



**Original Article**

**Comparison of Presepsin, Procalcitonin, Interleukin-8 and C-Reactive Protein in Predicting Bacteraemia in Febrile Neutropenic Adult Patients with Haematological Malignancies**

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**Abstract.** Bacterial infections represent life-threatening complications in patients with febrile neutropenia (FN). Diagnostic biomarkers of infections may help to differentiate bacteraemia from non-bacteraemia FN. We aimed to evaluate the utility of procalcitonin (PCT), presepsin (PS), C-reactive protein (CRP) and interleukin-8 (IL-8) as biomarkers of bacteraemia in adult FN patients with haematological malignancies. Concentrations of PCT, PS, CRP and IL-8 were prospectively measured in 36 FN episodes experienced by 28 oncohaematological patients. 11 out of 36 episodes were classified as bacteraemia. PCT was the best biomarker to predict bacteraemia with the area under the curve (AUC) ROC of 0,9; specificity 100% and positive predictive value 100%, while the most sensitive was IL-8 (90,9%) with AUC ROC of 0,88 and negative predictive value 95,2%. All patients with PCT concentrations above 1,6 µg/l had bacteraemia. Patients with IL-8 concentrations superior to 170 pg/ml had a 40 times higher risk for bacteraemia than the ones with lower levels. Patients with PS concentrations superior to 410 pg/ml had 24 times higher risk for bacteraemia than the patients with lower levels. PCT has higher accuracy than CRP, IL-8 and PS in predicting bacteraemia in adult hematologic patients with FN.

**Keywords:** Febrile neutropenia; Sepsis; Bacteraemia; Presepsin.

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**Introduction.** Febrile neutropenia (FN) refers to the occurrence of fever during a period of severe neutropenia (neutrophils  $<0.5 \times 10^9/L$ ). Particularly in the setting of chemotherapy-induced FN, these patients are very prone to bacterial infections.<sup>1,2</sup> Only 20% of FN episodes have a microbiologically-proven infection.

In most cases, the therapeutic approach is based on the clinical picture and the laboratory evaluation of surrogate markers. Among them, CRP, PCT and IL - 8 have been extensively evaluated as diagnostic biomarkers of infection.<sup>3,4</sup> Soluble CD14 subtype, also known as PS, is a novel biomarker of microbial

infection.<sup>5</sup> PS is a surface marker in monocytes/macrophages that binds to the lipopolysaccharide (LPS)-LPS binding protein. Following the infection and the phagocytosis of the CD14-pathogen complex, PS is generated and released.<sup>6</sup> An increasing number of studies have shown the ability of PS to serve as a valuable marker in sepsis diagnosis.<sup>3</sup> However, there is no clear evidence that PS may have a role in identifying infections in adult oncohaematological patients with FN.<sup>7</sup>

The aim of the present study was to analyse the utility of PCT, PS, CRP and IL-8 as biomarkers of bacteraemia during febrile episodes that occurred in neutropenic patients with haematological malignancies, with the goal to define reliable tools that predict bacteraemia.

## Methods and Patients.

**Study design.** This prospective observational study has been performed at the Haematology and Clinical Immunology Unit of the University of Padua, Italy over ten months (from April 2017 to January 2018).

**Participants.** Consecutive patients were considered eligible for the study if they met the following criteria:

- admission to our Unit for high dose chemotherapy alone or followed by autologous bone marrow stem cell transplantation
- the occurrence of FN as defined according to the Infectious Diseases Society of America (IDSA) guidelines.<sup>2</sup>
- patients under 18 years old, those with documented viral or fungal infections, patients with fever before neutropenia onset and patients who received antibiotic treatment before neutropenia onset were excluded from the study.

Episodes of FN were classified according to the International Immunocompromised Host Society into three groups:<sup>8</sup>

Group 1 – microbiologically documented infection or bacteraemia, defined as the presence of live bacteria in the bloodstream,

Group 2 – local infection – focal signs, defined as localized, clinically documented infection of one organ or organ system without bacteraemia,

Group 3 – fever of unknown origin (FUO), defined as an episode of fever without a recognizable cause of infection (clinically documented site of infection and microbiologically isolation).

