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Usefulness of procalcitonin in differentiating *Candida* and bacterial blood stream infections in critically ill septic patients outside the intensive care unit

Filippo Pieralli[1] · Lorenzo Corbo[1] · Arianna Torrigiani[2] · Dario Mannini[2] · Elisa Antonielli[1] · Antonio Mancini[1] · Francesco Corradi[2] · Fabio Arena[3] · Alberto Moggi Pignone[4] · Alessandro Morettini[2] · Carlo Nozzoli[1] · Gian Maria Rossolini[3,5,6,7]

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Abstract We aimed to explore the role of procalcitonin (PCT) for the diagnosis of *Candida* spp. bloodstream infections in a population of critically ill septic patients admitted to internal medicine units. This is a retrospective case–control study considering all cases of candidemia identified in three internal medicine units, from January 1st 2012 to May 31st 2016. For each case of candidemia, two patients with bacteremic sepsis were included in the study as control cases. The end point of the study was to evaluate the diagnostic performance of PCT for the diagnosis of *Candida* spp. blood stream infections in patients with objectively documented sepsis. Sixty-four patients with candidemia and 128 controls with bacteremia were enrolled. Median and interquartile range (IQR) PCT values are significantly lower in patients with candidemia (0.73; IQR 0.26–1.85 ng/mL) than in those with bacteremia (4.48; IQR 1.10–18.26 ng/mL). At ROC curve analysis, values of PCT greater than 2.5 ng/mL had a negative predictive value (NPV) of 98.3% with an AUC of 0.76 (0.68–0.84 95% CI) for the identification of *Candida* spp. from blood cultures. At multivariate analysis, a PCT value <2.5 ng/mL showed an odds ratio of 8.57 (95% CI 3.09–23.70; $p < 0.0001$) for candidemia. In septic patients at risk of C*andida* infection, a PCT value lower than 2.5 ng/mL should raise the suspicion of candidemia, adding value for considering prompt initiation of antifungal therapy.

Keywords Procalcitonin · Sepsis · *Candida* · Critical illness

✉ Filippo Pieralli
filippopieralli@gmail.com

1 Internal Medicine Unit 1, Careggi University Hospital, Azienda Ospedaliero-Universitaria Careggi, Largo Brambilla 3, 50134 Florence, Italy

2 Internal Medicine Unit 2, Careggi University Hospital, Florence, Italy

3 Department of Medical Biotechnologies, University of Siena, Siena, Italy

4 Internal Medicine Unit 3, Careggi University Hospital, Florence, Italy

5 Department of Experimental and Clinical Medicine, University of Florence, Florence, Italy

6 Clinical Microbiology and Virology Unit, Careggi University Hospital, Florence, Italy

7 Don Carlo Gnocchi Foundation, Florence, Italy

Introduction

Candida species (spp.) are among the most common causes of invasive bloodstream (BSI) and deep tissue infection. Data from the ECDC point prevalence survey of healthcare-associated infections and antimicrobial use in acute care hospitals in Europe, carried out in 2011–2012, shows that *Candida* spp. are the third most frequent cause of bloodstream infection in Italy [1]. Long considered an opportunistic pathogen, it is now recognized as an active component of disease featuring several virulence factors among which is the ability to form a characteristic biofilm in which the microorganisms grow as a highly structured and organized functional community (REF). Overall, it is estimated that this infection is accountable for up to 50% mortality among critically ill patients worldwide [2–5].

To date, the gold standard for diagnosis of invasive candidiasis remains growth in blood cultures; yet it has been recognized that this method features a relatively low sensitivity (yielding a positive result only when blood samples collect a sufficient concentration of viable

Candida from systemic circulation) and a 3- to 5-day lag time for identification, which can represent a delay in initiation of antifungal therapy and impact on patient outcome [6, 7]. It has been estimated that, relying on conventional culturing methods, approximately 50% of candidemia cases remain undiagnosed [7].

