

Prevalence of multi-resistant bacteria associated with febrile neutropenia in pediatric oncology patients

Prevalencia de bacterias multirresistentes asociadas a neutropenia febril en pacientes oncológicos pediátricos

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ABSTRACT

Introduction: Antimicrobial resistance (AMR), particularly that associated with extended-spectrum beta-lactamase (ESBL)-producing and carbapenemase-producing bacteria, represents a critical global public health threat. Febrile neutropenia is a frequent and potentially life-threatening complication in cancer patients undergoing chemotherapy; in the pediatric population, it is of particular concern given its significant impact on morbidity and mortality. This study aimed to determine the prevalence of multidrug-resistant (MDR) bacteria associated with febrile neutropenia, with the purpose of informing the revision and updating of institutional empirical antibiotic therapy protocols. **Methodology:** An observational, descriptive, cross-sectional, and retrospective study was conducted at the Baca Ortiz Pediatric Hospital in Quito, Ecuador. All eligible records were analyzed, constituting a census of 184 pediatric oncology patients with at least one episode of febrile neutropenia and a positive blood culture between 2019 and 2023. Inclusion criteria were temperature ≥ 38 °C and an absolute neutrophil count (ANC) $\leq 500/\text{mm}^3$. **Results:** Female patients accounted for 51.6% of the study population. Leukemia was the predominant oncologic diagnosis (84.8%), and more than 90% of patients presented severe neutropenia, concentrated primarily within this diagnostic group. Gram-negative bacteria predominated: *Klebsiella pneumoniae* (16.8%) and *Escherichia coli* (16.3%) were the most prevalent Enterobacteriaceae, and *Pseudomonas aeruginosa* (7.6%), the most frequent non-fermenting Gram-negative bacillus. Resistance analysis was performed on 160 bacterial isolates, after excluding 24 fungal isolates. The prevalence of ESBL-producing bacteria was 16.0% (95% CI: 10.0%–22.0%), and that of carbapenemase-producing bacteria was 8.0% (95% CI: 3.0%–12.0%). **Conclusion:** Multidrug-resistant Gram-negative bacteria predominated in pediatric oncology patients with febrile neutropenia, with an ESBL prevalence of 16.0% and a carbapenemase prevalence of 8.0% among bacterial isolates. These findings may contribute to the review and updating of institutional empirical antibiotic therapy protocols for this patient population and a critical determination for the optimization of empirical treatment strategies in this group.

Keywords: Microbial drug resistance; Extended-spectrum beta-lactamases; Gram-negative bacteria; Febrile neutropenia; Neoplasms.

RESUMEN

Introducción: La resistencia antimicrobiana (RAM), especialmente la asociada a bacterias productoras de betalactamasas de espectro extendido (BLEE) y carbapenemasas, constituye una amenaza global prioritaria. La neutropenia febril es un evento crítico frecuente en pacientes oncológicos bajo tratamiento quimioterápico que, en la población pediátrica, adquiere particular relevancia por su impacto en la morbimortalidad. Este estudio tuvo como objetivo determinar la prevalencia de bacterias multirresistentes asociadas a neutropenia febril, con el fin de contribuir a la actualización de protocolos de terapia antibiótica

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empírica institucional. **Metodología:** Se realizó un estudio observacional, descriptivo, transversal y retrospectivo en el Hospital Pediátrico Baca Ortíz de Quito, Ecuador. Se trabajó con la totalidad de registros elegibles, un censo de 184 pacientes oncológicos pediátricos con al menos un episodio de neutropenia febril con hemocultivo positivo entre el 2019 y el 2023. Los criterios de inclusión fueron temperatura ≥ 38 °C y recuento absoluto de neutrófilos $\leq 500/\text{mm}^3$. **Resultados:** El 51,6 % de los pacientes fueron mujeres. La leucemia constituyó el diagnóstico oncológico predominante (84,8 %), y más del 90 % presentó neutropenia severa, concentrada principalmente en este grupo. Las bacterias Gram-negativas fueron predominantes, entre ellas destacaron *Klebsiella pneumoniae* (16,8 %) y *Escherichia coli* (16,3 %) como enterobacterias. La *Pseudomonas aeruginosa* (7,6%) destacó como bacilo no fermentador. El análisis de resistencia se realizó sobre 160 aislamientos bacterianos; se excluyeron 24 aislamientos fúngicos. La prevalencia de bacterias productoras de betalactamasas de espectro extendido fue del 16,0 % (IC 95 %: 10,0-22,0 %) y la de productoras de carbapenemasas del 8,0 % (IC 95 %: 3,0-12 %). **Conclusión:** En pacientes pediátricos oncológicos con neutropenia febril predominaron las bacterias Gram-negativas multirresistentes, con una prevalencia de betalactamasas de espectro extendido (16,0 %) y de carbapenemasas (8,0 %) sobre los aislamientos bacterianos. Estos hallazgos podrían contribuir a la revisión y actualización de los protocolos de terapia antibiótica empírica institucional para este grupo poblacional; por tanto, resultan determinantes para la actualización de protocolos de tratamiento empírico en este grupo poblacional.

