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Outcome and Risk Factors of Febrile Episodes Treated with Broad Spectrum Antibiotics and Polyclonal IgM–Enriched Immunoglobulin in Pediatric Oncology Hematology Patients: A Retrospective Study

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Abstract

Objective Preparations with high-titer immunoglobulin-M (HT-IgM) have been used to treat neonatal and adult sepsis as adjuvant to antibiotics. Limited data are available of this use in pediatric oncohematological patients. We retrospectively assessed the characteristics and outcome of febrile episodes treated with broad-spectrum antibiotics and HT-IgM.

Methods This study included febrile episodes diagnosed after chemotherapy or hematopoietic stem cell transplantation (HSCT) treated with antibiotics and HT-IgM. Study period was from January 2011 to March 2019.

Results Seventy febrile episodes in 63 patients were eligible. In 40% of episodes ($n = 28$), blood cultures identified a causative organism: Gram-negative ($n = 15$), Gram-positive ($n = 8$), polybacterial ($n = 4$), fungi ($n = 1$). Twenty-six percent of Gram-negatives were extend spectrum β-lactamase (ESBL)-producers. In 44% of episodes, a deep-organ localization was present, mostly pulmonary. Severe or profound neutropenia, hypotension, and hypoxemia were present in 89, 26, and 21% of episodes, respectively; 20% of episodes required intensive care and 20% of episodes required the use of inotropes. Overall, 90-day mortality was 13% and infection-attributable mortality resulted 8.6%. More than half of the patients received HT-IgM within 24 hours from fever onset. HT-IgM-related allergic reactions occurred in three episodes. Risk factors for 90-day mortality were as follows: hypotension and hypoxemia at fever presentation, admission to intensive care unit (ICU), use of inotropes, presence of deep-organ infection, and escalation of antibiotic therapy within 5 days.

Conclusion The combination of broad-spectrum antibiotics and HT-IgM was feasible, tolerated, and promising, being associated with a limited infectious mortality. Further prospective controlled studies are needed to assess the efficacy of this combination over a standard antibiotic approach.

Keywords
- immunoglobulin M
- pediatric malignancy
- infectious complications
- febrile neutropenia

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Introduction

Infectious complications, such as febrile neutropenia, bacteremia, and septic shock, are frequently observed in pediatric patients after chemotherapy or hematopoietic stem cell transplantation (HSCT). The pathogenesis of these infections is primarily related to the compromisation of innate immunity (mucosal and skin barriers and neutropenia) induced by chemotherapy that allows commensal bacteria to spread and invade blood and deep organs. The approximate rate of occurrence is 0.76 febrile episodes every 30 days of severe neutropenia.[1] To avoid the risk of death associated with bacterial infections, the recommendation is to treat empirically every febrile episode with broad spectrum antibiotics.[2]

Pentaglobin (Biotest, Germany) is a commercial preparation of polyvalent immunoglobulin (Ig) with high-titer of IgM (HT-IgM) obtained from a plasma pool of thousands of donors. It contains IgM and IgA and has a lower content of IgG (IgM, 12%; IgA, 12%; and IgG, 76% of total Ig content, equal to 50 mg/mL) compared with conventional intravenous Ig (IVIg) which contains predominantly IgG (more than 95%). This composition confers to HT-IgM particular features, most of which are attributable to IgM. Several studies, both in vitro and in vivo, showed that the opsonizing activity of HT-IgM against different bacterial strains is higher than that of preparations containing predominantly IgG due to the better efficiency of fixing complement.[3,4] In fact, the pentameric structure of IgM allows to bind C1q a thousand times more powerfully than IgG, triggering complement-mediated bacterial lysis and enhancing phagocytosis more effectively.[5,6] HT-IgM preparation contains neutralizing antibodies against several bacterial toxins, such as the exotoxin released by *Staphylococci spp*. and *Streptococci spp*., and antibodies directed against lipopolysaccharide, that have an important role in the pathogenesis of Gram-negative sepsis.[7] Moreover, HT-IgM has an immunomodulating activity related to the presence of antibodies neutralizing different proinflammatory cytokines, such as TNF-α and anaphylatoxins (C3a and C5a), and to antiapoptotic action on leukocytes that it exerts.[7,8] Recently, a beneficial effect of HT-IgM administration on microvascular perfusion parameters was demonstrated in humans.[9,10] This is in line with positive effects of IgM on septic encephalopathy and the integrity of the function of the blood–brain barrier[10–12] and could help to protect from sepsis related multiorgan failure.

