Original Article

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Clinical Characteristics and Outcomes of Non-Neutropenic Fever in Children with Cancer: An Urban-Single Institution Experience

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ABSTRACT

OBJECTIVE: To evaluate the clinical characteristics and outcomes of pediatric cancer with non-neutropenic fever (NNF) in pediatric cancer patients in the absence of a central venous catheter.

METHODS: This single-center retrospective cohort study enrolled pediatric patients with cancer (age < 18 years) who received chemotherapy treatment at the Department of Pediatrics, Faculty of Medicine Vajira Hospital, Navamindradhiraj University, Bangkok, Thailand, from January 2016 to July 2020. Clinical characteristics and outcomes of NNF episodes were described. Descriptive statistics were analyzed.

RESULTS: Fifty-one patients were reviewed, but the 97 NNF episodes were documented from 32 patients. Only One (of the 51 patients) had subcutaneous port. The most frequent cancer diagnosis was acute lymphoblastic leukemia (51%). NNF occurred in 3.8 per 1,000 days of chemotherapy period (95% confidence interval [CI] 3.1–4.6). The most frequently clinically documented infections were respiratory tract infection (35%), urinary tract infection (11%), and gastrointestinal infection (10%). The causative pathogens could not be demonstrated in 67.1% of NNF episodes. The commonly identified pathogens were viruses (12.3%), gram-negative bacteria (10.3%), and gram-positive bacteria (5.2%). Empiric treatment with antibiotic was initiated in 92.8% of the total episodes. Ceftriaxone was the most common antibiotic of choice. Only one episode had a positive hemoculture. Four (4.1%) episodes required intensive care unit admissions, and only one NNF-related mortality due to the human Bocavirus pneumonia and multi-organ failure occurred. The mortality rate of NNF was 3.1%.

CONCLUSION: NNF episodes are common and life-threatening complications among pediatric cancer patients and generally lead to hospitalization. The incidence of NNF was 3.8 per 1,000 days of chemotherapy (95% CI 3.1–4.6). The causative pathogen in 67% of NNF episodes was unknown, and the commonly identified pathogens were viruses. However, many patients did not identify any causative bacteria, and they received intravenous antibiotics and were hospitalized. The results of our study suggest that patients with severe symptoms may indicate early evaluation and prompt management for viral infection, especially in a patient with a negative bacterial culture and poor respond to antibiotic treatment. This study reveals baseline information for future cohorts to provide guideline management of this common complication during cancer treatment.

KEYWORDS: cancer, chemotherapy, fever, non-neutropenic fever, pediatric

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INTRODUCTION

Over the past few decades, there has been progress in the treatment of pediatric patients with cancer, including chemotherapy regimens, radiation and hematopoietic stem cell transplantation, to improve the treatment outcomes and survival rates of childhood cancer[1-2]. However, these treatment options are associated with immunosuppression caused by multiple factors such as neutropenia, hypogammaglobulinemia, T-cell dysfunction, and mucosal barrier injury[3]. Infection is an important cause of treatment-related mortality in these patients[4]. Febrile illness in children with cancer is a common complication that requires urgent evaluation and management during treatment[5]. Several consensus clinical practice guidelines are established for the management and predictive factors of severe adverse events of fever with neutropenia (absolute neutrophil count [ANC] < 500 cells/mm^3)[6-7]. In 2017, the International Pediatric Fever and Neutropenia Guideline Panel, a group of experts in pediatric oncology and infectious diseases, formulated evidence-based recommendations and classified febrile neutropenia (FN) into groups with low and high risks for the develop of poor outcomes using multiple factors and suggest that the low-risk FN group may consider outpatient management, careful monitor and follow-up[8]. Regardless, cancer patients without neutropenia are also immunocompromised. One study[9] reported a significant greater incidence of bacteremia in pediatric patients with non-neutropenic fever (NNF) than in patients with FN (23.6% vs. 9.4%, respectively), particularly associated with the presence of central venous catheter exit site infection. However, there is no standard evidence-based recommendation guideline for the management approach in patients with fever with an ANC ≥ 500 cells/mm^3. Recently, a meta-analysis that evaluated fever episodes with ANC ≥ 500 cells/mm^3 in pediatric cancer patients revealed that the pooled-average bacteremia rate was 8.2% among total 4,106 NNF episodes, and the management of febrile non-neutropenic patients differed across studies[10]. The authors also addressed a relatively risk factors of bacteremia included type of central venous catheter, ill appearing patients, and higher body temperature. A recent study[11] on developing the possible risk prediction model for bloodstream infection in febrile pediatric cancer patients who had central venous catheters with ANC ≥ 500 cells/mm^3 suggested that the low-risk group may consider outpatient care without antibiotics. In contrast, the high-risk group may be hospitalized for broad-spectrum antibiotics. Studies on the incidence, outcome, and consensus management guidelines among pediatric patients with NNF are limited, especially in Thailand.

