

Diagnostic value of procalcitonin serum levels in comparison with C-reactive protein in allogeneic stem cell transplantation

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Background and Objectives. Infections represent the major complications following allogeneic stem cell transplantation (SCT). A promising marker for a more specific and early detection of bacterial or fungal infections is procalcitonin (PCT).

Design and Methods. Maximum values (m) and increase (Δ) of PCT and C-reactive protein (CRP) were prospectively analyzed during 214 clinical events in a cohort of 61 patients undergoing allogeneic SCT. Systemic reactions during bacterial or fungal infections were classified according to the ACCP/SCCM criteria.

Results. mPCT and mCRP (normal $<0.5 \mu\text{g/L}$ and $<5 \text{mg/L}$, respectively) levels were high during bacterial and fungal infections (median $2.3 \mu\text{g/L}$ and 188mg/L), moderately elevated during fever of unknown origin (median $1.5 \mu\text{g/L}$ and 82mg/L) and low during clinical events for which there was no evidence of bacterial or fungal infections (median $0.4 \mu\text{g/L}$ and 55mg/L). The area under the receiver operator characteristic (ROC) curve was 0.70 for mPCT, 0.76 for mCRP, 0.76 for ΔPCT and 0.83 for ΔCRP . Cut-off concentrations for optimum prediction of bacterial or fungal infection were: mPCT $> 1 \mu\text{g/L}$, mCRP $> 100 \text{mg/L}$, $\Delta\text{PCT} > 1 \mu\text{g/L}$ and $\Delta\text{CRP} > 50 \text{mg/L}$. An increase of PCT during a bacterial or fungal infection was usually detected 1 day after the onset of fever, while the rise of CRP occurred 1 day before. mPCT was strongly correlated with the severity of systemic reaction during infection (sepsis vs severe sepsis/septic shock: $p=0.0002$).

Interpretation and Conclusions. The diagnostic value of PCT was not superior to that of CRP in the detection of bacterial or fungal infections after allogeneic SCT. However, PCT assays may be useful in studies which compare the severity of infectious complications.

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Key words: procalcitonin, C-reactive protein, sepsis, stem cell transplantation.

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Infectious complications remain a major cause of morbidity and mortality after allogeneic stem cell transplantation (SCT). The identification of these complications is still based on clinical criteria, mainly the occurrence of fever. Diagnosis and outcome might be improved by using early, sensitive and specific laboratory parameters for bacterial or fungal infections. C-reactive protein (CRP) is a commonly used and well-documented sensitive marker, however it lacks specificity and is increased in various non-infectious complications following allogeneic SCT.¹⁻³ Procalcitonin (PCT), the 116 amino acid precursor molecule of calcitonin,⁴ has been described as a promising marker to distinguish bacterial and fungal infections from viral infections and non-infectious complications with high specificity.⁵⁻⁹ Clinical studies have revealed an early increase of PCT levels during systemic infections in neutropenic patients^{8,9} and a correlation of PCT levels with the severity of the systemic inflammatory response.^{5,7,10} It is currently unknown whether these characteristics of PCT are influenced by severe immunosuppression and aplasia in patients undergoing allogeneic SCT. The present study compares the diagnostic value of PCT with that of CRP in detecting infectious and other treatment-related complications following allogeneic SCT in a large number of patients.

Design and Methods

A total of 61 patients consecutively transplanted from allogeneic donors between December 1997 and July 1999 in the bone marrow transplant unit of the Hannover Medical School were analyzed. There were 37 male and 24 female patients with a median age of 33 years (range 4 - 59). Underlying diseases were chronic myeloid leukemia (CML, first or second chronic phase:

n=11, accelerated phase: n=1), acute myeloid leukemia (AML, first or second remission: n=10, first or second relapse: n=8), acute lymphoblastic leukemia (ALL, first or second complete remission: n=4, partial remission, first or second relapse: n=8), myelodysplastic syndrome (n=3), severe aplastic anemia (n=6), lymphoma (n=5), multiple myeloma (n=1), thalassemia major (n=1), paroxysmal nocturnal hemoglobinuria (n=1) and solid tumors (n=2). Six patients received a second transplantation because of primary or secondary graft failure.

