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Clinical description of pediatric oncology oncology patients with febrile neutropenia admitted to the intensive care unit of the national pediatric oncology unit

Abstract

Objective: To describe the clinical characteristics of pediatric oncology patients who were diagnosed with Febrile Neutropenia (NF) admitted for the first time to the Intensive Care Unit (ICU) of the National Pediatric Oncology Unit (UNOP).

Methods: This is a descriptive and retrospective study where a total of 211 patients who developed NF and required admission to the ICU, between the years 2017 to 2021, were characterized.

Results: The average age was 8 years, 46% were male and 54% female. 72.77% had a severe level of neutropenia and leukemia (81.99%) was the prominent oncologic diagnosis. Within all treatments, 38.39% of the patients were in the induction phase. An associated infectious agent was identified in 33.18%. Gram-negative bacteria were the most frequent causative infectious agent (13.74%). The mean length of stay in the ICU was 6.75±5.79 days. 91.62% of patients did not require mechanical ventilation and the most frequent complication associated with NF was sepsis in 65.88% of cases.

Conclusion: Most cases of Febrile Neutropenia are severe, hematological malignancies (ALL and AML) are the most frequent underlying disease for the development of NF and Gram-negative bacteria are the most frequent causative infectious agent. Most patients do not require mechanical ventilation and the most frequently associated complications are Sepsis and Pneumonia.

Keywords: febrile neutropenia, intensive care unit, national pediatric oncology unit, neutropenia, leukemia

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Introduction

Oncological diseases in children and adolescents are a major problem worldwide, as they are one of the main causes of death in this age group. According to the Pan American Health Organization (PAHO),[1] these pathologies represent the second leading cause of death in the region in people under 18 years of age. Based on statistics from the Annual Report of the Journal of the National Cancer Institute (JNCI),[2] the most common types of cancer in the pediatric segment are leukemias, central nervous system (CNS) tumors and lymphomas. Due to the evolution of the disease itself or the side effects of its treatment, these patients may present different types of immune compromise, sometimes leading to serious complications, such as Febrile Neutropenia (NF). According to specialized publications on the subject, this disease is considered a medical emergency, since the delay in adequate treatment can cause an increase in the morbidity and mortality of affected patients.[3–6]

The definition of neutropenia varies according to different authors, however, most of them agree in defining it as an absolute neutrophil count lower than 1,500 cells/mm3.[7] Depending on the level of neutrophils found, this disease can be classified as mild (1,000- 1,500 cells/mm^3), moderate (500-1,000 cells/mm^3) or severe (< 500 cells/mm^3).[8] NF is defined as Neutropenia concomitant with the presence of a temperature greater than 38˚C in two shots separated by one hour or greater than 38.3˚C in a single shot.[9] According to recent studies conducted in Latin America.[4,10] each pediatric oncology patient may present an average of 6 to 8 episodes of NF during chemotherapy treatment; and between 30% to 42% of these patients will have at least one admission to the Intensive Care Unit (ICU). In addition, it has been established that mortality in North America ranges between 4% and 10%.[11] In many cases, fever may be the only sign of the existence of an occult infection, so it is important that empirical antimicrobial treatment be initiated immediately and subsequently modified according to culture results and the clinical situation of the hospitalized patient.[12,13]

The etiology of NF episodes varies in different regions of the world, and may even vary in different hospitals in the same region or country. For this reason, knowledge of the most frequent etiologic agents, as well as the possible complications that may develop, is of great importance. In recent decades, the relative increase in infections by Gram-positive bacteria, associated with the prolonged use of vascular catheters and prophylactic antibiotics against Gram-negative bacteria, is striking.[8,11] In the guidelines of the International Society of Pediatric Oncology (SIOP)[5] in its section called Pediatric Oncology in Developing Countries (PODC), it indicates that infections caused by Gram-negative bacteria continue to be relatively more frequent in low-income countries, such as Guatemala. All the above mentioned has led to the realization of several studies in different countries that help to determine the most frequent types of microorganisms according to the hospital units, since this allows to establish adequate therapeutic conducts and thus help to prevent their mortality.

Recently, in a study conducted in Colombia, Medina and Ramos[14] described the characteristics of the pediatric population admitted to the ICU for NF. In the indicated study, the male gender presents a higher occurrence with 62% of the cases and the mean age was 7.9 years. Acute Lymphoid Leukemia (ALL) is observed as the most frequent primary oncologic disease with 46% and severe neutropenia was present in 60% of the sample analyzed. Among the infectious agents identified, *Klebsiella pneumoniae* was the most frequent.

