ACIN
ASOCIACIÓN COLOMBIANA DE INFECTOLOGÍA

infectio

ORIGINAL PAPER

Clinical and microbiological characterization of pediatric patients with acute lymphoblastic leukemia presenting with febrile neutropenia

Eileen Viviana Fonseca-Sepúlveda[1,*], Luisa Fernanda Imbachi-Yunda[2], Kelly Cristina Márquez-Herrera[3], Germán Camacho-Moreno[4], Carlos Alberto Pardo-González[5], Adriana Linares-Ballesteros[6]

Abstract

Introduction: Fever and neutropenia are common clinical manifestations at the onset of pediatric acute lymphoblastic leukemia (ALL). This study aimed to describe the clinical and microbiological characteristics and outcomes of pediatric patients with ALL presenting with febrile neutropenia (FN) as the initial manifestation.
Materials and methods: This retrospective study included children with ALL and FN within 72 h of diagnosis, prior to treatment. A descriptive analysis of the clinical and laboratory data was performed.
Results: Over 10 years, 134 (24%) patients with ALL presented with FN initially. Empiric broad-spectrum antibiotics were administered to 91% (122/134) of the patients. Blood cultures identified pathogens in 4.1% (5/122) of the patients FN-related complications occurred in 7.4% (10/134); no mortality was recorded.
Discussion: FN was the initial manifestation of ALL. Management followed chemotherapy-associated FN guidelines; however, microbiological isolates, resistance patterns, and complications differed significantly from those of chemotherapy-induced FN. In conclusion, further studies are needed to characterize FN at ALL diagnosis and establish optimal management guidelines for non-chemotherapy-associated FN.

Keywords: febrile neutropenia; precursor cell lymphoblastic leukemia-lymphoma; pediatrics.

Caracterización clínica y microbiológica de pacientes pediátricos con leucemia linfoblástica aguda que debutan con neutropenia febril

Resumen

Introducción: La fiebre y la neutropenia son manifestaciones clínicas comunes al inicio de la leucemia linfoblástica aguda pediátrica (LLA). El objetivo de este estudio fue describir las características clínicas y microbiológicas y los desenlaces de pacientes pediátricos con LLA que presentan neutropenia febril (NF) como manifestación inicial de la enfermedad.
Materiales y métodos: Estudio retrospectivo en niños con LLA y NF dentro de las primeras 72 horas del diagnóstico, previo a cualquier tratamiento. Se realizó un análisis descriptivo de datos clínicos y de laboratorio.
Resultados: En 10 años, 134 pacientes (24%) con LLA presentaron NF inicialmente. El 91% (122/134) recibió antibióticos empíricos de amplio espectro. Los hemocultivos identificaron patógenos en 4.1% (5/122). Se reportaron complicaciones relacionadas con NF en 7.4% (10/134); no hubo mortalidad asociada.
Discusión: La NF es una manifestación inicial de LLA. Su manejo siguió guías para NF asociada a quimioterapia, pero los aislamientos microbianos, patrones de resistencia y complicaciones difirieron significativamente de la NF inducida por quimioterapia. Como conclusión, se requieren más estudios para caracterizar la NF en el diagnóstico de LLA y establecer pautas óptimas de manejo para NF no asociada a quimioterapia.

Palabras clave: neutropenia febril; leucemia-linfoma linfoblástico de células precursoras; pediatría.

1 HOMI, Fundación Hospital Pediátrico La Misericordia, Bogotá, Colombia. https://orcid.org//0000-0001-9763-6782
2 HOMI, Fundación Hospital Pediátrico La Misericordia y Universidad Nacional de Colombia, Bogotá, Colombia. https://orcid.org//0000-0002-6250-5667
3 HOMI, Fundación Hospital Pediátrico La Misericordia, Bogotá, Colombia. https://orcid.org//0000-0001-5698-6161 (Filiación pasada)
4 HOMI, Fundación Hospital Pediátrico La Misericordia y Universidad Nacional de Colombia, Bogotá, Colombia. https://orcid.org//0000-0003-0472-798X
5 HOMI, Fundación Hospital Pediátrico La Misericordia y Universidad Nacional de Colombia, Bogotá, Colombia. https://orcid.org//0000-0003-1798-2947
6 HOMI, Fundación Hospital Pediátrico La Misericordia, Bogotá, Colombia. https://orcid.org/0000-0001-7429-6850
* Autor para correspondencia:
Correo electrónico: evfonsecas@gmail.com