The conditioning regimens included total body irradiation (12 Gy) in 22 cases. Busulfan-based myeloablative regimens were used in 28 transplants. Dose-reduced regimens were used in 7 patients and consisted of fludarabine 100 mg/m² and melphalan 180 mg/m². In 4 cases only cyclophosphamide was used for conditioning. Regimens for second transplant after graft failure were fludarabine 100 mg/m² + melphalan 140 mg/m² (n=2) and fludarabine 100 mg/m² + total nodal irradiation (7.5 Gy) (n=4). Bone marrow (n=22) and peripheral blood stem cells (collected by leukapheresis after stimulation with granulocyte colony-stimulating factor, n=45) were derived from HLA-compatible siblings (n=46), from HLA-mismatched family donors (n=6) or matched unrelated donors (n=15). Prophylaxis of graft-versus-host disease (GvHD) consisted of T-cell depletion of the allografts in 32 cases, which was combined with cyclosporine monotherapy in 10 cases. Other GvHD prevention strategies consisted of cyclosporine with short course methotrexate (n=16) or with prednisolone (n=5). Cyclosporine monotherapy was administered in 8 cases. Anti-lymphocyte antibodies were administered during conditioning (ATG-Fresenius, n=37, ALG-Merieux, n=14) and as therapy for severe GvHD (ATG-Fresenius, n=1, ALG-Merieux, n=1). All patients received standard supportive care including isolation in HEPA filtered or laminar flow rooms, empirical broad-spectrum antibiotic therapy in case of fever, low dose heparin for prevention of veno-occlusive disease (VOD) and immunoglobulins for cytomegalovirus (CMV) prophylaxis, if the donor or recipient was seropositive.

Clinical events

Fever was defined as a body temperature of >38°C measured on two occasions at least 4 h apart or one measurement of $\geq 38.5^\circ\text{C}$. Clinical events were defined as follows: bacteremia and fungemia were defined by at least one positive blood culture except for coagulase negative staphylococci which required at least two positive blood cultures. Pneu-

monia was diagnosed by a new onset of pulmonary infiltrates on chest X-ray which could not be explained by cardiac failure or generalized fluid retention. Local infection was defined as localized inflammation, which was not pneumonia. Acute GvHD was diagnosed and staged according to the Glucksberg score¹¹ and oral mucositis according to the WHO toxicity score.¹² VOD was diagnosed according to the Seattle criteria.¹³ Graft rejection was defined as a persistent decrease of leukocytes to lower than $0.5 \times 10^9/\text{L}$ after engraftment. CMV viremia was diagnosed by measurement of CMV pp65 antigen in peripheral blood mononuclear cells. Non-infectious events were termed as *others* if they were recorded ≤ 3 times.

Bacterial and fungal infections were categorized into microbiologically defined infection (MDI, i.e. proven microbial pathogen with or without microbiologically defined site of infection) and clinically defined infection (CDI, i.e. diagnosed site of infection without proven microbiologic pathogenesis).¹⁴ Acute GVHD grade I-IV, VOD, oral mucositis, graft-rejection, CMV-viremias and others were considered as clinical events without evidence of bacterial or fungal infection. Fever could be associated with all clinical events defined above with or without evidence of bacterial or fungal infections. Fever of unknown origin (FUO) was defined as the onset of fever without evidence of one of these clinical events.

To correlate the severity of septic episodes with PCT and CRP, systemic reactions in adults were categorized into sepsis, severe sepsis and septic shock according to the criteria of the *American College of Chest Physicians / Society of Critical Care Medicine (ACCP/SCCM)* consensus conference.¹⁵ Sepsis was defined as clinically or microbiologically defined infection with fever together with tachycardia (>90 beats per minute) or tachypnea (respiratory rate >20 breaths per minute). Severe sepsis was defined as sepsis associated with hypotensive systolic blood pressure of <90 mmHg or a reduction by >40 mmHg from baseline in the absence of other causes of hypotension or hypoperfusion (e.g. lactic acidosis, oliguria, or an acute alteration in mental status). Septic shock was defined as sepsis associated with hypotension, despite adequate fluid resuscitation and hypoperfusion.

The analysis of the patients' records included the time from the first day of conditioning to the day of discharge or death, which was a median of 36 days (range 11-106 days). Measurement of PCT and CRP was continued even when a transfer to the intensive care unit was necessary. A total of 260

clinical events occurring during the hospital stay were identified. Increases of PCT or CRP levels were only analyzed if they could be assigned to not more than one clinical event. This reduced the number of analyzed events to 214 with a median of 3 clinical events per patient (range 0 to 14). During a clinical event we analyzed the maximum level (i.e. mPCT and mCRP) and increase (i.e. Δ PCT and Δ CRP) of PCT and CRP. The increase of PCT and CRP was measured as the difference between the corresponding maximum level and the last minimum value. In cases when the onset of the clinical event occurred concurrently with decreasing marker values, Δ PCT or Δ CRP was denoted as zero. There were 14 cases involving only an increase in PCT and 13 cases involving only an increase in CRP which could not be attributed to a clinical event. PCT- or CRP-increases which could not be assigned to a clinical event were included in the analysis of sensitivities, specificities, positive (PPV) and negative (NPV) predictive values. The day of the first signs or symptoms of a clinical event was used for analysis of the course of the parameters during the clinical event.

