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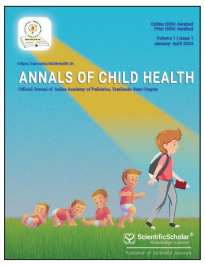

Original Article

Clinical Profile of Febrile Neutropenia in Children with Hematological Malignancies

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ABSTRACT

Objectives: The objective of this study was to assess the risk factors for adverse events during febrile neutropenia episodes in children with hematological malignancies.

Material and Methods: This observational study was carried out in a tertiary care hospital in Madurai over 1 year. Children diagnosed with hematological malignancies and presenting with febrile neutropenia were included ($n = 40$). A complete blood count was sent for all children who presented with fever >101 F or 100.4 F for >1 h. If absolute neutrophil count <500 mm^3, they were included in the study. Clinical and hematological profiles, along with microbiological investigations, were collected. Descriptive statistics in the form of mean, standard deviation, frequency, percentage, and inferential statistics – Chi-square test was done.

Results: The mean age of children was 6.45 ± 2.08 years. B-cell acute lymphoblastic leukemia was the most common malignancy (80%). Most cases occurred during high-risk stratification (77.5%) and within 7 days of chemotherapy (52.5%). Cytarabine (22.5%) and methotrexate (22.5%) were the most common chemotherapy drugs leading to febrile neutropenia. Clinical features included IV-line cellulitis (22.5%), oral mucositis (22.5%), and gastrointestinal involvement (22.5%). Profound neutropenia (38.9%), low hemoglobin (<5 g/dL) (71.6%), platelet count (<50,000/cu.mm) (46.7%), and microbiologically documented infections (47.2%) were associated with poor outcomes. Gram-negative bacilli, particularly *Klebsiella* (10%) and *Pseudomonas* (5%), were commonly isolated. Chances of poor outcome were higher in profound neutropenia (38.9%) compared to severe neutropenia (9.1%) ($P < 0.05$). Those with microbiologically confirmed infection (47.2%) had poor outcomes compared to clinically documented infection (4.3%) ($P < 0.05$).

Conclusion: Risk factors for adverse outcomes include short intervals between chemotherapy and neutropenia, profound neutropenia, low hemoglobin, low platelet count, and microbiologically documented infections.

Keywords: Febrile neutropenia, Hematological malignancies, Microbiologically documented infections

INTRODUCTION

Out of the common causes of mortality in the pediatric population, childhood malignancies are on a rising trend.[1] The rising incidence of the pathology thus requires a time-sensitive and more effective approach to diagnosis and intervention. Nearly one-third of childhood malignancies are hematological.[2]

A broad classification of the common hematological malignancies encountered in childhood are as follows – acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), chronic myeloid leukemia, Juvenile myelomonocytic leukemia, Hodgkin's lymphoma, non-Hodgkin's lymphoma, and Langerhans cell histiocytosis.[3]

Patients commonly present with symptoms including weakness, fatigue, fever, bleeding manifestations, bone pain, and either abruptly or gradually.[4] Children with ALL frequently exhibit signs and symptoms of extramedullary disease or bone marrow involvement.[5] Bone marrow failure due to infiltration by blasts manifests as anemia, thrombocytopenia, and neutropenia. History of prior treatment in the form of transfusion or drugs prescribed, especially steroids, should be taken as these factors may interfere with diagnosis.

Neutropenia in hematological malignancies can be due to the chemotherapeutic agents or the disease process itself. When such neutropenic patients encounter a pathogen, they develop fever. Prompt initiation of an empiric and broad-spectrum antibiotic is the single most important lifesaving intervention in these patients.

Thus, a high index of suspicion is needed in these patients as fever might be the only presenting complaint in many patients. A detailed history and physical examination with special attention to clues suggesting the etiology or focus of the infection is a necessity to risk stratify the patient and treat appropriately. Hence, this study is done to evaluate the clinical profile of febrile neutropenia in children with hematological malignancies.

Aims and objectives

The study aims to evaluate the clinical profile of febrile neutropenia in children with hematological malignancies. The objective is to assess the risk factors for adverse events during the febrile neutropenia episodes in hematological malignancies.

