RESEARCH ARTICLE

Frequency of risk factors for bacteremia in children with cancer, neutropenia and fever in a tertiary level hospital in western Mexico

Juan Carlos Lona Reyes,[1] Miriam Marín Aguilera,[2] Araceli Cordero Zamora,[1] Jesús Gaitán Meza[1]

ABSTRACT

Background. We undertook this study to identify risk factors (RF) for bacteremia in children with cancer, neutropenia and fever (CNF) in order to establish more timely diagnoses.

Methods. We conducted a cross-sectional study in regard to RF for bacteremia in pediatric patients with CNF. We compared the prevalence of bacteremia depending on the presence or absence of independent variables and calculated the prevalence ratio (PR) with 95% confidence intervals. Multivariate analysis was performed to identify conditions that increase the likelihood of the diagnosis of bacteremia.

Results. We included 149 patients with CNF. Average age was 7.3 years; 45% were females. The underlying disease was leukemia ($n = 113$) or solid tumors ($n = 36$). Of the patients, 25.5% suffered from bacteremia; 65% of isolated bacteria were gram-negative. Variables associated with bacteremia identified by multivariate analysis were thrombocytopenia (OR 2.3, 95% CI 1.02-5.4, p 0.04), central venous catheter (CVC) (OR 2.6, 95% CI 1.16-5.9, p 0.02) and history of chemotherapy with vincristine (OR 2.8, 95% CI 1.22-6.4, p 0.01).

Conclusions. In a multivariate model, platelet count $\leq 50,000/mm^3$, CVC and the use of vincristine were associated with an increased likelihood of diagnosis of bacteremia in children with CNF.

Key words: neutropenia, bacteremia, risk factors.

INTRODUCTION

Pediatric patients with oncological diseases frequently present with neutropenia due to defects in cell production related to the underlying disease and chemotherapy treatment or the accelerated reserve utilization and changes in core body distribution.[1,2] This cytopenia causes a state of immunosuppression that increases the likelihood of acquiring infectious processes, especially when the absolute neutrophil count decreases to <500 cells/mm3.[3-9] One of the main causes of death in children with cancer and neutropenia are infectious diseases. The prevalence of bacteremia has been reported in 8 to 36% of patients.[3,5,10]

In children with cancer, neutropenia and fever (CNF), different factors that increase the likelihood of developing bacteremia have been studied. Conditions such as age, type of oncological disease, presence of invasive devices or blood disorders (including thrombocytopenia and monocytopenia) have been identified as risk factors (RF).[5-12] The objectives of this study were to measure the prevalence of bacteremia in the total sample and in function of the presence or absence of RF in pediatric patients with CNF, to compare the frequency of occurrence of bacteremia and to identify the factors associated with bacteremia.

PATIENTS AND METHODS

Design

A cross-sectional study was performed to identify the frequency of occurrence of known risk factors for bacteremia in children with CNF. Sampling was obtained by

1 Infectología Pediátrica, Hospital Civil de Guadalajara Dr. Juan I. Menchaca, Guadalajara, Jalisco, México
2 Epidemiología, Hospital Rural Oportunidades, Villamar, Michoacán, México

nonrandom consecutive cases from June 19, 2008 to June 19, 2009. We included in the study all pediatric patients diagnosed with cancer who were hospitalized and during their admission had an axillary temperature ≥38.5°C and serum neutrophils ≤1,000 cells/mm^3. We did not include patients who had not received chemotherapy or who did not have blood culture tests.

Variables

For registration and intake of variables, a questionnaire was designed that was completed on the first day of hospitalization. The information was obtained from medical records or through an interview with a family member or guardian. We included data such as gender, age, type of cancer, laboratory results (serum neutrophils, monocytes and platelet counts), clinical variables (temperature >39°C, presence of gastroenteritis, presence of acute respiratory infection), presence of central venous catheter (CVC), recent chemotherapy drugs administered and the interval between the last chemotherapy and the fever.

Neutropenia was classified as profound if total neutrophils were ≤100 cells/mm^3; severe if >100 and ≤500 cells/mm^3 and moderate if >500 cells/mm^3. Thrombocytopenia was considered if the platelet count was ≤50,000/mm^3 and monocytopenia if monocytes were ≤100 cells/mm^3. Samples taken for blood cultures at the time of admission to the hospital were incubated in an automated detection system for microbial growth (Bact/Alert 3D). Diagnosis of bacteremia was established if the same bacterium was isolated on two or more positive blood cultures.