The use of HT-IgM as adjuvant therapy in patients with bacteremia and/or sepsis is debated because of conflicting results in adult and neonatal settings,[13–19] and there are limited data on their use in pediatric oncohematological patients. We retrospectively analyze the characteristics, outcomes, and risk factors of febrile episodes treated with broad-spectrum antibiotic therapy and HT-IgM in children with hematological oncological diseases.

Materials and Methods

This study was conducted in two Italian pediatric Hematology Oncology Units from January 2011 to March 2019 and focused on the characteristics and the outcome of neutropenic febrile episodes treated with broad-spectrum antibiotics and HT-IgM, administered within 72 hours from fever onset as adjuvant therapy. In these centers, the policy was to start early HT-IgM when the patient was considered by the clinician in charge at higher risk for complicated infections for one of the following risk factors: high fever (>39°C) not responding to antipyretics, hemodynamic instability (hypoxemia <95%, tachypnea, and hypotension), history of previous sepsis, and colonization by Gram-negative antibiotic-resistant bacteria. HT-IgM was administered according to the package indications at the dose of 5 mL (250 mg)/kg/day at maximum infusion rate of 0.4 mL/kg/hour, after premedication with antihistamine. Retrospective data collection was approved by Ethics Committee and was performed according to Italian regulation for the general data protection.

Fever was defined as body temperature ≥38°C not related to allergic reaction, blood hemocomponents infusion, or drug administration; neutropenia was defined as an absolute neutrophil count (ANC) < 1,000/mm^3, severe neutropenia as an ANC <500/mm^3, and profound neutropenia as an ANC <100/mm^3. For the purposes of this study, any modification of initial empiric antibiotic regimen by addition of one or more antibiotic within 5 days was considered as escalation therapy, whereas any reduction of the initial empiric antibiotic regimens within 7 days was considered as deescalation therapy.

The following information were extracted from clinical chart and laboratory database: demographic characteristics (age at febrile episode and gender); type of underlying disease (diagnosis and treatment phase) and HSCT; characteristics of the febrile episode (duration of fever, presence of hypotension [BP < 5th percentile for age] or hypoxemia [SaO_2 <95%], need for admission to intensive care unit (ICU), inotrope administration, concomitant deep-organ infection, and type of organ involvement); microbiological data (type of organism isolated in the blood cultures performed at the diagnosis of the episode); antibiotic resistance profile of the isolated bacteria (extend spectrum β-lactamase [ESBL] or carbapenemase production for Gram-negative bacteria and vancomycin resistance for Gram-positive bacteria); type of empiric antibiotic therapy (regimens for Gram-negative non ESBL-producers, for ESBL-producers, and for carbapenemase-producers); antibiotic prophylaxis, antifungal and antiviral prophylaxis, and therapies; and timing of HT-IgM administration (<24 hours, 24–48 hours, and >48–72 hours from fever onset), dose, and HT-IgM-related side effects.

Descriptive statistics, such as the absolute frequencies and percentages for categorical variables, median values, and ranges for continuous variables, was used to present the data.

Overall survival curve was estimated using the cumulative incidence method, considering the time interval between date of fever onset and date of death, the 90-day follow-up date, or next episode for patients who died, survived without episode, or developed a further episode, respectively. The occurrence of a further episode was considered as competing event. A risk factor analysis for 90-day survival was performed assessing the following factors: age,

gender, underlying disease, HSCT, treatment phase, severity of neutropenia, presence of hypotension, hypoxemia and signs of infection, admission to ICU, use of inotropes, proven bacteremia, escalation or deescalation of the antibiotic therapy, antifungal and antiviral treatment, and timing of HT-IgM administration.

