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ORIGINAL ARTICLE

Microbiological characterization and antimicrobial susceptibility pattern of infections associated with febrile neutropenia in pediatric hemato-oncological patients

Caracterización microbiológica y de susceptibilidad antimicrobiana de las infecciones asociadas a neutropenia febril en pacientes hemato-oncológicos pediátricos

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What do we know about the subject matter of this study?

Microbiological documentation is a fundamental tool for timely, appropriate, and rational empirical antibiotic therapy in febrile neutropenia. In Latin America, epidemiological surveillance is heterogeneous and sometimes limited, which leads to greater infectious complications in this population.

What does this study contribute to what is already known?

This study is representative of the local population, it provides a basis of microbiological behavior in febrile neutropenia, both locally and nationally and even in Latin American communities with similar population conditions to ensure the adequate use of antibiotics.

Abstract

Febrile neutropenia (FN) is the most frequent hemato-oncological emergency, with high morbidity and mortality in pediatrics. The objective of the study was the microbiological characterization and antimicrobial susceptibility of infections associated with FN in pediatric hemato-oncological patients. **Patients and Method:** Retrospective cohort study with patients aged between 1 month and 18 years, with onco-hematological pathology according to ICD-10 codes, hospitalized in a tertiary healthcare center in Bucaramanga, Colombia. Based on the medical records of the period 2013-2017, the episodes of FN were identified, and the isolated microorganisms and their susceptibility pattern were described. Biochemical identification and antimicrobial susceptibility testing were performed with the Dade Behring Microscan® automated system. The resistant microorganism classification was performed based on the Minimum Inhibitory Concentration (MIC) and the interpretation of the laboratory according to the cut-off points of the Clinical and Laboratory Standards Institute recommendations. **Results:** Of 130 patients, 14.7% of the cultures obtained were positive. Bloods-

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tream infection was observed in 17.5% of the episodes. The isolated microorganisms were mainly Gram-negative bacteria (75.8%). Enterobacteriaceae (EB) were the most frequent, led by *Klebsiella pneumoniae, Escherichia coli*, followed by *Pseudomonas aeruginosa* and coagulase-negative *Staphylococci*. Of the EBs, 40.5% showed resistance to Piperacillin/Tazobactam, 33.3% to Cefepime, and 8.2% to Meropenem. According to the antimicrobial resistance pattern, it was observed that 16.4% of the positive EB cultures had an extended-spectrum beta-lactamase pattern and 5% a pattern suggestive of carbapenemases. All Gram-positive cocci were sensitive to Vancomycin. **Conclusion:** In the studied patients, the predominant pathogenic microorganisms were Gram-negative ones with resistance indices similar to those of developing countries.

Introduction

In developing countries, cancer is the first cause of non-accidental death in children, with febrile neutropenia (FN) as one of the most frequent emergencies with the highest morbidity and mortality in patients with hematological and/or oncological pathology. In order to control invasive bacterial infections, broad-spectrum antibiotic therapy, should be started quickly after cultures collection. According to the management guidelines, microbiological documentation is an invaluable tool to perform a rational empirical therapy according to the institutional reality; since the evolutionary dynamics of microorganisms, the inappropriate and irrational use of broad-spectrum antibiotics for prophylactic or therapeutic purposes, superinfections, and migration of new microorganisms and strains between institutions are factors that lead to changes the etiology and the pattern of antimicrobial susceptibility[1-4].

The objective of the study was to describe the epidemiological, microbiological, and antimicrobial susceptibility pattern characterization of FN-associated infections in pediatric patients with hematological and/or oncological pathology in Bucaramanga, Colombia.

Patients and Method

Descriptive retrospective cohort study, which included patients aged between 1 month and 18 years with hematological and/or oncological pathology, according to ICD-10 code, who were hospitalized in the *Clínica Materno Infantil San Luis* (Bucaramanga, Colombia). The clinical records from 2013 to 2017 were reviewed to detect episodes of FN, data was collected in the REDCap software, and the description of the isolated microorganisms and their susceptibility pattern was made.

All patients under 18 years of age, with oncologic or hematologic diagnosis susceptible to FN (all those with a diagnosis of hematologic and oncologic pathology defined as a high-risk patient in the clinical history, with rapid progression of the disease, or advanced stage lymphomas), hospitalized in the period studied were included. We excluded all newborns and those patients whose FN was secondary to non-hematological or oncological pathologies (rheumatological, nutritional, metabolic, endocrinological, infectious, pharmacological other than antineoplastic, and immunological).

An episode of FN was defined as documentation in the medical record of temperature ≥ 38°C along with an initial absolute neutrophil count < 1500 cells/mm3, with evidence of decrease to < 500cell/mm3 over the next two consecutive days.

The antibiograms reported in the history of the institution's microbiology laboratory were used. Biochemical identification and antimicrobial susceptibility tests were performed with the MicroScan® (Dade Behring, U.S.A.) automated system and the appropriate microbiological quality control. The classification of resistant microorganisms was performed considering the Minimum Inhibitory Concentration (MIC) and the interpretation performed by the laboratory according to the cut-off points of the Clinical and Laboratory Standards Institute (CLSI) recommendations.

Clinically significant microorganisms were considered those whose isolation was from patients with associated symptomatology. Thus, microorganisms isolated in blood cultures with clinical significance were those that met the criteria of the Center for Disease Control and Prevention (CDC, 2018, Appendix 1) for bloodstream infection[5]. Microorganisms isolated in urine and stool cultures with clinical significance were from patients with urinary and gastrointestinal symptomatology, respectively, at the time of sample collection.