Statistical analysis

Because variables of gender, age, type of cancer and the presence of CVC may be permanent and be related to more than one event of neutropenia and fever (NF), a descriptive analysis was performed for all variables for only the first event and a descriptive analysis of nonpermanent variables for all the events. Mean and standard deviation were calculated for quantitative variables. Frequency of qualitative variables was calculated and expressed as percentage.

For the inferential analysis of qualitative variables, we calculated the prevalence ratio with 95% CI and χ^2 as a contrast test of hypothesis. For quantitative variables, we used Student t test to identify significant differences between patients with and without bacteremia.

Multivariate analysis was performed with information from NF first-time events using IBM-SPSS Statistics v.20 program. To build the model, variables were used through bivariate analysis showing a value of p <0.15 and were then excluded step by step until the final model.

RESULTS

During the study period, there were 271 events registered of 149 CNF patients. Of all the patients, 57% ($n = 85$) had a single event, 24% ($n = 35$) had two events, 5% ($n = 8$) had three events and 14% ($n = 21$) had four or more events.

The average age of the patients was 7.3 years (SD ± 4.2 years); 45% ($n = 67$) were females and 55% ($n = 82$) males. For the underlying disease, the results were 59.7% ($n = 89$) of acute lymphocytic leukemia, 24.2% ($n = 36$) of solid tumors and 16.1% ($n = 24$) of acute myeloid leukemia.

Bacteremia was diagnosed in 25.5% of the patients ($n = 38$) and in 24.3% of CNF events ($n = 66$); 18.1% of the isolates ($n = 12$) were polymicrobial. Microorganisms were gram negative in 65% ($n = 54$), gram-positive in 29% ($n = 24$) and yeast in 6% ($n = 5$) (Table 2).

Bacteremia frequency depends on the risk factors listed in Table 1. In CNF first-time events we found significant differences in the prevalence of bacteremia for monocytopenia variables ($p = 0.01$), platelet count ($p = 0.006$), CVC ($p = 0.01$), chemotherapy-fever interval <3 days ($p = 0.04$) and a history of having received chemotherapy with methotrexate ($p = 0.03$) or vincristine ($p = 0.04$).

In Table 3, prevalence ratios and 95% CI of the variables (p <0.15) that were used in the multivariate analysis are shown. Multivariate analysis was performed using logistic regression. To construct the model, variables were used according to bivariate analysis (p <0.15). In the first model, seven variables were included. Step by step insignificant variables were excluded. The final model is shown in Table 4.

DISCUSSION

The results of the study provide insight into the epidemiology and the demographic and clinical characteristics of pediatric patients with oncological and CNF diseases who were treated at a specialty hospital in the western region of Mexico. Prevalence of bacteremia for all CNF events

(24.3%) was higher than that reported by Klaassen et al (12%)[4] but had a similar result to the frequencies reported by Amman et al. (24%)[7] and Rackoff et al. (21%).[20]

Gram-negative bacteria were predominant (65%, n = 54), which is different from the information published by Cordonnier and colleagues who noted that the major causative organisms of bacteremia in children with NF were gram-positive cocci (21%).[19] Paul et al. observed in Schneider Children's Medical Center (Petach Tikvah, Israel) from 1988 to 2004, a change in the relationship of isolates of gram negative and gram positive of 1.2 to 0.7. They identified that the increase of coagulase-negative Staphylococcus isolates and modification of hospital days influenced this variation.[21] In this study, the ratio of isolates of gram negative and gram positive was 2.2 and the proportion of isolates of coagulase-negative Staphylococcus was 14.4% (n = 12). The most frequently isolated bacteria were Pseudomonas sp. (21.6%).

The importance of determining the bacteria causing bacteremia in children with CNF is its usefulness in decision-making, notably in the selection of empirical treatment regimens. Independent risk factors in multivariate analysis were thrombocytopenia (OR 2.3, 95% CI 1.02–5.4, p = 0.04), presence of CVC (OR 2.6, 95% CI 1.16-5.9, p = 0.02) and use of vincristine (OR 2.8, 95% CI 1.22–6.4, p = 0.01).