The most frequently isolated agent with 18%, followed by *E. coli* with 12%, *S. aureus* 8% and finally *S. epidermidis* in 4%; in 58% of the cases, no causative agent was identified.

To date, there are no studies of this type available in Guatemala that describe the most frequent etiologic agents and the complications that may develop during NF episodes in pediatric oncology patients admitted to the ICU; therefore, the present research constitutes an important contribution to improve this situation. The National Pediatric Oncology Unit (UNOP) was considered for this study, since it is a center specialized in the treatment of pediatric cancer that provides free services and treatment to oncology patients from all over the country. The objective of this research is to describe the clinical characteristics of pediatric oncology patients diagnosed with NF who were admitted for the first time to the ICU at UNOP, so that this information, which is specific to the reality of Guatemala, can be used as a tool to improve the care of future cases.

Materials and methods

General and specific objectives

General objective: To describe the clinical characteristics of pediatric patients. Oncology patients diagnosed with febrile neutropenia admitted for the first time to the Intensive Care Unit of the National Pediatric Oncology Unit (UNOP).

Specific objectives:

i. Classify patients' neutropenia as mild, moderate or severe.

ii. To determine the diagnosis and oncologic treatment associated with febrile neutropenia.

iii. Identify the most frequent infectious agents associated with febrile neutropenia.

iv. To determine the length of stay in the Intensive Care Unit of these patients.

v. Identify patients who required mechanical ventilation and the time they spent on mechanical ventilation.

vi. Identify the complications secondary to Febrile Neutropenia that these patients developed during their stay in the Intensive Care Unit.

Variables

i. Demographics: age, sex and origin of hospital admission.

ii. Level of neutropenia identified on admission to the Intensive Care Unit.

iii. Clinical diagnosis of the oncologic patient.

iv. Oncological treatment according to your diagnosis.

v. Type of microorganisms isolated from pediatric oncology patients.

vi. Length of stay in the Intensive Care Unit.

vii. Duration of mechanical ventilation.

viii. Complications secondary to fever and neutropenia that these patients developed during their stay in the Intensive Care Unit.

Population and sample

Inclusion criteria:

a. Patients under 18 years of age.

b. Patients with a diagnosis of Febrile Neutropenia who were admitted for the first time to the Intensive Care Unit at UNOP.

c. Patients admitted between the dates of January 1, 2017 through December 31, 2021.

Exclusion criteria

a. Pediatric patients diagnosed with febrile neutropenia who remained in the emergency, intermediate care, bedridden or day hospital.

b. Pediatric patients who were admitted to the Intensive Care Unit and did not develop febrile neutropenia.

Sample calculation

a. The sample was convenience sampling.

Design

Type of study: Descriptive, retrospective.

Population: Patients admitted for the first time to the ICU at UNOP, between January 1, 2009 and January 1, 2009. from 2017 to December 31, 2021.

Instruments and materials

The computer, the Microsoft Excel program and the physical medical records of the patients were the instruments and materials used. For data collection, the physical medical records were used, which were found in the file archive at UNOP. Subsequently, the researcher's computer was used, with a security code to fill out the data collection sheet in Microsoft Excel (version 2204 © Microsoft Corporation).

Procedure

Authorization was requested from the hospital to conduct the study and an official letter was obtained from the institution authorizing the use of patient information for research purposes. The first patient classification was obtained from a digital database provided by the UNOP ICU. This database included all patients admitted per month from 2017 to 2021. Then, from this database a list was obtained where only the first admission of each patient was included, making a total of 1232 patients admitted for the first time to the ICU. Subsequently, we proceeded to review the records to extract the relevant information only from those patients who met the study inclusion criteria previously described. Only a total of 712 medical records were reviewed because 331 records were not in the UNOP archive and 189 patients were classified as deceased and, due to the institution's regulations, these records were not accessible. To collect data on the deceased patients included in the study, only the digital database submitted by the ICU was used.

Without using personal identifiers to preserve the anonymity of each patient, the relevant information was extracted from 211 patients who met the previously described inclusion criteria. The data obtained were tabulated in a data collection sheet in Microsoft Excel (version 2204 © Microsoft Corporation). The data collected were: age, gender, hospital origin of the patient, initial level of neutropenia, oncologic diagnosis and treatment, isolated microorganisms, use of mechanical ventilation, time under mechanical ventilation, length of stay in the intensive care unit and complications developed.

