Revista Latinoamericana de
Infectología Pediátrica

ARTÍCULO ORIGINAL

doi: 10.35366/104660

Bloodstream infections in pediatric patients with febrile neutropenia in a reference center from Bucaramanga, Colombia

Infecciones del torrente sanguíneo en pacientes pediátricos con neutropenia febril en un centro de referencia de Bucaramanga, Colombia

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ABSTRACT

Febrile neutropenia (FN) represents an important cause of mortality in patients with cancer due to the underlying serious invasive infections, mainly associated with bloodstream infections (BSIs), to which they are susceptible because of immunosuppression. The purpose of this study is to describe BSI in pediatric patients with onco-hematologic pathologies and FN, as well as establish their association with adverse outcomes and mortality. Retrospective cohort analytical study of patients between 1 month and 18 years with onco-hematological pathology who were hospitalized in a reference center in Bucaramanga, Colombia between 2013 and 2017, presenting FN, with positive blood cultures.130 patients with FN were included, for a total of 315 episodes. The incidence of BSI was 29.23/100 patients with FN. Intravascular devices were responsible for 15% of these infections. Gram-negative bacilli (GNB) (74.19%) were the main cause, led by *Klebsiella pneumoniae* (30.65%) and *Escherichia coli* (24.19%). When performing a bivariate analysis, an association was found between the presence of bacteremia and a higher probability of presenting hemodynamic instability, requirement for inotropics, need for ICU and death, in accordance with the literature. The GNBs were the main cause of BSI in patients with FN, as well as a greater association with mortality in the population studied.

Keywords: Bacteremia, bloodstream, infections, febrile neutropenia, febrile neutropenia induced by chemotherapy, hematological diseases.

RESUMEN

La neutropenia febril (NF) representa una importante causa de mortalidad en los pacientes con cáncer, debido a las graves infecciones invasivas subyacentes, principalmente asociadas a las infecciones del torrente sanguíneo (IS) a las que son susceptibles por la inmunosupresión. El objetivo de este estudio es describir las IS en pacientes pediátricos con patologías oncohematológicas y NF, así como establecer su asociación con resultados adversos y mortalidad. Estudio analítico de cohorte retrospectivo de pacientes entre un mes y 18 años con patología oncohematológica que fueron hospitalizados en un centro de referencia de Bucaramanga, Colombia entre 2013 y 2017, presentando NF, con hemocultivos positivos. Se incluyeron 130 pacientes con NF, para un total de 315 episodios. La incidencia de IS fue de 29.23/100 pacientes con NF. Los dispositivos intravasculares fueron responsables de 15% de estas infecciones. Los bacilos gramnegativos (BGN) (74.19%) fueron la principal causa, encabezados por Klebsiella pneumoniae *(30.65%) y* Escherichia coli *(24.19%). Al realizar un análisis bivariado, se encontró una asociación entre la presencia de bacteriemia y una mayor probabilidad de presentar inestabilidad hemodinámica, requerimiento de inotrópicos, necesidad de UCI y muerte, de acuerdo con la literatura. Los BGN fueron la principal causa de IS en los pacientes con NF, así como una mayor asociación con la mortalidad en la población estudiada.*

Palabras clave: *Bacteriemia, torrente sanguíneo, infecciones, neutropenia febril, neutropenia febril inducida por quimioterapia, enfermedades hematológicas.*

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How to cite: Bello-Suárez AK, Cuesta-Armesto MH, Silva-Sánchez MP, Anteliz-Díaz AK, Sarmiento-Wilches PE. Bloodstream infections in pediatric patients with febrile neutropenia in a reference center from Bucaramanga, Colombia. Rev Latin Infect Pediatr. 2022; 35 (1): 12-21. https://dx.doi.org/10.35366/104660

Received: 15-02-2022. Accepted: 01-03-2022.

