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Procalcitonin is useful in driving the choice of early antibiotic treatment in patients with bloodstream infections

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Abstract. – OBJECTIVE: To evaluate whether PCT levels could be used to distinguish among different bacterial and fungal etiologies in patients with documented bloodstream infection (BSI).

PATIENTS AND METHODS: Monocentric retrospective cohort study on patients admitted to the Fondazione Policlinico Gemelli Hospital between December 2012 and November 2015 with BSI. Those who had undergone PCT determination within 48 hours of when the first positive blood culture was sampled were included in the study.

RESULTS: Four hundred and one patients were included in the study. Both the 24h and 48h PCT values were significantly higher in patients with Gram-negative (GN) BSI than in those with Gram-positive (GP) or candida BSI (*p* at ANOVA = 0.003). A PCT value of > 1 ng/ml was found in 31.5% of patients with GN BSI. Less than 7% of people with candida BSI had PCT level of > 1 ng/ml. At multivariable regression analysis, GN BSI, septic shock, and plasma creatinine were significantly correlated with PCT values.

CONCLUSIONS: PCT may be of value in distinguishing GN BSI from GP, and fungal BSI and PCT values of > 1 ng/ml could be used to prevent unnecessary antifungal treatment.

Key Words:
Procalcitonin, Bloodstream infection, Candidemia, Antibiotic stewardship.

Introduction

Sepsis is a leading cause of critical illness worldwide. It is associated with a mortality rate[1] of up to 40% if a septic shock is present[2]. Retrospective analyses of national and international databases[3-7] have revealed that the incidence of sepsis has increased over time. Moreover, the incidence of sepsis caused by multidrug-resistant microorganisms, particularly Gram-negative (GN) bacteria, has been rising for the past few decades[8].

When sepsis is suspected, timely initiation of an appropriate therapy is associated with better survival[1]. However, prompt and accurate detection of sepsis remains a challenge. Several sepsis biomarkers have been identified and investigated to determine their utility in enabling rapid and accurate clinical decisions regarding antibiotic treatment[9].

Procalcitonin (PCT) is the prohormone of calcitonin. It is produced ubiquitously in response to endotoxins and cytokines. PCT is rapidly induced (levels peak within 4-12 h after infection) and has a long half-life, but PCT levels decrease rapidly once the infection is under control[10].

Many researches, including randomized clinical trials (mostly conducted in intensive care unit [ICU] settings) and meta-analyses, have demonstrated that PCT levels can potentially be used to diagnose sepsis[11], predict prognosis[12] and provide information about disease severity[13]. Moreover, PCT levels can be used to reduce the duration of antibiotic therapy[14-15]. However, few studies have evaluated the predictive value of PCT with respect to discriminating among sepsis etiologies[16]. The aim of the present work was to evaluate whether PCT levels could be used to distinguish among different bacterial and fungal etiologies in patients with documented bloodstream infection.

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Patients and Methods

In this monocentric retrospective cohort study, we reviewed all cases of patients admitted to the Fondazione Policlinico Gemelli Hospital between December 2012 and November 2015 with clinical sepsis and bloodstream infection (BSI). Patients who had PCT determination within 48 hours of the first positive blood culture sampling were included in the study. Notification of our study was sent to the Ethics Committee of the hospital.

Clinical sepsis was defined in accordance with the International Sepsis Definitions Conference[17]. BSI was defined as the recovery of any bacterial or fungal species in one or more blood cultures. Patients positive for staphylococcus other than *S. aureus* were included in the study when the same species with the same resistance pattern grew from at least two consecutive samples. BSIs were stratified according to etiology: Gram-positive (GP) BSI, GN BSI, candida BSI, and mixed BSI (GP and GN bacteria in the same blood culture, GP bacteria and candida in the same blood culture, or GN bacteria and candida in the same blood culture). If the patient developed more than one episode of BSI, we considered only the first episode.

We also collected demographic and clinical data at the onset of sepsis from electronic medical records. They included age, gender, hospital ward, hospitalization in the 3 months before BSI, antimicrobial therapy in the 3 months before BSI, clinical severity (with or without septic shock at onset), Acute Physiology and Chronic Health Evaluation (APACHE II) score, and serum creatinine level (mg/dl).

Serum PCT assessment was performed within a 24- or 48-h window around blood cultures. We excluded cases in which the PCT assessment took place > 48 h before or after the diagnosis of BSI.

