MAJOR ARTICLE

A Prospective Study on the Epidemiology of Febrile Episodes during Chemotherapy-Induced Neutropenia in Children with Cancer or after Hemopoietic Stem Cell Transplantation

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Background. The purpose of our study was to evaluate the incidence and clinical characteristics of febrile episodes during neutropenia following chemotherapy in children with cancer.

Patients and methods. A prospective, 3-year single-center observational study of periods of neutropenia was performed. Epidemiology and clinical diagnoses of febrile episodes occurring during the neutropenic periods were evaluated, taking into consideration different categories of anticancer treatment based on the type of tumor and phase of therapy.

Results. A total of 703 febrile episodes were observed during 614 (34%) of 1792 neutropenic periods (34%), for a total of 28,001 days at risk, accounting for a rate of 0.76 episodes per 30 days at risk. The highest proportions of neutropenic periods with primary febrile episodes were observed after autologous hemopoietic stem cell transplantation (58%), aggressive treatment for acute leukemia or non-Hodgkin lymphoma (48%), and allogeneic hemopoietic stem cell transplantation (44%); the lowest proportion (9%) was observed during maintenance chemotherapy for acute leukemia ($P < .001$). The most frequent clinical diagnosis was fever of unknown origin (in 79% of cases), followed by bacteremia (10%); invasive mycosis was diagnosed in only 2% of cases.

Conclusions. The overall incidence of febrile neutropenia and severe infectious complications in children with cancer is low, with differences according to the aggressiveness of chemotherapy. This fact must be considered when designing clinical trials on the management of infectious complications in children with cancer.

Fever is a well-known complication in neutropenic patients with cancer. Available data on the incidence of fever during chemotherapy-induced neutropenia in adults and children with cancer are generally derived from randomized clinical trials [1–4], but no information is provided on the overall incidence regardless of specific eligibility criteria. In fact, in most of the studies, the denominator represents the number of patients who are eligible for the study but not the total number of subjects who are potentially at risk (i.e., all patients with a given disease or condition). Moreover, in most clinical trials, patients are enrolled only once; thus, data on additional infectious episodes occurring in the same patient are not evaluated. These facts might determine errors in the estimation of the expected number of events observed in a given period [3, 5]. Moreover, in everyday practice, information based only on reports of clinical trials might also not fully be appropriate for the development of treatment strategies. The aim of this 3-year prospective, observational study was to evaluate the incidence and clinical characteristics of febrile complications during neutropenic periods in children receiving antineoplastic chemotherapy and in children who recently underwent hemopoietic stem cell transplantation (HSCT).

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Table 1. Categories of anticancer treatment according to type of tumor and phase of treatment.

Treatment category	Underlying disease(s) and phase(s) of treatment
Not-yet-defined risk for ALL	Induction therapy for ALL before day 77, according to the I-BFM protocol
Aggressive treatment for acute leukemia or non-Hodgkin lymphoma	Induction therapy for high-risk ALL after day 78, according to the I-BFM protocol; any treatment for acute nonlymphoblastic leukemia, B-cell non-Hodgkin lymphoma, or relapse and/or resistance of acute leukemia or non-Hodgkin lymphoma
Moderately aggressive treatment for acute leukemia or lymphoma	Induction therapy for standard-to-medium risk ALL after day 78, according to the I-BFM protocol; any treatment for non-B-cell non-Hodgkin lymphoma; front-line or second-line therapy for Hodgkin disease
Maintenance treatment for acute leukemia or lymphoma	Maintenance chemotherapy for acute leukemia or lymphoma
Allogeneic hematopoietic stem cell transplantation	Conditioning regimen and immunosuppressive treatment for allogeneic hematopoietic stem cell transplantation
Autologous hematopoietic stem cell transplantation	Megatherapy with autologous stem cell transplantation
Aggressive treatment for solid tumor	Protocols for high risk neuroblastoma, bone and soft-tissue sarcomas, CNS tumor in patients aged <3 years and/or with disseminated disease and/or unfavorable histologic or biologic findings; any treatment for relapse and/or resistance of a solid tumor
Moderately aggressive treatment for solid tumor	Protocols for non–high-risk neuroblastoma, Wilms tumor, non–high-risk CNS tumor, or miscellaneous tumor

NOTE. ALL, acute lymphoblastic leukemia; I-BFM, International Berlin-Frankfurt-Münster Study Group.

