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ORIGINAL ARTICLE

Procalcitonin: The Laboratory Costs of Misused Tests

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SUMMARY

Background: **The study aimed to assess the compliance of procalcitonin (PCT) testing protocols for sepsis diagnosis and antibiotic therapy guidance and evaluate the economic impact of unnecessary or inappropriate testing.**
Methods: **The time intervals between tests were evaluated for all PCT requested in a tertiary hospital between January 2022 and December 2023. A cost of 20 €/test was calculated for each PCT.**
Results: **A total number of 5,420 PCT tests were requested. A budget of 108,400 € was spent. Almost 22% of the tests were conducted within 12 hours of the first measurement, and 6% were performed more than 10 days apart, resulting in 33,580 € (30%) spent. A total of 845 patients did not have a follow-up test, and 16,900 € were spent in these cases. The median number of PCT was 3.33 tests/patient. For 23 cases, more than 10 PCT tests/patient were performed; a total of 338 tests, with the cost of 6,760 €.**
Conclusions: **In total, out of the 108,400 € spent on PCT tests, at least 33,580 € (30%) could have been saved by adherence to the most basic protocols regarding PCT testing: longer than 24-hours interval between measurements and follow-up of initially elevated results.**
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INTRODUCTION

Procalcitonin (PCT) is a biomarker used in sepsis patients and antibiotic therapy guidance. Sepsis is a disorder of organ function indicating a pathobiology that is more complex than an infection in the absence of an accompanying inflammatory response. The evaluation of organ failure severity has been approached through the implementation of diverse scoring systems which aim to quantify abnormalities in accordance with clinical observations, laboratory data, or therapeutic interventions. The most widely used score, at present, is the sequential organ failure assessment (SOFA), which was originally developed as the sepsis-related organ failure assessment [1]. The PCT cutoff value for sepsis diagnosis has yet to be agreed upon. In published studies, the cutoff value was not listed, or it has been used with values ranging from 0.5 to 2.0 μg/L [2]. Additionally, elevated PCT serum levels have also been observed in non-infectious inflammatory conditions [3]. Three distinct meta-analyses

of PCT as a diagnostic tool for sepsis demonstrated a sensitivity and specificity range of 77 - 85% and 75 - 83%, respectively, but with a high heterogeneity [4-6]. Although PCT may be more accurate than CRP in patients with suspected sepsis, neither the 2016 IDSA/ ATS guidelines nor the 2017 ERS/ESICM/ESCMID/ ALAT guidelines recommend the use of PCT for diagnosing ventilator-associated pneumonia [7,8].

In other studies, the use of PCT for antibiotic therapy stewardship was evaluated. Antibiotic prescription is encouraged if PCT > 0.5 μg/L, but the availability of the test did not influence the prescription of antibiotics in emergency departments [9]. Studies on stopping or changing antibiotic treatment by using PCT values have also been published [10-12].

However, a recent systematic review and meta-analysis evaluated the impact of a PCT-guided approach on mortality and the duration of antibiotic therapy in critically ill patients. The findings indicated that a PCT-guided strategy to reduce the duration of antibiotic therapy by one day and to improve survival has low levels of evidence, particularly in randomized controlled trials where protocol adherence was low and when PCT was combined with CRP. Additionally, the review considered other factors, including industry sponsorship, algorithm adherence, and the simultaneous availability of CRP [13]. Lack of compliance with PCT algorithms may mean failure to request a follow-up test when needed [14] or may be defined as an over-use of the test (repeated tests too early) that may lead to a waste of resources.

Using PCT values for better outcomes either for patients or healthcare systems depends on the adherence to testing algorithms: the right patient at the right time. The aim of the study was to evaluate the compliance of PCT requests with published algorithms in a tertiary hospital and to evaluate the costs of unnecessary PCTs tests performed.

MATERIALS AND METHODS

A retrospective analysis of the PCT tests requested for patients in a tertiary hospital between January 2022 and December 2023 was performed. Data were extracted from the laboratory informational system (LIS). Data are available upon request from the corresponding author. The study has been approved by the Institutional Ethics Committee.