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INTRODUCTION

The immunocompromised state among hemato-oncology patients carries a high risk of infection, mainly of the bloodstream, with bacterial and fungal causes predominantly.[1] The high risk of infection depends on the intensity and duration of the immunocompromised state.[2] The effect of myelosuppressive and antineoplastic therapies is a major predisposing factor for BSI given its predominant effect in cells with high replication rate of both tumor origin and healthy tissue.[3] In addition, the loss of mucocutaneous barriers as a result of chemotherapy and the use of medical devices, neutropenic patients have low or no response to the high proliferation rate of pathogenic microorganisms.[4] Fever is the body's mechanism to alert the immune system that an inflammatory process is taking place and because this process is limited in these patients, fever is a reflection of an advanced infectious process, with possible bacteremia in this patient population 1) Febrile neutropenia (FN) is the main cause of mortality, leading to the need for intensive therapy and therefore constitutes a significant infectious emergency.[1]

The purpose of this study is to establish the incidence of bloodstream infections in pediatric patients with hemato-oncology pathologies and FN in the studied population, as well as the antimicrobial susceptibility of the isolated microorganisms, and to evaluate the association of bacteremia with adverse outcomes and mortality.

MATERIAL AND METHODS

A descriptive, retrospective cohort-type study was performed at the *Clínica Materno Infantil San Luis* (CMISL) (Bucaramanga, Colombia). All the patients aged one month to 18 years, hospitalized with an hemato-oncology pathology according to the CIE-10 code, and who presented FN between January 2013 and December 2017 were included. FN was defined as the simultaneous record of fever (axillary temperature > 38 ºC), and absolute neutrophil count under 500 cel/mm^3. All newborns and the patients whose FN was secondary to non-hematological nor oncological pathologies were excluded. The data from the medical records were collected in REDCap®.

The results of blood cultures were recorded, and episodes with positive isolations meeting the criteria for bacteremia according to the Center for Disease Control and Prevention (CDC)[5] *(Annex 1)*, were selected. Subsequently, the description of the isolated microorganisms and their susceptibility pattern based on antibiograms was performed *(Annex 2)*.

The study was considered without risk and was approved by the research committee of the Universidad Industrial de Santander and CMISL in which verbal informed consent and assent were performed. The authors declare no conflict of interest.

Statistical analysis. The variables were described by percentages, proportions and ratios. In quantitative continuous variables, the median with the respective interquartile range was calculated, since they are all non-parametric.

For bivariate analysis of results associated with bacteremia, the following variables were used: need for PICU, length of stay in the PICU, need for inotropes, need for antibiotic staggering, need for mechanical ventilation, recurrent bloodstream infection, length of hospitalization, readmission, and mortality associated with infection. Pearson's χ^2 test, was used for categorical variables, Fisher's exact test for low-number categorical variables, and Mann-Whitney test for continuous quantitative variables. In all analyses, a value of $p < 0.05$ was considered statistically significant with a 95% confidence interval. The Stata 14.0 program was used for the statistical analysis.

RESULTS

In the period from 2013 to 2017, 130 pediatric oncologic patients with FN were included, identifying 315 episodes of FN. Of these, 72 (22.85%) episodes had positive blood cultures. Upon applying the CDC criteria, the cumulative incidence of BSI was 29.23% (n = 38/130) of patients with FN during the study period, corresponding to 55 episodes, 5 of which presented more than one infection of the bloodstream during the episode. *Table 1* describes the characteristics of these population.

A total of 60 BSIs were detected throughout the period, for a total of 62 isolated microorganisms; two of them were secondary to two microorganisms found in the same blood culture, considered pathogenic: *S. pneumoniae - Fusarium spp*. and *P. aeruginosa - K. pneumoniae*. One fulminating case

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was found due to invasive fungal infection caused by *Fusarium spp*. in 2017, an emerging fungus in immunocompromised patients.[2] The isolated microorganisms are described in *Table 2* and *Figure 1* and the antimicrobial resistance of the isolated microorganisms in *Figure 2*.

The central venous catheters (CVC) related BSIs were found in 12 bacteremias (20.00%, $CI_{95\%}$ 6.52-22.61), with rate of 0.00032 cases per 1,000 device days and a mortality of 7.62 cases per 1,000 cancer patients with FN and CVC during the period studied. According to the type of catheter, half were associated with totally implantable CVC and the other half with Nontunneled CVC. Of Nontunneled CVC-related BSIs, 4 (66.67%) cases were linked with insertion site infection; five cases (83.34%) corresponded to subclavian catheters and one case (16.67%) to internal jugular catheter.

