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Procalcitonin levels in surgical patients at risk of candidemia

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Summary *Objective:* Although the majority of cases of sepsis in intensive care unit (ICU) patients are due to bacterial infection, fungal infections are common and their early identification is important so that appropriate treatment can be started. Biomarkers have been used to aid diagnosis of bacterial infections, but their role in fungal infections is less defined. In this study we assessed the value of procalcitonin (PCT) levels for the diagnosis of candidemia or bacteremia in septic patients.
Methods: We prospectively recorded PCT levels in 48 critically ill surgical patients with signs of sepsis and at high risk for fungal infection, and compared levels in patients with candidemia and bacteremia.
Results: Bacterial species were isolated from blood cultures in 16 patients, *Candida* species in 17, and mixed bacterial and *Candida* species in 2 patients. PCT levels were less elevated in patients with candidemia (median 0.71 [IQR 0.5—1.1]) than in those with bacteremia (12.9 [2.6—81.2]). A PCT value less than 2 ng/ml enabled bacteremia to be ruled out with a negative predictive value of 94%, and had a similar positive predictive value for candidemia.
Conclusions: Our data indicate that a low PCT value in a critically ill septic patient is more likely to be related to candidemia than to bacteremia.

Introduction

Sepsis represents a major cause of morbidity and mortality in the intensive care unit (ICU).[1] Late diagnosis of sepsis and delayed or inadequate antibiotic therapy are associated with higher mortality rates.[2—4] Clinical and hematological signs of sepsis (e.g., fever and leukocytosis) have a relatively high sensitivity but low specificity for sepsis,

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while other signs (e.g., arterial hypotension or hyperlactatemia) appear relatively late and are also non-specific for sepsis.

Although the majority of cases of sepsis are due to bacterial infection, fungal infections are also common. Indeed, *Candida* spp. is the third or fourth most commonly isolated microorganism in the bloodstream of ICU patients and its associated mortality is reported to be as high as 40–60%,[1,5–7] even with newly available antifungal agents. As for bacterial infection, early diagnosis remains a key point in the treatment of fungal infections; however, fungal infections may be even more difficult to diagnose as blood cultures frequently remain negative and it takes a considerable time to grow these organisms, even in disseminated infections.[8,9]

Unfortunately, there is no clinical feature that can help separate *Candida*-related sepsis from bacterial sepsis, yet this distinction is important because the treatment of these two conditions is completely different. A number of studies have highlighted the potential value of procalcitonin (PCT) as a marker of sepsis, particularly in the ICU setting.[10–14] PCT is a polypeptide with a molecular weight of approximately 13 kDa, produced primarily by the liver and peripheral mononuclear cells, under the stimulus of cytokines and lipopolysaccharide.[15,16] PCT levels have been found to have good sensitivity and specificity in the diagnosis of bacterial sepsis, and to have a good correlation with sepsis-related organ dysfunction and death.[17] However, few data are available regarding PCT levels in *Candida*-related sepsis and most of the data that are available were obtained in non-critically ill patients.[18–22] To evaluate the value of PCT as a marker of *Candida*-related sepsis, we measured PCT levels in a surgical ICU population at high risk of candidemia.

Patients and methods

The study was approved by the Institution Review Board. Informed consent was waived in view of the purely observational design of the study. We prospectively screened all patients admitted to the surgical ICU of Verona University Hospital between January 2003 and December 2005. We enrolled all patients older than 18 years who were admitted to the ICU for at least 48 h and who had signs of sepsis[23] and one or more major risk factors for fungal infection: Use of a triple lumen central venous catheter; administration of parenteral nutrition; acute renal failure (defined as a urine output <0.5 ml/Kg for at least 2 h despite adequate fluid resuscitation or an acute increase in serum creatinine of at least 0.5 mg/dL); prior antibiotic therapy with at least two agents since hospital admission; *Candida* colonization of at least two normally sterile sites; neutropenia (white blood cell [WBC] count $<500/mm^3$ for more than seven days), or immunosuppression.[7,24,25] We excluded patients who were receiving antifungal prophylaxis.