Finally, an interpreted reading of the antibiograms of the positive cultures was performed to identify the phenotypic pattern of antimicrobial resistance of the main bacteria causing infections in in-hospital care.

Antimicrobial resistance phenotype was considered as the combination of a causative bacterial agent and resistance to a given antibiotic. Appendix 2 shows the definitions of the interpreted antimicrobial resistance patterns.

Based on the WHO definition, microorganisms were classified into multidrug-resistant (MDR), when presenting resistance to 3 or more types of antimicrobial agents available in most of the world and considered potentially effective against the respective pathogen, and non-MDR those that did not meet these criteria; in order to establish their behavior in the studied population. Methicillin-susceptible and methicillin-resistant GPC, multi-susceptible GNBs, and low-spectrum and high-spectrum penicillinase patterns were considered as non-MDR phenotypes. Vancomycin-resistant GPC, ESBL-producing pattern, CPE pattern, and MDR pattern by combined mechanisms (MDRcm) were considered MDR phenotypes[6,7].

The study was considered risk-free, approved by the research committee of the *Universidad Industrial de Santander* (UIS) and the CLSI; in which verbal informed consent and assent were applied. There were no conflicts of interest.

A descriptive analysis was made of the epidemiological measures of incidence, mortality, lethality, as well as a description of the variables by patient level, episodes, cultures, bacteremia, and antibiogram interpretation. For bivariate analysis, the Pearson's Chi2 test was used for categorical variables, Fisher's exact test for categorical variables with low numbers, and the Mann-Whitney test for continuous quantitative variables. In all analyses, a P-value < 0.05 was considered statistically significant, with a 95% confidence interval, using the Stata 14.0 software.

Results

Of 1423 susceptible patients, 130 met the inclusion criteria (1240 did not present FN; 48 did not meet full FN criteria, 2 met exclusion criteria according to the methodology, and 3 did not sign informed consent). In the studied period, 315 episodes of FN classified as high risk were identified, up to 9 episodes per patient, with a median of 2,42 episodes per patient and a cumulative incidence of patients with a first episode of FN of 9,1 (CI 95%: 7,68-10,75). The cumulative period mortality was 1,96 deaths per susceptible patient, with a case fatality of 21,53 deaths per FN patient during the entire period.

Of the total number of FN episodes, 1454 cultures were obtained, ranging from 1 to 33 cultures per episode, with a median of 4 (IQR 3-5); 14,7% (n = 214; CI 95%13,0-16,6) were positive, resulting in a total of 110 episodes with positive cultures and 220 isolated microorganisms (202 cultures reported a single agent; 9 cultures, two agents). Table 1 shows the characteristics of the patients studied.

The clinical infection was present in 62,2% of the episodes on admission, being respiratory (n = 104; 33,1%) and gastrointestinal (n = 88; 28,1%) the most frequent. There was no central nervous system involvement in any of the cases. All children received initial empirical antibiotics; the most commonly used first-line antibiotics were TZP (n = 153; 48,6%), FEP (n = 118; 37,5%), and VAN (n = 68; 21,6%).

Within the types of cultures performed, the most frequent were blood cultures (n = 877; [60,3%], 109 positive), urine cultures (n = 355 [24,4%], 17 positive), and stool cultures (n = 124; [8,5%], 53 positive).

Of the isolates, 91,8% corresponded to bacteria, with a predominance of GNBs, followed by GPC, 7,3% to fungi, 0,5% to parasites, and the remaining to Mycobacterium tuberculosis. The predominant specific microorganisms isolated in descending order of frequency were: *Klebsiella pneumoniae*, *Escherichia coli*, CoNS, *Pseudomonas aeruginosa*, *Streptococcus viridans*, and *Staphylococcus aureus*. Of the GNBs isolated, almost 90% were EB, and *K. pneumoniae* predominating in slightly more than 40% of the cases, while in the GPC, CoNS accounted for almost half of the isolations. Regarding fungi, *Candida tropicalis* species predominated. No cultures were obtained for anaerobes and no technology was available for virus detection. Figure 1 describes the specific microorganisms isolated.

When applying the CDC criteria, 38 patients presented bloodstream infection, representing 55 episodes (17,5% [55/315] of the total episodes and 50,5% [55/109] of the episodes with positive cultures). Of the remaining patients, 9,1% (n = 5/55) had more than one bloodstream infection during the episode, for a total of 60 bacteremias (62 microorganisms). In addition, in 14 (n = 14/315, 4,4%) and 52 (n = 52/315, 16,5%) episodes, microorganisms with clinical significance were obtained in urine and stool cultures, respectively. Table 2 describes the different microorganisms isolated in blood cultures, stool cultures, and urine cultures.

Of the total isolated, 86,8% (n = 191) reported antibiograms. Antibiotic resistance was not reported in all cases according to the microorganism, and no antibiogram result were reported for the genus *Streptococcus spp*. Table 3 details antibiotic resistance by specific microorganism of clinical importance due to its frequency and pathogenicity. Of the EB, 40,46% showed resistance to TZP, 33,34% to FEP, and 8,15% to MEM.

Regarding GNBs, almost 60% of the EB were of non-MDR phenotypes. Within the MDR phenotypes, a quarter of the EB presented an ESBL-producing pattern, with the appearance of outbreaks of the pattern

suggestive of CPE. Of the non-fermenting GNBs, 60% were multi-susceptible and 30% presented MDR phenotypes, corresponding to 10% with a pattern suggestive of CPE and 20% with an MDRcm pattern.

