Accuracy of a sequential approach to identify young febrile infants at low risk for invasive bacterial infection

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ABSTRACT

Introduction Much effort has been put in the past years to create and assess accurate tools for the management of febrile infants. However, no optimal strategy has been so far identified. A sequential approach evaluating, first, the appearance of the infant, second, the age and result of the urinanalysis and, finally, the results of the blood biomarkers, including procalcitonin, may better identify low risk febrile infants suitable for outpatient management.

Objective To assess the value of a sequential approach ('step by step') to febrile young infants in order to identify patients at a low risk for invasive bacterial infections (IBI) who are suitable for outpatient management and compare it with other previously described strategies such as the Rochester criteria and the Lab-score.

Methods A retrospective comparison of three different approaches (step by step, Lab-score and Rochester criteria) was carried out in 1123 febrile infants less than 3 months of age attended in seven European paediatric emergency departments. IBI was defined as isolation of a bacterial pathogen from the blood or cerebrospinal fluid.

Results Of the 1123 infants (IBI 48; 4.2%), 488 (43.4%) were classified as low-risk criteria according to the step by step approach (vs 693 (61.7%) with the Lab-score and 458 (40.7%) with the Rochester criteria). The prevalence of IBI in the low-risk criteria patients was 0.2% (95% CI 0% to 0.6%) using the step by step approach; 0.7% (95% CI 0.1% to 1.3%) using the Lab-score; and 1.1% (95% CI 0.1% to 2%) using the Rochester criteria. Using the step by step approach, one patient with IBI was not correctly classified (2.0%, 95% CI 0% to 6.12%) versus five using the Lab-score or Rochester criteria (10.4%, 95% CI 1.76% to 19.04%).

Conclusions A sequential approach to young febrile infants based on clinical and laboratory parameters, including procalcitonin, identifies better patients more suitable for outpatient management.

INTRODUCTION

The rate of serious bacterial infections (SBI) is higher among febrile infants under 3 months of age compared with older children,[1] and their management is recommended to be more aggressive.

However, most of these infants have a benign viral disease[1][2] and, in selected patients, inhospital admission and antibiotic treatment may be avoided. In order to manage young febrile infants as outpatients, it is necessary to identify those patients at low risk for SBI and, mainly, invasive bacterial infection (IBI).

Several attempts have been made in order to identify patients with low-risk criteria for SBI.[3–6] Usually, low-risk criteria include a combination of clinical and laboratory data. However, the contribution of each parameter in predicting SBI is different. As the most common SBI in this age group is urinary tract infection (UTI),[4] the yield of urinalysis, compared with blood markers or other tests, is the highest. Blood biomarkers are more helpful in predicting bacteraemia or meningitis. However, the value of these tests is controversial. Recent studies have shown that white blood cell (WBC) count has a poor value in the diagnosis of bacteraemia and other bacterial infections in these infants.[7][8] In fact, WBC count has been relegated in the more recently developed scores to identify patients at higher risk for SBI[9][10] and newer biomarkers as C reactive protein (CRP)[10] and, mainly, procalcitonin (PCT)[11] seem to be more useful to identify febrile young infants with bacterial infections.[2][12]

The traditional approach to these infants has included the assessment of both clinical and laboratory data together for decision-making on the most adequate management (ie, admission and/or treatment). A sequential approach ('step by step') which takes into account in the first instance the appearance of the infant, and in sequence the age, the result of the urinanalysis and, finally, the results of the blood biomarkers (including PCT) may be a more practical approach for decision-making regarding these infants.

The main objective of this study was to assess the accuracy of a step by step approach to febrile young infants in order to rule in and, mainly, rule out IBIs, thus identifying infants suitable for an outpatient management.

The secondary objective was to compare this approach with other previously reported strategies for the management of the febrile infant in the paediatric emergency department (PED), such as the Rochester criteria and the Lab-score.

METHODS

Study design and selection of participants

This study was part of a retrospective multicentre study assessing the accuracy of different blood biomarkers in diagnosing IBIs and SBIs in well-appearing infants less than 3 months of age with fever without source (FWS) presenting to the PED.[13]

Original article

The study was carried out in five Spanish and two Italian PEDs with very similar protocols for the management of infants less than 3 months of age with FWS: urine dipstick testing, blood biomarkers (CRP, PCT and WBC), as well as blood and urine cultures are recommended in all patients. A lumbar puncture is individually recommended, according to the age of the infant, the general appearance and the laboratory tests results. Chest x-ray is practiced on individual basis.

