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ORIGINAL ARTICLE

Utility of basic clinical and laboratory parameters to predict Serious Bacterial Infection in children younger than 3 months old hospitalized for Febrile Syndrome without Source

Utilidad de los parámetros clínicos y de laboratorio básicos para predecir infección bacteriana seria en menores de 3 meses que se hospitalizan por síndrome febril sin foco

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

The diagnosis and treatment of a child younger than 3 months with fever of unknown origin (FUO) is still controversial in clinical practice. There are several strategies and criteria to define low risk of serious bacterial infection (SBI), but there are no criteria to determine high risk children for SBI, and that include C-reactive protein value or other available biomarkers.

What does this study contribute to what is already known?

Although it was not possible to establish clinical or laboratory parameters that would allow the identification of children under 3 months at high risk of SBI, it does reaffirm their usefulness as low-risk indicators among patients hospitalized due to FUO. It is necessary to assess other clinical and laboratory elements, which would allow pediatricians to differentiate between patients at high risk of SBI from those with viral infections.

Abstract

In 20% of children with febrile syndrome, it appears as fever of unknown origin (FUO) syndrome. Management strategies in this group have high sensitivity but low specificity. **Objectives:** To characterize serious bacterial infections (SBI) in children younger than three months old hospitalized because of FUO syndrome and to evaluate the utility of clinical and laboratory parameters in the identification of patients that are at high risk of SBI. **Patients and Method:** Prospective study in

Keywords:
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patients aged < 3 months hospitalized due to FUO syndrome between January 2014 and November 2015 in two pediatric hospitals in the Metropolitan Region. Inclusion criteria: age 4 days - 3 months, fever > 38ºC longer than 72 hours after onset without demonstrable cause. Exclusion criteria: antimicrobial use up to 7 days before admission, preterm infants < 34 weeks, birth weight < 2 kg, and immunocompromised. Demographic, clinical, and laboratory tests data were recorded as well as blood count and CRP, discharge diagnosis, and ruled out, probable or confirmed SBI. **Results:** 32% of the patients were discharged with diagnosis of SBI, 28% with diagnosis of viral or probably viral infection, 34% with diagnosis of not specified FUO syndrome, and 6% due to other causes. There were no significant differences in the CRP value, altered WBCs count, toxic aspect, or hours of fever at the admission when comparing groups with and without SBI ($p < 0.05$). The combination of clinical and laboratory parameters showed 27% of sensitivity, 90% of specificity, 60% of PPV, and 71% of NPV. **Conclusion:** It was not possible to establish clinical and laboratory parameters that allow the identification of children younger than 3 months old at high risk of SBI, however, they maintain their value as low risk indicators. It is necessary further investigation of other clinical and laboratory elements that allow discriminating SBI from viral infections.

Introduction

Fever is a physiological response to infectious and non-infectious agents[1,2]. It is one of the most frequent reasons for consultation in pediatrics, accounting for 40 to 60% of emergency department consultations and between 20 and 30% of outpatient consultations[3,4].

Most of the children with fever present clinical signs of an apparent infectious focus, however, around 20% present Fever of Unknown Origin (FUO), defined as a > 38ºC fever for more than 72 hours without an evident cause after a thorough anamnesis and physical examination[5,6].

In most cases, FUO occurs due to self-limiting viral infections, however, and especially in infants under 3 months of age, these may not be clinically distinguishable from serious bacterial infections (SBI) such as occult bacteremia (OB), pneumonia, osteoarticular infection, acute bacterial meningitis (ABM), and urinary tract infection (UTI) which is the most frequent cause of SBI at all ages[5-7].

Early diagnosis of SBI is essential to reduce the morbidity and mortality associated with etiological diagnoses. However, identifying SBI in children under three months of age is difficult, since in this group the symptoms are nonspecific and can be identified in the early stages of the disease where the severity of SBI is not yet evident[11,12].

