Epidemiology of bacteremia in the pediatric oncology service, report 2022, Hospital de Solca-Guayaquil.

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Abstract

Introduction: Infections are one of the main complications in the pediatric oncology population due to the use of myeloablative treatments. Continuous monitoring of the microorganisms involved and their susceptibility to antibiotics has become as crucial as their rational use to avoid resistance to treatment. The objective of the present study was to establish the epidemiology of hospital pathogens and, with these data, to establish an initial, efficient, and effective empirical management protocol.

Methods: Blood cultures taken from febrile neutropenic children hospitalized in the pediatric department of the Solca Hospital in Guayaquil during the year 2022 were analyzed. The cultures were taken directly from peripheral blood and retro cultures from samples of venous devices. The identification of the microorganisms and their sensitivity was carried out in the institution's microbiology department.

Results: A total of 1019 cultures were analyzed: 165 were positive (16.19%), 147 were new microorganisms, and 18 were follow-up cultures. Bacteria were identified in 101 cases (68.71%), and fungi were identified in the remaining 46 (31.29%). The main microorganisms isolated were the gram-negative bacteria *Klebsiella pneumoniae*, the most frequent (16.33%). Among gram-positive staphylococci, the majority are coagulase-negative staphylococci. *Staphylococcus aureus* 7.48%. The primary fungus isolated was *Candida parapsilosis* (17.69%). No Aspergillus spp. were isolated.

Conclusions: The results differed from the previous year's epidemiology; specific changes forced the use of new antibiotics.

Keywords:

MeSH: Blood Culture, Neutropenia, Febrile Neutropenia, Chemotherapy-induced Febrile Neutropenia, Child.

Abbreviations

AMK: amikacin.
CFZ: Cefazolin.
CFX: cefotaxime.
CFP: Cephoperazone.
IMI: imipenem.
MERO: meropenem.
TAZO: Piperacillin Tazobactam.

Supplementary information

No supplementary materials are declared.

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Author contributions

Eliezer Arellano Rojas: Conceptualization, data curation, formal analysis, acquisition of funds, research, writing - original draft.
Eduardo Barrio Nuñez: Conceptualization, Data curation, Formal analysis, Juan Pablo Masías Toapanta: Fund acquisition, Research, Methodology, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review and editing.
All the authors have read and approved the final version of the manuscript.

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Introduction

Infections are one of the main complications in the pediatric oncology population and are mainly associated with states of immunosuppression [1, 2] and the need to use invasive devices, such as central venous access or implantable venous chamber systems [3].

The use of increasingly myeloablative chemotherapies leads to more profound and more prolonged neutropenic states, with which complications related to health care appear, with aggressive microorganisms [4, 5]. Likewise, the development of antibiotic resistance is a cause of growing concern. It is currently a public health problem, requiring continuous surveillance of the main germs and their sensitivity and the rational use of medications [6, 7].

The optimal and timely decision regarding empirical antibiotic and antifungal treatment [7, 8] is not always easy or straightforward and depends on many variables, especially those related to the epidemiology of each institution.

This study aimed to identify for 12 months the main microorganisms associated with infections in febrile pediatric oncology patients of the Solca Hospital and their sensitivity to establish efficient and effective initial empirical management.

Materials and methods

Study design

The present study is cross-sectional. The source is retrospective.

Scenery

The study was conducted in the Hospital de Solca-Guayaquil, Ecuador, pediatric oncology service. The study period was from January 1, 2022, to December 31, 2022.

Participants

Pediatric oncology patients with febrile neutropenia were included. Cases with incomplete data were eliminated from the analysis.

Variables

The variables were the type of microorganism, sensitivity to antibiotics in the case of bacteria, sensitivity to antifungals in the case of fungi, and comparison with the historical file 2008-2022.

Data sources/measurements

The source was indirect; an electronic form was completed using data from the institutional medical history of the patients who entered the hospitalization period. A review of the registry of the pediatric oncology unit and the microbiology laboratory was carried out. The information was treated confidentially; no personal data were included to identify the study subjects.