Patients were retrospectively included from 31 December 2010 backwards, up to a maximum of 3 years earlier (1 January 2008), depending on when PCT was introduced in each hospital. Regardless of the date of PCT introduction, the study period for each hospital was required to be a multiple of 12 months in order to avoid possible epidemiological variations throughout the year.

Inclusion criteria
Infants younger than 3 months of age presenting with FWS to the PED who had PCT, CRP, WBC count, urine dipstick, as well as urine and blood culture performed at the time of initial evaluation were included in the study.

Exclusion criteria
Patients were excluded from the study if they met any of the following:
▶ Patients in whom presence of fever was not certain, that is, patients who were afebrile in the PED and whose body temperature was not measured at home with a thermometer. Patients who were afebrile in the PED, but in whom fever was measured at home were included.
▶ Patients in whom the medical history and/or the physical examination performed upon arrival in the PED allow the source of the fever to be identified; patients with certain diarrhoea or certain respiratory symptoms/signs (tachypnoea, breathing difficulties, wheezing, grunting, nasal flaring, retractions, rhonchi, rales, or focal areas of decreased breath sounds). Those reporting only a mild nasal congestion or few diarrhoeal stools will be included (no evident source for the fever).
▶ Patients in whom a blood culture, urine culture or urine dipstick was not obtained or CRP, PCT or WBC count was not measured.

Data collection
The following data were recorded for the included patients at each centre: demographics (age, sex), month when care was provided, medical history, time elapsed between moment when fever was first detected and when the infant was brought to the hospital, temperature registered at home and at the PED, whether the child appeared ill upon arrival or not, results of any tests performed and final diagnosis.

The following additional data were also provided:
▶ Total number of patients admitted during the study period
▶ Number of infants under 3 months of age with FWS admitted during the study period.

Definitions
▶ FWS: axillary or rectal temperature at home, or rectal temperature in the PED, of ≥38°C, without catarrhal or other respiratory signs/symptoms (such as tachypnoea) or a diarrhoeal process in patients who had a normal physical examination.
▶ Well-appearing: defined by a normal paediatric assessment triangle in those centres in which these data are

systematically recorded in the paediatric medical records. For the other centres, infants were considered to be not well-appearing if the physical exam recorded in the patient medical chart indicated any clinical suspicion of sepsis. The exclusion expressions included, but were not limited to: 'poor/bad general appearance', 'irritable', 'cyanosis', 'hypotonic' and 'cutis marmorata'.
▶ IBI: isolation of a bacterial pathogen from the blood or cerebrospinal fluid (CSF).
▶ SBI: isolation of a bacterial pathogen from the blood, CSF, urine or stools.
  – Definite cases of SBI: patients with leucocyturia and a positive urine culture, and those with a positive blood or CSF culture.
  – Possible SBI:
    • Infants with a urine culture yielding mixed growth or growth of >10 000 cfu/mL of a single bacterial species without leucocyturia were considered possible cases of UTI.
    • Patients with pneumonia without positive blood culture.

Urine samples for culture were collected by bladder catheterisation or suprapubic aspiration in the Spanish centres, and mainly using sterile collection bags changed every 30 min, as per local protocol, in the two hospitals in Italy. When bags were used, two different positive samples with a concordant bacterial growth >100 000 cfu/mL were required for a definitive diagnosis of UTI.