In CVC related BSIs, the microorganisms isolated in order of frequency were *Staphylococcus aureus,*

Table 1: Characteristics of the studied population in relation to the presence of BSI.

Variables	Bacteremia[a] N = 55 n (%)	No bacteremia N = 260 n (%)	Total	p (< 0.05)
Gender				
Female	28 (50.91)	129 (49.62)	157	0.86
Male	27 (49.09)	131 (50.38)	158	
Age (years)[b]	6 (2-10)	6 (3-9)	315	0.98
Cancer type				
ALL	38 (69.09)	150 (57.69)	188	0.12
AML	9 (16.36)	48 (18.46)	57	0.71
Lymphomas	2 (3.64)	24 (9.23)	26	0.28
Solid tumors	4 (7.27)	29 (11.15)	33	0.48
Other	2 (3.64)	9 (3.46)	11	1.00
Days between chemotherapy and fever[b]	7 (12.73)	10 (5-14)	270	**0.02**
Temperature[b]	38.5 (38.2-39.0)	38.5 (38.1-38.8)	315	0.13
Use of implantofix	30 (54.54)	112 (43.08)	142	0.12
Comorbidities[c]	26 (47.27)	72 (27.69)	98	**0.01**
Previous AB[d]	30 (54.54)	133 (51.15)	163	0.89
AB prophylaxis[e]	31 (56.36)	169 (65.00)	200	0.23
ANC at start[f]	40 (4-200)	85 (20-286)	315	0.49
Days of severe neutropenia[b]	10 (5-15)	6 (4-9)	302	**< 0.01**
CRP at the beginning of the episode[b]	192 (96-192)	48 (24-96)	304	**< 0.01**
Clinical infectious focus				
ORL	3 (5.45)	29 (11.15)	32	0.32
Respiratory	17 (30.90)	81 (31.15)	98	0.97
Gastrointestinal	20 (36.36)	55 (21.15)	75	**0.02**
Skin	10 (18.18)	20 (7.69)	30	**0.02**
Unknown	16 (29.09)	103 (39.62)	119	0.14
Microbial isolation	55 (100.00)	52 (20.00)	107	**< 0.01**
GPC	12 (21.82)	11 (4.23)	23	**< 0.01**
GNB	44 (80.00)	39 (15.00)	83	**< 0.01**
Fungus	6 (10.91)	3 (1.15)	9	**< 0.01**
Unusual resistances[e]	15 (27.27)	6 (2.31)	21	**< 0.01**

BSI = bloodstream infections; CI = confidence interval; ALL = acute lymphoid leukemia; AML = acute myeloid leukemia; AB = antibiotic; ANC = absolute neutrophil count; CRP = C-reactive protein; ORL = otorhinolaryngological; GPC = Gram-positive cocci; GNB = Gram-negative *Bacilli*.
[a] CDC = Center for Disease Control and Prevention, criteria 2018 *(Annex 1)*. [b] Median interquartile range (IQR). [c] Comorbidities: down syndrome, other chromosomopathies, congenital heart disease, chronic pneumopathy, malnutrition, hypothyroidism, epilepsy, psychomotor delay, renal insufficiency, others. [d] Last three months. [e] Trimetroprim sulfamethoxazole.
[f] GNB producers of extended *spectrum* Beta-lactamase (ESBL), with a suggestive pattern of carbapenemase production, a suggestive pattern of multi-drug resistance, Gram positive vancomycin resistant *cocci*.

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Table 2: Isolated microorganisms in FN episodes with BSI in the study (N=62).

