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Procalcitonin variations after Emergency Department admission are highly predictive of hospital mortality in patients with acute infectious diseases

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Abstract. – BACKGROUND AND AIM: To evaluate the diagnostic and prognostic usefulness of procalcitonin (PCT) in patients admitted to the Emergency Department (ED) with signs of infections and to assess the prognostic value of repeated measurements in predicting hospital mortality.

MATERIALS AND METHODS: A prospective, observational study was conducted in our 400-bed General Teaching Hospital. 261 patients arriving in ED with signs/symptoms of infection were enrolled. PCT was performed upon arrival in the ED (T0), and 5 days after antibiotic therapy (T5). Blood cultures were performed in all patients upon arrival in the ED.

RESULTS: Mean T0 PCT value was 7.1±17.9 ng/ml, and at T5 3±9.1 ng/ml ($p < 0.0001$). Mean PCT in septic non-survivors was increased at T5 compared to T0 but not significantly. The PCT increase at T5 was an independent factor of mortality (OR = 1.29, $p < 0.02$) in septic patients. Compared to baseline mean delta % PCT decrease at T5 was 28%. Patients with a decrease delta % PCT > 28% showed a lower number of deaths, with a statistical significant difference if compared to those patients with a < 28% decrease ($p < 0.004$). ROC curve of delta % PCT for prediction of death has an AUC = 0.82 ($p < 0.03$).

CONCLUSIONS: PCT is a useful marker for diagnosis of systemic and local infections, and for prognostic stratification in patients with acute infectious diseases at their arrival in ED. PCT variations after antibiotic therapy are highly predictive for in-hospital mortality. PCT normalization during antibiotic therapy suggests a good response to infection possibly leading to less infection-related deaths.

Key Words:
Procalcitonin, Infections, Sepsis, Emergency Department, Critical Care Unit.

Introduction

Emergency physicians are faced with the challenge to quickly and correctly confirm the diagnosis of infections, to discriminate local infections from sepsis, and to appropriately decide treatment within a very short period of time. In addition, patients often present with atypical symptoms and guidelines are not specific for the diagnosis of infectious disease. Overall mortality for infectious diseases is 25.9% annually and reaches 40-80% for septic patients worldwide[1-4].

The need of quick, sensitive and reliable tests are fundamental to the diagnosis of infections in the Emergency Department (ED). Unfortunately, routinely available laboratory tests (with a quick turn-around-time, high sensitivity and specificity) to aid in the differential diagnosis are lacking. C reactive protein (CRP) is often considered a rather non-specific marker of the acute phase inflammatory response rather than infection "per se" and even scores used as complementary tools are usually non-specific[5-7].

Procalcitonin (PCT) is a protein precursor of calcitonin[8], and its concentration appears to be correlated with the severity of infection[9-12]. The usefulness of PCT as diagnostic and prognostic marker has been reviewed in some meta-analyses, but the results are still somewhat controversial[13-15]. Although some data have been published on the use of PCT in detecting infectious diseases in ED[16-21], there is relatively little information regarding the diagnosis of sepsis in patients presenting to the ED, and of serial PCT measurements to follow the course of infection[22].

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The aims of this study were: (1) to evaluate the diagnostic usefulness of PCT measurement in patients admitted to the ED with signs of systemic or local infection in order to determine the ability of this marker to diagnose infectious diseases, and (2) to evaluate the potential utility of repeated PCT measurements in predicting hospital mortality.

Materials and Methods

A prospective, observational study was conducted in our 400-bed General Teaching Hospital. 261 patients were enrolled in the study (121/140 M/F, mean age 72.7±15.1 years). Patient characteristics are shown in Table I.

Patients arrived in ED from October 2008 to September 2009 with signs of infections on the basis of anamnestic data, physical examination, vital parameters, instrumental and laboratory tests. The Systemic Inflammatory Response Syndrome (SIRS) criteria were obtained for each patient. The sequential organ failure assessment (SOFA) score was used to describe the severity of organ dysfunction. Sepsis diagnosis was formulated according to the guidelines of ACCP/SCCM International Sepsis Definition Conference[4]. Our study was approved by our institutional Ethics Review Board (University Sant'Andrea Hospital, Rome) in accordance with Helsinki Declaration. Each patients gave informed consent prior to enter the study.

