A Prospective Multicenter Study of Leukopenia in Infants Younger Than Ninety Days With Fever Without Source

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Background: Little is known about the value of leukopenia for assessing the risk of having a bacterial infection in young febrile infants.

Methods: Infants younger than 90 days with fever without source were prospectively recruited between October 2011 and September 2013 in 19 Spanish Pediatric Emergency Departments. We analyzed the prevalence of invasive bacterial infection (IBI, positive blood or cerebrospinal fluid culture) and non-IBI (urinary tract infections and any other microbiologically confirmed bacterial infection excluding IBIs) by leukocyte count and general appearance.

Results: Among the 3401 infants recruited, 680 were diagnosed with non-IBIs (19.9%) and 107 with IBIs (3.1%). Overall, 244 infants had leukopenia (<5000 cells/mcL), 2369 a normal leukocyte count and 790 leukocytosis (>15,000 cells/mcL). Among the 3034 well-appearing patients, those with leukopenia had a lower prevalence of non-IBI [8.1% vs. 14.7%; odds ratio (OR) 0.51 (95% confidence interval (CI): 0.29–0.88)] and a similar prevalence of IBI [2.5% vs. 2.0%; OR, 1.20 (95% CI: 0.44–3.44)] compared with those with a normal leukocyte count. Among the 367 not–well-appearing infants, those with leukopenia had a similar prevalence of non-IBI [8.9% vs. 14.7%; OR, 0.57 (95% CI: 0.16–1.79)] and a higher prevalence of IBI [17.8% vs. 6.9%; OR, 2.90 (95% CI: 1.06–7.78)]. In the subgroup of well-appearing infants 22–90 days old without leukocyturia according to urine dipstick results, prevalence of both non-IBIs and IBIs was similar in patients with leukopenia and those with a normal leukocyte count.

Conclusion: Leukopenia in well-appearing young febrile infants should not be considered a risk factor for having a bacterial infection.

Key Words: young febrile infant, leukopenia, invasive bacterial infection, white blood cell count

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In the management of a febrile infant younger than 90 days, several laboratory tests are routinely performed to identify those with a higher risk of having a bacterial infection. Several studies have proven that, in this population, elevated C-reactive protein (CRP)[1] and especially elevated procalcitonin (PCT) levels are better predictors of a bacterial infection than leukocytosis.[2–4] In line with these findings, the white blood cell (WBC) count has been omitted from more recent management protocols, such as the lab score[5,6] and the step-by-step approach.[7] However, the WBC count and the band count are the only blood tests included in the classical Philadelphia[8] and Rochester[9] criteria, still in use in many Pediatric Emergency Departments (PEDs).

Previous studies have also concluded that nowadays total WBC count has limited value for screening particularly for both bacteremia and bacterial meningitis in this age group, but these authors focused specifically on the value of leukocytosis as a risk factor.[10,11] Little is known about the value of leukopenia in these patients. Moreover, while the Rochester criteria consider a WBC count <5000/mm^{3} to be an abnormal result,[9] the Philadelphia criteria do not.[8] In 2012, a retrospective single-center study including 1365 infants ≤90 days old with fever without a source (FWS) and a WBC count performed found no differences in the prevalence of bacterial infection among well-appearing infants with leukopenia and those with a normal WBC count.[12]

On the other hand, all clinical guidelines still recommend lumbar puncture, antibiotic treatment and admission for the youngest infants, even if all blood biomarker values are normal,[13–16] and hence, such values have limited impact on decisions concerning how to manage these patients. In line with this, a recent study determined that the best secondary cut-off age to identify infants ≤90 days old with a higher risk of having a bacterial infection was 21 days.[17] Similarly, young infants with a suspected urinary tract infection (UTI) because of the presence of leukocyturia will be managed in a different way to those with a normal urine dipstick. Therefore, we considered interesting to analyze the value of leukopenia among well-appearing infants >21 days old without leukocyturia, as this is the specific subgroup of patients in whom the blood test results are most likely to modify their subsequent management in clinical practice.

Our objectives were (1) to compare the prevalence of both invasive bacterial infection (IBI) and non-IBI in well-appearing infants ≤90 days old with FWS and leukopenia and in those with a normal WBC count or leukocytosis; (2) to compare these prevalence rates in the subgroup of infants 22–90 days old with a normal urine dipstick result.