Palabras clave: farmacoresistencia microbiana, betalactamasas de espectro extendido, bacterias Gram-negativas, neutropenia febril, neoplasias.

1. Introduction

Research on the prevalence of multidrug-resistant bacteria associated with febrile neutropenia in oncology patients has been an extensively addressed topic in the scientific literature, contributing valuable data on the epidemiology and management of these conditions in vulnerable populations. Antimicrobial resistance (AMR) constitutes a global health crisis that threatens the advances achieved by modern medicine. In this context, the World Health Organization (WHO) updated its Bacterial Priority Pathogens List (BPPL) in 2024. It includes 24 pathogens grouped into 15 antibiotic-resistant families, classified into three categories: critical, high, and medium priority [1,2]. Within the critical priority category, there are ESBL-producing Enterobacteriaceae, *Klebsiella pneumoniae*, and carbapenem-resistant *Acinetobacter baumannii* [1,2]. These pathogens are directly implicated in the findings of the present study. Microorganisms included in these groups are associated with high morbidity and mortality and substantially increase the cost of medical care [1].

This growing concern has underscored the urgent need to investigate the impact of AMR in high-risk populations, particularly pediatric oncology patients. Febrile neutropenia is a frequent and potentially life-threatening complication in cancer patients undergoing chemotherapy; in the pediatric population, it is of particular relevance due to its association with significant morbidity and mortality [3,4].

This study aimed to determine the prevalence of multidrug-resistant bacteria associated with episodes of febrile neutropenia in pediatric oncology patients treated at the Baca Ortíz Pediatric Hospital between 2019 and 2023, thus contributing to the revision and updating of institutional empirical antibiotic therapy protocols.

2. Materials and Methods

2.1 Study design

A non-experimental, quantitative, descriptive study was conducted using an observational, cross-sectional, and retrospective design based on the analysis of electronic medical records of previously treated patients, with no direct intervention on study participants.

2.2 Setting, population, and sample

The study was carried out at the Oncohematology Service of the Baca Ortíz Pediatric Hospital (Ministry of Public Health), Quito, Ecuador, a national tertiary referral center for the pediatric population. Electronic records from January 2019 to December 2023 were analyzed. Data collection was completed

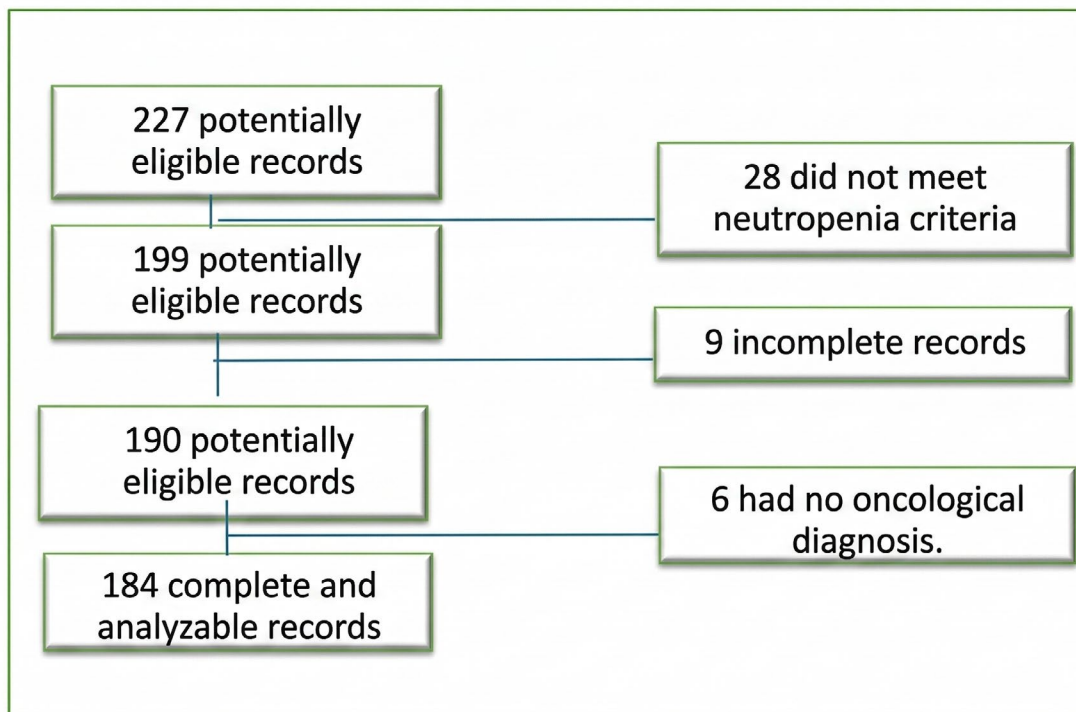
in December 2024. The study was approved by the Institutional Review Board for Human Research (CEISH-HPBO) under code 021-CEISH-HPBO-PA-2024.

