The Role of Procalcitonin in Febrile Neutropenic Patients: Review of the Literature

Y. Sakr, C. Sponholz, F. Tuche, F. Brunkhorst, K. Reinhart

Abstract

Background: Procalcitonin (PCT) has been increasingly used as an inflammatory marker to identify patients with systemic infection. Moreover, PCT guidance allowed significant reduction of antibiotic therapy in patients with respiratory disease. The aim of this qualitative review was, therefore, to evaluate the role of PCT measurements in febrile neutropenic patients in differentiating between various causes of fever and to investigate the value of PCT levels in terms of diagnosing infection or predicting outcome in these patients.

Patients and Methods: A MEDLINE search was performed using the keyword 'procalcitonin' crossed with 'febrile neutropenia', 'neutropenia', 'fever', 'bone marrow transplantation', and 'stem cell transplantation', and limited to human studies published between January 1990 and October 2006. Bibliographies of identified articles were also searched. Predefined variables were collected from the articles, including year of publication, study design, number of patients included, age group, disease group, markers other than PCT, and study results.

Results: From the 30 articles included, PCT seems to be able to discriminate fever due to systemic forms of infection from non-infectious etiologies. Patients with fungal infection may have a delayed increase in PCT levels. PCT has a minimal role, if any, in discriminating Gram-negative from Gram-positive infections. PCT may be useful in outcome prediction in patients with febrile neutropenia but is not superior to interleukin-6 or C-reactive protein concentrations for this purpose.

Conclusions: Despite lack of standard definitions, heterogeneity of study populations, and small numbers of patients included in some studies, our review provides important insight into the value of PCT as a diagnostic and prognostic tool in patients with febrile neutropenia.

Infection 2008; 36: 396–407
DOI 10.1007/s15010-008-7374-y

Introduction

The consensus guidelines of the Immunocompromised Host Society (IHS) [1] define neutropenia as a neutrophil count of 500 cells/mm^3 or less or a count of < 1,000 cells/mm^3 with a predicted decrease to < 500 cells/mm^3. Fever in a neutropenic patient is defined as a single measurement of oral temperature of more than 38.3 °C or a temperature of ≥ 38.0 °C for ≥ 1 h [1]. Unfortunately, the presence of fever is neither specific for infection nor is it pathognomonic of any particular type of infection; it may be caused or influenced by drugs and non-infectious agents [2]. Fever of unknown origin is a clinical entity which is defined as an illness of more than 3 weeks duration, with fever greater than 38.3 °C (101 °F) on several occasions [3]. The most frequent causes of fever of unknown origin are infection (36.6%), non-infectious inflammatory disease (15.9%), and neoplasm (11.2%) [4]. In neutropenic patients, fever of unknown origin is defined as at least 3 days of fever and is mostly caused by opportunistic bacterial infections [5].

Infection in neutropenic patients may be difficult to diagnose. Inadequately treated infection can rapidly lead to a fatal outcome, and early diagnosis is therefore crucial. Several studies have highlighted the usefulness of procalcitonin (PCT) measurements for identifying infectious processes [6], characterizing the severity of the underlying illness [7, 8], guiding therapy [9–12], and predicting outcome [13–15]. Recent meta-analyses have suggested that PCT may be superior to C-reactive protein (CRP) in discriminating infection from other causes of inflammation in critically ill patients [6, 16]. The origin of PCT in the inflammatory response is not yet fully understood but it is believed that PCT is produced ubiquitously during infections [17], by tissues like the liver [18], among others [19]. The expression of PCT in white blood cells is only increased transiently during the differentiation from monocytes to macrophages, and is less dependent on

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Received: September 24, 2007 · Revision accepted: February 14, 2008
Published online: August 30, 2008

infectious stimuli, e.g., lipopolysaccharide (LPS) [20, 21]. Therefore, concerns have been raised about possible impairment of PCT production in patients with neutropenia, which may limit its usefulness as a marker of infection.

The aim of this qualitative review was, therefore, to evaluate the role of PCT measurements in differentiating between various causes of fever in febrile neutropenic patients and to investigate the value of PCT levels in terms of diagnosing infection or predicting outcome in these patients.