All patients included in the study received antibiotic prophylaxis with levofloxacin and G-CSF at neutropenia onset. AML patients were also started on posaconazole prophylaxis, all patients with ALL and those undergoing autologous bone marrow transplantation received co-trimoxazole. Fluconazole was administered to ALL patients during induction therapy.

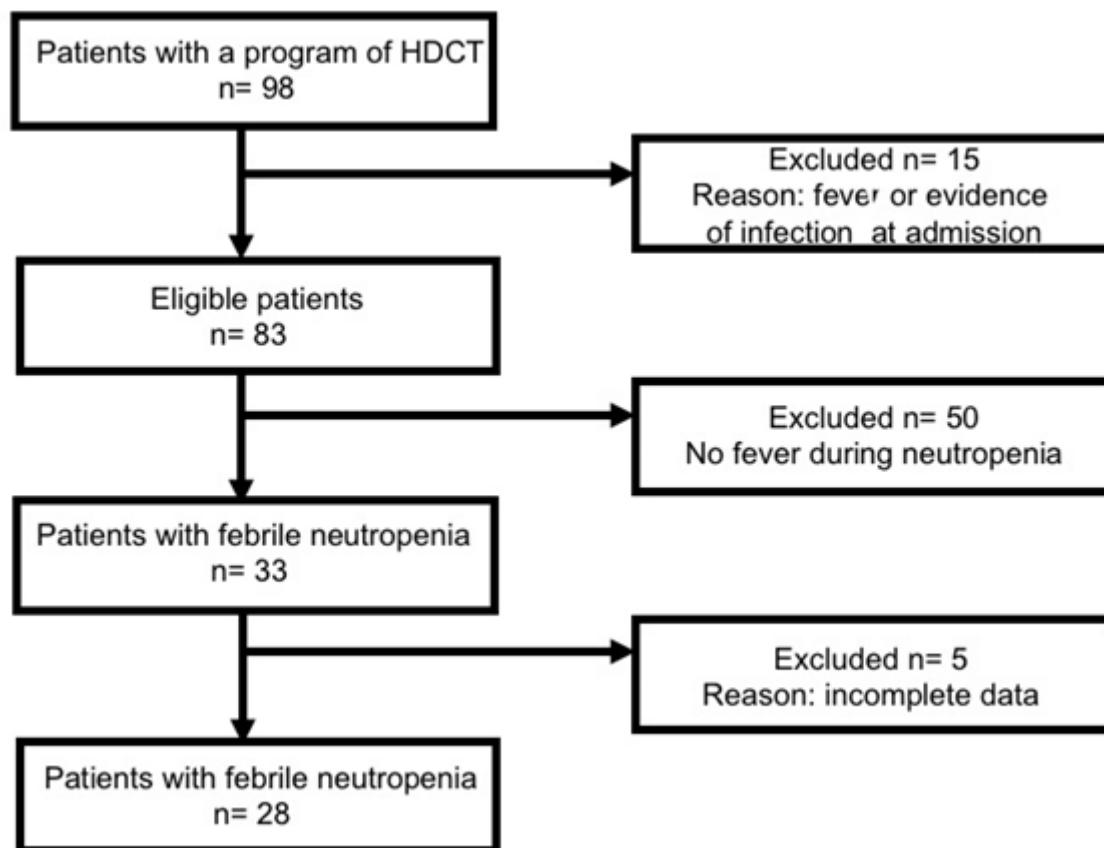
All subjects underwent central venous catheter (CVC) or peripheral intravenous central catheter (PICC) placement for chemotherapy. The study was approved by the Hospital Ethical Board, and written consent was obtained from each patient.

