ORIGINAL ARTICLE

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Febrile events in acute lymphoblastic leukemia: a prospective observational multicentric SEIFEM study (SEIFEM-2012/B ALL)

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Abstract

The purpose of the present study is to estimate the current incidence of febrile events (FEs) and infectious episodes in acute lymphoblastic leukemia (ALL) and evaluate the outcome. We analyzed data on all FEs in a cohort of patients affected by ALL admitted to 20 Italian hematologic centers during 21 months of observation from April 1, 2012 to December 31, 2013. Data about treatment phase, steroids, neutropenia, type and site of infection, and outcome of infection were collected. The population comprehended 271 ALL adult patients. Median age was 46 years old (range 19–75), M/F 1.1:1. We collected 179 FEs occurring during 395 different phases of treatment in 127 patients (45.3% incidence): remission induction treatment 53.1%, consolidation/maintenance 35.7%, treatment for a first or second relapse 44.3%, and refractory disease 85.7%. The incidence of FUO (fever of unknown origin) was 55/395 (13.9%). In the remaining cases, bacteria caused 92 FEs (23.2%), fungi 17 (4.3%), viruses 5 (1%). Mixed infections occurred in 10 cases mainly fungal+bacterial (9/10 cases). Neutropenia was mostly present at onset of FE

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(89.9% of FEs). Mortality rate was 11.7% (21/179) while 16 deaths occurred with evidence of infection (8.9%). Age > 60 years, neutropenia, poor performance status, steroids, refractory disease, and mixed infections significantly correlated with infection-related mortality. A statistically significant association with mortality was observed also for pulmonary localization and bacteremia. Our study describes the real-life epidemiological scenario of infections in ALL and identifies a subset of patients who are at higher risk for infection-related mortality.

Keywords Acute lymphoblastic leukemia · Febrile events · Epidemiology · Infections

Introduction

Febrile events (FEs) and infectious complications often make hematologic malignancies difficult to treat.

Several studies have defined the diseases and phases of treatment at higher risk for infection [1–6]. Infectious risk in acute lymphoblastic leukemia (ALL) has always been considered low but current epidemiology of FEs in such patients is not yet well elucidated. Most data regarding infections are derived from case reports or studies of specific subpopulations of ALL patients or pathogens (pediatric patients' cohorts, incidence after specific treatments) [7–13]. Moreover, bone marrow involvement and chemotherapy-associated toxicities contribute to infection risks associated with ALL. Particularly, higher doses of anthracycline and antimetabolite-based chemotherapy regimens are now frequently administered for longer periods. Steroids are also a cornerstone of the treatment of lymphoproliferative diseases, but have pleiotropic cumulative immunosuppressive and catabolic effects. Therefore, infection-related risks in the ALL population relative to other high-risk malignancies may be underestimated.

The aim of the present study was to investigate the current incidence of FEs and the infectious risk in ALL patients and to evaluate the outcome of such complications.

Patients and methods

Data collection

We prospectively collected data about FEs occurring in ALL patients in any phase of disease followed in Italian hematology centers participating to the study within the SEIFEM (Sorveglianza Epidemiologica Infezioni Fungine in EMatologia) group from April 1, 2012 until December 31, 2013. The study was approved by the ethics committee of each center. Case report forms were compiled and data concerning hematologic risk (immunophenotype, white blood cell count, cytogenetics, karyotype), treatment (phase of disease, chemotherapy regimen, previous hematopoietic stem cell transplant procedures), risk factors for infection (neutropenia, placement of CVC, positive surveillance swabs, use of antimicrobial prophylaxis and steroids, presence of comorbidities), characteristics of FE (signs and symptoms, etiology, radiologic abnormalities, treatment of infection) were analyzed. Patients that developed FEs during hematopoietic stem cell transplantation (HSCT) procedures (autologous or allogeneic) were withdrawn from the study so as not to bias the results as these practices are recognized as a higher risk for infectious complications. Similarly, patients receiving tyrosine-kinase inhibitors (TKI) monotherapy were excluded. Informed consent was obtained from all individual participants included in the study.

All the patients were treated according to NILG 10/07 [14] or GIMEMA protocols for ALL [15]. GMALL protocols were also used for T lineage ALL [16].

The diagnostic work-up at onset of fever did not significantly differ among the centers and included the use of microbiological data, CT scans, X-rays, bronchoalveolar lavage, and histological examination.

