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Evaluation of Procalcitonin in Adult Patients with Fever

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Abstract: ***Fever is one of the most common reasons for people to attend the emergency department and Infectious Diseases Service. While the fever is a symptom caused by infectious and non- infectious diseases the biggest challenge is to discriminate as soon as possible potentially life threatening conditions that have as main component the fever, like sepsis which is caused by an extreme systemic response to infection by microbial organisms. Recognition of sepsis and rapid treatment with appropriate antimicrobial drugs is important to maximize the chances of survival. There are a few laboratory tests that are used to assess for an ongoing infectious process, such as WBC, CRP, ESR, and blood cultures. These tests are not sensitive or specific for bacterial infection and sepsis. Procalcitonin is a relatively new diagnostic test which has been found useful in early identification of severe bacterial infections, and differentiating systemic inflammatory response syndrome from sepsis. Procalcitonin is a biomarker with excellent specificity for sepsis, while other laboratory values, such as WBC, CRP, sputum and urine culture, are non-sensitive, non-specific and unreliable. This is the first study conducted in the adult Albanian patients with fever in which we evaluated the levels of PCT, CRP and WBC in patients who presented or developed fever.***

Keywords: sepsis, procalcitonin, fever, infection

1. Introduction

The number of patients who presented to the Infectious Diseases Emergency room, is quite variable and depending on many factors (climate changes, epidemiological situation, health care structure, culture, etc.), but the majority of them have as main complaint high fever. Traditionally high fever has been considered as sign of infection, but in more than 50% of febrile patients it can also be caused by other non-infectious illnesses such as autoimmune or malignant diseases (1). In the emergency department (ED) the differentiation of causes of fever (bacterial, viral, parasitic or fungal infection is very difficult (1-4). Even more difficult is to differentiate whether we are dealing with an infectious disease or any other pathology similar to that in terms of clinical aspects. Cases without clear clinical signs and probably non infectious diseases, but presenting with high fever are common in the daily routine work of physicians in the ED or infectious diseases service. Currently neither clinical signs and symptoms, nor biomarker such as protein C- reactive (CRP) are considered as a potential marker for determining the etiology of fever. In the last decades PCT has been added as a marker in determining the diagnosis of febrile patients, especially those with sepsis. Physicians need to find solution for their patients, in sense of early diagnosis. Procalcitonin is a promising marker for identification of bacterial infections and it seems to be a very useful in monitoring the disease`s course and can be used as a diagnostic test for prevention, progress and treatment of sepsis, septic shock or multi-organ failure (MODS) (2,7,10,11). Also based on several literatures, PCT is a highly significant test in starting the antimicrobial therapy and its duration (3-13). Some authors suggest the use of PCT in ED as a rapid test, while others support the idea that the PCT is not able to differentiate sepsis from SIRS due to non-infectious causes (12,13,15,16).

2. Materials and Methods

This prospective observational study was conducted in the ED and admitted patients, at the Infectious Diseases Service (IDS) of "Mother Teresa" University Hospital Centre and at the American Hospital of Tirana, Albania between May 2010 and November 2013. The study included 302 adults older than 14 years old who were consecutively admitted to ED and IDS with fever (axillary temperature > 38ºC on more than two occasions), who, after a careful history and physical examination, underwent blood analysis and radiologic examination. The objective was to assess the value of PCT in patients with sepsis and to compare it with C-reactive protein and total white-blood cell count (WBC), in predicting severe bacterial infections. Infection was defined when clinical signs of systemic inflammatory response were present, determined by a definable source of infection (microbiology confirmed) and/or positive blood cultures or strong suspicion for infection. C-reactive protein was measured using a nephelometric method (BNA 100; Dade Behring, Marburg, Germany). Measurements of

samples for PCT determination were performed by Roche diagnostic elecsys 2010 immunoassay analyser.

Table 1: Interpretation of PCT values

Values of PCT in ng/ml	*Interpretation*
0-0.5	Not present sepsis condition
0.5-2	Suspicious for sepsis
>2	Present sepsis condition

3. Protocol

All patients in our study have been recorded in a well-defined database. At the time of admission signs and symptoms, clinical and laboratory data including PCT, CRP, WBC and other blood works were collected and scheduled within 24 hours. Samples were collected for cultures depending on the clinical symptoms. We used the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference definition of sepsis to identify patients with sepsis, severe sepsis, septic shock, and SIRS (11).

a) SIRS is defined as 2 or more of the following variables:

- Fever of more than 38°C (100.4°F) or less than 36°C (96.8°F)
- Heart rate of more than 90 beats per minute
- Respiratory rate of more than 20 breaths per minute or arterial carbon dioxide tension ($PaCO_2$) of less than 32mm Hg
- Abnormal white blood cell count (>12,000/µL or < 4,000/µL or >10% immature forms)

b) Sepsis is commonly defined as the presence of infection in conjunction with the systemic inflammatory response syndrome (SIRS);

4. Results

From 302 patients that has been enrolled in this study, 161 (53.3%) of them were males and 141 (46.7) females. Based on our protocol 76.49% were classified as sepsis and 23.5% of them as SIRS. The average age of patients with sepsis was 58.1 ± 15.7 years, while the average age of patients with SIRS was 47.3 ± 14.5 years.