Methods

We performed a search on MEDLINE using the keyword 'procalcitonin' crossed with 'febrile neutropenia', 'neutropenia', 'fever', 'bone marrow transplantation', and 'stem cell transplantation'. Our search was limited to human studies published in the English and German languages between January 1990 and October 2007. The abstracts of all articles were used to confirm our target population (patients with febrile neutropenia) and the corresponding full text articles were reviewed for the presence of data on PCT levels. Two investigators (CS and YS) independently identified the eligible literatures. Predefined variables were collected, including year of publication, study design (prospective/retrospective/case report), number of patients included, age group (adults or infants), disease group, markers other than PCT, and study results. Any inconsistencies between the two investigators in interpretation of data were resolved by consensus. To avoid publication bias, abstracts and full articles were eligible if PCT levels were reported. We also reviewed the bibliographies of available studies for other potentially eligible studies. Of 35 articles that quoted PCT levels in patients with febrile neutropenia, four articles were excluded because of insufficient data [7, 11, 22, 23], and one because of double publication [24]; 30 studies were, therefore, included in our review (Table 1). A quality assessment of the included studies was performed independently by two of the authors (YS and CS) using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) system [25].

Results

Quality Assessment

Six studies had more than 10 points on the QUADAS system (max = 14), 22 studies had 8–10 points, and 2 studies had less than 8 points (Table 1).

Value of PCT in Differentiating Between Infectious and Non-infectious Conditions in Febrile Neutropenic Patients

Procalcitonin levels increase moderately after the onset of fever in neutropenic patients, mainly in patients with infectious etiologies. *Engel* et al. [26] found increased PCT levels within 32 h of the onset of fever in neutropenic patients with clinically or microbiologically documented infections compared with those with unexplained fever (median 0.51 vs 0.26 ng/ml). PCT levels at the onset of fever were similar between groups irrespective of the cause of fever and remained below 0.5 ng/ml in more than half of the patients. The low incidence of bacteremic episodes in this study [26] might have contributed to these relatively low PCT levels. This finding underscores the value of PCT dynamics rather than absolute values in assessment of febrile episodes in neutropenic patients. In 61 patients who underwent stem cell transplantation, *Hambach* et al. [27] reported that PCT and CRP levels were highly elevated during bacterial and fungal infections (median 2.3 ng/ml and 188 mg/l, respectively), moderately elevated during fever of unknown origin (median 1.5 ng/ml and 82 mg/l), and low when there was no evidence of infection (median 0.4 ng/ml and 55 mg/l). The increase in PCT levels was observed within a median of 1 day after the onset of the clinical event, whereas CRP levels increased 1 day before the onset of clinical events. The authors [27] raised concerns about the utility of PCT in the early diagnosis of infection in this population. However, clinical events were defined in this study as evidence of infection irrespective of fever and CRP levels may have influenced these definitions. The higher incidence of bacteremia and fungemia in this study may explain the relatively high PCT levels in infected patients. In 350 patients following allogeneic hematopoietic stem cell transplantation, *Pihusch* et al. [28] found that CRP, interleukin (IL)-6, and PCT levels were increased after infectious complications, but only PCT differentiated between infection and other transplant-related complications. This study [28] was limited by the low sampling rate (once weekly) which may have overlooked the early changes in PCT levels after the onset of infection. Moreover, total body irradiation or administration of antithymocyte globulin may have influenced the level of inflammatory mediators in this population. *Schüttrumpf* et al. [29] measured PCT plasma concentrations prospectively in 111 patients with a hemato-oncological condition and a CRP concentration > 8 mg/l. Median CRP concentrations did not differ significantly between groups of patients with and without infection, but PCT concentrations were higher in patients with infection than in patients without infection. Interestingly, PCT concentrations were higher among infected patients without leukopenia when compared with patients with leukopenia. Nevertheless, the small number of patients in this subgroup and the discrepancy in the incidence of severe infections between neutropenic and non-neutropenic patients limit the value of this observation.