**Test methods.** Complete white blood cell count and CRP concentration were checked daily. As index tests, we considered CRP, PCT, PS and IL-8. PCT, PS and IL-8 were measured at the onset of neutropenia (baseline level), and after a single oral temperature measurement of  $\geq 38.3^{\circ}\text{C}$  or a temperature of  $\geq 38.0^{\circ}\text{C}$  sustained over a 1-h period. All subjects had blood samples collected for PCT, PS and IL-8 measurement between 90 and 120 minutes from fever onset, before any broad-spectrum empirical antibiotic therapy. PCT and PS were measured at the same time, while IL-8 was quantified on the following day. PCT, PS and IL-8 concentrations were determined by standardized assays (Liaison Brahms PCT II GEN, Roche Diagnostics, Germany, determination range 0,02-100  $\mu\text{g/l}$ ; Pathfast Presepsin test, Mitsubishi Chemical Europe, Germany, determination range 20-20000  $\text{pg/ml}$ ; Immulite 1000, Siemens, Germany, determination range 2-7500  $\text{pg/ml}$ , respectively). CRP was determined by the particle enhanced immunonephelometry provided by the Dimension Vista™ System (Siemens Healthcare Diagnostics Inc, Marburg, Germany). Blood culture was considered as a reference standard for diagnosing bacteraemia. Isolation of pathogens from blood cultures was performed using a BacT/Alert three-dimensional (3D) (bioMérieux Inc., Marcy l'Etoile, France) automated blood culture system. Each blood culture consisted of a set of four (FA Plus aerobic, FN Plus anaerobic, SA, and SN) bottles. Antibiotic sensitivity was studied with the VITEK 2 system by Biomerieux (Marcy l'Etoile, France). Only results of CRP and PCT were available to the clinicians during febrile neutropenia periods.

Common skin contaminants were considered significant only if they could be found in two consecutive BC samples or if there were concurrent skin, soft tissue, or catheter-related infections.

In subjects with a suspect of viral infection (like an influenza-like illness), a nasopharyngeal swab for PCR influenza testing was collected, as well as PCR or RT-PCR were performed to rule out respiratory syncytial virus, adenovirus, parainfluenza virus or human metapneumovirus infections. A suspect of fungal infections was evaluated in high-risk patients (not on posaconazole prophylaxis) by checking *Aspergillus* galactomannan antigen and the beta-D-glucan assay starting with the onset of neutropenia and continued until neutrophil recovery.

High-resolution chest CT was performed in all patients with respiratory symptoms and febrile neutropenia. CT scanning of other sites (head, sinuses,



**Figure 1.** Flow chart showing the selection of patients for inclusion in the study

abdomen/pelvis) was performed at the discretion of the clinician.

**Analysis.** Data were analysed for sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) derived from the receiver operating characteristic (ROC) curves. To establish the optimal cut-off values of index tests, authors constructed receiver operating characteristic (ROC) curves, and the areas under the curve (AUC) were determined. The ROC curve is a plot of the true-positive values (sensitivity) vs the false-positive values (1-specificity) for distinct index test cut-off values. The more the curve is located in the top left-hand corner of the graph, the higher the AUC and the higher the accuracy of the diagnostic test is. We performed several ROC analyses to evaluate the accuracy of each index test.

Cut-off values for each parameter determining bacteraemia were calculated from the areas under the ROC curves (AUC). The comparison between groups was made by the Mann-Whitney test, and the proportions of patients were compared by the chi-square test. The non-parametric analysis of variance was made with the Kruskal-Wallis test. Differences at the level of  $p < 0.05$  were considered statistically significant. The diagnostic accuracy was expressed as a proportion of correctly classified mucosal impedance measurements (true negative and true positive

measures) among all measures. We considered  $P \leq 0.05$  to be significant.

Statistical analysis was performed using IBM SPSS Statistics (version 19, SPSS Inc., IBM Company, Chicago, IL, USA).

**Results.** Ninety-eight subjects were admitted to our Unit for high dose chemotherapy over the ten months of the study. Fifteen subjects had a fever and/or evidence of viral infections ( $n = 13$ ) or a previous diagnosis of probable invasive aspergillosis ( $n = 2$ ) and therefore, were not considered eligible for the study. Fifty subjects did not experience fever during neutropenia. Full results were unavailable for five patients due to inappropriate sampling time or incomplete biomarkers analysis. Therefore 28 (29%) patients were analysed in this study (**Figure 1**).