The study population comprised pediatric patients aged 0 to 15 years with a confirmed oncologic diagnosis, who experienced at least one episode of febrile neutropenia with a positive blood culture during the specified period. All records meeting the selection criteria were included; therefore, there was a complete census of eligible cases.

Inclusion criteria were age between 0 and 15 years; confirmed oncologic diagnosis (solid tumors or hematologic malignancies); at least one episode of febrile neutropenia, defined as temperature $\geq 38^{\circ}\text{C}$ with an ANC $\leq 500/\text{mm}^3$ or $\leq 1,000/\text{mm}^3$ with an expected decline to below $500/\text{mm}^3$ within 24 to 48 hours; a positive blood culture; and a complete clinical record. Each patient was included only once, based on the first documented episode; recurrent episodes were not included.

Records were excluded if they contained incomplete data, lacked a final blood culture result, corresponded to patients older than 15 years, or did not strictly fulfill the criteria for febrile neutropenia or lacked an oncologic diagnosis. Of 227 potentially eligible records, 43 were excluded (28 because they did not meet febrile neutropenia criteria, 9 had incomplete records, and 6 for absence of an oncologic diagnosis), thus resulting in 184 records included in the final analysis. These represented the complete universe of eligible cases for the study period (Figure 1).

Figure 1. Participant selection flowchart. Of 227 potentially eligible records, 43 were excluded because they did not meet neutropenia criteria (n=28), had incomplete records (n=9), or absence of an oncologic diagnosis (n=6), thus resulting in 184 records included in the final analysis.



2.3 Variables

Variables analyzed included sociodemographic characteristics (age stratified in months, and biological sex), clinical characteristics (oncologic diagnosis [leukemia, lymphoma, and solid tumor]; neutropenia grade, classified as mild [ANC 1,000–1,500/ mm^3], moderate [ANC 500–1,000/ mm^3], and severe [ANC <500/ mm^3]; and oral or axillary temperature $\geq 38^{\circ}\text{C}$), and microbiological characteristics (microorganism isolated in blood culture; ESBL production; carbapenemase production; and classification as a multidrug-resistant organism). Categorical variables are presented with their respective categories; continuous variables were stratified for descriptive analysis.

2.4 Statistical analysis

Univariate descriptive analysis was performed for all variables using absolute frequency tables and percentages. To explore the distribution of microbiological variables according to oncologic diagnosis and neutropenia grade, contingency tables were constructed. Given the cross-sectional descriptive design and the census-based approach, 95% confidence intervals (CIs) were calculated for MDR prevalence estimates to assess the precision of findings. Records with incomplete data were excluded during the selection phase; therefore, no missing data were present in the final analysis. IBM SPSS Statistics version 23 was used for all statistical analyses.

2.5 Bias control

Strict inclusion and exclusion criteria were applied to minimize selection bias. Records with incomplete clinical histories, those lacking final blood culture results, patients older than 15 years, and those who did not strictly meet febrile neutropenia criteria or had non-oncologic diagnoses were excluded.