Regarding GPCs, 10% of CoNS were Methicillin-susceptible and 84% Methicillin-resistant; while almost 70% of *S. aureus* were Methicillin-susceptible and one-third Methicillin-resistant (MRSA), the latter, with hospital resistance phenotype. In 2017, a CoNS with MIC ≥ 2 for Vancomycin, susceptible to Linezolid was isolated from a central blood culture of a male adolescent with late relapsed acute myeloid leukemia and FN who was kept isolated and received targeted therapy with subsequent negative cultures. Few cases of *Enterococcus spp*. were documented, all of them susceptible to Vancomycin. Table 4 shows the frequency of interpreted clinically significant antimicrobial resistance patterns of the isolated microorganisms.

Given the predominance of EB, the trend of antimicrobial resistance patterns during the period studied, is shown in Figure 2. A decrease in the AmpC, No-MDR, and ESBL patterns was observed, although with a permanent circulation of the latter two and outbreaks of microorganisms with a pattern suggestive of CPE.

A global comparison was also made between multi-susceptible EB with those of ESBL and CPE patterns. There was a significant difference between these groups with respect to previous antibiotic use, prolonged neutropenia, profound neutropenia, and ICU days (Table 5). The latter corresponds to a global analysis that will enabler further studies.

Discussion

Microbiological isolations, obtained by cultures, were recorded in 35% of the episodes, and are consistent with those found in the literature[1,2]. Bacteria continue to be the main cause of infection documented during episodes of FN, accounting for 92% of the isolations in this study and up to 60% in previous studies.h GNBs were the most frequent agent with a preponderance of EB in almost 90%[1-3,8-10]. *K. pneumoniae* predominated in GNBs isolates, while CoNS predominated in GPC isolates.

Viruses, although not reported, are the main be-

Table 1. Characteristics of the patients studied.

Variables	Absolute values	Mesures (CI > 95% o IQR)
Female/Male	63/67	48.46 % / 51.54 %
Age (years)	3-16	6.3 (RIQ: 3.0-10.0)
Hematolymphoid Neoplasia	108	83.08% (77.52-88.65)
ALL	77	59.23% (50.47-67.44)
MLL	16	12.31% (6.82-23.51)
Non-Hodgkin lymphoma	14	10.78% (3.64-39.51)
Hodgkin lymphoma	1	0.77% (0.11-5.4)
Solid tumors	18	13.85% (8.85-21.01)
Another diseases	4	3.08% (0.84-12.39)
Implantable port catheter	58	45.08% (39.64-50.64)
Prophylaxis	22	16.92% (10.27-17.93)
Use of antibiotics the last 3 months	163	51.75% (46.18-57.25)
Comorbilities	98	31.11% (26.22-36.47)
Days between Chemotherapy and fever	0-40	10 (RIQ: 4-13)
Temperature (°C)	38.0-40.5	38.5 (RIQ: 38.2-38.9)
AN inicial count	0-1419	80 (RIQ: 14-280)
AN minimum value	0-470	20 (RIQ: 0-90)
Severe neutropenia days	1-58	7 (RIQ: 4-10)
Initial CRP	6-396	48 (RIQ: 24-192)
Procalcitonin	0.13-18.2	1.49 (RIQ: 0.38-8.7)

Comorbidities: Down Syndrome and other chromossomopathies, Congenital Heart Diseases, Chronic Lung Disease, Desnutrition, Hipothyroidism, Epilepsy, Neurological deficits, Kidney Disease, Electrolyte Disorder. Abbreviations: ALL: Acute Lymphoblastic Leukemia, AML: Acute Mielogenous Leukemia, °C: degrees Celsius, AB: Antibacterial, AN: Absolute neutrophils, CRP: C-Reactive Protein