In recent years, several studies have considered the use of surrogate diagnostic markers for earlier detection of invasive *Candida* infections, including β-1,3-D-glucan, mannan antigen in association with anti-mannan antibodies, and *Candida albicans* germ tube (CAGT) antibodies [8]. Unfortunately they apparently feature a high false positive rate (especially on single testing), require multiple determinations, and have limited availability across hospitals [8–11]. Another alternative that is receiving increasing attention is procalcitonin (PCT), a 116-amino acid prohormone of the calcium metabolism regulator calcitonin that is expressed in response to lipopolysaccharide- and bacteria-induced cytokines, and is down regulated in patients with viral infections [12, 13]. To date PCT is becoming broadly recognized as the serological marker of reference for the diagnosis, prognostication and management of septic bacterial infections across several settings [14–18]. So far, however, studies exploring the role of PCT in fungal sepsis are limited, and data supporting the usefulness of PCT in *Candida* spp. bloodstream infections are lacking or provide inconclusive results [14, 19–22].

Here we report a case–control study that aims to explore the role of PCT for the diagnosis of *Candida* spp. bloodstream infections in a population of critically ill septic patients admitted to internal medicine units.

Methods

This is a retrospective case–control study carried out in three internal medicine units (a total of 97 beds) of the University and General Hospital of Careggi, Florence, Italy, enrolling all cases of sepsis due to candidemia identified from January 1st 2012 to May 31st 2016. Sepsis, defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection according to the current definition, was classified either as bacterial or *Candida* spp. infection, based on the results of microbiological cultures. Bacterial and fungal blood cultures were performed using the BACTEC system (Benex Limited, Shannon, Ireland); identification of isolates and susceptibility testing were performed using standard laboratory techniques (MCM last).

Each case of candidemia was matched to two cases of bacterial blood stream sepsis, as to gender, age (±5 years) and time of hospitalization (±20 days) as control cases. Laboratory data were collected from the database of the Clinical Microbiology and Virology Unit of the Careggi hospital, which serves the three units of Internal Medicine involved in the study. Demographic, clinical and laboratory characteristics were collected from electronic medical records (ArchiMed Web Based DataBase© by B. Dannaoui). Neutropenic patients (neutrophils <1000/mm) were excluded from the study.

As foreseen by our hospital protocol, PCT measurements were performed as part of routine laboratory workup for all patients upon admission to the Internal Medicine ward (same day or following morning, according to scheduled nursing routine). PCT measurements considered for the analysis were those available within 24 h since blood sampling, which subsequently documented isolation of *Candida* or bacterial species. PCT was measured using the Vidas PCT kit (Brahms D-agnostics, Berlin, Germany) in accordance to manufacturer's instructions as described elsewhere [23].

The study protocol was submitted and approved by our Local Ethics Committee (SepsiMed Study protocol number 0018329), and the study was performed in agreement with the principles set in the Declaration of Helsinki.

The primary end point of the study is to evaluate the diagnostic performance of PCT for the diagnosis of *Candida* spp. blood stream infections in patients with objectively documented sepsis.

Statistical analysis

Variables were expressed as mean ± standard deviation or as median and interquartile ranges (25th–75th). In general, statistical comparisons were performed using Student's *t* test and one-way ANOVA models for the comparison of continuous normally distributed variables and Mann–Whitney *U* test for continuous not normally distributed variables. The Chi-square test or Fisher's exact test were used for the comparison of categorical variables. A whisker box-plot chart was used to graphically render results. A receiver-operating-characteristic (ROC) curve analysis was used to obtain the most accurate PCT cut-off for the identification of candidemia. Odds ratio (OR) of variables and 95% confidence intervals (CIs) were calculated using univariate and multivariate logistic regression analysis. Multivariate analysis was performed using a stepwise forward regression model, with an entry probability for each variable set at 0.05. All *p* values were two-tailed and considered significant when <0.05 (95% CI). All analyses were performed using SPSS statistical software 21.0 (SPSS, Chicago, Illinois, USA).

Results

Overall, the study enrolled 64 cases with confirmed candidemia and 128 controls with bacterial sepsis.