Data analysis

The data, according to their nature, were analyzed by means of descriptive statistics, measures of central tendency and dispersion, and absolute and relative frequencies were presented in tables and graphs.

Ethical considerations

In the study, a review of data in the physical records of each patient was performed. During data collection, patient identity data were not identified or reviewed to preserve patient privacy and confidentiality.

Results

A total of 211 patients who were first admitted to the ICU with a diagnosis of NF were included in the study. Table 1 illustrates the demographic characteristics of the patients.

Table 1 Demographic characteristics of the sample.

Features	Number of patients	% of patients
Age in years		
0- 3	50	23.70%
4-6	55	26.10%
7-9	22	10.40%
10-12	28	13.30%
13-15	37	17.50%
16-18	19	9.00%
Media		8 years
Maximum		17 years
Minimal		5 months
DE		5.08
Sex		
Female	114	54.00%
Male	97	46.00%
Origin of hospital admission		
Bedding	78	37.00%
Emergency	77	36.50%
Intermediate care	37	17.50%
Day hospital	19	9.00%

The classification of patients according to their level of neutropenia on admission to the ICU is described in Table 2. In most of the patients studied (72.77%) a neutrophil level below 500 cells/mm^3 was observed.

Table 2 Frequency according to level of Neutropenia

Neutropenia level	Number of patients	% of patients
Slight	21	10.99%
Moderate	31	16.23%
Severe	139	72.77%

Table 3 summarizes the oncologic diagnoses identified among the patients studied. Leukemia was the most common oncologic diagnosis in 81.99% (n=173) of the sample.

Table 3 Clinical diagnosis of oncologic patients admitted to the ICU.

Diagnostic Oncology	Number of patients	% of patients
Leukemia	**173**	**81.99%**
LLA	148	70.14%
LMA	25	11.85%
Lymphoma	**8**	**3.79%**
Hodgkin's lymphoma	6	2.84%
Non-Hodgkin's lymphoma	2	0.95%
Histiocytosis	**1**	**0.47%**
Pancytopenia	**3**	**1.42%**
Cancerous masses	**26**	**12.32%**
Bone	11	5.21%
Retina	5	2.37%
Soft Tissues	4	1.90%
Cerebral	3	1.43%
Liver	1	0.47%
Kidney	1	0.47%
Ovary	1	0.47%

Note: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia

Regarding treatment, the phase most commonly associated with the development of NF was the induction phase in 38.39% (n=81) of the patients, followed by the consolidation and maintenance phase. It was identified that 22.27% (n=47) were not under any treatment at the time of admission, as they were in the diagnostic phase. At least one infectious agent was isolated in 33.18% (n=70) of the sample. Only 22.27% (n=47) had at least one positive culture for bacteria and/or fungi. Within the positive cultures, 48.94% (n=23) were positive for anaerobes, 36.17% (n=17) for aerobes and 14.89% (n=7) for fungi. Table 4 describes the infectious agents isolated in their entirety.

Table 4 Infectious agents associated with febrile neutropenia.

Etiological agent	Number of patients	Percentage
None	**141**	**66.82%**
Bacteria	**39**	**18.48%**
Gram positive	10	4.74%
Clostridium difficile	6	2.84%
Streptococcus	2	0.95%
Staphylococcus	1	0.47%
Enterococcus	1	0.47%
Gram negative	29	13.74%
Escherichia coli	7	3.32%
Pseudomona aeruginosa	7	3.32%
Klebsiella pneumoniae	5	2.37%
Acinetobacter baumannii	5	2.37%
Enterobacter cloacae	2	0.95%
Pseudomona putida	1	0.47%
Salmonella choleraesuis	1	0.47%
Shigella	1	0.47%
Virus	**16**	**7.58%**
SARS-COV 2	11	5.21%
Parainfluenza	3	1.42%
Influenza	1	0.47%
Rhinovirus	1	0.47%
Coinfection	**7**	**3.32%**
Fungi	**5**	**2.37%**
Parasites	**3**	**1.42%**

Note: Coinfections described in Annex I.

Table 5 describes the mean number of days of ICU stay and hours under mechanical ventilation according to the level of Neutropenia of the patients. Severe Neutropenia was associated with a longer mean ICU length of stay (7.14 days). Of all patients studied, 91.62% (n=175) did not require mechanical ventilation. The 8.38% (n=16) who did require mechanical ventilation only had Moderate or Severe Neutropenia.