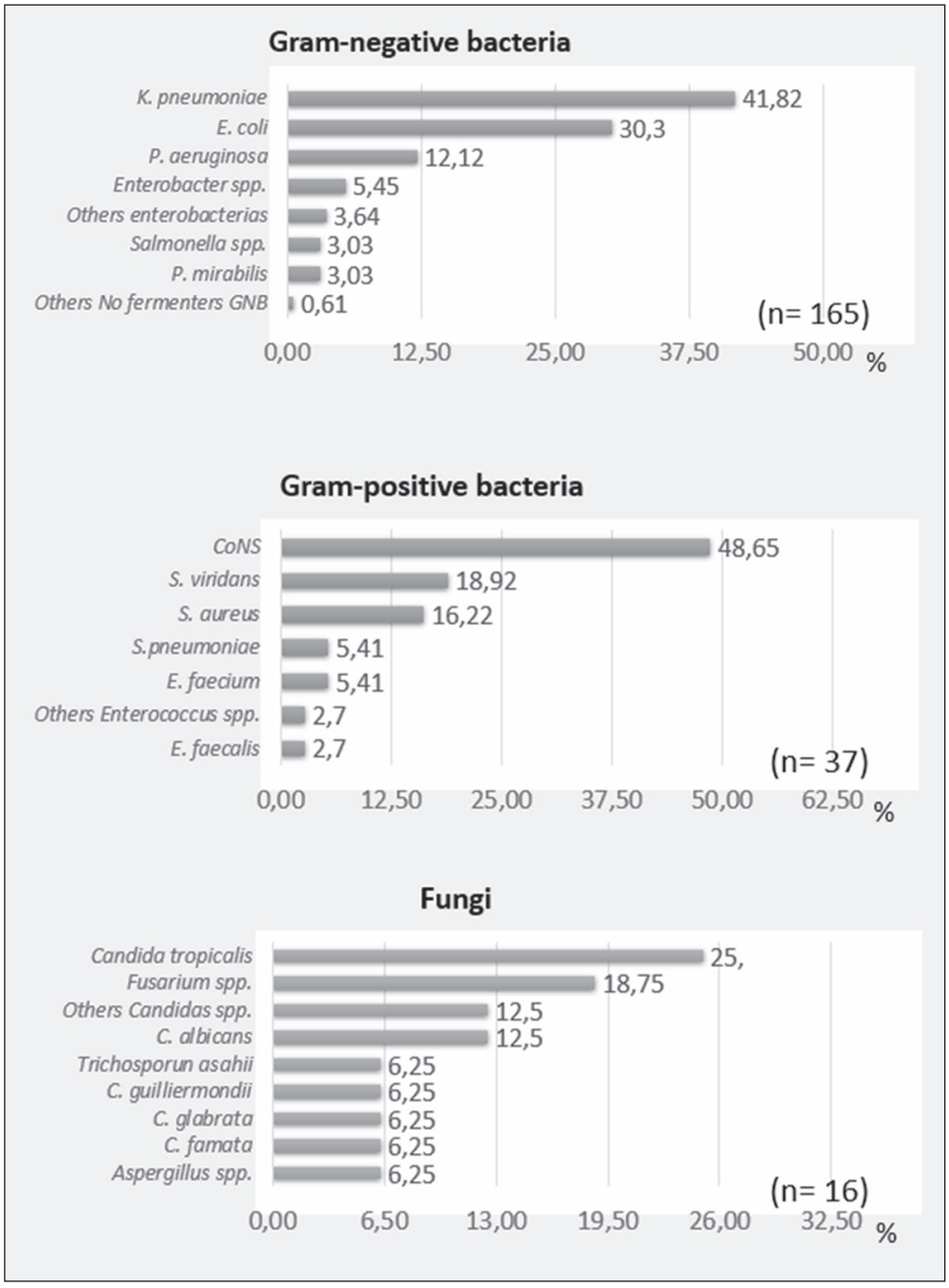

Figure 1. Specific isolated microorganisms in the study.

nign cause of fmild-moderate infections in patients with FN and their detection by molecular techniques is increasingly common[11,12]. Although fungi were less frequent, *Candida tropicalis* species has become relevant as a healthcare-associated infection in patients with prolonged and recurrent FN, possibly because it is a commensal organism in the mucocutaneous barrier in this population[13,14]. Furthermore, Fluconazole prophylaxis has increased the presence of other species resistant to it, such as *Candida krusei* and *Candida glabrata*[15,16].

Multi-susceptible EB was the most frequent phenotype pattern, with more than half of the isolations, followed by ESBL producers with a quarter. In regards to non-fermenting GNBs, the multi-susceptible pattern predominated, followed by MDRcm. For GPCs, Vancomycin susceptibility was prevalent (only one resistant case was reported); most *S. aureus* were Methicillin-susceptible, while CoNS were predominantly Methicillin-resistant. Infections by MDR bacteria are less common in children. However, the emergence of MDR agents, such as: EB with ESBL pattern, CPE,

Table 2. Clinically significant isolated microorganisms in the main cultures performed in the study

Pathogen classification	Microorganism	Frequency (n)	Frequency according to the microorganism classification (%)	Frequency according to total isolated microorganism (%)
Isolated microorganism in Blood Cultures (n = 62)				
Gram-negative microorganisms (n = 45, 72.58%)	*Klebsiella pneumoniae*	19	42.18	30.65
	Escherichia coli	15	33.33	24.19
	Pseudomonas aeruginosa	8	17.76	12.90
	Otros BGN aislados[a]	3	6.67	4.84
Gram positivos (n = 11, 17.74%)	*Staphylococcus epidermidis*	4	36.36	6.45
	Staphylococcus aureus	3	30.00	4.84
	Streptococcus mitis/oralis	2	18.18	3.23
	Otros CGP[b]	2	18.18	3.23
Hongos (n = 6, 9.68%)	*Candida tropicalis*	2	33.33	3.23
	Otras *Candida spp.*[c]	3	50.00	4.84
	Fusarium spp.	1	16.67	1.61
Microorganismos aislados en Coprocultivos (n=53)				
Gram negativos (n = 48, 90.57%)	*Klebsiella pneumoniae*	15	31.25	28.30
	Escherichia coli	15	31.25	28.30
	Proteus mirabilis	4	8.33	7.55
	Enterobacter cloacae	3	6.25	5.66
	Enterobacter spp.	2	4.17	3.77
	Salmonella spp.	2	4.17	3.77
	Pseudomonas aeruginosa	2	4.17	3.77
	Otros BGN aislados[a]	5	10.42	8.06
Fungi	*Candida albicans*	2	50.00	3.77
(n = 4, 7,55%)	Otras *Candida spp.*[c]	2	50.00	3.77
Parasites (n = 1, 1,89%)	*Giardia lamblia*	1	100.00	1.89
Isolated microorganism in Urine culture (n = 14)				
Gram-negative microorganisms	*Klebsiella pneumoniae*	6	46.15	42.86
(n = 13, 92.86%)	*Escherichia coli*	6	46.15	42.86
	Raoultella (K.) ornithinolytica	1	7.69	7.14
Fungi (n = 1, 7.14%)	*Candida tropicalis*	1	100.00%	7.14

[a]Other GNB in Blood culture: *Salmonella* spp, *Enterobacter cloacae*, *Enterobacter aerogenes*. Other GNB in Stool culture: *Citrobacter* spp, *Enterobacter aerogenes*, *Kluyvera ascorbata*, *Providencia alcalifaciens, Raoultella* (K.) *ornithinolytica*. [b]Other GPC: *Streptococcus pneumoniae, Enterococcus faecium*. [c]Other *Candida* spp: *Candida famata, Candida guilliermondii, Candida glabrata, Candida* spp.

