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ORIGINAL ARTICLE

Febrile syndrome in children younger than 29 days

Síndrome febril en niños menores de 29 días

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

Fever in children under 29 days of age is a red flag, which requires the detection of a serious bacterial infection, even in those patients who appear to be in good general condition and mild in severity. There is consensus to treat them as a case of sepsis and hospitalize them.

What does this study contribute to what is already known?

It describes a local experience and provides a bibliography and updated information on the subject. It highlights the importance of clinical observation and the possible influential causes for GGC and mild severity not to be good predictors of SBI.

Abstract

Acute fever of unknown origin (FUO) in children under 29 days is a worrying situation because of the risk of serious bacterial infection (SBI). **Objective:** to study the main clinical and laboratory characteristics of a group of hospitalized children under 29 days with diagnosis of FUO. **Patients and Method**: Retrospective study of children under 29 days hospitalized due to FUO. The clinical records of the patients were reviewed, recording age, sex, history of fever before consultation, temperature at admission, estimated severity at admission and discharge, discharge diagnoses, laboratory tests, and indicated treatments. Patients were classified according to the severity of the discharge diagnosis, as severe (S) and non-severe (NS). The inclusion criteria were term newborn, age less than 29 days, fever ≥ 38°C registered at home or admission, and history of < 4 days. **Results:** 468 children with FUO were admitted. Concordance between severity at admission and discharge was low (Kappa = 0.125; p = 0.0007). 26.1% of children were S and 73.9% NS. In the S group, urinary tract infection domínate (70.5%) and in the NS, FUO (67.6%). The cut-off levels for leukocytes/mm^3, C-reactive protein, and neutrophils/mm^3 showed negative predictive values to rule out severe bacterial infection. **Conclusions:** Most of the newborns presented mild severity at admission, but 24% of them had SBI, thus hospitalization and close clinical observation are always necessary. Laboratory tests, such as CRP, white blood cell and neutrophils count are not good predictors of SBI. Early treatment with antibiotics for patients who meet the low-risk criteria is debatable.

Keywords:
Fever;
Severe Bacterial Infection;
Febrile Newborn;
Acute Fever of Unknown Origin (FUO) Syndrome

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Introduction

For centuries, the population has recognized fever as an important symptom of disease, which contributes to the early medical care of febrile children, especially newborns (NB), in outpatient clinics or pediatric emergency units (PED), where fever is one of the main causes of consultation[1-4].

In studies carried out at the PED of the *Hospital Infantil Roberto del Río*, 45% of 75,000 pediatric consultations that included NBs were due to fever[1]. In the other cases, we observed that children under 29 days old accounted for 4.7% of 1,030 children under 36 months evaluated due to acute fever of unknown origin (FUO)[5] and that 48% of 550 children under 3 months old were hospitalized due to the same cause[6].

It is known that those children in this age group are immunologically immature and more susceptible to infection by microorganisms acquired during or after delivery, in the maternity ward or the community[4,6-9]. Moreover, since they are often oligosymptomatic, they may show few, if any, obvious signs of underlying disease on physical examination. It is not surprising then that, in cases of infection, fever may be the only initial sign, making difficult the early identification of severe bacterial infection (SBI) and its differentiation from non-severe ones[3-4,10-12].

Although the literature highlights that most NBs with acute FUO and good general condition (GGC) have mild and self-limited infections[3-4,7-11], due to the widespread concept that semiology in them has low sensitivity and specificity[2,8-12], GGC or the presence of an obvious viral infection[13-15] are not enough to rule out SBI such as acute bacterial meningitis (ABM), urinary tract infection (UTI), pneumonia (N), sepsis (S), acute gastroenteritis (AGE), occult bacteremia (OB), or acute osteoarthritis (AOA), which have a prevalence from 5% to 28%[12,16-24]. This information justifies highly active medical behaviors such as laboratory tests, hospitalization, and empirical and early initiation of antibiotic treatment, assuming that otherwise, the consequences for the child may be serious.

In the last decades of the 20th century, the guidelines or protocols that have been published based on epidemiological, clinical, and laboratory data, aimed at identifying patients at low risk of SBI[9], which, after being tested in children under 29 days of age, have questioned their usefulness. Some health professionals consider them unreliable and do not recommend them[25-30], unlike others[30-37] who use them as a support for deciding not to treat with antibiotics those patients who have GGC and meet the low-risk criteria.