PATIENTS AND METHODS

Patients. Patients who were eligible for this study included those who had received a diagnosis of acute leukemia (AL), a solid tumor, or a nonneoplastic disease requiring allogeneic HSCT; had been admitted for treatment at the Department of Hematology and Oncology of the G. Gaslini Children Hospital (GCH; Genoa, Italy); and had experienced at least 1 neutropenic period from 1 January 2002 through 31 December 2004.

Neutropenia was defined as an absolute granulocyte (PMN) count $<1.0 \times 10^6$ cells/L [6]. Two trained investigators reviewed the daily WBC counts of inpatients and outpatients and registered any new neutropenic period. Because the evaluation of WBC count during chemotherapy-induced neutropenia was performed at least every 3 days both for inpatients and outpatients, neutropenic periods of a duration <3 days were removed from the analysis; these periods were considered to be the result of individual or instrumental variability. Similarly, consecutive neutropenic periods separated by ⩽3 days were pooled. The duration of the neutropenic periods was calculated as the difference between the date of the last day of neutropenia (or date of death) and the date of the first day of neutropenia plus 1. For each period, data were collected on patient demographic characteristics, type of tumor, phase of antineoplastic chemotherapy, and administration of granulocyte colony-stimulating factor therapy within at least 3 days before the onset of neutropenia. Because of the lack of an internationally approved toxicity grading of therapeutic protocols, phases of antineoplastic therapy were arbitrarily classified into 8 categories on the basis of the type of underlying disease and phases of treatment (table 1). This classification system was based on the methods of available studies [7–14] reporting a relationship between tumor types and/or treatment phases and the risk of infectious complications.

Information regarding the occurrence and diagnosis of any febrile episode during each neutropenic period was then prospectively collected. Fever was defined as 1 oral or axillary temperature measurement ⩾38.5°C or 2 oral or axillary temperature measurements ⩾38.0°C that were separated by at least 1 h [15]. Febrile episodes were classified as microbiologically documented infection (MDI) with bacteremia, MDI without bacteremia, clinically documented infection, and fever of unknown origin (FUO) [15]. Invasive fungal infections were classified separately according to the European Organisation for Research and Treatment of Cancer/Mycoses Study Group criteria [16]. Finally, a second febrile and/or infectious episode that developed during the same neutropenic period as the primary episode was defined as a secondary infection. In cases of MDI, the isolated pathogen had to be different from that detected during the primary episode for the episode to be considered a secondary infection [17].

Standard of care during the study period. All patients were treated according to the protocols approved by the GCH ethics committee. Patients were admitted to single-bed rooms equipped with high-efficiency particulate air filters and received cotrimoxazole prophylaxis for *Pneumocystis jiroveci* pneumonia. Patients undergoing allogeneic HSCT also received antifungal prophylaxis with fluconazole [15]. From January 2004, prophylaxis with amoxicillin-clavulanate and fluconazole was

administered during the period of not-yet-defined risk therapy for acute lymphoblastic leukemia (table 1), according to International Berlin-Frankfurt-Münster Study Group–based protocols, and during aggressive treatment for AL or non-Hodgkin lymphoma (NHL) [15]. Unless specifically recommended by the antineoplastic protocol, granulocyte colony-stimulating factor therapy was not routinely administered. During a febrile episode, physical examination and blood cultures were performed; cultures of specimens from other sites, as well as appropriate imaging studies, were performed as clinically indicated. Other tests and imaging (including seriate galactomannan antigen detection and chest CT scan) were performed in accordance with the clinical evolution and microbiological documentation of the episode [15].