The mean age was 71.7 years and both genders were equally represented. In general, patients had several comorbidities, which however did not significantly differ among the two patient groups, except for pancreatitis and severe cognitive impairment that were more common in patients with candidemia, and for diabetes and chronic kidney disease (CKD) that were more common in patients with bacterial sepsis (Table 1). Notably, a concomitant or recent *Clostridium difficile* infection was more common in patients with candidemia compared to those with bacterial sepsis. Patients with candidemia had a lower score at malnutrition universal screening tool (MUST), indicating higher risk of or overt malnutrition [24]. The presence of medical devices (i.e., central venous catheter and urinary catheter) and total parenteral nutrition were more frequent among patients with candidemia. Patients with candidemia also had been exposed to antimicrobial drugs more frequently within the month preceding the septic index event. Furthermore, patients with candidemia more often suffered a severe clinical presentation of the infectious process, as indicated by a higher prevalence of severe sepsis; they had a longer duration of hospitalization and a tendency to higher in-hospital mortality compared to patients with bacterial sepsis (Table 1).

Among the patients of the control group with bacterial sepsis, the distribution of bacterial pathogens was the following: 70 (54.7%) Gram negative, 52 (40.6%) Gram positive, and 6 (4.7%) polymicrobial. Among the 64 patients with candidemia, 69 isolates of *Candida* spp were found, with species distribution featuring the most widespread to be *C. albicans* (42 isolates, 60.9%), while the remaining were due to *C. parapsilosis* in 16 (23.1%), *C. glabrata* in 8 (11.6%), *C. tropicalis* in 2 (2.9%), and *C. krusei* in 1 case (1.4%). Of note, there were five patients

Table 1 Demographic, clinical, healthcare-related variables and in-hospital outcome of patients with *Candida* and bacterial blood stream infection

	Candidemia ($n = 64$)	Bacteremia ($n = 128$)	p
Age (years)	71.0 ± 14.8	72.1 ± 14.6	0.69
Sex (female)	35 (54.7%)	70 (54.7%)	–
MUST	1.3 ± 1.6	0.4 ± 0.9	<0.001
Comorbidities			
Active cancer	16 (25.0%)	31 (24.2%)	0.140
Hematologic malignancy	5 (7.8%)	12 (9.4%)	0.204
Diabetes	13 (20.3%)	46 (35.9%)	0.011
Chronic liver disease	5 (7.8%)	9 (7.0%)	0.099
CKD (stages 3–5)	8 (12.5%)	40 (31.3%)	0.002
CHF (NYHA class III–IV)	10 (15.6%)	22 (17.2%)	0.158
COPD	15 (23.4%)	23 (18.0%)	0.100
Severe cognitive impairment	11 (17.2%)	6 (4.7%)	0.005
Acute pancreatitis (last 3 months)	5 (7.8%)	2 (1.6%)	0.036
Clostridium difficile infection	6 (9.4%)	3 (2.3%)	0.032
Charlson Comorbidity Index	3.5 ± 3.2	3.5 ± 2.9	0.896
Healthcare-associated factors			
CVC/PICC	45 (70.3%)	43 (33.6%)	<0.001
Urinary catheter	48 (75.0%)	50 (39.1%)	<0.001
Total parenteral nutrition	38 (59.4%)	12 (9.4%)	<0.001
Chronic steroid therapy	20 (31.3%)	32 (25.0%)	0.089
Any antimicrobial drug (previous month)	55 (85.9%)	45 (35.2%)	<0.001
Estimated creatinine clearance (mL/min)[a]	77.1 ± 30.0	53.7 ± 34.9	<0.001
Severe sepsis	26 (40.6%)	32 (25.0%)	0.012
APACHE II score	12.8 ± 4.8	13.0 ± 5.7	0.821
Length of stay (days)	23.0 ± 20.0	12.4 ± 10.0	<0.001
In-hospital death	10 (15.6%)	11 (8.6%)	0.066