Vital signs, Glasgow Coma Scale (GCS) score, WBC and platelet counts, arterial gases, blood creatinine, bilirubin, C-reactive protein (CRP) and PCT concentrations were recorded daily. The severity of organ dysfunction was evaluated using the SOFA score.[26] CRP was measured by the immunonephelometric method (BN, Dade-Behring, Marburg, Germany); PCT was measured with an automated chemiluminescence analyzer (Liaison, Byk Sangtec Diagnostica, Dietzenbach, Gremany). Chest X-rays and microbiological cultures (from urine, tracheal aspirate, bronchoalveolar lavage fluid, blood from central venous and arterial catheters, and other relevant samples) were obtained whenever deemed appropriate. Local protocols include collection of blood cultures (from central venous catheter, arterial line, and peripheral vein) when body core temperature exceeds 38 °C or decreases below 36 °C. Antipyretic drugs were not administered routinely.

Based on the blood culture results, we divided the patients into four groups: No organism isolated; bacteremia; candidemia; and mixed sepsis (candidemia and bacteremia present simultaneously or candidemia associated with localized bacterial infection). We defined different types of infection according to the criteria proposed by Calandra and Cohen.[27]

Statistical analysis

Data were analyzed using SPSS 11.0 software (SPSS Inc., Chicago, Illinois, USA). There were no missing data. Results are expressed as median values with interquartile range.

Demographic data, CRP, PCT and SOFA scores were analyzed using Mann–Whitney-U and chi^2 tests; values obtained on the day when the sample was taken for culture were used for the analysis. As linear regression is sensitive to outliers, we analyzed the log (PCT) for comparisons with the severity of organ dysfunction (using the SOFA score). All tests were two-tailed and statistical significance was considered for a p value <0.05.

Receiver operating characteristics (ROC) curves were constructed to evaluate the sensitivity and specificity of PCT for differentiating bacterial sepsis from *Candida* sepsis and the area under the curve (AUC) was calculated at selected cut-off values.

Results

One hundred and thirty surgical patients with sepsis were admitted to our ICU during the study period (Fig. 1); 48 of these patients had at least one risk factor for fungal infection. *Candida* and/or bacterial species were isolated from blood cultures in 35 of these 48 patients: Bacterial species in 16 patients, *Candida* spp. in 17 patients, and mixed

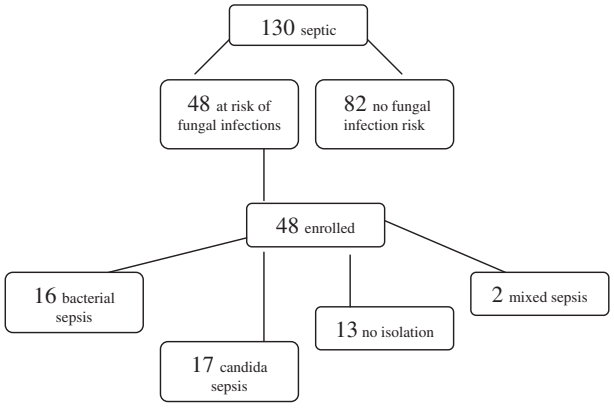

Figure 1 Enrollment process.

Table 1 Main demographic variables.

	Bacteremia	Candidemia	Mixed sepsis	No isolate	Total	*p* value
Variables						
Patients, *n* (%)	16 (33)	17 (36)	2 (4)	13 (27)	48	
Male, *n* (%)	8 (50)	11 (65)	1 (50)	8 (62)	28 (58)	0.841
Mortality, *n* (%)	10 (63)	9 (53)	1 (50)	6 (46)	26 (54)	0.852
Age (years)	61 [54—75]	65 [52—77]	70 [65—75]	60 [46—70]	63 [52—74]	0.492
SOFA score at ICU admission	8 [6—12]	6 [3—12]	6 [4—8]	6 [5—10]	7 [4—11]	0.497
APACHE score at ICU admission	14 [12—20]	12 [9—16]	15 [8—22]	16 [12—20]	14 [11—20]	0.191
Length of stay (days)	20 [9—27]	23 [14—48]	35 [20—50]	13 [10—19]	20 [11—28]	0.101
Origin of sepsis, *n* (%)						0.130
Abdominal	8 (50)	12 (71)	2 (100)	10 (77)	32 (67)	
Catheter	1 (6)	1 (6)	0 (0)	0 (0)	2 (4)	
Endocarditis	1 (6)	0 (0)	0 (0)	0 (0)	1 (2)	
Soft-tissues	6 (38)	4 (24)	0 (0)	3 (23)	13 (27)	

Results are presented as number (percentage) or median [interquartile range].

Candida spp and bacteria in two patients. No organism was isolated in 13 patients.