PCT levels were measured in serum samples with the chemiluminescent assay ADVIA Centaur BRAHMS (Thermo Fisher Scientific, Munchen, Germany) in accordance with the manufacturer's instructions. The functional sensitivity of the assay was 0.05 ng/ml, and the sensitivity within the measurement range was 0.05-150 ng/ml. The inter- and intra-assay coefficients of variation were < 10% and < 8%, respectively.

Blood cultures were performed in accordance with hospital protocol. Isolates were identified by matrix-assisted laser desorption ionization time-of-flight (MALDI-TOF) mass spectrometry (Bruker Daltonics GmbH, Billerica, MA, USA). The *in vitro* susceptibility of the isolates was assessed with the Vitek 2 system (BioMerieux, Marcy-l'Etoile, France) and the Sensititre broth microdilution method (Trek Diagnostic Systems, Thermo Fisher Scientific, Munchen, Germany). Results were classified in accordance with the European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints (http://www.eucast.org/clinical_breakpoints).

Statistical Analysis

We report variables with a normal distribution as mean ± standard deviation (SD) unless otherwise stated. Continuous variables were compared by the Mann-Whitney U test, while categorical variables were compared with the chi-square test or Fisher's test when appropriate. The PCT level was considered as the independent variable. We also built a multivariable model (linear regression analysis) to identify parameters significantly correlated with PCT levels. Any parameter associated with PCT level with a p-value of < 0.10 in univariate analysis was included in the multivariable analysis. We evaluated the diagnostic performance of PCT by means of receiver operating characteristic (ROC) curves. We selected the cutoff value for PCT to predict GN BSI by considering the sum of the highest sensitivity and specificity. Statistical analyses were performed with SPSS for Windows version 15 (IBM, Armonk, North Castle, NY, USA).

Results

We included 401 patients with BSI in the study. All patients had a PCT value available from a sample drawn within a 48-h window of positive blood culture. Demographic and clinical characteristics of the population study are shown in Table I. Of the 401 patients included in the study, 133 had GN BSI, 130 had GP BSI, 59 had candida BSI, and 79 had mixed BSI (19.7%). When we considered only patients with BSI and a PCT value within a 24-hour window ($n = 292$), 92 patients had GN BSI, 97 had GP BSI, 41 had candida BSI, and 62 had mixed BSI (21.2%). PCT mean values are shown in Table II. The 48 h PCT values were significantly higher in patients with GN BSI (10.4 ng/ml, SD 26.9 ng/ml) than in those with GP BSI (2.8 ng/ml, SD 14.6 ng/ml) or candida BSI (0.8 ng/ml, SD 4.9 ng/ml) (analysis of variance [ANOVA] $p = 0.003$). Differences in

Table I. Demographic and clinical characteristics of study participants (no. = 401).

Variables	Values
Men	226 (56.4)
Age, median (IQR) years	70 (60-80)
Ward of hospitalization	
Medical	279 (69.5)
Surgical	97 (24.1)
Intensive care	25 (6.2)
Hospitalization in the 3 months before sepsis	160 (39.9)
Antimicrobial therapy in the 3 months before sepsis	124 (30.9)

Values provided are n (%) unless otherwise indicated. IQR, interquartile range.

PCT between GP BSI and candida BSI patients were not statistically significant ($p = 0.15$)

More patients with GN BSI or mixed GP/GN BSI had PCT levels of > 2 ng/ml than those with GP BSI (chi-square $p < 0.001$) or candida BSI (chi-square $p = 0.002$). In patients with GP BSI, 48 h PCT values were slightly higher (2.8 ng/ml, SD 14.5) than in those with candida BSI (0.77 ng/ml, SD 4.90) (ANOVA $p = 0.29$). Less than 5% of people with candida BSI or mixed candida-bacterial BSI had a 48 h PCT level of > 2 ng/ml (Table III), and only 7% of people with candida BSI or mixed candida-bacterial BSI had a 24 h PCT level of > 1 ng/ml.

Among patients with GP BSI, those with BSI from *S. aureus* tended to have higher PCT values than patients with BSI from coagulase-negative staphylococci (3.83 ± 17.1 *vs.* 0.14 ± 0.53, $p = 0.10$). Patients with BSI due to methicillin-resistant *S. aureus* tended to have higher PCT values than those with BSI due to methicillin-susceptible *S. aureus* (6.46 ± 22.2 *vs.* 0.24 ± 0.58, $p = 0.12$).

Linear regression analyses revealed that APACHE II values were significantly correlated with PCT values ($p = 0.001$). Table IV shows the sensitivity and specificity of the cutoffs 1 ng/ml and 2 ng/ml. Figure 1 presents the ROC curves for 24 h-PCT > 1 ng/ml and 48 h-PCT > 1 ng/

Table II. Mean PCT values according to BSI etiology.