PCT and CRP measurements

Serum levels of PCT and CRP were prospectively measured daily in the morning from the day of admission to the day of discharge or death in the same samples. PCT was measured by PCT immunoluminometric assay (LUMItest; B.R.A.H.M.S Diagnostica, Berlin, Germany) and CRP by turbidimetry (N-Latex-CRP; Behringwerke AG, Marburg, Germany). Normal values were $<0.5 \mu\text{g/L}$ for PCT and $<5 \text{ mg/L}$ for CRP.

Statistical analysis

At the beginning of the analysis, frequencies of variables were calculated for descriptive purposes. The variables showed approximately normal distribution after logarithmic transformation. Differences between two groups were assessed by Mann-Whitney U-test and between multiple groups by analysis of variance (ANOVA) with subsequent correction for multiple comparisons according to Tukey-HSD. Dependent variables were analyzed by Wilcoxon's test. p values < 0.05 were considered statistically significant.

The diagnostic relevance was estimated as sensitivity (true positives: = patients with infection and marker $>$ cut-off level), as specificity (true negatives: = patients without infection and marker \leq cut-off level), as positive (true positives / all patients with marker $>$ cut-off level) and negative predictive value (true negatives / all patients with marker \leq cut-off level). Levels of sensitivity were

plotted against the levels of one-specificity at each cut-off point on a receiver-operator characteristic (ROC) curve. The area under the ROC curve, calculated by trapezoid integration, is a measure of the discrimination attained with the test between subjects with and without the disease. An area of 0.5 denotes no discrimination, whereas an area of one denotes full discrimination. The best cut-off value was chosen as the value which optimized sensitivity and specificity. Statistical calculations were performed using the Statistical Program for Social Science (SPSS).

Results

Analysis of PCT and CRP levels according to clinical events

PCT: Highest mPCT values were detected during infusion of anti-lymphocyte antibodies (Table 1) without significant difference between ATG-Fresenius and ALG-Merieux ($p=0.2598$, Mann-Whitney U-test). MDI and CDI were mostly associated with a high increase of PCT concentrations ($p=0.0001$, Wilcoxon's test). The exceptions were 6 cases of Gram-positive bacteremia with sepsis as a systemic reaction in which Δ PCT was 0. In the 3 cases of Gram-negative bacteremia Δ PCT was very low (median $0.2 \mu\text{g/L}$). FUO was associated with moderately increased PCT concentrations ($p=0.0001$, Wilcoxon's test). The increase of PCT levels was low during clinical events without evidence of bacterial or fungal infections ($p=0.001$, Wilcoxon's test). ANOVA showed significant differences between the categories no infection, FUO, CDI and MDI. Subsequent multiple testing showed no significant difference in mPCT levels between MDI and CDI ($p=0.7684$, Tukey-HSD). Therefore, CDI and MDI were summarized as *bacterial or fungal infections* for further analysis. mPCT levels differed significantly (multiple testing) between the categories no (bacterial or fungal) infection and infection as well as no infection and FUO, but not between FUO and infection (Figure 1a). The difference of mPCT levels during bacterial or fungal infections in aplasia ($\text{WBC} < 1.0 \times 10^9/\text{L}$, 40 events) and non-aplasia (14 events) was not significant ($p=0.6863$, Mann-Whitney U-test). The median Δ PCT was low in the 14 cases with PCT increases which could not be attributed to a clinical event (median mPCT $0.7 \mu\text{g/L}$ (range 0.5 - $5.8 \mu\text{g/L}$); median Δ PCT $0.3 \mu\text{g/L}$, (range 0.1 - $2.9 \mu\text{g/L}$).

CRP: The correlation of CRP levels with bacterial or fungal infections (in 2 cases Δ CRP was 0), FUO and clinical events without evidence of bacterial or fungal infection was similar to that of PCT

Table 1. Median maximum values and median increase of PCT and CRP levels according to clinical events. Wilcoxon's test was performed for groups with more than 6 cases to compare the marker at the maximum level with the last minimum level.