This study was designed to provide additional information on this patient population. This urban single-institution retrospective study aimed to analyze the incidence, clinical manifestations, management, and outcomes of pediatric cancer with NNF.

METHODS

Study population

All pediatric patients with cancer aged < 18 years who received chemotherapy treatment at an urban-tertiary hospital in Bangkok, Thailand, from January 1, 2016, to July 31, 2020, were eligible for inclusion. The study was approved by the Ethical Clearance Committee on Human Rights Related to Research to Research Involving Human Subjects, Faculty of Medicine Vajira Hospital, Navamindradhiraj University, Thailand (COA 180/2563).

NNF episode was defined as fever reported from home or body temperature recorded in the hospital at least 38°C for 1 hour or > 38.3°C once and ANC ≥ 500 cells/mm^3 [11].

Recurrent fever episodes during a 7-day period of treatment were counted as a single episode. Fever episodes in patients who received treatment or antibiotics for a previous documented infection or discontinued antibiotics for < 24 hours or ANC declined to < 500 cells/mm^3 within 24 hours were excluded from this study.

Data collection

The cohort included 51 consecutive pediatric patients with cancer who had been treated between study periods. All medical records were retrospectively reviewed to identify all NNF episodes encountered in both outpatient and inpatient settings. For eligible patients, demographic data, including age, sex, and cancer diagnosis, were collected. Treatment-related data regarding treatment protocol, catheter, or device type were recorded. For all the identified NNF episodes, fever characteristics, including vital signs, sepsis based on the 2005 International pediatric sepsis consensus conference criteria[12], choice of antibiotics administered, laboratory data, culture results (blood, urine, and other cultures), and clinical outcomes were collected.

Statistical Analysis

Data analyses were performed using the PASW Statistical Software version 28 (SPSS, Chicago, IL, USA) and STATA version 11 (College Station, TX, USA). Descriptive statistics were expressed as mean ± standard deviation, median (range), or percent. Categorical data were analyzed using Fisher's exact test. A p-value of less than 0.05 was considered statistically significant.

RESULTS

Fifty-one patients were reviewed, but the 97 NNF episodes over 25,506 days of chemotherapy were documented from 32 patients. Nineteen patients (37.2% of patient population) had occurrence of fever episodes while neutropenic (ANC < 500 cells/mm^3) or undertreatment of the previous document of infection. NNF occurred in 3.8 per 1,000 days of chemotherapy (95% confidence interval [CI] 3.1–4.6). Patient characteristics are summarized in Table 1. The most common cancer diagnosis was acute lymphoblastic leukemia. The mean patient age was 7.7 years (range, 0.3–15.3 years). Almost all patients did not use any central venous catheters (CVCs). Only one (of the 51 patients) had subcutaneous port. All patients received trimethoprim-sulfamethoxazole as *pneumocystis jirovecii* pneumonia (PJP) prophylaxis.

Table 1 Patient characteristics

Characteristics	Results (N=51)
Age at baseline, years, mean±SD	7.7 ± 3.7
Male:Female	27:24
Cancer diagnosis, n (%)	
Acute lymphoblastic leukemia	26 (51.0)
Solid tumor	10 (19.6)
Osteosarcoma	3 (5.9)
Rhabdomyosarcoma	2 (3.9)
Hepatoblastoma	2 (3.9)
Germ cell tumor	1 (2.0)
Neuroblastoma	1 (2.0)
Ewing sarcoma	1 (2.0)
Medulloblastoma	4 (7.8)
Lymphoma	4 (7.8)
Acute myeloid leukemia	4 (7.8)
Langerhans cell histiocytosis	2 (3.9)
Chronic myeloid leukemia	1 (2)
Type of CVC, n (%)	
No	50 (98.0)
Subcutaneous port	1 (2.0)
Patients with any NNF episodes, n (%)	32 (62.8)