MUST malnutrition universal screening tool, *CKD* chronic kidney disease, *CHF* chronic heart failure, *NYHA* New York Heart Association, *COPD* chronic obstructive pulmonary disease, *CVC* central venous catheter, *PICC* peripherally inserted central venous catheter, *APACHE II* acute physiology, age and chronic health evaluation II

[a] Creatinine clearance estimated by chronic kidney disease epidemiology collaboration (CKD-EPI) equation

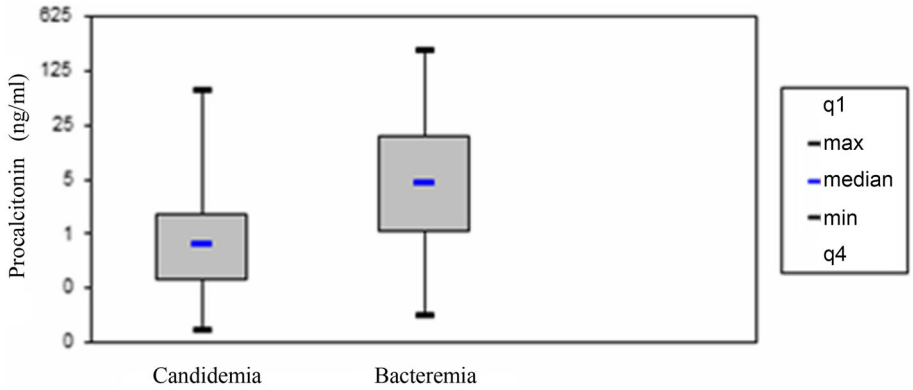

Fig. 1 *Whisker box-plot* distribution of procalcitonin values according to the etiology of sepsis based on the results of blood cultures

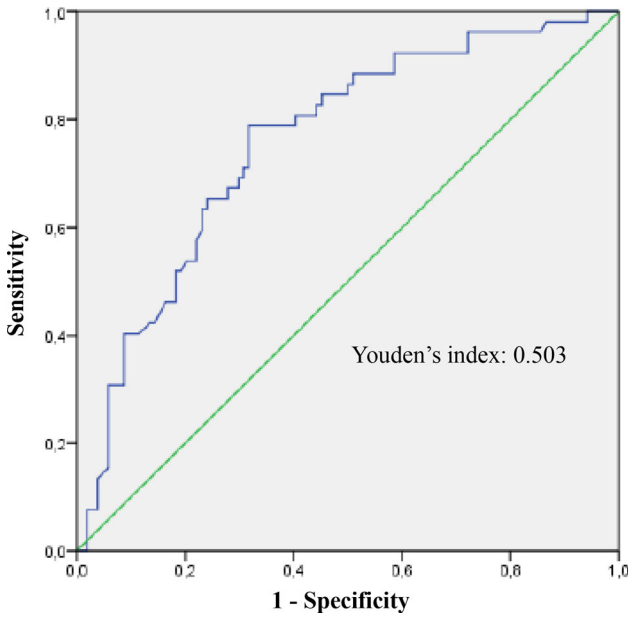

Fig. 2 Receiver-operating-characteristic (ROC) curve of procalcitonin for the identification of *Candida* spp. by blood cultures

with concomitant isolation of more than two *Candida* species in blood cultures: three cases with *C. albicans* and *C. glabrata*, one case of *C. albicans* and *C. parapsilosis*, and one case of *C. parapsilosis* and *C. krusei* co-infection.

Mean and median PCT values were significantly lower in patients with candidemia than in those with bacteremia. Mean PCT values were 3.37 ± 10.10 and 18.14 ± 38.23 ng/mL ($p < 0.001$), whereas median-interquartile range values were 0.73 (0.26–1.85) ng/mL and 4.48 (1.10–18.26) ng/mL ($p = 0.006$) in patients with candidemia and bacteremia, respectively (Fig. 1). At ROC curve analysis, values of PCT greater or equal to 2.5 ng/mL showed a sensitivity of 78.3%, a specificity of 72%, a positive predictive value (PPV) of 15.1%, and a negative predictive value (NPV) of 98.3% with an AUC of 0.76 (0.68–0.84 95% CI) for the identification of *Candida* spp. by blood cultures (Fig. 2). Results of univariate and multivariate analysis are shown in Table 2. Of note, at multivariate analysis, a PCT value <2.5 ng/mL showed a relative association (odds ratio) with candidemia of 8.57 (95% CI 3.09–23.70; $p < 0.0001$).