The Rochester, Boston, Philadelphia, and Pittsburgh criteria are the four strategies described for managing children with FUO under 3 months[5]. The objective of these criteria is to identify children at low risk of presenting an SBI using a combination of factors including medical record, physical examination, and basic laboratory tests, thus allowing outpatient management[13,14]. These criteria have good sensitivity but low specificity for detecting SBI, failing to diagnose even cases of AMB[15-17].

Clinically, the toxic aspect (TA) has been widely described to identify sepsis and AMB (5,8), however, TA itself has a 58.1% sensitivity and a 68.1% specificity for these infections[13].

A wide variety of hematological markers, such as white blood cell count, and biochemical ones, such as C-reactive protein (CRP) and procalcitonin (PCT), have been studied for the initial evaluation of sepsis[18]. It is therefore recommended that they be used in combination as a complement to the clinical assessment when evaluating the initial severity and follow-up of the infection[13,14].

Given this background, both the diagnosis and treatment of the child with fever under 3 months are still controversial in daily clinical practice. Although there are different strategies and criteria to define the low risk of SBI, there are no criteria to determine the high risk of SBI that include CRP value or other available biomarkers as PCT[17,19,20].

In addition, in Latin American and Chilean literature, the study of clinical and laboratory parameters in patients with FUO has been developed mainly in emergency units and covers up to 36 months of age, without specific reference to those under 3 months.

The objectives of this study are to characterize and describe the prevalence of SBI in patients under three months of age hospitalized due to FUO and to evaluate the usefulness of clinical (toxic aspect, duration of fever) and laboratory (CRP, hemogram) parameters in the identification of patients at high risk of SBI.

Patients and Method

Observational, prospective and analytical study that included all patients under 3 months of age hospitalized between January 2014 and November 2015 due to FUO in two pediatric hospitals of the Metropolitan Region, *Hospital Dr. Exequiel González Cortés* and *Hospital Dr. Luis Calvo Mackenna*, in the medical care units of Pediatric Hospitalization, Emergency Department (ED), General Pediatrics, and Intensive Care Unit. The following were considered as inclusion criteria: Patients aged between 4 days and 3 months, hospitalization due to FUO defined in the ED as a > 38ºC fever for more than 72 hours without an evident cause after a thorough anamnesis and physical examination in patients under 90 days, with laboratory tests (CBC, CRP, urinalysis, urine and blood cultures) performed or to be performed. The patients excluded were those with FUO who have not been discharged from maternity ward or neonatal unit, with history of hospitalizations, use of antimicrobials within 7 days before admission, preterm infants under 34 weeks, birth weight < 2 Kg, and immunocompromised.

Patients with FUO diagnosis were included at admission to the medical care unit and their legal guardians were asked to sign the informed consent. Subsequently, a clinical record was made for each patient, retrospectively recording demographic data, compliance with inclusion/exclusion criteria, presence of clinical signs consistent with TA and recorded in the medical care form and/or clinical record of the ED, duration, and intensity of fever (pre- and post-admission, total hours of fever, and highest temperature), CBC and CRP at admission or within the first 24 hours after hospitalization, discharge diagnosis (ruled out, probable, or confirmed SBI), and evolution during hospitalization.

All patients were treated according to the local regulations in force in each center and according to the clinical criteria of their treating physician. Data were tabulated in a Microsoft Excel spreadsheet. The study was approved by the Ethics Committees of both hospitals, which are in line with the Declaration of Helsinki.

