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ORIGINAL ARTICLE – CLINICAL ONCOLOGY

Comparison of procalcitonin and C-reactive protein as early diagnostic marker for the identification of transplant-related adverse events after allogeneic hematopoietic stem cell transplantation in pediatric patients

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Abstract

Purpose To evaluate serum procalcitonin (PCT) and C-reactive protein (CRP) as diagnostic biomarkers of transplant-related adverse events (TRAE) in pediatric patients undergoing hematopoietic stem cell transplantation (HSCT).

Methods This study analyzed PCT and CRP levels of 214 pediatric patients with a median age of 8.5 years (0.4–17.8 years) undergoing allogeneic HSCT with respect to major TRAE.

Results 26 patients (12.1%) did not experience TRAE (control group), and 188 (87.9%) experienced median 2 (range 1–4) TRAE. Median CRP and PCT were highly and significantly increased during sepsis/SIRS and bacteremia (17.24 mg/dl | 6.30 ng/ml; $p < 0.0001$ vs. prior values), graft rejection (14.73 mg/dl | 3.20 ng/ml; $p < 0.0001$), and liver GvHD (6.88 mg/dl | 2.29 ng/ml; $p < 0.01$). Strong CRP increases and slight/minimal/no PCT increases occurred during fungemia (8.85 mg/dl | 0.72 ng/ml; $p < 0.001$), intestinal GvHD (8.73 mg/dl | 1.06 ng/ml; $p < 0.0001$), VOD (10.84 mg/dl | 0.59 ng/ml; $p < 0.01$), mucositis (8.84 mg/dl | 0.81 ng/ml; $p < 0.0001$), and viremia (3.62 mg/dl; $p < 0.0001$ | 0.43 ng/ml; below normal limit). During skin GvHD, CRP and PCT were slightly increased (2.03 mg/dl | 0.93 ng/ml; $p < 0.0001$).

Conclusions CRP and PCT did not show congruent changes during TRAE. PCT was a clinically relevant marker for the early detection and differentiation of severe mucositis and sepsis/SIRS and bacteremia during the critical neutropenic period after HSCT. PCT helped to discriminate acute intestinal GvHD from adenovirus viremia and liver GvHD from hepatic VOD. Thus, PCT may be a valuable parameter to enable a prompt and appropriate treatment during these complications, improving patient outcomes.

Keywords Procalcitonin · PCT · C-reactive protein · CRP · Transplant-related adverse events · Pediatric patients · Hematopoietic stem cell transplantation · GvHD · VOD · Sepsis · SIRS · Viremia · Fungemia · Bacteremia

Abbreviations

ADV	Adenovirus
ALL	Acute lymphoblastic leukemia
AML	Acute myeloid leukemia
ATG	Anti-thymocyte globulin
BSA	Body surface area
CML	Chronic myeloid leukemia
CMV	Cytomegalovirus
CRP	C-reactive protein
EBV	Epstein-Barr virus
GvHD	Graft-versus-host disease
HHV-6	Human herpes virus 6
HSCT	Hematopoietic stem cell transplantation
HSV	Human herpes simplex virus
JMML	Juvenile myelomonocytic leukemia
kg	Kilogram
kg BW	Kilogram bodyweight
MDS	Myelodysplastic syndromes
MFD	Matched family donor
µg	Microgram

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µg kg^{-1} BW^{-1} d^{-1}	µg per kg body weight and day
µl	Microliter
MMFD	Mismatched family donor
MUD	Matched unrelated donor
n	Sample size
p	Probability value
PCT	Procalcitonin
SD	Standard deviation
VZV	Varicella zoster virus

Introduction

Major developments in transplantation and supportive care management have led to a significant reduction of transplant-related mortality of allogeneic hematopoietic stem cell transplantation (HSCT) in the recent years. In pediatric patients with acute lymphoblastic leukemia (ALL), transplant-related mortality dropped from over 30% (1984–1992) to approximately 5% with a significantly improved event-free survival (30–60%) (Mateos et al. 2013). Nevertheless, transplant-related adverse events such as sepsis/systemic inflammatory response syndrome (SIRS), fungal, bacterial, and viral infection, graft-versus-host disease (GvHD), veno-occlusive disease (VOD), mucositis, graft rejection, and engraftment failure not only represent a substantial burden for pediatric patients; they also pose a major challenge to treating physicians. Clinical symptoms of infectious complications are often difficult to distinguish from non-infectious ones such as GvHD. While higher immunosuppressive doses are a first-line therapy for GvHD, they can critically exacerbate infection. Therefore, early diagnosis and treatment are decisive for patient outcomes. The predictive value of a multitude of serum biomarkers including cytokines and different acute-phase proteins and their specific patterns in adverse events have been investigated (Baker et al. 1995; Fujita et al. 2008; Schots et al. 2003; Armand et al. 2007; Grossekathöfer et al. 2013; McDonald et al. 1984; Budde et al. 2017; Presland 2016; Tvedt et al. 2016; Sauer et al. 2003).

Procalcitonin (PCT) is a precursor molecule of the hormone calcitonin, which regulates calcium homeostasis. PCT transcription takes place in different organ tissues at variable quantities, but it is generally very weak in the absence of systemic and/or bacterial infection. It is hypothesized that during bacterial infection, the PCT transcription activity is enhanced either by a specific bacterial transcription factor that also enhances PCT transcription, or by displacing a constitutive negative enhancer of the PCT expression. Elevated PCT levels could be detected in the lymphocytes, monocytes, and neutrophils of severely infected patients. There is further evidence that cytokines secreted during bacterial infection trigger PCT release (Matwiyoff et al. 2012). C-reactive protein (CRP) is an acute-phase protein that is produced by hepatocytes during different infectious and non-infectious processes, and it is the most commonly used and recommended biomarker in hemato-oncological patients (Klastersky et al. 2016).

Several studies have been conducted that analyze the potential role of serum PCT and CRP as predictive and diagnostic biomarkers for transplant-related mortality and different transplant-related adverse events (mainly infectious complications) in adult and pediatric HSCT recipients, with somewhat contradictory conclusions. Nevertheless, there is evidence that serum PCT might be superior compared to CRP in identifying and discriminating transplant-related adverse events in pediatric patients (Lyu et al. 2013; Koya et al. 2012; Sato et al. 2014; Massaro et al. 2014; Shah et al. 2017; Miedema et al. 2011; Fleischhack et al. 2000; Hambach et al. 2002).

In this study, serum PCT and CRP levels of a total of 214 pediatric patients undergoing allogeneic HSCT for the treatment of hemato-oncological malignancies and non-malignancies were analyzed and correlated to post-transplant adverse events (graft rejection, mucositis, VOD, GvHD, sepsis/SIRS, and bacterial, viral, and fungal infection). The primary objective of this work was to assess the diagnostic and discriminative value of serum PCT and CRP in the early identification of transplant-related complications in these patients, and to evaluate which of the two biomarkers or their combination functions best in critical clinical situations.

Materials and methods

Study design

This retrospective study was conducted in accordance with the declaration of Helsinki and was performed under the waiver for retrospective anonymized studies in accordance with the ethics regulations of the Independent Ethics Committee of the University of Tübingen, Germany (Project no. 794/2018BO2). The data were collected retrospectively, entered in a standardized case-report form and anonymized.