The comparison between groups was performed using Chi-square or Fisher's exact test for categorical variables and by Mann–Whitney test for continuous variables. A p-value of <0.05 was considered statistically significant. All analyses were performed using the statistical software SAS version 9.4 (by SAS Institute Inc., Cary, North Carolina, United States).

Results

During the study period, 103 courses of HT-IgM were administered in 90 patients; of these, 27 courses were excluded from the study because HT-IgM was administered beyond 72 hours from fever onset and 6 courses were excluded because HT-IgM was administered in absence of fever as replacement therapy for hypogammaglobulinemia in patients considered by clinicians at risk for severe infection. Eventually, 70 episodes in 63 patients were eligible for the study. Six patients had multiple episodes: five patients had two episodes and one had three episodes.

The clinical and demographic characteristics of 70 febrile episodes are showed in ►**Table 1**. The most frequent underlying diseases were acute leukemia and non-Hodgkin's lymphoma ($n=46$, 65.7%), followed by other nonmalignant diseases ($n=13$, 18.6%) and other malignancy ($n=11$, 15.7%).

In 26 episodes (37.1%), patient had received an HSCT, allogeneic in 21 patients (80.8%) and autologous in 5 patients (19.2%); the stem cell source was bone marrow in 17 (65.4%), peripheral blood in 6 (23.1%), and cord blood in 3 patients (11.5%).

Forty febrile episodes (57.1%) occurred after the diagnosis of the malignancy, with an equal distribution between induction/reinduction phase ($n=20$, 50%) and other treatment phases ($n=20$, 50%). Twenty-three episodes (32.9%) occurred after HSCT at a median time of 6 days from transplant (range: 2–211). Four episodes (5.7%) occurred during chemotherapy for relapse. In two episodes, the treatment phase was a transfusion-dependence for severe bone marrow aplasia and in one the patient had an ALL in progression after HSCT on palliative care.

The median duration of febrile episodes was 5 days (range: 1–32 days).

Overall, 30 episodes (42.9%) were on antibiotic prophylaxis (ampicillin 15, amoxicillin/clavulanic acid 12, and ciprofloxacin 3), 39 episodes (55.7%) were on antifungal prophylaxis (fluconazole 22, liposomal amphotericin B 7, voriconazole 8, and micafungin 2), and 31 episodes (44.3%) were on antiviral prophylaxis (acyclovir 30 and foscarnet 1).

Moderate neutropenia, severe neutropenia, and profound neutropenia were present in 5 (7.1%), 10 (14.3%), and 52 episodes (74.3%), respectively. Median value of absolute neutrophil count in neutropenic episodes resulted 30/mm^3 (range: 0–990/mm^3).

Table 1 Characteristics of the population

Characteristics of febrile episodes ($n=70$)	n (%)
Age at fever diagnosis (y)	
Median	10.3
Range	0.4–18.0
Underlying disease	
Acute leukemia/non-Hodgkin's lymphoma	46 (65.7)
Solid tumors	11 (15.7)
Nonmalignant diseases	13 (18.6)
Diagnosis	
Acute lymphoblastic leukemia	24 (34.3)
Acute myeloid leukemia	20 (28.6)
Aplastic anemia	8 (11.4)
Osteosarcoma	3 (4.3)
Ewing's sarcoma	3 (4.3)
Atypical teratoid/rhabdoid tumor	2
Familial hemophagocytic lymphohistiocytosis	2
Non-Hodgkin's lymphoma	2
Hodgkin's lymphoma	1
Ganglioneuroblastoma	1
Embryonal rhabdomyosarcoma	1
Beta-thalassemia major	1
Congenital neutropenia	1
Severe combined immunodeficiency	1

Hypotension and hypoxemia were observed in 18 (25.7%) and 15 episodes (21.4%), respectively; 14 episodes (20%) required inotropes while in 14 episodes (20%), the patient was admitted to ICU. Concomitant organ infection was recorded in 31 episodes (44.3%). The most frequent single site of infection was pulmonary ($n=19$, 61.3%), followed by skin and soft tissue ($n=4$, 12.9%), gastrointestinal ($n=1$, 3.2%) and other sites ($n=3$, 9.7%). In four episodes (12.9%), there were infectious signs both at respiratory and gastrointestinal level.