Recibido: 10/05/2025; Aceptado: 21/07/2025

Cómo citar este artículo: E.V. Fonseca-Sepúlveda, *et al.* Clinical and microbiological characterization of pediatric patients with acute lymphoblastic leukemia presenting with febrile neutropenia. Infectio 2025; 29(4): 203-207
https://doi.org/10.22354/24223794.1247

Introduction

Fever and neutropenia are common clinical manifestations at the onset of pediatric acute lymphoblastic leukemia (ALL). Fever occurs in 45-52.8% of cases, while neutropenia is documented in 60-68% at disease presentation[1,2]. The simultaneous occurrence of these symptoms, known as febrile neutropenia (FN), is a frequent complication in oncology patients receiving high-intensity chemotherapy, as is the case in the management of ALL[3,4]. Furthermore, it is a condition that occurs in children with ALL at the time of diagnosis and before they receive oncological treatment.

FN secondary to myeloablative chemotherapy is an oncological emergency, and different consensus statements and clinical guidelines have outlined strategies that include risk stratification for each patient[5–8], early initiation (within one hour) of broad-spectrum antibiotics, and blood culture sampling, among other practices that together have helped reduce the mortality rate and associated complications during cancer treatment in children[3,9]. In contrast, FN as an initial presentation of ALL remains poorly described and understudied[10].

When fever presents as the initial symptom of the disease, it may be considered a clinical sign secondary to ALL and is not necessarily related to an underlying infectious disease. The simultaneous appearance of neutropenia and fever as initial manifestations of ALL represents a challenging scenario due to the reasonable risk of sepsis and severe infections[11,12]. The approach and management of FN as an initial manifestation of the disease, rather than solely because of chemotherapy, have not been studied, characterized, or addressed in the most recent guidelines on FN in pediatric cancer patients[5-8], limiting the definition to patients with FN secondary to chemotherapy alone.

This study aimed to assess the frequency of FN as an initial manifestation of ALL in pediatric patients and to characterize the clinical presentation, laboratory findings, approach, management, and outcomes to determine the importance of studying and expanding the information regarding this subtype of FN in pediatric patients.

Materials and methods

An observational, descriptive, and retrospective study was conducted from 2008 to 2018 at a national referral institution for the management of childhood cancer. Patients younger than 18 years with a confirmed diagnosis of ALL who presented with FN at the onset of the disease were included. All patients who presented with fever and neutropenia prior to urgent consultation, within 72 h after hospital admission, and before medical interventions such as chemotherapy, broad-spectrum antibiotic use, or vascular device insertion were considered. Patients with incomplete medical records or prior management for > 72 h at other hospital institutions were excluded.

Neutropenia was defined as an absolute neutrophil count (ANC) ≤ 1500 cells/mm3, and fever as a temperature measurement >38.3°C axillary or two measurements >38.0°C axillary taken with at least one hour apart[11].

The demographic and clinical characteristics of each patient were recorded. The clinical outcomes included admission to the pediatric intensive care unit (PICU) and mortality. ANC at the time of admission was recorded and classified according to the severity of neutropenia: mild (1500 to >1000 cells/mm3), moderate (1000 to >500 cells/mm3), severe (<500 cells/mm3), and profound (<100 cells/mm3). All microbiological isolates identified through blood cultures and other types of cultures such as stool and urine cultures, as well as respiratory viral panels were included in the analysis, and the type of microorganism isolated from each patient was described. Isolates found in blood cultures were classified as clinically significant or contaminants. A contaminating blood culture was defined as one in which microorganisms that are part of the normal skin or respiratory tract microbiota were isolated, found only in one blood culture, and not related to the clinical picture of the patient.

All localized infections were characterized and defined as those in which the origin site of the infection was identified according to clinical findings and diagnostic aids (e.g., chest X-ray, urinalysis, abdominal ultrasound, etc.), including pneumonia, skin and soft tissue infections, appendicitis, and gastroenteritis.