MDR *Pseudomonas* species, and Vancomycin-resistant *Enterococcus* (VRE), is a current public health problem[10].

These resistance patterns vary according to the epidemiological context in each institution. Indeed, locally Rueda et al. characterized FN in children at the *Hospital Universitario de Santander* from 2007 to 2008, with 35 episodes of high-risk FN and 6 positive blood cultures, whose microorganisms described were multi-susceptible (multi-susceptible *K. pneumoniae*, Oxacillin-susceptible *S. aureus*, multi-susceptible *Acinetobacter baumannii*, and *Candida parapsilosis*)[17]. Although the sample was small, this is the only study in Bucaramanga.

At Colombian level, in 2018 a descriptive study of oncological patients with septic shock hospitalized at the National Cancer Institute of Bogota was published, where GNBs predominated (56,9%), followed by GPCs (31%), where the most isolated pathogen was *K. pneumoniae*[18]. In a previous study in that institution, GPC were predominant, they did not report resistance to Vancomycin, 20% of the *S. aureus* and 40% of the

Table 3. Antibiotic resistance of the specific microorganisms of clinical relevance in the study

Gram-negative microorganisms			
Antibacterial	*K. pneumoniae* (n = 69) n (%)	*E. coli* (n = 20) n (%)	*P. aeruginosa* (n = 20) n (%)
Ampicillin	51/54 (94.44)[a]	39/45 (86.67)	-
C1G	27/40 (67.50)	15/41 (48.39)	-
TZP	36/65 (55.38)	10/47 (25.53)	3/19 (15.79)
Cefoxitine	8/63 (12.70)	8/46 (17.39)	-
Aztreonam	23/53 (43.40)	7/43 (16.28)	5/17 (33.33)
C3G	29/63 (46.03)	10/43 (23.26)	-
Cefepime	29/65 (44.62)	10/47 (21.28)	6/19 (31.58)
Gentamicin	15/65 (23.08)	10/47 (21.28)	9/19 (47.37)
Amikacin	1/64 (1.56)	5/48 (10.42)	6/19 (31.58)
Ciprofloxacin	24/65 (36.92)	8/45 (17.78)	5/19 (26.32)
Meropenem	9/64 (14.06)	2/47 (4.26)	6/19 (31.58)
Ertapenem	8/64 (12.50)	2/47 (4.26)	-
Gram-positive microorganisms			
Antibacterial	*S. aureus* (n = 6) n (%)	SCN (n = 20) n (%)	Enterococcus (n = 4) n (%)
Penicillin	4/5 (80.00)[a]	2/12 (16.66)[a]	3/4 (75.00)
Oxacillin	2/5 (40.00)	16/18 (88.89)	-
Ampiciline	4/5 (80.00)[a]	10/10 (100.00)[a]	3/4 (75.00)
SAM	2/5 (40.00)	12/14 (85.71)	-
Erythromycin	2/5 (40.00)	2/16 (12.50)	-
Gentamicin	1/5 (20.00)	9/15 (60.00)	2/2 (100.00)
Clindamycin	2/5 (40.00)	13/18 (72.22)	-
Vancomycin	0/5 (0.00)	1/18 (5.56)	0/4 (0.00)
TMP-SMX	2/5 (40.00)	10/17 (58.82)	-
Linezolid	0/5 (0.00)	0/16 (0.00)	2/4 (50.000)

In each cell, the denominator corresponds to the number of reports of resistance of the microorganism to the specific antibiotic. They correspond to expected resistance patterns (natural or acquired): Klebsiella pneu-moniae is naturally resistant to Ampicillin and Staphylococcus spp. are acquired resistant (by BLAZ beta-lactamase) to penicillins and aminiopenicillins in 80-90% of cases. Abbreviation: C1G: First generation ceph-alosporins, TZP: Piperacillin Tazobactam, C3G: Third generation cephalosporins. SAM: Ampicillin Sulbac-tam, TMP-SMX: Trimethoprim-Sulfamethoxazole.

CoNS were Oxacillin-resistant, in contrast to our study where the frequency of microorganisms resistant to Methicillin was twice. While in GNBs, 23% of *E. coli* and 14% of *K. pneumoniae* presented ESBL pattern; and 12% of GNBs were resistant to carbapenems (Meropenem or Imipenem)[19].

In Medellín, in 2013, a study conducted at the *Hospital Pablo Tobón Uribe* was published in which the most frequent microorganisms were GNBs led by *E. coli* and *K. pneumoniae*, followed by *S. aureus*. Regarding bacterial susceptibility, the ESBL pattern was detected in 7,6% of the episodes (one strain of *K. pneumoniae* and two of *E. coli*) and there was only one episode with resistance to carbapenems. In the GPC, multi-susceptible *S. aureus* predominated in a 3:1 ratio against methicillin-resistant *S. aureus*, none was resistant to Vancomycin[20]. Very similar results were reported in previous years at the *Centro Hematológico Infantil de la Universidad de Antioquia* and at the *Hospital San Vicente de Paúl*[21]. In contrast, a study in the city of Pasto reported greater isolation of GPC compared with GNBs, led by *S. aureus* and CoNS[22].

