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ORIGINAL ARTICLE

Microorganisms isolated from blood cultures and resistance profile in children with cancer and high-risk febrile neutropenia. Red PINDA, Chile, 2016-2021

Microorganismos aislados de hemocultivos y su perfil de resistencia en niños con cáncer y neutropenia febril de alto riesgo. Red PINDA, Chile, 2016-2021

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

The epidemiology of bacteria isolated from blood cultures in children with cancer and their resistance profile is changing over time. Systematic epidemiological surveillance is essential, favoring the rational use of antimicrobials.

What does this study contribute to what is already known?

Prospective, multicenter study that determines the frequency of microorganisms isolated from blood cultures and their antimicrobial resistance profile in children with febrile neutropenia. The most prevalent species are viridans group *Streptococci* (VGS) and *Escherichia coli*, highlighting the increase of resistance to third-generation cephalosporins in enterobacteria, the decrease of resistance to amikacin in *Pseudomonas* spp., and to penicillin in VGS.

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Abstract

Bacteremia is a major cause of morbidity and mortality in patients with cancer and episodes of high-risk febrile neutropenia (HRFN). **Objective:** To identify the frequency of microorganisms isolated from blood cultures (BC) and their antimicrobial resistance (R) profile in children with HRFN, compared with the same data from previous studies of the same group. **Material and Method:** Prospective, multicenter, epidemiological surveillance study of microorganisms isolated from BC in patients under 18 years of age, from 7 PINDA network hospitals, between 2016 and 2021. **Results:** 284 episodes of HRFN with positive BC were analyzed out of 1091 enrolled episodes (26%). Median age 7.2 years [3.0-12.3]. The main isolates were gram-negative bacilli (GNB) 49.2%, gram-positive cocci (GPC) 43.8%, and fungi 3.6%. The most frequently isolated microorganisms were viridans group *Streptococci* (VGS) (25.8%), *Escherichia coli* (19.8%), *Pseudomonas* spp. (11.2%), *Klebsiella* spp. (10.9%), and coagulase negative *Staphylococci* (CoNS) (10.9%). There was an increase in R to third-generation cephalosporins ($p = 0.011$) in GNB and to oxacillin in CoNS ($p = 0.00$), as well as a decrease in R to amikacin in non-fermenting GNB ($p = 0.02$) and to penicillin in VGS (p = 0.04) **Conclusion:** VGS is the main agent isolated in BC from pediatric patients with cancer and episodes of HRFN, followed by *E. coli, Pseudomonas* spp., and *Klebsiella* spp. Having epidemiological surveillance of microorganisms isolated from BC and their antimicrobial R profile is essential to favor the rational use of antimicrobials.

Keywords:
Febrile Neutropenia;
Antimicrobial Resistance;
Bacteremia;
Bloodstream Infections

Introduction

Febrile neutropenia (FN), is defined as the presence of an absolute neutrophil count (ANC) < 500 cells/mm^3 associated with fever[1,2]. It is a frequent complication associated with high morbidity and mortality in pediatric cancer patients and, depending on certain predictive factors, it is classified into FN of high or low risk of developing invasive bacterial infection (IBI)[2], which determines differences in its management, evolution, and prognosis.

Among the main infections presented by these patients, bacteremia[3] stands out, representing almost half of the documented infections[4]. The main sources of bacteremias in children with cancer are the digestive tract due to mucositis secondary to chemotherapy and skin and soft tissue damage due to the use of vascular access devices[5].

The choice of antimicrobial therapy and its early administration are crucial in the prognosis of FN episodes in children with cancer[6,7]. The evolution in the epidemiology of bacteria isolated from blood cultures (BC) has changed over time, making systematic epidemiological surveillance essential. Thus, in the 1970s, coagulase-negative *Staphylococci* (CoNS) predominated as the cause of morbidity, with a lower frequency of gram-negative microorganisms[3]. In the 1990s, gram-negative bacilli (GNB) bacteremia became predominant, reaching 60-70% of cases, with *Escherichia coli*, *Klebsiella* spp., and *Pseudomonas aeruginosa* standing out[7]. In the last decade, an increase of gram-positive cocci (GPC) has again been observed, with viridans group *Streptococci* (VGS) becoming especially relevant[8], with less representation of *Staphylococcus aureus* both globally and locally, reaching 8.7% of isolates in Chilean hospitals in the 2010 decade[3,7].