The increase in serum PCT levels is more pronounced in bacteremic patients than in those with local, viral, or fungal infection [26, 27, 30–36]. Typically, PCT peaked 24 h after the onset of fever and declined thereafter if infection resolved [37–39], but not in cases of unresolved fever. Several studies [26, 27, 30, 31, 35, 40–42] reported a cut-off point of serum PCT to discriminate bacteremic from non-bacteremic infection ranging from 0.5 to 1.3 ng/ml with a sensitivity ranging from 44 to 88% and a specificity from 61 to 88% (Table 2). Nevertheless, *de Bont* et al. [43] found similar PCT levels in patients with and without bacteremia in a cohort of 66 patients with

Table 1
Studies reporting PCT levels in neutropenic patients.

No.	Author	Year	QUADAS points (max. 14)	Total	Age gr.	Disease group	PCT assay and other markers	Results
1	*al-Nawas and Sha*h [50]	1996	8	122	Adults	Chemotherapy for hematological malignancy, HIV infection or organ transplantation	PCT-LUMI CRP WBC	PCT on D0–3 similar in both groups, D3–6 higher in immunocompetent than immunosupressed, similar values on D6–9 Pts with leukopenia had lower PCT levels; no difference between Gram-positive, and Gram-negative or culture negative infections
2	*Lestin* et al. [58]	1998	8	112	Adults	Hematological cancer and chemotherapy	PCT-LUMI CRP IL-6 Neopterin TNF alpha	PCT similar in SIRS/sepsis vs local infection PCT low in FUO PCT correlates to CRP, IL-6, neopterin, and TNF-alpha
3	*Engel* et al. [26]	1999	11	97	Adults	Cytotoxic chemo-therapy for hemato-logical malignancy	PCT-LUMI IL-8	Peak PCT on D2–3 after the onset of fever Similar in Gram-positive and Gram-negative infection PCT higher in bacteremia vs FUO
4	*Ruokonen* et al. [31]	1999	10	28	Children	Hematological cancer + chemo-therapy	PCT- LUMI IL-6 Neoptrin Endotoxin TNFa	PCT increased only in infected children Considerable overlap between groups for other markers CRP increased in all and remained high
5	*Fleischhack* et al. *[38]	2000	8	76	Children	Hematological malignancy or solid tumor	PCT-LUMI CRP IL-6 IL-8 sIL-2R sTNFR II	On admission; PCT Gram-negative > (Gram positive = pneumonia) > localized/FUO Peak PCT at 24 h at 5 days decreased but not normalized Pneumonia almost normal PCT CRP Gram-negative > Gram-positive > pneumonia but all increased significantly CRP correlated to PCT IL-6 increased in Gram-negative and normalized rapidly Prediction of Gram-negative bacteremia and FUO, weak sensitivity and specificity, PCT best
6	*Blijlevens* et al. [59]	2000	10	12	Adults	Bone marrow transplantation	PCT-LUMI CRP	PCT similar in infected vs non-infected events CRP higher in infected vs non-infected events
7	*de Bont* et al. [43]	2000	11	66	Adults	Chemotherapy for hematological malignancy or solid tumor	PCT-LUMI CRP WBC	WBC count higher in bacteremia and sepsis syndrome vs no bacteremia CRP lower no bacteremia vs bacteremia PCT similar in bacteremia and no bacteremia

Table 1
Continued.

No.	Author	Year	QUADAS points (max. 14)	Total	Age gr.	Disease group	PCT assay and other markers	Results
8	*Giamarellos-Bourboulis* et al. [40]	2001	12	115	Adults	Hematological malignancy or solid tumor	PCT-LUMI	PCT similar before CT and in neutropenia PCT similar in Gram-positive and Gram-negative infection PCT similar in severe sepsis or without bacteremia
9	*Svaldi* et al. [49]	2001	10	73	Adults	Hematological malignancy and fever with or without neutropenia	PCT-LUMI WBC	PCT higher in Gram-negative vs Gram-positive infection PCT similar in neutropenic vs non-neutropenic pts PCT higher in severe sepsis/septic shock vs sepsis vs local infection
10	*Christofilopoulou* et al. [34]	2002	12	14	Adults	Malignancy + fungal infection; proven/probable	PCT-LUMI	PCT elevated in the 5 deaths from D1–10
11	*Hambach* et al. [27]	2002	10	61	Adults	Allogenic stem cell transplantation	PCT-LUMI CRP	PCT higher in proven infection vs FUO and local infection PCT similar in aplastic and non-aplastic pts CRP higher in proven infection vs FUO and local infection CRP higher in aplastic vs non-aplastic pts
12	*Schüttrumpf* et al. [39]	2003	10	95	Adults	Hematological and solid malignancy	PCT-LUMI CRP	CRP was elevated in all patients; infection > FUO > drug/tumor All drug/tumor had normal PCT (< 0.4 μg/l) PCT was elevated; all infection > FUO > drug/tumor CRP differed between infection and no infection
13	*Dornbusch* et al. [45]	2003	10	24	Infants	Malignancy + mono-poly AT + fever No infection/infection	PCT-LUMI CRP	PCT increase at D1, peak on D2 during sepsis PCT increase at D1 of therapy and normalized within 4 days CRP increased markedly with infection on D1
14	*Sauer* et al. [46]	2003	10	47	Children	Bone marrow transplantation	PCT-LUMI CRP Endotoxin	PCT higher in sepsis and death in sepsis vs non-septic pts PCT higher in survivors of severe sepsis vs sepsis survivors CRP higher in sepsis survivors and non-survivors vs non-septic pts CRP similar in severe sepsis vs sepsis Endotoxin similar in all groups