Table 2: The value of procalcitonin

PCT	*Nr. of patients*	*Minimum*	*Maximum*	*Average*	*Standard deviation*
(0.5-2 ng/ml)	71	0.06	1.83	0.37	0.32
(>2 ng/ml)	231	2.19	102.00	15.29	25.95

We noted a significant statistical high PCT level in patients with sepsis 15.3 ± 25.5 µg/ml compared to patients with SIRS 0,37 ± 0,32 µg/ml.

Table 3: Average value of PCT, CRP and WBC

	Procalcitonin	*CRP (range 0-5)*	*WBCc (range 4-10× 10^3)*
Sepsis patients	15.29	35.7	13.7 × 10^3
SIRS patients	0.37	19.4	11.6× 10^3

Statistically significant correlation between WBCc and procalcitonin levels in sepsis patients were observed ($p< 0.001$). When comparing WBCc and procalcitonin levels, we did not find any statistically significant correlation in SIRS' patients;

SIRS, Pearson Correlation ($r=-0.316$, $p<0.14$)
Sepsis, Pearson Correlation ($r=-0.605$, $p<0.001$)

The final diagnoses are shown in Fig 1. and from them: 117 patients (38.7%) were confirmed with bacterial infection; 114 patients (37.7%) were suspected of having strong suspicions for bacterial infection; 71 patients (23.5%) with SIRS weren't identified infectious agent as a cause of fever.