Operational definitions

- *Serious Bacterial Infection (SBI):*
  - *Probable:* Acute febrile illness with suspected bacterial etiology determined by leukocytosis (> 15,000/mm^3), leukopenia (< 5,000/mm^3), absolute basophil count > 1,500/mm^3 [6], neutrophil count > 10,000/mm^3 [21], or in infant under 1 month: I:T ratio > 0.1, I/M > 0.2 (22.23), CRP > 90 mg/l[24], or shock during its evolution, in which it is not possible to specify a origin or isolate bacteria from sterile body fluids.
  - *Confirmed:*
    - *Bacteremia:* Positive blood culture for pathogenic bacterium (coagulase-negative staphylococci will be interpreted as contamination)[25].
    - *Urinary tract infection:* Urine culture with > 10,000 CFU's collected through intermittent catheterization, or > 100,000 CFU's collected using a bag urine collector, and abnormal urine sediment[5].
    - *Pulmonary consolidation due to pneumonia:* on chest X-ray[6].
    - *Osteoarticular infection:* well-justified clinical suspicion associated with elevated inflammatory markers. Positive findings in cultures of sterile tissue or fluid and/or in bone scan imaging[26].
    - *Bacterial meningitis:* compatible cerebrospinal fluid (Gram-positive bacteria, > 10 WBCs in patients aged between 1 and 3 months and > 20 in newborns, > 70% polymorphonuclear leukocytes, glycorrhachia < 40 mg/dL) or positive CSF culture[5].
    - *Viral or aseptic meningitis:* compatible cerebrospinal fluid (Gram-negative bacteria, > 10 WBCs in patients aged between 1 and 3 months and > 20 in newborns, with a marked presence of mononuclear cells and normal glycorrhachia > 50 mg/dL or > 50% of plasma glucose).

- *Toxic Aspect:* Clinical evaluation, within the first 24 hours after admission, presenting any of the following criteria: cyanosis, hypoactivity or lethargy, hyper- or hypoventilation, poor perfusion, tachycardia, dehydration (without pathological losses), grayish skin, marble or mottled appearance, irritability, altered state of consciousness, or hypotonia[5,6,19].

- *Altered CRP level:* In children under 28 days > 10 mg/L[27] and in patients aged between 1 and 3 months > 90 mg/L[24].

- *Altered WBC count:* leukocytosis (> 15,000/mm^3) or leukopenia (< 5,000/mm^3)[6], neutrophil count > 10,000/mm^3 [21] and absolute basophil count > 1,500/mm^3 [6], or immature-to-total neutrophil ratio (I:T) > 0.1 and immature-to-mature neutrophil ratio (I:M) > 0.2 in newborns[22,23]. The I:T formula represents the total immature neutrophils divided by the total neutrophils (segmented plus immature), while the I:M ratio corresponds to the total immature neutrophils divided by the total segmented (excluding immature).

Statistical analysis

The demographic and clinical characteristics of patients with and without SBI were analyzed as means and standard deviation or median and interquartile range depending on whether or not they followed a normal distribution, and as a percentage in the case of qualitative variables. The comparison between groups was made using the Mann-Whitney U test and Fisher exact test, considering a statistically significant $p < 0.05$ difference. Odds ratios (OR) and 95% confidence intervals (CI) were calculated for each of the possible predictor variables of SBI using logistic regression models, adjusting for potential confounders. Statistical analysis was performed using Stata 12 software.

Results

Between January 2014 and November 2015, 100 patients who met the inclusion criteria were included. The median age was 30.5 days with an interquartile range (IQR) between 17 and 46. 69% were men, 55% aged under 28 days, and most of them were admitted during autumn (39%). There were statistically significant differences in the baseline characteristics at admission of patients with and without SBI except for the type of breastfeeding and birth weight (table 1).

32% of patients were discharged with a probable and/or confirmed diagnosis of SBI, and out of which the most frequent diagnosis was UTI (78.12%), followed by bacteremia (12.5%), and omphalitis (6.2%). On the one hand, there were no patients discharged with a diagnosis of acute bacterial meningitis or pneumonia and, on the other hand, 28% of infants were discharged with a diagnosis of viral or probably viral infection, among which the most frequent diagnosis was acute gastroenteritis (17%), upper respiratory tract infection (17%), lower respiratory tract infection (17%), viral exanthem (17%), and viral meningitis (13.8%). 34% of patients were discharged with no specified FUO diagnosis and 6% of patients were discharged with FUO diagnosis due to other reasons such as overdress the child, fever after vaccination and underfeeding (table 2). There were no significant diffe-