There were no significant differences among the four groups (bacteremia, candidemia, mixed, no isolate) in demographic variables, risk factors for fungal infection, severity of organ dysfunction, length of ICU stay, source of sepsis, or mortality rate (Tables 1 and 2). The epidemiology of the 47 microbiological isolates is shown in Table 3: Methicillin-resistant *Staphylococcus aureus* (MRSA) and *Candida albicans* and *parapsilosis* were the most commonly isolated microorganisms.

PCT and CRP concentrations and SOFA scores were higher in patients with bacteremia than in those with candidemia (Table 4). The maximum PCT value was 2.1 ng/mL in the patients with *Candida* sepsis, and more than 200 ng/mL in patients with bacterial sepsis.

PCT levels were also significantly higher in patients with bacteremia compared to those in whom no organism was isolated [12.9 (2.6—81.2) *vs* 1.6 (0.5—5.3) ng/mL, $p = 0.008$]. PCT levels were higher in the two patients with mixed bacterial and *Candida* sepsis than in those with just candidemia [4.3 (2.0—13.8) *vs* 0.71 (0.5—1.1) ng/mL, $p = 0.012$], but were similar in the patients with just candidemia and in those with no organism isolated [0.7 (0.5—1.1) vs 1.6 (0.5—5.3) ng/mL, $p = 0.195$]. CRP levels were higher in patients with no organism isolated than in those with just candidemia (171 [110—295] vs 94 [66—129] mg/L ($p < 0.016$).

The area under the ROC curve (Fig. 2) was larger for PCT (0.97, $p < 0.001$) than for CRP (0.80, $p = 0.031$); the differences were statistically significant using a ROCcomp analysis ($chi^2 = 0.016$). A PCT cut-off value of 2 ng/mL separated *Candida* sepsis from bacterial sepsis with a sensitivity of 92%, a specificity of 93%, and positive and negative predictive values of 94%. The best cut-off value for CRP to separate bacterial sepsis from *Candida* sepsis was 100 mg/L, with a sensitivity of 82% and a specificity of 53%. The combination of CRP (with a cut-off value of 100 mg/L) and PCT (with a cut-off of 2 ng/mL) did not increase sensitivity or specificity for a diagnosis of *Candida* sepsis.

Log (PCT) values did not correlate with the SOFA score in patients with bacterial sepsis ($r^2 = 0.199$, $p = 0.083$) but did correlate in those with *Candida* sepsis ($r^2 = 0.36$, $p < 0.01$) (Fig. 3).

Discussion

The incidence of fungal infections as a cause of nosocomial infection is probably increasing.[1,5—7] Patients admitted to the ICU, perhaps particularly surgical ICU patients, have often received recent treatment with broad spectrum antibiotics and been exposed to invasive procedures or devices,

Table 2 Distributions of risk factors for fungal infection[7] in patients with candidemia, with bacteremia, and with no isolate.

Risk factor	Candidemia (*n*)	Bacteremia (*n*)	No isolate (*n*)	*p* value
ICU admission	17	16	13	—
Parenteral nutrition	9	11	8	—
Triple lumen catheter	5	6	5	0.35
Acute renal failure	10	8	4	0.77
Recent surgery	16	16	13	0.43
Antibiotic therapy	17	15	13	0.64
Colonization of 2 sites	3	1	0	0.89
Severe trauma	1	2	0	0.18
Immunosuppression	0	0	0	—

Table 3 Isolated microorganisms.

Isolated microorganism	Frequency *n* (%)
Bacteremia	
Methicillin-resistant *Staphylococcus aureus* (MRSA)	5 (28)
Pseudomonas aeruginosa	3 (17)
Escherichia coli	3 (17)
Enterococcus	2 (10)
Acinetobacter baumanii	2 (10)
Corynebacterium	1 (6)
Kokuria varians	1 (6)
Bacteroides vulgatus	1 (6)
Total	18
Candidemia	
Candida albicans	6 (32)
Candida parapsilosis	6 (32)
Candida glabrata	4 (21)
Candida tropicalis	3 (15)
Total	19

