Validation of the "Step-by-Step" Approach in the Management of Young Febrile Infants

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abstract

BACKGROUND: A sequential approach to young febrile infants on the basis of clinical and laboratory parameters, including procalcitonin, was recently described as an accurate tool in identifying patients at risk for invasive bacterial infection (IBI). Our aim was to prospectively validate the Step-by-Step approach and compare it with the Rochester criteria and the Lab-score.

METHODS: Prospective study including infants ≤90 days with fever without source presenting in 11 European pediatric emergency departments between September 2012 and August 2014. The accuracy of the Step-by-Step approach, the Rochester criteria, and the Lab-score in identifying patients at low risk of IBI (isolation of a bacterial pathogen in a blood or cerebrospinal fluid culture) was compared.

RESULTS: Eighty-seven of 2185 infants (4.0%) were diagnosed with an IBI. The prevalence of IBI was significantly higher in infants classified as high risk or intermediate risk according to the Step by Step than in low risk patients. Sensitivity and negative predictive value for ruling out an IBI were 92.0% and 99.3% for the Step by Step, 81.6% and 98.3% for the Rochester criteria, and 59.8% and 98.1% for the Lab-score. Seven infants with an IBI were misclassified by the Step by Step, 16 by Rochester criteria, and 35 by the Lab-score.

CONCLUSIONS: We validated the Step by Step as a valuable tool for the management of infants with fever without source in the emergency department and confirmed its superior accuracy in identifying patients at low risk of IBI, compared with the Rochester criteria and the Lab-score.

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Dr Gomez conceptualized and designed the study, developed the design of the data collection forms, coordinated and supervised data collection, carried out the analyses, and drafted the initial manuscript; Dr Mintegi conceptualized and designed the study, collaborated in the revision of the data, and reviewed and revised the manuscript; Dr Bressan conceptualized and designed the study, was involved in data collection, and reviewed and revised the manuscript; Drs Da Dalt and Gervaix were involved in the design of the study, were involved in data collection, and reviewed and revised the manuscript; Dr Lacroix was involved in data collection and reviewed and revised the manuscript; and all authors approved the final manuscript as submitted.

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WHAT'S KNOWN ON THIS SUBJECT: A sequential approach to young febrile infants on the basis of clinical and laboratory parameters, including procalcitonin, was recently described. When applied to retrospectively collected data, this tool revealed a good accuracy in identifying patients at low risk of invasive bacterial infection.

WHAT THIS STUDY ADDS: This prospective validation of the Step-by-Step algorithm reveals better sensitivity than the Rochester criteria or the laboratory score to identify low risk patients suitable for outpatient management. It is a useful tool for managing febrile infants in the emergency department.

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In the last 2 decades, several studies have been conducted to find the best set of criteria to identify those young febrile infants who are at a low risk of having a bacterial infection. These infants are candidates for outpatient management without receiving empirical antibiotic treatment. Since the classic Rochester,[1] Philadelphia,[2] and Boston[3] criteria were published, the management of infants younger than 90 days old with fever without source (FWS) has evolved. Regardless of the protocol used, current adherence to any of them in clinical practice is low.[4,5] Changes in the epidemiology of bacterial pathogens in the last decades[6,7] and introduction of biomarkers such as C-reactive protein (CRP) and, more recently, procalcitonin (PCT) could justify this low adherence rate and make several authors advocate for a more individualized approach. The latter includes new biomarkers and a reduction in lumbar puncture rates, antibiotic treatments, or in-hospital admission for many well-appearing infants outside the neonatal period.[8–10]

The "Step by Step" is a new algorithm developed by a European group of pediatric emergency physicians. Its primary objective was to identify a low risk group of infants who could be safely managed as outpatients without lumbar puncture nor empirical antibiotic treatment. This approach (Fig 1) evaluates sequentially the general appearance of the infant, the age, and result of the urinalysis and, lastly, the results of blood biomarkers, including PCT, CRP, and absolute neutrophil count (ANC). We retrospectively tested the Step-by-Step approach in 1123 infants[11] and found that it is able to accurately identify different groups of patients according to their risk of suffering from a noninvasive or invasive bacterial infection (IBI). In addition, this approach seemed to better identify low risk patients suitable for an outpatient management compared with the Rochester criteria or the more recently developed Lab-score.[12,13]

The objective of this study was to prospectively validate these results in a larger multicenter population.