Biases

To avoid interviewer, information, and memory biases, the leading researcher always maintained the data with a guide and records approved in the research protocol. Observation and selection bias was avoided by applying participant selection criteria. Two researchers independently analyzed each record in duplicate, and the variables were registered in the database once their agreement was verified.

Study size

The sample was probabilistic. Guayas-Ecuador has 4,391,923 inhabitants, with 25.7% of children ranging from zero to 14 years old, corresponding to 1,128,724 children. According to the Ecuadorian Institute of Statistics and Censuses (INEC), in 2021, 6,331 new cases of cancer were registered in children and adolescents up to 19 years of age in Ecuador. These new cases represent 9.4% of the new cancer cases registered in the country that year, which would represent 106,100 cases for the province of Guayas. The percentage of children with neoplasms who develop febrile neutropenia is 25 to 35%, which corresponds to a total of 26,525 cases (25%). Using the EPI info ™ program (Version 7.2.5, CDC, Atlanta, USA, September 2022.) with an expected frequency of 50%, a confidence limit of 5%, a 99% confidence interval, and the sample size. There are 647 cases for the number of samples collected. For the number of analyzable positive samples with a total of 26,525, with a frequency of culture positivity of 16% (historical file of 2021) with a confidence limit of 5% and a confidence level of 90%, the sample size was 145 cases.

Quantitative variables

Descriptive statistics were used. The results are expressed as frequencies and percentages.

Statistical analysis

Noninferential statistics are used. For the descriptive analysis, the incidence of positive blood culture was calculated. Annual reference tables have been available since 2008 for the same institution. However, no statistical tests are carried out to compare proportions between years. The 95% confidence interval for a proportion is presented.

Results

Participants

The study included 1019 cultures from hospitalized patients in the study period.

Prevalence of blood culture positivity

There were 165 positive blood cultures, representing 16.19% (95% CI 13.9% – 18.5%). Of these, 18 were follow-up cultures where microorganisms already detected were found. Without considering the follow-up tests, bacteria were identified in 101 blood cultures (68.71%), and fungi were identified in the remaining 46 (31.29%). The summarized prevalence is presented in Table 1.

Table 1 . Positivity of blood cultures of the study group.

Variable	N=1019	95% CI
Prevalence	165 (16.19%)	13.9%-18.5%
Follow-up	18 (1.8%)	1.0% - 2.6%
bacteria	101 (9.91%)	8.08% - 11.75%
Fungus	46 (4.51%)	3.24%- 5.79%

CI: confidence interval for a proportion.

Epidemiology of the blood cultures studied.

Among the bacteria, 54 gram-negative bacteria were identified (36.73%): 24 *Klebsiella pneumoniae*, 8 *Acinetobacter baumannii*, 6 *Burkholderia cepacia*, 5 *Escherichia coli*, 5 *Pseudomonas aeruginosa*, 2 Enterobacter aerogenus, 2 *Enterococcus faecium*, 1 *Serratia marcescens* and 1 *Stenotrophomonas maltophilia*. It is essential to mention that 16 were carbapenemase-producing strains with a marked predominance of *Klebsiella pneumoniae* and, to a lesser extent, *Escherichia coli* and *Acinetobacter baumannii*. Regarding the identification of extended-spectrum beta-lactamases (ESBL), they occurred in 11 cases, mainly in *Klebsiella pneumoniae* and *Escherichia coli*.

In the remaining 47 cultures, gram-positive bacteria were isolated (31.97%), 11 were Staphylococci aureus, and the remaining 36 were coagulase-negative staphylococci: 21 hominis, seven epidermidis, seven hemolyticus, and one saprophyticus.

Forty-six fungi were isolated; 44 corresponded to the genus Candida: 26 paraphimosis, 13 guilliermondii, three tropical, and two albicans, and the remaining 2 to *Cryptococcus neoformans*. (Table 2).

Table 2. Results of crops blood with isolation detected.