In a prospective multicenter study, Santolaya et al. identified factors associated with invasive bacterial infection in children with CNF. Among the factors identified are platelet count <50,000/mm^{3} (OR 1.7, 95% CI 1.4-2.2) and interval since the last chemotherapy <7 days (OR 1.3, 95% CI 1.1-1.16).[6] In this study we observed that during the hospital admission of CNF patients, thrombocytopenia increased the probability of the diagnosis of bacteremia in 31%. No association with chemotherapy and fever interval <7 days was probably because in the reference study, NF association with invasive bacterial infections, including bacteremia, was sought.

Ammann et al., using a bivariate analysis, identified that the presence of CVC is related to bacteremia through gram-negative bacillus (OR 4.4, 95% CI 1.7-13).[7] In the present study, using multivariate analysis, we identified that CVC increases 1.6 times the risk of diagnosis of bacteremia. Different studies have reported that up to 51%

of CVC in children with cancer may be complicated by bacteremia. Among the conditions that increase the probability of the presence of infection is a total neutrophil count <500 cells/mm^{3}.[22]

In the study conducted by Klaassen et al. whose objective was to evaluate a system for predicting the risk of serious bacterial infections in patients with NF, monocyte count of ≤100 cells/mm^{3} was a predictor of low risk, with sensitivity and specificity of 84 and 42%, respectively.[4] In our study, multivariate analysis showed no statistical significance for the variable of monocytopenia (OR 6.8, 95% CI 0.85-55.6). However, this variable was not excluded from the model because the result may be a consequence of the size of the sample and not by absence of association. Of all patients included in the study and who had bacteremia, 97.4% had serum monocytes ≤100 cells/mm^{3}. The main adverse effects related to vincristine are myelosuppression, mucositis, hepatotoxicity and peripheral neuropathy. The frequency of drug-related toxicity was measured in 13%.[23] In the study conducted at the Hospital Civil de Guadalajara, they identified an 80% increase in the likelihood of diagnosis of bacteremia if the patient received vincristine during their last chemotherapy treatment.

Langholz et al., in a retrospective analysis of clinical trials, identified that regardless of race or gender, each year the age increased there was an increase in the probability of vincristine toxicity (p <0.001).[23] In this study, to assess the effect of age, the sample was dichotomized for two cutoffs (ages ≥1 year and ≥12 years) and there were no changes in the multivariate model when these variables were included.

Frequency of bacteremia in children with CNF was 25.5%. The most frequently identified microbial agents were gram-negative bacilli (65%). In a multivariate model, the risk factors were platelet count ≤50,000/mm^{3}, CVC and the use of vincristine, all associated with increased likelihood of bacteremia.

FUNDING

Table 1. Prevalence of bacteremia in children with CNF according to function of independent variables (p value using χ^2)

Variable	First event of CNF (n = 149)			Total of events of CNF (n = 271)		
	Bacteremia in the presence of exposure	Bacteremia in the absence of exposure		Bacteremia in the presence of exposure	Bacteremia in the absence of exposure	
	n (%)	n (%)	p	n (%)	n (%)	p
Sex						
Male	21 (25.6)	17 (25.4)	0.97	ND	ND	
Female	17 (25.4)	21 (25.6)				
Type of cancer						
Solid tumor	9 (25.7)	29 (25.4)	0.97	ND	ND	
Myelocytic leukemia	6 (25.0)	32 (25.6)	0.95	ND	ND	
ALL	23 (25.6)	15 (25.4)	0.98	ND	ND	
Neutropenia						
Moderate	1 (7.7)	37 (27.4)	0.12*	9 (34.6)	57 (23.5)	0.20
Severe	15 (26.8)	23 (25.0)	0.81	17 (22.4)	49 (25.4)	0.60
Profound	22 (27.8)	16 (23.2)	0.52	40 (24.0)	26 (25.5)	0.77
Monocytopenia	37 (29.1)	1 (4.5)	0.01*	63 (26.6)	3 (9.1)	0.03
Thrombocytopenia	25 (36.2)	13 (16.5)	0.006*	45 (30.2)	21 (17.5)	0.01
Fever >39°C	23 (29.1)	15 (21.4)	0.28	36 (27.7)	30 (21.3)	0.21
Gastroenteritis	9 (24.3)	29 (25.9)	0.85	14 (23.7)	52 (24.5)	0.89
Respiratory infection	1 (11.1)	37 (26.4)	0.31	7 (28.0)	59 (24.0)	0.65
CVC	21 (36.2)	17 (18.7)	0.01*	ND	ND	
Qx-Fever interval <7 days	22 (28.9)	12 (20)	0.23	34 (28.8)	26 (20.5)	0.13
Qx-Fever interval <3 days	17 (36.2)	18 (20)	0.04*	26 (37.1)	35 (19.9)	0.05
Previous chemotherapy						
Arabinoside C	11 (23.9)	27 (26.2)	0.77	20 (27.4)	46 (23.2)	0.48
Cyclophosphamide	5 (33.3)	33 (24.6)	0.46	7 (19.4)	59 (25.1)	0.46
Daunorubicin	5 (20)	33 (26.6)	0.49	9 (22.5)	57 (24.7)	0.76
Doxorubicin	2 (15.4)	36 (26.5)	0.38	4 (13.3)	62 (25.7)	0.13
Etoposide	7 (23.3)	31 (26.1)	0.76	16 (28.1)	50 (23.4)	0.46
L-asparaginase	5 (26.3)	33 (25.4)	0.93	9 (27.3)	57 (23.9)	0.67
Methotrexate	4 (11.4)	34 (29.8)	0.03*	10 (17.5)	56 (26.2)	0.18
Vincristine	18 (36)	20 (20.2)	0.04*	27 (27.8)	39 (22.4)	0.32