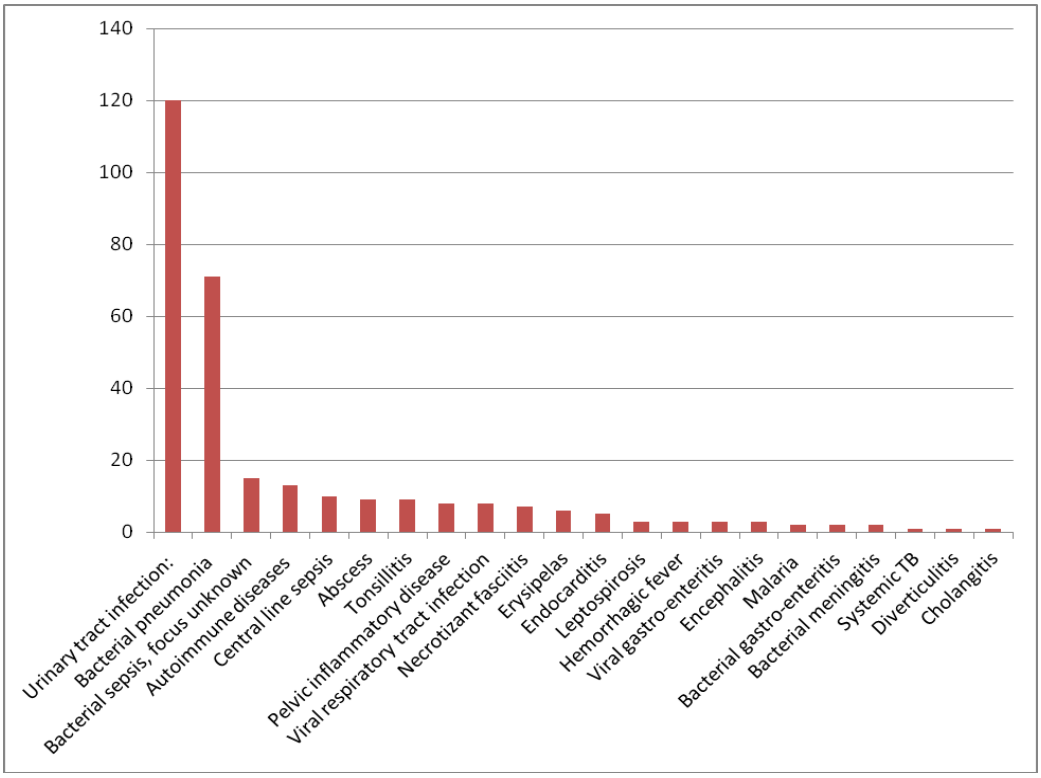

Figure 1: Final diagnosis of patients (n = 302) tested with PCT, PCR and WBCc

5. Discussion

Fever is one of the important features of infectious diseases. The cause of fever is difficult to be made on the ED service. Been one of the component of sepsis and SIRS it's of paramount importance the use of specific and sensitive markers in order to distinguish as soon as possible the SIRS and septic shock from an non- infection cause. The use of blood cultures for identifying the presence of bacteria requires time, which makes it inaccessible for clinical use in the ED. In our study we provided a thorough comparison between PCT, WBCc and CRP. Procalcitonin is a 116 amino acid precursor protein prohormone of calcitonin, normally produced by the thyroid gland under physiological conditions, but it's grow more rapidly during bacterial infections (1). Procalcitonin is reported as an important marker to differentiate sepsis from other non-infectious pathologies accompanied with SIRS (3-14). In normal metabolic condition, calcitonin mostly is produced by the C cells of thyroid medulla and neuroendocrine cells of the lungs, and in the lower level by parenchymal cells (including liver, lung, muscle and adiposities) too (1,7,8). It is not found in serum of healthy people, but high concentrations of PCT have been reported in patients with bacterial infections and septic inflammation (1,7,8,15). After an infection attack, there is a rapid increase of PCT synthesis and release as a consequence of bacterial products and endotoxins or proinflammatory cytokines and other factors, reflecting the inflammatory response to infection (3,4,11). This growth and especially the PCT course correlates with gravity of systemic bacterial infection. In clinically healthy people, PCT levels in the 95% of the population does not exceed the value of 0,05 ng/m. In bacterial infections it begins to rise within 3 hours and arrives it maximum values after 6-12 hours (1). Procalcitonin appears to play a physiological role including cytokines cycle regulation, attracting leukocytes to the site of inflammation, modulation of oxide nitrogen synthesis and non - steroidal analgesic effect (8,9). Etiologic diagnosis of febrile patients who present to ED is complex and sometimes difficult (15). Because most microbiological test results are not available for 24 h, a sensitive and specific marker of systemic infection would be useful. The use of blood cultures for identifying the presence of bacteria requires at least 3-5 days, which makes it inaccessible for clinical use in the ED or for the early goal-directed therapy. C-reactive protein levels, erythrocyte sedimentation rate, and WBC values are also available parameters for the diagnosis of inflammation, but their sensitivity and specificity is lower than PCT in differentiation of acute bacterial infection from the other types of inflammation (15,16). It is well known that CRP is a very sensitive marker and it may be increased in viral infections and other insults such as trauma or autoimmune diseases. Procalcitonin appears to play a physiological role including cytokines cycle regulation, attracting leukocytes to the site of inflammation, modulation of oxide nitrogen synthesis and non - steroidal analgesic effect (5,6). We can conclude that the overall accuracy of PCT markers is higher than WBCc and CRP both to differentiate bacterial infections from other non-infective causes of systemic inflammation. CRP levels and WBC values are also available parameters for the diagnosis of inflammation, but their sensitivity and specificity is lower than PCT in differentiating acute bacterial infection. Our results showed that PCT values in suspected sepsis groups were significantly higher than non-suspected sepsis groups ($P < .001$). It could be a useful tool in the emergency room for differential diagnosis among patients with signs of SIRS. From our data the PCT concentration provides important diagnostic value in distinguishing between patients with sepsis or SIRS. This was the first study in our country to investigate the PCT as a marker of sepsis in febrile patients.

The relatively high costs of PCT measurements discourage the application of PCT in resource-poor settings. We didn't found patients with sepsis, where the PCT value was below 0.5 ng/mL. In fact, all the patients had values of PCT >2.0 ng/mL. Furthermore, in cases of sepsis with multiorgan failures (MODS), we found the highest values of PCT. In the group of patients with SIRS the average value of PCT was < 2.0 ng/mL. In both groups WBC and CRP were higher than normal range, and we can't say the same for the PCT. We observed the correlation between PCT and WBC in patients group with sepsis and this can be related with the presence of microbial causes associated with aggressive growth of PTC, while in cases with SIRS this correlation wasn't noticed.

Our study has some limitations. Only a limited number of patients with culture confirmed bacteremia were available for the purpose of this study. As expected, the majority of patients enrolled had negative blood culture, because they have started antibioticotherapy before presenting in ours hospitals.

6. Conclusions

We, as clinicians need to diagnose our patient as soon as possible. This study demonstrated that PCT and CRP are valuable markers for the discrimination of fever in adult patients attending ED and IDS and they perform better than WBC in the diagnosis of sepsis.. PCT appears more accurate on bacterial infections than CRP. This is the reason why we suggest that every ED should use PCT as a diagnostic test in order to determine bacterial sepsis, but the high cost of PCT test limits its application in low income countries. We think that PCT has more advantages in relation to the time of acquisition, cost and the evaluation of progressive disease, compared to blood culture which is considered to be the gold standard of sepsis diagnosis. Finally, the combinations of the laboratory parameters, such as PCT, CRP and WBC, seem to be predictive in diagnosis of early sepsis. A combination of several sepsis biomarkers may be more effective, but this requires further evaluation.

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