Risk Factors of Serious Bacterial Infection in Previously Healthy Children Older Than 90 Days Old With Fever and Neutropenia

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Background: The main objective was to determine the clinical or analytical factors that independently predict risk of serious bacterial infection (RSBI) in immunocompetent patients older than 90 days given a diagnosis of fever and for whom neutropenia was an incidental finding. The secondary objective was to describe the prevalence of serious bacterial infections (SBIs).

Methods: This is a 3-year-long, multicenter, prospective analytical and observational study carried out at 6 pediatric emergency departments. Data for epidemiological, clinical, and analytical variables were collected.

Results: One hundred forty patients with febrile neutropenia (60.7% mild, 39.3% moderate to severe) were recruited. Serious bacterial infection incidence was 15.0% (95% confidence interval [CI], 9–21): 1 Invasive Bacterial Infection (*Staphylococcus epidermidis* bacteremia), 10 urinary tract infections, 8 pneumonias, and 2 cellulitis. Median total neutrophil counts per microliter showed no statistically significant differences ($P = 0.512$; 1000 [750–1200] in SBI patients vs 1100 [800–1300] in non-SBI patients). Higher RSBI was observed in patients with neutrophils less than 20% relative to total leukocytes (SBI, 15, 26.3%) than in those with neutrophils of 20% or greater (SBI, 6, 7.2%) (odds ratio, 4.6; 95% CI, 1.7–12.7). In patients with greater than 5000 leukocytes/μL, a percentage of neutrophils less than 20% was related to a greater RSBI with a trend toward statistical significance (odds ratio, 6.1; 95% CI, 0.7–51.1; $P = 0.066$). The clinical variables did not show a significant association with RSBI.

Conclusions: None of the clinical or analytical variables assessed were associated with the RSBI. However, according to a post hoc analysis, in patients with greater than 5000 leukocytes/μL, a neutrophil percentage less than 20% could be an independent risk factor for SBI. A thorough physical examination and basic diagnostic tests (urinalysis and chest x-ray) may help to establish a diagnosis of SBI in the vast majority of cases.

Key Words: febrile neutropenia, serious bacterial infection, inmunocompetent, fever

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Neutropenia, defined as a total neutrophil count less than 1500 cells per microliter (cells/μL),[1] can be classified as congenital or acquired. In patients given a diagnosis of congenital neutropenia, the risk of bacterial infections begins during the neonatal period[2,3] and, without proper treatment, can become a lifelong issue. Acquired neutropenia can be secondary to infections, with transitory and self-limiting suppression of the bone marrow caused by a viral infection being the most common cause.[4] Other frequent causes are hematologic malignancies and pharmaceuticals such as chemotherapy agents.

Febrile neutropenia is a frequent complication[5] in cancer patients, especially among those receiving chemotherapy. There is a general consensus on how febrile neutropenia should be handled in cancer patients, including the early administration of broad-spectrum antibiotics.[6]

There are few publications on the risk of serious bacterial infection (RSBI) in previously healthy patients[7–11] in whom the neutropenia was an incidental finding when performing diagnostics on a febrile patient. Some prospective studies[8,12–15] show an association between febrile neutropenia in previously healthy children and viral infections. These tend to be of a transitory nature and run a generally benign course without complications. There is not currently a consensus or unified protocols regarding the most suitable approach for this group of patients. Some clinical guides have used the experience garnered from managing cancer patients with febrile neutropenia.[16] However, given the low RSBI in previously healthy patients with fever, good overall condition, and isolated neutropenia, some authors suggest the possibility of not prescribing empirical antibiotic therapy and performing clinical follow-up for these patients on an outpatient basis.[8,12,15,16]

The main objective of this study is to determine whether previously healthy patients older than 90 days with fever and incidentally detected neutropenia present clinical or analytical factors that may serve as an independent predictor for RSBI. As a secondary aim, we will describe the prevalence of SBIs in this group of patients.

METHODS

Design

This was an observational, prospective, analytical, and multicenter study carried out for a 3-year period within the framework of the Research Network of the Spanish Society of Pediatric Emergency Care (RISeuP-SPERG).