Patients were treated in the same ED and by the same medical group. After an initial evaluation in the ED, patients were transferred to our critical care unit (CCU). Emergency physicians did not follow PCT results to guide clinical treatment of patients because these results were blinded. Length of stay in the CCU was 8 ± 5.6 days.

Vital parameters were recorded at ED arrival (T°C was recorded every 6 hours daily during hospitalization). Instrumental tests [chest X-ray, ECG, blood gas analysis in each patient, and, in selected cases, abdomen and cardiac ultrasonography, and computed tomography (CT) scan] were performed.

Blood cultures or other biological fluids cultures were performed in patients at the arrival in ED, at 30, and 90 minutes before antibiotic therapy. For blood cultures 5 to 10 ml blood samples was decanted into a blood culture container for a final dilution of 1:10, and sent immediately to the microbiology laboratory.

Blood tests as hemocromocytometric exam, urea, creatinine, electrolytes, transaminases, c reactive protein (CRP), coagulation parameters were performed as routine ED tests. CRP measurement was repeated at day 5 (T5).

Exclusion criteria were: age ≤ 18 years, autoimmune diseases[23], tumors[24], viral[25] or parasitic in-

Table I. Clinical and demographic features of the patients.

Characteristics	Total (261)	Sepsis (96)	Local infections (165)
Age (yrs)	72.7 ± 15.1	72.6 ± 9.5	73.4 ± 10.2
Gender (male/female)	121/140 (46/54%)	39/57 (41/59%)	82/83 (49/51%)
Comorbidities			
Coronary artery disease	54 (18%)	10 (10%)	44 (27%)
Hypertensive disease	118 (39%)	39 (41%)	79 (48%)
Peripheral vascular disease	16 (5%)	4 (4%)	12 (7%)
Cerebrovascular disease	46 (15%)	16 (17%)	30 (18%)
COPD	81 (26%)	14 (14%)	67 (41%)
Diabetes mellitus	73 (24%)	20 (21%)	53 (32%)
Chronic Heart Failure	40 (13%)	9 (9%)	31 (19%)
Renal dysfunction	40 (13%)	14 (14%)	26 (16%)
Chronic liver dysfunction	15 (5%)	2 (2%)	13 (8%)
Gastrointestinal disease	11 (4%)	2 (2%)	9 (5%)
Vital findings			
T°C	37.1 ± 0.9	37.6 ± 1.0	36.8 ± 0.8
Oxygen Saturation%	91.5 ± 8.3	90.7 ± 10.2	91.8 ± 7.3
Respiratory rate (breaths/minute)	20.2 ± 5.1	22.6 ± 4.9	19.2 ± 5
Heart Rate (beats/minute)	94 ± 18.7	103.1 ± 18.9	90.6 ± 18
Systolic blood pressure	127.3 ± 31.8	116 ± 32	133.1 ± 30.7

COPD: chronic obstructive pulmonary disease; T°C: Temperature ° Celsius.

fections[26], pancreatitis[27], trauma[28], patients who, within 1 week before presentation, had already started antibiotic therapy at the time of enrolment or before admission in the ED, patients unable to give informed consent.

An event was considered to be death during hospitalization.

Procalcitonin Assay

PCT was performed at the arrival in the ED (T0), and 5 days later (T5) from the antibiotic-therapy beginning. The 5th day was chosen because the drug minimum inhibiting concentration should be guaranteed for at least 3 consecutive days (the steady state is reached in two days).

Venous blood withdrawal was performed for each patient with lithium heparinized tubes. After clotting time, each sample was analyzed without storage and performed on the mini-Vidas (bio-Merieux, Marcy L'Etoile, Craponne, France), using the ELFA technique (Vidas, Brahms PCT). The lowest concentration measured by the assay is 0.05 ng/ml (95% percentile). This is considered the cut-off for healthy individuals on the basis of manufacturer's instructions. Interassay and intrassay of the procalcitonin assay used. Following manufacturer's instructions the repeatability (intrassay precision) and interassay reproducibility (interassay precision) were calculated using a protocol based on the recommendations of CLSI EP5-A2 document[23]. Intrassay coefficients of variation as determined in our laboratory (15 human serum samples in duplicates in 5 parallel determinations) were, depending on the sample concentration, between 2.0% and 3.2%.