Table 1. Baseline characteristics of study sample

	Total (n = 100)	Con SBI (n = 32)	No SBI (n = 68)	p-value
Hospital, n (%)				0.665[b]
- HEGC	58 (58.00%)	20 (62.50%)	38 (55.88%)	
- HLCM	42 (42.00%)	12 (37.50%)	30 (44.12%)	
Gender, n (%)				**0.000[b]**
- Male	69 (69.00%)	30 (93.75%)	39 (57.35%)	
- Female	31 (31.00%)	2 (6.25%)	29 (42.65 %)	
Age (days), Median (IQR)	30.5 (17-46)	42 (20.5-60)	28 (16-38)	**0.0067[a]**
Age group, n (%)				0.084[b]
- Less than 28 days	55 (55.00%)	22 (68.75%)	33 (48.53%)	
- 28 days and more	45 (45.00%)	10 (31.25%)	35 (51.47%)	
Birth weight (gr), Median (IQR)	3380 (3108-3792.5)	3499 (3290-3822.5)	3265 (3050-3702.5)	0.0515[a]
Season at admission, n (%)				**0.041[b]**
- Summer	29 (29.00%)	5 (15.62%)	24 (35.29%)	
- Autumn	39 (39.00%)	17 (53.12%)	22 (32.35%)	
- Winter	7 (7.00%)	4 (12.50%)	3 (4.41%)	
- Spring	25 (25.00%)	6 (18.75%)	19 (27.94%)	
Type of feeding, n (%)				0.578[b]
Exclusive breastfeeding	60 (60.00%)	17 (53.12%)	43 (63.24%)	
- Breastfeeding + formula	31 (31.00%)	12 (37.50%)	19 (27.94%)	
- Only formula	9 (9.00%)	3 (9.38%)	6 (8.82%)	
Vaccination at 2 months, n (%)				**0.034[b]**
- With vaccine	89 (89.00%)	25 (78.12%)	64 (94.12%)	
- Without vaccine	11 (11.00%)	7 (21.88%)	4 (5.88%)	

HEGC: Hospital Dr. Exequiel González Cortés; HLCM: Hospital Dr. Luis Calvo Mackenna; IQR: interquartile range; SBI: serious bacterial infection. p-values correspond to Mann-Whitney test (a) or Fisher exact test (b), bold font indicates statistical significance ($p < 0.05$).

rences at admission regarding the CRP level, abnormal leukocytes levels, toxic aspect, or hours of fever when comparing the groups with and without SBI ($p > 0.05$). Also, there were no significant differences when excluding probable SBI from the analysis (table 3).

Regarding the clinical evolution (table 4), the median hospital stay was 5 days (IQR 4-7), where 9% of patients required admission to the ICU, and 95% of patients required antimicrobials with a median stay of 6 days (IQR 4-10). Concerning the use of antimi-

Table 2. Discharge diagnosis

Group (% of total)			Diagnosis	n
SBI	(32%)		UTI	25
			OB	4
			Omphalitis	2
			Probable SBI	1
No SBI	(68%)	Viral or probably viral infection (28%)	AGE	5
			URTI	5
			Viral rash	5
			Viral meningitis	4
			LRTI	2
			Other	7
		Febrile syndrome due to other reasons (6%)	Underfeeding	3
			Overdress	2
			Fever after vaccination	1
		No specified febrile syndrome (34%)	-	34

SBI: serious bacterial infection; UTI: urinary tract infection; OB: Occult bacteremia; AGE: Acute gastroenteritis; URTI: upper respiratory tract infection; LRTI: lower respiratory tract infection.