	Total	median mPCT (range) in µg/L	median mCRP (range) in mg/L	median ΔPCT (range) in µg/L	median ΔCRP (range) in mg/L
Events with evidence of bacterial or fungal infection	54	2.3 (0.2-172.5)	188 (8-432)	1.7 * (0-172.0)	129 * (0-419)
MDI	41	2.1 (0.2-172.5)	195 (8-432)	1.7 * (0-172.0)	158 * (0-419)
fungemia (<i>Candida</i>)	4	3.6 (3.1-9.1)	251 (195-293)	2.9 (2.3-5.0)	188 (132-277)
bacteremia	37	1.6 (0.2-172.5)	191 (8-432)	1.3 * (0-172.0)	138 * (0-419)
Gram-positive	34	1.7 (0.2-172.5)	191 (8-432)	1.4 * (0-172)	138 * (0-419)
Gram-negative	3	0.6 (0.4-0.7)	193 (103-282)	0.2 (0-0.3)	161 (98-223)
CDI	13	2.8 (0.2-18.0)	170 (61-314)	1.7 * (0-17.7)	93 * (0-272)
pneumonia	9	3.5 (0.9-18.0)	173 (61-314)	3.0 * (0.4-17.7)	103 * (0-272)
local infection [†]	4	0.3 (0.2-1.2)	119 (87-290)	0 (0-0.8)	77 (35-135)
FUO	50	1.5 (0.2-32.6)	82 (5-470)	0.7 * (0-31.4)	40 * (0-431)
Events without evidence of bacterial or fungal infection	60	0.4 (0.1-24.4)	55 (5-429)	0 * (0-4.0)	7 * (0-282)
acute GvHD grade >I	6	2.5 (1.0-4.4)	169 (81-293)	0.4 (0-4.0)	0 (0-76)
acute GvHD grade I	11	0.5 (0.2-24.4)	29 (5-226)	0 (0-0.3)	0 (0-19)
VOD	4	1.6 (0.2-5.2)	142 (128-429)	0 (0-0.7)	0 (0-51)
oral mucositis grade >I	24	0.3 (0.1-11.7)	50 (16-328)	0 (0-1.1)	20 * (0-282)
graft rejection	4	0.4 (0.2-0.7)	65 (13-91)	0 no range	0 no range
CMV viremia	4	0.25 (0.1-0.8)	14 (5-57)	0 (0-0.2)	0 (0-19)
others [§]	7	0.7 (0.1-2.4)	37 (5-93)	0.2 (0-2.2)	6 (0-20)
Anti-lymphocyte antibody infusion	50	5.7 (0.2-351.0)	94 (8-392)	5.5 * (0-350.8)	82 * (3-383)
ATG-Fresenius	37	4.4 (0.2-61.2)	86 (19-244)	4.1 * (0-61.1)	76 * (8-232)
ALG-Merieux	13	10.1 (0.4-351.0)	186 (8-392)	9.9 * (0-350.8)	85 * (3-383)

[†]local infections were single inflammatory skin induration (n=2), bacterial laryngitis (n=1), sinusitis (n=1) [§]others were transplantation (n=2), oral herpes virus mucositis (n=2), rotavirus enteritis (n=2), toxic epidermolysis (n=1) * p<0.05, Wilcoxon's test.

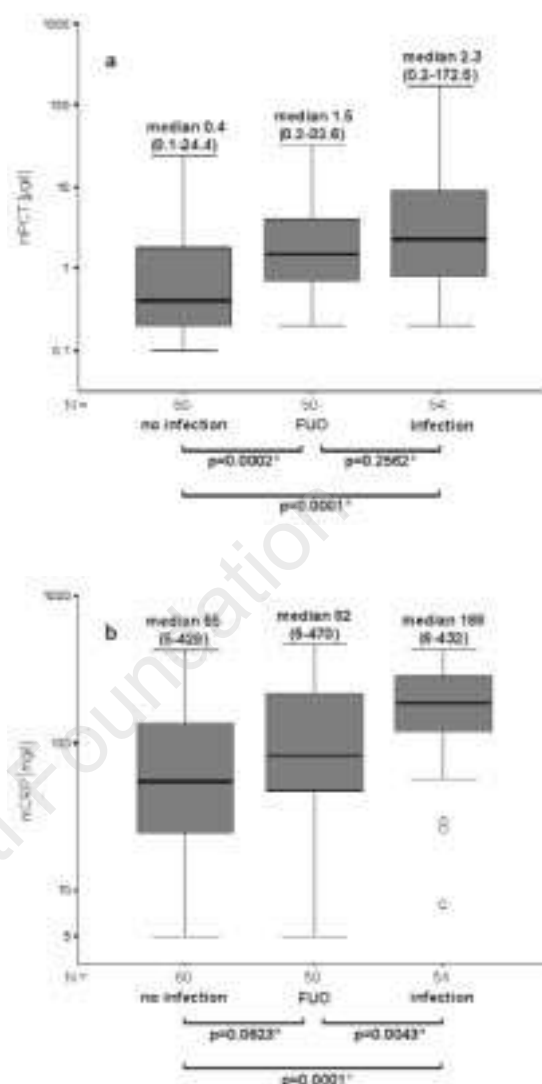


Figure 1. mPCT (a) and mCRP (b) levels (depicted as box-plots) during clinical events without evidence of bacterial or fungal infection, FUO and bacterial or fungal infections. Statistical significance between the groups was calculated with ANOVA analysis after logarithmic transformation of the parameters. *Tukey-HSD. Each box-plot depicts the median (middle line), the values from the upper to lower quartiles (central box) and the upper/lower quartile $\pm 1.5 \times$ interquartile range (horizontal lines) of one category. Outliers (i.e. values outside these borders) are depicted as circles.

