

# Management of febrile neutropenia in pediatric cancer patients

## Abstract

**Introduction:** Febrile neutropenia (FN) is the most common complication that threatens the life of patients undergoing chemotherapy. It is considered an oncological emergency and its therapeutic decisions must be timely and accurate.

**Objective:** To evaluate the therapeutic approach given to pediatric cancer patients with episodes of neutropenia and fever.

**Material and methods:** Descriptive, observational, cross-sectional and retrospective study in children with acute lymphoblastic leukemia (ALL), acute myeloblastic leukemia (AML), Burkitt's lymphoma (BL) and lymphoblastic lymphoma (LL) who attended the hematology service from 2014 to 2018. Age, gender, underlying diagnosis, treatment phase, absolute neutrophil count, clinical manifestations, blood culture collection and results, initial antimicrobial therapy, treatment changes, complications, days of hospital stay and mortality were analyzed. Descriptive statistics was used, with measures of central tendency, percentages and frequencies with the SPSS v22 program.

**Results:** We identified 104 episodes of FN in 70 patients with cancer. The mean age was 7 years and majority of patients were male (n=49, 70.0%). ALL was the most frequent underlying malignancy (n=59, 84.3%) and the highest amount of FN episodes occurred during the induction phase (n=74, 71.2%). Fever of unknown origin was observed in 29 (27.9%) episodes. Blood cultures were collected in 14 (13.5%) cases. The most commonly isolated microorganisms in blood culture were Gram-positive bacteria (n=10, 76.9%).  $\beta$ -lactams and aminoglycosides were the most common antibiotics used.

**Conclusions:** Febrile neutropenia is a frequent complication in the pediatric population with hemato-oncological diseases in our hospital. The therapeutic approach that patients receive is adequate.

**Keywords:** febrile neutropenia; leukemia; lymphoma; pediatrics

## Introduction

Febrile Neutropenia (FN) is defined as an absolute neutrophil count (ANC) <500 cells/microliter or <1,000 cells/microliter with a projected nadir of  $\leq$ 500 cells/microliter in the next 24 hours and fever  $>101^{\circ}\text{F}$  ( $>38.5^{\circ}\text{C}$ ) or two measurements  $>100.4^{\circ}\text{F}$  ( $>38.0^{\circ}\text{C}$ ) in one hour.<sup>1,2</sup>

Febrile neutropenia is the most common complication that threatens the lives of patients undergoing chemotherapy. In the United States, it is estimated that a total of 60,294 episodes of NF per year were recorded.<sup>3</sup>

In the context of oncological patients, neutropenia is more commonly associated with cytotoxic therapy.<sup>4</sup>

Bacterial infections are commonly caused by six main etiologies: three Gram-negative (E. coli, Klebsiella sp and Pseudomonas aeruginosa) and three Gram-positive (S. aureus, S. epidermidis and S. viridans).<sup>5</sup>

In order to give an adequate approach, a complete medical history and physical examination should be performed, as well as a complete blood count, a blood culture (taken before the start of antibiotic therapy) and a risk category should be established.<sup>6</sup>

According to the guidelines of the National Comprehensive Cancer Network (NCCN), patients who develop NF can be classified as low

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or high risk of complications. This classification takes into account comorbidities, functional status, temperature, source of infection, organ failure, etc.<sup>7</sup>

The 2017 update to the “Guideline for the Management of Fever and Neutropenia in Children with Cancer and Hematopoietic Stem-Cell Transplantation Recipients”, published in the Journal of Clinical Oncology,<sup>8</sup> recommends empirical therapy according to the patient’s risk as follows:

- High risk; use monotherapy with an antipseudomonal  $\beta$ -lactam, a fourth-generation cephalosporin, or a carbapenem. In unstable patients, a second agent against Gram-negative bacteria or a glycopeptide can be added.
- Low risk: Consider initial or step-down outpatient management if infrastructure allows careful monitoring and follow-up

The Infectious Diseases of America (IDSA) guideline establishes that patients with febrile neutropenia must receive their initial doses of empirical antibacterial therapy within an hour after triage.<sup>9</sup>

Regarding hospital stay, it has been established that, during the first episode of FN, patients will be 1-10 days under surveillance and receiving intrahospitalary care. However, time usually increases with later episodes.<sup>10</sup>

The mortality rate in recent studies of febrile neutropenia in pediatric patients has ranged between 0.7% and 3.9%.<sup>11</sup>

Repeated episodes lead to multiple sequelae such as infections by resistant microorganisms, prolonged hospital stays and decreased quality of life. They also constitute an important cause of mortality, so their detection and timely management have been considered a challenge. Therefore, the objective of this study was to evaluate the therapeutic approach given to pediatric cancer patients with episodes of neutropenia and fever in our hospital.