Type	Microorganism	n	Percentage according to	
			Type of microorganisms	Total of bacteremia
GNB (N = 46, 74.19%)	*Klebsiella pneumoniae*	19	41.30	30.65
	Escherichia coli	15	32.61	24.19
	Pseudomonas aeruginosa	8	17.39	12.90
	Enterobacter aerogenes	1	2.17	1.61
	Enterobacter cloacae	1	2.17	1.61
	Salmonella spp.	1	2.17	1.61
GPC (N = 10, 16.13%)	*Staphylococcus epidermidis*	4	40.00	6.45
	Staphylococcus aureus	3	30.00	4.84
	Streptococcus mitis/oralis	2	20.00	3.23
	Streptococcus pneumoniae	1	10.00	1.61
	Enterococcus faecium	1	2.17	1.61
Fungus (N = 6, 9.68%)	*Candida tropicalis*	2	33.33	3.23
	Candida guilliermondii	1	16.67	1.61
	Candida famata	1	16.67	1.61
	Other *Candida spp.*	1	16.67	1.61
	Fusarium spp.	1	16.67	1.61

FN = febrile neutropenia; BSI = bloodstream infections; GNB = Gram-negative *Bacilli*; GPC = Gram-positive cocci.

Pseudomonas aeruginosa, Klebsiella pneumoniae, Escherichia coli, Streptococcus pneumoniae and Enterococcus faecium.

Table 3 lists the outcome variables associated with bacteremia.

DISCUSSION

The incidence and microbiological characterization of FN-associated infections are essential to carry out institutional management protocols in accordance with the epidemiological reality in order to optimize the empirical treatment of patients with FN, and to evaluate their outcomes.

The incidence of BSIs was 29.23 per 100 patients with FN, corresponding to 17.46% of the total number of episodes during the period studied. This finding is compatible with some reports that describe bacteremia in 10-25% of all patients with FN.[1,4,6] Others also report that among infections with microbiological isolation, bacteremia is the most frequent, accounting for approximately 20-25% of FN episodes and 74-85% of all infections with positive cultures.[7,8]

In our cohort, a total of 60 bacteremias were obtained during the entire period, of which 20.00% were associated with CVC. The nontunneled CVC and totally implantable CVC kept the same ratio. This allows us to call attention to the management and care of these invasive devices as potential sources of preventable infections. However, the rate of CVC-related BSI is 0.00032 cases per 1,000 days of use of the device, a figure significantly lower than those reported worldwide. Cumulative rates of central catheter-related infections of 4.1/1,000 device-days have been documented in adult ICUs in high-income countries. In 2014, the European Centers for Disease

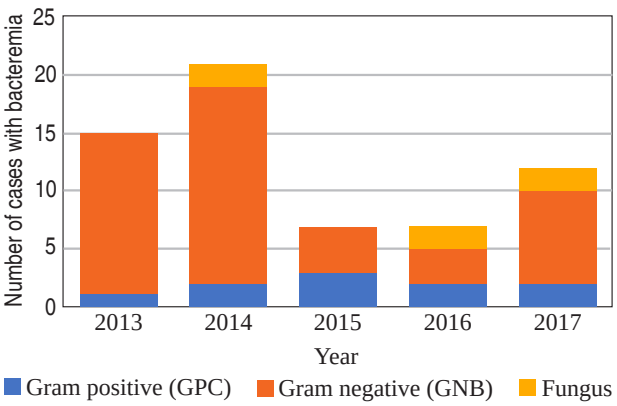

Figure 1: Annual distribution of isolated microorganisms in febrile neutropenia episodes with BSI in the study population (N = 62).

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Control and Prevention (ECDC) documented an incidence rate of 3.3 cases/1,000 device-days. In contrast, only a few specific studies from some countries in Latin America identified that infections associated with central catheters correspond to 12.5 cases/1,000 catheter-days.[9-11]