Statistical analysis. Statistical analyses were performed on the basis of the 8 predefined treatment categories, not the type of underlying disease. Descriptive statistics were reported in terms of absolute frequencies and percentages. Distribution of data regarding PMN count and duration of neutropenia were described in terms of a median value and interquartile range (IQR) because of the nonnormal (Gaussian) distribution of these values [18]. Accordingly, comparisons between 2 groups were performed using the nonparametric Mann-Whitney *U* test; the Kruskall-Wallis test was used for comparisons among >2 groups. Pearson's χ^2 test was applied to compare proportions.

The rate of febrile episodes (FR) during neutropenia was evaluated as the ratio of the total number of febrile episodes to the number of person-days accumulated during the same period and was expressed as the number of episodes per 30 person-days at risk. Because of the longitudinal nature of FR data (i.e., clustered within each patient), statistical testing and 95% CI estimation were based on the negative binomial likelihood (likelihood ratio χ^2 test), which improves the validity of statistical comparisons, allowing for the within-patient correlation [19]. All tests were 2-tailed, and $P < .05$ was considered to be statistically significant. All statistical analyses were performed using Stata software, release 8.0 (Stata).

The GHC is a tertiary care research hospital, and all of the patients or their guardians signed a consent form allowing for the use of their clinical and nongenetic data for clinical research purposes. The procedures followed were in accordance with our institution's ethical standards and with the Helsinki Declaration. According to Italian guidelines, no other specific informed consent was required for the purposes of this study.

RESULTS

Overall, 1803 periods of neutropenia were documented; 11 (0.6%) were excluded from the analysis, because they lasted <3 days, leaving 1792 evaluable neutropenic periods. These periods occurred in 366 patients (213 [58%] were male), with a median age at study entry of 5.8 years (IQR, 2.6–10.5 years). The distribution of the underlying diseases was as follows: 112 patients (31%) had AL or NHL, 76 (21%) had neuroblastoma, 48 (13%) had bone or soft-tissue sarcomas, 42 (11%) had a CNS tumor, 19 (5%) had Hodgkin disease, 14 (4%) had Wilms tumor, and 41 (11%) had miscellaneous malignant tumors. The remaining 14 children (4%) had a nonneoplastic disease requiring allogeneic HSCT. One hundred eleven neutropenic periods (6% of all periods) occurred during per-protocol granulocyte colony-stimulating factor therapy. The median duration of neutropenia was 11 days (IQR, 7–20 days) for a total of 28,001 days at risk, with differences among the 8 treatment categories ($P < .001$, by Kruskall-Wallis test) (table 2). The longest duration of neutropenia (median duration, 18 days) was observed during the first period of chemotherapy for acute lymphoblastic leukemia.

Incidence and diagnosis of febrile episodes. Overall, 614 neutropenic periods (34%) were complicated by fever (table 2); of these, 35 (32%) occurred during the 111 granulocyte colony-stimulating factor treatments. For 89 periods (14%), a secondary febrile episode was documented, for a total of 703 febrile episodes and an overall FR of 0.76 (95% CI, 0.70–0.81). The median age of patients at the onset of febrile neutropenia was 5.7 years (IQR, 3.1–10.7 years); the median age of patients who experienced a neutropenic period that was not complicated by fever was 6.9 years (IQR, 3.8–10.7 years; $P = .004$, by Mann-Whitney *U* test).

Details on the epidemiology and diagnosis of primary and secondary febrile episodes are reported in table 2. The distribution of primary episodes was significantly different among the treatment categories considered ($P < .001$, by Pearson's χ^2 test). In particular, the highest proportion of neutropenic periods with primary episodes (58%) was observed after autologous HSCT, followed by after aggressive treatment for AL or NHL (48%) and after allogeneic HSCT (44%). The lowest proportion of neutropenic periods with primary episodes (9%) was observed during maintenance chemotherapy for AL or NHL.

The median PMN count at the onset of the primary febrile episodes was 0.05×10^6 cells/L (IQR, 0.00–0.20×10^6 cells/L), and fever occurred a median of 3 days (IQR, 1–6 days) after the onset of neutropenia. There were no statistically significant differences among the treatment categories with regard to these factors ($P = .384$ and $P = .168$, respectively, by Kruskall-Wallis test).