The outcome of infection was evaluated at 30 days from the first fever onset.

Definitions

Performance status (PS) was graded according to the Eastern Cooperative Oncology Group Scale [17].

Neutropenia was defined as an absolute neutrophil count < 500 cells/mm^3 or < 1000 cells/mm^3 with a prediction of decline to < 500 cells/mm^3.

Fever was defined according to IDSA guidelines as a single increase of blood temperature to 38.3 °C or either ≥ 38 °C for 1 h or more [18]. Hypothermia (< 35 °C) was considered as possible sign of infection and thus investigated.

Fever of unknown origin (FUO) was described when fever occurred in the absence of a specific infectious focus detected by physical, radiological, or microbiological examination.

Bloodstream infections (BSI) were defined by the presence of one or more positive blood cultures together with clinical signs. In case of skin contaminants, a minimum of two positive blood cultures was necessary. When the pathogen was only traced in blood, we defined it primarily (e.g., catheter-related BSI included). Secondary BSI was defined as the detection in bloodstream of an organism causing infection in another body site.

Invasive fungal infections were defined according to the European Organization for Research and Treatment of Cancer/Mycoses Study Group (MSG) [19].

Steroid treatment was identified with administration of prednisone/prednisolone for at least 10 days at a dosage of 25 mg minimum (or equivalent dosage).

We considered mortality due to infection when patients died with clinical evidence and/or microbiological signs of infection.

Statistical analysis

Number and percentage were calculated for demographic data, FEs, treatment data and for characteristics of patient at FE onset.

Number and percentage of FEs and related deaths were reported by identified agent and by phase of treatment.

Univariate and multivariable logistic regression were used to investigate the association between death and patient risk factors. A multivariate logistic regression model was used to explore independent risk factors for infection-associated mortality. Risk factors associated with mortality were reported as odds ratios (ORs) and 95% confidence intervals (CIs). Statistical analysis was carried out using SAS software (version 9.2; SAS Institute, Milan, Italy). A two-sided P value of less than 0.05 was considered statistically significant.

Results

Characteristics of patients and distribution of FEs

Over the observation period, 20 Italian participating centers enrolled all patients diagnosed with ALL at any phase of disease, except HSCT procedures. We screened 271 patients. The population was predominately male (51.1%) with a median age of 46 years (range 19–75). A total of 395 treatment phases were recorded in the 271 patients. The characteristics of the 127 patients that developed a FE are shown in Table 1.

We registered 179 FEs with an incidence of 45.3% (179/ 395). The distribution per phase of treatment was the following: 53.1% (84/158) during remission induction treatment, 35.7% during consolidation/maintenance (54/151), 44.3% during treatment for a first or second relapse (35/79), and 85.7% for refractory disease (6/7).

FEs occurred after a median of 7 days after the end of chemotherapy (range 1–100) and mostly during neutropenia [61, 89.9%—on average after 6 days (range 1–28)]. A CVC was placed in 140 cases (78.2%). Patients were receiving corticosteroids in 123 cases (68.7%) of FEs. The distribution of different type of FEs per phase of treatment is shown in Table 2. As shown, the incidence did not differ significantly

Table 1 Demographic characteristics of patients ($n = 127$)

	No. (%)
Male sex/female sex	65/62 (51.1/48.9)
Median age, years (range)	46 (19–75)
Lineage	
B	103 (81.1)
T	24 (18.9)
Philadelphia chromosome	29 (22.8)
Characteristics of patients presenting FEs, $n = 179$ total, no (%)	
Phase of treatment	
• Induction	84 (46.9)
• Consolidation/maintenance	54 (30.2)
• Relapse/refractory	41 (22.9)
Conventional chemotherapy	159 (88.8)
Conventional chemotherapy+TKI	20 (11.2)
Characteristics of patients at FE onset, $n = 179$ FEs, no (%)	
Hypercytemia (WBC > 30.000)	59 (32.9)
CNS or other sanctuary site	17 (9.49)
HEPA filters rooms	91 (50.8)
Previous allogeneic HSCT	6 (3.3)
Neutropenia (PMN < 500)	161 (89.9)
PMN < 100 for more than 10 days	124 (69.2)
CVC	140 (78.2)
Steroids	123 (68.7)
Diabetes	18 (10.1)
CRI*	5 (2.7)
Hepatopathy	
HBV/HCV	8 (4.4)
Other (NASH**, non-viral hepatitis)	12 (6.7)

*Chronic renal insufficiency

**Non-alcoholic steatosis hepatitis

during the different phases of treatment except for fungal and mixed infections.