Overall, blood cultures were positive in 28 episodes (40%). The most frequent isolated agents were Gram-negative bacteria ($n=15$, 53.6% as single isolation, $n=19$ as polymicrobial isolation, and 59.4% of total isolated microorganisms), followed by Gram-positive ($n=8$, 28.6% as single isolation, $n=12$ as polymicrobial isolation, and 37.5% of total isolated microorganisms). In four episodes (14.3%), blood cultures were polymicrobial (two episodes with one Gram-negative and one Gram-positive, one episode with two Gram-negative, and one episode with two Gram-positive), whereas one episode (3.6%) was associated with candidemia. ►**Table 2** lists the organisms isolated.

In five episodes, the isolated microorganism was a Gram-negative ESBL-producer strain. Neither Gram-negative carbapenemase-producers nor Gram-positive vancomycin-

Table 2 Microorganisms isolated from initial blood cultures

Isolated microorganisms ($n = 32$)	
Bacteria	31 (96.9)
Gram-negative	19 (59.4)
Escherichia coli	7 (21.9)
Pseudomonas aeruginosa	6 (18.8)
Klebsiella pneumoniae	4 (12.5)
Acinetobacter spp.	1
Enterobacter cloacae	1
Gram-positive	12 (37.5)
Streptococcus mitis	4 (12.5)
Staphylococcus epidermidis	2
Staphylococcus haemolyticus	2
Staphylococcus hominis	1
Streptococcus salivarius	1
Enterococcus faecium	1
Rothia spp.	1
Fungi	1
Candida parapsilosis	1

resistant strains were isolated. Rate of Gram-negative ESBL-producers bacteria resulted 26.3%.

►**Table 3** shows the antibiotic therapy that lasted for a median of 14 days (range: 5–49 days). Most episodes ($n = 68$, 97.1%) were treated with a combined antibiotic therapy.

In 26 episodes (37.1%), the empiric antibiotic therapy was escalated within 5 days, mainly by substitution of broad-spectrum penicillin or third/fourth-generation cephalosporin with meropenem ($n = 22$) or adding metronidazole ($n = 4$). In five episodes (7.1%), a deescalation strategy was used within 7 days from antibiotic onset through the withdrawal of vancomycin ($n = 3$), teicoplanin and amikacin ($n = 1$), and ceftazidime and amikacin ($n = 1$).

Moreover, an empiric antifungal therapy was started in 38 febrile episodes (54.3%) between 5 and 7 days after the beginning of fever by adding liposomal amphotericin B ($n = 25$), echinocandins ($n = 9$), or voriconazole ($n = 4$). An antiviral therapy was started during the course of febrile episode in six HSCT patients (8.6%) for cytomegalovirus-DNAemia ($n = 4$, ganciclovir) and adenovirus-DNAemia ($n = 2$, brincidofovir).

HT-IgM was started within 24 hours from fever onset in 40 febrile episodes (57.1%), between 24 and 48 hours in 24 (34.3%) and between 48 and 72 hours in 6 (8.6%). Median time between fever onset and HT-IgM administration was 1 day (range: 0–3 days). In 58 episodes (82.9%) it was used the standard dosage of 5 mL (250 mg)/kg/day for 3 consecutive days, whereas in 12 (17.1%), a dosage of 3 to 4 mL/kg/day was administered. HT-IgM-related allergic reactions occurred in three febrile episodes (4.3%). One patient presented cough, vomit, and widespread skin marbling shortly after the start of the first infusion; one patient had mild dyspnea during the second infusion which was completed, and generalized itching and diffuse crampy pains during the infusion of day third which was withdrawn; one patient presented an erythematosus rush at hands and mouth after the start of the first infusion. The two more severe allergic reactions were treated with systemic corticosteroids and the withdrawal of HT-IgM infusion, while the mild skin reaction without systemic signs was treated only by repeating antihistamine.

