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Original Article

Comparison of the Power of Procalcitonin and C-Reactive Protein to Discriminate between Different Aetiologies of Fever in Prolonged Profound Neutropenia: A Single-Centre Prospective Observational Study

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Abstract. Management of fever in prolonged, profound neutropenia remains challenging with many possible infectious and non-infectious causes. We investigated whether procalcitonin (PCT) is superior to C-reactive protein (CRP) in discriminating between different aetiologies of fever in this setting.

CRP and PCT were tested daily during 93 neutropenic episodes in 66 patients. During this study period, 121 febrile episodes occurred and were classified into four categories based on clinical and microbiological findings: microbiologically documented infection (MDI); clinically documented infection (CDI); proven or probable invasive fungal disease (IFD); fever of unknown origin (FUO). Values of PCT and CRP at fever onset as well as two days later were considered for analysis of their performance in distinguishing aetiologies of fever.

At fever onset, no significant difference in PCT values was observed between different aetiologies of fever, whereas median CRP values were significantly higher in case of IFD (median 98.8 mg/L vs 28.8 mg/L, p=0.027). Both PCT and CRP reached their peak at a median of 2 days after fever onset. Median PCT values on day 2 showed no significant difference between the aetiologies of fever. Median CRP values on day 2 were significantly higher in IFD (median 172 mg/L versus 78.4 mg/L, p=0.002). In MDI median CRP values rose > 100 mg/L, whereas they did not in CDI or FUO.

PCT has no added value over CRP for clinical management of fever in prolonged, profound neutropenia. When performing reassessment 2 days after fever onset, CRP has better discriminatory power between aetiologies of fever.

Keywords: Febrile neutropenia; Procalcitonin; C-reactive protein; Prolonged profound neutropenia; Invasive fungal disease.

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Introduction. Febrile neutropenia occurs very frequently in patients with prolonged, profound neutropenia caused by treatment with intensive myelosuppressive chemotherapy for haematological malignancies, exceeding 80% of cases.[1-3] Management remains challenging as the presence of fever in this patient population is neither specific for infection nor is it pathognomonic of any type of infection. It may also be caused by reactions to drugs and blood products, non-infectious inflammatory responses secondary to the malignancy, administration of chemotherapy, antithymocyte globulin (ATG) or engraftment and graft versus host disease (GvHD) after allogeneic hematopoietic stem cell transplantation (HSCT). In more than 60% of cases, there is no documented infectious aetiology and unresolved febrile neutropenia often results in multiple empirical modifications of antibacterial therapy and/or addition of antifungal therapy. Unfortunately, indiscriminate use of broad-spectrum antibiotics can lead to important collateral damage including toxicity, selection of multidrug-resistant pathogens and an increased predisposition to other infections such as Clostridium difficile or yeasts/fungi.[4] In case of invasive fungal disease, prompt diagnosis and early initiation of antifungal therapy is known to improve survival.[5]

In clinical practice, C-reactive protein (CRP) is currently used in the decision-making process when treating patients with febrile neutropenia. However, it is part of the nonspecific acute-phase response to most forms of tissue damage, infection, inflammation and malignant neoplasia.[6] Procalcitonin (PCT) is a 116-aminoacid precursor peptide for the hormone calcitonin expressed by the *CALC1*-gene.[7] During infection, the combination of microbial products (e.g. lipopolysaccharides) and pro-inflammatory cytokines results in an up-regulation of the gene expression of the *CALC1*-gene and PCT is released from nearly all tissues and cell types in the body.[8] PCT promptly increases within 6 to 12 hours upon stimulation and circulating PCT levels halve daily when the infection is controlled by the host immune system or antibiotic therapy.[9]

Procalcitonin (PCT) has demonstrated superior diagnostic accuracy when compared to CRP as a biomarker of infection in non-haematological populations.[10-13] It has been used successfully in algorithms for antimicrobial therapy in acute respiratory infections and management of sepsis in intensive care units. In 2008 Sakr *et al.* reviewed the available literature on the use of PCT in febrile neutropenia, concluding that this biomarker may be helpful in differentiating infection and sepsis from non-infectious causes of fever.[14] However, due to the heterogeneity of study populations, the specific value of PCT assessment in adults with prolonged, profound neutropenia following intensive chemotherapy remains uncertain.