MATERIAL AND METHODS

An observational study was conducted in a tertiary care hospital in Madurai. The study period was for 1 year. All children who are already diagnosed and under treatment for hematological malignancies presenting with febrile neutropenia during the study period were included in the study. Those who did not give consent were excluded from the study. Forty children who met the selection criteria during the study period were chosen. Ethical clearance was obtained from the Institutional Ethical Committee, Madurai Medical College.

A complete blood count was sent for all children with hematological malignancies who presented with fever >101 F or 100.4 F for >1 h. If absolute neutrophil count (ANC) <500 mm^3, they were included in the study. Clinical profiles, hematological profiles, and microbiological investigations were conducted for the child. The details were collected in a pre-tested semi-structured interviewer administered questionnaire.

The data were entered in Microsoft Excel and were analyzed using the Statistical Package for the Social Sciences version 24. Descriptive statistics, such as frequencies and proportions, were used, and inferential statistics, such as the Chi-square test, were used. $P < 0.05$ was considered significant. Data were expressed in tables and figures wherever necessary.

RESULTS

The mean age of the children was 6.45 ± 2.08 years [Figure 1]. About 65% were male and 35% were female. The most common hematological malignancy was B-cell ALL (80%), followed by T-cell ALL (15%) [Figure 2]. About 77.5% of the episodes were in children who were risk stratified as high risk. About 87.50% were in newly diagnosed malignancy, and the mean interval between the onset of symptoms and diagnosis of hematological malignancy was 5.10 ± 2.48 months [Table 1].

About 37.5% had a previous history of febrile neutropenia. Fifteen children had a history of more than 1 episode of febrile neutropenia in the past. Among them, six children reported one previous episode, followed by six reported two previous episodes and three had three previous episodes. Among the children who had three previous episodes of febrile neutropenia, one child had a diagnosis of Burkitt lymphoma, which expired during the febrile neutropenic episode recorded during the study. The other two children had been diagnosed with B-cell ALL, and both of them recovered with intensive care unit (ICU) care. About 20% were in the consolidation phase of chemotherapy, 20% in the induction IA phase, 22.5% in the induction IB phase, 15% in the reinduction phase, 5% in the maintenance phase, 15% in relapse protocol and radiotherapy, and 2.5% was not yet started chemotherapy. About 52.5% of the febrile neutropenia episodes occurred within 7 days of chemotherapy. The most common chemotherapy drugs used for treatment were cytarabine (22.5%) and methotrexate (22.5%), followed by vincristine (20%). The main clinical features of the children with hematological malignancies presented with neutropenia were IV line cellulitis (22.5%), oral mucositis (22.5), and gastrointestinal involvement (22.5%) [Table 2].

About 55% had severe neutropenia, and 45% had profound neutropenia. About 45% had microbiologically documented infection, whereas the remaining 55% had only clinically documented infection. Among the appropriate cultures sent for children with febrile neutropenia, 32.5% were positive for microbes. The most common organisms found in blood culture were coagulase-negative Streptococci (10%), *Klebsiella* (10%), and non-fermentative Gram-negative bacilli (10%), followed by *Staphylococcus aureus* (5%) and *Pseudomonas* (5%). The organism isolated from pus culture in one child was *Escherichia coli* (2.5%). About 22.5% (9) of the children died, 12.5% recovered following intensive

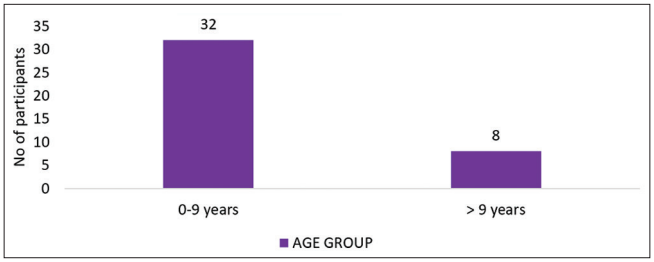

Figure 1: Age group of the study participants.