FUO was the most frequent clinical diagnosis associated with the primary febrile episodes, accounting for 79% of such episodes, followed by MDI with bacteremia (10%). The remaining 3 possible diagnoses together accounted for <10% of cases; in particular, invasive fungal infection was diagnosed in only 2% of primary episodes. The distribution of the different diagnoses associated with febrile episodes among the 8 treatment cate-

Table 2. Epidemiology and clinical diagnoses of febrile neutropenia in children with cancer, by treatment category.

Variable	Induction therapy for ALL before day 77	Aggressive treatment for AL or NHL	Moderately aggressive treatment for AL, NHL, or HD	Maintenance treatment for AL or NHL	Allogeneic HSCT	Autologous HSCT	Aggressive treatment for ST	Moderately aggressive treatment for ST	All
No. neutropenic periods	93	252	167	58	123	171	727	201	1792
Duration of neutropenia, median days (IQR)	18 (8–29)	11 (7–19)	13 (8–23)	15 (8–28)	14 (5–23)	14 (8–22)	10 (7–16)	11.5 (7–17)	11 (7–20)
Primary febrile episodes									
No. (%) of neutropenic periods with a primary febrile episode	23 (25)	120 (48)	36 (21)	5 (9)	54 (44)	99 (58)	232 (32)	45 (22)	614 (34)
Duration from onset of neutropenia to onset of the febrile episode, median days (IQR)	3 (2–18)	4 (1–7)	3.5 (0–7)	5 (1–7)	4 (0–8)	2 (1–4)	3 (0–6)	2 (0–5)	3 (1–6)
Absolute PMN count at the onset of fever, median 10^6cells/L (IQR)	0.05 (0.05–0.30)	0.05 (0.04–0.14)	0.20 (0.05–0.46)	0.09 (0.09–0.33)	0.05 (0.00–0.34)	0.00 (0.00–0.05)	0.05 (0.02–0.20)	0.07 (0.05–0.39)	0.05 (0.00–0.20)
Diagnoses, no. (%) of primary febrile episodes									
FUO	18/23 (78)	91/120 (76)	27/36 (75)	5/5 (100)	36/54 (67)	76/99 (77)	198/232 (85)	32/45 (71)	483/614 (79)
MDI with bacteremia	1/23 (4)	17/120 (14)	3/36 (8)	0/5 (0)	11/54 (20)	11/99 (11)	13/232 (6)	3/45 (7)	59/614 (10)
MDI without bacteremia	1/23 (4)	2/120 (2)	1/36 (3)	0/5 (0)	4/54 (7)	4/99 (4)	4/232 (2)	3/45 (7)	19/614 (3)
CDI	2/23 (9)	5/120 (4)	5/36 (14)	0/5 (0)	1/54 (2)	6/99 (6)	16/232 (7)	5/45 (11)	40/614 (6)
Invasive mycosis	1/23 (4)	5/120 (4)	0/36 (0)	0/5 (0)	2/54 (4)	2/99 (3)	1/232 (<1)	2/45 (4)	13/614 (2)
Secondary febrile episodes									
No. of secondary febrile episodes/no. of primary febrile episodes (%)	4/23 (17)	45/120 (38)	0/36 (0)	0/5 (0)	18/54 (33)	5/99 (5)	16/232 (7)	1/45 (2)	89/614 (14)
Diagnoses, no. (%) of secondary febrile episodes									
FUO	2/4 (50)	24/45 (53)	0/0 (0)	0/0 (0)	12/18 (67)	1/5 (20)	13/16 (81)	1/1 (100)	53/89 (59)
MDI with bacteremia	0/4 (0)	13/45 (29)	0/0 (0)	0/0 (0)	3/18 (17)	3/5 (60)	2/16 (13)	0/1 (0)	21/89 (24)
MDI without bacteremia	0/4 (0)	0/45 (0)	0/0 (0)	0/0 (0)	1/18 (5)	0/5 (0)	1/16 (6)	0/1 (0)	2/89 (2)
CDI	1/4 (25)	2/45 (4)	0/0 (0)	0/0 (0)	1/18 (5)	1/5 (20)	0/16	0/1 (0)	5/89 (6)
Invasive mycosis	1/4 (25)	6/45 (13)	0/0 (0)	0/0 (0)	1/18 (5)	0/5 (0)	0/16 (0)	0/1 (0)	8/89 (9)
Total no. of febrile episodes	27	165	36	5	72	104	248	46	703
Total no. of days at risk	1982	4183	2816	995	2108	2754	10,034	3129	28,001
Rate, no. of febrile episodes per 30 days of neutropenia (95% CI)	0.41 (0.27–0.59)	1.18 (1.01–1.38)	0.38 (0.27–0.53)	0.12 (0.04–0.27)	1.02 (0.80–1.29)	1.13 (0.93–1.37)	0.76 (0.67–0.86)	0.45 (0.33–0.61)	0.76 (0.70–0.81)