Abbreviations: CVC, central venous catheter; N, number; NNF, non-neutropenic fever; SD, standard deviation

The characteristics of the 97 NNF episodes are demonstrated in Table 2. The median body temperature was 38.6°C (range, 38–41°C). Fifty-six NNF episodes (57.7%) occurred in the inpatient setting. Most of the patients with NNF episodes (80.5%) present in outpatient settings, including clinics and emergency departments, were admitted. Patients with high presenting fever were more likely to be admitted. The mean temperature was higher in hospitalized patients (38.98°C, SD=0.73) compared with patients who were treated in outpatient settings (38.33°C, SD=0.17) (p = 0.01). The most frequently clinically documented diagnoses were respiratory tract infection (33%), urinary tract infection (UTI) (11.3%), and gastrointestinal tract infection (10.3%). However, 28% of NNF episode causes were unknown, and 32 (32.9%) febrile episodes were caused by identified microorganisms including virus (n=12), gram-negative bacteria (n=10), gram-positive bacteria (n=5), and mycoplasma (n=5). In over 30% of NNF episodes,

Table 2 Clinical characteristics of 97 non-neutropenic fever episodes

Characteristics	Results	
Median time to last chemotherapy, days (range)	6	(0-110)
Location of presentation, n (%)		
Inpatient	56	(57.7)
Pediatric clinic	26	(26.8)
Emergency department	15	(15.5)
Episode with absence of central line using, n (%)	97	(100)
Presenting signs or symptoms, n (%)		
URI symptoms	25	(25.8)
GI symptoms	15	(15.5)
Skin	12	(12.4)
LRI symptoms	8	(8.2)
Urinary tract infection symptoms	2	(2.1)
Seizure	1	(1.0)
No source on exam	34	(35.1)
Sepsis, n (%)	9	(9.2)
Hemoglobin (g/dl), median (range)	10.2	(5.0-13.7)
White blood cell count (cells/mm^3), median (range)	5,979	(1,000-22,500)
Platelet (cells/mm^3), median (range)	25,6500	(78,000-524,000)
Absolute neutrophil count (cells/mm^3), n (%)		
500-999	7	(7.2)
1000-5000	50	(51.5)
> 5000	40	(41.2)
Identified pathogens, n (%)		
Virus*	12	(12.3)
Gram negative bacteria	10	(10.3)
Gram positive bacteria	5	(5.2)
Mycoplasma species	5	(5.2)
Hemoculture		
Positive	1	(1)
No growth	84	(86.6)
Not done	12	(12.4)
Initial empiric antibiotics, n (%)		
Ceftriaxone	29	(29.9)
Ceftazidime plus amikacin	13	(13.4)
Piperacillin/Tazobactam	9	(9.3)
Antiviral agents	9	(9.3)
Meropenem	6	(6.2)
No antibiotic	7	(7.3)
Others	21	(24.6)
Median time to antibiotic, minutes (range)	82.5	(5-250)

Abbreviations: g/dl, grams per deciliter; GI, gastro-intestinal; LRI, lower respiratory traction infection; mm3, cubic millimeter; n, number; URI, upper respiratory tract infection

*influenza virus, varicella-zoster virus, respiratory syncytial virus, human bocavirus