Approaches to the febrile infant undergoing comparison in the present study
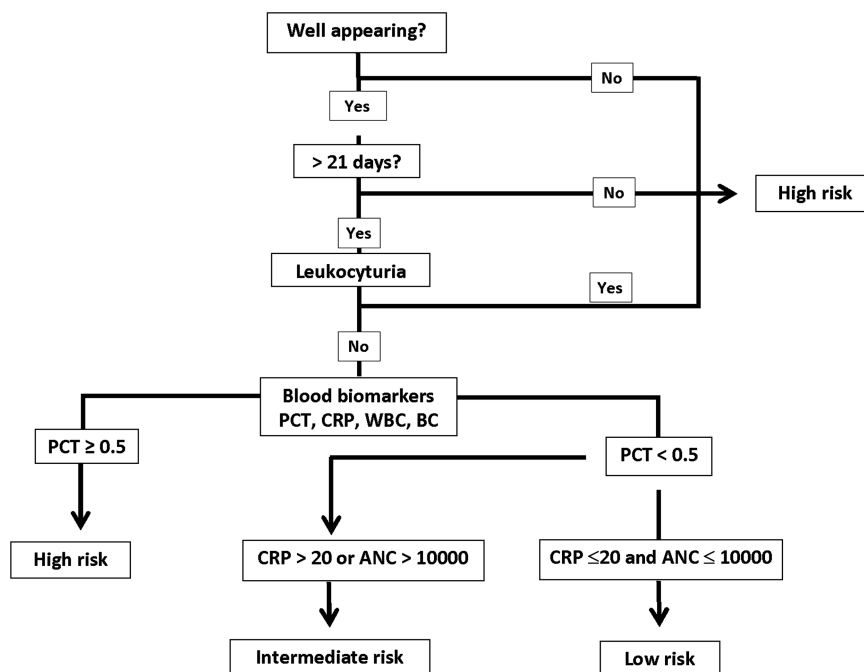#### Different low-risk criteria
In the three different approaches, to be classified as a low-risk patient, the infant had to appear well and be older than 21 days of age. As the risk for SBI is higher for febrile infants younger than 3-weeks-old,[14] and no guideline recommends an outpatient management for these patients, we excluded infants younger than 3 weeks of age of the low-risk group regardless the approach used.

Besides being well appearing and being older than 21 days, to be classified in the low-risk patient for each strategy, the infant had to fulfil all of the following.
▶ Sequential approach (figure 1):
  – Having a urine dipstick without leucocyturia
  – Having the following biomarkers values: PCT<0.5 ng/mL, CRP ≤20 mg/L and absolute neutrophil count (ANC) ≤10 000/mm³. We chose these biomarkers following the results of the original study.[13]
▶ Lab-score:[9] it takes into account PCT, CRP and urine dipstick. According to the Lab-score 2 points are attributed to PCT ≥0.5 ng/mL or CRP ≥40 mg/L, 4 points to PCT ≥2 ng/mL or CRP ≥100 mg/L and 1 point to a positive urine dipstick (ie, positive leucocyte esterase and/or positive nitrite). Consequently, Lab-score values ranged from 0 to 9 points. Values over or equal to 3 are related with a higher risk for having an SBI. To be included in the low-risk group, Lab-score must be lower than 3.
▶ Rochester criteria:
  – Having a urine dipstick without leucocyturia
  – Having the following biomarkers values: WBC=5000–15 000/mm³.

We defined failures of the different approaches to the studied population as follows:

Figure 1   Young febrile infants. Step by step approach.

▶ Major failures: Infants classified as a low-risk patient following the different approaches who were finally diagnosed with an IBI (ie, false negatives for IBI).

▶ Other failures: Patients meeting all the low-risk criteria with a positive urine culture and patients not meeting all the low-risk criteria with negative blood and urine cultures (and CSF, if performed).

Statistical analysis

All data were entered in a Microsoft Office Database by the research coordinator at each centre and then reviewed by the principal investigators. Normally distributed data were expressed as mean±SD; non-normally distributed data were expressed as median and IQR; categorical variables were reported as percentages. For non-normally distributed data, comparison was performed employing Mann–Whitney U test; comparison of normally distributed data was performed using independent-samples t test. For categorical data, the χ^2 test was used. Parameters displaying $p<0.05$ were considered statistically significant.

Sensitivity, specificity, positive and negative likelihood ratios (LR) for each Lab-score cut-off point were calculated. The commercial statistical software package used was SPSS V.19.0.

The study was approved by the Ethical Committee of the Spanish coordinator centre (Cruces University Hospital, according to Spanish legislation) and by the two independent Review Board of the participating Italian centres, that is, Padova and Treviso hospitals.

RESULTS

Five Spanish and two Italian PEDs participated in the study. Due to differences in the date on which the measurement of

Figure 2   Application of the 'step by step' approach to the studied population.