Death occurred in nine patients within 90 days from fever onset. Six patients died of septic shock and multiorgan failure (4 within day 30 and 2 after day 30, at days 32 and 37 from fever onset); all but one had a documented bacteremia: Gram-negative in two patients (one *Pseudomonas aeruginosa* and one *Escherichia coli* ESBL-producer), Gram-positive in one (*Staphylococcus haemolyticus*) and polymicrobial in two (one *E. coli* ESBL-producer and *Enterococcus faecium* and one *Klebsiella pneumoniae* and *P. aeruginosa*). The remaining three patients died of cytomegalovirus (CMV) pneumonia and encephalitis ($n = 1$, at day 48 from fever onset), cerebral hemorrhage ($n = 1$, at day 66), and pulmonary aspergillosis and chronic GvHD ($n = 1$, at day 68). The median time from the onset of fever to death was 32 days (range: 5–68 days). The 90-day infection-attributable mortality was 8.6%. The 30-day overall survival (OS) was 94.3% (confidence interval [CI]: 87.1–98.2%) and 90-day OS was 87.1% (CI: 78.1–93.7%; ►**Fig. 1**).

Table 3 Antibiotic therapy

First-line antibiotic therapy ($n = 70$)	*n* (%)
Monotherapy	2
Cefepime	1
Piperacillin/tazobactam	1
Combination therapy	68 (97.1)
Amikacin + ceftazidime (or cefepime or piperacillin/tazobactam or ampicillin/sulbactam or ceftriaxone or cefotaxime) + vancomycin (or teicoplanin) without or with metronidazole (6, 8.5%)	44 (62.7)
Amikacin + meropenem + vancomycin (or teicoplanin) without or with metronidazole (3, 4.3%)	14 (20)
Meropenem + vancomycin (or teicoplanin) Without or with metronidazole (4, 5.8%)	7 (10.1)
Amikacin + ceftazidime (or piperacillin/tazobactam)	3 (4.3)