## Material and methods

The present work is an analytical, observational, transversal and retrospective study of pediatric patients with cancer and febrile neutropenia treated at the Gynecology-Pediatrics and Family Medicine Hospital (GP-FMH) No. 31 of the Mexican Institute of Social Security (IMSS) from July 2014 to August 2018.

A thorough search in the registry of clinical files was carried out, locating patients with diagnosis of acute lymphoblastic leukemia (ICD-10 C910), acute myeloid leukemia (ICD-10 C92.0), lymphocytic lymphoma (ICD-10 C835) and Burkitt's lymphoma (ICD-10 C837).

We reviewed and identified those cases in which the diagnosis of febrile neutropenia was confirmed and included in our analysis all those that were aged 0 to 16 years. Files that had incomplete information were excluded.

We collected information on the following variables: age, gender, underlying diagnosis, treatment phase, absolute neutrophil count, clinical manifestations, nosological diagnosis, blood culture collection, microbial isolates, initial antimicrobial therapy, treatment changes, complications, days of hospital stay and mortality.

This study was conducted in accordance with the ethical principles of the Helsinki Declaration and our institution's Local Research Committee.

Descriptive statistics were used: measures of central tendency for quantitative variables and frequencies and percentages for qualitative variables; the information collected was analyzed in the statistical program SPSS version 22.

## Results

Our search allowed us to identify 61 cases with ALL diagnosis, nine patients with AML, three with LL, and one with BL. After the application of inclusion and exclusion criteria, two patients with ALL were eliminated, one with AML and the LB case. Therefore, we analyzed 70 files in total.

During the study period, 104 FN events were recorded. Of the total of patients included, 49 were men (70.0%) and 21 women (30.0%). The median age of the patients was 7 years (range of 2 to 16 years). The age medians by diagnosis and other general characteristics can be found in Table 1.

The average number of events that each patient presented was 1.5 (range 1-6). Majority (n=74, 71.1%) of episodes occurred during the induction phase. The frequency of events according to treatment phase and diagnosis are summarized in Table 2.

Regarding the type of symptoms, the most common manifestations were respiratory (n = 22, 21.15%), digestive (n = 21, 19.8%) and dermatological (n = 15, 14.4%). In four (3.8%) episodes, patients had mixed symptoms. In 13 (12.5%) cases, they presented fever without

symptoms. The frequency of each type of clinical manifestations is recorded in Figure 1.

**Table 1** General characteristics according to diagnosis

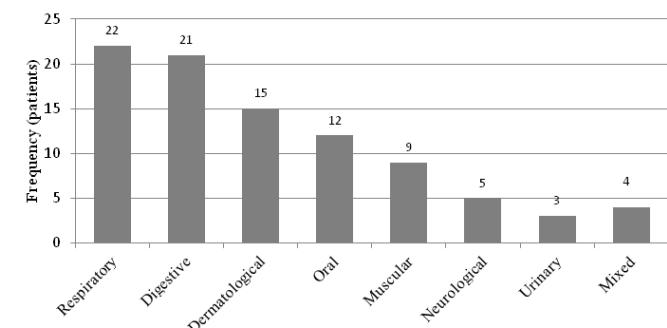
Characteristic	ALL	AML	LL
<b>Patients</b>	59	8	3
Male *	45 (76.3)	3 (37.5)	1 (33.3)
Female *	14 (23.7)	5 (62.5)	2 (66.7)
<b>Age (years) *</b>	7	5.5	4.5
<b>FN episodes *</b>	93 (87.7)	8 (8.5)	3 (3.8)
<b>Most common symptoms</b>	Respiratory	Digestive	Digestive
<b>Absolute neutrophil count *</b>	199 x 10 <sup>3</sup>	254 x 10 <sup>3</sup>	158 x 10 <sup>3</sup>
<b>Deaths</b>	9 (15.3)	2 (25)	1 (33.3)