METHODS

Study Design

We conducted a multicenter prospective study including 11 European pediatric emergency departments (PEDs): 8 Spanish, 2 Italian, and 1 Swiss centers. Infants ≤90 days old attending with FWS between September 2012 and August 2014 were included. This study was approved by the Clinical Research Ethics Committee of the Basque Country and by the institutional review board at each study site. Written informed consent was requested from the parents or caregivers of the patient.

After data collection, the Step-by-Step approach was applied to the study sample to analyze its accuracy. The Rochester criteria and the Lab-score were also applied, and the diagnostic performances of the 3 sets of criteria were compared (Supplemental Table 6).

Clinical Management of the Patients

A urine dipstick, a urine culture collected by an aseptic technique (bladder catheterization or suprapubic aspiration), white blood cell (WBC) count, CRP, PCT, and a blood culture were requested for each patient. The decision to perform any other test was made at the discretion of the physician in charge. The patients were admitted and/or received antibiotic treatment according to the management protocol of each center.

Exclusion Criteria

1. Clear source of fever identified after a careful medical history and/or physical examination in the PED.
2. No fever on arrival at the PED and fever that had been only subjectively assessed by parents on touch, without the use of a thermometer.
3. Absence of 1 or more of the mandatory ancillary tests (blood culture, urine culture collected by an aseptic technique, urine dipstick, PCT, CRP, or WBC count).
4. Refusal of the parents or caregiver to participate

Data Collection

Deidentified data were collected through a standardized electronic form to be completed online and included age, sex, duration and degree of fever, general appearance of the patient on arrival at the PED, relevant medical history, results of laboratory tests, diagnosis, treatment, and site of care (managed as outpatient or admitted). The parents or caregivers of those infants managed as outpatients received a follow-up telephone call within 1 month after the initial visit at the PED to check the course of the episode. In case that after 3 telephone calls, it was not possible to contact with the caregivers, the electronic registries of the PED and the Public Health System were used to identify and review any posterior visit to the primary care center or to any other hospital.

Definitions

- FWS: Temperature measured at home or at the PED ≥38°C, in patients with a normal physical examination and no respiratory signs/symptoms or a diarrheal process.
- Previously healthy infant: born at term, not treated for unexplained hyperbilirubinemia, not hospitalized longer than the mother, not receiving current or previous antimicrobial therapy, no