Currently, most health professionals still respect the consensus of studying febrile NBs according to the sepsis protocol, which includes hospitalization and antibiotic treatment until the culture report is available[9,22]. There is no consensus on early antibiotic treatment. For some health professionals, those patients who present GGC and meet the low-risk criteria, do not require antibiotics; a rigorous monitoring of the clinical evolution and cultures would be sufficient, whether hospitalized[30-37] or exceptionally at home, if the parents request it[33,35] and declare themselves capable of assuming this responsibility, on the condition of maintaining telephone contact with the treating physician and return to the hospital for a medical control in the following 24 hours or sooner, in the case of cultures (+) or clinical worsening.

The objective of this work is to study the clinical and laboratory characteristics of children younger than 29 days old, hospitalized with the diagnosis of acute FUO in a Pediatric Department.

Patients and Method

A cohort of children under 29 days old successively hospitalized diagnosed with acute FUO (ICD 10 R50.9), randomly selected, between 01/1/2007 and 12/31/2015, in the Pediatrics Department of the *Hospital Clínico Roberto del Río*, in Santiago, Chile.

Patients were identified based on the daily report of pediatric hospitalizations. The inclusion criteria were term NB, aged under 29 days, and a < 4-day history of fever ≥ 38°C recorded at home or in the PED. Those patients with compromised general condition, chronic diseases, hospitalizations, and/or recent treatments (< 7 days) with antibiotics were excluded.

The study had a retrospective design, without a prior hypothesis, in order to examine this population for possible associations. A random dichotomization of the children was applied based on their severity according to the diagnosis at the discharge and, according to this diagnosis, we classified them into "severe" (S) and "not severe " (NS) for the analysis. As in a previous study[6], patients considered S were those discharged with diagnoses of Acute Bacterial Meningitis (ABM); pneumonia (N); Bacteremia occult (OB), acute Pyelonephritis (APN), Osteoarthritis (OA), acute Bacterial gastroenteritis (ABG), and Sepsis(S); and among the NS, we included the remaining patients.

The clinical records of the patients were reviewed, recording age, sex, days of fever before consultation, temperature at admission to the PED, estimated severity at admission and discharge, discharge diagnoses, laboratory tests, indicated treatments, and days of hospital stay.

We classified as "severity at admission", that estimated and recorded in the PED and the clinical history at admission to the hospital. At discharge and for all comparison purposes, we assigned the estimates "mo-

derate to severe severity" to the S and "Mild or no severity" to the NS.

We define as traumatic lumbar puncture (TLP) when counting 400 or more erythrocytes per mm^3 in the cerebrospinal fluid (CSF) and as failed lumbar puncture (FLP) when CSF was not extracted.

We posed "acute FUO" when the anamnesis and physical examination failed to identify the cause of fever. As in most studies, we consider fever when the rectal (gold standard) or axillary temperature is ≥ 38°C[9,23].

For the diagnosis of UTI, a count of ≥ 10,000 colony-forming units per mm^3 was required in urine sample collected by urinary catheterization. We considered pyuria when there were ≥ 10 leukocytes in the urine, per high-power field; as pleocytosis when ≥ 25 leukocytes were identified in CSF; and as SBI when a pathogenic microorganism was isolated in blood, urine, CSF, synovial fluid, stools, or bones.

Statistical methods

The descriptive statistics were defined using means and proportions, with their measures of dispersion, standard error, and 95% confidence intervals (SE and 95% CI). To study the possible association resulting from the comparison of already dichotomized groups, the odds ratio (OR) was used as a measure of association, with 95% CI, controlling the results according to variables with clinical meaning.

To analyze the effect of confounders on the study results, the Mantel-Haenszel stratified analysis was used. For statistical significance tests, the U-Mann Whitney test was used to compare the medians of continuous variables and the Chi-square test for proportions. For the analysis of the significance of possible confounders, the Mantel-Haenszel Chi-square test was used. To study the concordance between the assignment of "severity" at admission and the one from the discharge diagnosis, the Kappa statistic was used, using the percentage of observed concordance, its correction determined by the expected concordance by chance, and the calculation of the SE for the examination of the null hypothesis kappa = 0. For categorical variables, Fisher's exact test was used. The level of statistical significance was arbitrarily set at $p < 0.05$. The behavior study of the laboratory tests was done by constructing ROC curves, after using the cut-off points proposed locally.