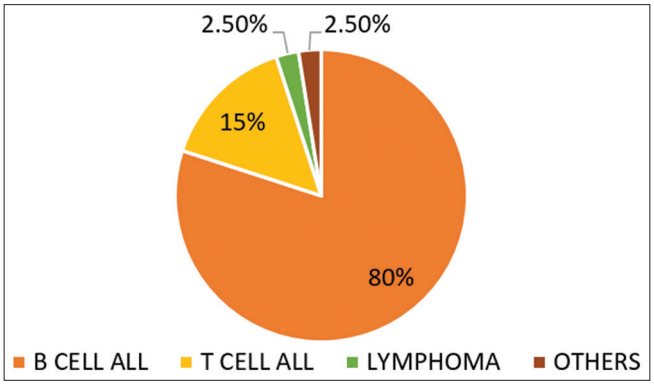

Figure 2: Diagnosis of the study participants. ALL: Acute lymphoblastic leukemia.

Table 1: Demographic features and diagnosis in the study participants (*n*=40).

Demographic features and diagnosis	Frequency (*n*=40)	Percentage (in %)
Age group (in years)		
0–9	32	80
>9	8	20
Gender		
Male child	25	65
Female child	15	35
Diagnosis		
B-cell ALL	32	80
T-cell ALL	6	15
Lymphoma	1	2.5
AML	1	2.5
Risk stratification		
High	31	77.5
Standard	9	22.5
Disease characteristic		
Newly diagnosed	35	87.5
Relapsed	5	12.5

ALL: Acute lymphoblastic leukemia, AML: Acute myeloid leukemia

treatment care (ICU care), and the remaining 65% recovered following medical care at the ward and discharged. The mean time taken for recovery of febrile neutropenia with care in the ward was 5.08 ± 2.29 (2–12) days, and from ICU was 9.40 ± 4.43 (3–20) days [Table 3].

Table 2: Clinical features and chemotherapy in the study participants (*n*=40).

Clinical features and chemotherapy	Frequency (*n*=40)	Percentage (in %)
Past episodes of neutropenia		
Yes	15	37.5
No	25	62.5
Number of previous episodes		
0	25	62.5
1	6	15
2	6	15
3	3	7.5
Phases of chemotherapy		
Induction 1B	9	22.5
Consolidation	8	20
Induction 1A	8	20
Reinduction	6	15
Others (relapse, RT)	6	15
Maintenance	2	5
Not started chemo	1	2.5
Interval since last drug usage		
Less than 7 days	21	52.5
More than 7 days	18	45
Not started chemo	1	2.5
Chemotherapy drug used		
Methotrexate	9	22.5
Cytarabine	9	22.5
Vincristine	8	20
Daunorubicin	7	17.5
Cyclophosphamide	2	5
L asparaginase	5	12.5
Clinical features		
IV line cellulitis	9	22.5
Oral mucositis	9	22.5
GI involvement	9	22.5
LRTI/ARDS	5	12.5
Fever only	5	12.5
URTI	2	5
Bed sores	1	2.5

GI: Gastrointestinal, RT: Radiotherapy, LRTI: Lower respiratory tract infection, ARDS: Acute respiratory distress syndrome, URTI: Upper respiratory tract infection, RT: Radio therapy, IV: Intra venous

With respect to gender, there was no statistically significant difference in case of outcome ($P > 0.05$). On comparing the type of hematological malignancy with the outcome of febrile neutropenia, it was observed that 5 (15.6%) children of B cell ALL, 2 (33.3%) children of T-cell ALL, 1 (100%) child with Burkitt lymphoma, and 1 (100%) of AML died which was not statistically significant ($P > 0.05$). About 16.1% of episodes in the high-risk category required ICU care, 61.3% of the episodes in the high-risk category, and 77.8% in standard risk recovered with care in the ward itself. About 25% of those in Induction 1A, 22.2% in Induction 1B, 25% in the

Table 3: Microbiological profile and outcome of the study participants (*n*=40).

Microbiological profile and outcome	Frequency (*n*=40)	Percentage (in %)
Absolute neutrophil count		
Severe (100–500/cu.mm)	22	55
Profound (<100/cu.mm)	18	45
Infection profile		
Clinically documented infection	23	57.5
Microbiologically documented infection	17	42.5
Culture growth		
No growth	23	67.5
Coagulase negative Streptococci	4	10
Klebsiella	4	10
Non-fermentative Gram-negative bacilli	4	10
Staphylococcus aureus	2	5
Pseudomonas	2	5
Escherichia coli	1	2.5
Outcome		
Recovered with care in the ward	26	65
Recovered with ICU care	5	12.5
Death	9	22.5

ICU: Intensive care unit

maintenance phase, and 16.7% in the reinduction phase died. One child died even before starting chemotherapy. However, there was no statistical difference with respect to phases of chemotherapy and outcome ($P > 0.05$) [Table 4].