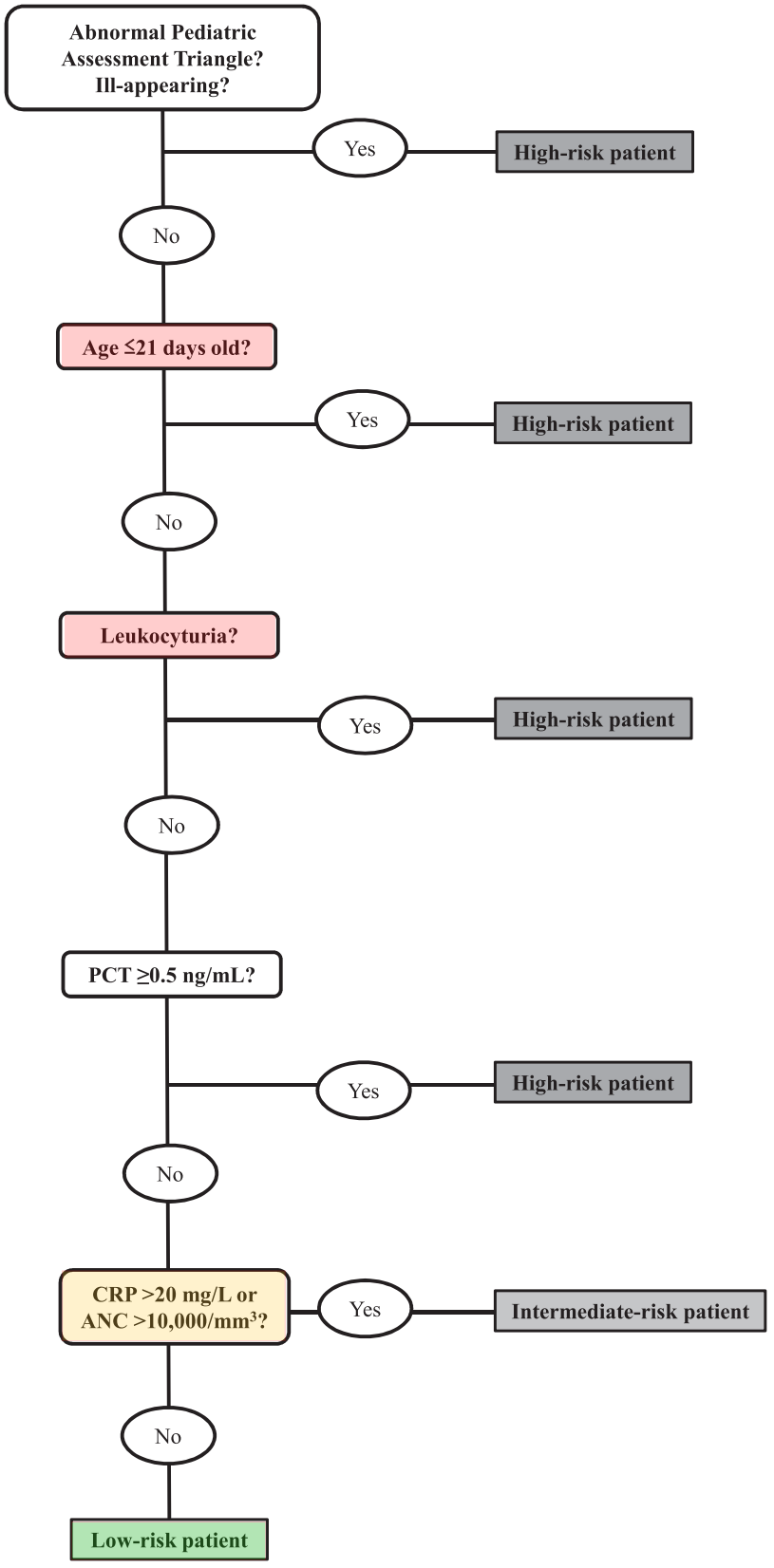

FIGURE 1
The Step-by-Step approach.

previous hospitalization, and no chronic or underlying illness.

- Well-appearing: Defined by a normal Pediatric Assessment Triangle[14] in those PEDs in which this data are systematically recorded. For the other PEDs, infants were considered as not well-appearing if the findings of the physical examination documented in the medical record indicated any clinical suspicion of sepsis.
- IBI: Isolation of a bacterial pathogen in a blood or cerebrospinal fluid culture. *Staphylococcus epidermidis, Propionibacterium acnes, Streptococcus viridans*, or *Diphtheroides* were considered contaminants.
- Non-IBI: Urinary tract infections (UTIs; urine culture with growth of ≥10 000 cfu/mL with leukocyturia associated) and bacterial gastroenteritis (isolation of bacteria in stool culture). When a registered patient received a diagnosis highly suggestive of having a bacterial etiology but with no positive bacterial culture, the case was discussed among the principal investigators to decide the most appropriate classification.
- Possible bacterial infection: Infants classified as possible UTI (positive urine culture without leukocyturia) and those finally diagnosed with a pneumonia or an acute otitis media with no positive bacterial culture.
- Sepsis: We used the sepsis criteria published by Goldstein et al[15] with only the following modification: Well-appearing patients with fever and leukocytosis were not diagnosed with a sepsis if they did not have any other sepsis criteria (tachycardia, bradycardia, tachypnea, or signs of organ dysfunction).
- Occult bacteremia: Presence of a pathogenic bacterium in the blood of a well-appearing infant with FWS.