Sample size: A total of 227 potentially eligible records were initially identified. Of these, 43 were excluded for failure to meet selection criteria: 28 did not fulfill febrile neutropenia criteria, 9 were incomplete, and 6 lacked an oncologic diagnosis. The final sample comprised 184 complete records.

3. Results

A total of 184 electronic records meeting the established criteria were identified ([Figure 1](#)). Each record corresponded to a single patient with one episode of febrile neutropenia and one positive blood culture; therefore, the unit of analysis was simultaneously the patient and the microbiological isolate. Recurrent episodes from the same patient were not included. Accordingly, prevalence per patient and prevalence per isolate are equivalent, both calculated on a denominator of 184 cases.

Female patients accounted for 51.6% of the cohort and male patients for 48.4%. The most frequently represented age group was 121 to 180 months old (10 to 15 years), comprising 33.2% of the population. Leukemia was the predominant oncologic diagnosis (84.8%), followed by lymphoma and solid tumors ([Table 1](#)).

Table 1. Distribution by diagnosis

Diagnosis	Frequency	Percentage
Leukemia	156	84.8 %
Lymphoma	14	7.6 %
Solid tumor	14	7.6 %
Total	184	100.0%

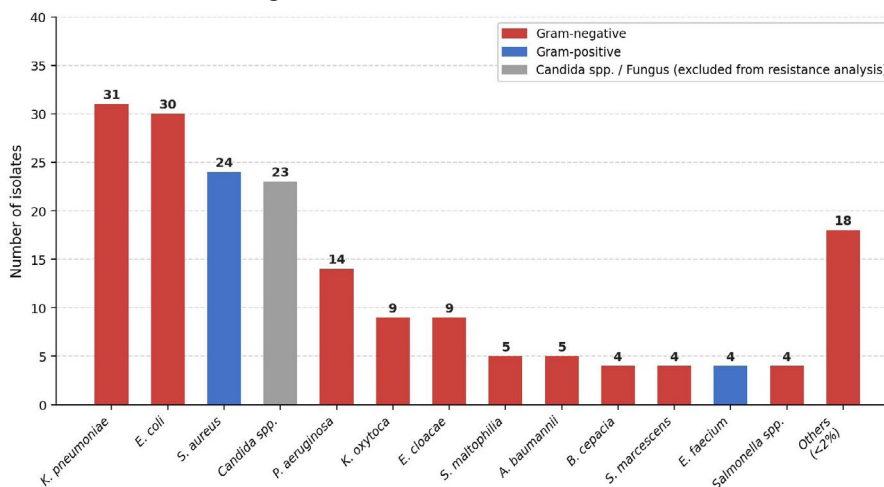
More than 90% of patients presented severe neutropenia. 78.3% belonged to the leukemia group, while patients with lymphoma and solid tumors predominantly exhibited mild to moderate neutropenia ([Table 2](#)).

Table 2. Sample distribution by level of neutropenia and cancer diagnosis

		Leukemia	Lymphoma	Solid tumor	Total	
Neutropenia level	MILD	Count	4	1	0	5
		Percentage	2.2 %	0.5 %	0.0 %	2.7 %
	MODERATE	Count	8	3	1	12
		Percentage	4.3 %	1.6 %	0.5 %	6.5 %
	SEVERE	Count	144	10	13	167
		Percentage	78.3 %	5.4 %	7.1 %	90.8 %
Total	Count	156	14	14	184	
	Percentage	7.6 %	8.4 %	7.6 %	100.0 %	

Of the 184 total isolates, 160 (87.0%) were bacterial and 24 (13.0%) were fungal, including *Candida* spp. (23 cases, 12.5%) and *Rhodotorula* sp. (1 case, 0.5%). Fungal isolates were excluded from the bacterial resistance analysis. Among bacterial isolates, Gram-negative organisms predominated (127 cases, 69.0%). *Klebsiella pneumoniae* (kpn) was the most frequently isolated microorganism with 31 cases (16.8%), followed by *Escherichia coli* (eco), 30 cases (16.3%); *Pseudomonas aeruginosa* (pae), 14 cases (7.6%); *Enterobacter cloacae* (ecl), 9 cases (4.9%); *Klebsiella oxytoca* (kox), 9 cases (4.9%); and *Acinetobacter baumannii* (aba), 5 cases (2.7%). Among Gram-positive bacteria (33 cases, 17.9%), *Staphylococcus aureus* (sau) was the most frequently isolated species with 24 cases (13.0%). All remaining microorganisms had individual frequencies below 2.5% (Figure 2).