Table 5 ICU stay and time under mechanical ventilation according to Neutropenia level.

Level of Neutropenia	ICU stay in days		Mechanical ventilation in hours	
	Media	±DE	Media	±DE
Slight	5.86	3.44	-	-
Moderate	5.61	3.2	131.75	24.45
Severe	7.14	6.45	156	102.25
TOTAL	6.75	5.79	149.94	76.36

The study identified 40 different complications associated with NF. These occurred concomitantly in 72.51% of the cases. Sepsis and pneumonia occurred concomitantly in 15.64% (n = 33) of the patients. Table 6 describes the 10 complications that occurred most frequently among the patients studied.

Table 6 Complications most frequently associated with patients with febrile neutropenia.

Complications	# of patients	Percentage
Sepsis	139	65.88%
Pneumonia	66	31.28%
SLT	43	20.38%
Mucositis	37	17.54%
Neutropenic colitis	24	11.37%
SDA	21	9.95%
Death	20	9.48%
Ventricular dysfunction	17	8.06%
COVID	11	5.21%
Pancreatitis	8	3.79%

Note: TLS, tumor lysis syndrome; ADD, acute diarrheic syndrome; ADS, acute diarrheic syndrome; ADD, acute diarrheic syndrome

Table 7 Combination of infectious agents that compose the co-infections.

Etiological agents	Number of patients
Rhinovirus + Enterovirus	4
Candida + Aspergillus	1
Candida Tropicalis + Clostridium Difficile	1
Enterovirus + Kocuria Rosea	1

The complications that were associated with some infectious agent (39.90%) were classified into 15 types and are represented in Figure 1.

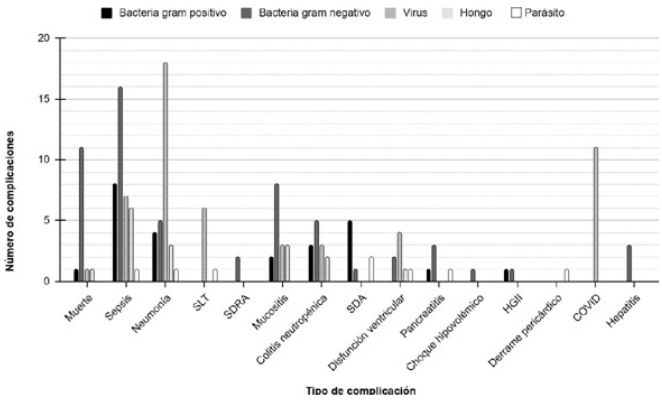

Figure 1 Complications developed according to infectious agents.

NOTE: TLS, tumor lysis syndrome; ARDS, acute respiratory distress syndrome; ADD, acute diarrheal syndrome; LGE, lower gastrointestinal bleeding (LGE).

Discussion

Febrile neutropenia (NF) is one of the main complications in pediatric oncology patients. Knowing the clinical characteristics, the most frequent etiologic agents and the complications that may develop can be of great help to establish adequate therapeutic behaviors and thus help prevent mortality. This research characterizes a total of 211 patients who developed NF and required admission for the first time to the ICU at UNOP, between the years 2017 to 2021.

According to the data analyzed, the female gender reached the highest frequency with 54% of the total, a finding that differs from different international studies[10,11,14,15] where the male gender presents a higher frequency. However, regardless of the results, it has not been demonstrated that the gender of the patients is a risk factor for the development of NF.[10] A higher age concentration of patients was observed between 4 and 6 years of life with 26.1% of the cases. The average age observed was 8 years with a standard deviation of 5.09 years, results similar to those described in the study conducted by Medina[14] in Colombia, where the average age was 7.9 ± 3.1 years.

Among the oncological diagnoses identified in the study, as a disease prior to the development of NF, hematological neoplasms were the most frequent (81.99% of the total); Acute Lymphoblastic Leukemia (ALL) being the most common type of these, representing 70.14% of the total cases observed and Acute Myeloid Leukemia (AML) the remaining 11.85%. This behavior is similar to that described in multiple international studies[6,8,10,11,14,15] where Acute Lymphoblastic Leukemia (ALL) is also the most prevalent with a frequency ranging between 42% and 80.8%. Of these patients, 36.6% were in the induction phase at the time of developing NF and 22.27% had no treatment whatsoever, as they were in the diagnostic phase. This finding differs from that described in the study performed at the Children's Hospital of Mexico, where patients who developed NF were more frequently in the maintenance phase.[6] Both findings are consistent with the Consensus of the Latin American Society of Pediatric Infectious Diseases 2021,[4] which describes that NF can develop at any time during the clinical course or phase in the treatment of oncology patients. However, it is important to highlight that our study takes into account only to patients admitted to the ICU for the first time, which explains why the highest frequency of admission is observed in the initial phases of the disease.