The analysis was comprised of a single patient cohort of pediatric patients with hemato-oncological malignancies and non-malignancies who underwent allogeneic HSCT at the University Children's Hospital Tübingen. All pediatric patients who received a first or second allogeneic HSCT were consecutively enrolled. The cohort was subsequently divided into two groups of patients without transplant-related complications as described below (control group; CG) and patients who experienced at least one of the defined complications (adverse events group; AEG) during the observation period. The observation period started on the day before the start of the conditioning chemotherapy

before HSCT and ended on the day of clinical discharge after HSCT.

Control group

Patients who did not experience transplant-related adverse events after HSCT, including acute GvHD, VOD, graft rejection, sepsis/SIRS and bacteremia, mucositis, viremia, and fungemia, were defined as the control group. Their median PCT and CRP values during the whole post-transplant period were used for comparison with the values of patients who did experience at least one of the aforementioned transplant-related adverse events.

Criteria for the assessment of post-transplant adverse events

The diagnosis and severity criteria of the European Society for Blood and Bone Marrow Transplantation were used to diagnose VOD (Corbacioglu et al. 2018; McDonald et al. 1986). Clinical diagnosis of acute GvHD followed the recommendations for GvHD grading and staging (Przepiorka et al. 1995; Glucksberg et al. 1974). Sepsis/SIRS were diagnosed according to the criteria of the International Sepsis Consensus Conference on Pediatric Critical Care 2005 and later revisions and amendments (Goldstein et al. 2005; Kawasaki 2017; Dellinger et al. 2013). Bacteremia was diagnosed by at least one positive blood culture. Viremia was diagnosed by positive PCR testing (> 600 copies/ml) from blood for cytomegalovirus (CMV), adenovirus (ADV), HHV-6, Epstein–Barr virus (EBV), varicella zoster virus (VZV), human herpes simplex virus (HSV), and Parvovirus B19. Local, non-invasive infections were defined as a positive microbiological or virological test of infection in the throat, urine, or feces. Proven, probable, or possible invasive fungal infections were defined according to the definitions of the Infectious Diseases Working Party of the German Society for Hematology and Medical Oncology (AGIHO) (Ruhnke et al. 2018). Diagnosis and staging of mucositis were performed using the WHO grading scale (Bensinger et al. 2008; Sonis et al. 2004; World Health Organization 1979).

Platelet recovery was defined as independence of platelet substitution for at least 7 consecutive days and a platelet count of > 20.000/µl. Leukocyte and granulocyte engraftment were defined as the first 3 consecutive days during which the absolute blood counts included leukocyte counts of > 1000/µl and granulocyte counts of > 500/µl, respectively. Graft rejection was defined as a recurrent pancytopenia with leukocytes < 1000/µl and granulocytes < 500/µl in the peripheral blood after successful engraftment, and a mixed chimerism with ≥ 60% autologous cells as confirmed by weekly PCR testing. Non-engraftment was identified by missing granulocytes engraftment in the peripheral blood within the first 28 days after HSCT and confirmed by bone marrow biopsy (Spitzer 2001; Schmid et al. 2008). Engraftment syndrome is a constellation of clinical symptoms including fever, maculopapular rash, fluid retention and weight gain, capillary leak, diarrhea, encephalopathy, and renal or hepatic dysfunction (Spitzer 2001; Schmid et al. 2008).

Blood sampling and laboratory analyses

PCT plasma levels were measured as part of routine blood analyses on the day before the start of conditioning chemotherapy, three times a week during the conditioning period, and at least three times a week after HSCT until in-patient discharge. CRP was measured daily as part of routine blood analyses beginning on the day before starting the conditioning and continuing until in-patient discharge. Laboratory analyses were performed at the Central Laboratory of the University Hospital Tübingen. Serum PCT (in lithium heparin anticoagulated peripheral blood) was determined from time-resolved amplified cryptate emission using a solid-phase bound monoclonal katacalcin antibody and a polyvalent calcitonin antibody. Normal PCT values were defined as ≤ 0.5 ng/ml. Serum CRP (in lithium heparin anticoagulated peripheral blood) was determined via immunoturbidimetry using an anti-CRP antibody and by measuring the change of extinction of the sample at 340 nm. Normal CRP values were defined as ≤ 0.5 mg/dl.

Concomitant medication

All patients received a standard prophylaxis against viral, fungal, and bacterial infections (virostatics, fungistatics, and metronidazole), and GvHD (cyclosporine A, methotrexate, mycophenolate mofetil, anti-thymocyte globulin (ATG), and thymoglobulin).

Aciclovir was administered (starting on the day before starting the conditioning chemotherapy; 3 × 250 mg/m^2 body surface area (BSA); as a short infusion) in patients receiving grafts from a matched unrelated donor (MUD). In patients undergoing haploidentical HSCT from a mismatched family donor (MMFD), the same antiviral prophylaxis was administered, when both donor and recipient were CMV negative. When both or one of them was CMV positive, ganciclovir (2 × 5 mg/kg BW per day) was given during conditioning until the day of HSCT, and beginning on day + 1 after HSCT, the patients received foscarnet (1 × 90 mg/kg BW per day).

Independent of the type of transplantation, all patients received antifungal prophylaxis with liposomal amphotericin B (1 × 1 mg/kg BW per day) during conditioning chemotherapy. During fever of unknown origin, the dose was adjusted

to 3 mg/kg BW per day. On day + 1 after HSCT, the antifungal prophylaxis was changed to caspofungin (1×50 mg/m^2 BSA per day; max. 50 mg).

All patients received an antimicrobial prophylaxis until the first occurrence of fever with metronidazole (21 mg/kg BW in two separated doses). In addition, all patients received a *Pneumocystis carinii* prophylaxis with cotrimoxazole (sulfamethoxazole/trimethoprim; 5 mg/kg BW per day in two separated doses; max. 2×80 mg trimethoprim).

Beginning on the fourth day after HSCT, almost all patients received granulocyte colony-stimulating factor at 5 µg per kg of body weight and day (µg kg^{-1} BW^{-1} d^{-1}) until stabilization of leukocytes (> 1.000/µl peripheral blood) and neutrophils (> 500/µl peripheral blood).

Statistical analysis

A total of 214 patients met the inclusion criteria and were enrolled in the analysis. PCT and CRP serum concentrations of each patient were determined before the start of conditioning chemotherapy. The "before" values were identified as the last determined concentrations before occurrence of first clinical symptoms of a transplant-related adverse event (1–7 days before diagnosis). "During" values referred to the highest serum levels that were determined during the time in which an adverse event was diagnosed according to the described criteria. "End" values were defined as the highest PCT or CRP serum concentration after clinical and laboratory-chemical symptoms of the respective episode of an adverse event had completely resolved.

PCT and CRP levels of these points in time were determined as median, mean ± standard deviation (SD), and range (minimum to maximum values), and are presented in the figures as bar charts (median ± 95% confidence interval).

Due to frequent non-normality (too small or unequal sample sizes) of data sets as tested by the Shapiro–Wilk normality test, non-parametric statistical tests were applied. Distributions of patient characteristics were compared between both groups using a Fisher's exact test.

Only clinically relevant changes, i.e., increases beyond the upper normal limits of median CRP and PCT values of the respective subgroup (e.g. patients with viremia), were included in the final statistical analyses for comparison against "before" values or results of the control group.

Median values of the control group were chosen to display parameter concentrations without clinical symptoms and to enable a differentiation of normal and pathological values. Results of the control group values were compared to "before", "during" and "end" values using a Mann–Whitney *U* test. A Wilcoxon matched-pairs signed rank test was used to compare before and during values.