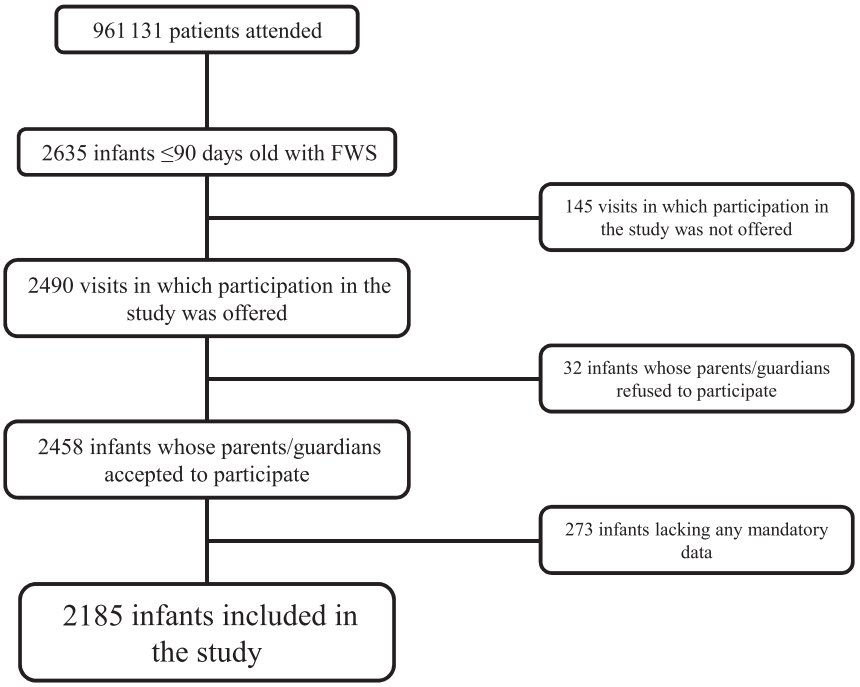

FIGURE 2
Flow diagram to indicate the included and excluded patients.

TABLE 1 Epidemiologic and Clinical Characteristics, Complementary Tests, and Management of Patients

Age (median and interquartile range), d	47 (29–65)
≤21 d old, %	16.7
Sex (boy), %	59.5
Duration of fever (median and interquartile range), h[a]	5 (2–12)
Highest temperature measured at home (median and interquartile range), °C[b]	38.5 (38–38.8)
Temperature upon arrival to the PED (median and interquartile range), °C[c]	38.1 (37.8–38.5)
Previously healthy, %	85.9
Classified as well appearing, %	87.7
PCT, CRP, WBC count, urine dipstick, urine culture collected by sterile method, blood culture, %	100
Lumbar puncture performed, %	27.4
Flu test, %	12.5
Antibiotic treatment, %	49.0
Admitted, %	58.5
Pediatric/neonatal ICU	1.6

[a] Evolution time was available in 2103 patients.
[b] Highest temperature measured at home was recorded in 2019 patients.
[c] Temperature upon arrival to the PED was recorded in 2174 patients.

Statistical Analysis

Normally distributed data were expressed as mean ± SD, nonnormally distributed data as median and interquartile range, and categorical variables were reported as percentages. We calculated the relative risk (RR) for presenting an IBI or a non-IBI in those infants presenting the risk factor evaluated on each step.

To compare the performance of this approach with the Rochester criteria and the Lab-score, we calculated the prevalence of IBI and non-IBI and the 95% confidence interval (95% CI) among those infants classified as low risk patients according to each protocol. We also calculated the sensitivity, specificity, positive and negative predictive values (PPVs and NPVs) and positive and negative likelihood ratios (LRs) of the low risk criteria used on each protocol and the IBI missed according to each of the 3 approaches.

The statistical analysis was carried out using the IBM SPSS Statistics for Windows (version 21; IBM SPSS Statistics, IBM Corporation).

RESULTS

Overall, 966 413 patients attended, including 2635 infants ≤90 days old with FWS (0.27%). Of them, 2185 infants (82.9%) were finally included in the study (Fig 2). Table 1 reports descriptive statistics for the main epidemiologic variables, complementary tests performed, and initial management. Of the 2185 included infants, 504 were diagnosed with a bacterial infection (23.1%), including 87 patients (3.9%) with an IBI and 417 (19.1%) with a non-IBI (Table 2). = valeur pré-test!

Applying the Step-by-Step approach, the prevalence of IBI and non-IBI in the different subgroups of patients is shown in Fig 3, as well as the corresponding RR for patients with each risk factor. The first part of the algorithm (evaluating general appearance, age, and presence of leukocyturia) identified 79.3% of the IBI (including 22 of 26 patients with sepsis and 9 of 10 with bacterial meningitis) and 98.5% of the non-IBI.