Table 4. Frequency of the antimicrobial resistance interpreted patterns of the isolated microorganisms in the NF episodes of the study[a]

Antimicrobial Resistence Interpreted Pattern	Frequency (n)	Frequency according to the microorganism (%)	Frequency ac-cording of the total number of isolates (n = 220) (%)	Frequency according to the total number of episodes (n = 315) (%)
No antibiogram report	29	100.00%	13.18%	9.20%
Staphylococcus aureus (n = 6, 2.64%)				
MSSA	4	66.67%	1.82%	1.27%
MRSA Hospital phenotype	2	33.33%	0.91%	0.63%
Coagulase Negative *Staphylococcus* (n = 19, 8.68%)				
MR-CoNS	16	84.21%	7.27%	5.08%
MS-CoNS	2	10.53%	0.91%	0.63%
VR-CoNS	**1**	5.26%	**0.45%**	0.32%
Enterococcus spp (n = 3, 1.37%)				
AR-E	2	66.67%	0.91%	0.63%
AS-E	1	33.33%	0.45%	0.32%
Enterobacteriaceae family (n = 143, 65.30%)				
MS EB	51	35.66%	23.18%	16.19%
ESBL EB	**36**	25.17%	**16.36%**	11.43%
ESBL Kp	21	14.66%	9.55%	6.67%
ESBL Ec	8	5.59%	3.64%	2.54%
Low-spectrum Penicillinase EB	21	14.66%	9.55%	6.67%
High-spectrum Penicillinase EB	12	8.39%	5.45%	3.81%
AmpC EB	12	8.39%	5.45%	3.81%
CP-EB[b]	**11**	7.69%	**5.00%**	3.49%
No fermenters Gram Negative Bacteria (n = 20, 9.13%)				
MS-NFB	12	60.00%	5.45%	3.81%
MDRmc-NFB	**4**	20.00%	**1.82%**	1.27%
CS-NFB	2	10.00%	0.91%	0.63%
CP-NFB	**2**	10.00%	**0.91%**	0.63%

[a]The definitions of the interpreted patterns of antimicrobial resistance can be found in Annex 2. [b]2.10% (n=3) were confirmed by the Boronic-Acid Test and Carba-NP Test. Abbreviation: MSSA: Methicillin-sensitive Staphylococcus aureus. MRSA: Methicillin-resistant Staphylococcus aureus. AR-E: Ampicillin-resistant En-terococcus, AS-E: Ampicillin-sensitive Enterococcus. MS-EB: Multisensitive Enterobacteriaceae, ESBL-EB: Enterobacteriaceae standard producer of Extended Spectrum Beta-lactamase. Kp: Klebsiella pneumoniae. Ec: Escherichia coli. CP-EB: Entero-bacteria pattern suggestive of carbapenemase producing. NF: Gram-negative non-fermenting bacilli. MS-NFB: multisensitive NFB, MDRmc-NFB: NFB pattern suggestive of multidrug resistance combined mechanisms, CS-NFB: BNF sensitive to 4th generation cephalosporin, CP-NFB: NFB with pattern suggestive of carbapenemase producing.

Table 5. Unusual EB Resistance Patterns-Associated variables in the NF Episodes in the Study

Variable	Multisensitive (n = 51) n (%)	BLEE phenotype (n = 36) n (%)	CPE phenotype (n = 11) n (%)	Valor de p
Previous antimicrobial use	26 (50.98)	30 (83.33)	2 (18.18)	< 0.001
Invasive dispositive use	26 (50.98)	19 (52.78)	5 (45.45)	0.698
Prolonged period of Neutropenia	14 (31.11)	20 (76.92)	11 (100.00)	< 0.001
Profound Netropenia	44 (86.27)	36 (100.00)	11 (100.00)	0.021
ICU admission	18 (35.29)	13 (36.11)	4 (36.36)	0.077
ICU stay[a] (days)	8.5 (4-13)	23 (4-23)	1 (1-1)	0.005

Results are pesented in rows. [a]Median (IQR)