Graphs and statistical tests were created with GraphPad Prism version 7.03 for Windows (GraphPad Software. Inc., La Jolla, CA, USA). *P* values < 0.05 (*), < 0.01 (**), < 0.001 (***), and < 0.0001 (****) were defined as statistically significant and are symbolized in the bar charts.

Results

Observation period

The median observation period in the control group and the adverse events group was 79 days (range 25–245 days) and included the time of measurement directly before the start of conditioning, until the day of clinical discharge.

Patient characteristics

The patient group consisted of 214 consecutive pediatric patients (120 males; 56.1%) with a median age of 8.5 years (range 0.4–17.8 years) who underwent allogeneic HSCT for hemato-oncological malignancies and non-malignancies. The patients received stem cell transplants from an MMFD ($n = 105$; 49.1%), a matched family donor (MFD; $n = 38$; 17.8%), a mismatched unrelated donor (MMUD; $n = 2$; 0.9%), or an MUD ($n = 69$; 32.2%). Of these 214 patients, 188 (87.9%) patients with a median age of 8.8 years (range 0.4–17.8 years) experienced exclusive adverse events (AE group) including graft rejection ($n = 13$; 6.1%), skin GvHD ($n = 50$; 23.4%), intestinal GvHD ($n = 16$; 7.5%), liver GvHD ($n = 5$; 2.3%), VOD ($n = 13$; 6.1%), sepsis/SIRS and bacteremia ($n = 38$; 17.8%), viremia ($n = 55$; 25.7%), fungemia ($n = 16$, 7.5%), and mucositis °III and °IV ($n = 95$; 44.4%). The remaining 26 patients (12.1%) did not experience transplant-related adverse events and were defined as the control group.

From the 188 patients of the AE group, 166 (88.3%) experienced more than one (median 2, range 1–4) AE during their in-patient stay after HSCT. An example of this is a patient developing a skin GvHD and later, at a separate time, a CMV infection. Episodes in which patients were diagnosed with more than one of these AE at the same time were not analyzed. A significant difference in the distribution of underlying diseases, therapy regimens, or donor types in the two patient groups was not detected. During the observation period, 8 of the 214 (3.7%) pediatric patients died, all from multi-organ failure. Patient characteristics are summarized in Table 1.

Control group

The CG consisted of 26 of the 214 (12.1%) pediatric patients and comprised a median age of 7.4 years (range 0.6–17.7 years). The median PCT value of the CG was

Table 1 Patient characteristics

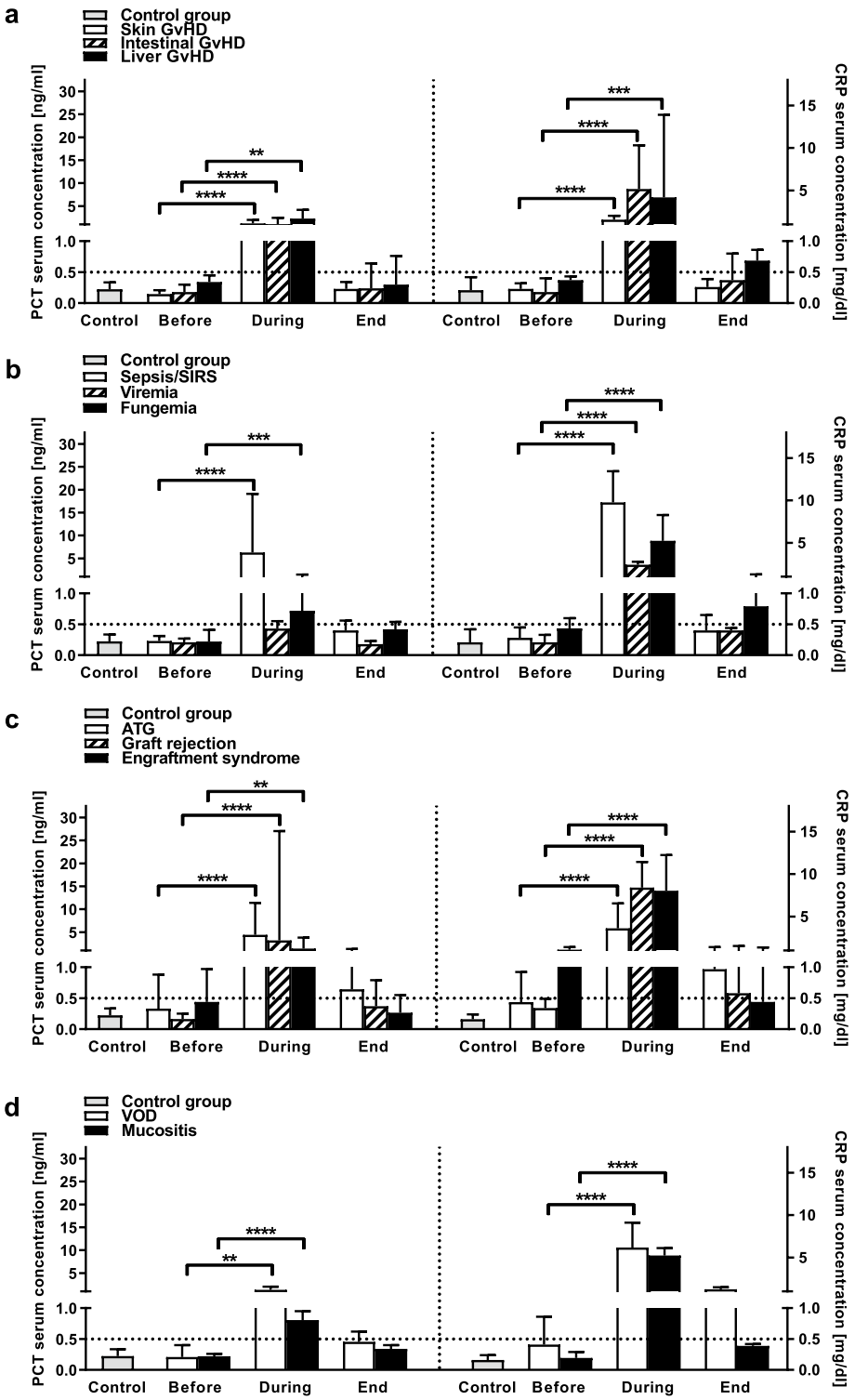
Total	Total		Adverse events group		Control group		*p*
	n	(%)	*n*	(%)	*n*	(%)	
	214	(100.0)	188	(87.9)	26	(12.1)	
Age (years)							
Median	8.5		8.8		7.4		
0–2	23	(10.7)	17	(9.0)	6	(23.1)	0.0423
3–6	62	(29.0)	56	(29.8)	6	(23.1)	0.6453
7–12	63	(29.4)	53	(28.2)	10	(38.5)	0.3580
13–17	66	(30.8)	62	(33.0)	4	(15.4)	0.0741
Sex							
Male	120	(56.1)	107	(56.9)	13	(50.0)	0.5530
Female	94	(43.9)	81	(43.1)	13	(50.0)	0.5530
Diagnosis							
Acute lymphoblastic leukemia (relapse)	64	(29.9)	58	(30.9)	6	(23.1)	0.4986
Acute myeloid leukemia (relapse)	27	(12.6)	27	(14.4)	0	(0.0)	0.0519
β-Thalassemia major	10	(4.7)	9	(4.8)	1	(3.8)	> 0.9999
Chronic myeloid leukemia	4	(1.9)	3	(1.6)	1	(3.8)	0.4067
Ewing's sarcoma	3	(1.4)	2	(1.1)	1	(3.8)	0.3233
Fanconi anemia	5	(2.3)	4	(2.1)	1	(3.8)	0.4802
Juvenile myelomonocytic leukemia	6	(2.8)	5	(2.7)	1	(3.8)	0.5448
M. Tay-Sachs	4	(1.9)	3	(1.6)	1	(3.8)	0.4067
Myelodysplastic syndromes	15	(7.0)	12	(6.4)	3	(11.5)	0.4020
MHC II defect	3	(1.4)	2	(1.1)	1	(3.8)	0.3233
Metachromatic leukodystrophy	6	(2.8)	3	(1.6)	3	(11.5)	0.0250
Neuroblastoma	22	(10.3)	19	(10.1)	3	(11.5)	0.7364
Rhabdomyosarcoma	5	(2.3)	4	(2.1)	1	(3.8)	0.4802
Severe combined immunodeficiency	5	(2.3)	4	(2.1)	1	(3.8)	0.4802
Severe aplastic anemia	8	(3.7)	7	(3.7)	1	(3.8)	> 0.9999
Sickle cell anemia	3	(1.4)	3	(1.6)	0	(0.0)	> 0.9999
Other	24	(11.2)	23	(12.2)	1	(3.8)	0.3225
Conditioning							
Reduced-intensity conditioning	23	(10.7)	20	(10.6)	3	(11.5)	> 0.9999
Myeloablative conditioning	191	(89.3)	168	(89.4)	23	(88.5)	> 0.9999
Total body irradiation	20	(9.3)	18	(9.6)	2	(7.7)	> 0.9999
HSCT donor							
Matched family donor	38	(17.8)	36	(19.1)	2	(7.7)	0.1817
Matched unrelated donor	69	(32.2)	59	(31.4)	10	(38.5)	0.5051
Mismatched unrelated donor	2	(0.9)	2	(1.1)	0	(0.0)	> 0.9999
Mismatched family donor	105	(49.1)	91	(48.4)	14	(53.8)	0.6779
Death							
Died during observation period	8	(3.7)	8	(4.3)	0	(0.0)	0.5998