Table 3. Clinical evolution of SBI and NO SBI patients

	Total (n = 100)	Con SBI (n = 32)	No SBI (n = 68)	p-value
Hospitalization days, median (IQR)	5 (4-7)	5 (4-6)	5 (4-7)	0.662[b]
Antimicrobials, n (%)	95 (95%)	32 (100%)	64 (95.52%)	1.000[b]
Antimicrobials days, median (IQR)	6 (4-10)	7 (4-10)	5.5 (4-9.5)	0.511[a]
Admission to ICU, n (%)	9 (9%)	2 (6.06%)	7 (10.45%)	0.714[b]

IQR: interquartile range; ICU: Intensive Care Unit, SBI: serious bacterial infection. p-values correspond to Mann-Whitney test[a] or Fisher exact test[b]

Table 4. Clinical and laboratory parameters

	Total (n = 100)	Con SBI (n = 32)	No SBI (n = 68)	p-value
Altered CRP, n (%)	24 (24%)	10 (31.25%)	14 (20.58%)	0.327[b]
Altered WBC, n (%)	44 (44.90%)	12 (37.5%)	32 (47.05%)	0.2840[b]
Total hours with fever, median (IQR)	18.5 (5-37.5)	19 (5-44)	18 (6-37)	0.982[a]
Toxic aspect, n (%)	22 (22%)	9 (28.13%)	13 (19.12%)	0.443[b]

SBI: serious bacterial infection; IQR: interquartile range; CRP: C-reactive protein; WBC: White blood cells. p-values correspond to Mann-Whitney test[a] or Fisher exact test[b]

Table 5. SBI predictive value of clinical and laboratory parameters

Model	Crude OR	Adjusted OR
Total hours with fever	0.999 (IC: 0.983 - 1.016)	0.995(IC: 0.977 - 1.013)
Toxic aspect	1.558 (IC: 0.587 - 4.136)	1.279 (IC: 0.451 - 3.627)
Altered CRP	1.3 (IC: 0.499 - 3.387)	1.423 (IC: 0.525 - 3.855)
Altered WBC count	0.589 (IC: 0.249 - 1.392)	0.504 (IC: 0.205 - 1.241)
Combined		
- Fever hours	0.996 (IC: 0.979 - 1.013)	0.989 (IC: 0.969 - 1.009)
- Toxic aspect	1.957 (IC: 0.692 - 5.540)	1.482 (IC: 0.494 - 4.445)
- Altered CRP	1.714 (IC: 0.609 - 4.819)	2.241 (IC: 0.741 - 6.778)
- Altered WBC	0.481 (IC: 0.192 - 1.206)	0.383 (IC: 0.145 - 1.014)

CRP: C- Reactive Protein, WBC: White blood cells. OR (odds ratio) are obtained by logistic regression models considering only the indicated variable (crude model) or adjusted (by sex, age and hospital). The model considers all the above variables in a single model (hours of fever, toxic aspect, alteration of CRP and leukocytes).

crobials, we could observe that 96% of patients of the group without SBI received this treatment. There were no statistically significant differences in the characteristics described between patients who developed and those who did not develop SBI.

To evaluate the predictive value of the laboratory and clinical parameters under study, we created logistic regression models with raw data (using only one of the predictor variables of interest) and models adjusted by age, sex, and hospital of admission. Also, we create a model that included all the variables of interest jointly and assessed the predictive value of these variables in a raw and adjusted form. In this analysis, none of the clinical and laboratory variables of interest showed a significant odds ratio (OR) to predict the development of SBI (table 5). The combination of clinical and laboratory parameters for the diagnosis of SBI showed 27% of sensitivity and 90% of specificity, with 60% of PPV and 71% of NPV.

Discussion

Just as fever is one of the main reasons for consultation in pediatric ED, the FUO is one of the entities that lead to most uncertainty in the clinician, since although there are tools to identify patients at low risk of SBI, there are no tools to reliably identify those patients who will benefit from aggressive management and differentiate them from those with viral infections that could be treated on an outpatient basis.

In this study, 100 children under the age of 3 months with FUO were included, highlighting the high proportion of male patients (69%), as well as SBI in males under three months (93.75%). This has been described in previous studies as a trend but without statistical significance[8,34,35].