Another point to highlight is the importance of surveillance of antimicrobial resistance over time, with the presence of extended-spectrum ß-lactamase (ESBL)-producing GNB, vancomycin-resistant enterococci, methicillin-resistant CoNS[5], in addition to penicillin-resistant VGS, and third-generation cephalosporins. The phenomenon of antimicrobial resistance is a growing problem in our country and around the world. The relationship between the use of antimicrobials in hospitals and the community and the emergence of bacterial resistance is widely recognized. Infections by multidrug-resistant bacteria reduce therapeutic options and are associated with longer hospital stays, mortality, and costs[3,9].

The objective of the study was to determine the frequency of microorganisms isolated from BC and their antimicrobial resistance profile in children with cancer and high-risk FN (HRFN) episodes between 2016 and 2021, compared with equal data from previous studies.

Material and Method

Design

Descriptive, prospective, multicenter, epidemiological surveillance study. The databases of FONDECYT regular project n°1161662 (2016-2019), FONDEF ID18I10293 (2020), and FONDECYT regular project n°1200964 (2021) were used. The original projects were approved by the Human Research Ethics Com-

mittee of the Faculty of Medicine, University of Chile, codes 217-2015, 036-2018, and 016-2020 respectively, and with the approvals from each participating institution and the informed consent/assent signature for the participation of children, when they were older than 10 years. Patients with a diagnosis of cancer who were seen in one of the seven hospitals of the National Child Program of Antineoplastic Drugs (PINDA) network due to episodes of HRFN[10] were included in the study. The participating hospitals were *Hospital Exequiel González Cortés*, *Hospital Sótero del Río*, *Hospital Roberto del Río*, *Hospital San Juan de Dios*, *Hospital San Borja Arriarán*, and *Hospital Dr. Luis Calvo Mackenna* in the Metropolitan Region, to which *Hospital Gustavo Fricke* in Viña del Mar was added since 2020.

All children with episodes of HRFN and positive BC were selected for this study. Epidemiological characteristics (age, sex, and baseline diagnosis), the frequency of isolated microorganisms, and their resistance profile were described, and the results were compared with the findings of three previous studies, conducted by the same PINDA Infectious Diseases Committee, in the periods 1994-1998, 2004-2009, and 2012-2015[7,11,12]. Patients undergoing hematopoietic stem-cell transplantation were excluded.

Definitions

a) Febrile neutropenia: ANC < 500 cells/mm^3 along with an axillary temperature measurement ≥ 38.5°C or two measurements ≥ 38.0°C spaced at least one hour apart; b) High-risk febrile neutropenia: episode of FN meeting at least one of the following criteria: diagnosis of non-lymphoblastic leukemia, relapsed leukemia, non-Hodgkin lymphoma, stage IV neuroblastoma, presence of low blood pressure, C-reactive protein ≥ 90 mg/L, or the following two criteria: platelet count ≤ 50,000 mm^3 plus chemotherapy received within ≤ 7 days relative to the onset of the FN episode.

Microbiological study

All patients on admission underwent automated BC (BacT/ALERT®, bioMérieux, Inc, Durham, NC, USA) using samples obtained from peripheral blood and central venous catheter. Each episode of FN was considered an event. For each event, different microbiological isolates were reported when they were microorganisms with a defined pathogenic role. The isolation of CoNS in a single peripheral BC was excluded from the registry and analysis, as it was considered a probable contamination[13]. The antimicrobial resistance study was performed using the VITEK®2 system (bioMérieux) and the agar diffusion method (Kirby-Bauer test), with cut-off points according to the Clinical Laboratory Standard Institute (CLSI) M100, which is updated annually.

