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Serum Procalcitonin, Use of Antibiotics, and Patient Outcome

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ABSTRACT

Objective: To evaluate the impact of serum procalcitonin (PCT) testing on use of antibiotics and patient outcome.

Design: A retrospective chart review evaluation of the patients who had a serum procalcitonin test performed at one medical center.

Setting: One academic medical center, Mount Sinai Medical Center, Miami Beach.

Participants: One hundred and forty four consecutive patients who had procalcitonin determined beginning in January 2014.

Measurements: We analyzed patient age, mortality, length of stay in intensive care unit and total hospital stay, presence of positive blood culture, and if on antibiotics at forty- eight and one hundred and twenty hours after PCT determination.

Results: There were seventy two patients with a positive PCT determination (>0.5 ng/ml) and seventy two patients with negative PCT (<0.5 ng/ml). Patients with a positive serum PCT had a longer hospital length of stay, longer length of stay in Intensive Care Unit (ICU), were more likely to have a positive blood culture, more likely to be on antibiotics at 120 hours after PCT, and had higher mortality, ($p<.05$).

Conclusion: Serum PCT level appears to predict severity of illness, mortality, and continued use of antibiotics. Negative PCT did not predict stopping of antibiotic treatment at forty-eight hours after the test.

INTRODUCTION

Early identification of bacterial infections and adequate antibiotic use have been major challenges for healthcare providers since the development of the antibiotic era. Clinicians have focused their efforts on early empirical treatment of inflammatory processes that, in most cases, are presumed to be bacterial. Early antibiotic treatment of inflammatory processes of unclear etiology was initially thought to improve patient outcomes and mortality. This would help as long as the inflammation is caused by a bacterial infection. However, over the course of the most recent decades, empiric antibiotic treatment of non-bacterial processes has led to unnecessary antibiotic exposure and emergence of antimicrobial resistance, which is an increasing problem. Under this perspective, research efforts have been focusing on identifying biomarkers that can discriminate the inflammatory response to bacterial infection from other types of inflammation. Moreover, there is a need for biomarkers that could guide physicians in individualizing antibiotic therapy according to the patients' condition and response to treatment.

There are no reliable biologic markers, routinely used in the United States, to diagnose or confirm the presence of a bacterial process and most of the therapeutic decisions are made empirically, which is progressively leading our medical practice towards antimicrobial resistance and poor patient outcomes.

Procalcitonin (PCT), the precursor molecule for calcitonin, with very low hormonal activity, has been shown to rise during bacterial infections and other major illnesses such as shock, but remain very low, or undetectable, in viral and non-infectious inflammatory processes [1]. It has been proven to act as a biologic marker that can discriminate the inflammatory response to bacterial infection from other types of infections such as viral illnesses or systemic inflammatory response syndromes (SIRS). Moreover, PCT is associated with the severity of the disease and can also be used as a predictor for sepsis, severe sepsis and septic shock [2,3]. Thus, PCT could help clinicians decide which patients are likely infected with bacteria and could benefit from early empirical antibiotic therapy. Its use could avoid indiscriminate use of antibiotics, reduce antibiotic exposure as well as costs and may contribute to slowing the emergence of resistant microorganisms, depending on physician utilization and acceptance. We investigated if the

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use of PCT levels helped in determining antibiotic therapy and patient outcomes.