Etiology	No.	24 h PCT, mean (SD)	No.	48 h PCT, mean (SD)
Monomicrobial				
Gram-positive bacteria	97	3.4 (16.6)	130	2.8 (14.5)
Gram-negative bacteria	92	12.2 (28.6)	133	10.4 (26.9)
Candida	41	1.07 (5.9)	59	0.8 (4.9)
Mixed				
Gram-positive and -negative bacteria	43	11.1 (26.9)	49	9.7 (25.4)
Gram-positive bacteria + candida	16	3.1 (12.2)	24	2.1 (10.0)
Gram-negative bacteria + candida	3	0.1 (0.1)	6	0.1 (0.1)
Total	**292**	**6.9 (22.0)**	**401**	**5.8 (20.3)**

BSI, bloodstream infection: PCT, procalcitonin.

Table III. Patients with PCT values > 1 ng/ml or > 2 ng/ml according to BSI etiology.

Etiology	24 h PCT			48 h PCT		
	No.	> 1 ng/ml, n (%)	> 2 ng/ml, n (%)	No.	> 1 ng/ml, n (%)	> 2 ng/ml, n (%)
Monomicrobial						
Gram-positive bacteria	97	8 (8.2)	8 (8.2)	130	10 (7.7)	10 (7.7)
Gram-negative bacteria	92	29 (31.5)	22 (23.9)	133	38 (28.5)	26 (19.5)
Candida	41	3 (7.3)	2 (4.9)	59	3 (5.1)	2 (3.4)
Mixed						
Gram-positive and -negative bacteria	43	11 (25.6)	10 (23.3)	49	11 (22.4)	10 (20.4)
Gram-positive bacteria and Candida	16	1 (2.3)	1 (2.3)	24	1 (4.2)	1 (4.2)
Gram-positive and -negative bacteria	3	0 (0)	0 (0)	6	0 (0)	0 (0)
Total	**292**			**401**		

BSI, bloodstream infections. PCT, procalcitonin.

Table IV. Demographic and clinical characteristics of study participants (no. = 401).

PCT	GN BSI *vs* all other causes	
	> 1 ng/ml	> 2 ng/ml
24 h		
Sensitivity	0.29	0.23
Specificity	0.93	0.93
PPV	0.78	0.74
NPV	0.59	0.57
+LR	4.01	3.21
−LR	0.77	0.94
48 h		
Sensitivity	0.26	0.19
Specificity	0.94	0.94
PPV	0.79	0.73
NPV	0.59	0.57
+LR	4.26	3.13
−LR	0.79	0.86

PPV, positive predictive value; NPV, negative predictive value; +LR, positive likelihood ratio; −LR, negative likelihood ratio; GN BSI, bloodstream infection caused by Gram-negative bacteria; PCT, procalcitonin.

ml. Areas under the ROC curve were 0.72 (95% confidence interval 0.66-0.77) and 0.71 (95% confidence interval 0.65-0.76), respectively. We built a multivariable regression model to identify parameters that correlated with PCT values even when adjusted for potential confounders (Table V). GN BSI, septic shock, and plasma creatinine were significantly correlated with both 24 h- and 48 h-PCT values.

Discussion

In the present study, we found that in people with BSI PCT levels correlated with etiology. Mean PCT values were significantly higher in people with GN BSI (and mixed GN BSI) compared to those with GP BSI or Candida BSI. Patients with PCT > 1 ng/ml were more likely to have GN BSI, while very few cases of Candida BSI had 24 h- or 48 h-PCT values > 1 ng/ml. Approximately 8% of people with GP BSI had 24 h- or 48 h-PCT values > 1 ng/ml. In mixed BSI, PCT values seemed to be driven by the presence of GN bacteria. Differences in PCT values between patients with GP bacteria or fungal microorganisms were not statistically significant. ROC analysis suggested that PCT values had moderate accuracy in predicting GN BSI. However, we should note that a PCT value of > 1 ng/ml was found in only one-third of patients with GN BSI.