Data processing was performed using the IBM Statistical Package for the Social Sciences 22 system (IBM Corp., Armonk, NY, USA). In the statistical analysis, quantitative variables are reported as mean ± standard deviation (SD) or median and interquartile range (IQR), depending on the nature and distribution of the continuous variables. Absolute and relative frequencies were used for nominal variables. The study was approved by the institution's ethics research committee (record number CEI-75-17).

Results

During the study period, 557 new ALL cases were reviewed, and FN was found to be the initial manifestation of the disease in 134 (24%) cases. The median age of the patients was 5 years (IQR = 3-8.2), with 68 patients (50.8%) being male.

Clinical and Laboratory Characteristics

The median duration of fever presented by the patients before hospital admission was 5 days (IQR = 2.5-10). The ANC upon admission had a median of 240 cells/mm3 (IQR = 80-510); 99 patients (73.8%) had an ANC of <500 cells/mm3.

Microbiological Characteristics

Of 122 patients (91.0%) from whom blood cultures were obtained, 11 (9%) had positive cultures, of which 5 (4.1%) were considered clinically significant: 2 patients (1.6%) had

Staphylococcus aureus (oxacillin-sensitive), and 3 patients (0.8% each) had *Pseudomonas aeruginosa* (natural phenotype), *Streptococcus pyogenes* (natural phenotype), and *Streptococcus viridans* (natural phenotype). The remaining six cultures were considered contaminants, with three cases (3.2%) showing *Staphylococcus epidermidis* and three blood cultures showing growth of *Staphylococcus hominis*, *Streptococcus sanguinis*, and *Staphylococcus epidermidi*s plus *Staphylococcus hominis*, each in different patients. Urine cultures were performed on 44 patients (32.8%), revealing only two isolates (4.5%): *Escherichia coli* (natural phenotype) and *Proteus mirabilis* (natural phenotype). Stool cultures were performed on 15 patients (11.1%), without documenting any isolates.

Among the 17 patients (12.6%) who presented with respiratory symptoms, a respiratory viral panel study (screening for influenza, respiratory syncytial virus, adenovirus, and parainfluenza) was conducted, detecting seven positive cases (41.2%): three with influenza (42.8%), two with adenovirus (28.5%), one with parainfluenza (14.2%), and one (14.2%) with simultaneous detection of influenza and respiratory syncytial virus.

In total, 122 patients (91.0%) received empirical broad-spectrum antibiotics. The most commonly used antibiotic was cefepime, used in 87 patients (71.3%), followed by a combination of cefepime and vancomycin in 12 cases (9.8%), piperacillin-tazobactam in 12 patients (9.8%), ceftriaxone in 6 patients (4.9%), and meropenem with vancomycin in one case (0.8%). Narrow-spectrum antibiotics, such as cephalothin, oxacillin, and clindamycin, were used in one patient (0.8%). The median duration of antibiotic treatment was 7 days (IQR 7.7-9).

Documented Infections

43 patients (32.0%) presented with localized infections. The types of infections included pneumonia in 14 (32.6%), skin and soft tissue infections in 7 (16.3%), upper respiratory infections in 6 (14%), acute gastroenteritis and acute otitis media/otitis mastoiditis in 5 each (11.6% each), urinary tract infections, appendicitis, and acute gastroenteritis with upper respiratory infections in 2 each (4.6% each). Six patients (4.5%) were admitted to the PICU with signs of septic shock. The type of infection and ANC are described in Table 1.

Severity of Neutropenia

Infections and antibiotic use variables according to the ANC subgroup are described in Table 1. The five patients with clinically relevant positive blood cultures had an ANC <500 cells/mm3. A differential behavior was observed in relation to the use of empirical antimicrobial therapy and the ANC: empirical antimicrobial therapy was used in 100% of patients with ANC <100 cells/mm3, 95.3% with ANC <500 cells/mm3, 70.8% with ANC between 500-1000 cells/mm3, and 81.8% with ANC >1000 and <1500 cells/mm3.

Outcomes

A total of 39 patients (29.1%) were admitted to the PICU, 10 (25.6%) of whom were admitted due to FN complications (septic shock). Among these patients, eight had profound neutropenia, one had moderate neutropenia, and one had severe neutropenia. Two (5%) patients admitted to the PICU had positive blood cultures: one with *Pseudomonas aeruginosa* and the other with *Streptococcus pyogenes*.