Procalcitonin is the precursor molecule of the hormone calcitonin. It is a 116 amino acid peptide with very low hormonal activity, with a molecular weight of 14.5 kDa. Proteolytic cleavage of immature regions produces calcitonin. PCT is encoded by a gene named CALC-1, located on chromosome 11. In the normal individual, this gene's expression is limited to the parafollicular cells of the thyroid gland, which produce calcitonin to reduce the serum levels of calcium when necessary, in opposition to the parathyroid hormone effect. The production of PCT is suppressed in non-neuroendocrine tissues under normal conditions. Due to mechanisms that are not yet well understood, bacterial infections induce a significant increase in the CALC-1 gene expression in parenchymal and well differentiated cells, causing a substantial increase in serum levels of PCT[1]. PCT is detectable in serum within 4-6 hours, reaching peak levels at 12-48 hours. It has also been shown to rise in direct proportion to the severity of the bacterial process. Given its specificity for bacterial inflammation, PCT has been widely studied as a sepsis biomarker and compared to the numerous other molecules that have been shown to rise during bacterial infections, including C reactive protein (CRP), white blood cell count (WBC), interleukin-6 (IL6), erythrocyte sedimentation rate (ESR) and adrenomedullin (ADM) [4,5]. Studies have proven that the vast majority of molecules compared to PCT tend to elevate in the non-infected individual, and were considered unsuccessful in differentiating bacterial inflammation from different causes of systemic inflammatory response syndrome (SIRS), postulating PCT as the most reliable diagnostic biomarker for bacterial infections, sepsis, severe sepsis and septic shock[2]. Chirouze et al studied how accurately a low serum PCT level would predict the absence of bacteremia in adults with acute fever [6]. They calculated sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for nine different cutoff values of PCT. The highest NPV was 98.8% for the cutoff value of 0.4 ng/mL (95% CI, 0.95-1), concluding that 0.4 ng/mL is the PCT diagnostic threshold. The Cochrane Database Systematic review performed recently by Schuetz et al; found no increased risk for mortality with PCT-based treatment algorithms when compared to standard empirical antibiotic regimens, in addition to a consistent reduction in the days of antibiotic exposure and prescription rates [7]. A different meta-analysis published by Uzzan et al; examined 25 studies that used PCT and sensitivities ranged from 42% to 100% and specificities ranged from 48% to 100% depending on the cutoff value used in each study, proposing a diagnostic cutoff value of around 0.6 ng/mL. The global conclusion presented was that the likelihood of infection in a patient with an elevated PCT level is about 16-fold higher than for a patient with low levels of PCT, introducing it as a reliable diagnostic marker for sepsis and they even recommended its inclusion as a diagnostic tool in the sepsis guidelines [8].

In 2013 our institutions infectious disease specialists requested to have serum procalcitonin added to our laboratory testing. It was predicted a negative test would result in less antibiotic use.

We added this test for use by our infectious disease specialists and intensivists. Procalcitonin testing costs approximately $100 per test. We performed this analysis to assess the value of the test for controlling use of antibiotics.

METHODS

This study was reviewed and approved by the Institutional Review Board of Mount Sinai Medical Center. We conducted a retrospective analysis by chart review to determine if the use of procalcitonin had an effect in the decision to stop antibiotic therapy. We evaluated: if the reported PCT level reduced the use of antibiotics, the duration of antibiotic days, length of intensive care stay, total hospitalization days, and mortality. We evaluated patients for positive or negative blood cultures.

This was a retrospective analysis by chart review of cases where a procalcitonin level was measured. Data were collected from the Microbiology Laboratory Data Bank and our Computerized Medical Record. Statistics were generated for the study population using means (and SEM) for continuous variables and/or medians and interquartile ranges. All variables were tested for normalcy. Two-sample comparison for continuous, normally distributed, variables was analyzed with the Student's t test with Bonferroni's adjustment for repeated testing. Non-normally distributed variables were tested using the Man U Whitney non-parametric test. Proportions were by Chi-square analysis. Differences were considered significant at values of $P < 0.05$.

RESULTS:

Our laboratory identified the patients as having a PCT assay in 2014. One hundred and forty-four patients' charts that had PCT levels were evaluated. Normal PCT was <0.5 ng/ml. Seventy-two patients had a high PCT and 72 patients had a normal PCT. PCT levels averaged 1.54±0.2 m/ml. The mean age of the study population was 73.2±1.2 years, and their average hospital length of stay was of 32.6±1.2 days. See Table 1 for data and statistics.