	Microorganism	n	%
Bacteria		**101**	**68.71**
Gram -	Klebsiella species	24	16.33
	Acinetobacter baumannii	8	5.44
	Burkholderia cepacia	6	4.08
	Escherichia coli	5	3.40
	Pseudomonas aeruginosa	5	3.40
	Enterobacter aerogenus	2	1.36
	Enterococcus faecium	2	1.36
	Serratia marcescens	1	0.68
	Stenotrophomonas maltophilia	1	0.68
Gram +	*Staphylococcus aureus*	11	7.48
	Staphylococcus hominis	21	14.29
	Staphylococcus epidermidis	7	4.76
	Staphylococcus hemolyticus	7	4.76
	Staphylococcus saprophyticus	1	0.68
Fungus		**46**	**31.29**
Yeasts	*Candida parapsilosis*	26	17.69
	Candida guilliermondii	13	8.84
	Candida tropicalis	3	2.04
	Candida albicans	2	1.36
	Cryptococcus neoformans	2	1.36
Total		**147**	**100**

Antibiotic sensitivity

Regarding sensitivity to antibiotics, 100% of the recorded coagulase-positive staphylococci were sensitive to vancomycin, linezolid, and tigecycline; 91% were sensitive to trimethoprim-sulfamethoxazole, 55% to clindamycin and only 37% to oxacillin.

Regarding coagulase negativity, sensitivity to vancomycin, linezolid, and tigecycline was 100%: 80% to trimethoprim, 29% to clindamycin, and 23% to oxacillin.

The susceptibility of gram-negative microorganisms was 95% for colistin, 94% for tigecycline (excluding Pseudomonas), 74% for carbapenems (meropenem and imipenem), 78% for aminoglycosides, 65% for ciprofloxacin, 60% for ceftazidime, 55% for piperacillin-tazobactam and 51% for cefepime (Table 3).

Table 3 . Percentage of sensitivity of the main microorganisms bacterial.

Microorganisms			Antibiotics															
	n	%	Amikacin	Ampicillin sulbactam	Cefazolin	Cefepime	Cefoxitin	Ciporfloxacin	Imipenem	Meropenem	Piperacillin/Tzobactam	Tigacillin	Colistine	Oxacillin	Clindamycin	Vancomycin	TMS
Staphylococcus coagulase negative	36	21.8	-	-	-	-	-	-	-	-	-	100		23	29	100	80
Klebsiella pneumoniae	24	14.5	78	13	35	35	48	53	61	61	43	95	100	-	-	-	-
Staphylococcus aureus	9	5.5	-	-	-	-	-	-	-	-	-	100	-	37	55	100	91
Acinetobacter baumannii	8	4.8	88	64	75	75	45	75	88	88	63	88	88	-	-	-	-
Pseudomonas aeruginosa	5	3.0	100		60	60		80	80	80	80	-	100	-	-	-	-
Escherichia coli	5	3.0	100	15	20	20	25	20	60	60	40	100	100	-	-	-	-
Enterobacter aerogenus	2	1.2	100	75	63	75	13	88	100	88	75	100	100	-	-	-	-

Antifungal sensitivity

The antifungal susceptibility found in this study was 100% for voriconazole, 89% for fluconazole, 87% for caspofungin, and 59% for amphotericin (Table 4).

Table 4 . Percentage of sensitivity of the primary fungus.

Microorganisms			Antifungals			
	n	%	Amphotericin	Caspofungin	Fluconazole	Voriconazole
Candida parapsilosis	26	16	52	84	88	100
Candida guilliermondii	13	7.88	62	85	92	100
Candida tropicalis	3	1.8	66	100	66	100
Candida albicans	2	1.21	100	100	100	100

Discussion

Of the 1,019 blood cultures taken in 2022, 165 were positive (16.2%). There were 147 new isolates and 18 follow-up cultures. Gram-negative bacteria were 44%, gram-positive bacteria were 28%, and fungi were 28%. This incidence is related to myeloablative chemotherapy treatments that lead to neutropenias of greater intensity and duration, increased hospitalization time, and consequently, an increase in infections.

Among the gram-positive bacteria, there is a predominance of coagulase-negative staphylococci, which are poorly sensitive to oxacillin and clindamycin and 100% sensitive to vancomycin, linezolid, and tigacycline. This high frequency is due to the increase in the use of long-term intravascular devices, the intensity of neutropenia caused by chemotherapy, and antibiotic prophylaxis for gram-negative bacteria. It is under discussion whether these coagulase-negative Staphylococci were pathogenic or contaminating since differentiation by isolation time or colony counting was not frequently done since taking samples in children is difficult and causes injuries at the puncture sites. These factors act as sources of infection. When treatment was considered, we individualized the patient, preferring vancomycin.