MATERIALS AND METHODS

Study Design

We conducted a multicenter observational prospective study developed with the Spanish Pediatric Emergency Research Group of the Spanish Society of Pediatric Emergencies (RISeuP-SPERG) and involving 19 hospitals that are members of this research network. We included infants ≤90 days old attending the emergency departments with FWS between October 2011 and September 2013. Informed consent was requested from the parents or caregivers of the patients before including them in the study. This study was approved by the Clinical Research Ethics Committee of the Basque Country, and additionally, approval was granted by the institutional review board at each participating institution, for the study and for data sharing with the coordinating institution and with the centralized data center.

Exclusion Criteria

We excluded from the study infants meeting any of the following criteria:

(a) the medical history and/or the physical examination performed upon arrival at the PED enabled identification of the source of the fever

(b) a blood culture was not performed

(c) the urine sample for culture was not collected by an aseptic technique

(d) the WBC count was not obtained

(e) they were afebrile on arrival at the PED and fever had been subjectively assessed by parents without using a thermometer ("I felt that he/she had a temperature.").

(f) the parents or caregiver refused to participate.

Data Collection

Two standardized forms were created to be completed online using Google Drive (Google Inc., Mountain View, CA):

- A patient registration form for each infant included in the study, collecting the following data: demographic data (age and sex), the highest temperature measured at home and the temperature on arrival at the PED, time between first detection of fever and arrival at the PED, appearance of the patient on arrival at the PED, relevant medical history, results of the laboratory tests including microbiological analyses, definitive diagnosis, treatment received and site of care (managed as an outpatient or admitted).

- A second form to collect the following additional data each month concerning patients attending the PED: total number of children, total number of infants ≤90 days old and total number of febrile infants ≤90 days old (both included and excluded).

The parents or caregivers of all patients were telephoned within a month after the initial visit at the PED to check on the course of the infant after he/she was discharged from the PED.

To maintain patient confidentiality, the forms did not include any data that would have allowed identification of any patients. The research coordinator was the only person who had access to the 2 resulting online databases and was responsible for downloading regular backups of both databases and reviewing them for possible errors in data entry. The participating researcher in each center was responsible for reviewing episodes with potential errors.

Definitions

- FWS: axillary or rectal temperature ≥38°C (100.4°F) measured either at home or at the PED, in patients who had a normal physical examination and did not have catarrhal or other respiratory signs/symptoms (such as tachypnea) or a diarrheal process.

- Previously healthy: to be classified as previously healthy, the patient was required to meet all the following criteria: born at term (after ≥37 weeks of gestation), not treated for unexplained hyperbilirubinemia, not hospitalized longer than the mother, was not receiving and had not received antimicrobial therapy, no previous hospitalization and no chronic or underlying illness.

- Well appearing: defined by a normal Pediatric Assessment Triangle in the case of hospitals in which these data are systematically recorded in the pediatric medical records. For the other departments, infants were considered not to be well appearing if the findings of the physical examination documented in the medical record indicated any clinical suspicion of sepsis. These finding included but were not limited to "ill appearing," "irritable," "cyanosis," "hypotonic" and "cutis marmorata."

- IBI: isolation of a bacterial pathogen in a blood or cerebrospinal fluid culture and any other isolation of a single pathogen in fluids from normally sterile sites, such as pleural or synovial fluids. *Staphylococcus epidermidis*, *Propionibacterium acnes*, *Streptococcus viridans* or *Diphtheroides* were considered contaminants when isolated in immunocompetent patients without heart disease, ventriculoperitoneal shunt, central catheters or other indwelling devices.

- Non-IBI: this definition includes UTIs and bacterial gastroenteritis (with isolation of bacteria in stool culture).

- UTI: growth of ≥100 CFU/mL of a single pathogen cultured from urine collected by suprapubic aspiration, ≥10,000 CFU/mL cultured from urine collected by urethral catheterization together with leukocyturia and/or nitrituria or ≥50,000 CFU/mL cultured from urine collected by urethral catheterization, regardless of the result of the urine dipstick test.