Patients admitted to the ICU presented a Severe Neutropenia level in most cases (72.77%), as reported by Medina[14] and Navarrete[8] in their studies where Severe Neutropenia was present in 60% and 93%

of the cases, respectively. The mean length of stay in the ICU was 6.75±5.79 days for all cases. However, for those cases with Severe NF a mean of 7.14±6.45 days was observed, of these, 8% of patients had a prolonged ICU stay of at least 15 days. A large majority of patients did not require mechanical ventilation; 8.38% who did require mechanical ventilation had Severe Neutropenia. The mean duration of mechanical ventilation, when required, was 149.94 ± 76.36 hours. The findings described in this paragraph reflect that a neutrophil count below 500 cells/mm3 may lead to the requirement of advanced therapies and a longer stay in the ICU because of it, consistent with what Medina[14] highlights in his study.

Due to the retrospective nature of this study, it was not possible to establish with certainty whether etiological studies had been performed in all patients; nevertheless, it was possible to identify at least one infectious agent in 33.18% of the sample. This finding is consistent with that mentioned in the current literature, which mentions that in patients with NF the causal infectious agent is detectable in only 20-30% of cases.[11] Bacteria were the most frequently evidenced microorganisms (17.99%) compared to viruses (7.57%), fungi (2.37%) and parasites (1.41%). This agrees with Kebudi and Kizilocak,[3] whose article published in the journal "Current Pediatric Reviews", state that the main type of infectious agent associated with NF is bacteria. The study shows that the Gram-negative bacteria were observed more frequently (13.74%) compared to Gram-positive bacteria (4.74%), which is in accordance with the SIOP-PODC guidelines[5] that mention that Gram-negative bacteria continue to be the most frequent cause in low-income settings, such as Guatemala. A wide variety of causative bacteria were identified, with *Escherichia coli and Pseudomona aeruginosa* being the most frequently observed bacteria, with 3.32% each; results consistent with other studies.[8,11,14,16] The second most frequently identified group of etiologic agents was viruses with 7.58% of the total, of which *SARS COV 2* was the most frequently observed virus with 5.21%; it is noteworthy that this virus was also identified as the most frequently identified individual infectious agent, which is to be expected since this study includes results from the COVID-19 pandemic. Similarly, most of the viruses identified were respiratory viruses, which is similar to a Vietnamese study by Nguyen[16] et al. where respiratory viruses were found to be commonly associated with NF.

The study found that twenty patients died as a result of NF-related complications, with a mortality rate of 9.48%. It is important to mention that mortality was calculated only from the statistics presented by the ICU, since there was no access to the physical records of the deceased patients. In a study by Basu[17] et al. based on data from the United States, a mortality of 3% was obtained, whose variation can be explained by the significant socioeconomic difference between these two countries.

This study has several limitations. Among them, we can mention the lack of certainty regarding the performance of etiological studies in all patients, to better identify the causal infectious agents. Likewise, the concurrence of the COVID-19 pandemic in the time range of the study may have biased the results of the most commonly isolated infectious agents.

Conclusion

72.77% of NF cases develop secondary to severe neutropenia. Hematologic malignancies (ALL and AML) are the most frequent underlying disease with 81.99%. Gram-negative bacteria are the most frequent causative infectious agent with 13.74%. The mean length of stay in ICU is 6.75±5.79 days. A 91.62% of patients did not require mechanical ventilation and the most frequent complication associated with NF was sepsis in 65.88% of cases, followed by pneumonia in 31.28%.

This study presents important features and highlights the most likely causes to be considered to assist physicians in the diagnosis, treatment, and prognosis of associated complications in future cases of NF presenting at this institution.

Recommendations

This study could have gone deeper in the identification of the specific complications that caused the death of patients who died in the ICU and even analyzed all those cases that could have resulted in death, given the availability of the respective records. It is recommended that, in future studies, the subject of mortality associated with NF could be better developed.

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None.

Conflicts of interest

There are no conflicts of interest with third parties. The authors declare that they have no links with pharmaceutical manufacturing or marketing companies. There was no sponsorship for this study.

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