PROCALCITONIN TO DISCERN THE ETIOLOGY OF FEVER IN CHILDREN RECEIVING ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION

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Introduction: Differentiating the etiology of fever in the presence of infection (FI) from fever not caused by infection (FNI) is critical for the rational use of antibiotics in hematopoietic stem cell transplantation (HSCT) pediatric recipients. We aimed to determine whether procalcitonin (PCT) was useful in discriminating FI and gram-negative bacterial infections from FNI in these patients.

Materials and Methods: A retrospective chart review was conducted from December 2010 to June 2016 in Centro Médico Imbanaco in Cali, Colombia. We examined children receiving allo-HSCT who developed fever between days −5 and the day of engraftment. PCT levels were reported for the first febrile episode. Each episode was classified as FI or FNI. We used receiver operating characteristic (ROC) curve analysis to evaluate test performance.

Results: A total of 82 patients received allo-HSCT during the study period. The average age of the patients was 9.6 years (SD ±5 years), and 54% were male. Seventy-two (88%) developed fever 0 days post allo-TPH (median). PCT was measured at least once during the febrile episode in 54 patients.
No significant differences in PCT were observed between FI and FNI. In gram-negative bacterial infections versus FNI, the first value of PCT had an area under the curve of 0.7 on the ROC curve. A PCT cutoff of 0.99 had an 88% sensitivity and a 56% specificity, a 1.97 positive likelihood ratio (LR), and a 0.23 negative LR.

Conclusion: PCT can help discriminate FI from fever caused by gram-negative infections. This biomarker may be useful in developing strategies for the rational use of antibiotics for this population.

Introduction

- Fever is common in children receiving allogeneic hematopoietic stem cell transplantation (allo-HSCT).
- Discriminating infection (IF) from non-infection-related fever (NIF) is critical for the judicious use of antibiotics in these patients.

Objective

- To determine whether procalcitonin (PCT) helps in discriminating IF (overall and gram negative) versus NIF in children receiving allo-HSCT

Methods

- A retrospective chart review of children and adolescents (0–18 years) receiving allo-HSCT was conducted from January 1st, 2010 to May 1st, 2016 at Centro Médico Imbanaco in Cali, Colombia.
- The transplant protocol consisted of cyclophosphamide administration on post-transplant days +3 and +4.
- Patients who developed fever between day −5 and the engraftment were included.
- PCT levels were documented for the first febrile episode.
- Each episode was classified as IF (gram negative, gram positive, viral, or fungal) or NIF (alloreactivity, drug-induced fever, or fever without a source).
- A receiver operating characteristic (ROC) curve was constructed to evaluate test performance.

The authors declare no conflicts of interest.

Results

- Eighty-two patients received allo-HSCT during the study period.
- Seventy-two (88%) of them developed fever.
- Fifty-four patients with fever had at least one PCT measured during their febrile episode, and these patients comprised the study population.
- The demographics are shown in Table 1.

Table 1. Demographic variables and pretransplant diagnosis

Variable	Non-infection-related fever (n=27)	Infection-related fever (n=27)	p value	Total (n = 54)
Age Mean (sd)	9,0 (4,4)	10,2 (5,5)	0,36	9,6 (5,0)
Sex n(%)				
Male	15 (55,6)	14 (51,8)	0,785	29 (53,7)
Pretransplant diagnosis, n(%)				
Acute lymphoblastic leukemia	9 (50)	9 (50)		18 (33)
Myeloid leukemia	4 (44,4)	5 (55,6)		9 (17)
Bone marrow failure	10 (62,5)	6 (37,5)		16 (30)
Hemoglobinopaties	1 (25,0)	3 (75)	0.78	4 (7)
Metabolic disorders	0 (0)	1(100)		1 (2)
Primary immunodeficiencies	2 (66,7)	1 (33,3)		3 (6)
Others	1 (33,3)	2 (66,7)		3 (6)

- The median day of onset of fever was day 0 for NIF and day +2.5 for IF.
- Most patients developed their first febrile episode between days −5 and +7 (Figure 1).

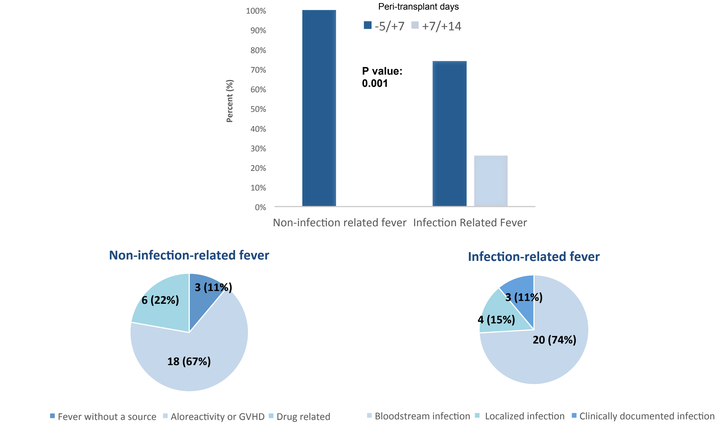

Figure 1. Peri-transplant time at occurrence of fever and its cause

- PCT levels were higher for IF and gram-negative infections than for NIF (Tables 2 and 3).

Table 2. PCT levels for NIF vs. IF

Variables' median (IQR)	Non-infection-related fever (n=27)	Infection-related fever (n=27)	p value
PCT value 1*	0.67 (0.09;3.06)	1.22 (0.13;4.46)	0.44
PCT value 2	0.52 (0.14;1.11)	1.85 (0.16;7.51)	0.34

*In ng/mL

Table 3. PCT levels for NIF vs. gram-negative infections

Variables' median (IQR)	Non-infection-related fever (n=27)	Gram-negative infections (n=13)	p value
PCT value 1*	0.67 (0.09; 3.06)	2.24(1.15; 10.47)	0.09
PCT value 2	0.52 (0.14; 1.11)	8.78 (4.66; 71.12)**	N/A

*In ng/mL **Samples obtained in three patients

- For gram negative vs. NIF, the first PCT value had an AUC of 0.7 in its ROC curve (Figure 2).
- At a cutoff of 0.99, PCT had a sensitivity of 88%, a specificity of 56%, a positive likelihood ratio (LR) of 1.97, and a negative LR of 0.23.

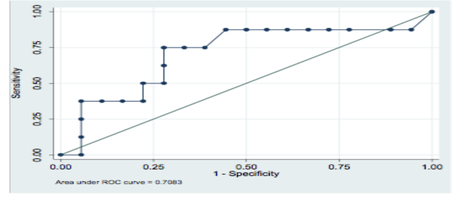

Figure 2. ROC curve for PCT in gram negative infections vs. NIF

- The PCT levels were similar between NIF and gram-positive infections (Table 4).

Table 4. PCT levels for NIF vs. gram-positive infections

Variables' median (IQR)	NIF-related fever (N=27)	Gram-positive infections (N=9)	p value
PCT value 1*	0.67 (0.09; 3.06)	1.22 (0.55; 4.46)	0.551
PCT value 2	0.52 (0.14; 1.11)	1.85 (0.05; 6.25)**	NA

*In ng/mL **Samples obtained in three patients

Conclusion

- The majority of children receiving HSCT develop fever in the peritransplant period.
- PCT may help discriminate IF from NIF, especially in gram-negative infections.
- Because patients are usually neutropenic during this period, discriminating gram-negative infections from NIF is of particular relevance.
- This biomarker may be useful in developing strategies to offer a more judicious use of antibiotics to this fragile population.