CRP, IL-8, PCT and PS were measured in 36 episodes of FN occurred in 28 patients (17 males and 11 females). All subjects received high-dose chemotherapy. Induction or consolidation chemotherapy for acute leukaemia was the reason for treatment in 17 patients (13 acute myeloid leukaemias, AML- and four acute lymphoblastic leukaemias, ALL). Four patients with multiple myeloma and one patient with non-Hodgkin lymphoma (NHL) received autologous stem cell transplantation. In 6 patients, salvage chemotherapy for NHL was administered.

**Table 1.** Characteristics of patients according to FN subtypes.

|   | Bacteraemia (n=11) |            | local infection (n=14) | FUO (n=11)   | ANOVA (p)    |
|---|--------------------|------------|------------------------|--------------|--------------|
|   | Gram +             | Gram -     |                        |              |              |
| Age, yrs, media ± SD                      | 51.2 ± 4.5         | 63.6 ± 2.3 | 55.4 ± 2.4             | 52.09 ± 2.1  | <b>0.025</b> |
| Sex, M/F                                  | 2/2                | 5/2        | 10/4                   | 5/6          | 0.53         |
| mucositis (yes/no)                        | 2/2                | 2/5        | 4/10                   | 3/8          | 0.85         |
| hospital stay, days, median (range)       | 32 (21-75)         |            | 35 (9-63)              | 30 (22-72)   | 0.67         |
| Hb, g/l, median (range)                   | 80 (72-98)         |            | 84 (70-100)            | 85 (75-115)  | 0.1          |
| WBC x 10 <sup>9</sup> /l, median (range)  | 0,11 (0,02-1)      |            | 0,3 (0,1-1,1)          | 0,4 (0,01-1) | 0.13         |
| N x 10 <sup>9</sup> /l, median (range)    | 0.01 (0-0,35)      |            | 0.03 (0-0,5)           | 0.08 (0-0,5) | 0.1          |
| L x 10 <sup>9</sup> /l, median (range)    | 0.07 (0-0,6)       |            | 0.23 (0-0,6)           | 0.22 (0-0,4) | 0.3          |
| M x 10 <sup>9</sup> /l, median (range)    | 0 (0-0.04)         |            | 0.01 (0-0,1)           | 0.02 (0-0,1) | <b>0.02</b>  |
| PLTS x 10 <sup>9</sup> /l, median (range) | 15 (3-38)          |            | 15 (4-53)              | 22 (5-36)    | 0.6          |

There were no differences between groups of hematologic diseases in terms of age and sex (ANOVA p=0,9 and p=0,7, respectively). Ten subjects were neutropenic at diagnosis before starting chemotherapy. Biomarkers at onset of neutropenia were as follow: PCT 0.03 ± 0.01 µg/l; PS 125 ± 97 pg/ml; CRP 4.4 ± 2.6 µg/l; IL-8 44 ± 27 pg/ml. Distribution of FN subtypes was as follows:

Group 1 – Among 11 episodes of bacteraemia, 7/11 showed growth of gram-negative bacteria (*Klebsiella pneumoniae* in 4 cases, *Escherichia coli* in 2 cases, *Klebsiella oxytoca* in 1 case). In 4 out of 11 episodes, cultures grew gram-positive bacteria (*Enterococcus faecalis* in 2 cases, *Propionibacterium* and *Staphylococcus hominis* in the other cases)