Table 1
Continued.

No.	Author	Year	QUADAS points (max. 14)	Total	Age gr.	Disease group	PCT assay and other markers	Results
15	*Persson* et al. [35]	2004	11	60	Adults	Hematological malignancy or solid cancer	PCT-LUMI CRP IL-6 SAA IL-8	Very low sensitivity for all markers PCT higher with non-CNS bacteremia and peaked at 20–30 h otherwise minimal change
16	*von Lilienfeld-Toa*l et al. [41]	2004	10	31	Adults	Hematological malignancy	PCT-LUMI CRP IL-6	PCT on D2 bacteremia > all others. PCT/CRP/IL-6 similar between Gram-negative and Gram-positive CRP not different between groups
17	*Ciaccio* et al. [47]	2004	4	54	Infants	Hematological malignancy	PCT-QTest	PCT > 0.5 ng/ml in all patients in all groups
18	*Ortega* et al. [32]	2004	8	77	Adults	Allogenic stem cell transplantation	PCT-LUMI	Culture positive infections had higher PCT levels Invasive aspergillosis had higher PCT
19	*Giamarellou* et al. [30]	2004	10	181	Adults	Hematological malignancy	PCT-LUMI CRP	Localized infections had similar PCT to FUO PCT high in all groups, sepsis > bacteremia > others PCT discriminated sepsis and not bacteremia
20	*Jimeno* et al. [37]	2004	10	104	Adults	Chemotherapy for solid cancer	PCT-LUMI	PCT higher in bacteremia than others Patients with treatment failure had high PCT levels Negative correlation between PCT on admission and MASCC scores PCT increased > 50%, mainly in bacteremia, less in others Combination with scores improved sensitivity but decreased specificity
21	*Erten* et al. [60]	2004	8	36	Adults	Hematological malignancy	PCT-LUMI CRP	PCT and CRP similar in culture positive and negative infection PCT and CRP higher in severe attacks than mild attacks PCT did not correlate to fever duration
22	*Stryjewski* et al. [36]	2005	10	56	Infants	Hematological malignancy or solid tumor and chemotherapy	PCT-LUMI IL-6 IL-8	IL-8 not IL-6 increased with sepsis PCT peaked at 24 h, PCT > 500 pg/ml and IL-8 at 48 h > 20 pg/ml

Table 1
Continued.