For *Staphylococcus aureus*, we used vancomycin or linezolid; when tigecycline was used, we discontinued vancomycin. Although linezolid penetrates lung tissue better, it is used in cases where the patient presents nephrotoxicity. In outpatients, TMS and clindamycin have good sensitivity. Except in specific situations, we do not use ciprofloxacin due to the cross-resistance it induces.

Taking as a reference previous studies carried out at the SOLCA-Guayaquil Hospital, the sensitivity of gram-positive bacteria to vancomycin, linezolid, and tigecycline has remained at 100% for over 15 years. Sensitivity to clindamycin and oxacillin has been gradually decreasing, but sensitivity to TMS has improved (Table 5).

Gram-negative bacteria represented 44% of the total isolates, similar to the 1980s when a predominance of infections caused by gram-negative bacilli was reported [5, 6].

Regarding the sensitivity of gram-negative bacteria compared to the 2021 results, excellent sensitivity to amikacin stands out at 78% (previously 93%), tigecycline at 94%, and colistin at 95% (previously 100%). These two are last-line drugs. Sensitivity to third- and fourth-generation cephalosporins is maintained but decreasing: for cefepime, 51% (previously 58). Regarding carbapenems (imi and meropenem), 74%. (previously 85%). Piperacillin tazobactam 55% (previously 73%), ciprofloxacin 65% (previously 75%). Sensitivities that are related to the frequency of its use. Ceftazidime maintains a sensitivity of 60%, but we do not have it available (Table 6). *Acinetobacter baumannii* was sensitive to 73% cefepime, 73% imipenem, 73% meropenem, 73% pipertazo, 73% ciprofloxacin, colistin, and 100% tigecycline. *E. coli* maintained good sensitivity to amikacin, imipenem, meropenem, tigacycline, colistin, and piper tazo 100% and little sensitivity to cefepime 38% and ciprofloxacin 25%. *Klebsiella pneumoniae* was 100% sensitive to colistin and 95% sensitive to tigacycline 78%. to amikacin, with a sensitivity to imipenem and meropenem of 61%. Pipertazo 43%, cefepime 35% and cipro 48%. Only two multisusceptible *Enterobacter aerogenes* were isolated. Pseudomonas were sensitive 100% to amikacin, 60% to ceftazidime, 60% to cefepime, 100% to colistin, 80% to ciprofloxacin and pipertazo, and 80% to imipenem and meropenem.

It is striking that despite the frequent use of antimicrobials, the isolated germs maintain an acceptable sensitivity to the drugs used. The orderly management of antibiotics following a predetermined empirical scheme, modified according to the isolates, infectious focus, and severity of the host's condition and characteristics, has been satisfactory.

Table 5. Sensitivity of gram-positive bacteria 2008-2022 and cost per day of treatment.

Gram +	2008	2009	2010	2011	2013	2014	2018	2019	2021	2022	USD/day
Vancomycin	100	100	100	100	100	100	100	100	100	100	$4.79
Linezolid	100	100	100	100	100	100	100	100	100	100	$35.19
AMP-SUB	58	65	18	64	50	28					
Clindamycin	69	83	59	82	61	41	45	28	67	35	
Erythromycin	59	78	39	82	61	48	45				
Oxacillin	54	65	18	73	fifty	31	9	17	25	24	
TMS	42	83	63	82	89	62	100	61	83	80	$0.37
Tigecycline	100	100	100	100	100	100	100	100	100	100	$71.99

AMP-SULB: ampicillin sulbactam. TMS: trimethopin sulfamethoxazole.

Table 6. Sensitivity of gram-negative bacteria 2007-2022 and cost per day of treatment.

