Is there a role for procalcitonin determination in avoiding unnecessary exposure to antibiotics in a non-intensive care setting?

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SUMMARY

The use of procalcitonin (PCT) as a tool to assist clinicians in using antibiotics in intensive care patients has been postulated. Here we evaluate the efficacy of procalcitonin determination in helping clinicians in the decision to start or discontinue an antibiotic treatment in patients admitted to infectious disease wards. A retrospective observational single centre study was conducted in two infectious disease wards. Descriptive and inferential statistical analysis was carried out and receiver operating characteristic curves and area under the curve (AUC) were used to assess the accuracy of PCT and C-reactive protein (CRP) in separating patients undergoing antibiotic treatment or otherwise. In all, 164 patients were analysed of whom 99 (60.4%) were not on antibiotic treatment at the time of PCT determination, whereas 65 (39.6%) took antibiotics. Regarding the accuracy of PCT and CRP in determining a subsequent antibiotic prescription in patients without an ongoing antibiotic treatment, no statistically significant difference between the two markers was detected [AUC, 0.75; confidence interval (CI) 95%: 0.66-0.84; *vs* 0.69; CI 95%: 0.59-0.79 for PCT and CRP, respectively; p=0.32]. Conversely, in patients with an ongoing antibiotic treatment a statistically significant difference between PCT and CRP AUC in their ability to determine an antibiotic interruption was observed [0.77 (CI 95%: 0.65-0.89) *vs* 0.59 (CI 95%: 0.45-0.73) (*p*=0.03)]. PCT determination appeared to be more helpful than CRP in determining discontinuation of an antibiotic treatment in non-intensive care patients. However, PCT should supplement and not supplant a careful clinical evaluation.

Keywords: procalcitonin, PCT, C-reactive protein, CRP, antibiotics.

INTRODUCTION

It has been estimated that approximately 30% of antibiotic prescriptions are unnecessary or incorrect, leading to a progressive increase in antibiotic resistance [1]. Consequently, a growing interest in the discovery and application of novel tools able to assist the clinical decision regarding antibiotic prescription have been observed [2]. When a clinician is facing with the problem of introducing or discontinuing an antibiotic regimen, limited help comes indeed from the traditional markers of inflammation, which are burdened by sub-optimal sensitivity and specificity for the diagnosis of bacterial infections [3, 4].

Therefore, there was a growing interest in procalcitonin (PCT) for identification and management of bacterial infections. Unlike the widely recognized high accuracy of PCT in differentiating

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bacterial from viral infections, the value of PCT to empiric rule out Gram-negative from Gram-positive bacteraemia or candidemia, is too weak to guide therapeutic decisions [4-7]. Several trials showed that use of PCT-based algorithm to withhold antibiotics in mild ill patients with respiratory tract infections and for early end of treatment in critically ill patients with sepsis resulted in lower antibiotic exposure and improved survival [8-10]. However, in a recent trial by Huang et al. no benefit in terms of reduction of antibiotic prescription was observed due to the low adherence to PCT-guided stewardship [11]. Moreover, the possible application of PCT as a stewardship intervention has not well established in setting other than sepsis or respiratory tract infections [12].
As for every biomarker, false positive and negative results can occur also in PCT determination. Circulatory shock, severe trauma, surgery, burns, pancreatitis, end stage renal disease and some autoimmune disorders can increase PCT levels, while localised infections as mediastinitis, empyema or abscesses are often associated with low PCT levels [13-17].
In this study, we assessed the usefulness of procalcitonin as an aid in deciding to start, withhold or stop an antibiotic prescription in patients hospitalised outside the intensive care unit.