- Interassay coefficients of variation as determined in our laboratory (measurements of the same samples on 7 different days) were, depending on the sample concentration, between 3.0% and 5.5%.
- Assay sensitivity (95Th percentile on 200 normal subjects) is < 0.05 ng/ml.

Statistical Analysis

Data are expressed as mean ± standard deviation (SD). Comparison of two means was performed using the Student's *t* test, and comparison of two proportions using χ^2 test. Pearson's test has been used for coefficients of correlation.

To determine the prognostic value of PCT for death in septic patients and in total population the receiver-operating characteristic (ROC) curve and area under (AUC) the ROC curve were constructed and the *p*-value was obtained by Wald test.

A logistic multivariate model was performed to select the variables most predictive of patient outcome (in terms of mortality). 95% Confidence Intervals (CI) for Odd's Ratios (OR) were calculated using the Wald method.

We calculated the difference between PCT values at T0 and T5, and this is indicated as delta PCT (PCT). The changes between the two values (time 0-5 days later) is calculated as a proportion of ΔPCT/PCT at time 0 and expressed in percentage.

p value < 0.05 was considered to be statistically significant in all tests.

The analyses were performed using SAS System 8.2 software for Windows (TS2M0, Chicago, IL, USA).

Results

Patients' characteristics are shown in Table I.

In 96 patients (36.7%) the diagnosis was sepsis, while 165 patients had local infections [7 urinary infections (2.6%), 13 skin infections (4.9%), 131 respiratory infections (50.1%), 14 gut infections (5.3%)].

Data on the etiology of infections provided by blood cultures were: Gram negative bacterial infections in 51 subjects (19.5%), Gram positive infections in 22 subjects (8.4%), fungal infections in 14 subjects (5.3%), and in 66.7% of cases blood cultures were negative (174 subjects). All patients with local infections showed negative blood cultures, but also 33 (12.6%) patients with the diagnosis of sepsis.

T0 PCT levels were higher (14.7 ng/ml) in Gram negative infections. The more frequent types of Gram negative detected germs were *Escherichia coli, Pseudomonas aeruginosa*, and *Proteus*; of Gram positive were *Staphylococcus aureus* or *hemolyticus*, and of fungi were *Candida* species.

22 patients with local infections had positive cultures of biological fluids (sputum, drainage liquid, wound/cutaneous swabs and urine) but not of blood cultures.

36 patients died in hospital: 32 sepsis, and 4 patients with respiratory infections. In the group of patients who died during hospitalization the germs isolated in blood cultures were: 8 Gram + (*Staphylococcus* type), 23 Gram – (the most frequent germs were *Enterococcus* species), 5 *Candida* species.

PCT Measurements

Mean PCT values at T0 were 7.1±17.9 ng/ml, and statistically decreased at T5 (3±9.1 ng/ml) ($p < 0.0001$). PCT septic patients mean values at T0 were 16±26.3 ng/ml with a significant statistical decrease at T5 (6.9±13.4 ng/ml) ($p < 0.003$), and in local infections PCT mean values at T0 were 2.1±6.8 ng/ml statistically decreased at T5 (0.7±3.7 ng/ml) ($p < 0.01$). PCT measured in septic patients was statistically different than PCT measured in patients with local infections, both at T0, and at T5 ($p < 0.0001$) (Figure 1).

At T5 mean PCT values in non-survivors patients were high (9.1±15.2 ng/ml) in the entire study population, while in survivors they were lower (2±7.3 ng/ml) with a statistical difference between the two groups ($p < 0.02$).

Similarly, septic patients mean PCT values in non-survivors patients were high at T5 (10.7±16.2 ng/ml) compared to T0 (6.1±11.8 ng/ml, p = n.s.) but they were not statistically different.

There was a statistical difference between PCT T0 mean values of septic survivors vs non-survivors (20.8±29.8 ng/ml *vs* 6.1±11.8 mg/ml, $p < 0.0001$), and also between PCT T5 mean values of septic survivors vs non-survivors (5.1±11.6 ng/ml *vs* 10.7±16.2 ng/ml, $p < 0.02$).