The PCT serum levels were measured from serum samples using the Alinity instrument (Abbott, USA). All samples were collected on serum separator tubes and measured within two hours from collection. PCT results were analyzed by the levels stated by Kopteridis et al. [15]. Demographic data of the patients were also registered.

The PCT values were sorted into two main categories: results from patients diagnosed with sepsis according to SOFA score and non-sepsis patients. Also, the results were sorted according to the number of PCT tests requested per patient: one request and two or multiple requests/patients. To evaluate the time interval elapsed from one measurement to another, the mean time between two consecutive measurements was calculated. To evaluate the cost, a mean price/test of 20 €/PCT test was set.

RESULTS

Samples for PCT measurement were collected from 2,983 patients, out of which 1,389 were female patients and 1,594 were male patients. The age median of the patients was 68 years [IQR: 24]. Some patients had only one PCT request, and others had two or more. Among patients with multiple procalcitonin determinations, the most requests were represented by the intensive care unit department (ICU), with 1,607 determinations, followed by the emergency department, with 1,374 determinations, and the nephrology department, with 466 determinations. The median number of PCT tests was 3.33 tests/patient. For 23 patients, more than 10 PCT tests/ patient were performed, a total of 338 tests with the cost of 6,760 €. In total, 5,420 PCT requests were analyzed (total cost of 108,400 €). Results with the number of tests performed/patient are shown in Table 1.

In the group of patients that had more than one test performed, 511 PCT tests were collected from patients with sepsis diagnosis and 1,868 from patients without sepsis diagnosis. The most common causes of sepsis starting point were renal diseases in 199 cases and pulmonary infections in 170 cases. Results are shown in Table 2.

The time interval between the initial PCT measurement and consecutive samples (second, third, etc.) and the cost of tests is shown in Table 3.

DISCUSSION

In patients that had more than two tests performed, the emphasis lies on the time that has elapsed between two measurements: 22% of the PCT requests were made within less than 12 hours, with a direct cost of 10,200 € (9.4% of total PCT cost), which may be considered wasted, since a clinical useful change was unlikely to occur during that time interval. Also, 324 tests were requested after more than 10 days from the previous sample, so another 6,480€ (6% of total PCT cost) were wasted in this case. Clinical studies involving over 1,000 patients admitted to intensive care units (ICUs) have shown that the use of a decision-making algorithm based on the relative decrease in plasma PCT levels during hospitalization allows for a significant reduction in the duration of antibiotic therapy and the duration of ICU stay, without causing apparent adverse effects in patients with severe sepsis and septic shock [15]. In patients with ventilator-associated pneumonia (VAP), the

Table 1. Number of PCT tests performed per patient.

PCT concentration (µg/L)	PCT level	1 PCT test/patient	Two or more PCT tests/patient
< 0.25	1	783	892
0.25 - < 0.5	2	248	488
≥ 0.5	3	189	481
≥ 1.0	4	656	1,683
		T: 1,876	T: 3,544

PCT levels were taken from the paper published by Kopteridis et al. [15].

Table 2. Number of PCT tests performed for sepsis and non-sepsis patients.

PCT concentration (ng/dL)	PCT level	PCT requests for sepsis patients	PCT requests for non-sepsis patients
< 0.25	1	51	478
0.25 - < 0.5	2	42	275
≥ 0.5	3	57	257
≥ 1.0	4	361	858
		T: 511	T: 1,868

Table 3. Time between consecutive PCT measurements in patients that had two or more PCT tests done.