PATIENTS AND METHODS

From January 2015 to December 2017, we conducted a retrospective observational single centre study at the two infectious disease wards of the "Luigi Sacco" academic hospital in Milan, Italy. Our infectious disease service consists of 78 beds units with about 1500 admissions/year. All patients with a PCT determination and a concomitant C-reactive protein (CRP) measurement during their hospitalization were included in the study. If a patient had more than one PCT determination, only the first value was considered for the analysis. The algorithm by Schuetz et al. was considered the reference in clinical practice in our infectious disease wards [18]. Moreover, in our hospital in all wards other than intensive care unit PCT is available under approval of a laboratory expert following telephone clinical case discussion.
Clinical data were collected from clinical case folders, anonymised and imputed in an electronic *ad hoc* database. Patients were analysed and clustered as two separate groups based on being or not exposed to an antibiotic treatment at the time of first PCT determination. Fever was defined as a body axillary temperature >37.4°C. PCT measurements were performed using Brahms reagents on a Cobas e411 platform (Roche Diagnostics). The threshold of detection of PCT in our laboratory was <0.1 ng/mL. The diagnostic groups were as follows: infectious diseases (bacterial and non-bacterial infections) and non-infectious diseases (autoimmune disease, neoplastic disease, fever of unknown origin, others).
A descriptive and inferential statistical analysis was carried out and receiver operating characteristic (ROC) curves and area under the curve (AUC) were used to assess the accuracy of PCT and CRP in separating patients undergoing or not antibiotic treatment. To compare the ROC curves of PCT and CRP in different groups we used the method reported by DeLong et al. [19]. The SAS software v9.4 was used for statistical analyses. A P value <0.05 was considered as statistically significant.
The study was approved by the Comitato Etico Interaziendale Area 1, Milano (protocol no. 46941/2018).

RESULTS

Characteristics of the 164 recruited patients are shown in Table 1. The number of patients with a PCT determination were 22 (13.5%) in 2015, 64 (39%) in 2016 and 78 (47.5%) in 2017. Ninety-nine patients (60.4%) were not on antibiotic treatment at the time of PCT determination, whereas the remaining 65 (39.6%) took antibiotics. Figure 1A describes the recruited patients divided in subgroups according to the subsequent therapeutic decision. At the time of PCT determination, 17.7% of patients with a PCT value >0.25 µg/L had an end-stage renal disease (eGFR <30 mL/min/1.73 m^2) and no patients had a cardiogenic shock, burns, surgery or severe trauma.
In the group of patients without an antibiotic prescription at the time of the first PCT determination, 72 (72.7%) had fever. An antibiotic treatment was not started in 41 (41.4%) of those patients, of whom almost 70% was subsequently diagnosed as affected by a non-infectious disease [autoimmune diseases (31.7%), cancer (19.5%) and FUO

Table 1 - Main characteristics of the 164 recruited patients.

Age, years [median (IQR)]	63 (43-77)
Men, n (%)	102 (62.2%)
Number of comorbidities per patient, median (IQR)	2 (1-3)
Types of comorbidities	
Diabetes, n (%)	22 (13.4%)
Chronic obstructive pulmonary disease, n (%)	20 (12.1%)
Hypertension, n (%)	68 (41.5%)
Cardiovascular disease, n (%)	55 (33.5%)
Chronic kidney disease, n (%)	18 (11.0%)
Cancer, n (%)	59 (34.9%)
Autoimmune disease, n (%)	25 (15.2%)
Human immunodeficiency virus infection, n (%)	34 (20.7%)
Chronic liver disease, n (%)	31 (18.9%)
Median hospital stay, days (IQR)	21 (12-33)
Median time to PCT determination from the admission, days (IQR)	
Patients without an ongoing antibiotic	5 (1-14)*
Patients on antibiotic treatment	7 (4-16)*

*A statistically significant difference (Mann-Whitney U test, p=0.04) in the median time of PCT determination in the two groups was detected.
List of abbreviations: IQR = Interquartile Range, PCT = procalcitonin.