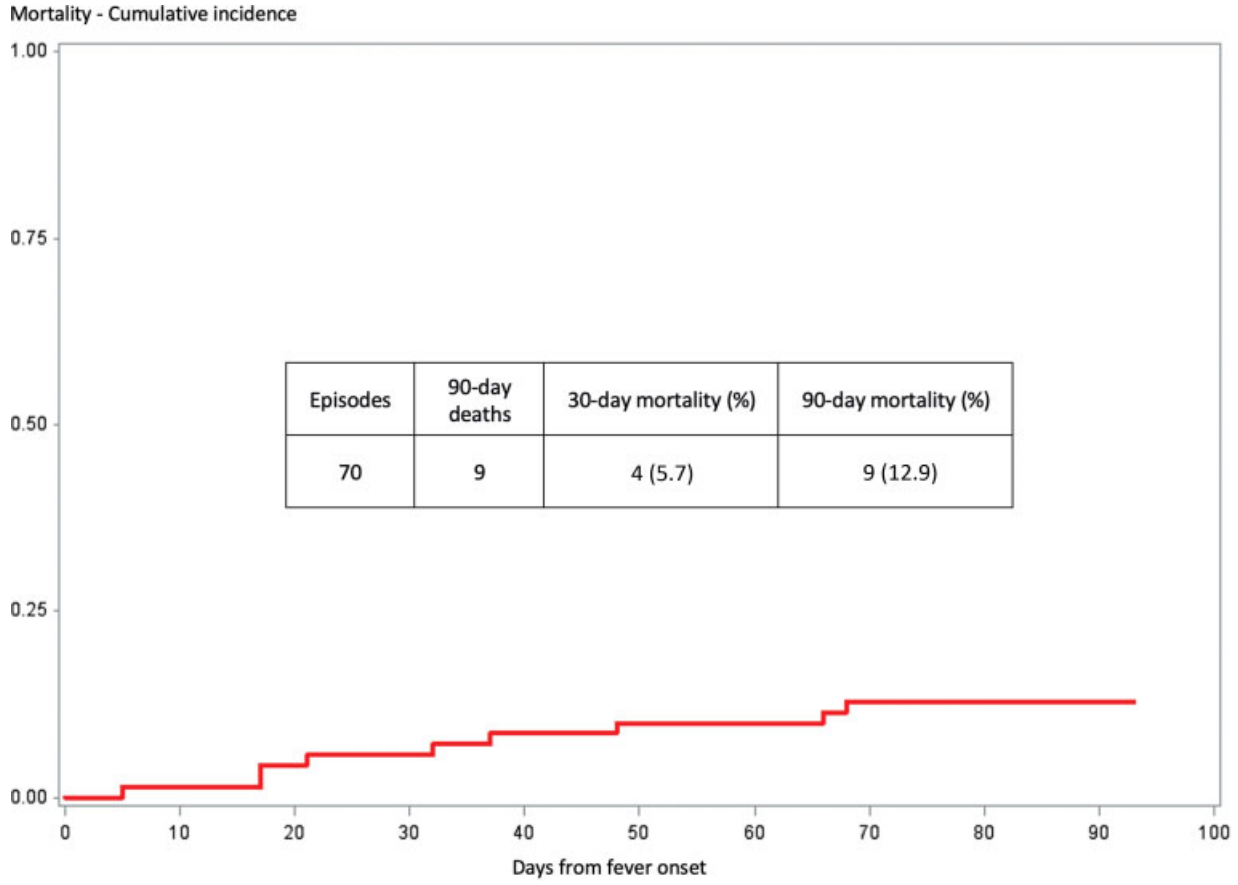

Fig. 1 The 90-day mortality is showed.

In univariate analysis, the factors associated significantly with a lower 90-day OS were related to the severity of the infection: the presence of hypotension or hypoxemia, need for the admission to ICU, use of inotropes, deep-organ involvement, and escalation of empiric antibiotic therapy within five days (►**Table 4**).

Discussion

The use of polyclonal HT-IgM in pediatric oncohematological patients is based on the rationale of a severe impairment of both innate and acquired immunity which makes them highly vulnerable to infections. In this condition, antibiotic therapies, even if they include broad-spectrum and bactericidal drugs, may be only partially effective. HT-IgM provides one of the key components of innate immunity, that is, the natural IgM highly efficient in opsonizing pathogens and neutralizing toxins, and IgG specific for a wide range of antigens, reflecting the immunization of the several plasma donors. Moreover, the antiapoptotic effect of IVIg on leucocytes may contribute to support immune system and the benefits on microcirculation could protect tissues and organs from septic damage. Considering that polyclonal HT-IgM administration is not routinely used in the treatment of neutropenic febrile episodes in children with cancer,[2] its use in combination with antibiotics may contribute to improve the response rate through a synergic action and to reduce mortality in patients with severe bacterial infections.

In this study, we presented the largest series of febrile episodes treated with HT-IgM in addition to antibiotic therapy in pediatric oncohematological patients. First of all, we observed that HT-IgM administration was well tolerated, allergic reactions being recorded only in three episodes (4%), and causing the withdrawal of HT-IgM only in two of them.

Fifty-seven percent of the febrile episodes occurred during chemotherapy after a first diagnosis of malignancy. The distribution between more and less intensive chemotherapy phases (induction/reinduction vs. others) was equal (50 vs. 50%). The mechanisms that promote bacterial infections in early or late chemotherapy phases are the same, such as severe neutropenia, mucositis, lymphopenia, and hypogammaglobulinemia. The same factors are important in determining bacterial complication in the early preengraftment period after HSCT. In this study, 33% of the episodes occurred after HSCT at a median time of 6 days.