No.	Author	Year	QUADAS points (max. 14)	Total	Age gr.	Disease group	PCT assay and other markers	Results
23	*Persson* et al. [61]	2005	13	79	Adults	Anti-neoplastic chemotherapy due to hematological malignancy or solid tumor	PCT-LUMI CRP SAA IL-6	PCT: higher in fever with complications than without complications IL-6: higher in fever with complications than without complications CRP + SAA: similar in fever with complications and without complications
24	*Hitoglou-Hatz*i et al. [33]	2005	10	120	Infants	ALL	PCT-LUMI CRP ADA	CRP: higher in patients with infection than those without infection or neutropenia without fever PCT: higher in bacteremic episodes than non-bacteremic episodes Values not different in FUO, non-microbial infection and viral infection ADA: higher in febrile neutropenia with infection than febrile neutropenia without infection than neutropenia without fever
25	*von Lilienfeld-Toal* et al. [48]	2006	10	43	Adults	Chemotherapy for hematological malignancy or solid tumor	PCT–LUMI	PCT higher in systemic infection than non-documented infection No correlation between PCT at fever onset and duration of fever episode or duration of subsequent afebrile period PCT higher shortly before death
26	*Schüttrumpf* et al. [29]	2006	10	111	Adults	Hematological malignancy or solid tumor and CRP > 8 mg/l	PCT-LUMI CRP	PCT higher in infected than non-infected patients CRP lower in drug-related fever than in infected patients CRP similar in neutropenic and non-neutropenic patients PCT lower in neutropenic than non-neutropenic patients
27	*Fraunberger* et al. [54]	2006	4	38	Adults	Hematological malignancy and solid tumors	PCT-LUMI CRP IL-6	PCT, CRP and IL-6 higher at onset of fever compared to healthy controls IL-6 higher in non-survivors than survivors AUC in prediction of mortality PCT: AUC 0.637, sensitivity: 57.1%; specificity; 58.8% CRP: AUC 0.545, sensitivity: 57.1%; specificity; 58.8% IL-6: AUC 0.807; sensitivity: 71.4%; specificity; 76.5%

Table 1
Continued.

No.	Author	Year	QUADAS points (max. 14)	Total	Age gr.	Disease group	PCT assay and other markers	Results
28	*Kitanovski* et al. [42]	2006	10	32	Children	Hematological malignancy or solid tumors	PCT-LUMI CRP IL-6	PCT and IL-6: higher in systemic than local infection and FUO at all days CRP higher in systemic than local infection and FUO only at day 2 and 3, Day 1: similar
29	*Pihusch* et al. [28]	2006	9	350	Children and adults	Hematopoietic stem cell transplantation and transplant related complication (TRC)	PCT–LUMI CRP IL-6	Elevation of PCT, CRP and IL-6 after anti-thymocyte globulin PCT similar in neutropenic patients with or without infection Irradiation leads to CRP and PCT elevation PCT, IL-6 and CRP higher in infected than non-infected patients IL-6 increased with severity of infection aGVHD: levels of CRP, IL-6 and PCT unchanged Microangiopathic hemolytic anemia and venoocclusive disease: PCT and IL-6 unchanged CRP, IL-6 and PCT higher in non-survivors than survivors CRP and IL-6 decreased after steroid therapy, but not PCT Only PCT differentiated between infection and other TRC
30	*Secmeer* et al. [44]	2007	10	49	Children	Neutropenic fever after intensive chemotherapy	PCT–LIAISON CRP ESR	PCT and CRP higher in febrile patients than afebrile controls ESR similar in febrile patients and afebrile controls PCT, CRP and ESR similar in febrile-neutropenic patients with clinically or microbiologically proven infection and FUO

PCT: procalcitonin; CRP: C-reactive protein; IL-6: interleukin 6; LUMI: immunoluminometric assay; ICU: intensive care unit; SAA: serum amlyoid A; WBC: white blood cell; TNF: tumor necrosis factor; ELISA: enzyme-linked immunosorbent assay; ALL: acute lymphoblastic leukemia; aGVHD: acute graft vs host disease; FUO: fever of unknown origin; Tx: transplantation; CNS: coagulase negative staphylococci; ADA: adenosine deaminase; AUC: area under the curve; ROC: receiver-operating characteristics; ESR: erythrocyte sedimentation rate, * retrospective study design

Table 2
Diagnostic values in diagnosing bacteremia.