Three patients (2.2%) died. The first patient developed acute appendicitis and peritonitis during the induction phase of treatment, required multiple abdominal surgical interventions, developed a secondary infection, and ultimately succumbed to it. The second patient, in the advanced phase of induction chemotherapy, presented with a respiratory infection that progressed to respiratory failure, resulting in septic shock and death. The third patient experienced acute pancreatitis during the induction phase of oncologic treatment, followed by neutropenic colitis and septic shock, which led to death.

Discussion

FN is not only a secondary complication of myeloblative chemotherapy but also an initial manifestation of ALL in pediatric patients[1], and few studies have characterized this FN subtype[10]. This study explored the frequency of FN in children with ALL as an initial manifestation and clinically characterized this subpopulation.

Among the most significant findings highlighting FN as a subtype with unique characteristics are the low incidence of complications, low frequency of isolates in blood cultures, and absence of multidrug-resistant microorganisms and associated mortality. The study with the largest amount of data related to this type of FN was conducted by Khurana et al.[10], who evaluated the frequency of positive blood cultures in patients who presented with fever at the time of ALL diagnosis, finding positivity in only 1.6% of patients (all with severe neutropenia), which contrasts with the data from this cohort, where clinically significant microbiological isolates were found in 4.1% of cases with blood cultures.

Guidelines and consensus on the management of chemotherapy-associated FN agree on the use of broad-spectrum antibiotics as the first line with anti-pseudomonal coverage, given the mortality associated with infections by this microorganism and other Gram- negative bacteria[4,11,14,15]. In this study, the approach to FN at the onset of ALL mirrored the FN management guidelines associated with chemotherapy, despite the isolation of *Pseudomonas* spp. in only one case and no other Gram-negative bacilli. This raises the question of whether patients with FN as an initial manifestation of ALLwithout localized infections or septic shockmight benefit from an empirical antimicrobial strategy distinct from high-risk chemotherapy-associated FN.

Table 1. Description of clinical variables according to the severity of neutropenia.

Variable	ANC <100 N=34 (25,3%)	ANC 100-500 N=65 (48,5%)	ANC 500-1000 N=24 (17,9%)	ANC 1000-1500 N=11 (8,2%)
Septic shock	**6 (17,6)**	**3 (4,6)**	**1 (4,2)**	**0**
Localized Infection				
Yes	**11 (32,3)**	**21 (32,3)**	**7 (29,2)**	**4 (36,4)**
Pneumonia	8 (66,6)	4 (19,0)	2 (28,6)	0
Urinary tract infection	0	1 (4,8)	0	1 (25,0)
Appendicitis	1 (8,3)	1 (4,8)	0	0
Acute gastroenteritis	1 (8,3)	2 (9,5)	2 (28,5)	0
AURI[1]	1 (8,3)	4 (19,0)	1 (14,3)	0
Skin and soft tissue	0	4 (19,0)	0	3 (75,0)
AOM[2]/Otomastoiditis	0	4 (19,0)	1 (14,3)	0
Acute gastroenteritis and AURI	0	1 (4,8)	1 (14,3)	0
No	**23 (67,6)**	**44 (67,7)**	**17 (70,8)**	**7 (63,6)**
Atibiotic therapy	**34 (100)**	**62 (95,3)**	**17 (70,8)**	**9 (81,8)**
Cefepime	23 (67,6)	47 (75,8)	11 (64,7)	6 (66,7)
Cefepime and vancomycin	5 (14,7)	5 (8,1)	1 (5,9)	1 (11,1)
Ceftriaxone	2 (5,8)	3 (4,8)	1 (5,9)	0
Piperacillin-tazobactam	4 (11,7)	5 (8,1)	3 (17,7)	0
Clindamycin	0	1 (1,6)	0	0
Vancomycin and meopenem	0	1 (1,6)	0	0
Vancomycin	0	0	1 (5,9)	0
Oxacillin	0	0	0	1 (11,1)
Cephalothin	0	0	0	1 (11,1)
Blood cultures	**33 (97,1)**	**62 (95,2)**	**18 (75,0)**	**9 (81,8)**
Positive	2 (6,1)	8 (12,9)	1 (5,6)	0
Isolated microorganisms				
Pseudomonas aeruginosa	1	0	0	0
Streptococcus viridans	1	0	0	0
Staphylococcus aerus	0	2	0	0
Staphylococcus epidermidis	0	3	0	0
Staphylococcus hominis	0	1	0	0
Staphylococcus pyogenes	0	1	0	0
Staphylococcus sanguinis and Staphylococcus hominis	0	1	0	0
Staphylococcus epidermidis and Staphylococcus hominis	0	0	1	0
Admission to PICU				
Yes	**16 (47,1)**	**13 (20,0)**	**6 (25,0)**	**4 (63,4)**
No	18 (52,9)	52 (80,0)	18 (75,0)	7 (63,6)
Admission to PICU related to neutropenia	**7 820,5)**	**2 (3,0)**	**1 (4,1%)**	**0**