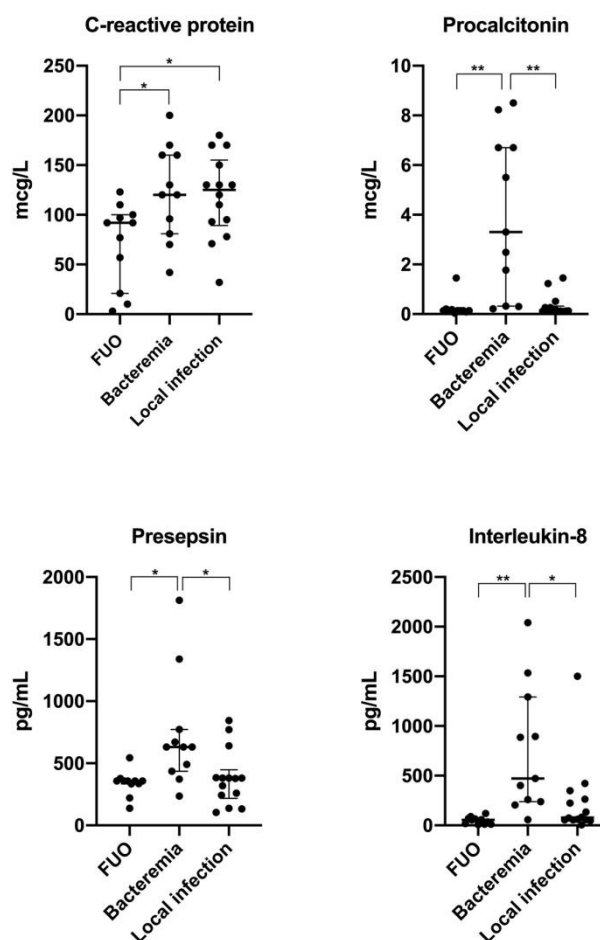
Group 2 –Local infections were diagnosed in 14 episodes as follow: pneumonia (6/14), sinusitis (4/14), endocarditis (1/14), pleuropericarditis (1/14), skin abscesses (1/14), and colitis (1/14).

Group 3 – 11 episodes were classified as FUO.

**Table 1** summarizes patients' characteristics for each group. There were no differences between groups when considering gender and presence of mucositis, while patients with gram-negative bacteraemia were significantly older. Days of hospitalization were similar between FN groups. There were no differences in hematologic parameters (Hb concentration, WBC and neutrophil count, as well as in platelets count). The only parameter that was significantly lower in the bacteraemia group was the monocytes count (**Table 1**).

Median concentrations and p values for each biomarker are presented in **Figure 2** and **Table 2**. PCT concentrations did not differ significantly from those measured at neutropenia onset in the local infection and FUO groups (not shown). Similarly, there were no statistically significant differences in PS and IL-8 values between FUO and local infection groups (**Figure 2**).

Subjects with bacteraemia showed significantly higher concentrations of all biomarkers compared to patients with FUO and those with local infections.



**Figure 2.** PCT, CRP, PS and IL-8 levels in neutropenic subjects. All markers were measured at 12-24 hours from febrile neutropenia onset. Median concentration of PCT (a), CRP (b), PS (c) and IL-8 (d) and interquartile ranges in each group are shown. Probability: \* p < 0.05 and \*\* p < 0.01

Only in the case of CRP, levels did not significantly differ in subjects with bacteraemia compared to local infection (**Figure 2**). Monocyte count lower than 0.01 x 10<sup>9</sup>/l inversely correlated with the concentrations of PCT, IL-8 and PS (r=-0.52, p=0.001; r=-0.45, p=0.005; r=-0.36, p=0.03 respectively).

To test whether CRP, IL-8, PCT and PS could

**Table 2.** CRP, IL-8, PCT, and PS levels in neutropenic subjects.

|                     | <b>FUO<br/>(n=14)<br/>Median (IQR)</b> | <b>Bacteraemia<br/>(n=11)<br/>Median (IQR)</b> | <b>Local infection<br/>n=11)<br/>Median (IQR)</b> |
|---------------------|--|--|---|
| <b>CRP (µg/l)</b>   | 92 (21-100)                            | 120 (81-160)                                   | 125 (89-155)                                      |
| <b>IL-8 (pg/ml)</b> | 55 (12-69)                             | 472 (239-1293)                                 | 78 (55-285)                                       |
| <b>PCT (µg/l)</b>   | 0.14 (0.14-0.18)                       | 3.3 (0.32-6.7)                                 | 0.14 (0.11-0.32)                                  |
| <b>PS (pg/ml)</b>   | 357 (334-357)                          | 631 (435-772)                                  | 380 (217-448)                                     |

**Table 3.** AUC, cut-off, sensibility, specificity, positive predictive value (PPV) and negative predictive value (NPV) for variables predicting bacteraemia.