NOTE. CDI, clinically documented infection; FUO, fever of unknown origin; HSCT, hemopoietic stem cell transplantation; IQR, interquartile range; MDI, microbiologically documented infection; PMN, granulocytes.

gories was statistically significant ($P = .039$, by Pearson's χ^2 test), with the highest proportion of bacteremia being observed after allogeneic HSCT (20% of primary febrile episodes in patients who underwent allogeneic HSCT), aggressive therapy for AL or NHL (14%), and autologous HSCT (11%).

Table 3 shows the proportions of the different diagnoses associated with the 614 primary febrile episodes, stratified by the PMN count at the onset of fever and by the duration of neutropenia prior to the onset of fever, using standard cutoff values. The majority of primary febrile episodes (70%) occurred in patients with an absolute PMN count $\leqslant 0.1 \times 10^6$ cells/L, and only 11% occurred in patients with a PMN count $>0.5 \times 10^6$ cells/L. During 27 episodes (40%) experienced by this latter group, the PMN count decreased to $<0.5 \times 10^6$ cells/L within 3 days after fever onset, and the PMN count remained stable or returned to $>1.0 \times 10^6$ cells/L during the remaining 42 episodes. Of these 42 primary febrile episodes, 33 were due to FUO, 4 were due to bacteremia, 2 were due to clinically documented infection, 1 was due to invasive fungal infection, and 1 was due to MDI. There were no differences in PMN count distribution among the types of diagnoses associated with the febrile episodes ($P = .34$, by Pearson' χ^2 test). If the duration of neutropenia to the onset of fever was considered, 81% of episodes occurred within the first 7 days of neutropenia; no statistically significant differences were observed among the possible clinical diagnoses ($P = .74$, by Pearson' χ^2 test).

We also evaluated the frequency of febrile neutropenia during only the first 30 days after HSCT (i.e., the pre-engraftment period). Among 50 patients who underwent HSCT procedures, 37 (75%) experienced episodes of febrile neutropenia within the first 30 days after the procedure.

A separate analysis was performed to measure the effect of the prophylactic program, which was adopted after January 2004, among children with AL or NHL. Febrile episodes were documented during 91 (40%) of 226 neutropenic periods in children who did not receive amoxicillin-clavulanate and fluconazole prophylaxis, and episodes were observed during 52 (44%) of 119 neutropenic periods in children who received prophylaxis ($P = .54$, by Pearson χ^2 test).

Data on the 89 secondary febrile episodes are also reported in table 2. Secondary febrile episodes occurred a median of 24 days (IQR, 5–42 days) after the onset of neutropenia. A secondary episode was observed more frequently after aggressive treatment for AL or NHL (37% of neutropenic periods with a primary febrile episode also involved a secondary episode), after allogeneic HSCT (33%), and during the first 77 days of treatment for acute lymphoblastic leukemia (17%). In addition, FUO was the most frequent clinical diagnosis associated with secondary febrile episodes (accounting for 59% of secondary episodes), but MDI with bacteremia (24%) and invasive mycoses (9%) accounted for higher proportions of secondary episodes than primary episodes ($P < .001$, by Pearson χ^2 test).