HSCT hematopoietic stem cell transplantation, *MHC* major histocompatibility complex, *n* sample size, *p* probability value. *P* value determined by Fisher's exact test

significantly below ($p = 0.0043$) the normal limit at 0.23 (range 0.09–1.11 ng/ml). The median CRP value was 0.16 (range 0.01–0.82 mg/dl) and thus also significantly below ($p < 0.0001$) the normal limit.

ATG administration

The T-cell antibody anti-thymocyte globulin (ATG) is part of various conditioning protocols prior to allogeneic HSCT: ATG is administered on three consecutive days between



day 12 and day 1 (depending on the conditioning protocol) before HSCT and leads to early increases of CRP and PCT on the subsequent day that both usually normalize within 3 days (Arber et al. 2000).

ATG was administered to 191 of 214 patients (89.3%) during the conditioning chemotherapy before HSCT, from which 149 (78.0%) subsequently developed temporary fever > 38.5 °C. Median PCT and CRP values significantly ($p < 0.0001$) increased to 1.17 ng/ml (range 0.05–38.0 ng/ml) and 4.60 (0.01–32.01 mg/dl), and subsequently declined within 3 days to 0.27 ng/ml (range 0.03–3.13 ng/ml) and 0.75 mg/dl (range 0.01–3.25 mg/dl), respectively.

◂**Fig. 1** PCT and CRP serum levels during transplant-related adverse events. The graph shows median + 95% confidence interval of serum levels of PCT (left) and CRP (right) in pediatric patients after allogeneic hematopoietic stem cell transplantation. Median values of pediatric patients during different transplant-related adverse events (graft rejection, VOD, mucositis, acute GvHD, sepsis/SIRS and bacteremia, viremia, and fungemia) were compared to median serum levels of patients, who did not experience any of these adverse events in the post-transplant period [control group; PCT: median 0.23 (range 0.09–1.11 ng/ml); CRP: median 0.16 (range 0.01–0.82 mg/dl)]. **a** During acute skin, intestinal and liver GvHD, PCT levels moderately ($p < 0.01$) and CRP levels strongly ($p < 0.001$) increased. **b** Median PCT levels strongly increased during sepsis/SIRS and bacteremia ($p < 0.0001$) and moderately increased during fungemia ($p < 0.001$). Median CRP levels strongly increased during sepsis/SIRS and bacteremia ($p < 0.0001$) and fungemia ($p < 0.0001$) and moderately increased during viremia ($p < 0.0001$). **c** Median PCT levels moderately increased after ATG administration ($p < 0.0001$), during graft rejection ($p < 0.0001$) and during engraftment syndrome ($p < 0.01$). Median CRP levels moderately increased after ATG administration ($p < 0.0001$) and strongly increased during graft rejection ($p < 0.0001$) and engraftment syndrome ($p < 0.0001$) **d** Median PCT levels slightly increased during VOD ($p < 0.01$) and mucositis ($p < 0.0001$), while CRP strongly increased during both VOD and mucositis ($p < 0.0001$). Dotted horizontal lines indicate upper normal limits of PCT (0.5 ng/ml) and CRP (0.5 mg/dl). Symbols indicate $*p < 0.05$, $**p < 0.01$, $***p < 0.001$, $****p < 0.0001$

Acute GvHD

Acute GvHD occurred in 71 (33.2%) of the 214 patients, of whom 50 patients (70.4%) had acute skin GvHD (median stage 2, range 1–3), 16 (22.5%) had acute intestinal GvHD (median stage 3, range 2–4), and 5 (7.0%) had acute liver GvHD (median stage 2, range 2–3). Of the 71 patients, 10 (14.1%) initially had GvHD manifestations on their skin and later in the intestine, three of the patients (4.2%) initially had skin GvHD and then developed liver GvHD, and one patient (1.4%) gradually developed skin, intestinal, and then liver GvHD.

During skin GvHD, the median PCT blood levels slightly increased (vs. "before": $p < 0.0001$; vs. control group: $p < 0.0001$) to 0.93 ng/ml (range 0.02–4.34 ng/ml). During intestinal and liver GvHD, the median PCT blood levels significantly increased (vs. "before": $p < 0.0001$; vs. control group: $p < 0.0001$) to 1.06 ng/ml (range 0.19–5.55 ng/ml), and to 2.29 ng/ml (range 1.02–4.20 ng/ml), respectively.

Median CRP blood levels during skin GvHD significantly increased (vs. "before": $p < 0.0001$; vs. control group: $p < 0.0001$) to 2.03 mg/dl (range 0.04–21.63 mg/dl). During intestinal and liver GvHD, the median CRP blood levels highly and significantly increased (vs. "before": $p < 0.0001$; vs. control group: $p < 0.0001$) to 8.73 mg/dl (range 3.24–32.37 mg/dl) and to 6.88 mg/dl (range 3.40–24.90 mg/dl), respectively (Fig. 1a).

Sepsis/SIRS and bacteremia

Sepsis/SIRS and bacteremia occurred in 38 (17.8%) of the 214 patients. During sepsis/SIRS and bacteremia, the median PCT blood levels significantly and highly increased (vs. "before": $p < 0.0001$; vs. control group: $p < 0.0001$) to 6.30 ng/ml (range 1.08–69.89 ng/ml). Likewise, the median CRP blood levels significantly and highly increased (vs. "before": $p < 0.0001$; vs. control group: $p < 0.0001$) to 17.24 mg/dl (range 1.48–49.47 mg/dl) (Fig. 1b).