*Variables used in multivariate analysis. CNF, cancer, neutropenia and fever; ALL, acute lymphocytic leukemia; Qx, chemotherapy. ND, not determined.

Table 2. Isolated microbes in hemocultures of pediatric patients with CNF

Specie	Number (%)	Specie	Number (%)
Pseudomonas sp.	18 (21.6)	*Streptococcus* sp.	2 (2.40)
Escherichia coli	13 (15.6)	*Empedobacter brevis*	2 (2.40)
Coagulase negative *Staphylococcus*	12 (14.4)	*Haemophilus influenzae*	1 (1.20)
Klebsiella pneumoniae	6 (7.22)	*Aeromonas hydrophila*	1 (1.20)
Candida sp.	5 (6.02)	*Morganella morganii*	1 (1.20)
Enterococcus sp.	5 (6.02)	*Chryseobacterium meningosepticum*	1 (1.20)
Enterobacter sp.	4 (4.81)	*Moraxella catarrhalis*	1 (1.20)
Acinetobacter sp.	3 (3.61)	*Achromobacter xylosoxidans*	1 (1.20)
Streptococcus viridans	3 (3.61)	*Sphingomonas paucimobilis*	1 (1.20)
Staphylococcus aureus	2 (2.40)	*Stenotrophomonas maltophilia*	1 (1.20)
		Total	83 100%

CNF, cancer, neutropenia, fever.
The number of isolated microbes exceeds the number of patients due to the cultivation of polymicrobes.

Table 3. Prevalance ratio and 95% CI of the independent variables (p value <0.15)

	First event of NF (n = 149)			Total events of NF (n = 271)		
Variable	PR	95% CI	p	PR	95% CI	p
Moderate neutropenia	0.3	0.04 - 1.9	0.12	ND	ND	
Monocytopenia	6.4	0.9 - 44.3	0.01	2.92	0.97 - 8.8	0.03
Thrombocytopenia	2.2	1.2 - 3.9	0.006	1.72	1.09 - 2.7	0.01
CVC	1.93	1.1 - 3.3	0.01		ND	
Qx-Fever interval <3 days	1.8	1.03 - 3.1	0.04	1.87	1.22 - 2.85	0.005
Vincristine	1.78	1.04 - 3.05	0.04	1.24	0.81 - 1.89	0.32
Methotrexate	0.38	0.15 - 1.0	0.03	0.67	0.36 - 1.23	0.18

NF, neutropenia and fever; CVC, central venous catheter; CI, confidence interval; Qx, chemotherapy; PR, prevalence ratio. ND, not determined.

Table 4. Multivariate analysis with logistic regression of variables associated with bacteremia in children with CNF

Variable	OR	95% CI	p
Monocytopenia	6.8	0.85 - 55.6	0.07
Thrombocytopenia	2.3	1.02 - 5.4	0.04
CVC	2.6	1.16 - 5.9	0.02
Vincristine	2.8	1.22 - 6.4	0.01

CNF, cancer, neutropenia and fever; OR, odds ratio; CI, confidence interval; CVC, central venous catheter.

CONFLICT OF INTEREST

The authors declare no conflicts of interest in carrying out of the study as well as results of the investigation.

Correspondence: Dr. Juan Carlos Lona Reyes
E-mail: carloslona5@hotmail.com

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