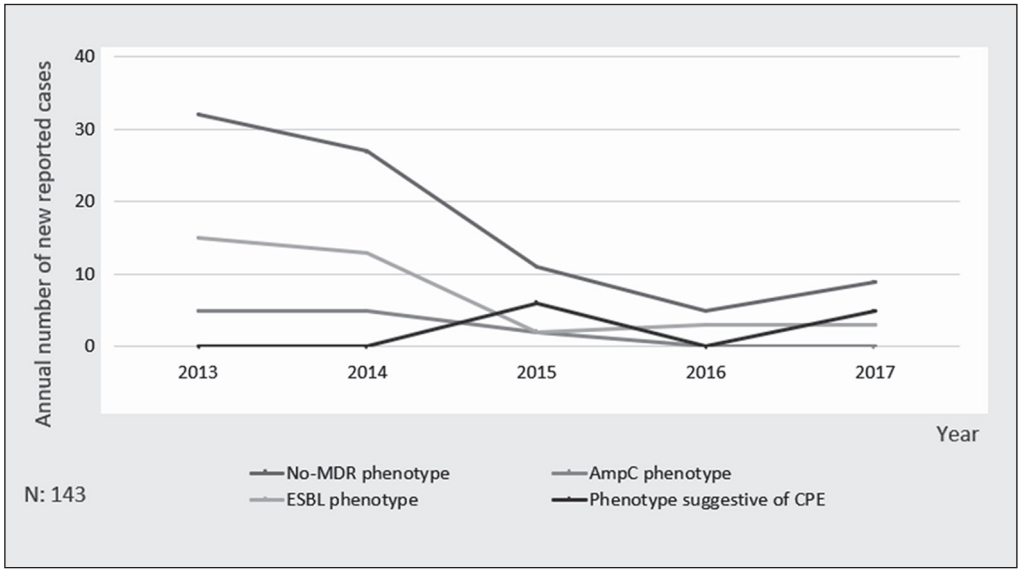

Figure 2. Antimicrobial resistance pattern trend of the Enterobacteriacea microorganism per Febrile Neutropenia episode in the study.

Similarly, in Latin America, although GNBs have been predominant, a microbial transition associated with the development of the country has been observed. In Cuba, a 2012 study showed that the predominant microorganisms were GNBs[23]. Meanwhile, Mexico in 2014 reported *E. coli*, *P. aeruginosa*, CoNS, and *K. pneumoniae* as the causative microorganism commonly isolated[24]; while by 2019, there was a predominance of GPC (*S. aureus*, *S. viridans*)[25]. Brazil instead, reported a predominance of encapsulated microorganisms (*S. pneumoniae*, *H. influenzae*), *S. aureus*, and GNBs[2].

In Chile, a country where microbiological behavior has been widely documented in referral institutions, a study of the causative agents of bacteremia in children with cancer and high-risk FN in five hospitals in Santiago between 2012 and 2015 found an equal predominance of GNBs (46,6%) and GPC (45,1%), with *E. coli* as the most frequent, closely followed by CoNS with 86,4% resistance to Oxacillin[26].

Similar results were obtained in the same centers between 2004 and 2009, where the frequency of isolation of GPC was predominant (56%), the most frequent agents were CoNS, *E. coli*, *S. viridans*, and *S. aureus*; with resistance to Oxacillin in 77% of CoNS and 14% of *S. aureus*[27]. Similar results were described by Cortez in 2008 and Ducasse in 2014[28,29]. Maldonado proposes that the small changes in resistance patterns across the years, correspond to the rigorous knowledge of local epidemiology that leads to the rational use of antibiotics, in contrast to the increased resistance observed in other countries[26].

In general, several studies worldwide (including countries such as the United States, Germany, the Netherlands, Italy, Australia, India, Israel, and Egypt) agree that there is a low frequency of MRSA, with a significant circulation of EB with ESBL pattern and emergence of VRE, CPE, and *Pseudomonas spp*. MDR species[13,30-35].

The risk of high levels of antibiotic resistance in this population responds to complex synergistic factors intrinsic to the host, pathogen, and environment (multiple hospitalizations, greater patient interventions, recurrent inappropriate use of empirical antibiotic therapy, associated comorbidities, among others)[36,37].

In this study, the behavior of pathogenic microorganisms was similar to that reported in other low- and middle-income countries, where EB were predominant, with an increase in MDR microorganisms. This behavior could be due to factors such as the limitations in infection control and prevention policies, new intensive chemotherapy treatments that increase the risk of bacterial translocation of enteric microorganisms through mucositis, selective pressure favored by some antibiotic prophylaxis, as well as the non-use of prophylaxis with fluoroquinolones, among others[14,38,39].

On the other hand, high-income countries have a predominance of GPC, due to interventional medicine which. Although favoring the timely and adequate management of FN, it also increases GPC colonization of the invasive dispositives and brings on infection for these agents. *S. aureus* has increased as the main cause of severe infections with progression to septic shock, *S. epidermidis* has become the main pathogen of central-line associated bloodstream infections (CLABSDI), and sin bloodstream infections related to mucosal barrier injuries *S. viridans* has increased[3,40]. Therefore, the evaluation of resistance patterns allows us to study new

infection control strategies and support the implementation of Antimicrobial Stewardship Programs according to the epidemiological context.

Strengths and Limitations

This study represents the local conditions of the Bucaramanga metropolitan area since it was carried out in a reference institution during a broad study period. Due to the large sample obtained, it contributes to the literature on infectious diseases in children with hemato-oncological diseases in our country and Latin America. There was no selection bias given the rigorous application of the inclusion and exclusion criteria. However, because it was a retrospective descriptive study, there could be information bias.

Conclusions

The behavior of microorganisms and their antimicrobial susceptibility pattern varies in each region and among each institution. Our study shows that in pediatric patients with hematological and/or oncological pathology and FN, in a reference institution in Colombia, there is a predominance of Gram-negative microorganisms as causative agents of infection, being more common EB, with an important circulation of ESBL pattern microorganism and outbreaks of CPE and they have similar resistance phenotypes to those observed in other low and middle-income countries.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

Financial Disclosure

Authors state that no economic support has been associated with the present study.