Among the isolated microorganisms, the GNBs are predominant. As main agents, *K. pneumoniae, E. coli* and *P. aeruginosa*, accounted for 79.14% of the causes of bacteremia in the studied population, while 16.13% were by GPCs and almost 10% by fungus. According to the recent literature, the GPCs predominate among the bacteria isolated in the blood cultures (46.9-82.0%), mainly the SCNs.[7] However, in some Latin American countries, the GNB's cause more than 80% of bacteremia, with infections due to *E. coli, K pneumoniae* and *P. aeruginosa* prevailing.[7] Fungus were less frequent, but they gain great importance mainly in patients with prolonged and recurrent FN.[1,2] A predominance of *Candida spp*. was observed, as in the other series.[3] It is important to highlight that fluconazole prophylaxis has increased the presence of other resistant species such as *Candida krusei* and *Candida glabrata*.[12,13] *Table 4* describes the incidence of bacteremia in different studies, and the predominant isolated microorganisms.[14-22]

According to the interpretative reading of the antibiograms, it is determined that within the *Enterobacteriaceae* (EB), there is a predominance of multisensitive microorganisms and those with usual resistances, which together correspond to almost 40% of cases, compared to unusual resistances. A study conducted at a Melbourne pediatric hospital and another in Hospital Clinic from Barcelona documented that antibiotic resistance occurs most frequently in patients with FN and EB-BSI; as demonstrated in this study, where patients with FN and BSI had a higher risk of unusual resistance than those who did not have bacteremia (27 vs 2% respectively, p = 0.01).[23,24] Another study in a Pediatric Hospital in Chile reported that the majority of resistant EB strains corresponded to ESBL producers, compatible with the results shown in this study, since they are the first cause of unusual resistance (15%) and slightly less than 5% of the isolations were from EB with a pattern suggestive of CBP.[17]

It has been noted that in those centers in which quinolone prophylaxis is not used, a predominance of GNB has been seen as a bacterial cause of infection in patients with FN, also important is the fact that the prophylaxis used in the patients studied was with TMP-SMX, and only in a few special cases ciprofloxacin was used.[4] However, the use of prophylactic quinolones has also been associated with increased resistance in GNB, the latter correlated with the predominance of microorganisms with low resistance patterns.[25]

Using a bivariate analysis to assess the associations between bacteremia and some triggers, it was found that those children with FN and BSI, had a greater probability of presenting adverse