Fever of unknown origin

The incidence of FUO was 13.9% (55/395), representing 30.7% of all FEs and did not differ significantly according to phase of treatment from 15.8% (25/158) at remission induction, 13.9% (21/151) during consolidation/maintenance, 10.1% (8/79) during relapse, and 14.2% (1/7) during refractory disease.

Bacterial infections

Quinolone antibiotic prophylaxis was administered in 44.6% of FEs.

Table 2 Microbiologically documented infections according to phase of treatment

Phases of treatment (no. febrile episodes)	Bacterial (%)	Fungal (%)	Viral (%)	Mixed (%)	FUO (%)
Induction (84/158)	44 (27.8)	9 (5.6)	2 (1.2)	4 (2.5)	25 (15.8)
Consolidation/maintenance (54/151)	28 (18.5)	2 (1.3)	3 (1.9)	/	21 (13.9)
Relapse (35/79)	18 (22.7)	4 (5.1)	/	5 (6.3)	8 (10.1)
Refractory (6/7)	2 (28.5)	2 (28.5)	/	1 (14.2)	1 (14.2)

The incidence of bacterial infections according to phase of treatment was 27.8% (44/158) during remission induction, 18.5% (28/151) during consolidation/maintenance, 22.7% (18/79) during relapse, and 28.5% (2/7) during refractory disease.

For FEs with a bacterial etiology, 77 microbiologically proven bacterial infections were registered during 395 phases of treatment, with an overall incidence of 19.4%. The incidence was 22% if mixed bacterial infections are included; bacteria were thus involved in 48.6% of all FEs.

Most documented infections presented as a primary bloodstream infections (61/77, 79.3%), followed by 5 primary pneumonias (5/77, 6.4%), 7 (7/77, 9.1%) infections of genitourinary tract, and 4 (4/77, 5.2%) infections of gastrointestinal tract.

In 59 cases, FEs were caused by a single bacterium, predominantly Gram-negative (38/59, 64.4%). In 18 cases of bacterial FEs, two or more bacteria were isolated. Both Gram-positive and Gram-negative pathogens were isolates in 12 cases, whereas two of more Gram negative were isolates in 5 cases, and one patient had two Gram-positive species.

No clinical or radiological signs of infection or isolate were recovered in 15 FEs. Because these FEs responded to empiric antimicrobial treatment, we classified these cases as clinically documented infection, with possible bacterial origin.

Fungal infections

Seventeen cases of invasive fungal disease (IFD) were observed during 395 cycles of treatment (4.3% overall incidence). When EORTC/MSG standardized diagnostic criteria are applied, 6 cases (35.3% IFDs) were proven, 8 cases (47.1%) were probable IFD, and 3 cases (17.6%) were possible IFD. As for the proven/probable IFDs, molds were isolated in 9 cases (all *Aspergillus spp*, 2.2%), while yeasts were isolated in 5 cases (all *Candida spp*, 1%). Molds caused 8 cases of pneumonia and one case of sino-nasal infection, while yeasts were associated with three episodes of candidemia and two cases of chronic disseminated candidiasis.

Co-infections were present in 10 IFD episodes, including 9 cases with bacteria, and 1 case with both bacteria and virus. Considering these mixed infections, the combined incidence of fungal infection was 6.8%.

Antifungal prophylaxis during remission induction chemotherapy was employed in 37 cases (in 4 cases with posaconazole, in 1 case with itraconazole, in 19 cases with fluconazole, in 13 cases with liposomal amphotericin B). Prophylaxis against *P. jirovecii* was used in 32.9 % of patients.

The IFD incidence per phase of treatment was 5.6% for induction phase (9/158), 5.1% for relapse phase (4/79), 1.3% (2/151) for consolidation/maintenance, and 28.5% (2/7) for refractory disease.

Viral infections

We registered four viral infections (incidence 1%). One patient developed viral infections during induction remission treatment, and three patients during consolidation/maintenance. *Cytomegalovirus* was detected by polymerase chain reaction (PCR) in 3 cases and *H1N1* in one case. In 50% cases, the patient had received antiviral prophylaxis with acyclovir or valacyclovir.