After taking into account PCT, CRP, and ANC values, we identified a subgroup of 991 low risk infants (45.3% of the studied population) with a prevalence of IBI of 0.7%. Supplemental Table 7 reveals the characteristics and initial management of the 7 infants who would have been classified as low risk patients and who were finally diagnosed with an IBI.

Nine other infants were diagnosed with a clinical sepsis without microbiological confirmation and 2 with a viral sepsis. All of them would

have been identified by the general appearance and age criteria.

Prevalence of bacterial infection among infants classified as low risk patients according to each set of criteria and number of IBIs that would have been misclassified are shown in Table 3. Prevalence of potentially missed IBI was higher when using the Lab-score or the Rochester criteria than the Step by Step ($P < .05$). Prevalence of non-IBI was also higher but differences only reach statistical significance when compared with the Lab-score. Prevalence of possible bacterial infection was similar in all the risk groups. Number needed to test with the Step by Step instead of with the Rochester criteria or the Lab-score to avoid missing an IBI was 102 infants and 81 infants, respectively. Table 4 reveals the diagnostic accuracy measures for each of the 3 approaches for identifying IBIs. The Step by Step had the lowest negative LR (0.17).

To compare specifically the performance of the complementary tests recommended by each set of criteria, we performed an "ad hoc" secondary analysis on those infants who met none of the clinical risk factors included in any of the 3 approaches (ie, well-appearing and previously healthy infants older than 28 days old). Although no lower age cutoff is defined by Rochester criteria, the Lab-score was validated for infants older than 7 days old, and the Step by Step considers 21 days old as a high risk cutoff. However, in clinical practice, and regardless of the protocol used, infants younger than 28 days old are usually more aggressively managed. Our results revealed that the Step by Step confirmed to be the most accurate tool of the 3 analyzed strategies to identify children at low risk of IBI (Table 5).

TABLE 2 Bacterial Infections Diagnosed

IBIs	87 (3.9%)
Bacterial sepsis	26
Bacteremic UTI	25
Occult bacteremia	24
Bacterial meningitis	10
Cellulitis-adenitis syndrome with bacteremia	1
Septic arthritis	1
Non-IBI	417 (19.1%)
UTI	409
Bacterial gastroenteritis	5
Cellulitis-adenitis syndrome with negative cultures	1
Omphalitis with negative cultures	1
Myositis with negative cultures	1
Possible bacterial infections	98 (4.5%)
Possible UTI (positive urine culture without leukocyturia)	88
Pneumonia with negative cultures	7
Acute otitis media with negative cultures	3

DISCUSSION

Our results validate the Step-by-Step approach as an accurate tool to identify subgroups of young infants with FWS at different risk of IBI.

This approach includes both clinical and laboratory criteria, applying them in a sequential order, according to their clinical relevance, starting with the general appearance. Several studies have demonstrated that, as expected, febrile children who are not well appearing are at higher risk of bacterial infections, both in the general pediatric population[16] and in infants younger than 3 months.[17] In fact, clinical appearance is the factor that mostly increases this risk.[16,17]

The second item that the Step by Step evaluates is the age. Most classic guidelines consider 28 days old as the cutoff under which a complete sepsis workup and admission with empirical antibiotic treatment is recommended.[10,18–20] However, more recent studies suggest alternative cutoff points. A descriptive study developed in 1 of our study participating centers evaluated retrospectively 1575 infants ≤90 days old with FWS analyzing the bacterial infection rate week by week.[21] Infants 21 to 28 days old had a similar prevalence of bacterial infections compared with older patients and a lower rate than infants ≤21 days old. Some authors even found a significant reduction in SBI rate after the second week of life, but without establishing different management strategies according to this cutoff.[22] Of note, in our study, 4 of the 7 patients finally diagnosed with an IBI and classified by the Step by Step as low risk patients were 22 to 28 days old (Supplemental Table 7). This finding, not observed in our previous retrospective study,[11] suggests to be cautious when assessing patients in the fourth week of age and recommends further studies to safely identify the best secondary age cutoff point.