Viremia

Viremia occurred in 55 (25.7%) of the 214 patients. ADV viremia was detected in 14 (25.5%) patients, BKV in 19 (34.5%) patients, CMV in 16 (29.1%) patients, EBV in 7 (49.1%) patients, HHV-6 in 11 (20.0%) patients, and HSV in 2 (3.6%) patients. In 9 of the 55 patients (16.4%), simultaneous infection with two viruses was detected (ADV + CMV, ADV + EBV, and BKV + HSV). In 2 of the 55 patients (3.6%), a viremia caused by a simultaneous infection with ADV, HHV-6, and BKV was diagnosed. During viremia, the median PCT blood levels did not significantly ($p = 0.3866$) increase beyond the normal limit to 0.43 ng/ml (range 0.07–2.12 ng/ml), whereas the median CRP blood levels significantly increased (vs. "before": $p < 0.0001$; vs. control group: $p < 0.0001$) to 3.62 mg/dl (range 0.06–15.60 mg/dl).

The 14 patients, who experienced ADV viremia, had significantly elevated median CRP levels at 2.32 mg/dl (range 1.01–10.87 mg/dl; $p < 0.0001$) during viremia, whereas median PCT levels remained below the upper normal limit at 0.38 ng/ml (range 0.10–2.12 ng/ml) (Fig. 1b).

Fungemia

Fungemia occurred in 16 (7.5%) of the 214 patients. In 14 (87.5%) of the 16 patients, *Aspergillus* ssp. were detected; 13 of them had a positive proof of *Aspergillus* galactomannan antigen in the peripheral blood in at least two consecutive serum samples. Six of these 13 patients had an increase of galactomannan antigen only, while the seven others had additional clinical signs including cough, dyspnea, or fever. Three of them were diagnosed with an aspergilloma in the lung proven by a bronchoalveolar lavage. Two (12.5%) of the 16 patients with fungemia were diagnosed with *Fusarium* spp. fungemia proven by a bronchoalveolar lavage. In total, 5 of 16 patients (31.3%) had a proven invasive fungal infection, 7 (43.8%) had a probable invasive fungal infection with positive galactomannan antigen proof and positive clinical signs, and the remaining 4 patients (25.0%) had a possible invasive fungal infection with positive proof of galactomannan antigen only (Ruhnke et al. 2018). During fungemia, the median PCT blood levels slightly increased

(vs. "before": $p = 0.0007$; vs. control group: $p = 0.0002$) to 0.72 ng/ml (range 0.22–1.92 ng/ml), while median CRP levels significantly and highly increased (vs. "before": $p < 0.0001$; vs. control group: $p < 0.0001$) to 8.85 mg/dl (range 2.30–28.41 mg/dl) (Fig. 1b).

Graft rejection

Graft rejection occurred in 13 (6.1%) of the 214 patients. During graft rejection, the median PCT blood levels significantly (vs. "before" and vs. control group: $p < 0.0001$) increased to 3.2 ng/ml (range 1.04–99.7 ng/ml) and the median CRP blood levels significantly and highly increased (vs. "before" and vs. control group: $p < 0.0001$) to 14.73 mg/dl (range 5.45–30.19 mg/dl) (Fig. 1c).

Engraftment syndrome

Engraftment syndrome occurred in 10 (4.7%) of the 214 patients. During engraftment syndrome, the median PCT blood levels slightly increased (vs. "before" and vs. control group: $p < 0.01$) to 1.43 ng/ml (range 0.30–3.82 ng/ml), while the median CRP levels significantly and highly increased (vs. "before" and vs. control group: $p < 0.0001$) to 14.03 mg/dl (range 2.85–29.29 mg/dl) (Fig. 1c).

Veno-occlusive disease

VOD occurred in 13 (6.1%) of the 214 patients. During VOD, the median PCT blood levels slightly increased (vs. "before": $p = 0.0013$; vs. control group: $p = 0.0002$) to 0.59 ng/ml (range 0.20–3.27 ng/ml). Median CRP significantly and highly increased (vs. "before" and vs. control group: $p < 0.0001$) to 10.84 mg/dl (range 4.53–19.97 mg/dl) (Fig. 1d).

Mucositis

Mucositis occurred in 95 of 214 (44.4%) patients. Mucositis °III was diagnosed in 5 (5.3%) and °IV in 90 (94.7%) of them. During mucositis, the median PCT blood levels slightly increased (vs. "before": $p < 0.0001$; vs. control group: $p < 0.0001$) to 0.81 ng/ml (range 0.02–3.80 ng/ml), while the median CRP blood levels significantly and strongly increased (vs. "before": $p < 0.0001$; vs. control group: $p < 0.0001$) to 8.84 mg/dl (range 2.04–34.61 mg/dl) (Fig. 1d).

In summary, large and significant simultaneous elevations of PCT and CRP occurred during sepsis/SIRS and bacteremia, graft rejection, and liver GvHD. The combination of highly elevated CRP (> 8 mg/dl) and slight increases of PCT occurred during engraftment syndrome, fungemia, and intestinal GvHD. Large increases of CRP (> 8 mg/dl) with minimal increases of PCT occurred during VOD and mucositis. During skin GvHD, CRP and PCT were moderately (> 3 mg/dl) and mildly (> 0.9 ng/ml) elevated, respectively. During viremia, CRP values moderately increased, whereas PCT values remained below the normal limit. Detailed results are displayed in the supplementary Tables S1 and S2. Comparisons of the median PCT and CRP serum values during different transplant-related adverse events, which are clinically difficult to differentiate, are displayed in Fig. 2.

Discussion

Pediatric oncology patients undergoing HSCT are generally at high risk for infectious complications, GvHD, VOD, mucositis, and other transplant-related adverse events. Immediate and proper treatment is essential for positive patient outcomes. In this analysis, serum PCT and CRP values of pediatric HSCT recipients were correlated to transplant-related adverse events to evaluate their diagnostic or discriminative value during these complications.

ATG administration

The administration of ATG during the conditioning period before HSCT led to fever > 38.5 °C in 78% of the patients and a temporary significant increase of both CRP and PCT. These values declined within 3 days and were thus not clinically relevant for the analyses of post-transplant complications. The transient increases of the body temperature and serum levels of PCT and CRP are in accordance with previously published data. (Arber et al. 2000).

Sepsis/SIRS and bacteremia and mucositis

Mucositis is a severe and painful complication following high-dose chemotherapy that leads to ulcerations of the mucous membrane. It usually occurs within the first 7–14 days after HSCT, i.e., the critical neutropenic period after HSCT, in which patients are also at the highest risk for severe infection and sepsis. Both complications are regularly difficult to differentiate during fever in the early neutropenic period after HSCT. It is, therefore, of critical importance to differentiate life-threatening sepsis, which requires immediate antimicrobial therapy and intensive care, from less critical mucositis, which is treated with analgesics including morphine derivatives (Kawasaki 2017; Jacobs et al. 2013). In the present analysis, severe mucositis (mainly °IV) was characterized by highly elevated CRP (median 8.84 mg/dL) but only minimally increased PCT (median 0.81 ng/ml), whereas an increase of both PCT and CRP during febrile episodes occurred in