Mixed infections

Mixed infections occurred in 10 cases (incidence of 2.5%). Bacterial+fungal infections were the most common (9 cases) with a predominance of Gram-negatives (8/10). Bacterial+fungal+viral infection occurred in 1 case. In 5 cases, the patient had a relapsing disease, in 4 cases underwent remission induction treatment and in1 case during refractory disease.

Mortality

We evaluated mortality within 30 days from the onset of FE. Twenty-one deaths occurred of which 16/21 (76.1%) with evidence of infection (Table 3). The overall mortality rate was 7.7% (21/271). The mortality rate in FE population was 12.5% (16/127). Considering febrile events, an unfavorable outcome occurred in 8.9% cases (16/179) (death "with infection").

The highest rates of infection-associated mortality occurred in patients with refractory ALL (50%) with mixed infection (30%) (Table 3). Mortality rates did not significantly differ between patients with Gram-positive versus Gram-negative infections.

Table 3 Mortality with evidence of infection (16 pts)

	Deaths per febrile episode—no (%)
Agent	
Bacteria	8/92 (8.6)
Fungi	2/17 (11.7)
Virus	1/5 (20.0)
Mixed infections	3/10 (30.0)
FUO	2/55 (3.6)
Phase of treatment	
Remission induction treatment	4/84 (4.7)
Consolidation/maintenance	2/54 (3.7)
Relapse	7/35 (20.0)
Refractory disease	3/6 (50.0)

Risk factors for mortality

In univariate logistic regression age ($p = 0.0056$), the presence of CNS involvement at diagnosis of ALL ($p = 0.0015$), ECOG score > 1 at FE onset ($p = 0.02$), uncontrolled disease ($p \leq 0.001$), and mixed infection ($p = 0.0001$) were significantly associated with death (Table 4). On the contrary, a disease during first induction ($p = 0.006$) or in remission ($p = 0.02$) were associated with reduced odds of death.

Results were confirmed in multivariable analysis adjusted for patient age. Specifically, the presence of CNS/sanctuary site at the time of ALL diagnosis (OR 4.05, 3.31–4.96; $p < 0.001$), relapse or refractory ALL (OR 11.92, 9.27–15.32; $p < 0.001$), mixed infection (OR 3.87, 2.99–5.00, $p < 0.001$), pneumonia (OR 1.96, 1.62–2.36, $p < 0.001$), and possible exposure to high-dose steroids (OR 3.39, 2.77–4.16; $p < 0.001$) were associated with overall mortality. On the other hand, infection at the time of first induction chemotherapy was associated with a lower risk of death (OR 0.76, 95% CI 0.58–0.99, $p = 0.04$).

Deep and prolonged neutropenia prior to infection diagnosis was associated with an exponential risk of predicted probability of death, especially after 20 consecutive days (Fig. 1).

A separate logistic regression was also conducted for the 18 deaths occurred in the presence of infection. Univariate analysis confirmed the significance for age ($p < 0.001$), use of steroids (< 0.001), bacteremia ($p < 0.001$), and pneumonia ($p < 0.001$). A better PS was found protective (ECOG score < 1 a FE onset, $p < 0.001$).

Discussion

Hematologic malignancies are often burdened with infectious complications. In recent years, several studies have been conducted to estimate these events. However, they often concentrate on specific pathogens (e.g., bacteremia or fungal

Table 4 Risk factors for overall mortality (univariate and multivariable analysis)

Variable	Univariate analysis		Multivariable analysis[a]	
	OR (95% CI)	p value	OR (95% CI)	p value
Age (≥ 60)	3.63 (1.21–10.43)	0.0056	10.18 (8.11–12.78)	< 0.001
Lineage (B vs T)	0.95 (0.28–4.19)	0.93		
PH chromosome	1.33 (0.35–4.20)	0.60		
CNS/sanctuaries involvement at ALL diagnosis	5.34 (1.39–18.41)	0.0015	4.05 (3.31–4.96)	< 0.001
ECOG (2–4 vs 0–1)	2.85 (1.01–8.02)	0.02		
First induction	0.22 (0.05–0.75)	0.006	0.76 (0.58–0.99)	0.04
Consolidation/maintenance	0.21 (0.02–0.95)	0.02		
Relapse/refractory	12.69 (4.10–42.94)	< 0.0001	11.92 (9.27–15.32)	< 0.001
Steroids	2.08 (0.63–8.91)	0.19	3.39 (2.77–4.16)	< 0.001
CVC	0.87 (0.28–3.28)	0.81		
FUO	0.33 (0.06–1.24)	0.08		
Clinically documented infection	0.47 (0.01–3.45)	0.47		
Bacterial infection	0.79 (0.26–2.20)	0.62		
Fungal infection	1.71 (0.28–7.01)	0.42		
Viral infection	2.58 (0.04–33.74)	0.40		
Mixed infection	9.56 (1.93–45.50)	0.0001	3.87 (2.99–5.00)	< 0.001
Pneumonia (primary site and/or secondary)	2.16 (0.71–6.14)	0.10	1.96 (1.62–2.36)	< 0.001
Bacteremia (primary site and/or secondary)	1.57 (0.56–4.39)	0.32		