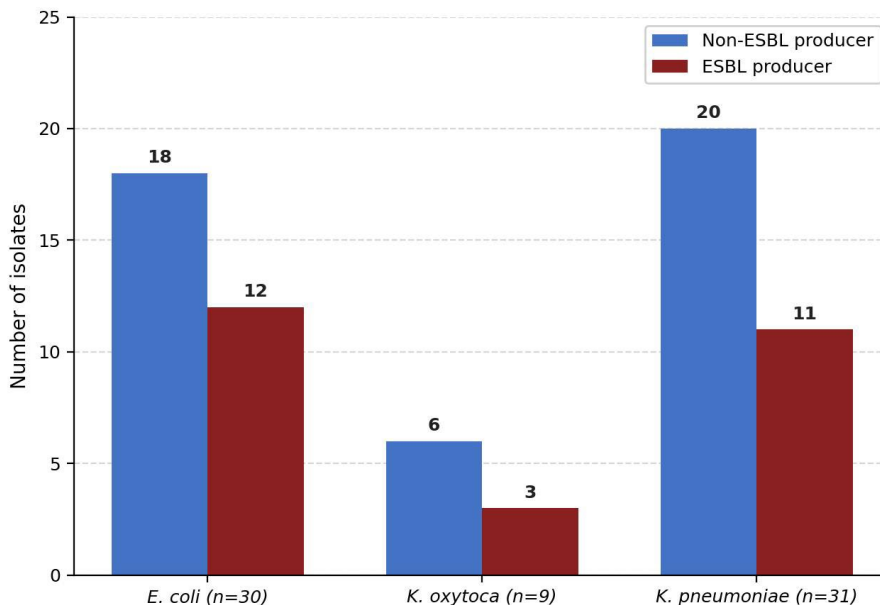
Figure 2. Frequency of microorganisms identified in blood cultures from patients with febrile neutropenia, according to microbiological classification (n=184). Red bars represent Gram-negative bacteria, blue bars Gram-positive bacteria, and grey bars fungi. Values above each bar indicate the absolute number of isolates. Fungal isolates were excluded from the bacterial resistance analysis.



Source: Authors' own elaboration.

Resistance analysis was performed on the 160 bacterial isolates, excluding the 24 fungal isolates. The prevalence of ESBL-producing bacteria was 16.0% (95% CI: 10.0%–22.0%), calculated on this denominator. Regarding species distribution, *Escherichia coli* (eco) had the highest frequency of ESBL production with 12 cases (40.0% of its isolates), followed by *Klebsiella pneumoniae* (kpn) with 11 cases (35.5%), and *Klebsiella oxytoca* (kox) with 3 cases (33.3%). It should be noted that kpn and kox are Enterobacteriaceae, while the remaining ESBL-producing cases corresponded to other Gram-negative bacteria with individual counts below 2 cases (Figure 3).

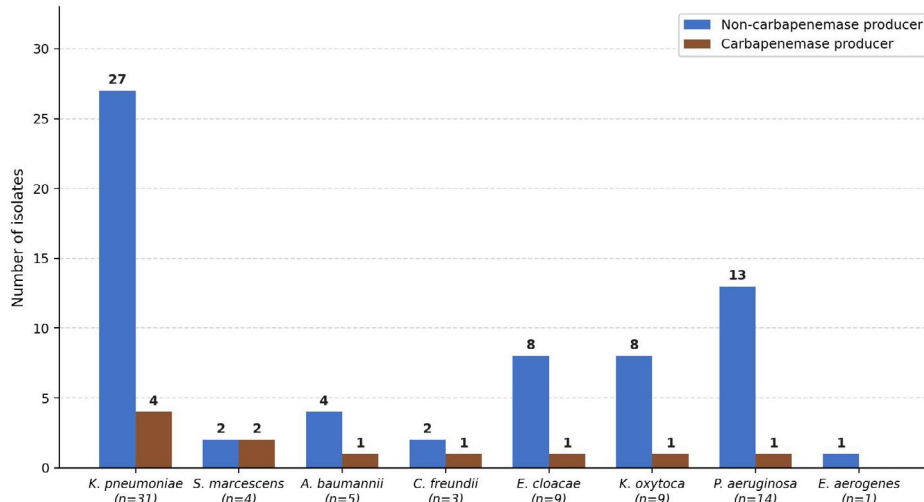
Figure 3. Distribution of ESBL-producing isolates by bacterial species. Blue bars represent non-producing isolates, red bars represent ESBL-producing isolates. Values above each bar indicate the absolute number of isolates. *E. coli* n=30 (40.0% ESBL-producing); *K. pneumoniae* n=31 (35.5% ESBL-producing); *K. oxytoca* n=9 (33.3% ESBL-producing).