The time interval between chemotherapy and the occurrence of neutropenia has an impact on the outcome, which was also statistically significant. Among children with profound neutropenia, 38.9% died, 16.7% recovered following ICU care, and 44.4% recovered following medical care from the ward. With severe neutropenia, 9.1% died, 9.1% were treated in ICU, and 81.8% recovered with medical care. Chances of poor outcome were higher in profound neutropenia compared to severe neutropenia ($P < 0.05$). On comparing hemoglobin count with the outcome of febrile neutropenia, it was observed that 71.6% of the children with hemoglobin <5 g/dL died compared to 12.1% of children with hemoglobin more than 5 g/dL, which was statistically significant ($P < 0.05$). Among 40 children with hematological malignancy with febrile neutropenia, 7 (46.7%) out of 15 children with platelet count <50000 died, 20% were treated at ICU, and 33.3% recovered with care from the ward. Among those children with platelet count >50,000, 8% died, 8% required ICU care, and 84% were discharged following medical care from the ward, which was statistically significant ($P < 0.05$). Hence, it was observed that low platelet count was associated with poor outcomes. With respect to infection profile, it was found that 47.2% of episodes with microbiologically documented infection died, 17.6% required ICU care, and 35.2% recovered following medical care from the ward. Among those with clinically documented infection, 4.3% died, 12.5% required ICU care, and 86.9% recovered following medical care from the ward. Those with microbiologically confirmed infection had poor outcomes compared to clinically documented infection ($P < 0.05$) [Table 4].

Among four children with coagulase-negative streptococci in culture, it was observed that all four were sensitive to cefotaxime, followed by carbapenem and linezolid (50%). Four children tested positive for *Klebsiella* infection. Among them, three children were sensitive to carbapenem, followed by amikacin, gentamicin, and ciprofloxacin (50%). For children with positive to non-fermentative Gram-negative bacilli, all four were sensitive to amikacin and ciprofloxacin, followed by gentamicin and cefotaxime (75%). All the children positive for *S. aureus* infection were sensitive to gentamicin, piperacillin, tazobactam, clindamycin, cotrimoxazole, erythromycin, and tetracycline. Among two children sensitive to *Pseudomonas*, both were sensitive to amikacin, gentamicin, ciprofloxacin, and cefotaxime. One child with a positive for *E. coli* was sensitive to both carbapenem and amikacin.

DISCUSSION

Among the 40 episodes, 80% of the episodes were presented in children with B-cell ALL, 15% of the episodes in T-cell ALL, and 2.5% each in lymphoma and AML. The results differ from the study done by Lakshmaiah *et al*., which analyzed 108 febrile neutropenic episodes in 72 children. Their study concluded that the occurrence of febrile neutropenia is higher in AML and the outcome is also poor in AML.[6] In our study, only one child with AML was included during the study period, and the child died following the first neutropenic episode due to DIVC.

Nearly 22.5% of the episodes in our study occurred in the induction 1B phase and 20% in the induction 1A phase, which accounts for a total of 42.5% of the episodes in the induction phase of chemotherapy. This data aligned with many different studies in India and also various countries in the world, where nearly 40–45% of the episodes occurred during the induction phase.

Most of the episodes of febrile neutropenia occurred following the administration of cytarabine and methotrexate. The interval between the chemotherapy and the occurrence of febrile neutropenia had an impact on the outcome. Lesser the time interval between the chemotherapy administration and occurrence of febrile neutropenia, poorer the prognosis. In our study, children who developed neutropenia within 7 days of chemotherapy had longer recovery periods, and seven out of nine children who died developed febrile neutropenia within 7 days of chemotherapy, which was statistically significant. The study done by Prasad *et al*. found

Table 4: Association of demographic, clinical, hematological, and microbiological profiles with outcome in the study participants.