[a] Adjusted for age
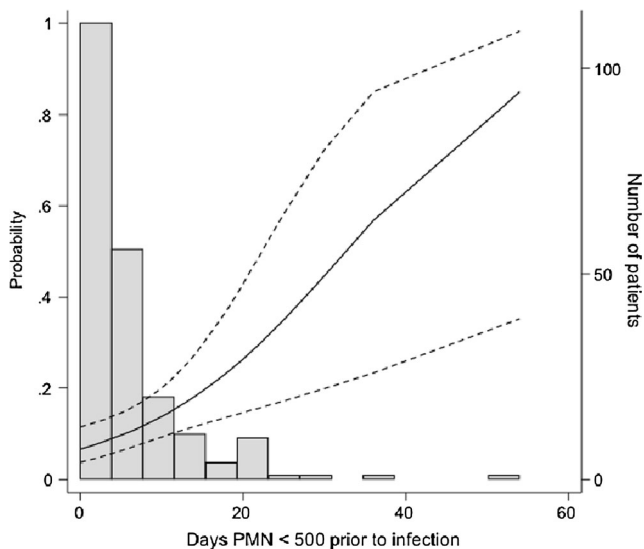
Fig. 1 Relationship between probability of all-cause mortality and duration of severe neutropenia prior to infection. The solid line represents the probability estimate death = exp(− 2.640 + 0.0809 × days PMN < 500)/(1 + exp(− 2.640 + 0.0809 × days PMN < 500)). Dashed lines are the 95% confidence intervals. Bars represent the number of patients per duration of neutropenia before infection

infections) or regard specific malignancies and treatment courses (e.g. acute myeloid leukemia during remission induction, HSCT) known to be at higher risk for infection [2, 5, 20–25]. Investigations concerning acute lymphoproliferative disorders are acquiring interest but remain still scarce [26].

In 2004, Offidani et al. retrospectively described the epidemiology of infectious complications in adult ALL patients in a monocentric experience [27]. However, the incidence and nature of such events might have changed in the recent years; therefore, our purpose was to describe the current incidence and outcome of infectious complications in ALL in a large cohort that included different phases and types of treatment and to define a risk profile for these patients. The strength of our study is that all patients were enrolled and followed prospectively during the same time period. We purposely excluded FEs occurring in ALL patients undergoing HSCT (autologous/allogeneic) to obtain a clearer picture of infection risk specific to ALL and its management. Infection risk in the ALL patients following HSCT is dominated by transplant related factors such as graft versus host disease (GVHD) involving the GI tract and prolonged marrow aplasia [28, 29]. On this basis, the impact of infectious agents may be higher during such procedure [30, 31]. Likewise, patients receiving TKI monotherapy were excluded in order not to bias our results.

To our knowledge, data about the incidence of FEs in different phases of treatment for ALL have not yet been elucidated. The previous HEMA chart study reported an incidence of febrile events during remission induction treatment for ALL of 32.6% [1]. In our cohort, the incidence during induction treatment was 53.1% and was similar during re-induction

for relapsed patients (44.3%). As expected, refractory patients had the highest incidence of FEs (85.7%), whereas patients in complete remission the lowest (35.7%). However, this quite noteworthy rate, if compared to the one observed in acute myeloid leukemia during consolidation/maintenance, could be explained considering the highly aggressive chemotherapy regimens even during consolidation or maintenance that are currently used for ALL.