Source: Authors' own elaboration.

Regarding carbapenemase production, a total of 12 cases were identified (8.0%; 95% CI: 3.0%–12.0%). *Klebsiella pneumoniae* (kpn) was the most frequently implicated species with 4 cases (33.3% of carbapenemase-producing isolates), followed by *Serratia marcescens* (sma) with 2 cases (16.7%). The remaining 6 cases were distributed among *Acinetobacter baumannii* (aba), *Citrobacter freundii* (cfr), *Enterobacter cloacae* (ecl), *Klebsiella oxytoca* (kox), *Pseudomonas aeruginosa* (pae), and *Enterobacter aerogenes* (eae) with one each (Figure 4).

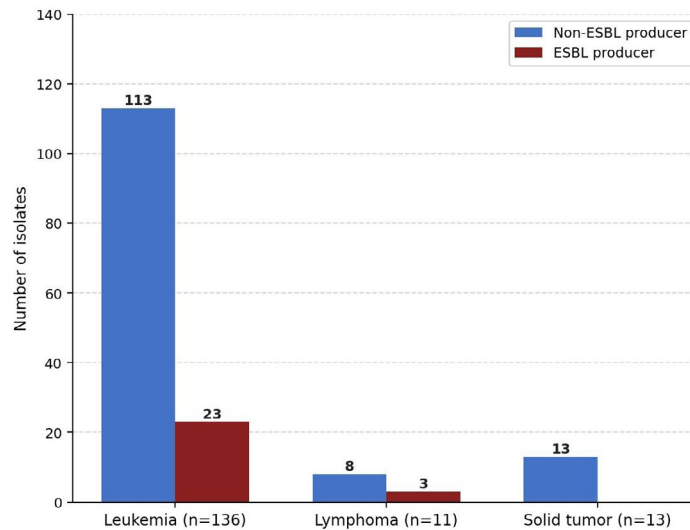
Figure 4. Distribution of carbapenemase-producing isolates by bacterial species (n=160) in pediatric oncology patients with febrile neutropenia. Blue bars represent non-producing isolates, red bars represent carbapenemase-producing isolates. Values above each bar indicate the absolute number of isolates. The overall prevalence of carbapenemase production was 8.0% (95% CI: 3.0%–12.0%).



Source: Authors' own elaboration.

When stratified by oncologic diagnosis, the prevalence of ESBL-producing organisms was 16.9% among patients with leukemia (n=23), 27.3% among those with lymphoma (n=3), and 0.0% among those with solid tumors (Figure 5).

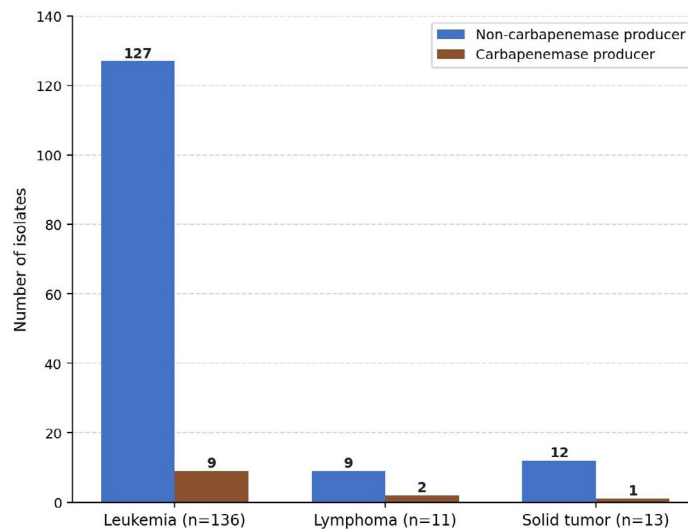
Figure 5. Distribution of ESBL-producing bacterial isolates by oncologic diagnosis (n=160). Blue bars represent non-producing isolates, red bars represent ESBL-producing isolates. Values above each bar indicate the absolute number of isolates. Leukemia: 16.9% ESBL; Lymphoma: 27.3% ESBL; Solid tumor: 0.0% ESBL.