- WBC count groups:
  - leukopenia: <5000/mm^3
  - normal WBC count: between 5000 and 15,000/mm^3
  - leukocytosis: >15,000/mm^3

Statistical Analysis

Normally distributed data were expressed as mean ± standard deviation and non-normally distributed data as median and interquartile range, whereas categorical variables were reported as percentages. Normal or non-normal distribution was determined using Kolmogorov–Smirnov test. The prevalence of bacterial infection in the different subgroups was compared using the χ^2 test. Relative risks (RRs) for having a bacterial infection were calculated for patients with leukopenia and those with leukocytosis, using those with a normal WBC count as the reference group. Sensitivity, specificity, positive predictive value and negative predictive value of leukopenia to identify infants with a bacterial infection were also calculated. The statistical analysis was carried out using the IBM SPSS Statistics for Windows (version 21, Armonk, NY).

RESULTS

During the study period, 1,612,212 children attended the 19 participating PEDs, including 4008 infants ≤90 days old with FWS (0.24%). After applying the exclusion criteria, 3401 (84.8%) infants were finally included in our analysis (Fig. 1). Median age of the infants was 46 days (18.2% were ≤21 days old) and 59.7% were boys. Median time since detection of fever was 5 hours (interquartile range: 2–12 hours). In relation to their past medical history, 86.4% of the included infants were considered previously healthy.

Overall, 784 infants (23.0%) were diagnosed with a bacterial infection: 107 (3.1%) of them with an IBI (38 bacteremic UTIs, 31 occult bacteremias, 20 sepsis, 17 bacterial meningitis and 1 adenitis with bacteremia associated) and 677 (19.9%) with a non-IBI (666 UTIs without bacteremia, 9 bacterial gastroenteritis and 2 omphalitis). *Escherichia coli* was the leading cause of IBI (45.7%), followed by *Streptococcus agalactiae* (22.4%) and *Staphylococcus aureus* (8.4%); whereas there were only 2 IBIs because of *Listeria monocytogenes* (1.8%). *E. coli* was the leading cause of nonbacteremic UTI (84.1%). Among the 3401 patients studied, 2368 (69.6%) had a normal WBC count, 243 (7.1%) had leukopenia and 790 (23.2%) had leukocytosis. The relation between the prevalence of bacterial infection and the WBC count result was influenced by the general appearance. Table 1 shows the prevalence of both IBI and non-IBI in the overall sample and in the subgroups of well-appearing and not–well-appearing infants by WBC count. Well-appearing patients with leukopenia had the same risk of having an IBI as those with a normal WBC count and
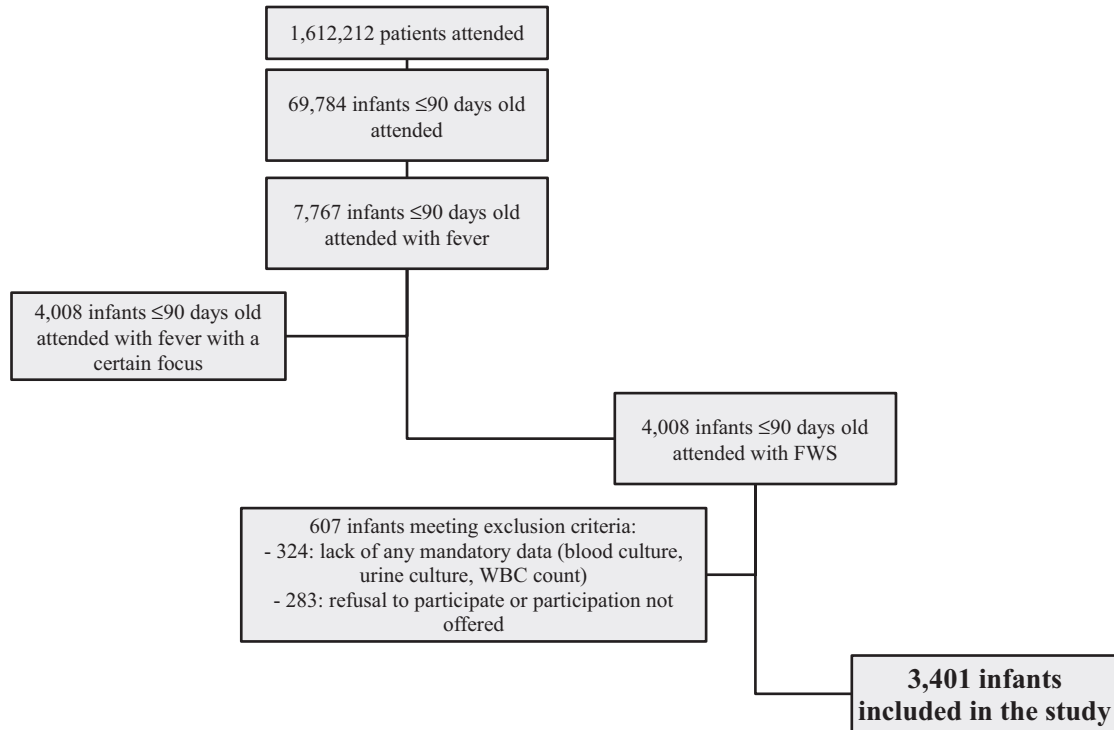
FIGURE 1. Flow of patients through the selection process.