Parameters	Recovered with care in ward (%)	Recovered with ICU care (%)	Death (%)	Chi-square test value	*P*-value
Gender					
Male	19 (73.1)	3 (11.5)	4 (15.4)	2.574	0.331
Female	7 (50)	2 (14.3)	5 (35.7)		
Diagnosis					
B-cell ALL	22 (68.8)	5 (15.6)	5 (15.6)	8.34	0.161
T-cell ALL	4 (66.7)	0	2 (33.3)		
Lymphoma	0	0	1 (100)		
Others	0	0	1 (100)		
Risk					
High	19 (61.3)	5 (16.1)	7 (22.6)	1.334	0.639
Standard	7 (77.8)	0	2 (22.2)		
Phases of chemotherapy					
Induction 1A	4 (50)	2 (25)	2 (25)	10.10	0.64
Induction 1B	7 (77.8)	0	2 (22.2)		
Maintenance	1 (50)	1 (50)	0		
Consolidation	6 (75)	0	2 (25)		
Not started chemo	0	0	1 (100)		
Others	4 (66.7)	1 (16.7)	1 (16.7)		
Reinduction	4 (66.7)	1 (16.7)	1 (16.7)		
Past episodes					
Yes	9 (60)	3 (20)	3 (20)	1.30	0.55
No	17 (68)	2 (8)	6 (24)		
Interval since the last drug					
<7 days	10 (47.6)	4 (19)	7 (33.3)	13.82	0.003*
More than 7 days	16 (88.8)	1 (5.6)	1 (5.6)		
Not started chemo	0	0	1 (100)		
Absolute neutrophil count					
Profound	8 (44.4)	3 (16.7)	7 (38.9)	6.35	0.035*
Severe	18 (81.8)	2 (9.1)	2 (9.1)		
Hemoglobin count					
Less than or equal to 5	1 (14.2)	1 (14.2)	5 (71.6)	12.40	0.002*
More than 5	25 (75.8)	4 (12.1)	4 (12.1)		
Platelet count					
<50000	5 (33.3)	3 (20)	7 (46.7)	10.72	0.002*
>50000	21 (84)	2 (8)	2 (8)		
Infection profile					
Microbiologically documented infection	6 (35.2)	3 (17.6)	8 (47.2)	10.85	0.003*
Clinically documented infection	20 (86.9)	2 (8.6)	1 (4.3)		

*Statistically significant by Chi-square test. ICU: Intensive care unit, ALL: Acute lymphoblastic leukemia

that receiving chemotherapy <7 days ago was a risk factor for adverse outcomes, but this result was not statistically significant in their study.[7]

Children who had profound neutropenia at presentation had a poor outcome, which was statistically significant. This result was similar to the results of the study done by Lehrnbecher *et al.*, where ANC of <100/cu.mm has been identified as a risk factor for adverse outcomes.[8]

In our study, along with neutropenia, a hemoglobin of <5 g/dL and a platelet count of <50,000/cu.mm have been identified to have an impact on the outcome, which was also statistically significant. The results from the studies by Santolaya *et al.*, Swiss pediatric oncology group (SPOG) adverse events rule were similar in that a platelet count <50,000/cu.mm is a risk factor for adverse outcomes.[9] The hemoglobin level taken as a cutoff for predicting adverse outcomes in other studies, such as Lehrnbecher *et al.*, was 7 g/dL, whereas, in our study, it is 7 g/dL.[8]

Microbiologically proven infections were found to have an adverse effect on the outcome. Children with microbiologically proven infections required admission to the ICU, and those who did not require ICU admission took

a longer time to recover. All nine children who died due to febrile neutropenia had a microbiologically proven infection. On the contrary, children with a clinically documented infection recovered earlier.

Out of the 13 culture positive sepsis, the most common organisms isolated from cultures are Gram-negative bacilli (64.7%). Among the Gram-negative bacilli, *Pseudomonas* growth was observed in 15%, *Klebsiella* growth in 30%, non-fermentative Gram-negative bacilli in 30%, and *E. coli* growth in 7.7%. These results are higher than the percentage of Gram-negative infections observed in the studies conducted in Maulana Azad Medical College by Dubey *et al*.[10] and by Lakshmaiah *et al*.[6], where the incidence was around 36–40%. These Gram-negative organisms are sensitive to the drugs in the order as follows – amikacin (69%), ciprofloxacin (61%), carbapenem (46%), and gentamicin (38%).