A statistical significant difference was showed also between non-survivors who increased their Δ%PCT (28/65) in comparison to non-survivors with decreased Δ%PCT (8/159) ($p < 0.0001$). The mean percentage of PCT increase in patients with events was 77.7% (28/36 deaths).

The mean Δ%PCT decrease was 28% in our whole population studied, and considering this percentage as a cut-off we demonstrated that those patients with a decrease > 28% showed a lower number of events (10), with a statistical significant difference if compared to those patients who had a decrease < 28% (26) ($p < 0.004$).

Among patients who normalized their PCT at T5 (< 0.05 ng/ml) (102/261= 39%) there was only one event.

To evaluate if the events were correlated to the increasing concentration of PCT we divided patients in the 5 groups of ACCP/SCCM criteria on the basis of PCT values at T5: Group 1 (< 0.05 ng/ml), Group 2 (> 0.05-0.5 ng/ml), Group 3 (> 0.5-2 ng/ml), Group 4 (> 2-10 ng/ml), and Group 5 (> 10 ng/ml). The results demonstrated that most events occurred in the two last groups (15 and 10 events respectively).

There was a significant correlation in septic patients between SOFA score and PCT at T0 when the outcome death was considered (r = 0.72, $p < 0.0001$); in the total population there was a weak but significant correlation (r = 0.21, $p < 0.0004$). The SOFA score mean value in sepsis was 3.9± 2.4, and 2.9±1.9 in the whole study

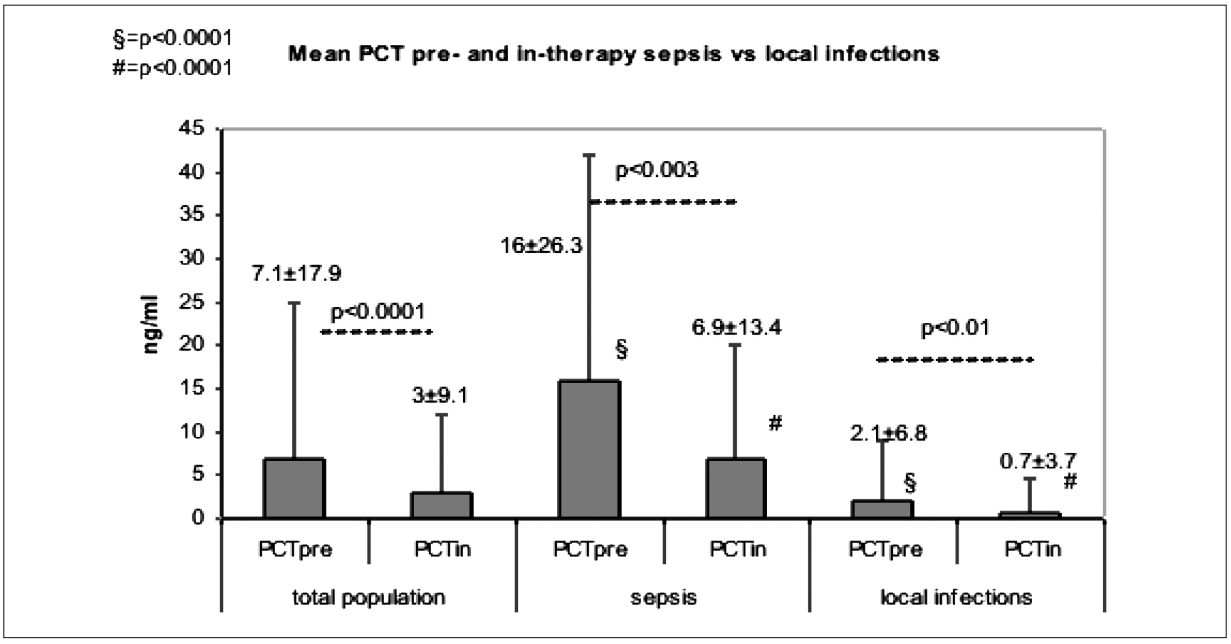

Figure 1. Mean (±SD) PCT values (ng/ml) at T0 (pre-therapy) and at T5 (in therapy) in total population, in sepsis, and in local infections.

Table II. ROC curve for PCT and CRP levels at T0, and at T5 for prediction of sepsis (a), for prediction of death in septic patients (b), and for prediction of death in total population (c).