Finally, the rate of febrile episodes per 30 neutropenic days was significantly different among the 8 treatment categories ($P < .001$, by likelihood ratio χ^2 test), with the highest values observed for neutropenic periods after aggressive treatment for AL or NHL (FR, 1.18), autologous HSCT (FR, 1.13), and allogeneic HSCT (FR, 1.02) (table 2).

Etiology and locations of documented febrile episodes. Table 4 shows the etiologies of microbiologically documented episodes. MDI with bacteremia was due to a single strain of gram-positive bacteria in 46 cases (57%) and to gram-negative bacteria in 33 cases (41%); 1 episode (2%) was caused by a mixed bacterial infection. MDI without bacteremia was due to gram-positive bacteria or gram-negative bacteria in 8 cases (38%) each; 1 episode (5%) was caused by a mixed bacterial infection, 1 (5%) was caused by a superficial mycosis, and 4 (14%) were due to viruses. Invasive fungal infections were clas-

Table 3. Distribution of clinical diagnoses of primary febrile episodes, by the different thresholds of absolute granulocyte (PMN) count and duration of neutropenia preceding the development of fever.

	No. (%) of febrile episodes					
Variable	All	FUO	MDI with bacteremia	MDI without bacteremia	CDI	Invasive mycosis
Total	614 (100)	483 (100)	59 (100)	19 (100)	40 (100)	13 (100)
PMN count						
$\leqslant 0.1 \times 10^6$ cells/L	448 (73)	345 (71)	51 (86)	12 (63)	32 (80)	8 (61)
>0.1 to 0.5×10^6 cells/L	98 (16)	84 (17)	3 (5)	4 (21)	3 (7)	4 (31)
$>0.5 \times 10^6$ cells/L	68 (11)	54 (12)	5 (9)	3 (16)	5 (12)	1 (8)
Duration of neutropenia						
⩽7 days	501 (81)	394 (81)	46 (78)	14 (74)	36 (90)	11 (84)
8–14 days	53 (9)	41 (9)	8 (13)	2 (10)	1 (3)	1 (8)
⩾15 days	60 (10)	48 (10)	5 (9)	3 (16)	3 (7)	1 (8)

NOTE. Because of rounding, percentages may not total to 100%. CDI, clinically documented infection; FUO, fever of unknown origin; MDI, microbiologically documented infection.

Table 4. Isolated pathogens in infections with documented etiologies.

Pathogen	No. of isolated strains
Gram-positive bacteria	
Any	57
Coagulase-negative staphylococci	11
Staphylococcus aureus	13
Viridans streptococci	15
Streptococcus species	2
Streptococcus pneumoniae	3
Enterococcus faecium	5
Enterococcus species	1
Bacillus sphaericus	1
Streptococcus pyogenes	1
Clostridium difficile	1
Nonspeciated	4
Gram-negative bacteria	
Any	40
Escherichia coli	13
Klebsiella pneumoniae	4
Enterobacter species	2
Pseudomonas aeruginosa	6
Pseudomonas species	4
Pseudomonas putida	1
Stenotrophomonas maltophilia	1
Salmonella species	1
Alcaligenes xylosoxidans	3
Citrobacter species	1
Proteus species	1
Neisseria cinerea	1
Nonspeciated	2
Fungi	
Any	14
Candida species	2
Candida albicans	1
Candida tropicalis	4[a]
Candida parapsilosis	1
Cryptococcus neoformans	1
Aspergillus fumigatus	1
Nonspeciated filamentous fungi	3
Nonspeciated yeasts	1
Viruses	
Any	4
Adenovirus	3
Epstein-Barr virus	1
Positive galactomannan antigen test result in the presence of clinical and radiological signs of infection	1

[a] One patient who previously received a diagnosis of infection with *C. tropicalis* fungemia without signs of localization was treated for 3 weeks and subsequently developed *C. tropicalis* arthritis.

sified as fungemia without deep organ involvement in 7 cases (33%), proven with deep organ involvement in 8 (38%), probable in 2 (10%), and possible in 4 (19%). Figure 1 describes the locations of MDIs and clinically documented infections. Blood represented the most frequent site of infection (in 55% of episodes), followed by the gastrointestinal tract (14%, including cases involving the mouth [5%], bowel [4%], and perianal cellulitis [5%]), skin and soft tissue (13%), and the respiratory tract (8%, including cases involving the upper respiratory tract [2%] and lungs [6%]).