Our study is one of the few prospective studies conducted on the clinical profile of febrile neutropenia in hematological malignancies. We want to emphasize the fact that every institute with a hemato-oncology unit should have a periodic assessment of the clinical variables, pattern of microbial infections, and mortality in febrile neutropenia.

CONCLUSION

Febrile neutropenia is common during the induction phase and the most common drug causing febrile neutropenia is methotrexate and cytarabine. The risk factors associated with poor outcomes are the time interval between chemotherapy and occurrence of neutropenia, profound neutropenia at presentation, culture-positive sepsis, hemoglobin <5 g/dL, and platelet count <50,000/cu.mm. Gram-negative bacteria are the most common organisms isolated from the culture, and most of them are sensitive to ciprofloxacin and amikacin. Although this study would need validation across other research-limited settings, it is hoped that the information gained from this study will be useful in deciding the treatment of children with febrile neutropenia and the risk factors of the outcome.

Ethical approval

The research/study was approved by the Institutional Review Board at MADURAI MEDICAL COLLEGE, number 24/(16.11.2021), dated November 16, 2021.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Nil.

Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript, and no images were manipulated using AI.

REFERENCES

1. Karanwal AB, Parikh BJ, Goswami P, Panchal HP, Parekh BB, Patel KB. Review of Clinical Profile and Bacterial Spectrum and Sensitivity Patterns of Pathogens in Febrile Neutropenic Patients in Hematological Malignancies: A Retrospective Analysis from a Single Center. Indian J Med Paediatr Oncol 2013;34:85-8.
2. Taj M, Farzana T, Shah T, Maqsood S, Ahmed SS, Shamsi TS. Clinical and Microbiological Profile of Pathogens in Febrile Neutropenia in Hematological Malignancies: A Single Center Prospective Analysis. J Oncol 2015;2015:596504.
3. Jacob LA, Lakshmaiah KC, Govindbabu K, Suresh TM, Lokanatha D, Sinha M, *et al.* Clinical and Microbiological Profile of Febrile Neutropenia in Solid Tumors and Hematological Malignancies at a Tertiary Cancer Care Center in South India. Indian J Cancer 2014;51:464-8.
4. Mandal PK, Maji SK, Dolai TK, De R, Dutta S, Saha S, *et al.* Micro-organisms Associated with Febrile Neutropenia in Patients with Haematological Malignancies in a Tertiary Care Hospital in Eastern India. Indian J Hematol Blood Transfus 2015;31:46-50.
5. Zhang Y, Zheng Y, Dong F, Ma H, Zhu L, Shi D, *et al.* Epidemiology of Febrile Neutropenia Episodes with Gram-Negative Bacteria Infection in Patients Who Have Undergone Chemotherapy for Hematologic Malignancies: A Retrospective Study of 10 Years' Data from a Single Center. Infect Drug Resist 2020;13:903-10.
6. Lakshmaiah KC, Malabagi AS, Govindbabu, Shetty R, Sinha M, Jayashree RS. Febrile Neutropenia in Hematological Malignancies: Clinical and Microbiological Profile and Outcome in High-Risk Patients. J Lab Physicians 2015;7:116-20.
7. Prasad M, Chinnaswamy G, Arora B, Vora T, Hawaldar R, Banavali S. Risk Predictors for Adverse Outcome in Pediatric Febrile Neutropenia: Single Center Experience from a Low and Middle-income Country. Indian J Cancer 2014;51:432-7.
8. Lehrnbecher T, Phillips R, Alexander S, Alvaro F, Carlesse F, Fisher B, *et al.* Guideline for the Management of Fever and

Neutropenia in Children with Cancer and Undergoing Hematopoietic Stem-cell Transplantation. J Clin Oncol 2012;30:4427-38.
9. Santolaya ME, Alvarez AM, Becker A, Cofré J, Enríquez N, O'Ryan M, *et al.* Prospective, Multicenter Evaluation of Risk Factors Associated with Invasive Bacterial Infection in Children with Cancer, Neutropenia, and Fever. J Clin Oncol 2001;19:3415-21.
10. Dubey AP, Singhal D, Prakash SK. Febrile Episodes in Childhood Malignancies. Indian Pediatr 2002;39:952-7.

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