	AUC^{ROC}	*p* value	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV % (95% CI)	NPV % (95% CI)
Sepsis (a)						
PCT T0	0.79	< 0.0001	76 (68-85)	69 (63-75)	53 (45-62)	86 (81-91)
PCT T5	0.81	< 0.0001	62 (52-72)	84 (78-89)	69 (59-78)	79 (73-85)
CRP T0	0.70	0.9	100	9 (5-13)	34 (28-39)	100
CRP T5	0.76	0.002	97 (94-100)	20 (14-27)	38 (31-45)	94 (86-100)
Death in sepsis (b)						
PCT T0	0.66	0.4	71 (55-87)	22 (12-32)	30 (20-41)	61 (41-81)
PCT T5	0.70	< 0.001	87 (75-99)	50 (38-62)	46 (33-58)	89 (79-99)
CRP T0	0.56	0.9	100	0	32 (23-42)	100
CRP T5	0.71	0.9	100	4 (0-9)	34 (23-44)	100
Death in total population (c)						
PCT T0	0.41	0.007	67 (51-82)	58 (52-63)	18 (11-24)	93 (89-97)
PCT T5	0.83	< 0.0001	86 (75-97)	76 (70-81)	36 (26-46)	97 (95-100)
CRP T0	0.62	0.9	100	7 (4-10)	13 (9-17)	100
CRP T5	0.84	0.9	100	17 (11-22)	15 (10-20)	100

population ($p < 0.0001$). The mean SOFA score was 5.1±2.8 in non-surviving septic patients.

CRP Measurements

Mean CRP values at T0 were 15.8±12.8 mg/dl, and at T5 they were 7.9±9 mg/dl with a significant statistical difference ($p < 0.0001$). There was a statistical difference between CRP mean values measured in septic patients at T0 and at T5 (21.4±14.2 *vs* 13.2±10.4 mg/dl, $p < 0.0001$), and also in local infections (T0 = 12.3±11.4 *vs* T5 = 5.2±6.9 mg/dl, $p < 0.0001$).

A weak but significant correlation has been found between PCT and CRP at T0 (r = 0.30, $p < 0.0001$), and at T5 (r = 0.24, $p < 0002$).

ROC Curves

AUC^{ROC} for the diagnosis of sepsis, for prediction of death in sepsis and in total population studied are showed in Table II.

Table III shows the AUC^{ROC} of Δ%PCT for prediction of death in septic patients and in whole population. Δ%PCT alone (AUC 0.88) or combined with PCT at T0 (AUC 0.89) is highly predictive of death in sepsis.

Multiple Regression Analysis

The results of a multiple logistic regression analysis to identify variables associated with sepsis or mortality in sepsis are summarized in Table IV. A T0 PCT level > 2 ng/ml, a T5 PCT level > 2 ng/ml, and a CRP T5 level > 0.5 mg/dl were strongly independently associated with the presence of sepsis (Table IV). Only T5 PCT was considered a significant predictor of death in sepsis (Table IV). Other parameters as heart rate > 90 beats/min, body temperature > 38°C/< 36°C, leukocytes > 12,000/< 4,000 cells/mm^3, respiratory rate > 20/min were not independently associated with sepsis or mortality in sepsis.

Table III. ROC curve for Δ% PCT, and for PCT pre & Δ% PCT for prediction of death in total population, for prediction of sepsis, and for prediction of death in sepsis.

Description	AUC	*p* value
Δ% PCT for prediction of death	0.824	0.03
Δ% PCT for prediction of sepsis	0.446	0.22
Δ% PCT for prediction of death in sepsis	0.884	0.00007
PCT pre & Δ% PCT prediction of death	0.728	0.1
PCT pre & Δ% PCT prediction of sepsis	0.833	0.00001
PCT pre & Δ% PCT prediction of death in sepsis	0.893	0.0004

Δ% PCT PCT variation (T5-T0) in percentage.

Table IV. Multivariate analysis for sepsis (a), and for death in sepsis (b).