EngelAuthor	Cut-off value	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Engel et al. [26]	PCT: 0.5 (ng/ml)	73	86	73	86
Giamarellos-Bourboulis et al. [40]	PCT: 1.0 (ng/ml)	78.6	63.6	84.6	–
Hambach et al. [27]	PCT: 1 (ng/ml)	70	61	54	76
	CRP: > 100 (mg/l)	83	61	58	85
von Lilienfeld-Toal et al. [41]	PCT: 0.62 (ng/ml)	72	77	62	84
	IL-6: 297 (pg/ml)	72	62	50	70
Persson et al. [35]	PCT: 1.3 (ng/ml)	79	87	63	94
	CRP: 143 (mg/l)	58	82	48	88
	IL-6: 71 (pg/ml)	68	72	41	89
Giamarellou et al. [30]	PCT: 1.0 (ng/ml)	44.2	64.3	82.1	18.8
	CRP: > 3.2 (mg/l)	34.6	21.4	62.1	8.3
Ruokonen et al. [31]	PCT: 0.5 (ng/ml)	54.5	88.2	–	–
Kitanovski et al. [42]	PCT > 1.04 (ng/ml)	87.5	80.8	58.3	95.5
	CRP > 124 (mg/l)	75	86.3	63.2	91.7
	IL-6 > 85.5 (pg/ml)	93.6	68.6	48.4	97.2
Secmeer et al. [44]	PCT: 0.4 (ng/ml)	33.3	92	50	92
	CRP: 50 (mg/l)	66.7	46.6	12	92

PCT: procalcitonin; CRP: C-reactive protein; IL-6: interleukin-6; PPV: positive predictive value; NPV: negative predictive value

chemotherapy-induced neutropenic fever; however, PCT was measured only at the onset of fever which might have resulted in any subsequent increases in PCT in infected patients being overlooked. Moreover, bacteremic episodes in this study [43] were mainly due to coagulase-negative staphylococcus, which has been reported to induce no significant increase in PCT levels [30, 35].

Patients with fever of unknown origin may have PCT levels within normal ranges [31, 32, 34, 38] or moderately elevated [27, 30, 35, 41], but usually values are far below those observed in bacterial infections [27, 30, 31, 34, 35, 38, 42]. In 28 children with febrile neutropenia, *Ruokonen* et al. [31] reported higher PCT levels in infected patients compared to patients with fever of unknown origin, 8 h after the onset of fever. IL-6 was also higher in infected children, whereas CRP, endotoxin, tumor necrosis factor (TNF)-alpha, and neopterin levels did not differ between infected children and those with fever of unknown origin. PCT showed good specificity but poor sensitivity in identifying infections in these patients; however, the small number of patients and short follow-up period (8 h) in this study are major limiting factors. *Fleischhack* et al. [38] also reported higher PCT levels in infected patients when compared to those with fever of unknown origin or those with afebrile newly diagnosed cancer in a cohort of 76 children with febrile neutropenic episodes; however, the infected group included patients with both localized and systemic infections. *Kitanovski* et al. [42] also demonstrated higher PCT and IL-6 levels in children with febrile neutropenia and bacteremia or local infection than in children with fever of unknown origin. However, after allogenic stem cell transplantation, *Persson* et al. [35] found no differences in PCT, CRP, serum amyloid A (SAA), or IL-6 levels in patients with febrile neutropenia and fever of unknown origin, compared to patients with bacteremia with coagulase-negative staphylococci. This observation, among others [30, 43], limits the value of PCT measurements in this specific population. *von Lilienfeld-Toal* et al. [41] described similar PCT levels in febrile patients after chemotherapy suffering from fever of unknown origin, non-microbial fever, and pneumonia, but higher levels in patients with bacteremia than in non-bacteremic patients. The dynamics of PCT over time seem to be important also in the context of management of patients with fever of unknown origin. In pediatric patients with febrile-neutropenia after intensive chemotherapy, *Secmeer* et al. [44] found no differences in PCT or CRP levels, or erythrocyte sedimentation rate between clinically or microbiologically documented infection and fever of unknown origin at the onset of fever; however, PCT levels declined more rapidly in non-infected compared to infected patients.

Value of PCT According to the Infecting Micro-organism

Higher PCT levels were reported more frequently in febrile neutropenic patients with documented bacterial infections than with viral or fungal infections [26, 27, 30, 32–36, 38, 45–48]. However, differences according to specific types of bacteria are less obvious. *Fleischhack*

et al. [38] reported higher PCT levels in 76 febrile neutropenic children infected with Gram-negative bacteria than in Gram-positive infected patients. Likewise, *Svaldi* et al. [49] found higher PCT levels in 73 febrile adult patients with Gram-negative infection when compared to those with Gram-positive infection. However, several studies reported similar PCT levels in patients with Gram-negative and those with Gram-positive infections in sepsis and immunodeficiency [50], febrile neutropenia after cytotoxic chemotherapy [26], and in adult neutropenic patients with hematological malignancy [41], or solid tumors [40].