(Table 1). In contrast to PCT, a moderate increase of CRP was found during oral mucositis ($p=0.0001$, Wilcoxon's test) and local infections. Only moderately elevated CRP levels were observed during infusions of anti-lymphocyte antibodies, again

with no significant difference between ATG-Fresenius and ALG-Merieux ($p=0.0665$, Mann-Whitney U-test). Again, ANOVA showed significant differences between the categories no infection, FUO, CDI and MDI. Multiple testing demonstrated that the difference of mCRP levels between CDI and MDI was not significant ($p=0.8654$, Tukey-HSD). mCRP levels differed significantly (multiple testing) between the categories designed as no (bacterial or fungal) infection and infection as well as FUO and infection, but not between the categories no infection and FUO (Figure 1b). The mCRP levels during bacterial or fungal infections were significantly higher during aplasia than during non-aplasia (median 227 mg/L vs 145 mg/L, $p=0.0032$, Mann-Whitney U-test). Moderate increases in CRP levels were observed in the 13 cases with CRP increases which could not be attributed to a clinical event (median mCRP 92 mg/L (range 11-252 mg/L); median Δ CRP 49 mg/L (range 6-168 mg/L).

ROC curves

Figure 2 depicts ROC curves illustrating the sensitivities and specificities of mPCT and mCRP (Figure 2a) as well as Δ PCT and Δ CRP (Figure 2b) for the detection of bacterial or fungal infections. The area under the ROC curve (AUC) was 0.70 for mPCT (95% confidence interval (CI), 0.61 to 0.78), 0.76 for mCRP (95% CI, 0.69 to 0.83), 0.76 for Δ PCT (95% CI, 0.67 to 0.84) and 0.83 for Δ CRP (95% CI, 0.77 to 0.89). Infusions of anti-lymphocyte antibodies were excluded from the analysis.

Predictive values

Table 2 shows the sensitivities, specificities and positive (PPV) and negative predictive values (NPV) of mPCT, mCRP, Δ PCT and Δ CRP for the detection of bacterial or fungal infections. A concentration of mPCT $> 0.5 \mu\text{g/L}$ had an 83% sensitivity and a 78% NPV, but a specificity and PPV of only 40% and 47%, respectively. The range of sensitivities, specificities, PPV and NPV using mCRP was similar to those using mPCT depending on the chosen cut-off level. Specificity and PPV were improved by using the increase of the parameters (Δ PCT and Δ CRP) instead of maximum levels (mPCT and mCRP), while sensitivity and NPV decreased. Diagnostic cut-off levels with the optimum sensitivity and specificity derived from the ROC curve were found to be mPCT $> 1 \mu\text{g/L}$, mCRP $> 100 \text{ mg/L}$, Δ PCT $> 1 \mu\text{g/L}$ and Δ CRP $> 50 \text{ mg/L}$. Specificity and PPV could be further improved by combining PCT and CRP. The best results were found for the combination of the optimum cut-off values for mPCT and mCRP as well as Δ PCT and Δ CRP leading to speci-