\* Number (percentage), + median, ALL, acute lymphoblastic leukemia; AML, Acute Myeloblastic Leukemia; LL, lymphoblastic lymphoma

**Table 2** Treatment phases

Treatment phase	ALL *	AML *	LL *
Induction	66 (71.0)	6 (75.0)	2 (66.7)
Consolidation	9 (9.7)	2 (25.0)	1 (33.3)
Maintenance	7 (7.5)	0	0
Relapse	11 (11.8)	0	0
Total	93 (100.0)	8 (100.0)	3 (100.0)

\*Number (percentage), ALL, acute lymphoblastic leukemia; AML, Acute Myeloblastic Leukemia; LL, lymphoblastic lymphoma



**Figure 1** Frequency of clinical manifestations

The nosological diagnoses were: 29 (27.9%) cases of fever of unknown origin (FUO), 18 (17.3%) of neutropenic colitis, 15 (14.4%) of pneumonia, 13 (12.5%) of mucositis, 10 (9.6%) of port catheter infection, nine (8.7%) of cellulitis, six (5.8%) of pharyngitis, three (2.9%) of sinusitis and one (1.0%) case of acute ischemic stroke. Eight cases (7.7%) had criteria for septic shock upon admission to the emergency room.

The Absolute Neutrophil Count (ANC) had a median of 193 x 10<sup>3</sup> (ranging from 37 to 530 x 10<sup>3</sup>).

A blood culture was taken in 14 episodes (13.5%); of these, 4 (28.6%) were collected before the start of antimicrobial therapy and the remaining 10 (71.4%) were taken afterwards.

Only one culture's result was not collected since the patient died a day after its obtaining. The remaining 13 cultures were positive; 3 (23.1%) were gram negative bacteria and 10 (76.9%) gram positive. No colonization by fungi was identified by this method. The isolated bacteria are listed in Table 3.

**Table 3** Isolated microorganisms in positive blood cultures

Microorganism	Frequency, n (%)
Pseudomonas aeruginosa	5 (38.5)
Staphylococcus aureus	4 (30.7)
Klebsiella pneumoniae	2 (15.4)
Escherichia coli	1 (7.7)
Streptococcus thoraleensis	1 (7.7)

The time between the start of symptoms and the first dose of antibiotics varied from two to 36 hours and had a median of five hours. Meanwhile, time between medical contact to antibiotic administration had a median of 1.3 hours.

Beta lactams (n=78, 75.0%) and aminoglycosides (n=72, 69.2%) were the most commonly used drugs. The frequency with which these and other drugs were used can be found in Table 4.

**Table 4** Antibiotic use distribution

Drug class	Frequency, n (%)
β -Lactams	78 (75.0)
Aminoglycosides	72 (69.2)
Vancomycin	16 (15.4)
Antifungals	5 (4.8)
Quinolones	5 (4.8)
Carbapenems	4 (3.8)
Macrolides	3 (2.9)
Trimethoprim + Sulfamethoxazole	3 (2.9)
Clindamycin	1 (1.0)
Metronidazole	1 (1.0)

In 27 cases (26.0%), the antimicrobial regime was not changed during the FN episode. The addition of an antifungal to antibiotic treatment occurred in seven (6.7%) cases.

There were no complications in 78.8% (n = 82) of the events. In the cases in which there were complications (n = 22, 31.4%), the most common was sepsis (n = 12, 17.1%). The frequency of the other complications can be seen in table 5.

**Table 5** Frequency of medical complications

Complication	Frequency, n (%)
Acute renal injury	5 (4.8)
Hospital-acquired pneumonia	4 (3.8)
Pleural effusion	3 (2.9)
Cardiac arrest	3 (2.9)
Gastrointestinal hemorrhage	2 (1.9)
Neurological sequelae	1 (1.0)
Muscular hypotrophy	1 (1.0)
Pulmonary aspergillosis	1 (1.0)

The average hospital stay was 12 days. Twelve deaths (17.1%) occurred as a result of an episode of FN (or its complications).

## Discussion

In the study's four-year period, a total of 104 episodes of chemotherapy-associated febrile neutropenia were recorded and treated in 70 patients of GP-FMH No. 31.

There was a marked predominance of the male gender (2.3: 1), which surpasses what was previously reported in international and national studies.<sup>12-14</sup>

The mean age was 7.6 years, higher than the study by Hakim et al.,<sup>15</sup> whose patients averaged 5.9 years, but less than the cohort of Vázquez et al.,<sup>16</sup> in Mexico, where it was 8.3 years.