The role of PCT in the diagnosis of fungal infections in febrile neutropenic patients is not well established. Several investigators [32, 34] have reported normal PCT levels at the onset of fungal infections with subsequent increases in patients with higher severity of illness. *Petrikkos* et al. [51] measured serum PCT, CRP, and mannan antigens in 91 neutropenic, human immunodeficiency virus (HIV) infected, critically ill patients with fungal and bacterial infection. CRP and PCT levels were higher in patients with bacterial infection than in those with fungal infection on the first and the third day after the onset of infection. Mean PCT levels never exceeded 1.5 ng/ml. The area under the ROC curve for predicting invasive fungal infection was 0.71 for PCT on days 1 and 3, and 0.62 and 0.67 on days 1 and 3, respectively, for CRP. *Christofilopoulou* et al. [34] measured serum PCT levels in a cohort of 14 patients with malignant disease and fungal infection; PCT was less than 0.5 ng/ml in nearly all patients on the first day of the fungal infection. However, higher PCT levels were observed in patients with an unfavorable course 3 and 10 days after the onset of severe fungal infection. Similarly, *Ortega* et al. [32] reported PCT levels in 5 patients with invasive aspergillosis in their study of 77 patients with febrile neutropenia after stem cell transplantation. All patients with aspergillosis had low PCT levels on the first day of infection (< 0.7 ng/ml), but high levels of PCT on day 5 of fungal infection (> 1.5 ng/ml). In this subgroup, PCT levels > 3 ng/ml on the fifth day of persistent fever discriminated invasive aspergillosis with a sensitivity of 80% and a specificity of 100%.

The correlation between the severity of fungal infections and high PCT levels was also demonstrated in several case reports. *Gerard* et al. [52] reported a case of disseminated candidiasis in a 4-year old liver transplant recipient, proven by positive blood cultures and ascitic fluid samples. PCT levels reached a maximum of 103 ng/ml and rapidly decreased during antifungal therapy. *Beaune* et al. [53] reported only slight increases in PCT levels in two patients with aspergillosis after chemotherapy; one patient showed increased PCT levels in association with convulsions due to neurological spread of the fungal infection, whereas PCT remained low in the second patient with pulmonary aspergillosis.

Relationship Between PCT, the Severity of Sepsis, and Outcome

Higher PCT levels were reported in systemic and more severe form of infections than in local and less severe infections. *Giamarellos-Bourboulis* et al. [40] found higher levels of PCT in febrile patients with severe sepsis after chemotherapy than in those with localized infection; PCT > 2.0 ng/ml discriminated severe sepsis from local infection with a sensitivity of 90% and a specificity of 86.9%. Interestingly, higher PCT levels were found in patients with fever of unknown origin who responded to antimicrobial therapy than in those who did not, suggesting a possible role of PCT in decisions regarding administration or adjustment of antimicrobial therapy in these patients. *Giamarellou* et al. [30] described higher PCT levels in patients with febrile neutropenia and severe sepsis than in patients with systemic or local bacterial infection. PCT levels > 5 ng/ml had a sensitivity of 83.3% and a specificity of 100% for diagnosing severe sepsis. CRP, at a cut-off of 3.2 mg/l, had a sensitivity of 100% and a specificity of 5%. *Svaldi* et al. [49] found higher PCT levels in febrile neutropenic patients with severe sepsis or septic shock than in those with sepsis; PCT levels were also higher in septic patients than in non-septic patients. The authors [49] also reported lower PCT levels in leukopenic than in non-leukopenic patients. This observation signifies that PCT levels between 0.5 and 2 ng/ml may be an indicator of serious and life-threatening conditions in febrile neutropenic patients. *Sauer* et al. [46] showed that PCT levels were higher in children with sepsis after bone marrow transplantation when compared to non-septic patients. Children developing septic shock and subsequent MOF had higher PCT values when compared to those with sepsis, and PCT levels were also higher in patients with severe sepsis than in those with sepsis without organ failure. At a cut-off level of 1.0 ng/ml, PCT had a sensitivity of 56% and a specificity of 87% for predicting sepsis. CRP levels were higher in sepsis patients compared to non-septic patients, but similar in severe sepsis compared to sepsis. At a cut-off value of 50 mg/l, CRP had a sensitivity of 100% but a poor specificity of 41% for predicting sepsis. CRP and PCT levels were higher in non-survivors compared to survivors.