When performing the adjusted statistical analysis to assess the modifying effect of sex, age range and their interaction on the variables studied, the analysis did not present a significant difference, thus it was not possible to define it as a risk factor for SBI on its own or along with other variables.

In addition, we know that febrile UTI is the main cause of FUO in children under three months of age who are hospitalized, which was also observed in this series, and which is more frequent in male patients under 30 days of age[36,37]. Considering that 55% of the total studied patients were aged less than or equal to 28 days at the time of admission, the febrile UTI diagnosis could explain the male predominance among patients who presented with SBI[38,39].

In this series, we found that the SBIs, probable and/or confirmed, represents 32% of the total. This figure is above 20% described in the international literature[5,28,29]. However, most of the studies on which this estimate is based have evaluated patients up to 36 months of age in the ED, unlike this study, which included only children under 3 months and hospitalized due to FUO.

The inclusion process of hospitalized patients may constitute a selection and naming bias that could explain the higher prevalence of SBI in our group versus those where the inclusion process occurred in the ED since patients at lower risk of SBI could be discharged from the ED with outpatient follow-up.

Among the causes of SBI, UTI is still the main cause, similar to that described in the national and international literature, where UTI represents 70-80% of SBI in children aged between 24 and 36 months[30-32]. We ob-

served a 12.1% frequency of bacteremia, higher than that described in the literature (1-2%)[8,10], and the frequency of viral infections is lower than that published[8]. This may also be due to the factors described above. An Argentinean study that included 201 patients under 24 months hospitalized due to FUO obtained similar figures to those described in our series, presenting 34.8% of patients with SBI[30].

In our series, there were no cases of bacterial pneumonia, which could be explained by the presence of clinical findings suggestive of a respiratory origin (cough, coryza, crepitation) at the time of the initial evaluation which leads to the hospitalization of these patients with a specific diagnosis and not as FUO. It is also important to emphasize the high percentage of viral meningitis in our series (13.8), which should be analyzed in the particular epidemiological national context during the second half of 2015, where there was an increase in viral meningoencephalitis cases in all age ranges[33].

Regarding clinical evolution, it is remarkable that 95% of patients received antimicrobials during 6 days (IQR 4-10) and that there are no significant differences when comparing groups with and without SBI. A study carried out in Philadelphia showed that 87% of blood cultures taken in the ED showed bacterial findings after 24 hours of incubation and 99% after 72 hours[40] while a study conducted at the *Hospital Dr. Exequiel González Cortés* showed that all pathogens identify in blood cultures of patients under 3 months with FUO were detected before 24 hours of incubation[41].

Although there are no established standards in the healthcare services participating in the study, nor is there a recommendation on observation times in children under 3 months with FUO, so the duration of antimicrobial treatment was determined by each treating physician, it is possible to suggest that 48 hours after taking blood cultures is enough to rule out OB. This makes evident a delay in the withdrawal of treatment and a delay in the discharge of patients without SBI, exposing them to a higher risk of healthcare-associated infections.

It was suggested that the symptoms and signs of TA as well as the course of the fever curve, could be predictors of increased risk of SBI, which was not demonstrated in this study.

On the one hand, a small Belgian study (n = 31) evaluated different clinical characteristics at the time of first emergency care, suggesting that these characteristics would have a role in ruling out SBI but not in confirming it[42]. On the other hand, an Australian study proposing diagnostic algorithms based on symptoms at the time of initial assessment found that some signs and symptoms alone may predict specific SBI such as UTI, bacteremia, and pneumonia[43].

In a Chilean study conducted with children under 36 months visiting the ED due to fever, the TA was an indicator of ABM and sepsis/bacteremia, but not other SBI such as UTI or pneumonia[8]. It is important to note that the definition of TA is subjective and observer-dependent and that no scales or scoring systems were used for this study.