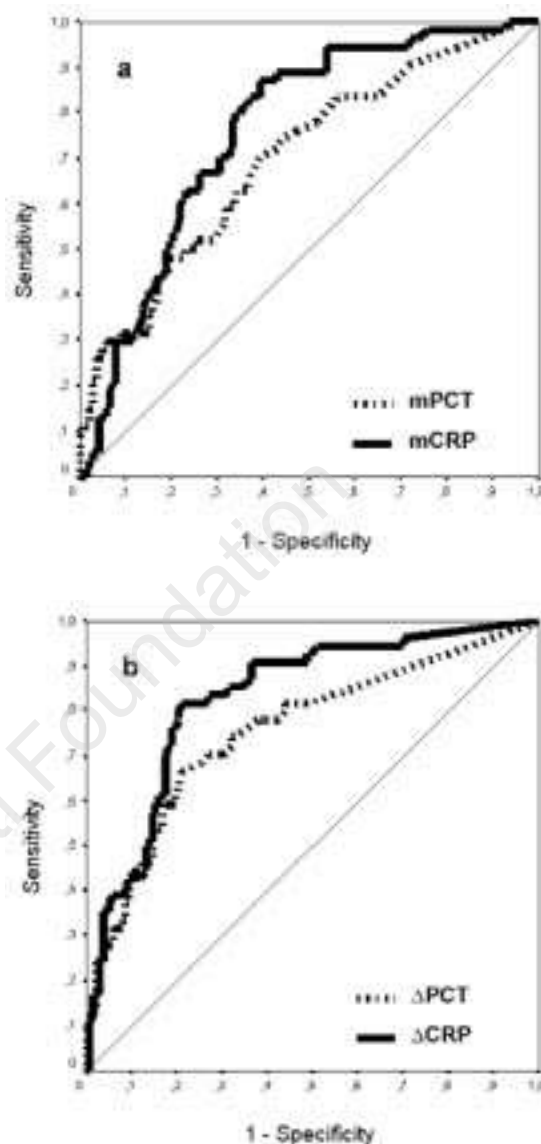


Figure 2. Receiver operating characteristic (ROC) curves comparing (a) mPCT and mCRP levels as well as (b) Δ PCT and Δ CRP levels for prediction of bacterial or fungal infection. The area under the curve (AUC) was 0.70 for mPCT, 0.76 for mCRP, 0.76 for Δ PCT and 0.83 for Δ CRP. Infusions of anti-lymphocyte antibodies were excluded from the analysis.

ficities of 77% and 88% and PPVs of 64% and 75%, respectively.

Course of PCT and CRP during bacterial or fungal infections

During bacterial or fungal infections PCT levels increased one day (median) after the onset of fever (range -4 to 3 days), reached a peak after one day (range 0 to 16 days) and declined to their next min-

Table 2. Comparison of the diagnostic values of maximum values as well as increases of PCT and CRP levels for the detection of bacterial and fungal infections at different cut-off levels. Diagnostic value was determined using sensitivity, specificity, positive and negative predictive values (PPV and NPV). Infusions of anti-lymphocyte antibodies were excluded from the analysis.

Screening value	Sensitivity %	Specificity %	PPV %	NPV %
mPCT > 0.5 µg/L	83	40	47	78
mPCT > 1 µg/L	70	61	54	76
mPCT > 2 µg/L	52	74	57	70
mPCT > 3 µg/L	44	82	61	69
mCRP > 5 mg/L	100	4	40	100
mCRP > 50 mg/L	94	41	51	91
mCRP > 100 mg/L	83	61	58	85
mCRP > 150 mg/L	68	74	63	78
mPCT > 0.5 µg/L and mCRP > 5 mg/L	83	44	49	80
mPCT > 1 µg/L and mCRP > 100 mg/L	63	77	64	76
ΔPCT > 0 µg/L	82	56	55	83
ΔPCT > 1 µg/L	59	81	67	75
ΔPCT > 2 µg/L	45	89	73	71
ΔPCT > 3 µg/L	36	91	73	69
ΔCRP > 0 mg/L	96	29	47	92
ΔCRP > 50 mg/L	83	71	65	87
ΔCRP > 100 mg/L	65	82	70	78
ΔCRP > 150 mg/L	43	89	72	71
ΔPCT > 0 µg/L and ΔCRP > 0 mg/L	80	59	56	81
ΔPCT > 1 µg/L and ΔCRP > 50 mg/L	56	88	75	75

Optimum diagnostic cut-off levels derived from the ROC curves are shown in bold.

imum levels 4 days after the PCT increase (range 1 to 10 days). In contrast, rising CRP levels were detected already one day (median) before the onset of fever (range -4 to 4 days). The peak levels were reached after a median of three days (range 0 to 10 days) and the next minimum levels six days after the increase of CRP levels (range 1-19 days).

Marker of severity of the systemic reaction

For adults, severity of systemic reactions during bacterial or fungal infections was classified according to the ACCP/SCCM criteria. The median mPCT and mCRP values gradually rose with increasing severity of the systemic reaction (Figures 3a and b). ANOVA analysis showed significant differences for mPCT and mCRP between the categories no sep-

sis, sepsis and severe sepsis/septic shock. Multiple testing demonstrated that the differences between all categories was significant except between no sepsis and sepsis for mPCT ($p=0.2694$, Tukey-HSD) and between sepsis and severe sepsis/septic shock for mCRP ($p=0.3901$, Tukey-HSD).

Discussion

In general, our data showed a good correlation between high PCT levels and the onset of bacterial or fungal infections in allogeneic SCT recipients. This confirms the findings of previous studies mainly in non-transplanted patients.⁵⁻⁹ In contrast to previous case reports^{16,17} we found high PCT levels in the four cases of severe fungal infections in our study. Six of 34 cases of Gram-positive and three of three Gram-negative bacteremias during aplasia with sepsis as systemic response were associated with no or almost no increase of PCT levels. This observation is difficult to explain. Although peripheral blood mononuclear cells have been described as a major source for PCT release in sepsis,¹⁸ it is unlikely that aplasia was the underlying reason for the failure to detect an increased PCT. As in a previous study with neutropenic patients after conventional chemotherapy,⁹ PCT levels seemed to be independent of the leukocyte counts. This is in agreement with a recent animal study which showed that PCT can be released from many tissues throughout the body in response to sepsis.¹⁹