Despite the most improved diagnostic procedures, FUO represents a considerable part of FEs in the population in study. There is still controversy if FUO are undetected infectious episodes or phenomena related to the hematologic malignancy or to its treatment. Given the pathophysiology of ALL that is characterized by a notable inflammatory burden, FUOs may be related to ALL itself and/or it could represent treatment-related fever. In any case, mortality rates registered during FUO were low (3.6%). Probably prompt empiric prescription of anti-infective drugs at fever onset might play a role in the reduction of mortality rates for FE misdiagnosed as FUO that are actually sustained by microorganisms. In our cohort, more than one third of FEs with a microbiological diagnosis was caused by bacteria (about 74% of the non-FUO events). Gram-negative bacteria accounted for the majority of documented infections, as opposed the predominance of Gram-positive pathogens reported in epidemiological studies published in the 1990s and early 2000 [32, 33]. However, no difference in terms of mortality was found. In fact, bacterial infections seem to have little impact on overall and infection mortality, as compared to IFI and mixed infections. The overall scarce utilization of quinolones prophylaxis may be supported by the short period of neutropenia that patients undergo during consolidation/maintenance therapy. In fact, the wider use was made during remission induction treatment. In the GRAAL group experience, the incidence of bacterial infections during remission induction treatment was slightly higher, with a predominance of Gram-positive bacteria. This might reflect the different local epidemiology as in Italy an increase of multiresistant Gram-negative bacteria has been observed. However, mortality rates were analogous [34].

The incidence of IFD was 4.3% (9.4% of FE) apparently in reduction compared to other previous studies [21] and from the one recently published by Mariette and colleagues (6.7%) [35] and comparable to the recent study by Nicolato et al [36]. However, our study included patients in different treatment phases of ALL, including phases at lower risk for infection (i.e., consolidation/maintenance). As expected, the latter was the category that presented the lowest incidence (Table 2). Mold infections were more common than yeast. Other species were found in the contest of mixed infections. The mold/yeast ratio was 1.8:1. Candida BSI infections were still evident in our study cohort (incidence

0.7%) but were lower than those reported in previous studies by the SEIFEM group [23].

Viral infections rates were low (incidence 1%, 2.7% of all FEs) but probably underestimated in our study. Subclinical viral infections are common and may be overshadowed by bacterial or fungal disease in some patients. However, mortality rates were relatively high among patients who had a microbiologically documented viral infection (Table 3).

Mixed infections caused primarily by bacteria and fungi accounted for 5.5% of all FEs. The presence of mixed infections likely reflects mucosal damage observed in leukemia patients undergoing chemotherapy. Mixed infections were also responsible for the highest mortality rates.

Mortality rates for/with infection were low compared to other hematologic malignancies, but still notable. Apparently, deaths caused by fungal infections and mixed infections are more frequent than in previous studies by the SEIFEM group [1]. This may be due to the chemotherapy regimens administered, as they are increasingly aggressive and prolonged. Conversely, deaths by FUO are lowering probably as a result of improved diagnostic procedures.

Beyond IFDs, other risk factors for mortality seem to be, as expected, an uncontrolled malignancy, older age (> 60 years old) and poor PS. However, the main role is played by neutropenia. In fact, during almost every FE (89.9%), the patient had neutrophil count lower than 500/mm^3 and all the deceased patients were neutropenic. Previous studies demonstrated the correlation with the depth and duration of neutropenia with the incidence of infections [37]. In our investigation, deeper and more prolonged neutropenia is associated with a higher risk of predicted probability of death. Steroid use is another distinct risk factor for mortality. In fact, a large use of steroids during all the treatment of ALL (also to contain refractory disease) is observed. Moreover, concomitant presence of pneumonia should be carefully considered in FE ALL patients. CNS localization at diagnosis of ALL does not seem to decisively affect the outcome in presence of infection but seems significant in the context of overall mortality.

In conclusion, our study illustrates the current incidence of fever and infectious complications in a disease formerly considered at low risk. The phases of treatment in which infectious episodes are more frequent are first induction/reinduction treatment and even higher in patients with refractory disease. Most microbiologically documented FEs in ALL patients were caused by bacteria; however, the incidence of IFD (4.3%) is sufficiently high to justify intensive diagnostic workup for fungal pathogens including molds during fever. Remarkably, mixed infections, often involving fungi, are the most concerning. Primitive or secondary pulmonary localization seems to be critical, together with bacteremia, as poor prognostic factor, as well as use of steroids and neutropenia. A poor

PS also appears prominent in the management of FEs in ALL. Together with steroid use, an uncontrolled malignancy and a poor PS seem to be crucial for mortality with evidence of infection.

Compliance with ethical standards

The study was approved by the ethics committee of each center.

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