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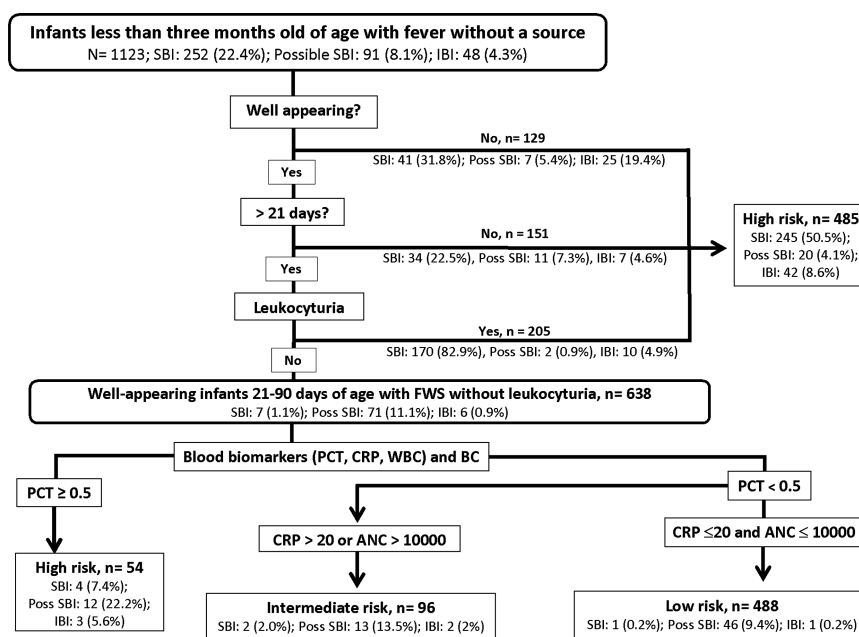
Table 1 The observed number of serious bacterial infections and invasive bacterial infections in low-risk patients defined by three different strategies

	Step by step, n=488	Lab-score, n=693	Rochester, n=458
Invasive bacterial infections	1; 0.2% (0%–0.5%)	5; 0.7% (0.1%–1.3%)	5; 1.1% (0.1%–2%)
Possible serious bacterial infections	46; 9.4% (6.8%–12.1%)	61; 8.8% (6.6%–10.9%)	48; 10.5% (7.6%–13.2%)
Definite serious bacterial infections	1; 0.2% (0%–0.5%)	70; 10.1% (7.8%–12.3%)	5; 1.1% (0.1%–2.0%)

PCT was introduced at each hospital, three of them contributed data on patients admitted during 1 year, another three data for 2 years and one data for 3 years. Over the study period, a total of 533 133 paediatric patients were admitted in the seven European PEDs, 1531 (0.28%) being infants under 3 months of age with FWS.

Of these, we sequentially excluded 408 patients (no blood culture obtained: 145; no urine culture obtained: 124; no urine dipstick performed: 7; incomplete data on biomarkers: 132). We finally included 1123 patients (59.8% boys). Of them, 994 (88.5%) were classified as well-appearing upon arrival to the PED and 994 (84.1%) were older than 21-days-old.

An SBI was diagnosed in 252 infants (22.4%), 48 of them being IBIs (4.2%). Final diagnoses for those infants diagnosed with an SBI were: ITUs (n=202), ITUs with bacteraemia associated (n=17), occult bacteremias (n=15), sepsis (n=9), bacterial meningitis (n=7) and bacterial gastroenteritis (n=2).

Among the 1123 patients included, using the three different approach strategies, febrile infants classified as low-risk patients for SBI were as follows:

- ▶ Sequential approach: 488 (figure 2)
- ▶ Lab-score: 693
- ▶ Rochester criteria: 458.

Prevalence of definite SBI, possible SBI and IBI (being the latter considered 'major failures' of the different approaches) among low-risk patients according to each approach is shown in table 1.

Applying the step by step approach in the study population, the prevalence of definite SBI, possible SBI and IBI in patients classified as high, intermediate and low-risk patients is shown in table 2, as well as the +LR for IBI for each risk group.

As it is shown in figure 2, the assessment of the appearance, age and leucocyturia before taking into account the performance of blood tests identifies a population at higher risk for IBI (IBI rate: 8.6%).

Of the 48 patients with IBI, one patient (2.0%, 95% CI 0% to 6.12%) was classified as a low-risk patient according to the step by step approach (vs five using Lab-score or Rochester criteria, 10.4%, 95% CI 1.76% to 19.04%) (see table 3).

Finally, infants classified as not low-risk patients in the three approaches were 635 using the step by step approach, 430 with the Labscore and 665 using Rochester. Among them, 339 (53.3% 95% CI 49.4% to 57.3%) were not diagnosed with an SBI using the step by step approach (vs 218; 50.6%—95% CI 45.9% to 55.4%—with the Labscore and 375; 56.3%—95% CI 52.6% to 60.1%—with the Rochester criteria).