This study has been approved by the Ethics and Research Committee of the North Metropolitan Health Service.

Results

468 term newborns were admitted to the study, 122 (26.1%) were in the S group and 346 (73.9%) were in the NS one. 86% of the S and 86.5% of the NS were born vaginally ($p > 0.05$), all without perinatal pathologies. 51% of the patients presented symptoms such as irritability, lack of appetite, and weakness, with no significant differences between the groups.

All NBs underwent complete blood count, blood culture, complete urinalysis, and urine culture with samples obtained by urinary catheter and, less frequently, chest X-ray (CXR) to 90% of cases, C-reactive protein (CRP) to 87.2%, LP to 70.1%, indirect immunofluorescence assay (IFA) to 80%, and stool culture + Rota-test to 12%. The patients remained in the observation area (OA) of the PED for 5 hours on average before being admitted to a crib in the pediatrics department.

The frequency of early administration of antibiotics was significantly higher in cases of TLP or FLP (OR:1.6, 95%CI:1-2.5; $p < 0.03$) and, when presenting in the blood count CRP ≥ 80mg/L (OR:8.8, 95%CI:1.2-66; $p < 0.03$); leukocytes ≥ 20,000/mm^3 (OR = 10.8, 95%CI:1.5-80; $p < 0.02$), or total neutrophils ≥ 9,500/mm^3 (OR:4.8, 95%CI:1.9-12, $p < 0.001$).

When comparing the general variables of the S and NS groups, we observed that the S were older ($p < 0.05$); the risk of severity was 2.7 times higher in males; 80% when at the admission presented temperature ≥ 38.5°C; 90% when the fever started ≥ 24 hours before consultation; 2.7 times when at admission they were classified with moderate to acute severity; 5 times when the fever continued after the first 24 hours of hospital admission; and 27 times in those hospitalized for 4 or more days (table 1). Of the NS, 62.7% were hospitalized for 48 to 72 h and 37.3% for 4 days.

To compare, moderate to acute severity is S and mild severity is NS. Out of 468 patients at admission, 422 (90.2%) were categorized as NS and 46 (9.8%) as S (table 2). On discharge, 346 (73.9%) were categorized as NS and 122 (26.1%) as S. When considering as the gold standard the severity categorization at discharge, we observed a sensitivity = 17.2 (95%CI: 10.9-25.1); specificity = 92.78 (95%CI: 89.5-95.3); predictive value (+) = 45.65 (95%CI: 32.8-59.1), and a predictive value (-) = 76.07 (95%CI: 74.4-77.6).

When using the Fisher's exact test we found that in the distribution of patients according to severity between admission and discharge, there were significant differences ($p = 0.002$), and using the Kappa coefficient, the concordance between the categorization of severity at admission and discharge was slight (Kappa = 0.125, 95%CI: 0.036-0.0214, $p = 0.0007$, $Z = 3.19$).

Table 3 describes the discharge diagnoses. Among all patients, the following stand out: acute FUO (50%), UTI (18.4%), acute URI (11.1%), sepsis (1.9%), ABM (1.7%), ABM + UTI (0.4%), and OB (1.1%). In the S group, UTI predominated (70.5%), of these 14.8%

were bacterial infections, 7.4% sepsis, and 2 children (1.6%) had simultaneous UTI + ABM. In the NS group, 67.6% were discharged with the diagnosis of acute FUO.

In order to compare the frequency of discharge diagnoses according to age, we divided the children into 2 groups, those aged ≤ 15 days and those aged > 15 days. Using Fisher's exact test, we compared the distribution of these diagnoses and observed that, in the S group, the prevalence of discharge diagnoses did not show significant differences ($p = 0.92$) but were significant in the NS group ($p < 0.001$).

Table 4 shows the cut-off values for CRP (mg/L), leukocytes and neutrophils per mm^3 used to calculate the fixed and variable indexes, considering as positive those patients with a severe diagnosis at discharge. We note that in the prevalence of SBI (0.26 or 26 %), only the specificity and the PV (-) seem "to be useful" to rule out SBI. The ROC curves obtained with the leukocyte and neutrophils count and CRP did not show a cut-off point that determines fixed indexes of clinical usefulness.