With this study, we wanted to compare the evolution of CRP and PCT with daily measurements in a large cohort of patients with prolonged, profound neutropenia. This differs from older studies where PCT values were often tested at intervals of 3 to 5 days or daily only for a few days around a febrile episode. With this design, we hoped to find medications or clinical situations that affect CRP and PCT values differently. Furthermore, we aimed to clarify whether PCT has superior reliability in comparison to CRP in the clinical management of febrile patients in the setting of prolonged profound neutropenia.

Material and Methods.

Study design. This single-centre prospective observational study was carried out at the adult haematology ward of the Antwerp University Hospital, which is equipped with high-efficiency particulate air (HEPA) filtration. Throughout 18 months (March 2015 until September 2016), consecutive patients admitted for induction/consolidation chemotherapy for acute leukaemia, intensive chemotherapy followed by autologous stem cell rescue or allogeneic HSCT for diverse haematological malignancies were enrolled. Patients could be included several times in the study for different admission periods. After written informed consent, CRP and PCT were measured daily on standard blood draws during the entire hospitalisation period. All patients received standard care, and no clinical decisions were based on PCT results as those were not available to treating physicians. The protocol was reviewed and approved by the local ethics committee. This study was conducted in agreement with the Declaration of Helsinki as well as the laws and regulations of the Belgian government, whichever provides the greatest protection for the patient.

Data collection. Results of daily CRP and PCT measurements were recorded, as well as administration of drugs that could potentially influence their values such as corticosteroids, cytarabine, antithymocyte globulin and immunosuppressive therapy in case of allogeneic HSCT. CRP was measured daily by nephelometry using the Dimension Vista® 1500 System (Siemens Healthcare, Munich, Germany). PCT was measured daily using the Elecsys® BRAHMS PCT Assay on the Modular E170 instrument (Roche Diagnostics, Rotkreuz, Switzerland). This automated test is performed in human serum using the ECLIA (ElectroChemiLuminiscence ImmunoAssay) technique with a detection limit of 0.02 µg/L and an upper limit of normal (ULN) of 0.5 µg/L.

Definitions and infectious work-up. Febrile neutropenia was defined as an axillary temperature of ≥38.3°C on a

single occasion or ≥38.0°C sustained over a 2 hour period during neutropenia defined as an absolute neutrophil count < 500/μL.[15] A new febrile episode was defined as a relapsing fever after more than 72 hours of apyrexia (<38.0°C).

For each febrile episode, the initial diagnostic workup consisted of a thorough physical examination, one set of aerobic and anaerobic blood cultures drawn by phlebotomy and one set via each lumen of the central venous line, urine culture and chest X-ray. Blood cultures were obtained repeatedly during the first three fever spikes, galactomannan antigenemia was measured twice weekly, and additional specific investigations were performed according to the clinical presentation. When fever persisted for more than four days, the diagnostic reassessment included a thoraco-abdominal CT-scan and bronchoscopy with BAL in the presence of a lung infiltrate.

Febrile episodes were classified into four categories based on clinical and microbiological findings without any knowledge of the analysed PCT values: 1) microbiologically documented infection (MDI, i.e. proven microbial pathogen with or without microbiologically defined site of infection); 2) clinically documented infection (CDI, i.e. diagnosed site of infection without proven microbiologic pathogenesis); 3) proven or probable invasive fungal disease (IFD); 4) fever of unknown origin (FUO).[16,17]

Statistical analysis. All data were analysed using a statistical software package (IBM SPSS Statistics 23, Chicago, IL). Continuous variables were compared using the Mann-Whitney (2-group comparison) or Kruskall Wallis (multiple-group comparison) non-parametric tests. Categorical variables were compared with the χ^2 or Fischer's exact test, as appropriate. A linear mixed model using R was performed to evaluate the effects of different variables on the values of CRP and PCT over time. A two-sided p-value of less than 0.05 was considered as statistically significant. The peak values of PCT and CRP were considered for analysis of their performance in distinguishing aetiologies of fever in receiver operating characteristic (ROC) curves and by calculation of sensitivity, specificity, positive & negative predictive values and efficiency. The best cut-off was defined on the basis of the highest calculated efficiency.