had a lower prevalence of non-IBIs [relative risk (RR), 0.55 (95% confidence interval (CI): 0.34–0.89)]. Among not–well-appearing infants, the presence of leukopenia did not increase the risk of having a non-IBI but did increase the risk of having an IBI [RR, 2.56 (95% CI: 1.18–5.58)].

    Among the 1934 well-appearing infants >21 days old without leukocyturia (56.8% of the overall sample), 97 patients (5%) were diagnosed with a bacterial infection, including 22 IBIs (1.1%: 15 occult bacteremias, 3 sepsis, 2 bacterial meningitis and 2 bacteremic UTIs). Table 2 presents the prevalence of bacterial infection for each subgroup. Infants with leukopenia had a similar prevalence of both non-IBI and IBI to those with a normal

WBC count. In this subgroup of well-appearing infants >21 days old without leukocyturia, we also performed a multivariate analysis to ascertain whether lumbar puncture was more frequently performed in infants with leukopenia and whether such patients were more frequently admitted. After adjusting for PCT (<0.5 or ≥0.5 ng/mL) and CRP (≤20 or >20 g/dL) levels, leukopenia remained an independent risk factor for both performing a lumbar puncture (OR: 2.1; 95% CI: 1.3–3.5) and admission (OR: 2.6; 95% CI: 1.8–3.8). Table 3 shows the sensitivity, specificity and positive and negative predictive values of leukopenia to identify infants with a bacterial infection in the different analyzed subgroups.

TABLE 1. Prevalence of Categories of Bacterial Infection by WBC Result and RRs for Presenting a Bacterial Infection in Infants With an Abnormal WBC Count

	All the Bacterial Infections		IBIs		Non-IBIs	
	Prevalence, % (95% CI, in %)	RR (95% CI)	Prevalence, % (95% CI, in %)	RR (95% CI)	Prevalence, % (95% CI, in %)	RR (95% CI)
All infants (n = 3401)						
Leukopenia (n = 243)	13.6 (9.2–17.8)	0.79 (0.57–1.10)	5.3 (2.5–8.1)	2.15 (1.20–3.86)	8.2 (4.7–11.6)	0.56 (0.36–0.86)
Normal WBC count (n = 2368)	17.2 (15.7–18.7)	—	2.5 (1.8–3.1)	—	14.7 (13.3–16.1)	—
Leukocytosis (n = 790)	43.4 (38.1–48.6)	2.52 (2.24–2.84)	4.4 (2.9–5.8)	1.78 (1.18–2.68)	39.0 (34.9–42.1)	2.65 (2.32–3.01)
Well-appearing infants (n = 3034)						
Leukopenia (n = 198)	10.6 (6.3–14.8)	0.63 (0.42–0.96)	2.5 (0.3–4.7)	1.28 (0.51–3.19)	8.1 (4.2–11.8)	0.55 (0.34–0.89)
Normal WBC count (n = 2123)	16.7 (12.8–20.6)	—	2.0 (1.3–2.5)	—	14.7 (13.2–16.2)	—
Leukocytosis (n = 713)	43.2 (39.5–46.8)	2.58 (2.28–2.93)	3.9 (2.5–5.3)	1.99 (1.24–3.18)	39.3 (35.6–42.8)	2.66 (2.32–3.06)
Not–well-appearing (n = 367)						
Leukopenia (n = 45)	26.7 (13.7–39.5)	1.23 (0.72–2.12)	17.8 (6.6–28.9)	2.56 (1.18–5.58)	8.9 (0.5–17.2)	0.60 (0.23–1.62)
Normal WBC count (n = 245)	21.6 (16.4–26.7)	—	6.9 (3.7–10.1)	—	14.7 (10.2–19.1)	—
Leukocytosis (n = 77)	45.5 (34.3–56.5)	2.10 (1.49–2.96)	9.1 (2.6–15.5)	1.31 (0.56–3.04)	36.4 (25.6–47.1)	2.47 (1.62–3.78)