Previous studies have demonstrated differences in BSI due to GN or GP bacteria or Candida. In a study that included 50 patients, Charles et al found that bacterial BSI was associated with PCT values significantly higher than fungal BSI[18]. In a further study[19], they found significantly higher

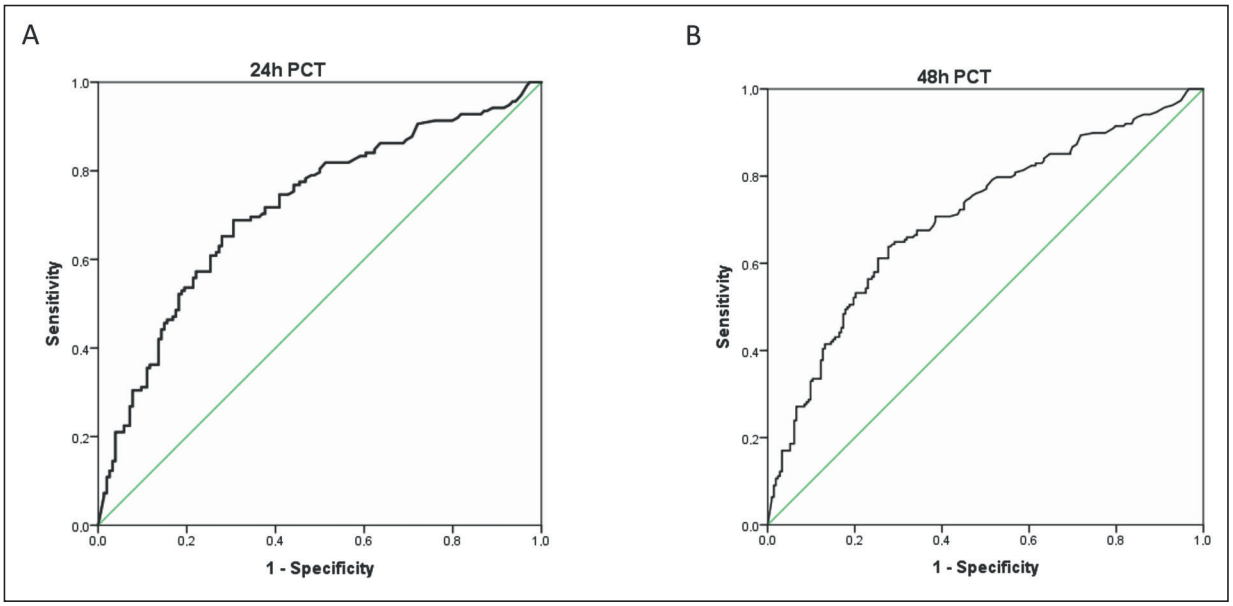

Figure 1. Receiver operator characteristic curves for 24 h-PCT > 1 ng/ml ***(A)*** and 48 h-PCT > 1 ng/ml ***(B)***.

Table V. Multiple linear regression analysis of variables correlated with PCT values.

Variables	24 h PCT		48 h PCT	
	HR	95% CI	HR	95% CI
Serum creatinine	3.2	1.8-4.5	2.9	1.8-4.0
Septic shock	21.4	13.0-29.9	19.1	11.8-26.5
GN BSI vs GP- or candida BSI	7.0	2.1-11.9	6.7	2.6-10.7
APACHE II	0.05	-3.2-9.7	-0.1	-1.6-8.6

CI, confidence interval; HR, hazard ratio; GN BSI, bloodstream infection caused by Gram-negative bacteria; PCT, procalcitonin; APACHE II, Acute Physiology and Chronic Health Evaluation II.

levels of PCT in bacteremia episodes due to GN bacteria compared to episodes due to GP bacteria. In two additional small study populations, one in surgical patients[20] and the other in ICU patients[21], levels of PCT were significantly lower in patients with candidemia than in those with bacteremia. Brodska et al[22] found that a cutoff of 15 ng/ml had a specificity of 87.8% in discriminating between GN and GP BSI. Two other works[23-24] detected lower levels of PCT in patients with Candida BSI compared to those with bacterial BSI. Unfortunately, the number of cases of fungal BSIs included in the studies cited above is very small. Leli et al[25], in a larger study population (1949 samples), confirmed significantly higher median levels of PCT in patients with GN BSI than in those with GP or fungal BSI.

Although the number of cases of staphylococcus BSI that we observed was not high, we found a trend toward higher levels of PCT in *S. aureus* infections compared to coagulase-negative (CoNS) BSI. We also observed a non-significant trend toward higher levels of PCT in methicillin-resistant *S. aureus* BSI than in methicillin-sensitive *S. aureus* BSI. This is in concordance with the results of a previous investigation of 116 patients, 95 with CoNS and 24 with *S. aureus* BSI[26]. As in previously published studies[27], GP BSI was associated with lower values of PCT than GN BSI. We did not perform an analysis of individual GN agents because the groups would have been too small to draw reliable conclusions.