Results.

Patient inclusion. During the 18-month study period, 66 patients were enrolled in this study and data was collected for 93 admissions. The median duration of each hospitalisation was 26 days, with a median duration of profound neutropenia of 12 days. During these 93 neutropenic periods, a total of 121 febrile episodes (FE) occurred. A total amount of 2535 patient days was evaluated for PCT and CRP values. Patient demographics and characteristics of neutropenic & febrile episodes can be found in **Table 1**. As an interim analysis performed after 40 admissions showed that ATG had an important impact on the PCT value, FE classified as fever of unknown origin that occurred within 48 hours after administration of ATG were separated for further analysis.

Table 1. Characteristics of patients, neutropenic and febrile episodes.

Patients	**n = 66**
Median age (range)	58 (17-76)
Male/female	38/28 (42.4%)
Underlying malignancy	
Acute leukaemia	26 (39.4%)
Multiple Myeloma	19 (28.8%)
Lymphoma	15 (22.8%)
Other	6 (9%)
Neutropenic episodes	**n = 93**
Treatment	
Induction/consolidation	35 (37.6%)
Autologous HSCT	30 (32.2%)
Allogeneic HSCT	28 (30.2%)
Median duration of neutropenia in days (range)	12 (4-78)
Median duration of hospitalisation in days (range)	26 (10-87)
Febrile episodes	**n = 121**
Microbiologically documented infection (MDI)	28 (23.1%)
Clinically documented infection (CDI)	18 (14.9%)
Proven or probable invasive fungal disease (IFD)	8 (6.6%)
Fever of unknown origin (FUO)	67 (55.4%)
Without ATG	57 (47.1%)
With ATG	10 (8.3%)
First / Recurrent febrile episode	82 /39 (32.2%)
Antibiotics / No antibiotics on-going at onset	34/87 (71.9%)
Severity of infection	
Hypotension	7 (5.8%)
Hypoxia	8 (6.6%)
Septic shock	3 (2.5%)
Death	3 (2.5%)
Median time to defervescence in days (range)	3 (1-23)
Microbiologically documented infection (MDI)	2.5 (1-16)
Clinically documented infection (CDI)	6 (2-11)
Proven or probable invasive fungal disease (IFD)	6 (3-23)
Fever of unknown origin (FUO)	2 (1-8)
With ATG	1 (1-3)
Without ATG	2 (1-8)

Comparison of PCT and CRP evolution during prolonged, profound neutropenia. In a first analysis, the individual curves of CRP and PCT evolution during the 93 hospitalisation periods were reviewed visually. In 31 out of 93 neutropenic episodes (33.3%) their pattern of evolution appeared similar, whereas in 61 neutropenic episodes (66.7%) their evolution was clearly different. CRP seemed to be a more volatile parameter, rising above its ULN (3 mg/L) during every single neutropenic episode. Its reactivity to stimuli was also quite pronounced with a median of 2 surges above 100 mg/L per neutropenic episode. In contrast, PCT did not rise above its ULN of 0.5 ng/mL in 50 out of 93 neutropenic episodes (53.8%).