[1]Acute upper respiratory infections; [2]Acute media otitis.

The definition of chemotherapy-associated NF varies across different guidelines[5–8], with most establishing a neutropenia parameter of an ANC of <500 cells/mm3. For this study, we used an ANC cutoff of <1,500 cells/mm3, which is a threshold defined in the literature for mild neutropenia[13]. Using this cutoff, we found that antibiotics were used in 81.8% of patients with mild neutropenia (ANC 1000-1500), representing high antibiotic use in a subgroup with low microbiological isolates and complications (no PICU admissions due to NF or infection). Similar antibiotic use was observed in patients with moderate neutropenia, who exhibited clinical behavior comparable to that of the mild group.

The highest rates of microorganism isolation, localized infections, and PICU admission due to infection or complications, such as septic shock, were found in patients with severe

neutropenia (ANC < 500/mm3). This suggests that empirical antibiotic management for this subgroup should align with high-risk chemotherapy-associated NF recommendations (anti-pseudomonal agents), adjusted based on culture results.

In this study, a simplified viral panel was used for patients presenting with respiratory symptoms. Currently, multiple polymerase chain reaction panels for the detection of respiratory viruses are available, and some consensus guidelines indicate them as routine Laboratory tests are performed in all cases of chemotherapy-associated FN, regardless of the presence of respiratory symptoms[8]; thus, their utility in this population remains to be determined.

Notably, most patients with non-chemotherapy-associated FN lacked antimicrobial resistance risk factors (e.g., prior broad-spectrum antibiotic exposure, bacterial colonization, prolonged hospitalization, and vascular access devices). Our findings suggest that these patients may be candidates for narrower-spectrum empirical antibiotics, minimizing future colonization by multidrug-resistant strains and early exposure to broad-spectrum agents.

In conclusion, FN is a presenting manifestation of ALL in children. Its clinical behavior differs significantly from that of chemotherapy-associated FN, with a lower frequency and distinct microbiological isolates, fewer complications, and no associated mortality. However, the management of this cohort adhered to the chemotherapy-associated FN guidelines. Our findings highlight the need for further multicenter studies to characterize FN at ALL onset and define tailored management strategies, including risk stratification and antibiotic approaches distinct from chemotherapy-associated FN.

Ethical considerations

Protection of persons. No apply.

Protection of vulnerable populations. This study did not include photographs or personal data of the patients and was approved by the institutional ethics committee (under the act. CEI-75-17).

Confidentiality. This study was approved by the institutional ethics committee and was a retrospective study that did not require informed consent from each patient.

Privacy. The authors guarantee the privacy of each medical record reviewed for this study.

Financing. This study was not supported by any funding. The authors are responsible for any publication costs that may incur.

Conflict of interests. The authors have no conflict of interest to declare.

Acknowledgments. No apply.

Authors´ contribution. Conceptualization: all authors. Data curation: EVF, LFI. Formal analysis: EVF, LFI. Methodology: all authors. Supervision: ALB, GCM, KCM. Writing – original draft: all authors. Writing – review & editing: all authors. All authors have read and approved the final version of the submitted manuscript.