The average number of events (1.5 per patient) was less than that found by Orozco in Mexico City children's hospital, where they registered 1.96 per child.<sup>17</sup>

Unlike the study by Düzenli et al.,<sup>18</sup> in which the majority of NF events occurred during reinduction (35.6%), the events of the present study occurred during the induction phase (71.2%).

FUO occupies the first cause of NF in this study, causing 27.9% of the episodes, which coincides with other cohorts, where it explains between 23% and 53% of events. Neutropenic colitis, the second cause of FN (17.3%), differs from these cohorts since it is only identified between 5.7 and 8.7% of the cases.<sup>15,17-19</sup>

The median of the ANC ( $193 \times 10^3$ ) varies considerably between studies, being reported lower in some cases, as in the study of Düzenli ( $100 \times 10^3$ ), and greater in others, as in the Vanderpuye study ( $200 \times 10^3$ ).<sup>18,20</sup>

Severe neutropenia ( $<200 \times 10^3$  ANC) was present in 19.3% events, lower than the study of Vathana et al., where it appeared in 44.4% laboratory findings.<sup>21</sup>

Blood culture collection, although subpar according to current treatment guidelines,<sup>8</sup> is comparable with international and national studies, where it has varied from 9.4% to 26%.<sup>17,22</sup> Likewise, the study by Meidani et al., showed that in 68.4% of the medical records, there was no result for culture of anybody fluid.<sup>23</sup>

Even so, blood culture results are vastly better than other studies, which have calculated rates between 0-2.6% regarding positivity, whereas 92.9% of cultures in this research were positive.<sup>23,24</sup> The high percentage of positivity could be explained due to the fact that no evidence of negative cultures was found reported in clinical files.

Regarding microbiological isolates, the predominance of *Pseudomonas aeruginosa* is atypical when compared to similar studies, since it has only been positive in 5.9 to 21.6% of blood cultures. The other isolated bacteria, with the exception of *S. thoraleensis* (which has not been identified in other series), have a comparable frequency.<sup>12,13,16,21</sup>

The time between the onset of fever and the administration of antibiotics had a median of five hours, significantly higher than what the current IDSA guideline recommends (<2 hours).<sup>8</sup> Cox et al., found that in their emergency department, 53% of patients received antibiotics during the first two hours of fever onset; only 5% of their patients took between 240-299 minutes to start treatment.<sup>14</sup> It should be mentioned that this delay in the start of antibiotic therapy is mainly due to the parental delay to seek medical assistance.

The time between the first medical contact and the first dose of antibiotic was 1.3 hours, which is somewhat close the current goal according to IDSA's guideline (<1 hour after triage). The implementation of an emergency treatment protocol, as well as adequate guidance aimed at parents could reduce the time of administration of antibiotics, as Keng et al., did in their hospital.<sup>25</sup>

The most used antibiotic regime was the combination of a  $\beta$ -lactam (mostly cephalosporins) with an aminoglycoside (amikacin). Similarly, in the study by Vathana et al., in Thailand, 77.1% of patients were treated with a combination of cefatazidime and gentamicin.<sup>21</sup> In the same way, Martínez et al., found that 63% of their patients were treated with that same antibiotic combination. The additional introduction of vancomycin or antifungal therapies (6.7%) was only necessary in a minority of patients in both studies.<sup>26</sup>

Almost a third of the patients in this study (31.4%) presented some type of complication, lower than the study from Rodríguez et al., conducted at the Federico Gómez Children's Hospital of Mexico, whose percentage increases to 50.0%.<sup>27</sup>

The mean hospital stay varied considerably from patient to patient, and averaged 12 days, almost double than the study from Lal et al., who calculated an average of 7.5 days.<sup>28</sup>

## Conclusions

Febrile neutropenia is a frequent complication in the pediatric population with hemato-oncological diseases in the GPH-FM No. 31. Currently, Fever of Unknown Origin is the most frequent nosological diagnosis and Gram positive bacteria are the main etiological agents. The therapeutic approach that patients receive is adequate. However, it is necessary to decrease time in antibiotic administration and to emphasize the collection of blood cultures prior to its start, in accordance with the current treatment guidelines.

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None.

## Conflicts of interest

The authors declare no conflict of interest.

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