Discussion

Few studies addressed the role of PCT testing in the diagnosis of *Candida* blood stream infections in patients with sepsis. This case–control study aims to investigate this marker's behavior in patients with candidemia and its performance as a diagnostic marker.

Findings from the study evidence significantly lower PCT values in patients with candidemia compared to those with bacteremia.

The reasons for this lower response in PCT values to fungal infections is not completely understood; however, it is likely that fungal infections might trigger a different pattern and extent of cytokines response from that elicited by Gram-negative or by Gram-positive bacteria and other pro-inflammatory cytokines [25, 26]. Another hypothesis could be that patients with fungal disease have an impaired immune response to infectious agents, which would be coherent with the clinical observation of the "frail phenotype" of patient suffering of invasive candidiasis [27]. It is a common clinical observation that patients with candidemia in internal medicine units more frequently have signs of malnutrition or a lower body mass index, have suffered a prolonged hospitalization with multiple contacts with predisposing drugs (i.e., antibiotics, steroids) and with the healthcare facilities. Indeed, *Candida* blood stream infection is often a late event in the course of the disease process.

In this study, a PCT value ≥2.5 ng/mL has a negative predictive value of 98% for candidemia, and at multivariate analysis a value below that threshold increases eightfold the probability of recovery *Candida* spp. in blood cultures (OR 8.57, 95% CI 3.09–23.70; $p < 0.0001$).

Similar results have been observed in septic patients admitted to intensive care units as reported by Charles and

Table 2 Relationship between procalcitonin and other clinical variables with the probability of candidemia at univariate and multivariate logistic regression analysis

	Univariate analysis			Multivariate analysis		
	OR	CI (95%)	*p* value	OR	CI (95%)	*p* value
Hospitalization greater than 5 days*	14.96	5.84–38.32	<0.001	10.62	3.26–34.45	<0.001
Admission from nursing home	3.89	1.08–13.96	0.043			
Admission from surgical ward	3.90	1.32–11.39	0.013			
Admission from home	0.20	0.10–0.41	<0.001			
Barthel index <30	2.78	1.40–5.54	0.004			
Previous hospital admission in the last 3 months	3.29	1.59–6.79	0.001			
Acute pancreatitis in the last 3 months	5.43	1.02–28.99	0.042			
Cognitive impairment	4.14	1.31–13.09	0.016			
Clostridium difficile infection	5.43	1.02–28.99	0.042			
CVC or PICC	5.00	2.38–10.51	<0.001			
Total parenteral nutrition	13.53	5.85–31.28	<0.001	11.36	2.22–58.34	0.004
Urinary catheter	5.96	2.75–12.93	<0.001	4.04	1.11–14.71	0.034
Nasogastric tube	5.62	2.12–14.88	<0.001			
Severe sepsis/septic shock	2.11	1.07–4.16	0.039			
Procalcitonin <2.5 ng/mL	5.96	2.70–13.16	<0.001	8.57	3.09–23.70	0.009
Antimicrobial drugs in the previous month[§]	2.78	1.39–5.53	0.004	3.37	1.08–10.14	0.037

CVC central venous catheter, *PICC* peripherally inserted central venous catheter

* It refers to patients hospitalized for more than 5 days prior to the septic index event due to documented *Candida* or bacterial infection

§ Use of two or more different classes of antimicrobial drugs in the month previous to the septic index event due to documented *Candida* or bacterial infection

coworker in a small retrospective study on 50 patients with sepsis (35 with bacteremia and 15 with candidemia) admitted to a single intensive care unit [20], and recently by Cortegiani et al. in a larger retrospective cohort of septic patients from a series of ICU patients as well [22]. The PCT cut-off values for the identification of candidemia reported in the studies by Charles and Cortegiani are <5.5 and <6.08 ng/mL, with negative predictive values of 96.3 and 100% for bacterial infections, respectively.