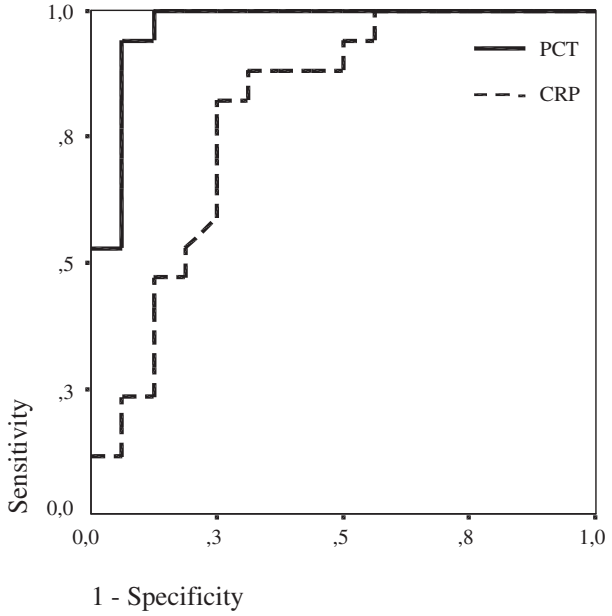

Figure 2 ROC-curves representing the sensitivity and specificity of PCT (solid line) and CRP (dashed line) for a diagnosis of candidemia.

all factors associated with a greater risk of developing fungal infections.[28–30]

Diagnosis of fungal infections still represents a challenge in ICU patients, and is usually based on a constellation of clinical signs, laboratory tests, and microbiological cultures. However, clinical signs and laboratory tests lack sensitivity and specificity and microbiological cultures take time.[31] Because the only absolute criterion for diagnosis of *Candida* infection is detection of microorganisms in the blood or in other sterile fluids, we elected to limit our observations to patients with candidemia and/or bacteremia. We had a relatively high proportion of *Candida non-albicans* in our Department, but this is unlikely to have affected our results.

We need reliable sepsis markers to facilitate early, accurate diagnosis. CRP levels have been widely used as such, alone or in combination with other variables,[10,11,13–15,32,33] but their role in candidemia is not well defined. In our study, CRP levels were increased in all patients, and to a greater extent in patients with bacterial sepsis than in those with *Candida* sepsis. However, no clear cut-off value to separate bacterial and *Candida* sepsis could be identified from analysis of ROC curves.

In our population of critically ill adult surgical patients with clinical signs of sepsis and risk factors for fungal infection, PCT levels were less elevated in patients with *Candida* sepsis than in those with bacterial sepsis. Interestingly, the PCT values of patients with no isolates were comparable to the PCT levels of patients with *Candida* sepsis although the median values were higher and interquartile ranges larger in this latter group. It may be that although no organisms were isolated, some of these patients may still have been infected as no organisms are isolated in as many as 40% of patients with sepsis.[1] A PCT value less than 2 ng/ml was considered a reasonable cut-off point to distinguish between sepsis due to *Candida* infection and sepsis of bacterial origin, as this value could rule out a bacterial infection with a negative predictive value of 94%, and had a similar positive predictive value for the presence of *Candida* sepsis.

PCT levels have been shown to have good sensitivity and specificity in the diagnosis of bacterial sepsis, and are also a good prognostic marker.[10–15,17] Several other studies have reported lower PCT levels in patients with fungal than in those with bacterial infections.[18,19,21] Distefano et al. compared PCT and CRP levels in low birthweight infants[21]; PCT levels were significantly lower in babies with fungal than in those with bacterial infections. Petrikkos and co-workers first evaluated serum PCT levels in fungal infections[18] and then the power of PCT and mannan antigen to distinguish

Table 4 Markers of sepsis and organ dysfunction at time of blood culture. Data are expressed as median [interquartile range].

	Bacterial sepsis	Candida sepsis	*p* value
n	16	17	
CRP (mg/L)	190 [115–316]	94 [66–129]	**0.002**
PCT (ng/ml)	12.9 [2.6–81.2]	0.71 [0.5–1.1]	**0.001**
SOFA	8 [7–13]	5 [3–8]	**0.010**
WBC ($\times 10^6$/ml)	14.3 [10.6–16.4]	11.6 [8.4–15.7]	0.336
T (°C)	38.0 [37.0–38.4]	37.8 [37.0–38.3]	0.493