The present study, to evaluate the influence of confounding factors on the evolution of CRP and PCT, utilises a linear mixed model fitting with the neutropenic episode as a random effect. The logarithm of the outcomes was modelled as residual assumptions are better met in this way. This model included the following parameters: temperature, white blood cell count (WBC), absolute neutrophil count (ANC), administration of ATG, corticosteroids, cytarabine, cyclosporine A, mycophenolate & methotrexate and presence of cytarabine-induced dermatitis or engraftment syndrome. We found that many of these factors had a statistically significant effect on both the CRP and PCT values. However, the only one with a clinically relevant large effect size was ATG: administration of ATG resulted in an 11-fold increase [95% CI (8.7, 15.1)] of the PCT value one day later versus only a 2-fold increase [95% CI (1.4, 2.9)] of the CRP value.

Comparison of PCT and CRP evolution during febrile episodes. **Figure 1** and **Table 2** show the kinetics of PCT & CRP for different aetiologies of febrile neutropenia.

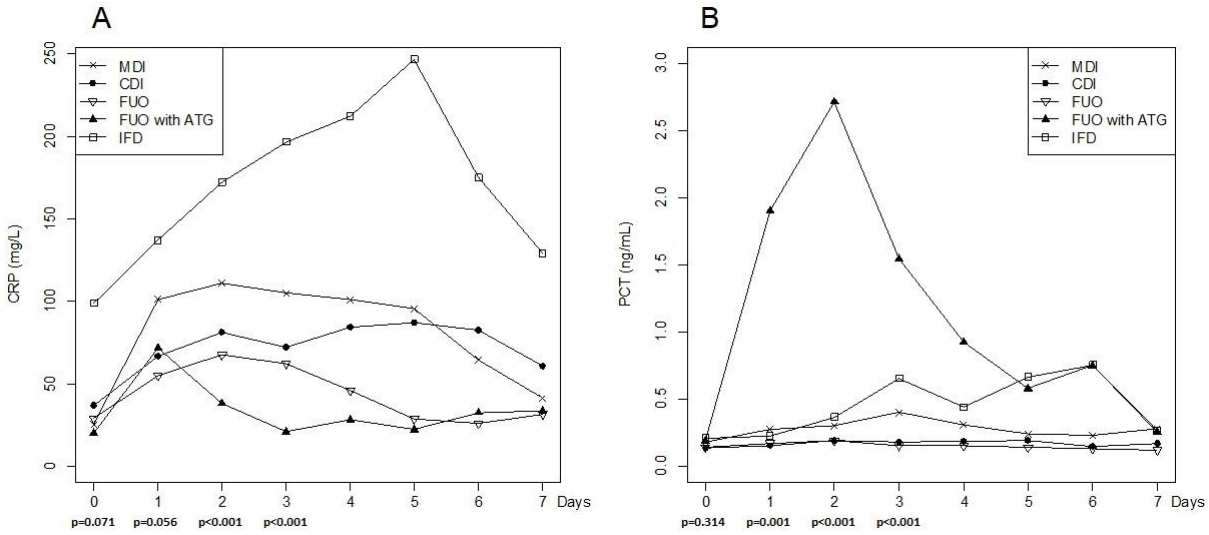
Initial diagnostic assessment. On the day of fever onset, no significant difference in PCT values was observed between the different categories (p=0.314). Nine FE presented with a PCT value ≥ 0.5 ng/mL: 2 MDI, 1 CDI, 4 FUO and 2 FUO with ATG. None of these FE was associated with severe clinical signs such as hypotension, hypoxia and the need for transfer to intensive care facilities. Thirteen FE, which were complicated by a severe clinical course, showed a median PCT value of 0.15 ng/mL (range 0.09 - 0.34 ng/mL) on the day of fever onset.

CRP values were significantly higher on the day of fever onset in patients suffering from IFD versus all other aetiologies (median 98,75 mg/L versus 28.8 mg/L, p=0.027). Thirteen FE presented with a CRP value ≥ 100 mg/L: 3 MDI, 1 CDI, 5 FUO and 4 IFD. Three of these FE ran a severe clinical course. Median CRP on the day of fever onset was 36.6 mg/L (range < 2.9 - 137 mg/L) in the thirteen FE complicated by a severe clinical course.