Table 5 shows the results of the blood cultures of the 468 patients. In the S group, 27/122 (22.1%) presented positive results and 12/346 (3.5%) in the NS one. In this group, 11 cases of coagulase-negative Staphylococci and one of *Streptococcus viridans* were considered as contaminants. In the S group, we highlight that 14.8% of UTIs had bacteremia. The IFA was performed in 91% of the patients in the S group and 97% in the NS one, with positive results in 9% and 3%, respectively. *Meningococcus B* was identified in two patients, one of them died due to sepsis within 12 hours of the fever onset.

Discussion

There is evidence that supports the recommendation to evaluate all febrile children younger than 29 days according to the Sepsis protocol since, at this age, fever should be interpreted as a sign that "alerts" about the risk of SBI, even when they appear to have GGC and mild severity[2,4,6-7,10,24,26-27].

Table 1. General characteristics of 468 children under 29 days old, hospitalized due to "Acute Fever Without a Focus"

Variables	G group n = 122	NG group n = 346	OR (95% CI)
Age in days			
Mean (s.d.)	16.7 (6.7)	14.2 (7.6)	p = 0.001
Sex			
Men	93 (76.2%)	189 (54.6%)	OR: 2.7 (1.7 - 4.3)
Women	29 (23.8%)	157 (45.4%)	P < 0.0001
T° at Admission (C°)			
≥ 38.5	59 (48.4%)	117 (33.8%)	1.8 (1.2 - 2.8)
< 38.5	63 (51.6%)	229 (66.2%)	p = 0.005
Fever hours at consultation			
≥ 24	63 (51.6%)	123 (35.5%)	OR: 1.9 (1.3 - 2.9)
< 24	59 (48.4%)	223 (64.5%)	p: 0.002
Severity at admission			
Moderate to serious	21 (17.2%)	25 (7.2%)	OR: 2.7 (1.4 - 5)
Mild	101 (82.8%)	321 (92.8%)	p < 0.002
Days of fever in hospital			
>1	42 (34.4%)	33 (9.5%)	OR: 5.0 (3 - 8.4)
≤ 1	80 (65.6%)	313 (90.5%)	p < 0.0001
Days in hospital			
≥ 4	115 (94.3%)	129 (37.3%)	OR: 27.6 (12.5 - 61.1)
< 4	7 (5.7%)	217 (62.7%)	p < 0.0001

95% CI: 95% confidence interval. OR: Odds ratio. G= moderate to serious severity; NG= mild severity.

Table 2. Distribución according to severity category at admission-discharge, of 468 children under 29 days old hospitalized due to "Acute Fever Without a Focus"

Admission	N°	%	Discharge	N°	%
NG	422	90.17	NG	321	76.07
			G	101	23.93
G	46	9.83	NG	25	54.35
			G	21	45.65

G= moderate to serious severity; NG= mild severity.

Table 3. Discharge diagnoses of 468 children under 29 days old, hospitalized due to "Acute Fever Without a Focus"

Discharge diagnosis	Total		G group		NG group	
	N°	%	N°	%	N°	%
Acute febrile syndrome	234	50	0	0	234	67.6
Urinary tract infection	86	18.4	86	70.5	0	0
Acute rhinopharyngitis	52	11.1	0	0	52	15
Pneumonia	17	3.6	6	4.9	11	3.2
Thirst fever	15	3.2	0	0	15	4.3
Viral exanthem	18	3.8	0	0	18	5.2
Viral meningitis	10	2.1	0	0	10	2.9
Sepsis	9	1.9	9	7.4	0	0
Bacterial meningitis	8	1.7	8	6.6	0	0
Occult bacteremia	5	1.1	5	4.1	0	0
Osteoarthritis	4	0.9	4	3.3	0	0
Acute gastroenteritis	4	0.9	1	0.8	3	0.9
Influenza A	2	0.4	0	0	2	0.6
UTI + Bacterial meningitis	2	0.4	2	1.6	0	0
Herpes simplex encephalitis	1	0.2	1	0.8	0	0
Omphalitis	1	0.2	0	0	1	0.3
Total	468	100	122	100	346	100

G = moderate to serious severity; NG = mild severity; UTI urinary tract infection.