Complications without evidence of bacterial or fungal infections were mostly not associated with a significant increase of PCT. Analogous to reports in solid organ transplants, PCT remained in the normal range during graft rejection.²⁰ In accordance with previous studies, PCT was not affected by the onset of local infections or oral mucositis.⁵ CMV viremia had no impact on the PCT levels in the four cases of evaluable CMV viremia. However, differences between CMV-disease or viremias of other origin cannot be excluded. In the four cases of evaluable VOD, PCT levels were already moderately elevated at the beginning of this complication, and exhibited no further increase. This indicates the importance not only of considering the absolute value but also the change in levels of the diagnostic marker. During acute GvHD, only higher grades (II-IV) of the disease were associated with moderate increases of PCT levels.

As in previous reports of patients undergoing allogeneic SCT, CRP was a reliable marker of bacterial and fungal infections.¹⁻³ Almost no increase of CRP levels was observed during events without evidence of bacterial or fungal infections. In con-

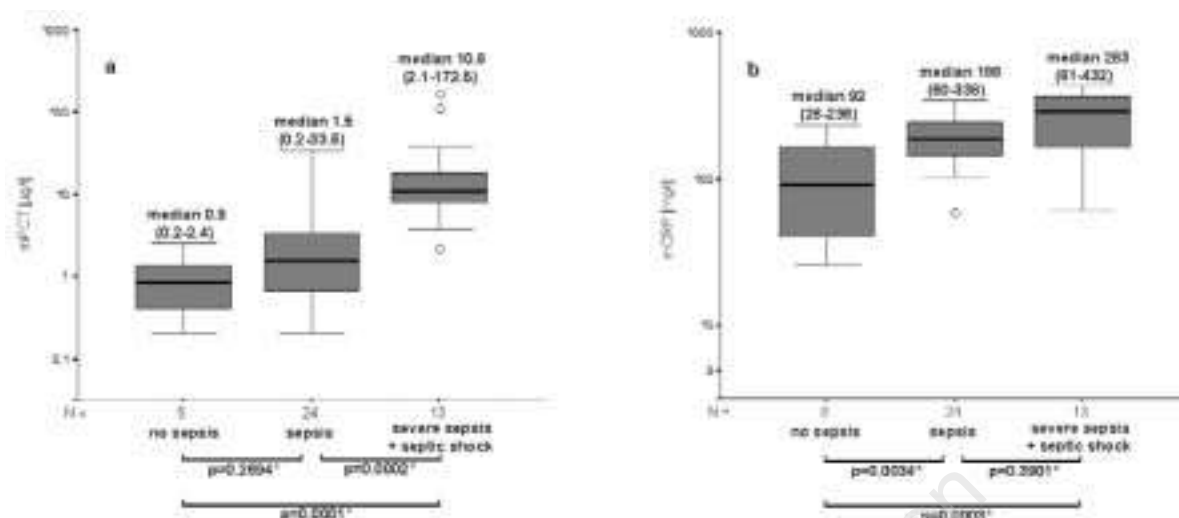


Figure 3. (a) mPCT and (b) mCRP levels (depicted as box-plots) in various grades of severity of the systemic reaction during bacterial or fungal infections according to the ACCP/SCCM criteria for adult patients. Statistical significance between the groups was calculated with ANOVA analysis after logarithmic transformation of the parameters. *Tukey-HSD. Each box-plot depicts the median (middle line), the values from the upper to lower quartiles (central box) and the upper/lower quartile $\pm 1.5 \times$ interquartile range (horizontal lines) of one category. Outliers (i.e. values outside these borders) are depicted as circles.

trast to PCT, but in accordance with previous studies, there was a moderate increase of CRP during local infections and oral mucositis.^{2,3} Previous data concerning CRP levels in acute GvHD are contradictory.¹⁻³ It is important to note that these previous studies only analyzed absolute values. In our study CRP values were already high at the beginning of acute GvHD (with high median absolute values), whereas the increase of CRP even during development of severe acute GvHD was low. Similar observations were made in VOD.

Very high PCT and CRP values were found during administration of anti-lymphocyte antibodies, indicating that PCT release is not only induced by infectious agents. Administration of anti-lymphocyte antibodies was mostly associated with a severe systemic response, including fever and hypotension comparable to sepsis and severe sepsis. PCT levels correlated with the severity of the systemic response (*data not shown*). One explanation for this observation might be a release of similar mediators during both bacterial sepsis and administration of anti-lymphocyte antibodies. A previous study on cytokine release during administration of anti-T cell antibodies revealed high levels of the inflammatory cytokine, interleukin (IL)-

6.²¹ IL-6, in turn, has been reported as a strong mediator of PCT synthesis in peripheral blood mononuclear cells¹⁸ and of CRP synthesis in the liver.²