The antimicrobials included in the GNB study were aminoglycosides (gentamicin, amikacin), third-generation cephalosporins (cefotaxime/ceftriaxone for enterobacteria and ceftazidime for non-fermenting GNB), fluoroquinolones (ciprofloxacin), piperacillin-tazobactam, and carbapenems (imipenem), while in GPC, the analysis included oxacillin in CoNS and *Staphylococcus aureus*, vancomycin in *Enterococcus* spp., and penicillin in VGS. Piperacillin/tazobactam resistance for Enterobacteriaceae and non-fermenting GNB, as well as the resistance to cefotaxime/ceftriaxone for VGS, are reported for the current period (2016-2021) without comparative analysis with previous periods where the data are not systematically available.

Statistical analysis

The databases were unified, and a descriptive analysis was performed using absolute and percentage frequency for categorical variables and median plus interquartile range [IQR] for continuous variables, evaluated for normality with the Shapiro-Wilk test. The Fisher test was used to compare frequencies and the 95% CI was reported using the Binomial Exact test. A value of $p < 0.05$ was considered significant. Stata/SE version 14.0 statistical software was used.

Results

Population studied

1,091 HRFN episodes were analyzed in patients under 18 years of age undergoing treatment for cancer in one of the seven centers included in the study between 2016 and 2021. Of these, 301 had positive BC (27.6%) and 17 episodes (5.6%) were excluded because they were considered probable contamination, therefore, the final sample analysis was 284 HRFN episodes with positive BC (26.0%) (figure 1). The median age of the patients was 7.2 years [3.0-12.3], male sex predominated with 53.5% of the cases. The main underlying pathologies were acute lymphoblastic leukemia (ALL) in 33%, acute myeloblastic leukemia (AML) in 28.5%, and relapse of ALL in 15% of cases.

Microbiology

There were 252 (87.5%) episodes with only one microorganism isolated in BCs and 36 (12.5%) episodes with two or more isolates, with a total of 329 microorganisms, consisting of 162 GNB (49.2%), 144 GPC (43.8%), and 12 fungal species (3.6%) (table 1). The most frequently isolated microorganisms were VGS (25.8%), *Escherichia coli* (19.8%), *Pseudomonas* spp. (11.2%), *Klebsiella* spp. (10.9%), and CoNS (10.9%) (table 2).