In relation to the evaluation of laboratory parameters, traditionally, white blood cell counts < 15,000/mm, > 5,000/mm and basophils < 1,500/mm^3 are considered low risk for SBI in children aged between 1 and 3 months[5,6,34]. In a prospective study of children under 3 months with fever higher than 40ºC, those with a WBC count ≥ 15,000/mm^3 had a three times higher risk of bacteremia when comparing with those with a leukocyte count < 15,000/mm^3, with a PPV for bacteremia of only 14%[44].

In newborns, it is relevant to consider leukocyte indices above the white blood cell count. A study of 166,092 infants with suspected early-onset neonatal sepsis showed that when the values of leukocytes, total neutrophils, I:T ratio, and platelets were normal, only 0.6% of the patients had a positive blood culture, with 95% NPV. Also, the presence of decreased WBC counts, low total neutrophils, and altered I:T ratio is associated with an increased risk of positive blood culture, with 20-40% PPV[45].

There is evidence that CRP, an acute phase marker, is superior to other diagnostic tests in predicting SBI, which is more sensitive and specific than leukocyte count[24]. An Italian study of 408 children aged between 1 and 36 months showed that a CRP value > 40 mg/L has 71.3% of sensitivity and 81.2% of specificity for SBI, while a CRP > 80 mg/L has 46% of sensitivity and 94.6% of specificity18. It has been seen that in patients under 1 month the cut-off CRP values are lower and that it is a late marker with low sensitivity[45-47]. A US study of 1,136 newborns showed that high levels of CRP (> 10 mg/L) are associated with the presence of SBI in early- and late-onset neonatal sepsis[27].

With this background, we analyzed the laboratory parameters in our study sample. For this purpose, we used the cut-off values previously established in the literature in order to determine whether altered leukocyte count and/or leukocyte indices, as well as altered CRP values, could be a predictive indicator of high risk of SBI. After the analysis, there was no significant difference between those patients with confirmed or probable SBI and those without SBI in any of the parameters analyzed both individually and jointly, as well as raw and adjusted data according to age, sex, and hospital of origin, presenting sensitivities under 30%. This makes these parameters ineffective screening tools in patients hospitalized due to this cause. This result differs from a Chilean study

that evaluated the usefulness of clinical and laboratory parameters for the diagnosis of SBI in children aged between 6 weeks and 36 months, in which there were statistically significant differences between the averages CRP values, absolute neutrophil, and leukocyte counts, however, it was no possible to establish cut-off points for these parameters[31].

In our series, since the clinical and laboratory evaluation did not show significant differences between patients with and without SBI, it was not possible to conclude that its presence is indicative of the bacterial etiology of the condition. Therefore, it is not possible either to propose new algorithms for local management, which so far include hospitalization for at least 2 days and broad-spectrum antibiotic treatment while waiting for culture results, with the personal, family, and economic cost that this implies both for the patient and for the health system.

This analysis allows us to state that, out of the tools available in the public health system, none of them can predict with certainty which patients hospitalized due to FUO are at higher risk of SBI, which supports the usefulness of the low-risk criteria used to date.

Studies are currently focused on finding other biomarkers that have utility as predictors of SBI such as IL-6, IL1β and TNFα[48,49]. The measurement of PCT (compared with CRP, leukocytosis, HSV, and left shift) has proved to have a better performance regarding sensitivity and specificity to predict SBI and to be an earlier marker than CRP and, therefore, more useful in short-evolution cases[18, 49-53].

Conclusions

In this study, it was not possible to establish that the clinical and laboratory parameters used in routine clinical practice to evaluate children under 3 months of age hospitalized due to FUO could be predictive of SBI, highlighting their role as low-risk indicators given their better PPV (71%). Out of the available inflammation markers, PCT has better sensitivity than CRP, but its cut-off values are not yet well defined. Future studies with RNA biomarkers or proteomic profiles will be essential to improve the prediction of SBI and its differentiation from viral infections.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

Financial Disclosure

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