Patients were divided in two groups based on the PCT levels. In the group with normal PCT the mean PCT was 0.144 (95% Confidence Intervals (CI): 0.12-0.17. In the patients with PCT >0.5 the mean PCT was 6.9 (95% CI: 3.8-10.1). There was no statistical difference in age of the patients in each group. Positive PCT predicted severity of

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illness and outcome. In the group with high PCT there was statistically increased hospital and ICU length of stay and mortality. Patients with positive blood cultures were more likely to have positive PCT. See Table 2. In comparing use of antibiotics in the group of normal and high PCT, there was no statistical difference in those on antibiotics at 48 hours. Negative PCT did not predict stopping of antibiotics. There was a difference in those on antibiotics at 120 hours. There was no difference between the groups with normal or high PCT in antibiotics prior to PCT assay, days on antibiotics prior to PCT, and antibiotics administered prior to blood cultures (Table 1).

TABLE 1:

	PCT<0.5	**PCT>0.5**	**P value**
N	72	72	
Age	75.2±1.7	72.2±1.8	0.11[a]
PCT	0.144±0.01 (95%CI: 0.12-0.17)	6.9±1.5 (95% CI: 3.8-10.1)	
LOS Hospital	17.4±1.7 (95%CI:13-21) Median: 11 d	38.5±7 (95%CI:24-53) Median: 16.5 d	0.006[b]
LOS ICU	11.2±1.5 (95%CI:8.1-14.2) Median:8	31.8±8 (95%CI:15-47) Median: 12	0.039[b]
Positive Blood culture	6 (8.3%)	21 (29.2%)	0.0023[c] (OR: 4.53; CI 95% 1.7-12.1)
On Antibiotics 48 hr	45 (63.3%)	53 (75.7%)	0.143[c]
On Antibiotics 120 hr	31 (42.9%)	43 (61.4%)	0.03[c]
Survived	60 (83.3%)	51 (70.7%)	0.041[c]
On Antibiotics before PCT	36/71	46/69	0.06[c]
Days on Antibiotics before PCT	6.8±1.4 (95%CI:3.7-9.8)	8.4±2.6 (95%CI:3-13)	0.65[c]
On Antibiotics before blood Culture Yes	8/54 (14.4%)	4/51 (7.9%)	0.37[c]

A Student's t test; b: Mann U Whitney test; c Chi square test

Patients with positive blood cultures were more likely to be continuing antibiotics at 48 hours and 120 hours. However, positive blood cultures failed to predict hospital and ICU length of stay (P= 0.9) (Table 2).

TABLE 2:

	Positive Blood culture	**Negative blood culture**	**P value**
N	27	117	
Age	74.2+2.4	73.3+1.4	0.85[a]
PCT	6.2+3.2	2.09+0.7	0.125a
PCT >0.5	21/27 (77.7%)	51/117 (43.5%)	0.0014[c]
LOS Hospital	30.5+11	33.8+7	0.9[b]
LOS ICU	22.9+7	22.4+5	0.9[b]
On Antibiotics 48 hr	23/26 (88.6%)	74/113 (65.4%)	0.0032[c]
On Antibiotics 120 hr	16/26 (61.5%)	58/114 (50.8%)	0.008[c]
Antibiotics started before Blood Culture	2/18 (22.2%)	66/100 (66%)	0.0006[c]

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LIMITATIONS OF THE STUDY:

This study is from one medical center and thus represents the clinicians and patients at one hospital. We started performing serum PCT in 2014 with restrictions due to the high cost of the test, approximately $100 per sample. Only our infectious disease attendings, intensivists, and pulmonary critical care physicians could order the test initially. As more physicians became aware of the test more physicians ordered the test. Internists with patients in the intensive care unit ordered the test. The only education done on the test was at medical grand rounds by one of our Infectious Disease specialists.

DISCUSSION:

In 2013 our institutions infectious disease specialists requested to have serum procalcitonin added to our laboratory testing. We added this test for use by our infectious disease specialists and intensivists. We performed this analysis to assess the value of the test for controlling use of antibiotics. We found that positive procalcitonin was a predictor of severity of illness. We found fewer patients with negative test on antibiotics at 120 hours after the test. When evaluating antibiotic use at forty-eight hours we did not see a statistical difference. Positive and negative blood cultures were strongly predictive of antibiotic use at 48 and 120 hours.

Based on these findings and analysis we will increase education efforts for our clinicians about use of PCT and the suggested therapy changes based on the results. We believe this can have multiple benefits including appropriate antibiotic usage, patient and staff satisfaction, and decreased expenses.

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