TABLE 2. Prevalence of Categories of Bacterial Infection Among the 1934 Well-appearing Infants >21 Days Old Without Leukocyturia on Urine Dipstick Testing by WBC Result and RRs for Presenting a Bacterial Infection in Infants With an Abnormal WBC Count

	All the Bacterial Infections		IBIs		Non-IBIs	
	Prevalence, % (95% CI, in %)	RR (95% CI)	Prevalence, % (95% CI, in %)	RR (95% CI)	Prevalence, % (95% CI, in %)	RR (95% CI)
Leukopenia (n = 156)	3.2 (0.4–5.9)	0.68 (0.28–1.65)	1.3 (0–3.0)	1.24 (0.29–5.39)	1.9 (0–4.0)	0.52 (0.16–1.64)
Normal WBC count (n = 1455)	4.7 (3.6–5.8)	—	1.0 (0.5–1.5)	—	3.7 (2.7–4.6)	—
Leukocytosis (n = 323)	7.1 (4.3–9.9)	1.50 (0.95–2.37)	1.5 (0.2–2.8)	1.50 (0.55–4.10)	5.6 (3.1–8.0)	1.50 (0.89–2.52)

TABLE 3. Test Performance of Leukopenia Compared with a Normal WBC Count in the Global Study Population and in the Different Evaluated Subgroups

	All the Bacterial Infections	IBIs	Non-IBIs
All the infants (n = 3401)	S: 7.5%; SP: 90.3%; PPV: 13.6%; NPV: 8.8%	S: 18.1%; SP: 90.9%; PPV: 5.3%; NPV: 97.5%	S: 5.4%; SP: 90.1%; PPV: 8.2%; NPV: 85.1%
Not–well-appearing infants (n = 367)	S: 18.5%; SP: 85.3%; PPV: 26.7%; NPV: 78.4%	S: 32.0%; SP: 86.0%; PPV: 17.8%; NPV: 93.1%	S: 10.0%; SP: 83.6%; PPV: 8.9%; NPV: 85.3%
Well-appearing infants (n = 3034)	S: 5.6%; SP: 90.9%; PPV: 10.6%; NPV: 83.3%	S: 10.6%; SP: 91.5%; PPV: 2.5%; NPV: 98.0%	S: 4.9%; SP: 90.9%; PPV: 8.1%; NPV: 85.3%
Well-appearing infants >21-day-old without leukocyturia (n = 1934)	S: 6.8%; SP: 90.2%; PPV: 3.2%; NPV: 95.3%	S: 11.8%; SP: 90.3%; PPV: 1.3%; NPV: 99.0%	S: 5.3%; SP: 90.2%; PPV: 1.9%; NPV: 96.3%

S indicates sensitivity; SP, specificity; PPV, positive predictive value; and NPV, negative predictive value.

There were 2 cases of IBIs among the 156 well-appearing infants without leukocyturia and with leukopenia: a 30-day-old boy with an occult bacteremia because of *Enterococcus faecalis* (4770 leukocytes/mm³; CRP, 9.5 mg/L; PCT, 0.05 ng/mL) and a 44-day-old boy with a UTI because of *E. coli* together with bacteremia (3000 leukocytes/mm³; CRP, 26.7 mg/L; PCT, 0.13 ng/mL).

Analyzing separately the 462 infants classified as not previously healthy, we obtained similar results as those obtained in the global population. Well-appearing patients with leukopenia had the same risk of having both an IBI and a non-IBI than those with a normal WBC count.

DISCUSSION

Our results confirm the findings of our preliminary retrospective single-center study and show that leukopenia should not be considered a risk factor neither for having an IBI nor for having a non-IBI in well-appearing infants ≤90 days old with FWS.

Recent studies have concluded that biomarkers such as CRP and especially the PCT are much more useful than the WBC count for identifying young infants at a higher risk of having a bacterial infection.[1–4] However, the WBC count is probably still the most frequently requested blood test when managing young febrile infants in the PED. Probably, there are 2 main reasons for this. First, the new biomarkers, particularly PCT, are not available in all PEDs. Although PCT is increasingly widely used in European PEDs, it is still not in use in most PEDs in the US. Second, the WBC count and the band count are the only 2 blood biomarkers included in the classical clinical guidelines (such as the Rochester criteria and Philadelphia criteria),[8,9] and these are still in use, despite being developed more than 25 years ago.