Diagnostic reassessment. Both PCT and CRP reached their peak value at a median of 2 days [95% CI (1,10) for PCT & 95% CI (1,7) for CRP respectively]. PCT values on day 2 were significantly higher in FUO after ATG versus all other aetiologies (median 2.72 ng/mL versus 0.21 ng/mL, p<0.001). In cases of MDI and IFD, median PCT values rose > 0.25 ng/mL on day 2. In contrast, in cases of CDI or FUO without ATG, they stayed lower. Thirteen FE that were complicated by a severe clinical course showed a median PCT value on day 2 of 0.35 ng/mL (range 0.09 - 7.67 ng/mL) versus 0.22 ng/mL (range 0.06 - 29.59 ng/mL) in all other uncomplicated cases (p=0.139).

CRP values on day 2 were significantly higher in IFD versus all other aetiologies (median 172 mg/L versus

Figure 1. Kinetics of CRP and PCT for different aetiologies of febrile neutropenia.



A: Kinetics of CRP for different aetiologies of febrile neutropenia based on the median value.
B: Kinetics of PCT for different aetiologies of febrile neutropenia based on the median value.

Table 2. Kinetics of PCT and CRP for different etiologies of neutropenic fever (median/range).

	PCT D0 (ng/mL)	PCT D2 (ng/mL)	CRP D0 (mg/L)	CRP D2 (mg/L)
Microbiologically documented infection (MDI)	0.18 (0.05 - 2.67)	0.30 (0.06 - 24.75)	25.4 (<2.9 - 225)	111 (20.7 - 253)
Clinically documented infection (CDI)	0.13 (0.08 - 0.52)	0.18 (0.08 - 4.29)	37.7 (9.5 - 101)	85.2 (25.3 - 215)
Proven or probable invasive fungal disease (IFD)	0.21 (0.07 - 0.31)	0.37 (0.09 - 7.67)	98.8 (18.5 - 155)	172 (75.4 - 276)
Fever of unknown origin (FUO) without ATG	0.14 (0.04 - 3.53)	0.18 (0.06 - 3.13)	29.1 (<2.9 - 162)	68.6 (4.1 - 225)
Fever of unknown origin (FUO) with ATG	0.19 (0.09 - 3.94)	2.71 (0.10 - 29.59)	20.3 (<2.9 - 44)	38.1 (23.3 - 82.4)
p-values				
distribution accross all categories	p=0.314	**p<0.001**	p=0.071	**p<0.001**
without 'FUO with ATG' group	p=0.733	**p=0.017**	p=0.154	**p=0.004**
IFD versus all other causes	p=0.906	p=0.483	**p=0.027**	**p=0.002**

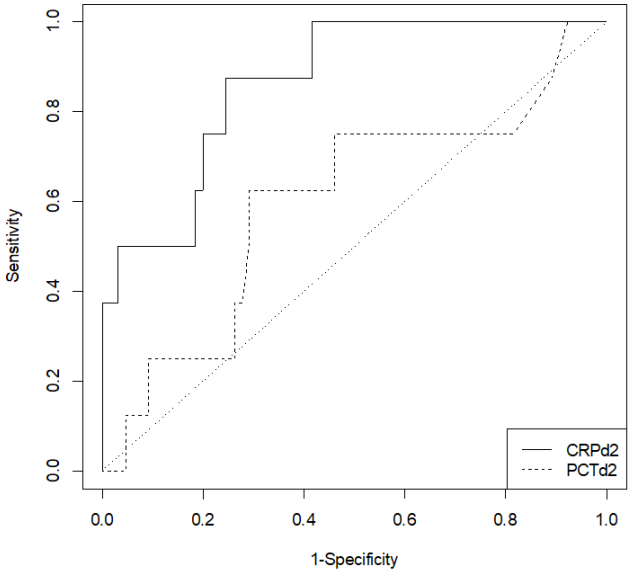
MDI = microbiologically documented infection, CDI = clinically documented infection, IFD = invasive fungal disease, FUO = fever of unknown origin, ATG = antithymocyte globulin.