patients reported presenting signs or symptoms of respiratory tract infection. Among the episodes with respiratory tract symptoms (n=33), nasopharyngeal swab for rapid diagnostic tests to identify influenza virus and respiratory syncytial virus (RSV) and multiplex polymerase chain reaction (PCR) test of qualitatively detecting of viral pathogens were done in 39.4% and 6.1% of episodes. The most common identified viruses were influenza virus (n=5), RSV (n=3), varicella-zoster virus (n=3), and human bocavirus (n=1). Blood culture was taken in 87 NNF episodes (89.7%). Only one blood culture-positive specimen was documented, and *Acinetobacter baumannii* was the only microorganism isolate identified, and the bacteremia rate was 1.03%. No episodes of gram-positive septicemia or fungemia occurred in this cohort. Fifteen bacteria were isolated from different sites including urine culture (n=10), stool or rectal swab culture (n=3), hemoculture (n=1), and sputum culture (n=1). The most commonly identified bacterial pathogens were *Salmonella spp.* (n=3), *Escherichia coli* (n=2), *Proteus mirabilis* (n=2), and *Enterococcus faecalis* (n=2). An empirical antibiotic was given in 92.8% of the NNF episodes. The most common initial empiric treatment with ceftriaxone monotherapy was administered in 29.9% of the total events, followed by ceftazidime plus gentamycin (13.4%). Additional antiviral agents were used in some patients with identified viral pathogens. The analysis suggests that only 20.6% (15/97) of NNF episodes were caused by the identified bacterial pathogens, and approximately 70% of identified gram-negative bacteria showed ceftriaxone susceptibility. We found that there was no significant association of antibiotic administration with mortality, needed of intensive care service or delay of the next chemotherapy cycle.

Among the hospitalized patients, the median length of stay was 5 days (range, 1–14 days). In this cohort, four patients who required ICU admission had septic shock (n=3) and pneumonia with respiratory failure (n=3). The clinical data of the patients with a severe condition that needed ICU admission are shown in Table 3. Viruses, including respiratory syncytial virus (n=2) and human bocavirus (n=1), were commonly identified pathogens in patients with severe pneumonia. One of the 32 patients who experienced NNF died, so the mortality rate was 3.1%. The NNF-related cause of death occurred in a 5-year-old boy with acute lymphoblastic leukemia who had severe human bocavirus pneumonia with multi-organ failure (table 3).

Table 3 Clinical courses of NNF patients with severe feature needed intensive care

	Case 1	Case 2	Case 3	Case 4
Age (year)	12.4	5.4	8	14
Sex	Male	Male	Female	Female
Diagnosis	ALL	ALL	ALL	ALL
Treatment protocol/ phase of treatment	TPOG ALL1301/ maintenance	TPOG ALL1302/ maintenance	TPOG ALL1303/ maintenance	TPOG ALL1302/ augmented consolidation
Comorbid	Down syndrome	None	Relapsed ALL	None
Type of central line	None	None	None	None
Presenting place	Inpatient	Outpatient	Emergency room	Inpatient
Day from latest CMT	9	27	18	6
Clinical presentations	Respiratory distress, wheezing	Oral ulcer	Respiratory distress	Severe abdominal pain
Sepsis	None	Yes	Yes	Yes
Initial ANC (cells/mm^3)	6,512	9,555	1,181	10,649
Lowest ANC (cell/mm^3)	6,512	9,555	599	1,400
Empirical antibiotics	IV Cefotaxime	IV Cefotaxime plus cloxacillin	IV Ceftazidime plus amikacin	IV Meropenem

Table 3 Clinical courses of NNF patients with severe feature needed intensive care (continued)

	Case 1	Case 2	Case 3	Case 4
Additional treatment	None	IVIg	None	
Reason for ICU	Respiratory failure	Progressive respiratory failure with shock	Respiratory failure	Septic shock
Identified pathogen	Yes, RSV	Yes, human bocavirus	Yes, RSV	No
Hemoculture	No growth	No growth	No growth	No growth
Final Diagnosis	RSV pneumonia	Human bocavirus pneumonia with multi-organ failure	RSV pneumonia	Severe necrotizing pancreatitis
Outcome	Discharge, full recovery	Dead	Discharge, full recovery	Discharge, full recovery

Abbreviations: ALL, acute lymphoblastic leukemia; ANC, absolute neutrophil count; CMT, chemotherapy; ICU, intensive care unit; IV, intravenous; IVIg, intravenous immunoglobulin; mm3, cubic millimeter; NNF, non-neutropenic fever; RSV, respiratory syncytial virus; TPOG, Thai pediatric oncology group

DISCUSSION

Fever is a common event among children with cancer during chemotherapy. Our cohort reports that NNF occurs in 3.8 per 1,000 days of chemotherapy in the absence of CVCs in children with cancer. NNF was common among patients aged 5–10 years, similar to previous studies[11,13].