The study was supervised and approved by the ethics and clinical research committee of each of the affiliated centers. The parents or legal guardians, along with children 12 years and older, signed an informed consent form. Patients were evaluated according to the protocols for febrile neutropenia at each center. Thus, inclusion in the study did not involve any change in the diagnostic or therapeutic approach or any additional interventions. Data were processed in compliance with that set forth in the current Spanish laws on data protection. The study complies with the rules of the Declaration of Helsinki. Neither the researchers nor the

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participating centers received any kind of compensation for carrying out this study.

Sample Selection

All children older than 90 days who presented with fever at the pediatric emergency department of one of the 6 participating hospitals (Supplementary Digital Content 1, http://links.lww.com/PEC/A956) and who had a neutropenia (defined as total neutrophil count in a peripheral blood sample less than 1500 cells/μL) on a blood test performed in accordance with the protocols of each center were included.

Patients with any of the following were excluded: those who did not sign the informed consent; known vitamin B12, folate, or copper deficiency; taking a pharmaceutical that produces neutropenia in the past 4 weeks (Supplementary Digital Content 2, http://links.lww.com/PEC/A957); known oncological pathology with or without current chemotherapy treatment; congenital infection with cytomegalovirus; known congenital neutropenia; primary autoimmune neutropenia; known cyclic neutropenia; neutropenia observed on a previous blood analysis; hypersplenism; myeloperoxidase deficiency; and other primary or acquired immunodeficiencies.

Study Protocol

A blood analysis was ordered for patients with fever, in accordance with normal clinical practice, in the situations in which the participating centers' protocols called for one. After obtaining the laboratory results and confirming the neutropenia, the informed consent was offered to those patients who met the inclusion criteria and did not present any exclusion criteria.

A notebook was filled in to collect the relevant epidemiological, clinical, and analytical information. Each subject was assigned a 4-digit numerical code to identify them in the study and to associate the information extracted from medical history, without including personal data that could allow his/her identification.

Follow-up was performed at 7 days after the initial evaluation, either through a telephone call if the patient had been sent home or by looking at their medical records if they were still at the hospital.

Each center appointed a collaborating researcher to submit the data in electronic format. The information was then grouped together into a single protected database, accessible only to the principal investigators of the coordinating hospital. A monthly backup was performed.

Variables

The recorded data included epidemiological information (age, sex, and medical and family history), clinical information (reason for visit, maximum temperature, time of clinical evolution, pediatric assessment triangle evaluation upon arrival at the Emergency Department, physical examination findings, final diagnosis, treatment and duration, hospital admission, and evolution), analytical findings (leukocyte count and differential, hemoglobin, platelets, C-reactive protein [CRP], and procalcitonin [PCT]), microbiological isolates in urine, blood and cerebrospinal fluid culture, and radiology reports if a chest x-ray had been performed. The neutrophil levels were expressed as total count and absolute count, and the neutropenia was categorized as mild (1000–1499 neutrophils/μL), moderate (500–999 neutrophils/μL), or severe (<500 neutrophils/μL).

The definitions used in the study protocol are available in Supplementary Digital Content 3, http://links.lww.com/PEC/A958.

In addition, the total number of patients and children older than 90 days seen at the Emergency Department, number of patients with neutropenia detected, and number of children older than 90 days with neutropenia who were excluded from the study were recorded on a monthly basis.

Statistical Analysis

The categorical variables are expressed as absolute frequencies and percentages, whereas the quantitative ones are expressed based on whether they were found to be normally distributed or not: mean and SD for symmetrically distributed variables and median and interquartile range for asymmetrically distributed ones.

The associations between RSBI and the different clinical and analytical variables were analyzed using the χ^2 test for categorical variables and the Student t test or Mann-Whitney U test for the quantitative variables. In addition, the quantitative variables were categorized after their distribution was graphically determined, to describe the RSBI in a practical manner.

The interaction between the variables was evaluated using stratified analyses, creating a multivariable logistic regression model to quantify the RSBI through the odds ratio (OR) and associated 95% confidence intervals (CIs). The variables shown to have an association on the univariable analysis were introduced into this model.

The statistical software package SPSS v.20 was used to process the data. Statistical significance was set at $P < 0.05$, and a value of $P < 0.10$ was considered as tending toward statistical significance.