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Anexo 1. Criterios del Center for Disease Control and Prevention (2018) para infection del torrente sanguíneo

- Criterio 1: Infección en paciente de cualquier edad en el que se documenta un organismo patógeno, en al menos uno de los especímenes de sangre obtenidos por hemocultivos o métodos microbiológicos no basados en cultivos realizados del torrente sanguíneo. No es necesario que existan signos o síntomas para cumplir con los criterios de infección del torrente sanguíneo confirmada por laboratorio.
- Criterio 2: Infección en paciente de cualquier edad que tiene al menos uno de los siguientes signos o síntomas: Fiebre (> 38°C), escalofríos o hipotensión y en el que se identifica un microorganismo comensal en al menos dos especímenes de sangre recolectados en dos ocasiones diferentes que incluyen: difteroides (*Corynebacterium spp. C. diphtheria*), *Bacillus spp.* (*B. anthracis*), *Propionibacterium spp.*, SCN (incluido *S. epidermidis*), *S. viridans*, *Aerococcus spp. Micrococcus spp. y Rhodococcus spp*.
- Infección en paciente menor de un año que tiene al menos uno de los siguientes signos o síntomas: fiebre (> 38°C), hipotermia (< 36°C), apnea o bradicardia, en el que se identifica un microorganismo comensal en dos o más muestras de sangre.

Center For Disease Control And Prevention. Bloodstream Infection Event (Central Line-Associated Bloodstream Infection and Non-central Line Associated Bloodstream Infection). [En línea]. Guidelines and recommendations. USA. CDC.gov. 2018. (Recuperado en 28 de Febrero 2019) Disponible en: https://www.cdc.gov/nhsn/pdfs/pscmanual/4psc_clabscurrent.pdf.

Anexo 2. Lectura interpretada realizada de los antibiogramas obtenidos en el estudio.		
Microorganismo	Patrón interpretado	Lectura interpretada
Staphylococcus aureus	SA-MS	*S. aureus* sensible a Meticilina/Oxacilina.
	SA-MR fenotipo comunitario	*S. aureus* resistente a Meticilina/Oxacilina, sensible a Clindamicina y TMP-SMX, Gentamicina.
	SA-MR fenotipo hospitalario	*S. aureus* resistente a Meticilina/Oxacilina, Clindamicina, TMP-SMX, Gentamicina., sensible solo a Vancomicina.
	VI-SA	*S. aureus* con resistencia intermedia a vancomicina. Requiere pruebas confirmatorias.
	VR-SA	*S. aureus* resistente a vancomicina. Requiere pruebas confirmatorias.
Staphylococcus coagulasa negativo	SCN-MS	S. Coagulasa negativo sensible a Meticilina.
	SCN-MR	S. Coagulasa negativo resistente a Meticilina, sensible a Vancomicina.
	SCN-VR	S. coagulasa negativo resistente a Vancomicina.
Enterococos	E-AS	Enterococos sensibles a Ampicilina.
	E-AR	Enterococos resistentes a Ampicilina y sensibles a Vancomicina.
	E-RV	Enterococos resistentes a Vancomicina.
Estreptococos	S-PS	Estreptococos sensibles a Penicilina.
	S-PI	Estreptococos con resistencia intermedia a Penicilina, sensibles a Ceftriaxona y Vancomicina.
	S-PR	Estreptococos resistentes a Penicilina, sensibles a Ceftriaxona y Vancomicina.
	S-CR	Estreptococos resistentes a Ceftriaxona y sensibles a Vancomicina.
Enterobacterias	EB-MS	Enterobacterias multisensibles. (La *K. pneumoniae* puede ser naturalmente resistente a ampicilina).
	EB-PPasa	EB con patrón sugestivo productor de penicilinasas: • Penicilinasa de bajo techo: Resistente a Ampicilina, Piperacilina, Ampicilina-Sulbactam, cefalosporinas de primera y segunda generación. • Penicilinasas de alto techo: Resistente a Ampicilina, Piperacilina, Ampicilina-Sulbactam, Piperacilina-Tazobactam, cefalosporinas de primera y segunda generación.
	EB-AmpC	EB con patrón sugestivo productor de AMPc (Resistente a cefalosporinas de primera, segunda, tercera generación y Cefoxitin resistentes).
	EB-BLEE	EB con patrón sugestivo productor de betalactamasas de espectro extendido (Resistente a cefalosporinas de primera, segunda, tercera y cuarta generación, Aztreonam resistente, pueden ser sensibles o resistentes a Cefoxitin).
	EB-PC	EB patrón sugestivo productor de carbapenemasas (Resistente a carbapenémicos: 3 o más carbapenémicos incluido Ertapenem, pueden tener comportamiento BLEE). Requiere pruebas de confirmación.
	EB-MDRmc	EB patrón sugestivo de patrón de multirresistencia de mecanismos combinados (Bomba de eflujo, porinas, etc. Requiere lectura interpretada del antibiograma por infectóloga investigadora).
Bacilos Gram-Negativos no fermentadores	BNF-MS	Bacilos Gram-Negativos no fermentadores multi-sensibles. (Podría existir resistencia intrínseca a Cefalosporinas de primera, segunda y tercera generación).
	BNF-CS	Microorganismos no fermentadores sensibles a cefalosporinas de cuarta generación (sensibles a Cefepime)
	BNF-PC	Bacilos Gram-Negativos no fermentadores con patrón sugestivo de carbapenemasas: resistencia a 3 o más Carbapenémicos. Requiere pruebas de confirmación.
	BNF-MDRmc	Bacilos Gram-Negativos no fermentadores con patrón sugestivo de patrón de multirresistencia por mecanismos combinados (Bomba de eflujo, porinas, etc. Requiere lectura interpretada del antibiograma por infectóloga investigadora).

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