However, differently from the studies cited above, our population is a typical representation of patients admitted to internal medicine units that differ from patients of acute settings as the ICU, as they feature a lower disease severity, older age, greater burden of comorbidities, and repeated contacts with healthcare facilities. Many patients with candidemia enrolled in studies from ICUs have undergone abdominal surgical intervention, which is a leading risk factor for candidemia in ICU, whereas this is not so common in Internal Medicine patients. It is well known that the severity of the inflammatory process and abdominal surgical interventions per se, may increase PCT levels independently from an underlying infectious process [28]. These observations could help explain the lower PCT cut-off value found in our study as discriminating between bacterial infection and *Candida* blood stream infections with respect to the studies carried out in ICUs.

Findings from our study seem of value, since *Candida* spp. is an increasingly recognized cause of severe infection in patients admitted to internal medicine units. Candidemia is associated with a very high mortality rate in this setting (ranging from 20 to 50%) [29], and a rapid diagnosis with prompt starting of antifungal therapy has been shown to be a crucial step to reduce mortality [6, 30, 31]. However, ultimate diagnosis that relies on results of blood cultures needs time (up to 4 days, depending on *Candida* species), and waiting can delay starting of antifungal therapy with a negative impact on outcome. The term pre-emptive therapy has been introduced to promptly start antifungal therapy whenever supported by the clinical appearance and the positivity of rapid non cultural microbiological tests, such as β-1,3-D-glucan, mannan antigen in association with anti-mannan antibodies, and *Candida* albicans germ tube (CAGT) antibodies [8]. However, these tests show limitations, mainly due to the high rate of false positive results, lack of specificity, turnaround time, and more importantly the limited availability in most hospitals. At the moment of the writing of this manuscript, β-1,3-D-glucan test (the most accepted and diffuse test) is available in no more than ten hospitals in our country.

Indeed, in septic patients admitted to internal medicine units, and a suggestive risk profile for *Candida* infection, a PCT value lower than 2.5 ng/mL should raise a high

probability of candidemia, and justify the prompt initiation of antifungal therapy, pending the results of microbiological tests and indirect tests such as β-1,3-D-glucan.

Taken together, the potential values of these findings are somewhat limited by the retrospective nature of this study: firstly, it limits the exportability of the results as compared to a prospective study; and secondly, it prevents further exploration of patient cases given the impossibility of gathering serial measurements of PCT that could have provided a complete picture on PCT temporal trend for *Candida*. On the other hand, due to the low prevalence of fungal infections, as for other studies in the ICU setting (where most of the literature is available), a prospective study would have hardly been feasible.

In conclusion, this is a study exploring the role of procalcitonin in differentiating *Candida* and bacterial blood stream infections in critically ill septic patients admitted to internal medicine units. Patients with candidemia have significantly lower values of procalcitonin compared to patients with bacteremia. A procalcitonin value of 2.5 ng/mL gives the most accurate cut-off to differentiate *Candida* from bacterial blood stream infection. A PCT level ≥2.5 ng/mL has a 98% negative predictive value and a 15% positive predictive value for candidemia-related sepsis. On the other hand, a value lower than that threshold is an independent predictor of candidemia determining a eightfold increase in the probability of finding *Candida* in blood cultures. Thus, in septic patients at risk for a *Candida* infection admitted to internal medicine units, a PCT value lower than 2.5 ng/mL should raise the probability of fungal infection, adding value for considering prompt initiation of antifungal therapy.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Statement of human and animal rights The study was performed in agreement with the principles set in the Declaration of Helsinki on human research ethics.

Informed consent Informed consent was not needed in accordance to current regulatory laws on retrospective observational studies in our country. Local ethics committee approval was obtained (SepsiMed Study protocol number 0018329).

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