RESULTS

During the study period, 399,605 emergency cases were seen, among which 320 were children older than 90 days with fever and neutropenia. Once those with exclusion criteria were omitted (Fig. 1), this left 140 patients in the study; 85 were classified as having mild neutropenia (60.7%), 44 were classified as having moderate neutropenia (31.4%), and 11 were classified as having severe neutropenia (7.9%). There were no deaths recorded or admissions to the ICU.

The characteristics of the children analyzed and the complementary tests carried out are shown in Table 1.

Twenty-one cases of SBI were diagnosed (15.0%; 95% CI, 9.1%–20.9%), one of them was an Invasive Bacterial Infection (IBI) (0.7%). These correspond to 10 urinary tract infections (UTIs) (all of them with *Escherichia coli* isolated in the urine culture), 8 cases of pneumonia, 2 cellulitis, and 1 occult bacteremia caused by *Staphylococcus epidermidis* (considered a true pathogen because of its growth during the first 24 hours in 2 separate blood cultures, in a patient initially suspected of having a lymphoproliferative syndrome, which was ultimately not confirmed). The analytical findings of the patients with SBI are shown in Table 2.

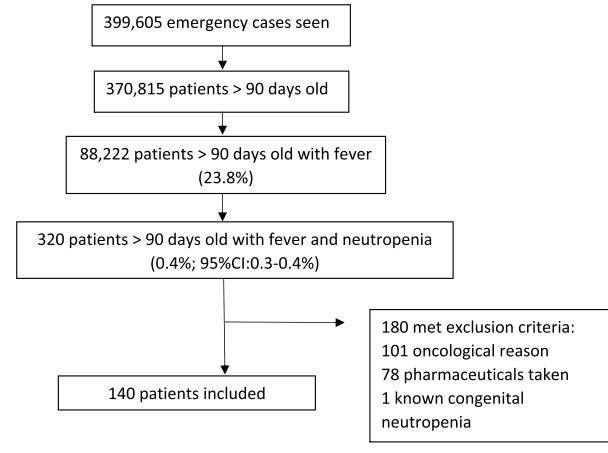

FIGURE 1. Flowchart for sample selection.

TABLE 1. Characteristics of the Children Older Than 90 Days With Fever and Neutropenia

Characteristics	n (%)
Sex (male)	86 (61.4)
Age,* y	21 mo (10–69 mo)
Recent infection, in 10 d prior	11 (7.9)
Family history of hematologic disease	2 (1.4)†
Fever‡	39.2 C (0.8)
Time of evolution of the fever*	66 h (24–96 h)
Stable PAT	125 (89.3)
Mucous membrane issues (aphthae/ulcers)	4 (2.9)
Petechiae	25 (17.86)§
Hepatosplenomegaly	2 (1.4)‖
Adenopathy	2 (1.4)‖
Blood analysis	
- Leukocytes, total/μL*	4350 (3178–6575)
- Neutrophils, total/μL*	1100 (800–1300)
- Hemoglobin, g/dL*	12.3 (11.2–13.2)
- Platelet count, total/μL*	192,000 (145,000–238,750)
- CRP, mg/dL*	0.8 (0.2–3.5)
- PCT, ng/mL*	0.3 (0.1–1.2)
Patients with blood culture collected	116 (82.9)
Patients with urine culture collected	55 (39.3)
Patients with CSF culture collected	4 (2.9)
Patients with chest x-ray performed	22 (15.7)
Hospital admission	30 (21.4)
Antibiotic treatment	36 (25.7)
Fever resolved by time of follow-up	124 (89.2)

*Results are expressed as median and interquartile range.

†No patient reported to have a family history of congenital blood disease. The 2 cases who reported a family history of hematologic disorders were tumoral in nature.

‡Results are expressed as mean and standard deviation.

§Punctiform petechiae in all the cases.

‖The 2 patients who presented with adenopathy and hepatosplenomegaly were ultimately given a diagnosis of lymphoblastic leukemia.

CRP indicates C-reactive protein; CSF, cerebrospinal fluid; PAT, pediatric assessment triangle; PCT, procalcitonin.

Univariable Analysis

Table 3 shows a comparison of the clinical and analytical characteristics of patients with febrile neutropenia, with and without SBI. No differences were found in total neutrophil values between these groups ($P = 0.512$). There were also no differences in RSBI when classifying neutropenia by severity (mild, 16.5%; moderate, 9.1%; severe, 27.3%; $P = 0.266$). The median neutrophil count (expressed as percentage of total leukocytes) was 15% in SBI patients and 24% in non-SBI patients ($P = 0.008$) (Fig. 2).