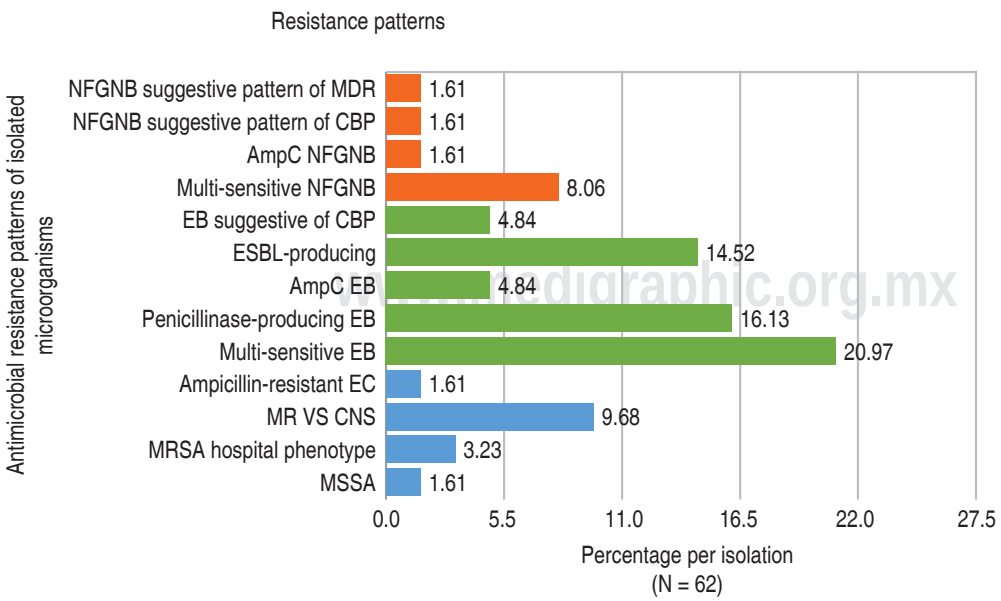

Figure 2:
Antimicrobial resistance pattern of isolated microorganisms in febrile neutropenia episodes with bloodstream infection in the study population.
Non fermenting Gram-negative bacilli (orange), *Enterobacteriaceae* (green) and Gram-positive cocci (blue) are evidenced. No resistance to vancomycin was reported in the GPC isolated in the study.
NFGNB = non fermenting gram-negative bacilli; MDR = multidrug resistance; CBP =: carbapenemase production; AmpC = AmpC β-lactamase producing; EB = *Enterobacteriaceae*; ESBL = extended-spectrum beta-lactamase; EC = *Enterococcus*; MR VS CNS = methicillin-resistant and vancomycin-sensitive coagulase-negative *Staphylococcus*; MRSA = methicillin-resistant *Staphylococcus aureus*; MSSA = methicillin-sensitive *Staphylococcus aureus*.

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Table 3: Association of outcomes to BSI in the patients studied.

Variable	Bacteremic episodes N = 55 n (%)	Episodes without bacteremia N = 260 n (%)	Total N = 315	OR (CI 95%)	p
Antibiotic stepping	27 (49.09)	78 (30.00)	105	2.25 (1.25-4.05)	**0.006**
Hemodynamic instability	16 (29.09)	25 (9.62)	41	3.86 (1.91-7.81)	**< 0.001**
Inotropic requirement	8 (14.55)	3 (1.15)	11	13.07 (3.52-47.97)	**< 0.001**
PICU admission	21 (38.18)	27 (10.38)	48	5.33 (2.73-10.41)	**< 0.001**
PICU stay (days)*	5 (4-12)	5 (3-9)	46	1.04 (0.96-1.13)	1.16
Mechanical ventilation	10 (18.18)	12 (4.62)	22	4.59 (1.91-11.05)	**< 0.001**
Hospital stay (days)*,‡	11(8-19)	7 (5-11)	224	1.03 (1.00-1.05)	**0.007**
Re-admission§	5 (9.09)	50 (19.23)	55	0.75 (0.28-2.02)	0.57
Infection-related mortality	16 (29.09)	12 (4.62)	28	8.48 (3.78-19.02)	**< 0.001**

BSI = bloodstream infections. OR = Odds ratio; CI = confidence interval; ICU = Intensive Care Unit.
* Median (RIQ). ‡ Hospital stay only due to FN. § Re-admission with identical main diagnosis febrile neutropenia (FN) within 30 days after discharge.

outcomes such as some degree of hemodynamic instability, inotropic requirement, need for antibiotic stepping, required ICU stays, and the use of invasive devices such as mechanical ventilation and CVC placement, as well as a longer hospital stays and death, compared to those who did not document bloodstream infection. Hsin-Pao found a statistically significant association between patients with BSI and change in antibiotic, hypotension, transfer to the ICU, length of hospitalization, and risk of mortality based on PRISM II.[26] In addition, most recently Hyo, showed that among the complications associated with *P. aureginosa* bacteremia, the need for mechanical ventilation was important. Some studies indicate that hypotension is an independent variable for deaths in populations similar to the one studied.[27]

Regarding mortality, in a multivariate analysis carried out by Paganini, bacteremia was identified as a mortality risk factor in patients with FN and malignant diseases.[2] For his part, Basu in 2005 identified that the diagnosis of bacteremia in patients with FN, increases the mortality by 10 times.[27] At the same time, the El-Mahallawy study shows a crude mortality of 10.40% in patients with documented bacteremia concomitant with FN in 2011, while in 2015, it decreased to 6%.[15,21] Not far from the findings, our study shows the risk of mortality increases 8 times more in patients with bacteremia vs. those without. Different studies demonstrate that a high incidence of resistance in GNBs contribute to a higher mortality in pediatric patients with FN (20-30%).[1,4,23] However, it would be interesting to perform a multivariate analysis to better delineate the factors associated with mortality in patients with FN and BSI.