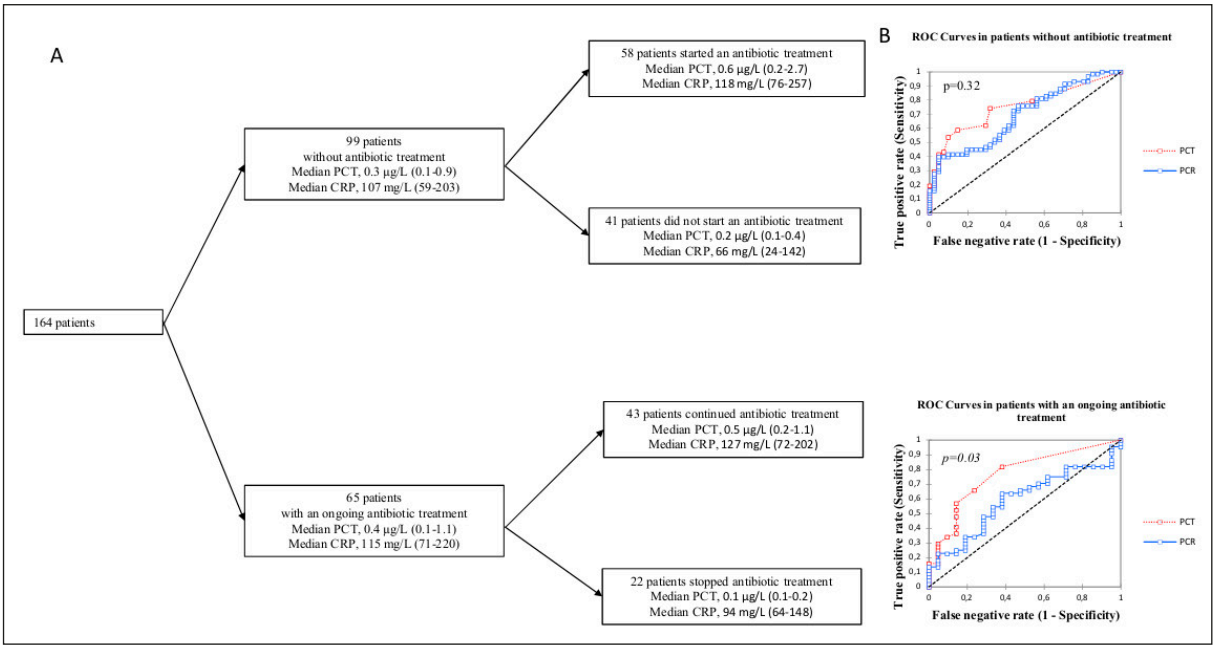

Figure 1 - **1A** Characteristics of recruited patients according to the therapeutic decisions during their hospitalization. PCT and CRP median (and interquartile) values are displayed for different groups. **1B** Comparison of PCT and CRP ROC curves in determining antibiotic interruption, in patients with an ongoing antibiotic treatment, and antibiotic introduction, in patients without an antibiotic treatment, by using the method proposed by DeLong et al. [4].
List of abbreviations: PCT = procalcitonin, CRP = C-reactive protein.

(17.1%)]. Of note, median PCT value of patients discharged with a diagnosis of autoimmune infection was 0.1 µg/L (IQR 0.1-0.3), while median CRP value was 111 mg/L (IQR 44-175). In the 65 patients with an ongoing antibiotic treatment at the time of PCT determination, 42 (64.6%) had fever. Afterwards, the antibiotic treatment was discontinued in 22 (33.8%) patients, who were monitored for a median of 9 days (IQR 4-15.5) until their discharge. Among them, no antibiotic treatment was reintroduced. Regarding the accuracy of PCT and CRP in determining a subsequent antibiotic prescription in patients without an ongoing antibiotic treatment, no statistically significant difference between the two markers was detected [AUC, 0.75; confidence interval (CI) 95%: 0.66-0.84; *vs* 0.69; CI 95%: 0.59-0.79 for PCT and CRP, respectively; p=0.32] (Figure 1B). Conversely, in patients with an ongoing antibiotic treatment a statistically significant difference between PCT and CRP AUC in their ability to determine an antibiotic interruption was observed [0.77 (CI 95%: 0.65-0.89) *vs* 0.59 (CI 95%: 0.45-0.73) (*p=0.03*)] (Figure 1B). The PCT cut-off with the best accuracy (0.72) for predicting antibiotic introduction in patients without an ongoing antibiotic treatment was 0.3 µg/L, with a sensitivity of 74% (CI 95% 61-84) and a specificity of 68% (CI 95% 53-80). The PCT cut-off with the best accuracy (0.75) for predicting antibiotic interruption in patients with an ongoing antibiotic treatment was 0.2 µg/L, with a sensitivity of 82% (CI 95% 68-91) and a specificity of 62% (CI 95% 41-79).

DISCUSSION

In our study conducted in non-intensive inpatients admitted in two infectious disease wards, PCT showed a relatively low diagnostic accuracy for predicting both introduction and interruption of antibiotics. This confirms that every therapeutic decision should be based on a careful combination of clinical and microbiological patient assessment [20]. Furthermore, the low accuracy values and suboptimal sensitivity and specificity of PTC estimated in our study is in agreement with those of a large meta-analysis, in which authors encouraged the use of PCT but not as single diagnostic tool for the diagnosis of bacterial infections [21]. Clinicians should also be aware of the limitations of the assay. Considering all the factors that could potentially alter the PCT levels during the patient's assessment is mandatory [13-17]. If on one hand, some infections (*i.e.*, fungal infections or compartmentalized infections) could be associated with low PCT levels, on the other, PCT could be elevated in other non-infectious conditions, including end-stage renal disease, burns, surgery and circulatory shock [22]. Moreover, current PCT evidences and PCT algorithms focus on patients with sepsis and respiratory tract infections [6, 8-10, 18, 22]. Whereas, in patients with immune-suppression, autoimmune diseases and with a previous antibiotic exposure the PCT-guided algorithms should be applied with caution [13-17].