A higher RSBI was observed in patients with a percentage of neutrophils less than 20% of total leukocytes (SBI, 15, 26.3%) than in those with a higher or equal percentage (SBI, 6, 7.2%) (OR, 4.6; 95% CI, 1.7–12.7).

Age, and leukocyte and platelet counts were also associated with the presence of SBIs. A greater frequency was observed in those younger than 12 months (26.1% vs 9.6%; OR, 3.3; 95% CI, 1.3–8.6) and in children with more than 5000 leukocytes/μL (25.9% vs 7.3%; OR, 4.4; 95% CI, 1.6–12.2) or more than 180,000 platelets/μL (21.5% vs 6.6%; OR, 3.9; 95% CI, 1.2–12.3).

Multivariable Analysis

An interaction between the total leukocyte count and the percentage of neutrophils in its association with the RSBI was identified. The stratified analysis revealed, with a trend toward statistical significance, that a neutrophil count less than 20% was related to a greater RSBI in children whose total leukocytes were greater than 5000/μL (OR, 6.1; 95% CI, 0.7–51.1; $P = 0.066$). However, no association was shown when total leukocyte count was 5000/μL or less (OR, 1.1; 95% CI, 0.1–10.0; $P = 0.955$).

The multivariable logistic regression model, which also incorporated age of less than 12 months and a platelet count greater than 180,000/μL, stratified by leukocytes, confirmed the effect of neutrophil count less than 20% on the RSBI in those patients with greater than 5000 leukocytes/μL, again with a trend toward statistical significance (Table 4).

DISCUSSION

This study analyzes possible risk factors for SBI in previously healthy children older than 3 months with fever and neutropenia. There are several prospective studies in the literature that describe the etiology and clinical course of febrile neutrophil in previously healthy children.[12,14,17] To our knowledge, this is the first prospective multicenter study focused on analyzing clinical and analytical characteristics as predictive factors for SBI in these patients, with the objective of fine-tuning the diagnostic and therapeutic approach.

Our results suggest that the total number of neutrophils is not a risk factor for SBI in previously healthy children. These results are consistent with that described by other authors, who establish that children without previous illnesses who have an isolated neutropenia and concurrent fever do not have a greater RSBI.[10,12,13,15,18] In line with previous studies,[12,13,15] our work shows that the degree of neutropenia (mild, moderate, severe) does not predict a greater risk of presenting a bacterial infection. However, our results point to a potentially higher RSBI in children with neutropenia if the neutrophils represent less than 20% of the total leukocytes and the total leukocytes is greater than 5000/μL. Anyway, this finding was a post hoc finding that had not been stated as a working hypothesis because published literature focuses on the total number of neutrophils and no publication has been identified that discusses the risk of SBI by deeming neutropenia as a percentage of total leukocyte count.

Therefore, it would be necessary to design more studies to further analyze this result. None of the clinical variables analyzed were associated with the RSBI.

It is worth mentioning that, in our sample, an "unstable" pediatric assessment triangle (PAT) evaluation was not identified as a risk factor for IBI/SBI. According to the articles published by Gomez et al[19,20] in relation to febrile infants, altered PAT seems to be associated with an increased risk of IBI. However, there seems to be no association with risk of SBI (non-IBIs). In one of the articles by Gomez et al,[19] infants in "poor overall condition" (defined as those deemed "unstable" on the PAT evaluation) and with leukopenia (<5000/μL) have a greater risk of IBI (Relative Risk, 2.56; 95% CI, 1.18–5.58) but do not have a greater risk for "non-invasive" bacterial infections (Relative Risk, 0.60; 95% CI, 0.23–1.62). In our study, the small sample size as well as the low incidence of IBIs (only 1 case of bacteremia) and SBIs may explain why no significant association was found. For the aforementioned reasons, it was not possible to analyze the value of altered PAT as a risk factor for IBIs and SBIs independently.