In line with the above and in order to diagnose, our patients were initially admitted and stay for a few hours in the observation area (SO) of the PED, with the main objectives of carefully and closely monitoring the clinical evolution, collecting samples for laboratory tests, and timely administration of the first dose of antibiotics to the most serious patients or those with suspected SBI due to altered laboratory tests[38-45] and, to a lesser extent, in the case of a febrile NB.

Although it is widely known that NBs are not very symptomatic, in this retrospective study we were unable to determine this characteristic, however, nonspecific symptoms such as lack of appetite, irritability, or weakness were reported in 51% of patients, with no significant differences between the S group and the NS one. We analyzed the usefulness of fever and severity classification at admission as predictors of SBI and found that the probability of this type of infection was higher when the fever had started ≥ 24 hours before consultation (OR: 1.9) and was ≥ 38.5°C (OR: 1.8).

Regarding the severity at admission, when compared with the actual severity according to the discharge diagnosis (gold standard), we observed a significant association between both severity states, indicating that, at discharge, the percentages of NS and S patients are significantly different between patients classified as S and NS at admission. Of those classified NS at admission, 76% were discharged as NS, and of those classified S at admission, 54% were discharged as NS.

The low concordance between these severity classifications mainly affected the severe patients, since 24% of them were classified as NS at admission. The fixed indexes also showed that the severity classification at admission is not a good predictor of severe infections, but it is a good one of mild infections. So the question is why clinicians do not "buy into" the non-severity classification at admission? The answer can be inferred from what has been observed in this and other previously published studies[2-3,6,9,10,21,24], which agree that GGC and mild severity at the time of consultation do

Table 4. Usefulness of leukocytes, total neutrophils, and CRP to recognize SBI in 468 children under 29 days old, hospitalized due to "Acute Fever Without a Focus"

Test	Sensitivity	Specificity	VP (+)	VP (-)	Prevalence
Leukocytes > 20000	0.16	0.98	0.71	0.77	0.26
IC95%	(10.3 - 24.2)	(95.5 - 99)	(53 - 84.7)	(75.4 - 78.2)	(22.2 - 30.3)
Neutrophils > 9500	0.28	0.92	0.56	0.78	0.26
IC95%	(20.1 - 36.7)	(88.9 - 95)	(44.3 - 66.6)	(76.4 - 80.3)	(22.2 - 30.3)
PCR > 80	0.18	0.98	0.78	0.74	0.29
IC95%	(11.5 - 26.1)	(95.3 - 99.2)	(59.2 - 89.4)	(71.9 - 75.3)	(25.4 - 34.7)

SBI= severe bacterial infection; PV= predictive value; 95% CI= 95% confidence interval; CRP= C-reactive protein.

Table 5. Microorganisms isolated in blood cultures of 27 children under 29 days old hospitalized due to "Acute Fever Without a Focus", from the G group and according to discharge diagnosis

Pathogens	UTI	Sepsis	Meningitis	Bacteriemia	Pneumoniae	Osteoartritis	Total
Escherichia coli	13			1			14
Staphylococcus aureus						4	4
Streptococcus agalactiae		2	1	1	1		5
Enterococcus faecalis				1			1
Pasteurella multocida			1				1
Neisseria meningitidis		1	1				2
Total	13	3	3	3	1	4	27

UTI: urinary tract infection G = moderate to serious severity.

not allow ruling out SBI in children under 29 days of age.

Among the causes that explain this, we should mention the limited capacity of newborns to react with specific signs and symptoms; the lack of social interaction which, due to the general and neurological immaturity of the neonate, makes it difficult to apply the severity criteria used in older children; the short evolution of the disease at the time of consultation (61% consulted in the first 24 hours of fever and of these, 80% in the first 12 hours), and very important, the experience of the physician who participates in the *triage*, considering the general characteristics and normal behavior of the NBs.

As described in the literature[38-43], laboratory studies showed that the number of leukocytes per mm^3, total neutrophils per mm^3 and CRP mg/L, with our cut-off levels, had low sensitivity for detecting SBI, although, with the prevalence of SBI found, their better specificity and PV (-) make them less likely.