The higher PCT values observed in GN BSI compared to GP BSI may be directly linked to the complicated and not fully understood pathobiology of sepsis. Pathogenic microbes have components called pathogen-associated molecular patterns (PAMPs), which include lipopolysaccharides, peptidoglycans, and beta-glucans. PAMPs play a key role in activating the innate immune defense system by binding to Toll-like receptors (TLRs). The final common result triggered by this binding is transcription of important proinflammatory cytokines such as tumor necrosis factor (TNF), interleukin (IL)-1-beta, IL-6, IL-8, and IL-12[28]. GN bacteria, GP bacteria, and fungi bind to different TLRs, and each TLR is associated with a different cytokine cascade and magnitude of response. For example, TLR4 is the main TLR involved in cell activation by GN bacteria through ligation to LPS. By contrast, TLR2 recognizes both GP bacteria and fungal components[29-30]. GN infections increase TNF alpha, IL-1, IL-6, IL-10, and IL-8 levels more than GP and fungal infections[31]. Several investigations[14, 32-33] have revealed that the cytokine cascade and bacterial LPS itself are the main inducers of PCT. Another possible explanation is the impairment of host defense mechanisms in patients with candidemia, which decrease the inflammatory response and, consequently, PCT induction[34].

We decided to use the cutoff values suggested by the manufacturers of the PCT assays that we utilized since previous studies have demonstrated their discrimination power. In Charles et al[18] and Martini et al[20] reports, the PCT cutoff was set to 1-2 ng/ml. Because the sensitivity of PCT is low but its specificity is relatively good, our study suggests that PCT values may be useful in excluding Candida BSI. PCT values in BSI may thus be very useful when deciding treatment strategies. In the present paper, the sensitivity and positive predictive value of PCT with respect to identification of GN etiological agents of BSI were not high. However, unlike most of the published studies, our study population included only patients with definitive BSI. The area under the ROC curve in our analysis was > 0.70, as in the study by Leli et al[25], confirming good power in discriminating among different etiologies. We

did not find any significant differences when we used different 24 h- and 48 h-window periods for PCT assessment. This indicates that PCT values may be useful for deciding upon therapeutic approach even when they are assessed up to 48 hours after the onset of BSI.

From a practical perspective, the results of the present study lead to two main conclusions. First, a PCT value of > 1 or 2 ng/ml may be useful in excluding Candida BSI and designating the probability of GP BSI as low. In fact, only three out of 41 cases (7.3%) of Candida BSI had a 24 h-PCT value of > 1 ng/ml and only three out of 59 cases (5.1%) of Candida BSI had a 48 h-PCT value of > 1 ng/ml. Second, a PCT value of < 1 or 2 ng/ml will not help in discriminating among different etiologies. Many patients, even those with GN BSI, had PCT values below the cutoff.

The rate of polymicrobial BSI in our work population was not negligible (19.7%), but the rate of mixed BSI including Candida was low (7.4%). Assessment of PCT levels may be only partially useful for bacterial BSI but more so for Candida BSI, by excluding it as a causative agent. This may lead to the reduction of empiric antimicrobial treatments to be administered. None of the previously published studies reported the rate of patients with PCT values below the cutoff in accordance with the different etiological agents. Thus, we were unable to make comparisons among the studies.

Our findings may be helpful to clinicians to decide empirical therapy in the first few hours when BSI is suspected. PCT levels may be a useful tool in ruling out candidemia when the PCT value is > 1 ng/ml. If our results are confirmed in further studies, starting an empiric therapy without an antifungal component may be supported in people with PCT > 1 ng/ml. This is especially true if the results of other biomarkers, such as beta-D-glucan, are available to physicians within hours after onset. This could strongly enhance the optimization of resources and reduce costs in hospitalized patients. The results of the present study are of particular value because most of the patients were in medical and surgical wards, rather than the intensive care unit.

This research has some limitations. First, we did not include a control group (patients in whom PCT was assessed but who did not have BSI). Second, the retrospective nature of the study and the heterogeneity of the population could have introduced bias. Finally, due to the monocentric design, our results are not generalizable nor should they be considered for infections other than BSI.

Conclusions

We showed that PCT may be of value in distinguishing GN BSI from GP and fungal BSI. The most important feature of a biomarker is its potential in influencing clinical decisions. If further studies confirm our findings, PCT values of > 1 ng/ml could be used to prevent unnecessary antifungal treatment.

Ethical Approval

For this type of study formal consent is not required.

Informed Consent

All patients admitted to our hospital are required to fill out a form to give their consent for the treatment of their personal data. The retrospective nature of this study does not allow us to obtain a specific informed consent from all individual participants.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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