Source: Authors' own elaboration.

Regarding carbapenemase production, prevalence was 6.6% among patients with leukemia (n=9), 18.2% among those with lymphoma (n=2), and 7.7% among those with solid tumors (n=1) (Figure 6).

Figure 6. Distribution of carbapenemase-producing bacterial isolates by oncologic diagnosis (n=160). Blue bars represent non-producing isolates, red bars represent carbapenemase-producing isolates. Values above each bar indicate the absolute number of isolates. Leukemia: 6.6%; Lymphoma: 18.2%; Solid tumor: 7.7%.



Source: Authors' own elaboration.

4. Discussion

Findings of the present study reveal a microbiological profile dominated by Gram-negative bacteria in pediatric oncology patients with febrile neutropenia. *Klebsiella pneumoniae* (kpn) was the most frequently isolated pathogen (16.8%), followed by *Escherichia coli* (eco) (16.3%), and *Pseudomonas aeruginosa* (pae) (7.6%). Within this group, kpn and eco are Enterobacteriaceae, whereas *P. aeruginosa* (pae) and *Acinetobacter baumannii* (aba) are non-fermenting Gram-negative bacilli—a taxonomically relevant distinction for empirical treatment selection. This pattern is consistent with trends documented in the contemporary literature [5,6,7]. Islas-Muñoz et al. [8] in a Mexican cohort of oncology patients reported *Escherichia coli* as the most frequent pathogen in bacteremia, accounting for 42.3% of isolates, while Babu et al. [9] in India identified a similar pattern with predominance of *E. coli*, *A. baumannii*, and *K. pneumoniae*. The convergence of these findings suggests a consistent epidemiological trend toward the predominance of Gram-negative bacteria—both fermenting and non-fermenting—in this patient population.

Regarding resistance profiles, the prevalence of ESBL-producing bacteria was 16.0% (95% CI: 10.0%–22.0%) and that of carbapenemase-producing bacteria was 8.0% (95% CI: 3.0%–12.0%), both calculated on 160 bacterial isolates after excluding the 24 fungal isolates. These figures are clinically significant, particularly given that ESBL- and carbapenemase-producing Gram-negative bacteria—including Enterobacteriaceae and non-fermenting bacilli—are listed under the critical priority category of the 2024 WHO Bacterial Priority Pathogens List [1,2]. The carbapenemase prevalence identified in this study falls at the lower end of the 3%–51% range reported by Balletto et al. [10] across different European regions, which may reflect differences in antibiotic stewardship policies and local epidemiological surveillance systems. Nevertheless, even low prevalences of carbapenem resistance carry substantial clinical implications in immunocompromised populations, given the limited therapeutic armamentarium available for their management [1,7].

The distribution of resistance by oncologic diagnosis demonstrated that patients with leukemia concentrated the highest frequency of infections due to ESBL-producing (16.9%) and carbapenemase-producing (6.6%) organisms. This finding is consistent with the greater chemotherapy intensity and depth of neutropenia characteristically observed in this disease [4]. More than 90% of patients in this cohort presented with severe neutropenia, a proportion exceeding that reported by Gavidia Mayora et al. [11] in Guatemala (72.77%). This difference may be explained by the characteristics of the population served at a national tertiary referral center.

Regarding infection etiology, literature documents a historical evolution in microbiological profiles: from the predominance of Gram-negative organisms in the 1960s and 1970s, to a shift toward Gram-positive bacteria from the mid-1980s onward [5]. Subsequently, there was a resurgence of multidrug-resistant Gram-negative organisms since the year 2000 driven by the dissemination of resistance genes encoding ESBLs and carbapenemases [6,7]. This study reflects the most recent phase, which is characterized by a predominantly Gram-negative profile and a significant presence of MDR mechanisms that must be taken into account in therapeutic decision-making.

It is important to note that, while these findings provide valuable information on the local epidemiology of bacterial resistance in pediatric oncologic febrile neutropenia, the development of empirical antibiotic therapy protocols requires integrating multiple clinical and institutional variables, including the local antimicrobial susceptibility profile, the patient's clinical status, tumor type, treatment intensity, and available resources. Therefore, results of the present study should be interpreted as a complementary input for the review of institutional guidelines, and not as independent evidence sufficient to modify protocols [2,5,7].