Gram -	2007	2008	2009	2010	2011	2013	2014	2018	2019	2021	2022	USD/day
AMK	65	85	87	42	90	87	94	97	80	93	78	$3.65
CFZ	70	75	75	90	84	70	71	67	78	60	60	$51.4
CFX	50	59	68	58	63	45	55	64				
CFP	59	67	70	95	61	65	58	67	78	58	51	$7.80
Cipro	87	86	85	69	67	70	73	73	78	75	65	$1.14
IMI	91	97	92	95	82	89	99	77	93	85	74	$76.98
MERO	96	98	95	95	86	93	99	87	93	85	74	$55.05
MUG	74	95	87	100	81	85	80	64	88	73	55	$59.80

AMK: amikacin. CFZ: Cefazolin. CFX: cefotaxime. CFP: Cephoperazone. IMI: imipenem. MERO: meropenem. TAZO: Piperacillin Tazobactam.

Table 7. Comparison 2021-2022.

Variable	2021	2022
Crops	734	1019
Effectiveness	16.20%	18.20%
Gram +	43%	28%
St. Aureus	12 (32%)	9 (20%)
S.Coag Neg	39 (68%)	36 (80%)
Gram -	53%	44%
Klebsiella	32%	44%
Acinetobacter	18%	16%
Enterobacter	16%	14.5%
E. Coli	eleven %	14.5%
Pseudomonas	8%	eleven %
KPC	0.4%	0.16%
ESBL	0.12%	0.11%
Candida	0.5%	0.46%
C. albicans	3	2
C. Guilliermondii	1	13
C. Parapsilosis	1	26

C: Candida

We noticed that some germs in successive cultures lose their sensitivity and the existence of multiresistance in patients with previous hospitalizations or referred from other hospitals.

Forty-six candida were isolated (2 albicans, 26 paraphimosis, 13 guilliermondii, three tropical, one *Cryptococcus neoformans*, and one Cryptococcus Laurentiis), representing a significant increase in fungal infections in our children with NF [9] (only 5 in 2021). Alternatively, with improvement in detection methods, no Aspergillus spp. were isolated [10, 11].

Currently, we think that the early use of fluconazole as treatment (or prophylaxis, as long as there is no interference with chemotherapy), even without detection of the germ, taking as parameters the persistence of fever for more than five days, prolonged neutropenia and findings in images, could decrease yeast isolation. Fluconazole could be temporarily replaced with amphotericin (liposomal is unavailable) at low doses (0.3 mg), monitoring its nephrotoxicity, or with caspofungin. The appearance of candida resistant to amphotericin and caspofungin draws attention.

In patients with profound and prolonged neutropenia, we performed surveillance cultures, originally nasal, pharyngeal, and perianal, but due to costs, they were limited to nasal and perianal cultures. We reviewed the results obtained at 6 months, and the conclusion was that the pharyngeal and nasal cultures could have been more productive. Most of the time, with normal flora, no methicillin-resistant staphylococci, penicillin-resistant pneumococci, or Aspergillus were isolated. In contrast, with the perianals, we were able to detect multiresistant gram-negative bacteria, Klebsiella ESBL and KPC, and Stenotrophomonas maltophilias, colonizing germs that could be responsible for the fever in prolonged febrile neutropenia that is difficult to manage. No resistant enterococci and only one Serratia were isolated. Vancomycin was used in specific cases and at the beginning of managing severe sepsis with unknown germ (Table 7).

Conclusions

The sensitivity of blood cultures was 16.2%, primarily gram-negative bacteria, of which Klebsiella was the most frequent. The initial empirical treatment scheme was piperacillin-tazobactam with or without amikacin progressing according to evolution to carbapenems, unlike in 2021, which used cefepime. The results were different, noting an increase in KPC and candida, which made it necessary to use higher-line antibiotics such as ceftazidime, avibactam, tigecycline, or colistin, and due to the incidence of candida, fluconazole was needed as prophylaxis and treatment and sometimes caspofungin or amphotericin. Vancomycin was used in specific cases and at the beginning of the management of severe sepsis with unknown germ.

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Statements

Ethics committee approval and consent to participate

The ethics committee of the Hospital de Solca-Guayaquil approved the study. With a protocol review exemption letter due to it being a retrospective database study.

Publication consent

Not needed when patient-specific images, X-rays, and studies are not published.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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