Finally, leukocyturia identifies those infants with a high probability of having a UTI but also a subgroup of infants with an increased risk of having a bacteremia.[17] Indeed 1 of the most frequent IBI in young febrile infants is UTI with associated bacteremia.[23,24]

In our study, general appearance, age, and urine dipstick identified almost 80% of the IBI patients and, more interestingly, 85% of the sepsis and 90% of the bacterial meningitis. The bacterial meningitis and 3 of the 4 bacterial sepsis not detected by this first part of the algorithm would have been identified by an elevated PCT value. Several studies have compared the performance of PCT and CRP in the management of

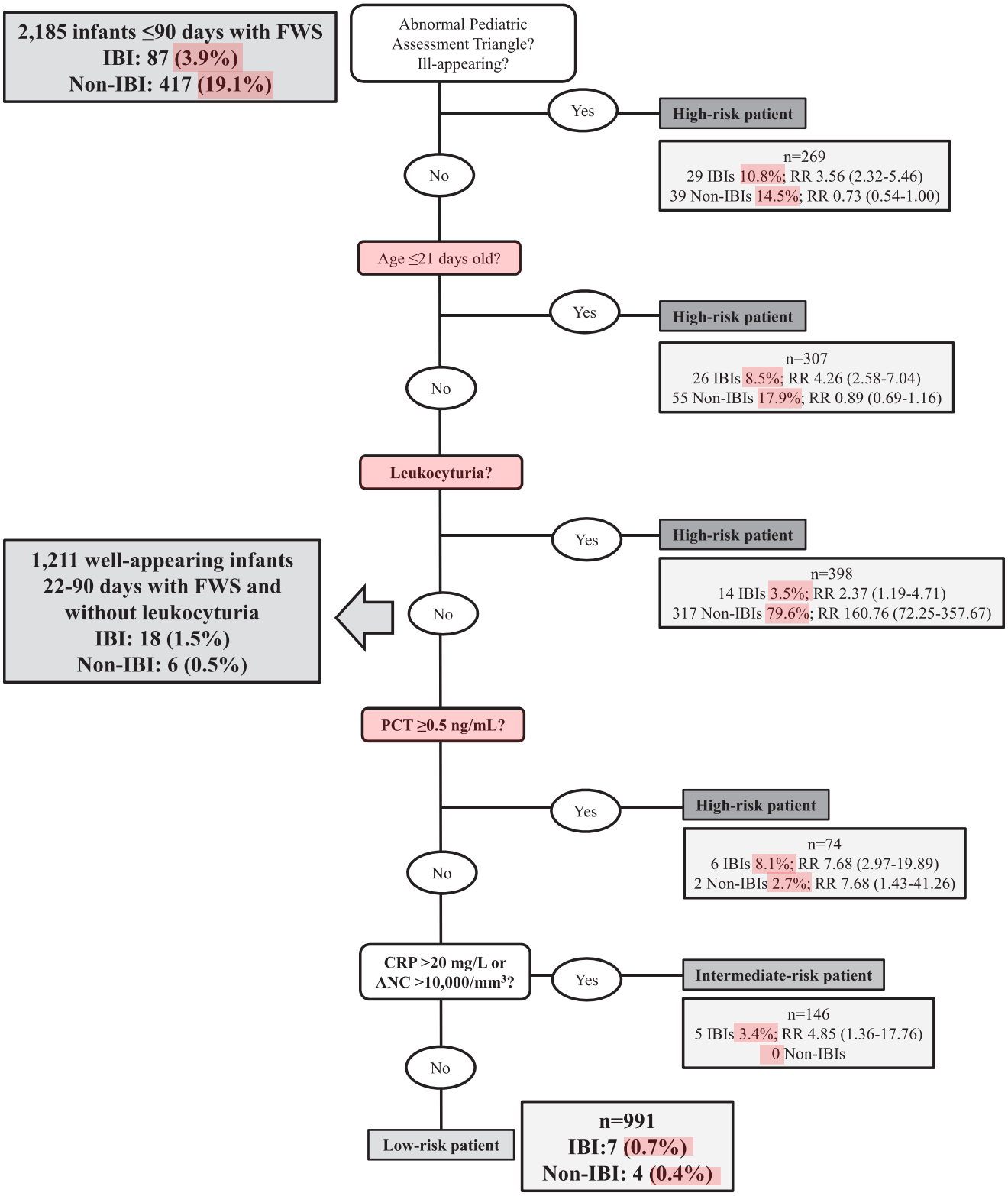

FIGURE 3
Prevalence of invasive and non-IBI in the different risk subgroups and OR for those infants presenting each risk factor.