DISCUSSION

The primary aim of this study was to quantify the incidence of febrile complications during neutropenic periods in children with cancer. To our knowledge, this information was not available in the literature and might be useful for the planning of management strategies in everyday clinical practice and to avoid possible errors in the sample-size estimation of randomized clinical trials [3, 5] of therapy or prophylaxis for infections in children with cancer.

Overall, we observed that fever complicates neutropenia in only 34% of cases and that <1 febrile episode (i.e., 0.76 episodes) should be expected for every 30 neutropenic days at risk. As expected, the incidence and rate of febrile complications varied according to treatment phase. For clinical purposes, we believe that the 8 treatment categories that we defined may be further grouped into 4 categories based on similar epidemiology. In particular, aggressive treatment for AL, NHL, or any HSCT (group 1) was associated with primary febrile episodes in >40% of neutropenic periods and a frequency of >1 episode per 30 days at risk. Aggressive treatment for a solid tumor (group 2) was associated with febrile episodes in 30%–40% of neutropenic periods and an FR of 0.5–1. All other types of antineoplastic treatments (group 3) were associated with febrile episodes in 20%–30% of neutropenic periods and an FR of 0.5–0.3. Finally, maintenance treatment for AL or NHL (group 4) was associated with febrile episodes in <10% of neutropenic periods and an FR of <0.3. For febrile neutropenia after allogeneic HSCT, the overall proportion of 44% of neutropenic periods with a febrile episode that was observed in our study might be considered to be very low. However, in this category, we included all of the neutropenic periods, regardless of when the period occurred after HSCT. Even if only the first 30 days after HSCT procedures are considered, our value of 75% is lower than the 98% reported by Mullen et al. [20] in a retrospective study involving only the preengraftment period, possibly because of differences in conditioning regimens.

In the absence of local epidemiological data, our information may be used to calculate the expected number of events when planning randomized clinical trials. We recognize that it is difficult to generalize results derived from a single center; however, our strategies for the treatment of patients with neutropenia are based on a wide review of international literature [15] and should not be significantly different from the strategies used in other, similar tertiary care pediatric cancer centers.

Even if the methodology of our study was somewhat unique, some comparisons with other studies that mostly involve adults are possible. For example, the percentage of neutropenic pe-