DISCUSSION

According to our data, the identification of young febrile infants with low-risk criteria for IBI can be improved using a sequential approach including PCT.

During the last decades, a lot of effort has been made in order to identify febrile young infants at low and high risk for SBI. The prevalence of SBI in young febrile infants is higher than in older populations and, in this way, the approach to these patients has to be cautious. On the other hand, hospitalising and treating with antibiotics all these infants has been related to unnecessary hospitalisations, nosocomial infections, emergence of resistant bacteria and adverse effects of antibiotics.[15]

The observation is that treatment for low-risk infants without antibiotics seems to be a better approach than continuing to treat all patients regardless of risk stratification.[3]

Previous studies have tried to validate different low-risk criteria in their own populations.[16–24] A significant number of patients with SBI, and mainly IBI, were missed by all these protocols limiting the applications of their results.

Nowadays, most of these patients come very early to the emergency department and most of them appear well[4] and these factors have to be taken into account in order to correctly identify low-risk patients. Therefore, we need strategies applicable in this population. The availability of new biomarkers and their use in young febrile infants[12] has led to the design of new diagnostic tools, combining different tests in order to manage properly these patients. Lacour et al[9] developed the Lab-score, which combines the value of two different biomarkers (CRP and PCT) and the presence/absence of leucocyturia for better identifying febrile infants at high risk for SBI. Although the Lab-score was prospectively validated in a different

Table 2 Prevalence of definite SBI, possible SBI and IBI, and +LR for IBI related to the risk classification of the 'step by step' approach

Risk classification of patients according to step by step approach	Definite SBI		Possible SBI		IBI			+LR for IBI (95% CI)
	n	(95% CI)	n	(95% CI)	N	% (95% CI)		
High risk before biomarkers (n=485)	245	50.5 (46.0 to 54.9)	20	4.1 (2.3 to 5.8)	42	8.6% (6.1% to 11.1%)	2.05 (1.89 to 2.22)	
High risk after biomarkers (n=54)	4	7.4 (0.4 to 14.3)	12	22.2 (11.1 to 33.3)	3	5.6% (0% to 11.6%)	7.91 (4.24 to 14.75)	
Intermediate risk (n=96)	2	2.0 (0 to 4.9)	13	13.5 (6.6 to 20.3)	2	2% (0% to 4.8%)	4.12 (1.81 to 9.37)	
Low risk (n=488)	1	0.2 (0 to 0.6)	46	9.4 (6.8 to 12.0)	1	0.2% (0% to 0.6%)	1	

IBI, invasive bacterial infection; LR; likelihood ratio; SBI, serious bacterial infection.

Table 3 Patients' characteristics, diagnosis and isolated pathogens of initially missed invasive bacterial infection (IBI) (infants classified as low risk and finally diagnosed with IBI (missed IBIs)), according to the three evaluated protocols

Protocol	Sex and age	Evolution time	Diagnose and bacterium
Step by step	Female, 79 days	6 h	Occult bacteraemia, *Enterococcus Fecalis*
Lab-score	Male, 32 days	8 h	Occult bacteraemia, *Staphylococcus Aureus*
	Female, 70 days	15 h	Occult bacteraemia, *Enterococcus Fecalis*
	Female, 58 days	1 h	Occult bacteraemia, *Streptococcus Agalactiae*
	Female, 79 days	6 h	Occult bacteraemia, *Enterococcus Fecalis*
	Female, 72 days	3 h	Occult bacteraemia, *Streptococcus Pneumoniae*
Rochester	Male, 32 days	8 h	Occult bacteraemia, *Staphylococcus Aureus*
	Female, 67 days	12 h	Occult bacteraemia, *Neisseria Meningitidis*
	Female, 70 days	15 h	Occult bacteraemia, *Enterococcus Fecalis*
	Female, 58 days	1 h	Occult bacteraemia, *Streptococcus Agalactiae*
	Female, 79 days	6 h	Occult bacteraemia, *Enterococcus Fecalis*

population,[10] its accuracy to rule in or rule out an IBI in young febrile infants less than 3 months has been only recently evaluated in a study of our research group.[25]

In our population, the Lab-score appears as a good tool to rule in an IBI but probably it is not the best approach to identify patients suitable to be managed as outpatients.