The correlation between PCT and outcome was investigated by several authors. *Fraunberger* et al. [54] reported similar PCT and CRP levels irrespective of ICU outcome in 38 febrile neutropenic patients during the initial onset of fever. In this study [54], only IL-6 levels were significantly higher in non-survivors compared with survivors. *Pihusch* et al. [28] documented elevated levels of CRP, PCT, and IL-6 in patients who died from transplant-related complications compared with patients surviving after hematopoietic stem cell transplantation. *Sauer* et al. [46] described higher PCT and CRP levels in non-survivors compared to survivors in children after bone marrow

transplantation and sepsis. *von Lilienfeld-Toal* et al. [48] reported a rise in PCT levels shortly before death in patients with febrile episodes and hematological malignancy. The small number of patients in the previous studies [28, 46, 48, 54] is a major limiting factor. Moreover, the independent influence of PCT on the risk of death in this population was not investigated. Further studies are also needed to assess the usefulness of incorporating PCT into scoring systems with the aim of improving their performance in terms of outcome prediction.

Discussion

The degree of neutropenia is a major risk factor for developing infection; the longer the duration of neutropenia and the more rapid the decline in white cells, the greater the incidence of infection [55, 56]. It is, therefore, important to start antibiotic therapy as early as possible in cases of infection. The presence of sepsis markers could assist in clinical decision making. *Südhoff* et al. [57] evaluated values of serum and plasma markers in febrile neutropenia in 2000 and concluded that, according to the literature, predictive values of CRP, pro-inflammatory cytokines, and soluble adhesion molecules seemed to be too low to influence initial treatment decisions, such as rapid institution of empirical broad-spectrum antibiotic therapy, in patients with neutropenic fever. There were relatively few data available for PCT at that time. Six years later, 30 studies have been published evaluating the role of PCT in febrile neutropenic patients. The present literature suggests that PCT may be helpful in differentiating infection and sepsis in neutropenic patients from non-infectious causes of fever and fever of unknown origin. Despite the consistent significant difference in PCT levels in the literature between patients with local infections and those without infection, the discriminative value of PCT has been reported mainly for systemic infections and bacteremia. The superiority of PCT over CRP and IL-6 in differentiating non-invasive local infections from non-infectious causes of fever and inflammation remains unclear and needs further evaluation and may only be demonstrated by using a PCT test with high sensitivity [9, 10].

Although it has been demonstrated that the use of PCT levels in the frame work of a predefined algorithm may prevent antibiotic overuse in non-neutropenic patients with community-acquired pneumonia and in patients with suspected respiratory tract infections [9, 12], whether this use of PCT is also valid in other clinical settings, e.g., in patients with neutropenia, has not been assessed. Of note, the results of the aforementioned studies [9, 12] were obtained using a modern PCT test with a functional assay sensitivity of 0.06 ng/ml, which is five times greater than the sensitivity of the PCT test that was used in all the studies included in this review.

On the basis of the reported PCT levels in febrile neutropenic patients, it is obvious that values less than 0.5 ng/ml are less likely to occur in patients with infection; however, during the early phase of fever (first 24 h) or with suspected fungal or viral infections normal values may be reported and sequential measurement of PCT should be obtained to rule out infection or to guide antimicrobial therapy. PCT values between 0.5 and 1.0 ng/ml commonly occur with local or uncomplicated systemic infections, whereas PCT values between 1.0 and 2 ng/ml are highly suggestive of bacteremia or severe fungal infections. Patients with severe sepsis and septic shock commonly have PCT levels above 2.0 ng/ml and should be considered at high risk of poor prognosis.

The lack of standard definitions, the heterogeneity of study populations (adults, infants, and children), and the small number of patients included in some studies are all possible limitations of our review. The available data are not sufficient to perform a meta-analysis in this subgroup of patients. Nevertheless, our review provides important insight into the value of PCT as a diagnostic and prognostic tool in this group of high-risk patients.

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