| <b>Variable</b> | <b>AUC<br/>(95% CI)</b> | <b>cut-off</b>           | <b>Sensitivity<br/>%</b> | <b>Specificity<br/>%</b> | <b>PPV<br/>%</b> | <b>NPV<br/>%</b> | <b>Accuracy</b> |
|-----------------|-------------------------|--------------------------|--------------------------|--------------------------|------------------|------------------|-----------------|
| CRP             | 0,63<br>(0,43-0,83)     | 115 µg/l                 | 64                       | 64                       | 43,8             | 80               | 63,8            |
| IL-8            | 0,88<br>(0,76-1)        | 170 pg/ml                | 90,9                     | 80                       | 66,7             | 95,2             | 83,3            |
| PCT             | 0,9<br>(0,89-1)         | 1,6 µg/l                 | 72,7                     | 100                      | 100              | 89,3             | 91,6            |
| PS              | 0,85<br>(0,68-1)        | 410 pg/ml                | 82                       | 84                       | 70               | 91,3             | 83,3            |
| Monocytes       | 0,79<br>(0,64-0,95)     | 0,01 x10 <sup>9</sup> /l | 64                       | 84                       | 64               | 84               | 60,8            |

predict bacteraemia, we determined optimal cut-off values by ROC analysis. The sensitivity, specificity, NPV, PPV, and diagnostic accuracy for distinct index test are presented in **Table 3**. ROC analysis showed that PCT yielded higher AUC values than other biomarkers, with CRP showing the lowest value (**Table 3**). In addition, the optimal cut-off value for PCT as a biomarker of bacteraemia was 1.6 µg/l, with a specificity of 100% and a sensitivity of 72.7% (**Table 3**). The optimal cut-off value for IL-8 was 170 pg/ml, with a sensitivity of 90,9% and a specificity of 80%. Finally, the optimal cut-off for PS was 410 pg/ml, with a sensitivity of 82% and specificity of 84 % (**Table 3**). CRP could not predict bacteraemia well. In fact, with a cut off value of 115 µg/l, CRP had the lowest AUC (0.63) with sensitivity and specificity of only 64% for both (**Table 3**). All patients with PCT concentrations above 1.6 µg/l had bacteraemia. Patients with IL-8 concentrations superior to 170 pg/ml had a 40 times higher risk for bacteraemia than the ones with lower levels. Patients with PS concentrations superior to 410 pg/ml had 24 times higher risk for bacteremia than the patients with lower levels. PS showed the highest sensitivity in predicting Gram-negative bacteraemia.

When combining two parameters for improving bacteraemia prediction (using scatter plot graph and chi-square test), like PCT (cut-off > 1,6 µg/l) and PS (cut-off > 410 pg/ml) or PCT and IL-8 (cut-off > 170 pg/ml), no significant changes in the sensitivity or negative predictive value compared to PCT alone were observed.

**Discussion.** In this study, we found that PCT has

higher specificity than PS, IL-8 and CRP in predicting bacteraemia during FN in subjects with haematological malignancies. PCT performed better even in term of the probability of bacteraemia above a definite cut-off. In fact, a 64 times higher probability of bacteraemia was found at a PCT cut-off value of 1,6 µg/ml, compared to 40 times and 24 times higher probability for IL-8 and PS, respectively for the best cut-off value of 170 ug/l and 410 pg/ml. Interestingly, patients with monocyte count under 0,01 x 10<sup>9</sup>/l, had 9 times higher probability for bacteraemia than patients with higher monocyte count. We found that CRP concentrations could not predict bacteraemia well. This is not unexpected as CRP levels could be influenced by the underlying malignant disease and tissue damage, all factors affecting its specificity.<sup>9</sup>

Presepsin, a molecule secreted from monocytes following phagocytosis, has gained interest over the past few years in virtue of its rapid increase in patients with sepsis.<sup>6</sup> A recent meta-analysis (18 studies, 3470 patients) has addressed the diagnostic accuracy of presepsin in sepsis.<sup>10</sup> Overall, data suggest that presepsin is a promising marker for the diagnosis of sepsis, but no better performance of presepsin over PCT could be demonstrated.