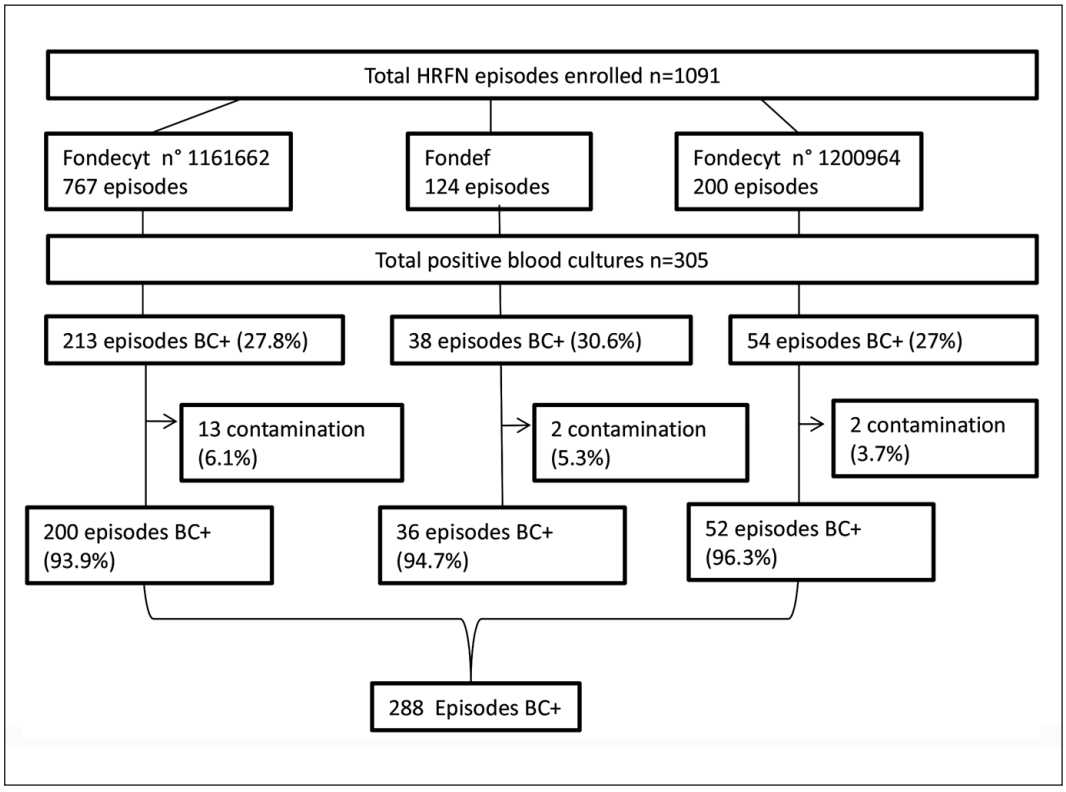

Figure 1. Episodes of high-risk febrile neutropenia included in the study in seven hospitals of PINDA network, Chile, 2016-2021

Figure 2 shows the relative frequency of the groups of microorganisms isolated in the study, compared with the periods 1994-1998, 2004-2009, and 2012-2015. A significant increase in the frequency of Enterobacteriaceae highlights, from 20.7% and 29.8% in the 1990s and 2000s, respectively, to 43.2% and 35.3% in the periods 2012-2015 and 2016-2021, respectively ($p = 0.00$). In addition, a fluctuation in the frequency of non-fermentative GNB, with increase in the study period compared with the period 1994-1998 ($p = 0.00$); a significant decrease of *S. aureus* and CoNS, from 16.7% to 3.3% ($p = 0.00$) and from 43.8% to 10.9% ($p = 0.00$) respectively, added to a significant increase of VGS, with frequencies that varied in the four periods analyzed of 4.4%, 16.6%, 13.6%, and 25.8% ($p = 0.00$).

Antimicrobial resistance

Of the 329 isolated microorganisms, antimicrobial resistance was reported in 97.4% of Enterobacteriaceae, 100% of non-fermenting GNB, and *Enterococcus* spp., 97.2% of CoNS, 91% of *S. aureus*, and 96.5% of VGS.

Table 3 shows the antimicrobial resistance in the study period and its comparison with the different periods analyzed. Enterobacteriaceae show 8.2% resistance to amikacin, 39.8% to cefotaxime/ceftriaxone, 1.4% to imipenem, and 18.2% to piperacillin-tazobactam, with an increase over time of resistance to cefotaxime/ceftriaxone ($p = 0.01$), maintaining a low and stable resistance to amikacin and carbapenems. Resistance to piperacillin-tazobactam was not analyzed in previous periods and therefore its trend is not comparable. Non-fermenting GNBs show 2.7% resistance to amikacin, 10.8% to ceftazidime, 10.3% to ciprofloxacin, 1.4% to imipenem, and 15.8% to piperacillin-tazobactam, with no increase in resistance over time to any type of antimicrobials and with a significant decrease in resistance to amikacin ($p = 0.02$). *S. aureus* shows 10% resistance to oxacillin, which is stable over time, while CoNS has 82.4% resistance to oxacillin, with a significant increase since the 1990s ($p = 0.00$), with stability from 2012 to date. Resistance to vancomycin is not described in either microorganism. Besides, *Enterococcus* spp. shows 50% resistance to vancomycin and has been stable since the 2012-2015 evaluation and VGS presents 48.7% resistance to penicillin, with a significant decrease from the 2000s to the 2016-2021 period ($p = 0.04$) and 19.2% resistance to third-generation cephalosporins, with no data from previous studies for comparison.

