ≥80% from the baseline or in those showing a serum PCT level ≤0.5 μg/L. This group showed significantly lower antibiotic consumption and significantly lower 28-day and 1-year mortality rates [41]. The hypothesis of the authors to explain this latter result was that PCT may enable to exclude the presence of bacterial infections leading to a more accurate diagnosis of non-infectious processes. This observation was further confirmed by a metanalysis of randomized trials in patients with respiratory infections [42] and in secondary analysis of a Swiss randomized trial. In this latter study, among the patients with congestive heart failure randomized to the PCT group, those having a PCT lower than 0.25 μg/L showed significative lower rate of adverse outcome [18]. In addition to lowering the antibiotic consumption, several cost-effectiveness analyses demonstrated that use of PCT-based algorithms is associated to decrease of both ICU and non-ICU length of stay [43] and overall hospital cost saving ranging from £368 to £3268 [19, 43]. Lastly, in a paper evaluating a cost-impact model based on meta-analysis data of randomized trials, the estimated cost savings produced by use PCT for acute respiratory infections compared with standard care in a cohort of 1 million of people could reach $700,000 [44].

An additional important result of this work was that in both ICU and non-ICU patients, an increase of PCT after 48 h of antibiotic treatment did not represent an indication for antibiotic escalation. In a Danish multicenter randomized trial, a PCT-based algorithm to escalate antibiotic treatment was not associated to an increased survival rate. In addition, this strategy led to higher antibiotic consumption and longer ICU stay, and therefore it is not advisable [29]. However, a recent randomized multinational trial showed that a reduction of PCT value ≥80% from the baseline to day 4 of observation was associated to a reduction in 28-day mortality. In addition, this study evaluated short-term change of PCT as a predictor of mortality and found that patients who died within 28 days had an average increase of 30% of PCT value form baseline. By comparison, patient who survived did not show any PCT value increase. It worth to be noted that the results of this study were not available at the time when the consensus took place [31].

The optimal cutoff of PCT ensuring the best sensitivity and specificity for diagnosis of infection is still a matter of debate. For lower respiratory tract infection, cutoffs of 0.15–0.25 μg/L are commonly considered adequate [14, 45]. However, different real-life experiences in patients with intra-abdominal infection and in ICU patients with bloodstream infection suggest that higher cutoff should be considered in these settings [32, 37]. In this latter case, higher cutoff values may be helpful to differentiate between bacterial and fungal infections [46, 47]. It is worth noting that all the available literature was produced using the high sensitive assays based on B·R·A·H·M·S· PCT antibodies, which have demonstrated strong reproducibility [48, 49]. The reproducibility of results of these assays is important especially when PCT-based algorithms are implemented for antimicrobial stewardship purposes. In this case, strict cutoff values are commonly used to decide start or discontinuation of antibiotic treatment.

Areas of further investigation and limitations

Further studies are needed to address several aspects of PCT use. Specific cutoff values should be investigated and identified particularly in intra-abdominal infections, including bacterial superinfections of acute necrotizing pancreatitis, taking into consideration the importance of a high analytical sensitivity of the assay used. Most of randomized clinical trials have been conducted in patients with acute respiratory infections. Thus, the application of specific algorithms of treatment escalation or de-escalation in other clinical scenarios has still to be evaluated. In addition, immunocompromised patients have been excluded from most clinical trials, and therefore most of the available evidences, including the findings of this consensus work, cannot be applied to immunocompromised hosts.

In conclusion, in this expert consensus, several aspects of PCT use have been evaluated and addressed. The experts considered PCT as an important marker of bacterial infection in both ICU and non-ICU patients. Its use may be appropriate in algorithms for antibiotic de-escalation and discontinuation. However, initiation or escalation of antibiotic therapy in specific scenarios, including acute respiratory infections, should not be based solely on PCT serum levels. Overall, in every clinical scenario, careful evaluation of clinical and radiological findings, evaluation of severity of illness and of patient's characteristics should be taken into proper account in order to correctly interpret PCT results.

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