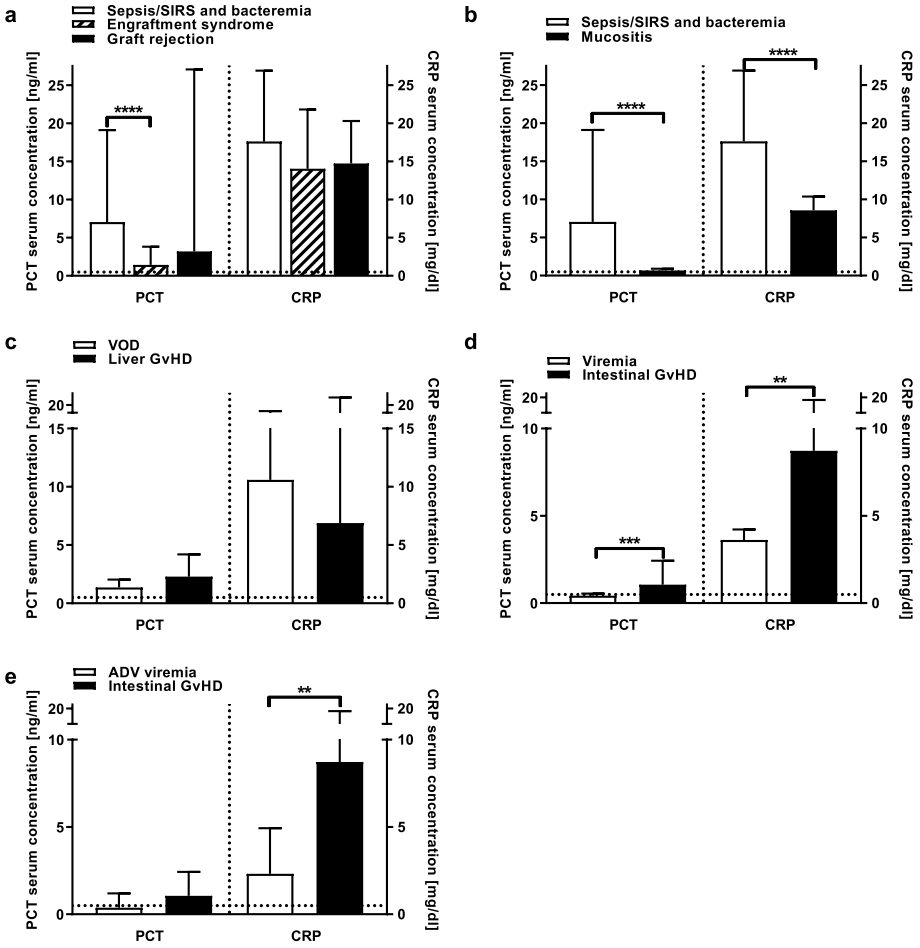


Fig. 2 Specific comparisons. The graph shows comparisons of median PCT and CRP serum values during different post-transplant conditions. **a** Sepsis/SIRS and bacteremia vs. engraftment syndrome vs. graft rejection: these three complications regularly occur during the early post-transplant period until day 30 after HSCT. Sepsis/SIRS and bacteremia were characterized by strong increases of both PCT and CRP; graft rejection was accompanied by strong increases of CRP and moderately-to-highly increased PCT values, while in contrast during engraftment syndrome, strong increases of CRP but only slight increases of PCT occurred (PCT: Sepsis/SIRS and bacteremia vs. graft rejection: $p=0.1640$; Sepsis/SIRS and bacteremia vs. engraftment syndrome: $p<0.0001$; engraftment syndrome vs. graft rejection: $p=0.0890$ | CRP: Sepsis/SIRS and bacteremia vs. graft rejection: $p=0.1996$; Sepsis/SIRS and bacteremia vs. engraftment syndrome: $p=0.3070$; engraftment syndrome vs. graft rejection: $p=0.9758$). **b** Mucositis vs. sepsis/SIRS and bacteremia: mucositis and sepsis regularly occur in the early aplastic phase in the first 14 days after HSCT and require distinctly different therapeutic interventions. Sepsis/SIRS and bacteremia were characterized by strong increases of both PCT and CRP, while mucositis was accompanied by strong increases of CRP but only minimal increases of PCT (CRP: $p<0.0001$ | PCT: $p<0.0001$). **c** VOD vs. acute liver GvHD: both complications occur during the early post-transplant period until day 30 after HSCT. While VOD was accompanied by strong increases of CRP and minimal increases of PCT, acute liver GvHD was characterized by moderate-to-strong increases of CRP and higher PCT increases compared to VOD (PCT: $p=0.0987$ | CRP: $p=0.1784$). **d** Viremia vs. acute intestinal GvHD. Both complications may occur during the early post-transplant period until day 30 after HSCT and require different therapies. While acute intestinal GvHD was characterized by highly elevated CRP and moderately increased PCT, viremia was accompanied by strong CRP increases and negative PCT (PCT: $p=0.0006$ | CRP: $p=0.0040$). **e** Especially, ADV viremia is often difficult to differentiate from acute intestinal GvHD. While acute intestinal GvHD was accompanied by highly elevated CRP and moderately increased PCT, ADV viremia was characterized by CRP increases and negative PCT (PCT: $p=0.0568$ | CRP: $p=0.0079$). Dotted horizontal lines indicate upper normal limits of PCT (0.5 ng/ml) and CRP (0.5 mg/dl). Symbols indicate $*p<0.05$, $**p<0.01$, $***p<0.001$, $****p<0.0001$

the course of sepsis/SIRS and bacteremia (median CRP 17.24 mg/dl; median PCT 6.30 ng/ml). These results were in accordance with a prospective study analyzing 116 episodes of febrile neutropenia occurring in 88 adult patients after HSCT or chemotherapy, showing that PCT was able to distinguish major bacterial infection from mucositis and GvHD. PCT was not considerably elevated beyond 1 ng/ml in patients experiencing mucositis or GvHD (Sarmati et al. 2010).

Viremia and intestinal GvHD

GvHD is a severe inflammatory complication after HSCT that usually occurs 14–28 days after HSCT, i.e., the time of T-cell regeneration. Acute GvHD requires intensive immunosuppressive treatment including corticosteroids or antiproliferative agents. Clinically, an acute intestinal GvHD is difficult to differentiate from for example a gastrointestinal viral infection with ADV. In both cases, the patients may present with fever, abdominal pain, diarrhea, nausea, and vomiting. Especially, ADV viremia is usually difficult to differentiate from an intestinal GvHD. According to international guidelines, it is necessary to do histopathological staining of intestinal biopsies to secure the diagnosis of an intestinal GvHD. However, PCR testing for ADV infection and molecular pathological analyses may take at least several hours up to several days as opposed to laboratory testing for PCT and CRP (max. 1–2 h), which may help to make or support an early therapeutic decision.

The results of this analysis show that viremia did not cause elevations of PCT beyond the normal limit (median 0.43 ng/ml), while CRP was significantly increased (median of 3.62 mg/dl). Especially during ADV infection of the feces and ADV viremia, PCT serum levels remained below the normal limit, while CRP levels significantly increased. In contrast to viremia, acute intestinal GvHD was accompanied by significantly elevated PCT and highly increased CRP.

This is in accordance with the existing data for adult patients after HSCT experiencing viral respiratory complications, as analyzed in a prospective study on 157 stem cell recipients (Lucena et al. 2017). In another retrospective analysis of 821 febrile episodes of a total of 316 pediatric patients undergoing chemotherapy or HSCT ($n=59$), it was shown that from a total of 27 episodes with documented viral infection, approximately 56% had PCT serum concentrations of ≥ 0.7 ng/ml, which is rather contradictory to our results (Gunasekaran et al. 2016).

