Use of procalcitonin as a tool for antibiotic stewardship

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“PCT dosing helps to reduce antibiotic therapy duration for serious infections – with no harm in terms of mortality”

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Since the first observations of its elevation as a result of inflammatory state, notably in cases of bacterial infection [1], procalcitonin (PCT) has been extensively studied and recognized as a valuable biomarker to support diagnosis and guide therapy in infectious diseases. Even after some shortcomings emerged – especially due to a low microbiological predictive power [2] – PCT retained its clinical value, especially after recent redefinition of sepsis as a clinical syndrome, due to its correlation with the SOFA score and with patient outcomes [3].

After more than 20 years of study, most evidence regarding PCT role and its potential comes from the intensive care unit (ICU) setting. Fewer data were produced in the field of primary care, internal medicine, and in the emergency department [4].

Antimicrobial stewardship (AS) approach, as proposed by major guidelines [5], must be considered a cornerstone of clinical practice for the purpose of promoting optimization of the use of antimicrobial regimens, with the aim of limiting multidrug resistance spread. In this regard, PCT-guided de-escalation or discontinuation of antibiotics, which are supported by extensive literature and already endorsed by local and international guidelines [6,7], perfectly fits in such strategy.

As for any biomarker in medicine, misuse may lead to a high volume of useless determinations. This in turn, can lead to perception of limited utility of PCT by clinicians and bears the risk of wasting its potential, to support saving policies in hospitals. An optimal use of PCT measurement may contribute to improve patient management and saving resources. It is, therefore, of the greatest importance to preserve PCT as a tool in the AS setting by means of correct use. The aim of this commentary is to discuss research fields that could be further investigated to improve the use of PCT, in the context of an AS approach.

We propose four areas for which further studies are strongly warranted to define optimal PCT utilization in clinical settings, outside of the ICU: selection of patients, definition of appropriate cut-off integration with microbiological data and inclusion in an AS approach.

Patient selection

As it is the case with any test in medical practice, the value of results highly depends on pretest considerations aimed at identifying patients who would take greatest benefit from being tested. More specifically, predictive value of a test is correlated to the pre-test prevalence of the disease. Most relevant data on correlation of PCT elevation to infection are available for bloodstream infections (BSI), sepsis and pneumonia; most data come from the ICU. Therefore, it would be very useful to identify study populations in whom suspicion of BSI, sepsis or pneumonia is high. Currently, clinical risk scores, such as SOFA for sepsis [3] and CURB-65 or PSI for pneumonia [6] are validated to predict severity of the disease. The predictive value of PCT in patients stratified according to these scores, could improve the performance of the measurement.

On the other hand, elevation during other infections (i.e., endocarditis and meningitis) is more variable, hence it is difficult to interpret PCT results [8,9]. Moreover, escalation strategies based on PCT-guided approaches are not

validated [10]. Further studies on the meaning of high PCT levels in patients for whom an infectious disease has been ruled out is another research area of great interest.

Predefinition of cut-offs

Since most data on PCT utilization come from intensive care settings, the performance of PCT measurement in medical wards should be further investigated. A highly accepted cut-off of <0.5 ng/ml is used to discourage both infectious diagnosis and antibiotic therapy initiation in ICU clinical trials [11,12]. Whether the same cut-off could be adopted for lower-intensity care settings, should be evaluated. Particularly, a cut-off of 1 ng/ml or even higher could increase the test specificity in non-ICU settings. As no large agreement exists on an algorithm for PCT measurement, quality evidence is needed to guide appropriate use. In the meantime, we suggest that AS teams in healthcare facilities provide rules on timing of determinations and interpretation of cut-off.

Integration with microbiology data

PCT should not be regarded as an alternative to rapid microbiological tests, nor as a tool to rule out BSI. Neither should it discourage blood cultures collection in case of negativity, since its negative predictive value for bacteremia is poor [2]. A decreasing trend of elevation exists from Gram-negative bacteria, to Gram-positive bacteria, to fungi [13]. PCT elevation proved useful if combined with low β -D-glucan levels to hint against fungal infections [14]. Whether PCT measurement may accelerate the identification of the cause of an infection, could be another interesting field to be investigated.

Antimicrobial stewardship approach

It has been largely demonstrated that the greatest utility of PCT is in guiding antibiotic de-escalation, based on PCT reduction. PCT dosing helps to reduce antibiotic therapy duration for serious infections – with no harm in terms of mortality [10,11]. It is not surprising that PCT potential to reduce length of therapy was also studied in terms of health economics, showing expenditure reduction [15]. A reduction in antimicrobial utilization is correlated to a reduced selective pressure on local microbiota.

Providing AS teams with PCT levels along with other data can improve patient care and optimize antimicrobial utilization with fewer negative effects both at patient and environmental level. Pharmacoeconomic studies on the benefits of PCT measurement in clinical practice, in different settings and different populations are strongly warranted.

In conclusion, we believe that PCT measurement, when applied to the right patient population and in the context of AS programs, can prove useful in reducing inappropriate antimicrobial therapies. We suggest that all clinicians comply with international or local guidelines, if available, such that PCT determination can be limited to appropriate cases, always estimating in advance if a positive or negative result will have a consequence in terms of clinical practice.

Further data from settings outside of ICUs are strongly needed to support infectious disease specialists and antimicrobial stewards in critically revising local PCT protocols and promoting a wise use of this biomarker. PCT is a useful weapon in the AS arsenal against antimicrobial resistance and should not be wasted.

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