Table 1. Classification of microorganisms isolated from blood cultures in children with cancer and episodes of high-risk febrile neutropenia in seven hospitals of PINDA network, Chile, 2016-2021

Microorganisms	n	%
Gram-negative bacilli	162	49.2
Gram-positive cocci	144	43.8
Fungus*	12	3.7
Gram-positive bacilli	5	1.5
Gram-negative cocci	4	1.2
Gram-negative coccobacilli	2	0.6
Total	329	

*Fungus: *C. parapsilosis* (n = 4); *C. tropicalis* (n = 4); *C. dubliniensis* (n = 1); *C. krusei* (n = 1); *C. lusitaniae* (n = 1) y *Rhodotorula mucilaginosa* (n = 1)

Table 2. Microorganisms isolated from blood cultures in children with cancer and episodes of high-risk febrile neutropenia in seven hospitals of PINDA network, Chile, 2016-2021

Microorganisms aislado	n	%
Group viridans *Streptococcus*	85	25.8
Escherichia coli	65	19.8
Pseudomonas spp.	37	11.2
Klebsiella spp.	36	10.9
Coagulase negative *Staphylococcus*	36	10.9
Candida spp.*	11	3.4
Enterobacter spp.	11	3.4
Staphylococcus aureus	11	3.4
Enterococcus spp.	7	2.1
Others**	16	4.8

**Candida* spp. *C. parapsilosis* (n = 4), *C. tropicalis* (n = 4), *C. dubliniensis* (n = 1), *C. krusei* (n = 1) y *C. lusitaniae* (n = 1). **Others: one isolation of: *Aeromonas* sp., *Arthrobacter oxydans, Burkholderia cepacia* complejo, *Capnocytophaga sputigena, Granulicatella adiacens, Haemophilus infuenzae, Lactobacilus rhamnosus, Micrococcus* sp., *Moraxella* sp., *Pantonea agglomeus, Proteus mirabilis, Ralstonia insidiosa, Rhodotorula mucilaginosa, Rothia mucilaginosa, Salmonella enterica* sp., *Streptococcus pneumoniae.*