Previous research indicating a poor accuracy of the WBC count when compared with other blood biomarkers has focused only on leukocytosis. In contrast, a recent study analyzing the value of the WBC count in identifying late-onset neonatal sepsis found that both a high and a low WBC count were associated with a higher rate of late-onset neonatal sepsis.[18] However, this study included infants admitted in a neonatal unit (mean gestational age of 29.6 weeks) rather than infants attending a PED, and the associations were weaker with increasing postnatal age and with increasing gestational age. Indeed, no association was found between a low WBC count and a higher risk of sepsis in infants with a postnatal age more than 30 days. Other studies published concerning the value of the WBC count in infants admitted in neonatal units, focusing on low-birth weight infants or neonates at risk of septicemia, concluded that an abnormal WBC count has a poor positive predictive value,[19] and that CRP is a better blood biomarker after 3 days of life. Nevertheless, little is known about the value of the leukopenia in young infants seen in the PED with FWS.

As we have mentioned, in clinical practice, many pediatricians manage patients with leukopenia more aggressively than those with a normal WBC count. According to our results, this does not seem to be necessary. Well-appearing infants with leukopenia had the same prevalence of IBI as those with a normal WBC count and actually a lower prevalence of non-IBI. In contrast, in not–well-appearing infants, leukopenia did increase the risk of having an IBI. Indeed, leukopenia is considered to be a risk factor for poor outcome in patients with sepsis.[20] Nevertheless, not–well-appearing infants with FWS will be managed aggressively, in any case, regardless the results of any ancillary test.

As noted previously, there are some other data that, taken alone, increase the risk of a bacterial infection and that are easy to evaluate before performing blood tests, such as the age and the urine dipstick result. The secondary cut-off age of 21 days found by Garcia et al[17] to identify an even higher risk subgroup of infants is also proposed in the step-by-step approach, a management protocol recently evaluated in a European multicenter study.[7] Given this, we performed a secondary analysis exploring the value of the leukopenia in the subgroup of well-appearing infants outside the first 3 weeks of life without leukocyturia. These are the infants in whom the blood test results have a marked impact on decisions concerning the management of the patient, in terms of hospital admission,

administration of antibiotics and the performance of more invasive tests, such as lumbar puncture. In this analysis, infants with leukopenia had the same prevalence of both IBI and non-IBI as those with normal WBC count.

Regarding leukocytosis, infants with an elevated WBC count presented a higher prevalence of IBI and non-IBI in the overall sample, but once again, there were no differences in the subgroup of well-appearing infants 22–90 days old with a negative urine dipstick.

The changes observed over the last decade in the epidemiology of bacterial infections in this age group could partially explain why the WBC count, included in the classical guidelines, is not useful nowadays for identifying at-risk groups of young febrile infants. Specifically, recent studies have demonstrated a shift in the bacterial species involved.[21,22] *L. monocytogenes*, classically considered 1 of the main pathogens in young infants, is nowadays an infrequent cause of bacterial infections in this age group. These studies have also shown that *E. coli* has replaced *S. agalactiae* as the leading cause of late-onset bacteremia among young infants, mainly related to UTIs. These patterns are also reflected in our sample.

The main limitation of our study is that, as we have seen, the value of leukopenia for identifying patients with a higher risk of having a bacterial infection depends on general appearance. In many but not all the participating hospitals, appearance was evaluated by experienced triage nurses or by the pediatric emergency physician in charge using the Pediatric Assessment Triangle, a rapid tool recommended by the American Academy of Pediatrics to assess the first general impression of any child. Appearance, work of breathing and circulation to the skin are assessed using specific predefined physical, visual and/or auditory findings. Given this, our results cannot be extrapolated to hospitals where patients are assessed by less experienced personnel, who may not make a correct assessment of the general appearance.

We conclude that well-appearing infants ≤90 days old with FWS and leukopenia can be managed in a similar way to those with a normal WBC count, avoiding unnecessary admissions and use of antibiotics when this is the only abnormal blood biomarker.

ACKNOWLEDGMENTS

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