We observed a significant better performance of PCT when compared to CRP in determining patients who can discontinue an ongoing antibiotic therapy. Therefore, a single PCT determination may be considered as an additional help to assist the clinician in the challenging decision to withhold an antibiotic treatment in a setting of clinical stability of the patient, as already previously recommended in patients admitted in intensive care unit [18]. Of note, no patients were re-exposed to another antibiotic regimen during hospitalisation after interruption of the first one.

In our study cohort, the great majority of the patients had a single PCT determination. Because patients admitted in our wards were not critically ill, a single PCT measurement could be considered appropriate according to the algorithm proposed by Schuetz et al. to decide if introduce or continue an antibiotic treatment [18]. The cut-offs for the best accuracy in the two sub-groups (0.3 and 0.2 µg/L) were similar to the threshold (0.25 µg/L) proposed in other studies for withholding antibiotics in non-critically ill patients [18, 23-25]. This could be an alternative to monitoring of PCT kinetics that allow discontinuing antibiotics when PCT value drop less than 80% of peak value [25]. Recently, a consensus of experts on the optimal PCT use suggested three new PCT algorithms based on the severity of the disease (mild and moderate outside the intensive care unit and severe in the intensive care unit) and on the probability of bacterial infection (uncertain or highly suspected) [22]. This disease severity-based approach could be helpful for clinician to avoid antibiotic in patients with mild disease and a PCT level <0.25 µg/L. On the contrary, in patients with

moderate or severe disease if an empiric antibiotic treatment is started despite low PCT level, the use of repeated test should guide the discontinuation of unnecessary antibiotic treatment [22].

Our findings show that PCT was frequently used in patients with fever. This suggests that quite often the physician's question leading to a PCT request was related to discriminate between bacterial infections and non-bacterial diseases [23]. As reported in other studies, patients discharged with a diagnosis of autoimmune diseases showed low median PCT levels, unlike those of CRP [3, 23]. Nevertheless, the current scientific evidence discourages this kind of PCT application [20, 21, 26]. Moreover, in the HiTEMP study, in which PCT algorithm was applied in a heterogeneous population of patients with fever, admitted to the emergency department, the use was not associated with a reduced antibiotic prescription showing a poor accuracy in the diagnosis of bacterial infection [27].

Our study accounts for some limitations. Firstly, the retrospective design and the limited size of population. PCT was not a part of routine laboratory tests panel in our infectious disease wards, but it could be performed after discussion with laboratory expert in order to avoid inappropriate requests. Moreover, critically ill patients (*i.e.*, septic shock or severe pneumoniae) were not admitted to our ward until they were haemodynamically stable and usually antibiotic therapy was already introduced by infectious disease consultant. This might explain the relatively low and selected number of PCT determination in three years in our wards. In addition, the limited experience and the consequent low adherence to PCT algorithm have been attributed to failure of several PCT studies [11, 27]. Nevertheless, the progressive increase in the number of the PCT determinations since 2015 could suggest a growing confidence in the use of this biomarker in our wards. Secondly, physicians in charge were not blinded to biomarker values and this may have influenced their therapeutic decisions in patient follow-up. Thirdly, the choice to request or not the PCT determination and its timing were based on clinician's judgment; therefore, if on the one hand it reflects the clinical practice, on the other hand it was not blinded and consequently not applicable to other settings and/or published algorithms.

In conclusion, in our retrospective preliminary evaluation a single PCT determination appeared to be more helpful than CRP in determining discontinuation of an antibiotic treatment in non-intensive care patients. However, given its limited diagnostic accuracy, the interpretation of PCT must be part of the clinical history and other signs and symptoms of patients. Thus, it should supplement and not supplant clinical evaluation. Cost-effectiveness and impact on patient outcome of this marker application need to be tested in future trials.

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Conflict of interest

The authors have declared that no competing interests exist.

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