Importantly, bacteremia was documented in 40% of episodes and the most frequent isolated agents were Gram-negative bacteria, 26% of them being ESBL-producers. The increase of antibiotic resistance is an emerging problem of the last years. Our rate is higher than that of 18% reported in a survey of the Fourth European Conference on Infections in Leukemia Group (ECIL-4)[20] and is more in line with the

Table 4 Univariate analysis of 90-day survival risk factors

		Survivors ($n = 61$) *n* (%)	Deceased ($n = 9$) *n* (%)	*p*-Value
Gender	F	29 (96.7)	1 (3.3)	0.07
	M	32 (80.0)	8 (20.0)	
Age (y)	Median	10.0	13.6	0.17
	Range	0.4–19.0	0.5–22.0	
Underlying disease	AL/NHL	41 (89.1)	5 (10.9)	0.48
	Other	20 (83.3)	4 (16.7)	
Presence of HSCT	No	40 (90.9)	4 (9.1)	0.28
	Yes	21 (80.8)	5 (19.2)	
Treatment phase[a]	CT	37 (92.5)	3 (7.5)	0.41
	HSCT	19 (82.6)	4 (17.4)	
	CT after relapse	4 (100.0)	0 (0.0)	
Severe neutropenia (ANC $<500/mm^3$)	No	5 (62.5)	3 (37.5)	0.06
	Yes	56 (90.3)	6 (9.7)	
Hypotension	No	48 (92.3)	4 (7.7)	0.04
	Yes	13 (72.2)	5 (27.8)	
Hypoxemia	No	51 (92.7)	4 (7.3)	0.02
	Yes	10 (66.7)	5 (33.3)	
Admission to ICU	No	53 (94.6)	3 (5.4)	0.001
	Yes	8 (57.1)	6 (42.9)	
Use of inotropes	No	53 (94.6)	3 (5.4)	0.001
	Yes	8 (57.1)	6 (42.9)	
Deep-organ involvement	No	39 (100.0)	0 (0.0)	0.0003
	Yes	22 (71.0)	9 (29.0)	
Positivity of blood culture	No	39 (92.9)	3 (7.1)	0.14
	Yes	22 (78.6)	6 (21.4)	
Escalation of antibiotic therapy within 5 days	No	41 (95.3)	2 (4.7)	0.02
	Yes	20 (74.1)	7 (25.9)	
Deescalation of antibiotic therapy within 7 days	No	57 (87.7)	8 (12.3)	0.5
	Yes	4 (80.0)	1 (20.0)	
Antifungal therapy	No	29 (90.6)	3 (9.4)	0.49
	Yes	32 (84.2)	6 (15.8)	
Antiviral therapy	No	57 (89.1)	7 (10.9)	0.17
	Yes	4 (66.7)	2 (33.3)	
Timing of HT-IgM administration	Within 24 hours	33 (82.5)	7 (17.5)	0.28
	Between 24and 72 hours	28 (93.3)	2 (6.7)	

Abbreviations: AL, acute leukemia; ANC, absolute neutrophil count; CT, computed tomography; F, female; HSCT, hematopoietic stem cell transplantation; HT, high-titer; ICU, intensive care unit; Ig, immunoglobulin; M, male; NHL, non-Hodgkin lymphoma.
[a]Three patients neither in chemotherapy nor in transplant phases were not included in the analysis.

results of an intercontinental study on antibiotic resistance rates among Gram-negative bacteremia in HSCT patients that ranged from 25 to 49%.[21]

Only two febrile episodes were treated with an antibiotic monotherapy, whereas in the great majority of cases, it was used a broad-spectrum antibiotic combination which included an aminoglycoside and/or a glycopeptide in addition to the cephalosporin, ureidopenicillin, or carbapenem to obtain a broad coverage. This is in line with the severity of septic episode, as determined by the physician in charge at the start of the episode, and the recommendations to use empirically a broad antibiotic coverage in centers with a high incidence

of multidrug-resistant bacteria in patients hemodynamically unstable or with a previous history of sepsis or colonized with antibiotic-resistant bacteria.[2,22,23] Interestingly, a carbapenem-based combination of antibiotics was used in 30% of episodes and superimposable to the rate of ESBL-producers bacteria isolated from the blood. We can infer that the knowledge of individual risk factors, colonization status, and infectious history allowed to personalize the empirical antibiotic treatment. Noteworthy, the initial empiric antibiotic regimen was modified within 5 days from its start in 37% of episodes mainly through the introduction of meropenem, to cover Gram-negative ESBL-producers. This reflects the clinical management of the febrile episode according to the persistence of fever, the lack of improvement of other signs and symptoms of infection, the isolation of a Gram-negative resistant strain.[2,22,23]