Among the literature reviewed, only the study by Husain et al[14] makes a reference to the variable "overall condition" (91% of the patients included therein being "well and active"). However, it does

TABLE 2. Analytical Values for Children With Serious Bacterial Infection

Patient	Diagnosis	Leukocytes/μL	Neutrophils/μL (% of Total Leukocytes)	Hemoglobin, g/dL	Platelet Count/μL	CRP, mg/dL	PCT, ng/mL
1	UTI	7400	1000 (13.5)	13.2	197,000	0.1	0.14
2	UTI	20,900	1400 (6.7)	11.9	299,000	0.1	—
3	UTI	5300	700 (13.2)	12.7	180,000	0.1	0.15
4	UTI	7900	1300 (16.5)	11.6	200,000	0.1	0.17
5	UTI	2100	300 (14.3)	11.4	176,000	0.98	0.5
6	UTI	12,400	1000 (8.1)	12.1	321,000	0.1	0.1
7	UTI	8700	1200 (13.8)	12.3	227,000	0.1	0.1
8	UTI	3700	1000 (27.0)	11.3	251,000	0.24	0.09
9	UTI	5820	1100 (18.9)	9.8	475,000	8.6	5.84
10	UTI	7500	320 (4.3)	11.1	211,000	0	0.09
11	Pneumonia	1400	800 (57.1)	11.5	184,000	33.3	41.62
12	Pneumonia	7300	1100 (15.0)	12.2	193,000	0.1	0.13
13	Pneumonia	5030	1200 (23.9)	11.8	226,000	1.54	—
14	Pneumonia	6200	260 (4.2)	11.2	232,000	3.9	1.76
15	Pneumonia	3200	1000 (31.3)	10.2	299,000	22.44	3.64
16	Pneumonia	2900	600 (20.7)	8.7	115,000	23.7	—
17	Pneumonia	9500	1300 (13.7)	9.9	371,000	20.3	—
18	Pneumonia	3000	1400 (46.7)	10.8	168,000	4	—
19	Bacteremia	7800	1200 (15.4)	13.2	3000	0.1	—
20	Cellulitis	8200	800 (9.8)	13.8	288,000	0.7	—
21	Cellulitis	7500	1200 (16)	10.2	275,000	5.0	—

CRP indicates C-reactive protein; PCT, procalcitonin; UTI, (upper) urinary tract infection.

not compare the children with bacterial infections (only 2 UTIs are described, no IBIs) and those with viral infections. Craig et al[21] analyzed the diagnostic value of various clinical signs and symptoms in children younger than 5 months with fever. They concluded that a change in overall condition was the most powerful predictive factor for SBI (bacteremia, pneumonia, UTI), being especially meaningful in patients with bacteremia. We consider that patients with an "unstable" PAT evaluation require a more aggressive diagnostic and therapeutic approach.

Another clinical aspect traditionally related with a clinical suspicion of IBI is the presence of petechiae. However, in our analysis, petechiae being present was not associated with a greater RSBI, quite on the contrary, because most patients with petechiae did not have an SBI. In their study, Barg et al[18] describe a greater frequency of rash in the group of patients with neutropenia and relate this finding to the prevalence of viral exanthems in healthy children with fever and neutropenia, as characterized by other authors.[9,12–14]

TABLE 3. Comparison of the Clinical and Analytical Characteristics Between Patients With Febrile Neutropenia With and Without Serious Bacterial Infection

	Serious Bacterial Infection			
	Yes	No	*P*	N
Age, mo	10.4 (6.9–22.1)	23.7 (10.4–92.2)	0.001	140
Fever, °C*	39.4 (0.7)	39.2 (0.8)	0.279	127
Evolution of the fever, h	72 (24–84)	60 (24–96)	0.755	140
Unstable PAT (N = 15)†	3 (14.3%)	12 (10.1%)	0.566	15
Petechiae, yes (N = 25)†	1 (4.8%)	24 (20.2%)	0.089	25
Total leukocytes, cells/μL	7300 (3450–8050)	4300 (3100–5730)	0.019	140
Neutrophils, cells/μL	1000 (750–1200)	1100 (800–1300)	0.512	140
CRP, mg/dL	0.7 (0.1–6.8)	0.3 (0.1–0.9)	0.766	137
PCT, ng/mL	0.17 (0.12–4.74)	0.30 (0.12–0.90)	0.772	58
Platelet count × 10^3, cells/μL	226 (182–293.5)	185 (143–237)	0.022	140

Values are expressed as median (interquartile range).