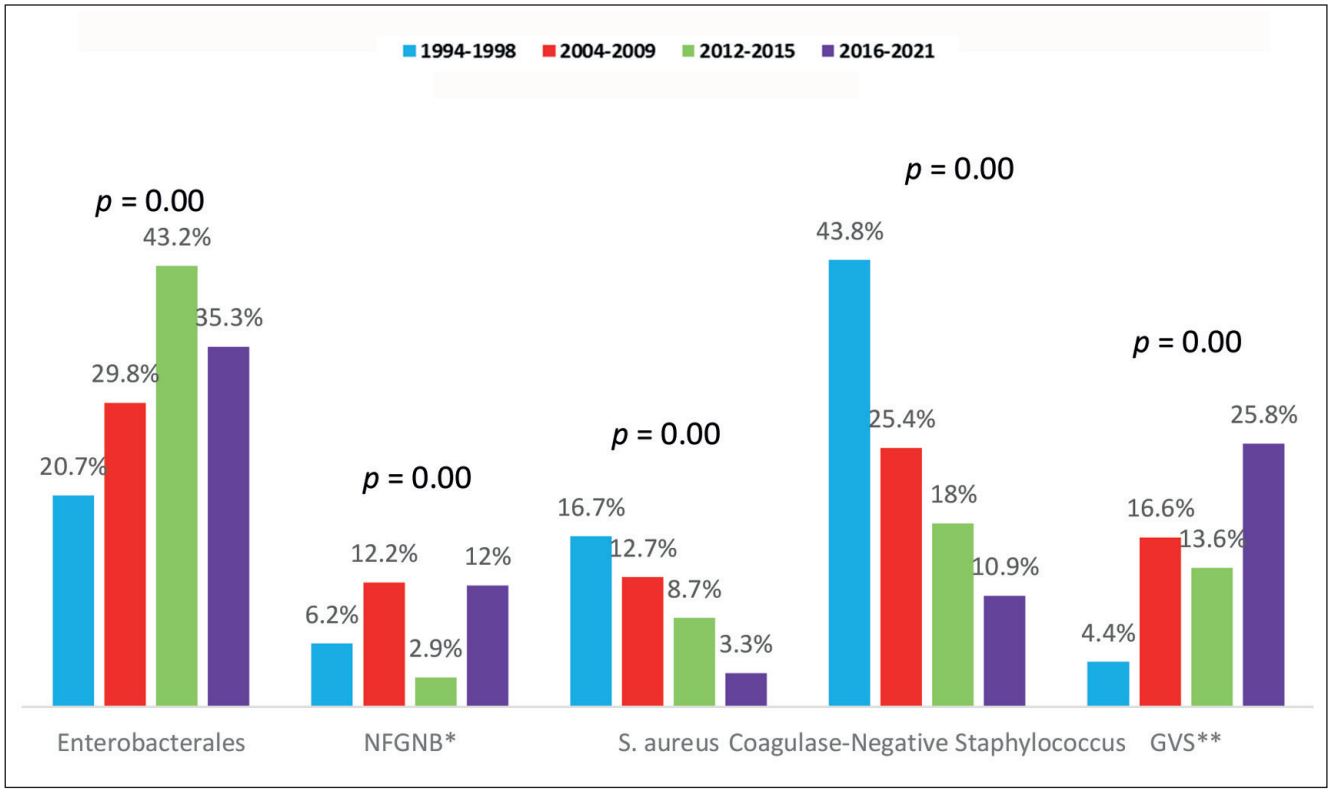

Figure 2. Relative frequency of microorganisms isolated from blood cultures in children with cancer and episodes of high-risk febrile neutropenia, PINDA network, periods 1994-1998, 2004-2009, 2012-2015 y 2016-2021. NFGNB*: Nonfermenting Gram-Negative Bacilli, **GVS: Group viridans *Streptococcus*

Table 3. Antimicrobial Resistance of microorganisms isolated from blood cultures in children with cancer and episodes of high-risk febrile neutropenia, PINDA network, periods 1994-1998, 2004-2009, 2012-2015 y 2016-2021

Microorganisms/ Antimicrobials	1994-1998 n = 707 % [95%CI]	2004-2009 n = 181 % [95%CI]	2012-2015 n = 206 % [95%CI]	2016-2021 n = 329 % [95%CI]	p
Enterobacterales					
Gentamicin	19 [12.8-25]	19 [7-30.2]	28 [17.6-37.6]	20.9 [13.7-29.7]	0.40
Amikacin	18 [11.9-33.7]	16 [5-26.2]	11 [4.8-18]	8.2 [3.8-14.9]	0.11
Cefotaxime/Ceftriaxone	24.3 [19.5-29.6]	34.3[25.3-44]	25.3 [19.1-32.3]	39.8 [30.5-49.6]	0.01
Imipenem	2.4 [0-7.2]	2.7 [0-7.9]	0	1.4 [0.03-7.4]	0.25
Piperacillin-tazobactam				18.2 [9-30.9]	
*NFGNB**					
Gentamicin	24 [9.3-37.8]	27 [4.3-49.1]	33 [13-66.6]	8.3 [1.8-22.5]	0.11
Amikacin	9.3 [0.6-18]	25 [3.8-46.2]	33 [13-66.6]	2.7 [0.06-14.1]	0.02
Ceftazidime	19 [5.5-33.3]	31 [8.5-54]	17 [8.6-50.8]	10.8 [3-25.4]	0.24
Ciprofloxacin	11 [0-24.3]	19 [0-37.9]	20 [3.6-62.4]	10.3 [2.9-24.2]	0.69
Imipenem	6.7 [0-19.3]	14 [0-32.6]	0	11.4 [3.2-26.7]	0.80
Piperacillin-tazobactam				15.8 [3.4-39.6]	
S. aureus					
Oxacillin	31 [23-39.7]	14 [0-28]	22 [3-41.4]	10 [0.3-44.5]	0.20
*CNS***					
Oxacillin	55 [46.7-62.6]	77 [64.1-89.4]	86 [75.4-97.4]	82.4 [65.4-93.2]	0.00
Enterococcus spp					
Vancomicin			67 [29.6-90.7]	50 [11.8-88.1]	1.00
*GVS****					
Penicillin	50 [18.8-81.2]	75 [40-93.7]	71 [52.7-88.9]	48.7 [37-60.4]	0.04
Cefotaxime/Ceftriaxone				19.2 [10.9-30]	

*NFGNB Nonfermenting Gram-Negative Bacilli; **CNS: Coagulase-negative *Staphylococcus*; ***GVS: Group viridans *Streptococcus*.