On the other hand, a deescalation of antibiotic therapy was performed only in 7% of episodes, mostly through the suspension of vancomycin after the isolation from blood of Gram-negative bacteria. This testifies the difficulties for the clinicians to narrow the spectrum of empirical antibiotic treatment in case of no rapid defervescence or no rapid resolution of severe neutropenia or the lack bacterial isolation. Besides, an empiric antifungal therapy, mainly with liposomal amphotericin B, was started in 54% of episodes, as suggested by guidelines in case of persistence of fever.[2,22]

Overall mortality due to infectious complications in oncohematological children is reported lower than that observed in this study. In fact, the 5-year cumulative infection-related mortality rate in pediatric patients with acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML) resulted 2.4[24] and 11%,[25] respectively, and overall mortality rate for febrile neutropenia in children with cancer was reported as 0.75%, with a significantly greater mortality associated with sepsis, pneumonia, meningitis, and mycosis.[26] Importantly, Gram-negative bacteria were prevalent in deceased patients and one-third of these were ESBL-producers. These results are in line with the higher mortality of sepsis caused by Gram-negative bacteria and with the higher difficulty in treatment of infections in which are involved resistant strains.[27,28]

In this study, focuse on patients was considered at higher risk of severe infection complications and infectious death. The 90-day mortality by sepsis-related organ failure and septic shock was 8.6% which is inferior to percentages reported in other studies. In a recent retrospective study, the mortality rate due to severe sepsis in pediatric oncohematological patients resulted 23%,[29] and previous studies reported mortality rates between 16 and 48%.[30–32]

The impact of the severity of infections on risk of death is confirmed by univariate analysis, where the factors significantly associated with 90-day mortality were the presence of hypotension, hypoxemia, localized-organ-infection signs, the admission to ICU, the administration of inotropes and the need for escalation of empiric antibiotic therapy.

Due to the retrospective nature of our study, we cannot assess if the use of HT-IgM has had a role in determining a better outcome, but our experience may serve a basis for future prospective studies. Our results are consistent with those reported by Carlone et al who found that the adjuvant therapy with HT-IgM in pediatric HSCT patients was associated with a significant reduction of infection-related mortality rate.[33] Furthermore, they also found a decrease in days of fever, number of antibiotics used to control infections, number of antibiotic therapy changes, and a lower incidence of relapsing febrile episodes during a 6-month follow-up.[33] A randomized controlled trial, performed in a pediatric intensive care setting, showed that the use of polyclonal HT-IgM as an adjuvant in the management of sepsis led to a significant reduction in mortality, length of stay, and occurrence of complications, especially disseminated intravascular coagulation.[34]

Despite some limitations, such as the retrospective design, the limited number of analyzed cases and the lack of control groups, this study suggests that the use of HT-IgM deserves further prospective investigation.

Conclusion

We observed that the adjuvant treatment of febrile episodes with HT-IgM in pediatric oncohematological patients is feasible and well tolerated and that the outcome, in terms of infection-related mortality, seems to be more favorable compared with other studies. The use of HT-IgM in this population is based on the rationale of a severe impairment of innate and adaptative immunity, situation in which the antibiotics could not be total effective because of the lack of a concomitant efficient immune response. Therefore, HT-IgM could be helpful in treating infections, providing components of both innate and specific immunity. The present study would represent a starting point, indeed future prospective randomized studies are necessary to determine the real benefit of this strategy for these children.

Conflict of Interest
None declared.

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