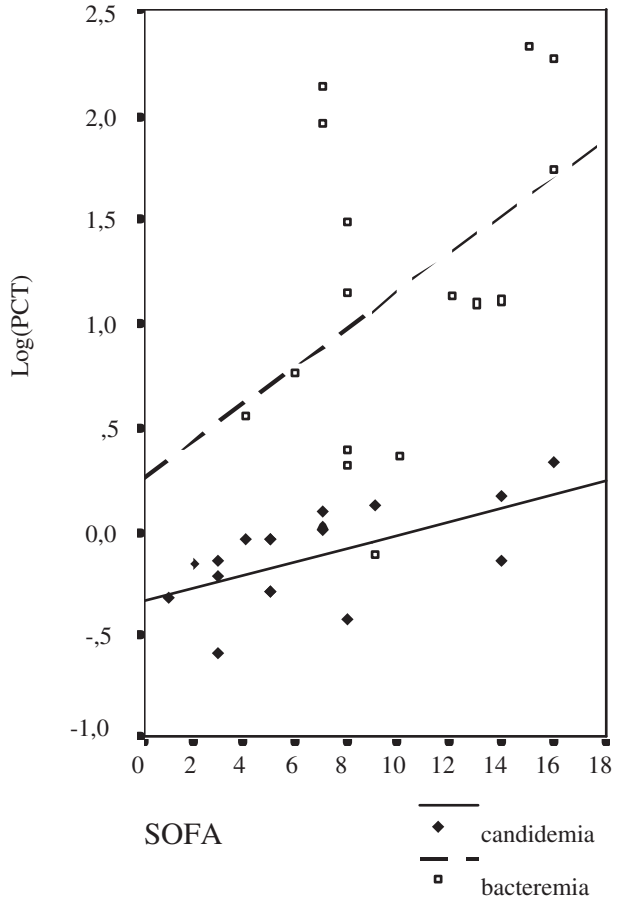

Figure 3 Linear regression line between log (PCT) and degree of organ dysfunction (SOFA-score). Note that statistical significance was reached for candidemia ($p = 0.01$) and not for bacteremia ($p = 0.08$).

fungal from bacterial infection.[19] These authors found that PCT levels were in the normal range (<0.5 ng/mL) in fungal infections, and higher than normal only in patients with an unfavorable outcome.[18] In a second study, they compared PCT and CRP levels in bacterial and fungal infections and proposed a cut-off value of PCT of 0.5 ng/mL plus the presence of mannan antigen to diagnose fungal infection.[19] This value is lower than ours, but their population was less severely ill. In addition, they analyzed *Candida* and *Aspergillus* infections together and, more importantly, the diagnosis of fungal infection was often suspected and not definitive.

Charles et al. retrospectively analyzed PCT levels in ICU patients with clinical signs of sepsis and candidemia.[22] They concluded that a cut-off value of 5.5 ng/mL for PCT could rule out *Candida* infection with a negative predictive value of 100%. This value is considerably higher than our value of 2.0 ng/mL; however, looking at their data, it is clear that 12 of 15 episodes of candidemia were associated with a PCT value within the range proposed by the studies of Petrikkos[18,19] and compatible with known PCT values for localized infection (i.e., less than 2.0 ng/mL), exactly the value we proposed. To reach a complete (100%) negative predictive value, Charles et al.[22] set their cut-off value to the maximum value they had in the candidemia group, i.e., 5.5 ng/mL, but such a high value can frequently be found in bacterial sepsis or in mixed sepsis. Moreover, in a recent multicenter study Charles et al.[34] proposed a new cut-off value for PCT in invasive candidiasis that is very similar to ours. We, therefore, believe that the cut-off value of 2 ng/mL is useful to separate fungal from bacterial infection, with 92% sensitivity, 93% specificity, and positive and negative predictive values of 94%.

Some studies have related PCT values in septic patients with the severity of organ dysfunction.[10,35] We also considered the relation between PCT levels and the degree of organ dysfunction, evaluated with the SOFA score on the day of culture sampling, in patients with candidemia and those with bacteremia. Our data were unable to confirm that, in bacterial sepsis, PCT levels were higher in patients with more severe organ dysfunction; however, in patients with *Candida* sepsis PCT levels increased with the degree of organ dysfunction.

The strengths of our study include that it was prospective and that we limited our observations to *Candida* infections confirmed by positive blood cultures. A limitation is that it was conducted in a single center, and had a relatively small sample size, although similar studies have also included relatively small numbers of patients.[18,19,21,22]

In conclusion, our data indicate that a low PCT value (less than 2.0 ng/mL) in a surgical patient with clinical signs of sepsis and risk factors for fungal infections is more likely to be related to candidemia than to bacteremia.

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None

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