In this study, we observed that children with leukocytes count ≥ 20000 per mm^3, neutrophils ≥ 9500 per mm^3, or CRP ≥ 80mg/L were treated early with antibiotics, which we consider to be correct management because, in these circumstances, the probability of SBI is significantly higher. Some authors described that the performance of these tests as predictors of SBI is significantly better when they are performed after the first 12 hours of fever, so they recommend repeating them after that time in those patients who are not receiving antibiotics[41]. Urine and CSF analyses are necessary and can be obtained quickly, unlike cultures, which take longer[44]. We do not use procalcitonin, however, there are reports in the literature on its usefulness[45].

During hospitalization, the cause of fever was identified in 50% of the patients and they were discharged with specific diagnoses and the other 50% with a diagnosis of acute FUO, although due to their good clinical evolution, they appeared to have mild infections, probably caused by unidentified viruses, as also occurred in the cases of viral meningitis and herpes simplex encephalitis. Therefore, they were included in the NS group which, as in previous experiences[3,6,8], included most of the studied children (73.9%).

We hope that, with the new techniques for the rapid identification of a greater variety of viruses and bacteria[46], a significant number of these patients can be monitored on an outpatient basis, as occurs relatively frequently in the private health system. This would avoid the risks and costs of hospitalization and unnecessary antibiotic treatment[6] administered to 63% of the children in the NS group, who progressed satisfactorily, like 37% of those not treated. We should bear in mind that, if 48 hours after hospitalization, the patients have preserved the GGC and the cultures are still (-), antibiotics should be suspended and should be discharged with controls in the outpatient clinic.

The prevalence of SBI was 26.1%, similar to that described in the literature[9,11] although it may be lower because we included some children with unconfirmed suspicion of SBI (negative cultures). We found a high frequency of UTI (72%), of which 14.8% had bacteremia and 2 had ABM, similar to that reported in a previous study[6]. The latter, previously described by others[17-19], justifies the study of CSF in all febrile NBs, even when there is a strong suspicion of UTI. Sepsis, OB, and ABM had a low frequency.

The patients in the S group had a longer hospital stay, mainly due to parenteral antibiotic treatment, however, they had a good evolution and without complications. When comparing the distribution by discharge diagnoses in children ≤ 15 days old and > 15 days old[27], we observed that in the S group, the frequency of sepsis was higher in those ≤ 15 days old and pneumonia in those > 15 days old, but the differences

were not significant. In the NS group, we did find significant differences.

As this is a retrospective study, we had limitations, especially in the description of clinical signs, however, it allowed us to know interesting aspects, which can be contributions for future prospective research.

In conclusion, we found that NBs with acute FUO are not very symptomatic and that most of them present mild infections; however, they should be hospitalized, evaluated with the sepsis protocol, and, according to many health professionals, treated with antibiotics. If NS patients, 48 hours after hospitalization, preserve the GGC and their cultures continue (-), antibiotics should be suspended and should be discharged with outpatient control.

UTI is the most frequent SBI and can be accompanied by bacteremia and also ABM[17-18]. Mild severity and GGC at admission, as well as CRP, leukocytes, and neutrophils count per mm^3, were poor predictors of SBI. We support the strategy of carefully observing those patients meeting low-risk criteria, reserving antibiotics for those with clinical deterioration or positive cultures[33,36]. Although the frequency of ABM is low, it is important to study the CSF and improve the LP technique in order to decrease the high frequency (39.6%) of traumatic or failed LP.

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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References