Our study has some potential limitations. As the study was retrospective, we were not able to assess all the variables, and were limited by the documentation by the treating physician. Additionally, we did not collect physiologic data, details of comorbidities, and were not able to determine the secondary BSIs to other infectious sources. Furthermore, viral and fungal infection could not be interpreted properly due to the lack of instruments needed for their detection. Our data report a single center experience, and therefore results are most likely related to local epidemiological conditions. However, our study provides an opportunity to investigate potential risk factors for BSI's in pediatric oncologic patients with FN.

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CONCLUSION

In the present study, GNBs were the main cause of bacteremia in patients with FN, and had a greater association with antibiotic resistance, hemodynamic complications, prolonged hospital stays, and mortality. Microbiological identification and characterization of bacteremia in hemato-oncology pediatric patients with FN is critical to have a knowledgeable use of available antibiotics

Table 4: Studies related to FN bacteraemia in pediatric patients with hematology-oncology disorders.

Article	Incidence	Bacteriemias, n	Microorganisms	n (%)
Greenberg[14] Israel (2005)	37.27% (41/110) patients	132	Gram-negative bacteria	86 (65.00)
			Klebsiella spp.	20 (15.20)
			CNS	15 (11.40)
			Pseudomonas spp.	14 (10.60)
			Streptococcus spp.	13 (9.80)
			Enterobacter spp.	12 (9.10)
			E. coli	11 (8.30)
El-mahallawy[15] Egypt (2011)		239	Gram-positive bacteria	180 (75.00)
			CNS	116 (48.50)
			Streptococcus spp.	29 (12.10)
			S. aureus	23 (9.60)
Cortez[16] Chile (2012)		95	Gram-positive bacteria	56 (59.00)
			CNS	29 (30.20)
			S. group viridans	13 (5.00)
			S. aureus	10 (4.00)
Solís[17] Chile (2012)	21.57% (181/839) episodes	181	Gram-positive bacteria	101 (56.04)
			CNS	45 (25.00)
			E. coli	36 (20.00)
			S. group *viridans*	25 (14.00)
			S. aureus	24 (13.00)
			Pseudomonas spp.	16 (9.00)
Miedema[18] Germany (2013)		248	Gram-positive bacteria	180 (73.00)
			CNS	96 (39.00)
			Streptococcus spp.	65 (26.00)
Reddy[19] India (2014)	4.13%(27/653)episodes	27	Gram-negative bacteria	25 (92.00)
			Klebsiella spp.	13 (48.00)
			Acinetobacter spp.	6 (22.00)
Al-Mulla[20] Qatar (2014)	37.83% (70/185) patients	111	Gram-positive bacteria	64 (57.00)
			CNS	42 (38.00)
			Klebsiella spp.	14 (13.00)
			Pseudomonas spp.	10 (9.00)
			E. coli	7 (6.00)
El-Mahallawy[21] Egypt (2015)		232	Gram-positive bacteria	168 (72.00)
			CNS	135 (58.20)
			Streptococcus spp.	16 (6.90)
			S. aureus	13 (5.60)
Tural Kara[22] Turkey (2019)		111	Gram-negative bacteria	(60.50%)
			E. coli	19 (16.70)
			CNS	19 (16.70)
			Klebsiella spp.	15 (13.20)
			Pseudomonas spp.	12 (10.50)
			Enterococcus spp.	9 (7.90)

FN = febrile neutropenia; CNS = coagulase-negative staphylococci.

and create protocols in line with institutional reality. This would be instrumental in reducing the risk of antimicrobial resistance, adverse effects of antibiotic therapy, decreasing mortality and reducing the cost of cancer care.

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Funding/Support: No funding was secured for this study.

Conflict of interest disclosures: The authors have no conflicts of interest relevant to this article to disclose.

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Annex 1: Bloodstream infection CDC's criteria (2018).