References

1. Vargas M, Linares A, Ruiz M, Tamara L, Sarmiento I, Moreno L. Signs, Symptoms and Findings in Complete Blood Cell Count at Diagnosis in Children with Acute Leukemia. Pediatr Res Child Heal. 2018;1:001–4.
2. Brix N, Rosthøj S. Bone marrow involvement is not manifest in the early stages of childhood acute lymphoblastic leukaemia. Dan Med J. 2014;61(8):1–6.
3. Koenig C, Lehrnbecher T. Diagnostics and therapy of paediatric patients with febrile neutropenia. EJC Paediatr Oncol. 2023;2(October):100116. DOI: 10.1016/j.ejcped.2023.100116
4. Davis K, Wilson S. Febrile neutropenia in paediatric oncology. Paediatr Child Heal. 2020;30(3):93–7. DOI: 10.1016/j.paed.2019.12.002
5. Martínez Campos L, Pérez-Albert P, Ferres Ramis L, Rincón-López EM, Mendoza-Palomar N, Soler-Palacin P, et al. Consensus document on the management of febrile neutropenia in paediatric haematology and oncology patients of the Spanish Society of Pediatric Infectious Diseases (SEIP) and the Spanish Society of Pediatric Hematology and Oncology (SEHOP). An Pediatr. 2023;98(6):446–59. DOI: 10.1016/j.anpedi.2023.03.012
6. Lehrnbecher T, Robinson P, Fisher B, Alexander S, Ammann RA, Beauchemin M, et al. Guideline for the management of fever and neutropenia in children with cancer and hematopoietic stem-cell transplantation recipients: 2017 update. J Clin Oncol. 2017;35(18):2082–94. DOI: 10.1200/JCO.2016.71.7017
7. Lehrnbecher T, Robinson PD, Ammann RA, Fisher B, Patel P, Phillips R, et al. Guideline for the Management of Fever and Neutropenia in Pediatric Patients with Cancer and Hematopoietic Cell Transplantation Recipients: 2023 Update. J Clin Oncol. 2023;41(9):1774–85. DOI: 10.1200/JCO.22.02224
8. Santolaya M, Contardo V, Torres JP, Lopez-Medina E, Rosanova MT, Álvarez AM, et al. Manejo de los episodios de neutropenia febril en niños con cáncer. Rev Chil Infect. 2021;38(6):857–909. DOI: 10.4067/s0716-10182021000600857.
9. Boccia R, Glaspy J, Crawford J, Aapro M. Chemotherapy-Induced Neutropenia and Febrile Neutropenia in the US: A Beast of Burden That Needs to Be Tamed? Oncologist. 2022;27(8):625–36. DOI: 10.1093/oncolo/oyac074
10. Khurana M, Lee B, Feusner JH. Fever at Diagnosis of Pediatric Acute Lymphoblastic Leukemia : Are Antibiotics Really Necessary ? J Pediatr Hematol Oncol. 2015;37:498–501. DOI: 10.1097/MPH.0000000000000417
11. Melgar M, Reljic T, Barahona G, Camacho K, Chang A, Contreras J, et al. Guidance statement for the management of febrile neutropenia in pediatric patients receiving cancer-directed therapy in Central America and the Caribbean. J Glob Oncol. 2020;6:508–17. DOI: 10.1200/JGO.19.00329
12. Lehrnbecher T, Robinson P, Fisher B, Alexander S, Ammann RA, Beauchemin M, et al. Guideline for the management of fever and neutropenia in children with cancer and hematopoietic stem-cell transplantation recipients: 2017 update. J Clin Oncol. 2017;35(18):2082–94. DOI: 10.1200/JCO.2016. 71.7017
13. Fioredda F, Calvillo M, Bonanomi S, Coliva T, Tucci F, Farrugia P, et al. Congenital and Acquired Neutropenia Consensus Guidelines on Diagnosis From the Neutropenia Committee of the Marrow Failure Syndrome Group of the AIEOP (Associazione Italiana Emato-Oncologia Pediatrica). Pediatr Blood Cancer. 2011;57:10–7. DOI: 10.1002/pbc.23108.
14. Downes KJ, Zaoutis TE, Shah SS. Guidelines for management of children with fever and neutropenia. J Pediatric Infect Dis Soc. 2013;2(3):281–5. DOI: 10.1093/jpids/pit035
15. Alali M, David MZ, Danziger-Isakov LA, Elmuti L, Bhagat PH, Bartlett AH. Pediatric febrile neutropenia: Change in etiology of bacteremia, empiric choice of therapy and clinical outcomes. J Pediatr Hematol Oncol. 2020;42(6):E445–51. DOI: 10.1097/MPH.0000000000001814.