The International Pediatric Fever and Neutropenia Guideline Panel reported the evidence-based clinical practice guideline for patients with FN[8]. It recommended considering initial or step-down outpatient management with a capable infrastructure to ensure safe outpatient monitoring and follow-up in patients with low-risk or severe adverse outcomes. However, specific management guideline of the patient with non-neutropenic fever is still unclear, and it varies across institution[14]. In multicenter retrospective review study by Esbenshade et al.[11] bacteremia occurred in 4.2% over 937 NNF episodes in pediatric oncology patients with central venous catheter, with 77.6% of episodes were outpatient at presentation. Overall 42% of NNF episodes (409/937) were received antibiotics. Following the approach to risk-stratified management of NNF in the study, there were 22/937 episodes (2.3%) of fever with high blood stream infection risk recommended to be admitted on broad spectrum antibiotics. Our study shows that the vast majority of patients with NNF presenting to the outpatient settings were hospitalized (80.5%). A high admission rate in our cohort may be caused by the providers' concern about the family's ability to observe and return to hospital service, and lack of risk-stratified approach management during the study period.

In this study, the causative pathogen could not be identified in 67.1%. The most common microbiologically proven infections were bacterial infections (gram-negative and gram-positive bacteria), followed closely by viral infections. Contrary to a previous study on children with cancer who had central line catheters[15], bacterial infection was greater than the fever of unknown origin, viral infection, and fungal infection in fever episodes with and without neutropenia. Additionally, this study documents a rate of bacteremia as low as 1.03% of NNF episodes, whereas a previous study reported 3.1%–8.2% [10-11, 16]. The lower rate of bacteremia may result from the lack of central line use in the study population. Although the bacteremia rate in our study population is relatively low, it was found that patients with severe symptoms were commonly caused by viral infection. Among our patients with severe symptoms requiring treatment in intensive care, 75% presented with viral pneumonia. Previous studies[17-18] reported that respiratory viral infections increase morbidity and mortality in children with cancer, which was similar to our study's patients.

Regarding the initial antibiotic therapy, ceftriaxone monotherapy constituted the most common antibiotic of choice. A similar finding was reported in a simple meta-analysis by Allaway et al. that empirical antibiotics therapy with ceftriaxone

is commonly prescribed in patients with NNF with a central line[10]. However, there was no significant association of antibiotic administration with mortality, intensive care admission or delay of the next chemotherapy cycle in our cohort.

In the present study, NNF-related mortality occurred in one out of thirty-two (3.1%). Fatal human bocavirus pneumonia with multi-organ failure in a boy with ALL was associated leading cause of death. Recent studies[19-20] showed that severe human bocavirus infection was rare. However, it could occur in patients with underlying chronic conditions, such as congenital heart disease, chronic lung disease, premature birth, cancer, and immune deficiency. A previous study evaluating NNF in children with cancer found a favorable outcome of NNF with an absence of NNF-related deaths[10]. The difference reported may be because of population differences or differences in specific clinical management across countries. NNF mortality among children with cancer may be unrecorded in Asian population.

As study limitations, the retrospective design may lead to incomplete data collection. Testing for potential causative pathogens may differ among NNF presenting episodes. More comprehensive information is more likely collected in inpatients than in outpatients. In addition, with a small sample size, single-center patients may not be representative of patients in other centers. Therefore, to obtain more accurate data, prospective multicenter research is warranted.

CONCLUSION

In conclusion, fever and infection are important and life-threatening complications among pediatric cancer patients with non-neutropenia and commonly lead to hospitalization. This study shows clinical characteristics and incidence of NNF in pediatric cancer in the absence of CVCs. In children with cancer, NNF occurs in 3.8 per 1,000 days of chemotherapy. A lower rate of bacteremia was registered in our study population. Viral infections are common among NNF episodes. However, many patients did not identify any causative bacteria; they received intravenous antibiotics and were admitted. The most clinically severe NNF episodes that required intensive care were caused by respiratory viral pathogens. The mortality rate was 3.1%, with human bocavirus pneumonia with multi-organ failure being the cause of death. The results of our study suggest that patients with severe symptoms may indicate early evaluation and prompt management for viral infection, particularly in a patient with a negative culture and poor respond to antibiotic treatment. Our study reveals clinical practice information, local distribution of pathogens, and significant effect of respiratory viral infection on pediatric patients with NNF in the absence of CVCs.

CONFLICT OF INTEREST

None

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DATA AVAILABILITY STATEMENT

Data available within the article or its supplementary materials

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