78.4 mg/L, p=0.002). In cases of MDI, median CRP values rose > 100 mg/L on day 2. In contrast, in cases of CDI or FUO (with/without ATG), they stayed lower. Thirteen FE that were complicated by a severe clinical course showed a median CRP value on day 2 after onset of fever of 182 mg/L (range 75.4 - 276 mg/L) versus 59.5 mg/L (range 4.1 – 259 mg/L) in all other uncomplicated cases (p<0.001).

When looking at the 28 episodes of MDI, 15 were caused by gram-positive bacteraemia, eight by gram-negative bacteraemia and the remaining five by urinary tract infection and viral or bacterial pneumonia. The median values of CRP and PCT did not differ depending on the underlying cause of MDI or specific bacterial isolate.

Differential diagnosis between FUO and IFD. ROC curves were computed to see whether PCT and/or CRP were able to discriminate between FUO and IFD. **Figure 2** demonstrates that the discriminatory power of CRP on day two after the onset of fever was superior to that of PCT. **Table 3** shows the predictive value of CRP for IFD at different cut-offs. With the cut-off set at 200 mg/L, CRP on day 2 has a positive predictive value of 66.7% and a negative predictive value of 94.2% for the diagnosis of IFD versus FUO. This leads to an efficiency of 92%.

Figure 2. ROC curves.



ROC curves for median CRP and PCT values on day 2 after onset of fever. The area under the curve for CRP is larger, reflecting a higher efficiency in predicting invasive fungal disease in comparison to PCT.

Discussion. The management of febrile neutropenia in patients with prolonged, profound neutropenia remains challenging as there are many possible infectious and non-infectious causes for fever. The possible risk of a fatal outcome from bacterial infection warrants immediate administration of broad-spectrum antibiotics. However, in many cases such antibiotic therapy might not be necessary and long periods of treatment with broad-spectrum antibiotics can result in toxicity, selection of multidrug-resistant pathogens and increased predisposition to infections by Clostridium difficile and yeasts/fungi. While the clinical condition of the patient is the most important element in the decision-making process leading to the initiation, reassessment and (dis)continuation of broad-spectrum antibiotics, laboratory parameters denoting infection/inflammation are also included. CRP is a very basic and widespread test to reflect inflammation but is not specific for infection. In this study, we investigated whether PCT could provide superior reliability in comparison to CRP in the clinical management of fever in patients with prolonged, profound neutropenia. To achieve this, we performed daily determinations of CRP and PCT whereas several other studies in the field have limited the number of PCT measurements and might have only provided a partial picture.

On the day of fever onset, both CRP and PCT were not able to differentiate between the aetiologies of febrile episodes nor were they able to predict the

Table 3. Predictive value of CRP on day 2 after onset of fever for IFD.

Cut-off (mg/L)	sensitivity (%)	specificity (%)	PPV (%)	NPV (%)	efficiency (%)
50	100	34.3	15.4	100	41.3
100	87.5	65.7	23.3	97.8	68.0
150	50.0	83.6	26.7	93.3	80.0
200	50.0	97.0	66.7	94.2	92.0

IFD = invasive fungal disease, PPV = positive predictive value, NPV = negative predictive value.

severity of the clinical picture (including hypotension, hypoxia and the need for transfer to intensive care facilities). As such, the decision whether or not to start antibiotics when febrile neutropenia occurs cannot be delayed even with low values of CRP and/or PCT. However, after two days of febrile neutropenia, reassessment needs to be performed to decide on (dis)continuation of broad-spectrum antibiotics. In our study, median CRP values at this time were significantly higher in the case of IFD as well as MDI in contrast to CDI and FUO where they stayed below 100 mg/L. The CRP value on day 2 was significantly higher in episodes of febrile neutropenia running a severe clinical course, whereas this was not the case for PCT. Median PCT values at this point were especially high in case of FUO with ATG, which confirms previous findings by Brodska *et al.* & Hambach *et al.*[18-19] In IFD and MDI they rose above 0.25 ng/mL, whereas they did not in case of CDI and FUO without ATG. However, these differences were not statistically significant, and PCT surpassed the threshold of 0.5 ng/mL only in 9 out of 23 FE (39.1%) caused by bacteraemia on day two after fever onset.