Parameters	Odds ratio	95% CI	*p* value
Sepsis (a)			
PCT T0	1.05	1.018-1.097	0.004
> 0.5 ng/ml	2.23	1.134-4.804	0.02
> 2 ng/ml	4.27	2.166-8.434	< 0.0001
PCT T5	1.07	1.004-1.140	0.03
> 0.5 ng/ml	4.15	2.022-8.541	0.0001
> 2 ng/ml	6.53	2.773-15.381	< 0.0001
CRP T0	1.02	0.989-1.055	0.19
CRP T5	1.08	1.035-1.137	0.0007
> 0.5 mg/dl	4.36	0.972-19.634	0.05
Gender (female)	0.34	0.159-0.730	0.005
Age	0.99	0.969-1-019	0.61
Cardiovascular Diseases	1.12	0.535-2.352	0.76
Diabetes	0.45	0.190-1.077	0.07
Hypertension	0.75	0.339-1.672	0.48
Chronic Kidney Failure	1.06	0.340-3.318	0.91
COPD	0.31	0.122-0.805	0.01
Death in sepsis (b)			
PCT T0	0.82	0.714-0.955	0.009
PCT T5	1.29	1.041-1.622	0.02
CRP T0	0.99	0.931-1.053	0.74
CRP T5	1.08	1.012-1.173	0.02
Gender (female)	2.77	0.559-13.783	0.21
Age	1.02	0.976-1.074	0.32
Cardiovascular Diseases	1.35	0.302-6.102	0.69
Diabetes	0.27	0.035-2.068	0.20
Hypertension	3.50	0.639-19.202	0.14
Chronic Kidney Failure	0.43	0.054-3.485	0.43
COPD	0.88	0.117-6.670	0.90

COPD: chronic obstructive pulmonary disease.

Discussion

From our data the evaluation of PCT concentration in patients presenting to the ED for acute infections provides important diagnostic value in distinguishing between patients with sepsis or local infections in the very early phases of the diseases. This is in accordance with many other reports[9-12].

The ED physician plays a central role in detecting acute and severe infections as well as in starting a quick and appropriate treatment. In fact, there is much evidence that the faster the ED physician starts antibiotics in patients with infections, the better is the outcome. Our results suggest that PCT is useful as an aid in the differential diagnosis to distinguish local infections from sepsis. The difference of the terms "systemic" from "local" infection is based on the evidence that the first is defined as an infection spread throughout the body and interesting more organs and tissues, while the second one is an infection confined to a local area of the body, i.e. an organ[4]. The term "systemic infection" can be considered a synonym of "sepsis" that includes an heterogeneous group of symptoms and signs which, often, leads to confusion in diagnosis. The AACP/SCCM conference in 1992 tried to formulate diagnostic criteria for sepsis, defined a systemic inflammatory response to infectious agents, but unfortunately some patients diagnosed as septic do not have documented infection especially in the early phases. So it could be of interest to understand the potential additional, but also early, diagnostic value of PCT in sepsis and local infection also in according to antibiotic treatment during hospitalisation.

Also of noteworthy importance is the prognostic role of PCT evaluation at baseline in infectious diseases. It is also of great impact for ED physician to stratify the prognostic risk and also to allocate the patients in hospital higher intensity care unit (ICU) beds.

Until now, although there was much literature showing the usefulness of PCT as diagnostic and prognostic factor in local infections, as well as sepsis in the ICU there was relatively scarce data

about PCT use in the emergency setting, especially with serial measurements[22,30-34]. Looking at the serial PCT assessment in hospital, our data show that PCT concentrations were significantly decreased ($p < 0.0001$) after 5 days of antibiotic therapy. Until now, published data have stressed the utility of PCT guided antibiotic-therapy mainly in local infections and based only on a unique measurement of PCT, and only recently Nobre et al[35] published results on serial measurement of PCT in septic patients during therapy. The Authors showed that serial PCT variations allow the physician to discontinue therapy when PCT decreases by 90% the initial value, but also other papers[36-38] have demonstrated the usefulness of serial PCT as a guide for antibiotic therapy, such as the PRORATA study recently published, and the proHOSP on lower respiratory tract infections.

In our study, PCT in septic patients was statistically decreased at T5 if compared to T0 ($p < 0.003$). The behaviour of PCT in local infections was similar (Figure 1). This is in accordance with literature data. In fact, Charles et al[39] showed that in septic patients on day 2 and 3 of antibiotic therapy there was a significant decrease of PCT levels. The Hellenic Sepsis Study group[22] also demonstrated that a decrease of PCT values during the first 48 hours of therapy is fundamental to obtain beneficial effects from antibiotics.