In order to identify young febrile infants at low risk for SBI, and mainly IBI, the step by step approach takes into account, first, the appearance of the infant, as being 'not-well appearing' has been related with higher risk of SBI and IBI.[2] Second, it does not include infants less than 21 days of age, as the higher risk for SBI in these infants has recently been published.[14] Third, patients with altered urine dipstick (UD) are also excluded from the low-risk patients group, as the presence of leucocyturia has been related with a higher risk for SBI and for IBI.[2] So, the first step is to select the patients for whom the results of the blood biomarkers will influence the most subsequent management: well appearing febrile infants between 21 and 90 days of age without leucocyturia.

The second step is to select which blood biomarker is more useful in this population. In this way, PCT plays a different role as it has been described in the original paper by Gomez and colleagues.[13] PCT was the only independent risk factor for having an IBI (OR 21.69 if PCT ≥0.5 ng/mL) and, comparing with CRP, PCT showed a better performance to rule in an IBI. Among patients with normal urine dipstick and fever of recent onset (less than 6 h), areas under the receiver operating characteristic (ROC) curve were 0.819 and 0.563, for PCT and CRP respectively, for detecting IBIs. However, since the inclusion of the PCT alone would lead to miss an important number of patients with IBI, we decided to add a final 'step' including ANC and CRP values. We decided to exclude WBC count because univariate analysis of the risk factors showed an increase in the rate for IBI only for CRP and ANC. Including ANC and CRP reduces this limitation, and the number of missed patients with IBI using the step by step approach is much lower than those applying Rochester criteria or Lab-score.

On the other hand, the number of patients without an SBI or IBI not well classified does not increase significantly. However, whatever diagnostic strategy we use, the rate of young febrile infants admitted and not finally diagnosed with an SBI is quite high, and so other strategies to identify better patients with SBI should be investigated in the future.

One specific issue is the management of children with pneumonia. Performance of a chest x-ray is not routinely recommended in this population as they are infants with fever without a source. Chest x-ray has to be performed if signs of respiratory distress or tachypnoea are detected. In our study, chest x-ray is practiced on individual basis as it is assessed in the Methods section and only two patients were diagnosed with pneumonia, none of them having a positive blood culture. Both of them were admitted to ward and treated with antibiotics.

Our study has several limitations. First, a prospective study would have allowed a better quality of the collected data. In this way, not all the patients were included as some of them had not all the tests performed. Probably, excluded patients had a lower rate for SBI and IBI. However, this fact does not seem to decrease the value of the step by step approach to identify patients with low risk for IBI more suitable to be managed as outpatients. This fact may be corrected in a prospective validation of this approach and must be taken into account when designing this validation. Second, the assessment of the appearance is very important in the proposed protocol. Probably, before considering an outpatient management, the appearance of the infant is better to be assessed by an experienced emergency physician. Finally, as it was reported in our initial study,[13] 90% of the urine cultures were collected by bladder catheterisation in the Spanish hospitals, whereas samples were mainly obtained by using urine collection bags in the Italian hospitals (two positive urine cultures from different and consecutive urine samples for the diagnosis of UTI being necessary). Although a higher UTI prevalence was reported in children enrolled in the Italian centres compared with the Spanish ones (suggesting a possible overestimation of UTI diagnoses), this bias does not, however, affect the results obtained for prediction of IBI.

We have tried to elaborate an adequate strategy to identify young febrile infants suitable for a secure outpatient management. We have compared the step by step approach with other approaches which were not specifically designed to identify these patients. However, in fact, those strategies are commonly used by paediatric emergency physicians, and our aim was to advertise to physicians about the possible risks of using some strategies for other objectives different from the original ones. The Lab-score should theoretically be applied to the entire sample as evaluation of appearance and age are not contemplated in the score. The Rochester criteria should be applied to all children (even younger than 21 days) as no age cut-off is contemplated in these criteria. It should also be specified that Rochester criteria were not applied in their entirety as band count was not determined (basically not used in Europe) and also the stool smear (not performed even in the presence of loose stool, but very few children presented loose-diarrhoeal stools). Such a comparison will allow for a better evaluation of

the characteristics of each approach and will even more highlight the advantages of the sequential approach as two more infants with IBI should not be detected less than 21-days-old. The step by step approach basically reflects a more comprehensive approach based on clinical reasoning (assessment based on priority related steps for more direct decision-making).

We can conclude that a sequential approach to young febrile infants like the step by step approach better identifies low-risk patients more suitable for outpatient management. This can help to identify a set of febrile young infants for being more safely managed as outpatients. Prospective multicentre studies are needed to validate these findings.

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