young febrile infants.[25–27] PCT is a better biomarker to rule in an IBI, and, due its more rapid kinetic,[28] it is a more suitable biomarker in young infants who, for the great majority, present to the PED with a very early onset fever.[17,26,27,29] However, in 6 of 7 patients potentially missed by the Step by Step, fever duration

TABLE 3 Prevalence of Bacterial Infection Among Low Risk patients According to Each Management Protocol

	Number of Infants Classified As Low Risk Patients, *n* (%)	Prevalence of Bacterial Infection Among Low Risk Patients			
		SBI			Possible BI, (95% CI)
		Overall, %, (95% CI)	IBI, %, (95% CI)	Non-IBI, %, (95% CI)	
Rochester criteria	949 (43.4)	2.1 (1.2–3.0) *n* = 20	1.6 (0.9–2.5) *n* = 16	0.4 (0–0.8) *n* = 4	5.6 (4.2–7.2) *n* = 54
Lab-score	1798 (82.2)	10.8 (9.4–12.3) *n* = 195	1.9% (1.3–2.6) *n* = 35	8.8% (7.6–10.2) *n* = 160	5.0 (4.0–6.1) *n* = 91
Step by Step	991 (45.3)	1.1 (0.5–1.8) *n* = 11	0.7 (0.2–1.2) *n* = 7	0.4 (0–0.8) *n* = 4	5.1 (3.8–6.5) *n* = 51

TABLE 4 Sensitivity, Specificity, PPVs, NPVs and Positive and Negative LR, with 95% CI, of Each Approach for Identifying IBIs

valeur pré-test 3,9%

	Sensitivity, %	Specificity, %	PPV	NPV	Positive LR	Negative LR
Rochester criteria	81.6 (72.2–88.4)	44.5 (42.4–46.6)	5.7 (4.6–7.2)	98.3 (97.3–99.0)	1.47 (1.32–1.64)	0.41 (0.26–0.65)
Lab-score	59.8 (49.3–69.4)	84.0 (82.4–85.5)	13.4 (10.4–17.2)	98.1 (97.3–98.6)	3.74 (3.07–4.56)	0.48 (0.37–0.62)
Step by Step	92.0 (84.3–96.0)	46.9 (44.8–49.0)	6.7 (5.4–8.3)	99.3% (98.5–99.7)	1.73 (1.61–1.85)	0.17 (0.08–0.35)

was less than 2 hours, which is far too short even for PCT to rise. This very short fever duration makes the evaluation of these patients even more challenging and highlights the important role of a short-term PED observation in the management of these patients.

The intermediate risk group includes patients with an elevated CRP or ANC. We excluded the WBC count, because neither leukocytosis nor leukopenia have proved to be good predictors of bacterial infection in young infants.[30–33]

In comparing the Step-by-Step approach with previously developed sets of low risk criteria, we only focused on the Lab-score and Rochester criteria. This is because the Boston and Philadelphia criteria recommended performing systematically a lumbar puncture in all febrile infants. This would have implicated a change in the management protocols in use in the participating centers. In addition, most of the more recent guidelines do not recommend performing this test systematically, favoring an individualized approach that takes into account general appearance, age, and blood tests results.[10,18–20,34]

Both the Rochester criteria and the Lab-score were developed to identify patients at risk for severe bacterial infection globally. We further categorized severe bacterial infection into IBI and non-IBI for the different implications in terms of management and possible outcome. The Step by Step appears the most accurate of the 3 approaches for ruling out an IBI presenting the highest sensitivity and NPV and the best negative LR. On the contrary, and as expected due to the relatively low prevalence of IBI (4.0%), specificity, PPV, and positive LR were poor for all the 3 approaches when considering all the risk criteria of each protocol all together. In addition, the Step by Step provides risk estimates for both IBI and non-IBI according to the risk group that patients fall into during their sequential assessment. There are some reasons behind its better performance. Since the development of the Rochester criteria, the epidemiology of bacterial pathogens in young febrile infants has changed. Improvement in the perinatal antibiotic prophylaxis has reduced the incidence of *S. agalactiae* early-onset sepsis,[35–37] *E coli* is nowadays the leading cause of bacteremia in this population,[6,7,17,24] and *Listeria* is rarely involved.[6,7,17,24] On the other hand, new biomarkers that have been shown to be better predictors of IBI have been included in many management protocols. Curiously, the Lab-score, developed less than 10 years ago, revealed a lower performance compared with previously published studies. This score was created to be applied in patients between 7 days and 36 months of age. Its derivation on this broad age range may account for its lower performance in younger infants, as bacterial pathogens and incidence of bacterial infections significantly varies with age. The same authors of this score found, in a validation study, that its sensitivity decreased with the age of the infant.[38]