Time elapsed	Number of samples	Cost
12 - 24 hours	510	10,200 €
24 - 48 hours	486	9,720 €
48 - 72 hours	235	4,700 €
72 - 96 hours	225	4,500 €
96 - 240 hours	459	9,180 €
> 240 hours	324	6,480 €
Total:	2,239	44,780 €

The cost/test of PCT was 20 €.

measurement of procalcitonin (PCT) at the onset of treatment and on day four (D4) could predict survival, thereby differentiating patients with a favorable versus an unfavorable outcome [11]. The persistence of elevated PCT levels at the fourth day of antibiotic therapy was indicative of an inability to control the infection [12,13]. In clinical practice, for patients who present elevations in biomarker levels by the third or fourth day of antibiotic therapy, doctors should consider the possibility of treatment failure and prompt an intensified diagnostic and therapeutic approach. However, it is important to exercise caution when using biomarkers as a standalone criterion to determine when to intensify the diagnostic process. An algorithmic approach to clinical practice based on the premise of an "alert PCT" (PCT ≥ 1 µg/L and not decreasing by > 10%/day) was evaluated in a randomized controlled trial, demonstrating no mortality benefit at the expense of increased utilization of broad-spectrum antibiotics, a longer duration of mechanical ventilation and ICU stay, and a higher incidence of prolonged antibiotic therapy [17]. Unnecessarily exposing patients to antibiotics leads to potential complications and multi-resistant microorganisms' emergence [17], and in one study [18], it has been reported that up to 30% of antibiotics prescribed to hospitalized non-critically ill adult patients were unnecessary prescribed.

Also, in the same study, it has been reported that antibiotics were used for a longer time than recommended or had been used for treatment of colonizing and contaminating microorganisms [18]. Similar findings regarding PCT test follow-up were found by other studies: in a group of patients with septic shock, 37.3% of the patients had inappropriate PCT measurements [19].

In the group that had a single PCT measurement, 54% of these values were < 0.25 µg/L. These values had been associated either to a therapeutic success in antibiotic treatment or to an improbability of a bacterial infection, depending on the clinical setting. In patients with severe community-acquired pneumonia, PCT had been evaluated as a means for assessing the presence of bacterial co-infection in influenza [7,8]. The preliminary results of studies conducted on documented cases of influenza infection indicate that PCT levels may be useful in ruling out the presence of a bacterial co-infection [10]. It may be assumed that these PCT tests were used to rule out bacterial infections by clinicians and were therefore appropriately used. However, for the remaining 845 tests in this group, although they had values > 0.5 µg/L, a second test was never requested, showing a lack of adherence to guidelines that state either that this value is suggestive for sepsis, bacterial infections, or misguided antibiotic therapy. The direct cost of the tests that may be considered wasted was 16,900€ (more than 15% of total PCT costs). It also can be said that in 46% of the cases, opportunities were missed.

A lack of adherence to guidelines for PCT testing protocols has been found in studies, and some of those studies discussed the causes of these findings. In the study by Schuetz et al., the lack of adherence to guidelines for antibiotic treatment in patients with respiratory infections was attributed to knowledge gap regarding the utility of PCT testing [20]. In a quality improvement project for better use of antibiotics in COVID-19 patients, in 72% of the cases, the antibiotics were never started or stopped after less than 48 hours if the COVID-19 positive patients had a PCT < 0.25 ng/dL [21]. Computer-based algorithms have also been used to try to limit the number of PCT requests, with savings of more than 11,000 € in one year and a half [22]. However, in critical COVID-19 patients, PCT was not the only test used for decision-making algorithm, because 9% of severe patients had low PCT, and other markers (i.e. IL-6, ferritin, NLR, etc) were recommended to sustain medical decisions [23,24].

CONCLUSION

In total, out of the 108,400 € spent on PCT tests, at least 33,580 € (30%) could have been saved by adherence to the most basic protocols regarding PCT testing: longer than 24-hours interval between measurements and follow-up of initially elevated PCT levels. Lack of adherence to guidelines leads to waste of resources. Better knowledge of the algorithms, better communication, and higher confidence in tests may improve the general use of resources, but further research should be made on factors that influence the adherence of clinicians to protocols.

Declaration of Interest:

All authors declare that they do not have a potential conflict of interest.

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