Sepsis/SIRS and bacteremia, graft rejection, and engraftment syndrome

Sepsis/SIRS and bacteremia, graft rejection, and engraftment syndrome are all major and life-threatening complications after HSCT, and usually occur during the early post-transplant period until day 30 after HSCT. They are accompanied by persistent high fever > 39.0 °C. In the present analysis, serum CRP values strongly increased during sepsis/SIRS and bacteremia, graft rejection, and engraftment syndrome, which is in accordance with published pediatric data (Sauer et al. 2003; Sauer et al. 2000). CRP could not be used as a discriminative biomarker during these complications. In contrast, PCT was strongly elevated during sepsis/SIRS and bacteremia, but it only moderately increased during graft rejection and minimally increased during engraftment syndrome. In a small prospective study of 30 pediatric patients (1–21 years of age), from which five developed engraftment syndrome after allogeneic HSCT, median maximum PCT values were 2.05 ng/ml (range 0.95–6.80 ng/ml), and thus comparable to our data (Shah et al. 2017).

Fungemia

The median PCT values in patients experiencing fungemia in this analysis were minimally elevated to 0.72 ng/ml, being accompanied by strong increases of CRP serum concentrations. This is in accordance with an analysis of 34 adult hemato-oncological patients undergoing chemotherapy or allogeneic HSCT, in which it was shown that during bacterial infection, CRP and PCT were both substantially elevated while the fungal infection was characterized by high CRP values and minimal or no increases of PCT (Markova et al. 2013). An analysis of 28 adult HSCT patients detected a more valuable role of PCT than C-reactive protein (CRP) in differentiating bacterial and fungal infections (Koya et al. 2012).

Liver GvHD and VOD

VOD usually occurs during the early post-transplant period until day 30 after HSCT and needs to be differentiated from acute liver GvHD. During both complications, patients may present with fever, elevated serum bilirubin, or right upper quadrant pain (liver pain). In the present analysis, it was shown that hepatic VOD was accompanied with highly elevated CRP (median 10.84 mg/dl) and minimally increased PCT (median 0.59 ng/ml), whereas GvHD of the liver showed significantly elevated serum levels of both PCT (median 2.29 ng/ml) and CRP (median 6.88 mg/dl). Although the number of patients with acute liver GvHD does not allow one to make a statistically reliable statement, it can be noted that 100% of the patients had significantly elevated PCT (> 1 ng/ml) and CRP (> 3 mg/dl) serum levels. Comparable pediatric or adult studies that included data on PCT serum levels during acute liver GvHD were not found.

Conclusion

In the present analysis, it was shown that PCT is superior to CRP in the diagnosis of different, clinically relevant transplant-related complications. In contrast to CRP, PCT helped to differentiate mucositis from sepsis/SIRS and bacteremia, acute intestinal GvHD from adenovirus viremia, and graft rejection from engraftment syndrome and sepsis/SIRS. Due to the small number of analyzed patients with liver GvHD, a definitive statement on the discriminative

value of PCT and CRP in differentiation of patients with VOD could not be made. However, it was shown that during hepatic GvHD, PCT and CRP were both elevated, while during hepatic VOD, serum PCT levels had only minimally increased. Larger prospective studies are needed to evaluate these findings.

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Compliance with ethical standard

Conflicts of interest The authors declare that they have no conflicts of interests.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

References

Arber C, Passweg JR, Fluckiger U, Pless M, Gregor M, Tichelli A, Schifferli JA, Gratwohl A (2000) C-reactive protein and fever in neutropenic patients. Scand J Infect Dis 32:515–520

Armand P, Kim HT, Cutler CS, Ho VT, Koreth J, Alyea EP, Soiffer RJ, Antin JH (2007) Prognostic impact of elevated pretransplantation serum ferritin in patients undergoing myeloablative stem cell transplantation. Blood 109:4586–4588

Baker KS, Allen RD, Roths JB, Sidman CL (1995) Kinetic and organ-specific patterns of cytokine expression in acute graft-versus-host disease. Bone Marrow Transpl 15:595–603

Bensinger W, Schubert M, Ang KK, Brizel D, Brown E, Eilers JG, Elting L, Mittal BB, Schattner MA, Spielberger R, Treister NS, Trotti AM (2008) NCCN task force report. Prevention and management of mucositis in cancer care. JNCCN 6(Suppl 1):S1–S21 **(Quiz S22–4)**

Budde H, Papert S, Maas JH, Reichardt HM, Wulf G, Hasenkamp J, Riggert J, Legler TJ (2017) Prediction of graft-versus-host disease: a biomarker panel based on lymphocytes and cytokines. Ann Hematol 96:1127–1133

Corbacioglu S, Carreras E, Ansari M, Balduzzi A, Cesaro S, Dalle JH, Dignan F, Gibson B, Guengoer T, Gruhn B, Lankester A, Locatelli F, Pagliuca A, Peters C, Richardson PG, Schulz AS, Sedlacek P, Stein J, Sykora KW, Toporski J, Trigoso E, Vetteranta K, Wachowiak J, Wallhult E, Wynn R, Yaniv I, Yesilipek A, Mohty M, Bader P (2018) Diagnosis and severity criteria for sinusoidal obstruction syndrome/veno-occlusive disease in pediatric patients: a new classification from the European society for blood and marrow transplantation. Bone Marrow Transpl 53:138–145

Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, Sevransky JE, Sprung CL, Douglas IS, Jaeschke R, Osborn TM, Nunnally ME, Townsend SR, Reinhart K, Kleinpell RM, Angus DC, Deutschman CS, Machado FR, Rubenfeld GD, Webb SA, Beale RJ, Vincent JL, Moreno R (2013) Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. Crit Care Med 41:580–637

Fleischhack G, Kambeck I, Cipic D, Hasan C, Bode U (2000) Procalcitonin in paediatric cancer patients: its diagnostic relevance is superior to that of C-reactive protein, interleukin 6, interleukin 8, soluble interleukin 2 receptor and soluble tumour necrosis factor receptor II. Br J Haematol 111:1093–1102

Fujita A, Ihira M, Suzuki R, Enomoto Y, Sugiyama H, Sugata K, Suga S, Asano Y, Yagasaki H, Kojima S, Matsumoto K, Kato K, Yoshikawa T (2008) Elevated serum cytokine levels are associated with human herpesvirus 6 reactivation in hematopoietic stem cell transplantation recipients. J Infect 57:241–248

Glucksberg H, Storb R, Fefer A, Buckner CD, Neiman PE, Clift RA, Lerner KG, Thomas ED (1974) Clinical manifestations of graft-versus-host disease in human recipients of marrow from HL-A-matched sibling donors. Transplantation 18:295–304

Goldstein B, Giroir B, Randolph A (2005) International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. Pediatr Crit Care Med 6:2–8

Grossekatthöfer M, Guclu ED, Lawitschka A, Matthes-Martin S, Mann G, Minkov M, Peters C, Seidel MG (2013) Ferritin concentrations correlate to outcome of hematopoietic stem cell transplantation but do not serve as biomarker of graft-versus-host disease. Ann Hematol 92:1121–1128

Gunasekaran V, Radhakrishnan N, Dinand V, Sachdeva A (2016) Serum procalcitonin for predicting significant infections and mortality in pediatric oncology. Indian Pediatr 53:1075–1078

Hambach L, Eder M, Dammann E, Schrauder A, Sykora KW, Dieterich C, Kirschner P, Novotny J, Ganser A, Hertenstein B (2002) Diagnostic value of procalcitonin serum levels in comparison with C-reactive protein in allogeneic stem cell transplantation. Haematologica 87:643–651