4.1 Limitations

This study has several limitations that should be considered when interpreting results. First, given the retrospective design, data quality was contingent upon the completeness of available electronic records, which may have required excluding 43 records due to incomplete data or absence of an oncologic diagnosis. Second, the single-center design limits the generalizability of findings to other institutional or geographic contexts, as antimicrobial resistance patterns may vary substantially across hospitals and regions. Third, the lymphoma and solid tumor subgroups had small sample sizes, thus resulting in wide confidence intervals for their stratified estimates and limiting the precision of comparisons across oncologic diagnoses. Finally, given the descriptive cross-sectional design, causal relationships could not be established, nor could the impact of bacterial resistance on clinical outcomes such as mortality or length of hospitalization be assessed.

5. Conclusions

This study identified a predominance of Gram-negative bacteria in blood cultures from pediatric oncology patients with febrile neutropenia. Enterobacteriaceae *Klebsiella pneumoniae* and *Escherichia coli* were the most frequently isolated pathogens, followed by the non-fermenting bacillus *Pseudomonas aeruginosa*. Leukemia was the predominant oncologic diagnosis; it also concentrated the highest proportion of cases with severe neutropenia and multidrug-resistant bacterial isolates.

The presence of ESBL-producing and carbapenemase-producing bacteria both included in the critical priority category of the 2024 WHO Bacterial Priority Pathogens List underscores the clinical relevance of these findings in a particularly vulnerable population. ESBL production was the most prevalent MDR mechanism, occurring at a higher frequency than carbapenemase production.

Results contribute to characterizing the local microbiological landscape of bacterial resistance associated with febrile neutropenia in pediatric oncology patients at the Baca Ortíz Pediatric Hospital and may serve as a basis for the revision and updating of institutional empirical antibiotic therapy protocols. Given the descriptive, single-center nature of the study, these conclusions should be interpreted with caution and supplemented by multicenter research to broaden their scope and applicability.

6. Abbreviations

Aeh: *Arcanobacterium haemolyticum*

Aug: *Acinetobacter ursingii*

Aba: *Acinetobacter baumannii*

Asb: *Aeromonas veronii biovar sobria*

Avv: *Aeromonas veronii biovar veronii*

Bcx: *Burkholderia cepacia*

Cru: *Candida rugosa*

Cal: *Candida spp.*

Cfr: *Citrobacter freundii*

Cgu: *Candida guilliermondii*

Cpa: *Candida parapsilosis*

Ctr: *Candida tropicalis*

Ecl: *Enterobacter cloacae*

Eco: *Escherichia coli*

Efm: *Enterococcus faecium*

Efa: *Enterococcus faecalis*

Inf: *Salmonella infantis*

Kox: *Klebsiella oxytoca*

Kpn: *Klebsiella pneumoniae*

Kpl: *Raoultella planticola*

Pae: *Pseudomonas aeruginosa*

Pma: *Stenotrophomonas maltophilia*

Rho: *Rhodotorula sp.*

Sal: *Salmonella spp.*

Sen: *Salmonella enteritidis*

Sma: *Serratia marcescens*
 Sau: *Staphylococcus aureus*
 Swa: *Staphylococcus warneri*
 Sam: *Salmonella typhimurium*
 Sep: *Staphylococcus epidermidis*
 Sin: *Streptococcus intermedius*
 Eae: *Enterobacter aerogenes*
 Koz: *Klebsiella ozaenae*
 Pal: *Providencia alcalifaciens*
 Pfl: *Pseudomonas fluorescens*
 Mmo: *Morganella morganii*
 AMR: Antimicrobial resistance
 ANC: Absolute neutrophil count
 ESBL: Extended-spectrum beta-lactamase
 MDR: Multidrug-resistant
 SPSS: Statistical Package for the Social Sciences

7. Administrative information

7.1 Author contributions

Cinthy Paredes-Barzola: Conceptualization, methodology, validation, investigation, and writing.

7.2 Conflicts of interest

The author declares no conflicts of interest.

7.3 Funding

No external financial support was received for this study.

7.4 Ethics statement

In accordance with the regulations governing Human Research Ethics Committees published in the Official Register of Ecuador, Agreement No. 00005-2022 (August 2022), this study received approval from the Institutional Review Board for Human Research (CEISH) of the Baca Ortiz Pediatric Hospital (CEISH-HPBO), under code 021-CEISH-HPBO-PA-2024.

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