The role of PS in hematologic FN patients is even less clear as only limited, and inconsistent results are available.<sup>11-15</sup> Only one study found evidence in favour of presepsin as a predictor of bacterial infection in FN. These authors concluded that PS could be used as a discriminator of infectious versus non-infectious origin of fever in children with oncohaematological disorders.<sup>14</sup> Unfortunately, in this study, Baraka et al.

did not provide details on the methodology of sample collection. Therefore the comparison between studies is difficult as the temporal profile of markers likely differs. Of interest, in our study, PCT was informative even if blood samples were collected by 2 hours from the onset of fever. One would have expected a different dynamics of inflammatory markers, particularly of PS and PCT, the latter rising later after the onset of inflammation.<sup>16</sup> The fact that there is evidence of a pre-activation of monocytes before the development of overt sepsis may explain our findings.<sup>17</sup>

In agreement with our results, a retrospective study by Ebihara et al. found that only PCT discriminates between neutropenic patients with infection and uninfected subjects. However, the major limitation of this retrospective study is that no baseline values were collected and therefore, these authors concluded that these biomarkers could not be used as diagnostic tools by themselves.<sup>15</sup> In a population of adult haematological patients with FN, Koh et al. demonstrated that PS levels increased significantly earlier than PCT, but they concluded that the ability of PS to discriminate septic shock from other conditions was inferior to that of PCT.<sup>11</sup>

We found that IL-8 was the most sensitive biomarker. At a cut-off value of 170 pg/ml, IL-8 correlated with all cases of gram-positive bacteraemia and 6/7 of gram-negative bacteraemia. Our result is consistent with recent evidence correlating IL-8 with bacteraemia in paediatric haematological patients, especially in Gram-negative bacteraemia.<sup>18-21</sup>

Interestingly, monocyte count lower than  $0,01 \times 10^9/l$  inversely correlated with the concentrations of PCT, IL-8 and PS, in agreement with a recent study by Koh et al.<sup>11</sup> As already suggested, monocyte count in the bloodstream is not representative of tissue monocytes during bacteraemia. On the other hand, a low monocyte count in FN may also explain the lower reliability of PS in compared to data from non-neutropenic subjects with infection and sepsis.

Our findings are apparently in contrast with the results of a recent study showing no added value of PCT over CRP in haematological patients with prolonged and profound neutropenia.<sup>22</sup> In particular, these authors found that only 39% of bacteraemia episodes had PCT above the average threshold at day two after fever onset. Also, they noted that CRP values at the same time were significantly higher in microbiologically documented infection compared to

clinically documented infection. A possible explanation for the discrepancy may relate to a different subgroup composition of febrile neutropenic patients between ours and Verlinden's study as we did not include allogeneic transplants whereas no patients with relapsed NHL were considered in Verlinden's study. Also, the timing of blood collection on the day of febrile neutropenia onset slightly differed in our study as sampling was performed by 90 and 120 minutes from fever onset, always before patients were started on antibiotic treatment, which may potentially affect procalcitonin levels.<sup>23</sup>

One may argue that, in real life, even a highly accurate and rapidly available marker does not change the therapeutic approach as the decision to start a patient on antibiotic therapy is always based on the clinical picture and standard protocols. A biomarker would be most useful as a screening test (i.e. a negative value confirms the absence of infection); hence it should be characterized by a high sensitivity, not supported by our and other studies.

Although there is general agreement over combination therapy in septic shock, international guidelines recommend against combination therapy in bacteraemia and sepsis without shock. However, in clinical scenarios of severe clinical illness, this position does not preclude the use of multidrug therapy to broaden the spectrum of antimicrobial treatment, and in this specific setting, the identification of highly specific markers of bacteraemia like PCT may be of help.

In agreement with previous studies, the neutrophil count did not predict bacteraemia compared to other febrile neutropenia subgroups.<sup>14,24</sup> Although sample size limits substantial conclusions, this result is not unexpected as all subjects with  $ANC < 0.1 \times 10^9/L$  are considered at high risk, and other factors like duration of neutropenia may contribute to the development of bacteraemia.<sup>2</sup>

Significant limitations of this study are the fact that it is a single-centre study with a relatively low number of febrile episodes (albeit comparable with the majority of previously published monocentric studies on this topic) and that comparison of our results with those from other studies is limited because of the heterogeneity of populations and methodologic approaches.

In conclusion, PCT has higher specificity than PS, IL-8 and CRP in predicting bacteraemia during FN in subjects with haematological malignancies.

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