Moreover, from our data PCT values in non-survivors increased during therapy, while, on the contrary, there was a significant PCT decrease in survivors. This is in accordance with Giammarello-Bourboulis et al[30] who showed that septic non-survivors patients have higher values of PCT in comparison to survivors, furthermore, in worsening septic patients repeated measurements of PCT showed a trend in increasing values. Similar findings are evident in our study where non-surviving patients with worsening infection showed an increase of PCT levels, while on the contrary patients who survived had a dramatic decrease of PCT both in whole population studied, and in septic patients. Charles et al[39] showed similar results in an ICU setting. PCT levels in septic patients were found to be significantly higher in non-survivors than in survivors on the third and fourth day of therapy. Also Boussekey et al[40] showed that in community pneumonia patients a rapid increase, from day 1 to 3, is a poor prognostic factor. Our data show also a singular phenomenon, in fact at T0 septic survivors showed mean PCT values significantly higher than non-survivors (20.8 *vs* 6.1 ng/ml) ($p < 0.0001$). In our opinion this could be due to the extreme variability in PCT levels measured in our study on a wider group of surviving patients in comparison to the group of non-survivors, and, also, to not "normally" distributed PCT values. Moreover, it should be noted that, in non-survivors, germs involved in sepsis were preferably *Enterococcus* species which represent a bacterial population thought to be treated easily in comparison to other species such as *Proteus, Pseudomonas* or *Klebsiella* which are considered "major" bacteria. This could lead the emergency physician to underestimate the potential risks of the "minor" bacteria such as *Enterococcus*. It could be hypothesized that PCT release is "dependent" on the type of germ involved in the infectious process. Furthermore, the elementary structure of these "minor" bacteria do not permit a good immune response to the release of PCT, so we could find lower levels of PCT at T0 in patients who do not survive to the infection.

Moreover, eleven septic non-surviving patients had negative blood cultures, this could be done to the eventual presence of the so-called "difficult" bacteria that need a longer timing of culture to develop, and that require a specific therapy in consideration of their poly-resistance to routine daily types of antibiotics. This could have lead to an initial lower level of PCT at T0 and, consequently, to an underestimation of the severity of sepsis in these patients with an antibiotic approach not aggressive enough to eliminate circulating germs in the organism.

When the difference of PCT at T0 and T5 is studied, we show that the prediction value of Δ% PCT, for death in both the total population studied and in septic patients, is of great importance; Δ %PCT appears to be a strong predictor of death in hospital, and its combination with PCT at T0 had an AUC even higher in predicting death in septic patients (AUC 0.89) than Δ%PCT alone.

When we calculate the mean Δ%PCT decrease (28%) in our whole studied population, and we consider arbitrarily this percentage as a "cut-off" value we demonstrate that those patients who had a decrease Δ%PCT > 28% at T5 had lower mortality rate, and the difference was significant if compared to those patients who did not had a decrease > 28% ($p < 0.004$). This is of importance because this could suggest the creation of a cut-off percentage of PCT decrease during therapy below which we could be relatively confident to not have infection-related deaths, and so to use it

to titrate and/or discontinue therapy. In a recent paper Karlsson et al[41] used an arbitrary cut-off of 50% PCT decrease, and in those patients in which the PCT decrease was > 50% mortality was lower compared to those with a PCT decrease < 50%.

Moreover, if we consider non surviving patients who increase their Δ%PCT in comparison to non-survivors who decrease it, we found a statistical significant difference between the two groups ($p < 0.0001$). This could indicate that Δ%PCT reduction after 5 days of antibiotic therapy could be really useful to discriminate those patients in which events occur more frequently; in fact in patients with events Δ%PCT is increased with a mean 77.7%. This result could be useful to understand that the timing of initiating and titrating antibiotic therapy in an emergency ward on the basis of the behaviour (increase or decrease) of PCT during patient's stay in ED/CCU is of great relevance.