*Values are expressed as mean (standard deviation).

†Values are expressed as absolute frequency (percentage).

CRP indicates C-reactive protein; PAT, pediatric assessment triangle; PCT, procalcitonin.

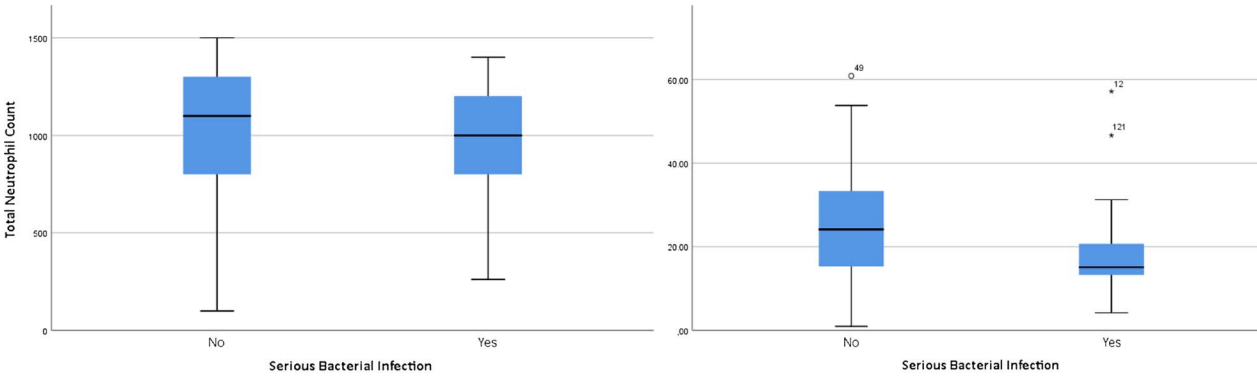

FIGURE 2. Comparison between total neutrophils and the percentage of neutrophils (relative to total leukocytes) in patients with and without serious bacterial infection.

As for the analytical parameters, we did not detect any association between the acute phase reactants (CRP and PCT) and the RSBI. No previous study has analyzed the value of CRP and PCT as predictors of SBI or IBI in healthy children with febrile neutropenia. We should bear in mind that the SBIs diagnosed in our sample are mostly UTIs and pneumonias. We detected elevated values in most patients given a diagnosis of pneumonia (CRP > 2 mg/dL in 6 of 8 patients and PCT > 0.5 ng/mL in 3 of 4 patients with PCT tested), but not in patients given a diagnosis of UTI. Few authors report CRP values in their publications.[9,13,15,18] In the article by Barg et al,[18] the CRP values were lower in the neutropenia group than in the control group (median of 0.56 vs 3.4 mg/dL; $P < 0.001$), probably because of the greater proportion of SBIs in that control group. We have only found references to PCT in the study by Pascual et al[13] (PCT ≤ 0.5 ng/mL in 91.8% of the patients included). According to the literature, the usefulness of this acute phase reactants to make a differential diagnosis between bacterial or viral etiology of community-acquired pneumonia[22,23] or to establish the diagnosis of acute pyelonephritis versus lower UTI[24] is not as well defined. These aspects, together with the limitations of the sample size and the low incidence of IBIs/SBIs, could explain why no significant association between these variables has been identified. In the case of the patient given a diagnosis of bacteremia, he had a fever of 1 hour's evolution when he was assessed in the emergency department and the blood test was drawn. This could justify that the CRP was not elevated. The PCT value was not available.

Nevertheless, given the limitations of our study, we consider that these results are not enough to assert that these parameters should not be taken into consideration in clinical decision making.