Jacobs S, Baggott C, Agarwal R, Hesser T, Schechter T, Judd P, Tomlinson D, Beyene J, Sung L (2013) Validation of the children's international mucositis evaluation Scale (ChIMES) in paediatric cancer and SCT. Br J Cancer 109:2515–2522

Kawasaki T (2017) Update on pediatric sepsis: a review. J Intensive Care 5:47

Klastersky J, De Naurois J, Rolston K, Rapoport B, Maschmeyer G, Aapro M, Herrstedt J (2016) Management of febrile neutropaenia: ESMO clinical practice guidelines. Ann Oncol 27:v111–v118

Koya J, Nannya Y, Ichikawa M, Kurokawa M (2012) The clinical role of procalcitonin in hematopoietic SCT. Bone Marrow Transpl 47:1326–1331

Lucena CM, Rovira M, Gabarrus A, Filella X, Martinez C, Domingo R, Torres A, Agusti C (2017) The clinical value of biomarkers in respiratory complications in hematopoietic SCT. Bone Marrow Transpl 52:415–422

Lyu YX, Yu XC, Zhu MY (2013) Comparison of the diagnostic value of procalcitonin and C-reactive protein after hematopoietic stem cell transplantation: a systematic review and meta-analysis. Transpl Infect Dis 15:290–299

Markova M, Brodska H, Malickova K, Valkova V, Cetkovsky P, Kolar M, Haluzik M (2013) Substantially elevated C-reactive protein (CRP), together with low levels of procalcitonin (PCT), contributes to diagnosis of fungal infection in immunocompromised patients. Support Care Cancer 21:2733–2742

Massaro KS, Macedo R, De Castro BS, Dulley F, Oliveira MS, Yasuda MA, Levin AS, Costa SF (2014) Risk factor for death in hematopoietic stem cell transplantation: are biomarkers useful to foresee the prognosis in this population of patients? Infection 42:1023–1032

Mateos MK, O'brien TA, Oswald C, Gabriel M, Ziegler DS, Cohn RJ, Russell SJ, Barbaric D, Marshall GM, Trahair TN (2013) Transplant-related mortality following allogeneic hematopoeitic stem cell transplantation for pediatric acute lymphoblastic leukemia: 25-year retrospective review. Pediatr Blood Cancer 60:1520–1527

Matwiyoff GN, Prahl JD, Miller RJ, Carmichael JJ, Amundson DE, Seda G, Daheshia M (2012) Immune regulation of procalcitonin: a biomarker and mediator of infection. Inflamm Res 61:401–409

Mcdonald GB, Sharma P, Matthews DE, Shulman HM, Thomas ED (1984) Venocclusive disease of the liver after bone marrow transplantation: diagnosis, incidence, and predisposing factors. Hepatology 4:116–122

Mcdonald GB, Shulman HM, Sullivan KM, Spencer GD (1986) Intestinal and hepatic complications of human bone marrow transplantation. Part I. Gastroenterology 90:460–477

Miedema KG, De Bont ES, Elferink RF, Van Vliet MJ, Nijhuis CS, Kamps WA, Tissing WJ (2011) The diagnostic value of CRP, IL-8, PCT, and sTREM-1 in the detection of bacterial infections in pediatric oncology patients with febrile neutropenia. Support Care Cancer 19:1593–1600

Presland RB (2016) Biology of chronic graft-vs-host disease: immune mechanisms and progress in biomarker discovery. World J Transpl 6:608–619

Przepiorka D, Weisdorf D, Martin P, Klingemann HG, Beatty P, Hows J, Thomas ED (1995) 1994 Consensus conference on acute GVHD grading. Bone Marrow Transpl 15:825–828

Ruhnke M, Behre G, Buchheidt D, Christopeit M, Hamprecht A, Heinz W, Heussel CP, Horger M, Kurzai O, Karthaus M, Loffler J, Maschmeyer G, Penack O, Rieger C, Rickerts V, RITTER J, Schmidt-Hieber M, Schuelper N, Schwartz S, Ullmann A, Vehreschild JJ, Von Lilienfeld-Toal M, Weber T, Wolf HH (2018) Diagnosis of invasive fungal diseases in haematology and oncology: 2018 update of the recommendations of the infectious diseases working party of the German society for hematology and medical oncology (AGIHO). Mycoses 61:796–813

Sarmati L, Beltrame A, Dori L, Maffongelli G, Cudillo L, de Angelis G, Picardi A, Ottaviani L, Cefalo MG, Venditti A, Amadori S, Arcese W, Andreoni M (2010) Procalcitonin is a reliable marker of severe systemic infection in neutropenic haematological patients with mucositis. Am J Hematol 85:380–383

Sato M, Nakasone H, Terasako-Saito K, Sakamoto K, Yamazaki R, Tanaka Y, Akahoshi Y, Nakano H, Ugai T, Wada H, Yamasaki R, Ishihara Y, Kawamura K, Ashizawa M, Kimura SI, Kikuchi M, Tanihara A, Kanda J, Kako S, Nishida J, Kanda Y (2014) Prediction of infectious complications by the combination of plasma procalcitonin level and localized infection before allogeneic hematopoietic cell transplantation. Bone Marrow Transpl 49:553–560

Sauer M, Tiede K, Volland R, Fuchs D, Zintl F (2000) Procalcitonin in comparison to C-reactive protein as markers of the course of sepsis in severely immunocompromised children after bone marrow transplantation. Klin Padiatr 212:10–15

Sauer M, Tiede K, Fuchs D, Gruhn B, Berger D, Zintl F (2003) Procalcitonin, C-reactive protein, and endotoxin after bone marrow transplantation: identification of children at high risk of morbidity and mortality from sepsis. Bone Marrow Transpl 31:1137–1142

Schmid I, Stachel D, Pagel P, Albert MH (2008) Incidence, predisposing factors, and outcome of engraftment syndrome in pediatric allogeneic stem cell transplant recipients. Biol Blood Marrow Transpl 14:438–444

Schots R, Kaufman L, Van Riet I, Ben Othman T, De Waele M, Van Camp B, Demanet C (2003) Proinflammatory cytokines and their role in the development of major transplant-related complications in the early phase after allogeneic bone marrow transplantation. Leukemia 17:1150–1156

Shah NN, Watson TM, Yates B, Liewehr DJ, Steinberg SM, Jacobsohn D, Fry TJ (2017) Procalcitonin and cytokine profiles in engraftment syndrome in pediatric stem cell transplantation. Pediatr Blood Cancer 64:e26273

Sonis ST, Elting LS, Keefe D, Peterson DE, Schubert M, Hauer-Jensen M, Bekele BN, Raber-Durlacher J, Donnelly JP, Rubenstein EB (2004) Perspectives on cancer therapy-induced mucosal injury: pathogenesis, measurement, epidemiology, and consequences for patients. Cancer 100:1995–2025

Spitzer TR (2001) Engraftment syndrome following hematopoietic stem cell transplantation. Bone Marrow Transpl 27:893–898

Tvedt TH, Lie SA, Reikvam H, Rye KP, Lindas R, Gedde-Dahl T, Ahmed AB, Bruserud O (2016) Pretransplant levels of CRP and interleukin-6 family cytokines; effects on outcome after allogeneic stem cell transplantation. Int J Mol Sci 17:1823

World Health Organization (1979) WHO handbook for reporting results of cancer treatment. World Health Organization, Geneva

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