1. Méndez Espínola B, Herrera P, Guerra H, Dattas JP, Muñoz B, Velasco J. Estructura de la consulta pediátrica en el Servicio de Urgencia. Hospital Infantil Roberto del Río. Rev. Chil. Pediatr 2005; 76(3):259-65.
2. Goldman R, MD, MHRM, FRGPC; Scolnik D, MD; Chauvin-Kimoff, MD, et al. Practice variations in the Treatment of Febrile Infants Among Pediatric Emergency Physicians. Pediatrics 2009; 124(2):439-45.
3. Jain S, MD, MPH; Cheng J, MD; Alpern E, MD, MSCE; at el. Management of Febrile NEONATES in US Pediatric Emergency Departments. Pediatr.2014;133:187-95.
4. Eric Bruno, MD; David Pillus, MD; David Cheng, MD; Gary Vilke, MD; Nicholas Pokrajac, MD. During the Emergency Department Evaluation of a Well-Appearing Neonate With Fever, Should Empiric Aciclovir Be Initiated? The Journal of Emergency Medicine 2018;54(2):261-5.
5. Méndez-Espinola M, Duffau G, Herrera O, Velasco J, Muñoz B. Síndrome febril Agudo sin causa aparente, en niños menores de 36 meses. Utilidad del recuento de leucocitos para la orientación etiológica en el servicio de Urgencia. Rev. Chil Pediatr 2007;78(6):623-84.
6. Méndez Espinola B; Herrera Labarca P. lactantes menores de 3 meses hospitalizados por síndrome febril. Rev. Chil. Pediatr 2015;76(3):259-65.
7. García S, Mintegi S, Gómez B, et al. Is 15 Days an Appropriate Cut- off Age for Considering Serious Bacterial Infection in the Management of Febrile Infants? Pediatr Infect Dis J 2012;31:455-8.
8. Bonadío W. Incidence of serious infections in afebrile neonates with a history of fever. Pediatr Infect Dis J 1987; 6(10):911-3.
9. Hernández D. Fever in Infants < 3 Months old: ¿What is the Current Standard? Pediatr Emerg Med Report 2011;16(1):1-15.
10. Bonadío W, MB. The history and physical assessments of the febrile infant. Pediatr Clin North Am. 1998;45(1):65-77.
11. Smitherman H, Macias C. Evaluation and management of fever in the neonates and young infant younger than three months of age. www.uptodate 2014.
12. Weber M, Carlin J, Gatchalian S, et al. Predictors of neonatal sepsis en developing countries. Pediatr Infect Dis 2003;22: 711-16.
13. Bonadío W, Huang F, Nateson S, et al. Meta-analysis to Determine Risk for Serious Bacterial Infection in Febrile Outpatient Neonates With RSV Infection. Pediatr Emerg care 2016;32(5): 286-9.
14. Byington Carrie, Enriquez F, Hoff C, et al. Serious-Bacterial Infection in Febrile Infants 1-90 Days Old With and