Criterion 1: patient of any age has a recognized a pathogen, identified from one or more blood specimens, obtained by a culture, or identified by non-culture based microbiologic testing. No additional elements such as sign or symptoms are needed to meet criteria.[2]

Criterion 2: patient of any age has at least one of the following signs or symptoms: fever (> 38 °C), chills, or hypotension and the same common commensal organisms is identified by a culture, from two or more blood specimens collected on separate occasions included: diphtheroids (*Corynebacterium spp.* not C. *diphtheria*), *Bacillus spp.* (not B. *anthracis*), *Propionibacterium spp.*, coagulase-negative *Staphylococci* (including *S. epidermidis*), *S. viridans*, *Aerococcus spp. Micrococcus spp.* and *Rhodococcus spp.*[2]

Criterion 3: patient ≤ 1 year of age has at least one of the following signs or symptoms: fever (> 38 °C), hypothermia (< 36 °C), apnea, or bradycardia and the same common commensal organisms is identified by a culture, from two or more blood specimens collected on separate occasions.[2]

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Annex 2: Interpretative reading of the antibiograms obtained in this study.

Microorganisms	Interpretative pattern	Interpretative reading
Staphylococcus aureus	M.S.S.A	Methicillin-sensitive *S. aureus*
	M.R.S.A community-phenotype	Methicillin-resistant *S. aureus*; clindamycin, trimethoprim/sulfamethoxazole and gentamicin sensitive
	M.R.S.A hospital-associated	Methicillin-resistant *S. aureus*, clindamycin, trimethoprim/sulfamethoxazole and gentamicin: vancomycin sensitve
	V.I.S.A	*S. aureus* with intermediate susceptibility to vancomycin. Confirmatory test are required
	V.R.S.A	Vancomycin-resistant *S. aureus*. Confirmatory test are required
Enterococcus	A.S.E.	Ampicillin-sensitive *Enterococcus*
	A.R.E	Ampicillin-resistant and vancomycin-sensitive *Enterococcus*
	V.R.E.	Vancomycin-resistant *Enterococcus*
Streptococcus	P.S.S.	Penicillin-sensitive *Streptococcus*
	P.I.S	*Streptococcus* with intermediate susceptibility to penicillin; ceftriaxone and vancomycin sensitive
	P.R.S	Penicillin-resistant *Streptococcus*; ceftriaxone and vancomycin sensitive
	C.R.S	Ceftriaxone-resistant *Streptococcus*, vancomycin-sensitive
Enterobacteriaceae	Pansensitive EB	Pansensitive enterobacteria (*K. pneumoniae* can be naturally resistant to ampicillin)
	Penicillinase-producing EB	Penicillinase-producing enterobacteria: Low level penicillinase: resistant to ampicillin, piperacillin, ampicillin-sulbactam, first and second generation cephalosporins High level penicillinase: resistant to ampicillin, piperacillin, ampicillin-sulbactam, piperacilli-tazobactam, first and second generation cephalosporins
	AmpC EB	AmpC positive *Enterobacteriaceae* (resistant to first, second and third generatrion cephalosporins and cefoxitin-resistant)
	ESBL producing EB	Extended-spectrum beta-lactamase-producing *Enterobacteriaceae* (resistant to first, second, third and fourth generation cephalosporins, resistant to aztreonam, can be cefoxitin-resistant or cefoxitin-sensitive)
	CP-EB	Carbapenemase-producing *Enterobacteriaceae* (resistant to carbapenems: three or more carbapenems, including ertapenem, can be ESBL producing EB). Confirmatory test are required
	MDR-EB	Multidrug resistance *Enterobacteriaceae* expressing combined mechanisms of resistance (efflux bomb, porins, etc.) antibiogram interpretative reading by infectologist is required
Nonfermenting Gram-negative *Bacilli*	Pansensitive NFGNB	Pansensitive nonfermenting Gram-negative *Bacilli* (intrisic resistance to first, second and third generation cephalosporins can exist)
	AmpC NFGNB	Non-fermenting microorganisms, resistant to first, second and third generation cephalosporins, resistant to cefoxitin, fourth generation cephalosporins-sensitive (cefepime-sensitive)
	CP-NFGNB	Carbapenemase-producing nonfermenting Gram-negative *Bacilli*: resistant to three or more carbapenems. Confirmatory test are required
	MDR-NFGNB	Multidrug resistance nonfermenting Gram-negative *Bacilli* expressing combined mechanisms of resistance (efflux bomb, porins, etc.) antibiogram interpretative reading by infectologist is required.