These findings contrast the results of three prior studies discussing the value and/or dynamics of PCT in this specific patient population. Gac *et al.* prospectively studied 29 patients with 39 instances of chemotherapy and found that all neutropenic episodes with bacteraemia reached a PCT value of 0.5 ng/mL at 15 days after the onset of chemotherapy.[20] Robinson *et al.* prospectively studied 194 consecutive febrile episodes during 125 neutropenic episodes in 90 patients. They observed that a PCT threshold of 0.5 ng/mL on day two after the onset of fever allowed the best discrimination of severe infections from infections due to coagulase-negative staphylococci (CoNS), superficial infections or fever of unknown origin.[21] Koivula *et al.* analysed 90 episodes of febrile neutropenia in 66 patients and concluded that an elevated level of PCT above 0.5 ng/mL within 24 hours after onset of fever was able to predict bacteraemia and Gram-negative bacteraemia with a sensitivity of 57% & 70% and a specificity of 81% & 77% respectively.[22]

Contrasting results have also been reported in the setting of allogeneic HSCT, where studies by Pihush *et al*[23] and Koya *et al*[24] concluded that PCT has a superior discriminatory power for detection of systemic infection and can differentiate infection from other transplant-related complications such as GvHD despite steroid therapy. However, these results contradict older studies by Blijlevens *et al.*, Hambach *et al.* and Ortega *et al.*[19,25-26] All three studies concluded that the diagnostic value of PCT was not superior to that of CRP in the detection of infections after allogeneic HSCT and did not facilitate the differential diagnosis of febrile episodes.

A possible explanation for these conflicting results could be the presence of severe neutropenia whereas peripheral blood mononuclear cells have been described as a major source for PCT release in sepsis.[27] Some authors reported low sensitivity of PCT levels in patients with a WBC count < 1 x 10E9/L and previous studies confirmed a correlation of PCT with low neutrophil count.[26,28] However, we could not confirm this correlation in our dataset. Another possible confounding factor could be the fact that in many studies PCT samples were frozen and analysed in batch at a later time. In our study, we performed daily measurements on fresh samples as this would be the way one would eventually implement it into real life daily practice and decision making.

From a practical point of view, MDI and CDI are usually already diagnosed by day two based on clinical examination, chest X-ray and microbiological cultures. As such the most important differential diagnosis at this point concerns FUO versus IFD, coupled with the decision to discontinue antibiotics and/or initiate antifungal treatment. Current guidelines suggest diagnostics for IFD to be performed after four days of persistent febrile neutropenia. However, in our study, a CRP value above 200 mg/L showed a positive predictive value of 66.7% and a negative predictive value of 94.2% for the diagnosis of IFD versus FUO (when MDI and CDI were ruled out by diagnostic workup). A high CRP in the absence of a clear focus of infection might prompt earlier investigation for IFD, leading to earlier treatment initiation and lower mortality. Given the low numbers of IFD in our study, these findings should be confirmed in a larger patient population.

Conclusions. In haematological patients with prolonged, profound neutropenia, PCT has no added value over CRP for clinical management of febrile neutropenia. Both CRP and PCT are not able to predict either aetiology or severity of infection at the onset of fever. When performing a reassessment of antibiotic therapy two days after the onset of fever, CRP has the better discriminatory power between aetiologies of fever and shows higher peak values in clinically severe infections. As such, there seems to be no reason to introduce PCT in the daily clinical decision-making process on antibiotic and antifungal therapy in prolonged, profound neutropenic patients suffering from febrile neutropenia.

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