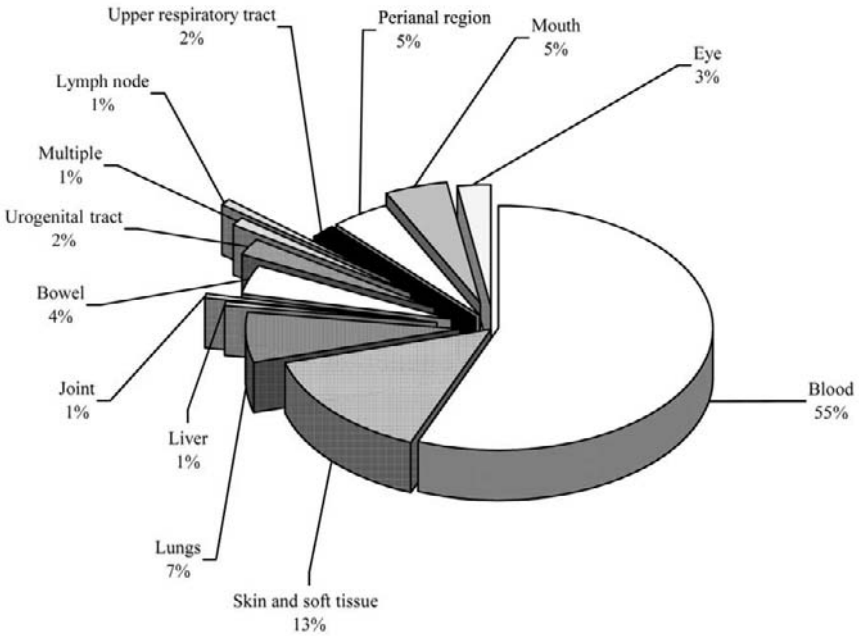

Figure 1. Location of microbiologically or clinically documented infections during 703 episodes of infection in neutropenic children with cancer

riods with febrile episodes observed in group 1 was similar to the percentage reported in the placebo arm in prophylactic studies involving leukemic children (50%) [1, 3] but is lower than the percentage observed in similar studies involving adults with AL or after HSCT (85%–100%) [4, 21]. On the other hand, the 20%–30% incidence of febrile neutropenia that was observed in group 3 is higher than the 8%–15% incidence reported in placebo-controlled prophylactic studies involving adults with low-risk solid tumors [2].

Our study also confirmed that the diagnosis and locations of febrile neutropenia in children differ from those described in adults (e.g., children have a higher incidence of FUO and a lower incidence of invasive mycoses) [22–27]. These discrepancies demonstrate the difficulty of translating data derived from series involving adults into the practice of pediatric care.

In our series, 89% of febrile episodes occurred in patients with a PMN count $\leq 0.5 \times 10^6$ cells/L, and most of these patients (72%) had a PMN count $\leq 0.1 \times 10^6$ cells/L. Moreover, in 27 (40%) of the 68 episodes that occurred in patients with a PMN count $>0.5 \times 10^6$ cells/L at the time of diagnosis, the PMN count decreased below this value within 3 days after the diagnosis. This observation is consistent with the guidelines of the Infectious Diseases Society of America [28], which define the cutoff value for starting empirical therapy of febrile episodes as a PMN count of 0.5×10^6 cells/L or a PMN count rapidly decreasing from $<1.0 \times 10^6$ cells/L. However, it should be mentioned that, among the small group of febrile episodes occurring in patients with a PMN count $>0.5 \times 10^6$ cells/L, 8 cases of documented infection were observed in patients with PMN counts that did not decrease below the cutoff value. On the basis of these data, the Infectious Disease Society of America definition seems to be appropriate, but patients with a PMN count in the "gray zone" of $1.0–0.5 \times 10^6$ cells/L should be carefully monitored, because some severe infections may still develop.

We also confirmed that severe infectious complications occur during long-lasting neutropenia [23, 29], but we observed that the majority of primary febrile episodes occurred shortly after the onset of neutropenia (median time from onset of neutropenia to the primary febrile episode, 3 days). Because this interval and the PMN count at fever onset were not different among the treatment categories, it might be hypothesized that, once the patient has become neutropenic, other factors, such as mucositis [30] or genetic factors [31, 32], could become prominent for the development of fever.

Lastly, the role of prophylaxis for the prevention of fever in patients with cancer and neutropenia should be considered. In this prospective observational study, the incidence of febrile neutropenia was not modified after the implementation of prophylaxis. However, this finding should be taken cautiously because of the small sample size and the low statistical power (13.5%) of the analysis. In fact, because of the small observed percentage of neutropenic periods with febrile episodes, >1000 neutropenic episodes per arm would be required to demonstrate any statistically significant difference.

A positive effect of antibacterial prophylaxis was reported in a recent meta-analysis [33] that mostly involved randomized trials including only 1 neutropenic period per patient. Our findings, as well as data from Cullen et al. [2], seem to suggest that the beneficial effect of prophylaxis might disappear in patients with repeated neutropenic periods. As a consequence, multicenter clinical trials that are able to recruit a very large number of patients with cancer should be implemented to evaluate the efficacy of repeated cycles of antibacterial prophylaxis.

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