The findings that deaths occur mainly in the two last groups of PCT values based on ACCP/SCCM criteria represents the confirmation of the prognostic power of this biomarker, and, interestingly, the events occur independently by the PCT group values after the cut-off of 2 ng/ml. In fact Group 4 has more events if compared to the Group 5, and it is probably due to the fact that this difference is, perhaps, given to the more aggressive therapeutic approach provided to patients who inspire in emergency physician a sensation of a more severe degree of infection, and this could represent a methodological error that could lead to a consequent worsening of patient's conditions in terms of long-term survival.

Therefore, it is of paramount importance to treat every patient in the same manner when a PCT > 2 ng/ml is measured. This could decrease future events, even in patients with severe sepsis, and not only in those with septic shock.

PCT during therapy is predictive of death (AUC 0.83, $p < 0.0001$) in the total studied population (CRP shows a similar AUC 0.84, but not significant). The AUC for sepsis diagnosis was greatest for PCT (AUC 0.79 at T0, and AUC 0.81 at T5) followed by CRP (AUC 0.70 at T0, and AUC 0.76 at T5) (Table II). PCT could be considered a sensitive tool to predict mortality both in total population, and it has a high sensitivity and specificity to discriminate sepsis from local infection.

PCT appears to be a strong independent factor, compared to the other covariates considered, for diagnosis of sepsis at T0 but also at T5, when PCT cut-off (internationally accepted) of > 2 ng/ml (OR = 6.53) is considered. Also CRP is independently associated with the diagnosis of sepsis if a cut-off level > 0.5 mg/dl is considered (OR = 4.36) (Table IV). Moreover, in septic patients the increase of PCT at T5 is an independent factor of mortality (OR = 1.29, $p < 0.02$), CRP has a similar behaviour even if it shows an OR slightly lower (OR = 1.08, $p < 0.02$) (Table IV).

In our study we showed a significant correlation between SOFA score and PCT at T0 measured in our non-surviving septic patients indicating that this biomarker, combined with a clinical score, could be useful to assess the severity of infection. The mean SOFA score was higher in septic patients in comparison to the general population studied ($p < 0.0001$). There was also a significant correlation between PCT and CRP at T0 and at T5 indicating that both are useful as diagnostic and prognostic markers of infectious disease but PCT is an earlier marker compared to CRP. The lower correlation between these two biomarkers at T5 in comparison to T0 could be explained by this different kinetics of these molecules, in fact PCT decreases more rapidly than CRP in response to therapy and this has been demonstrated also by Castelli et al[12]. CRP remains elevated for a longer time, while PCT gives rapid information on the trend of the disease during antibiotic therapy. This in particular seems really useful in the ED setting.

Regarding the limitations of the study: we did not employ a strict selection criteria for patient enrolment, but rather included all patients that arrived in ED with signs of infections. In particular, we also studied patients with very severe infections, and our ED/CCU mortality rate could be influenced by this. We measured PCT only two times, at arrival and after 5 days of antibiotic therapy to evaluate the kinetic response of the molecule to the antibiotics. In addition, we did not consider any change in therapy based on PCT results as these were blinded. Antibiotic therapy was discontinued when clinical and laboratory signs of infection disappeared.

Our results show that, in infections, antibiotic therapy decreases PCT and it could be useful to titrate the therapy and also to discontinue it when there is a decrease of PCT levels during hospitalization.

PCT is a useful marker for the early diagnosis of infectious diseases, both local or systemic, and to predict patient's death. From our findings it seems important to assess a rapid PCT measurement in a febrile patient at the arrival in ED, and also to standardize timing of serial measurements

in the ED in order to indicate the exact time to discontinue antibiotic therapy. So, for patients arriving in the ED with acute infections, PCT is a useful marker to diagnose sepsis and local infections, and to predict hospital mortality.

Moreover, assessment of PCT during 5 days after starting antibiotic treatment can allow the possibility to identify patients in which the decrease of PCT > 28% is a predictor of lower mortality.

Normalization of PCT suggests a good response of treated patients to infection possibly leading to less infection-related deaths.

Conclusions

In patients with acute infectious disease the monitoring of PCT after antibiotic treatment in the ED/CCU should be aimed to reach a decrease of PCT around 30% in the first days of therapy with an eventual normalization to obtain a complete survival of these patients.

It could also be useful to create a standardized cut-off PCT difference in percentage to develop a simple algorithm to monitor antibiotic therapy in ED.

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