Discussion

In this study, microorganisms isolated from BC in children with cancer and HRFN were analyzed, and their frequency and antimicrobial resistance were reported. We observed 49.2% of GNB, 43.8% of GPC, and 3.6% of fungi, which is stable nationally as reported by our group for the period 2012-2015 with 46.6% of GNB, 45.1% of GPC, and 6% of fungi[7] and differs from that reported in the international literature where the main pathogens are gram-positive, followed by gram-negative, and fungi remain in third place[9,15-18]. A study of the pediatric division of the University Hospital of Bern, Switzerland, shows CoNS (64.3%) and VGS (42.2%) as the main pathogens, followed by *Escherichia coli* (33.2%)[16].

The predominance of GPC in international experiences could be explained by the increasing use of levofloxacin prophylaxis for GNB worldwide[19], despite that a systematic review published in 2019, based on 114 randomized studies, makes only a weak recommendation for the use of antimicrobial prophylaxis, focused on patients undergoing intensive chemotherapy for AML and relapsed ALL, and establishes a strong recommendation against the routine use of prophylaxis in patients where periods of profound and prolonged neutropenia following chemotherapy cycles are not expected[20]. This is in addition to the strong recommendation, with moderate quality of evidence, published in the consensus on the management of FN in children with cancer of the Latin American Society of Pediatric Infectious Diseases, in which antimicrobial prophylaxis is not recommended, except in exceptional situations since there is no evidence of a decrease in mortality and an increase in bacterial resistance[21].

Among our findings, the low resistance of enterobacteria and non-fermenting GNB to amikacin, an antimicrobial that continues to show high utility in the management of bacteremia in pediatric patients with cancer and episodes of FN[21], stands out. Regarding

resistance against piperacillin-tazobactam, our study reported 18.2% in Enterobacteriaceae, higher than the 3% observed in a pediatric hospital in Denmark between 2004-2013[18]. Not having previous data on resistance to piperacillin-tazobactam does not allow us to know a trend of resistance in this population but gives us a baseline value for future evaluations, considering that the use of this antimicrobial allows limiting the indication of carbapenems and preserving its use for the management of infections by multidrug-resistant bacteria in the future[21].

In our experience, a significant increase in the frequency of VGS was observed, positioned as the main agent in the period 2016-2021. This microorganism is considered an emerging pathogen of clinical relevance in pediatric cancer patients[22] and has been the cause of bacteremia in 25-30% of cases in the last decade[23,24].

S.B. Han et al. reported resistance to penicillin in VGS of up to 70% in pediatric patients in a hospital in Seoul between 2009-2012[25], higher than the 48.7% reported in this study and in Canada, and similar to that reported by our group in the period 2012-2015 (57% [40-73])[8,23]. The progressive decrease in resistance to penicillin in VGS in our sphere could be because, in the 2000s, the management protocol of induction chemotherapy in patients with AML included the use of amoxicillin, a practice that has been discontinued in the last five years[26]. Finally, for *S. aureus*, lower resistance to oxacillin figures were observed in relation to that reported in the antimicrobial resistance bulletin of the Chilean Public Health Institute (ISP) in the 2012-2020 series which is > 35%[26]. Our result should be analyzed with caution, considering that it is based only on 11 strains of *S.aureus* and that the CLSI recommends not to present resistance results when the number of microorganisms is lower than 30.

The limitation of this study is that it has data from only one hospital in the region, which could represent a bias in the inference of data at the national level and its strength is the prospective and systematic collection of microbiological data, in a multicenter manner, which allows us to have active surveillance over time.

We can conclude that having systematic epidemiological surveillance of microorganisms isolated from BC and their antimicrobial resistance profile in children with cancer and FN could favor the rational use of antimicrobials and limit the spread of resistant strains, which goes hand in hand with the Chilean National Plan on Antimicrobial Resistance 2021-2025[26], which seeks to strengthen resistance surveillance systems, improve access to information, and promote related research.

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

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