The prevalence of SBIs in our population was 15%, a very similar figure to that described in other prospective studies carried out on patients with a similar profile (Alexandropoulou et al,[12] 14.7%; Karavanaki et al,[17] 14.9%). However, this number is considerably higher than the prevalence reported in other previous studies, which are mostly retrospective in nature.[10,13–15,18] This could be explained by the heterogeneity in the design of the published studies, in terms of variability in the inclusion criteria (children without fever,[10] only children with stable PAT evaluation[13] or in good overall condition,[9] only children with moderate to severe neutropenia,[9,10,13,15,18] only children with a blood culture[18]) and in the definition of SBI applied. For example, some authors[10,12,14] did not include pneumonia in the definition of an SBI. In fact, Melendez et al[10] did not consider pneumonia that had been diagnosed via x-ray as an SBI because of the difficulty in making a differential diagnosis between viral and bacterial etiologies in this pathology. In our study, pneumonia represents 38.1% (8/21) of the cases of SBI diagnosed. Given that this is an observational study, testing for respiratory viruses was not carried out systematically, and we therefore cannot rule out that some of these cases of pneumonia could have had a viral etiology. The profile of SBIs diagnosed in our patients is consistent with that described by other authors.[10,13–15,18] These are mostly focal infections (UTIs, pneumonia, cellulitis) that are diagnosed based on a thorough physical examination and routine diagnostic tests and require antibiotic therapy that targets the most common etiologic agents for each type of infection.

If we concentrate on IBIs, most of the studies we reviewed[13–15,18] did not report a single case; the prevalence in our study was 0.7%. These data show that the risk of IBI in healthy children with febrile neutropenia is less than that described in healthy children 3 to 36 months old with moderate leukocytosis (14,000–24,999 cells/μL) or extreme leukocytosis (≥25,000 cells/μL) (1.36% and 2.7%, respectively),[25] in infants younger than 3 months

TABLE 4. Multivariable Analysis for Risk of Serious Bacterial Infection

	Total Leukocytes					
	>5000 Leukocytes/μL			≤5000 Leukocytes/μL		
	OR	95% CI	*P*	OR	95% CI	*P*
Neutrophils < 20%	8.2	0.9–71.7	0.056	1	0.1–9.8	0.993
Age < 12 mo	1.6	0.4–6.3	0.495	1.9	0.3–12.2	0.477
Platelet count > 180,000/μL	7.0	0.7–66.2	0.088	1.2	0.2–6.9	0.805

The explanatory multivariable logistic regression model includes the variables with an association identified in the univariable analysis, stratified by the effect-modifying factor total leukocytes.

CI indicates confidence interval; OR, odds ratio.

with fever and leukopenia (5.3%),[19] and in cancer patients with febrile neutropenia (12.2%).[26]

Our study does have some limitations. The main limitation is the small sample size, although this was a multicenter study with a recruitment period extended to 3 years. This could be due to the low incidence of febrile neutropenia in healthy children, along with the rigorous inclusion and exclusion criteria. On a positive note, this same rigorousness is a strength of the study design, because it minimizes the selection bias. In addition, we do not have a control group, and therefore, we cannot estimate the relative risk for SBI in healthy children with febrile neutropenia in our sample.

Finally, because of it being an observational study, the participation of the patients included does not generate any type of intervention in addition to the diagnostic-therapeutic management indicated at the discretion of the physician in charge of the patient, in accordance with the current protocols. Therefore, it is possible that any SBI may have been missed. In the case of UTI, it seems unlikely because the protocols recommend screening for UTI by urine dipstick and a urine culture is not systematically required if the result of the dipstick is negative. In the literature reviewed, only the study by Barg et al[18] excludes patients who do not have a blood culture collected and does not report any cases of bacteremia in the group of patients with neutropenia. Finally, microbiological tests to diagnose viral etiologies were not systematically performed. Nevertheless, describing the etiology of febrile neutropenia was not one of the study's objectives because this is well described in the literature.[9,12,14,17] We deem that the results reflect the variability in the approach to these patients and the need to standardize clinical practice on the basis of scientific evidence.

CONCLUSIONS

None of the clinical or analytical variables assessed were associated with the RSBI. However, according to a post hoc analysis, in patients with greater than 5000 leukocytes/μL, a neutrophil percentage less than 20% could be an independent risk factor for SBI.

On the basis of our results and as suggested by other authors,[15,16,18] we consider that when presented with a previously healthy patient with fever and neutropenia, having a detailed physical examination, carrying out a urinalysis, and performing a chest x-ray would allow us to establish the diagnosis of SBI in the vast majority of cases. In our opinion, in patients deemed stable via PAT evaluation without a clinical and/or analytical or radiological suspicion of SBI, the administration of empirical antibiotic therapy and hospital admission are not justified, as long as outpatient follow-up and access to healthcare in case of clinical deterioration can be guaranteed.

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