PCT and CRP could not be used to discriminate between MDI and CDI, which might be explained by the fact that in the cases of only clinically defined infection the microbial detection was either not successful or just not performed. The diagnostic efficiency of PCT and CRP was decreased by the occurrence of high levels of both parameters in some cases of FUO. As these high levels might have been based on the lack of detection of an actual infectious agent, not much can be said about the true value of both markers in detecting all bacterial or fungal infections. However, by considering only the microbiologically and clinically defined infections in the analysis, the diagnostic value of both markers can be estimated and compared, although the specificity and PPV of both markers are, thereby, reduced. The optimum cut-off level for PCT and CRP was chosen as the value with the best sensitivity and specificity for bacterial or fungal infections. The AUCs in the ROC curves of PCT and Δ PCT were comparable with those of CRP and Δ CRP, respectively. The expected greater speci-

ficity of PCT could not be confirmed in the allogeneic transplant setting. The specificity and PPV of PCT levels were improved by using the increase rather than absolute values, although some sensitivity was lost. However, specificity and PPV clearly improved by using CRP and PCT in combination. This indicates that PCT might be helpful in detecting infectious complications when a large increase of CRP is observed.

In our study, the PCT levels during bacterial or fungal infections reached maximum levels and subsequent minimum levels more quickly than CRP levels, which is in agreement with the data in iatrogenic sepsis.²² In previous studies of neutropenic adults, which postulated PCT as an early marker of infection, PCT was only measured at a baseline and shortly after the onset of fever.^{8,9} Currently, there are few data available about the behavior of PCT before the diagnosis of a bacterial or fungal infection. In our analysis, PCT levels increased at a median of one day after the onset of fever, whereas CRP levels increased with the onset of fever or even before. If PCT is only measured once in the morning, it might be impossible to detect bacterial or fungal infections early enough to make a therapeutic decision. Our results therefore suggest that PCT is not an early marker of bacterial or fungal infection in patients undergoing bone marrow transplantation. A previous kinetic analysis of CRP showed increasing levels two days before manifestation of bacterial infection¹ or even earlier,² which confirms our finding that CRP is an early indicator suggesting clinical intervention.

Preliminary results of other studies suggest that increased PCT levels may reflect the severity of the systemic inflammatory response.^{5,7,10} We found a close relationship between high PCT levels and different grades of sepsis, when classifying these latter according to the ACCP/SCCM criteria.¹⁵ For instance, PCT was better than CRP at differentiating between life-threatening (severe sepsis and septic shock) and less severe septic conditions. In this regard PCT could be useful in studies comparing the severity of infectious complications.

In conclusion, PCT was found to be a specific marker for the detection of bacterial or fungal infections when appropriate cut-off levels were chosen. Our data using CRP as an internal control confirm the results of previous studies. The sensitivity and specificity of PCT for detection of bacterial or fungal infections were not superior to those of CRP. In particular, assaying PCT was not helpful in early detection of infectious complications. However, the combination of CRP with PCT was a

specific method for the detection of bacterial or fungal infections. PCT was useful in discriminating different grades of sepsis. PCT was better at reflecting the extent of the systemic reaction than the type of its underlying cause.

Contributions and Acknowledgments

LH: analysis of the data and writing the paper. ME, AS, KWS, JN: clinical management of the patients and collaboration in writing the paper. ED: documentation and collaboration in analysis of the data. CD: measurement of the parameters. CD, PK, AG: revising the article critically for important intellectual content and final approval of the version to be submitted. BH: clinical management of the patients, conception and design of the study and collaboration in analysis of the data and writing the paper. The order of authorship is a joint decision of the co-authors. The study was performed under the guidance of LH and BH. The other co-authors contributed equally to the work.

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Disclosures

Conflict of interests: none.

Redundant publication: no substantial overlapping with previous papers.

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PEER REVIEW OUTCOMES

Manuscript processing

This manuscript was peer-reviewed by two external referees and by Dr. Jordi Sierra, Deputy Editor. The final decision to accept this paper for publication was taken jointly by Dr. Sierra and the Editors. Manuscript received October 1, 2001; accepted April 10, 2002.

What is already known on this topic

C-reactive protein (CRP) and procalcitonin (PCT) serum levels are early indicators of bacterial and fungal infection in hematologic patients with fever.

What this study adds

This report compares CRP and PCT in a prospective series of allogeneic stem cell transplantation (SCT) recipients. Although the increase in PCT levels occurs later than the rise in CRP, the former indicator correlates better with the severity of bacterial or fungal infection.

Potential implications for clinical practice

The combination of PCT and CRP serum levels may be useful to raise the suspicion of bacterial or fungal origin of fever after SCT, with the former of the two parameters correlating with the severity of this type of complication.

Jordi Sierra, Deputy Editor