Of note, 3 of the 7 IBIs unidentified by the Step by Step attended the PED only 1 hour after the fever was firstly detected and in 3 other patients, fever was firstly detected on arrival at the PED (the reason for consultation was another complaint than fever). This very short fever duration makes the evaluation of these patients even more challenging and highlights the important role of a short-term PED observation in the management of these patients.

Our study has some limitations. First, the prevalence of SBI obtained in our study was similar to those reported in other recent European publications,[17,25,33] but higher than those reported in some US studies,[7,23,39–41] mainly due to an increased rate of UTI. This discrepancy can be explained by

TABLE 5 Performance of the Complementary Tests Recommended by Each Set of Criteria Among the 1247 Well-Appearing and Previously Healthy Infants Older Than 28 d

	Number of Infants Classified As Low Risk Patients, *n* (%)	Prevalence of Bacterial Infection Among Low Risk Patients			Possible BI, % (95% CI)
		SBI			
		Overall, % (95% CI)	IBI, % (95% CI)	Non-IBI, % (95% CI)	
Rochester criteria					
No leukocyturia	699 (56.0)	1.2 (0.4–2.1)	0.7 (0.1–1.3)	0.5 (0–1.1)	6.1 (4.4–7.9)
WBC count >5000/mcL and <15 000/mcL		*n* = 9	*n* = 5	*n* = 4	*n* = 43
Lab-score		11.2 (9.3–13.1)	1.0 (0.4–1.6)	10.1 (8.4–12.0)	5.1 (3.8–6.5)
Combination of urine dipstick, PCT, and CRP	1069 (85.7)	*n* = 131	*n* = 11	*n* = 120	*n* = 55
Step by Step					
No leukocyturia		0.5 (0–1.0)	0.2 (0–0.6)	0.2 (0–0.6)	5.2 (3.7–6.8)
PCT < 0.5 ng/mL	786 (63.0)	*n* = 4	*n* = 2	*n* = 2	*n* = 41
CRP ≤ 20 mg/L					
ANC ≤ 10 000/mcL					

different denominators, reflecting the difference in inclusion criteria between studies. Although we included only infants with FWS, excluding specifically those patients in whom a clear source of fever was identified (bronchiolitis, upper respiratory tract infection, etc) in many US studies, include a broader population of febrile infants.

Second, although part of the Rochester criteria, the absolute band count was not available in many of the participating centers and thus not included in our analysis. Including this item, the performance of the Rochester criteria could have varied.

Third, we have not been able to compare the Step by Step with other sets of criteria such as the Philadelphia or the Rochester criteria. According to 1 recent survey sent to the members of the American Academy of Pediatrics,[5] only 62% of the respondents reported using some set of published guidelines and among them, 20% cited using the Philadelphia protocol, 15% the Rochester criteria, and 13% the Boston criteria. As there seems to be no predominant criteria used in the United States and none of these classic risk criteria are frequently used in Europe, we chose the Rochester criteria for the reasons previously mentioned.

CONCLUSIONS

The Step-by-Step approach revealed a high sensitivity, being more accurate than the Rochester criteria and the Lab-score at identifying children at low risk of IBI, and appears to be a useful tool for the management of the febrile infant in the ED. However, as no perfect tool exists, the Step by Step is not 100% sensitive and physicians should use caution especially when assessing infants with very short fever evolution. For this subgroup of patients, we strongly advise for an initial period of close observation and monitoring in the ED, even when all the complementary test values are normal.

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ABBREVIATIONS

ANC: absolute neutrophil count
CI: confidence interval
CRP: C-Reactive protein
FWS: fever without source
IBI: invasive bacterial infection
LR: likelihood ratio
NPV: negative predictive value
PCT: procalcitonin
PED: pediatric emergency department
PPV: positive predictive value
RR: relative risk
UTI: urinary tract infection
WBC: white blood cell

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