Without Viral Infections. Pediatrics, 2004; 113:1662-6.
15. Oray-Schrom P, Phoenix C, Martin D, Amoateng-Adjepong Y. Sepsis Workup in Febrile Infants 0-90 Days of Age With Respiratory Syncytial Virus Infection Pediatr Emerg care 2003;19(5):314-9.
16. Edward M, Backer C. Bacterial meningitis in the neonate Clinical features and diagnosis. www.uptodate 2015.
17. Wallace S, Brown D, Cruz A. Prevalence of Concomitant Acute Bacterial Meningitis in Neonates with Febrile Urinary Tract Infection: A Retrospective Cross-Sectional Study. J Pediatr 2017;184:199-203.
18. O'Donovan D. Urinary tract infections in neonates. www.uptodate 2015.
19. Bonadío W, Maida G. Urinary Tract Infection in Outpatient Febrile Infants younger than 30 Days of Age: A 10-year Evaluation. Pediatr Infect Dis J 2014;33:342-4.
20. Speer M. Neonatal pneumoniae. www.uptodate 20.
21. Edward M. Clinical features, evaluation, and diagnosis of sepsis in term and late preterm infants. www.uptodate15.
22. Backer D, Avner J. Management of fever in young infants. Evidence versus common Practice. Pediatrics 2016;138(6): e 201620.
23. Greenhow T, Hung Y, Herz A. Changing Epidemiology of Bacteremia in Infants Aged 1 Week to 3 Months. Pediatrics 2012;129:e590-6.
24. Bonsu B, Harper M. Identifying Febrile Young s with Bacteriemia: ¿Is the Peripheral White Blood Cell Count an Accurate Screen? Ann Emerg. Med. 2003; 42:216-225.
25. Schwartz S, Raveh D, Toker O, Segal G, Godovitch N, Schlesinger Y. A Weeks-by- Weeks análisis of the low-risk criteria for serious bacterial Infection in febrile neonates. Arch. Dis. Child 2009;94(4): 287.
26. Bilavsky E, Ashkenazi-Hoffnung L, Yarden-Bilavsky H, Amir J, Livni G. A search for the "Holy grail" in the evaluation of febriles neonates aged 28 days or less: a prospective study. Scand J Infect Dis.2011;43(4):264.
27. Esposito S, Rinaldi VE, Argentiero A, et al. Approach to Neonates and Young Infants With fever Without a Source. Who Are at Risk for Severe Bacterial Infection. Mediators Inflamm 2018, V2018, ID 4869329, pages 1-11.
28. Baker D, Bell L. Unpredictability of Serious Bacterial Illness in Febrile Infants from Birth to 1 months of Age. Arch. Pediatr Adolesc. Med. 1999; 153: 508-11.
29. Kadish H, Loveridge B, Tobey J, Bolte R, Cornell H. Applying Outpatient Pediatr Protocols in febrile Infants 1-28 days of Age: ¿can the Threshold Be Lowered? Clin. Pediatr. 2000;39:81-8.
30. Bhattacharjee I. Reliability of low risk criteria for serious bacterial infection in febrile neonates. An analysis. Pediatr Infect Dis 2012;4:156-9.
31. Chiu CH, Lin T Y. Aplicación de los criterios de Rochester en neonatos febriles. Pediatr Infect Dis J 1998;17:267-9.
32. Chiu CH, Lin TY, Bullard MJ. Identificación of febrile neonates unlikely to have bacterial infection. Pediatr Infect Dis J 1997;16(1):59-63.
33. Baraff L. Management of febriles neonates: ¿What to do with low risk infants? Pediatr. Infect Dis 1994;13:943-5.
34. Chiu CH, Lin TY, Bullard MJ. Application of criteria identifying febrile outpatient neonates at low risk for bacterial infection. Pediatr Infect Dis J. 1994;13(11):946-9.
35. Ferrera P, Bartfield J, Snyder H. Neonatal Fever: Utility of the Rochester Criteria in Determining Low Risk for serious Bacterial Infections. Am J Emerg med 1997;15:299-302.
36. Gómez B, Mintegi S, Bressan S, Da Dalt L, Gervaix A, Lacroix L. Validation of the "Step-by-Step" Approach in the management of Young Febrile Infant. Pediatrics 2016; 138(2):1-10.
37. Marom R, Sakran W, Antonelli J, et al. Quick identification of febrile neonates With low risk for serious bacterial Infection: an observational study. Arch Dis Child Fetal Neonatal Ed. 2007;92(1): F15-8.
38. Kupperman N, Walton E. Inmature Neutrophils in the Blood Smears of Young febrile Children. Arch Pediatr Adolesc Med 1999;153:261-6.
39. Brown L, Shaw T,Wittlake W. ¿Does leucocytosis identify bacterial infections in febrile neonates presenting to the emergency department? Emerg med J 2005;22:256-9.
40. Cuello García C, Tamez Gómez I, Valdez Ceballos J. Leucocitos en sangre, eritrosedimentación y proteína C reactiva en pacientes de 0 a 90 días de edad con fiebre sin focalización. An Pediatr (Barc) 2008;68(2):103-9.
41. Bressan S, Andreola B, Cattelan F, Zangardi T, Perilongo G, Da Dalt L. Predicting Severe Bacterial Infection in Well-Appearing Febrile Neonates: Laboratory Markers Accuracy and Duration of Fever. Pediatr Infect Dis.J 2010;29: 227-32.
42. Bonsu B, Harper M. Utility of the Peripheral blood white blood cell count for identifying sick young infants who need lumbar puncture. Ann Emerg Med. 2003;41(2):206-14.
43. Cruz AT, Mahajan P, Bonsu BK, et al. Accuracy of Complete Blood Cell Counts to Identify febrile Infants 60 Days or Younger With Invasive Bacterial Infections. Jama Pediatr. 2017; 171 (11): 1-8
44. García-Prats, Cooper T, Schneider V, Stager Ch, Hansen T. Rapid Detection of Microorganisms in Blood Cultures of newborn Infants Utilizing an Automated Blood Culture System. Pediatr. 2000; 105 (3):523-7.
45. Jacquot A, Labaune JM, Baum TP, Putet G, Picaud JC. Rapid quantitative procalcitonin measurement to diagnose nosocomial infections in newborn infants. Arch.Dis Child Fetal neonatal. 2009;94:F345-8.
46. Mahajan P, Kupperman N, Mejias A, et al. Association of RNA Biosignature With Bacterial Infections in Febrile Infants Aged 60 Days or Younger. JAMA 2016;316: 846-57.