Febrile young infants with abnormal urine dipstick at low risk of invasive bacterial infection

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ABSTRACT

Objectives To develop and validate a prediction rule to identify well-appearing febrile infants aged ≤90 days with an abnormal urine dipstick at low risk of invasive bacterial infections (IBIs, bacteraemia or bacterial meningitis).

Design Ambispective, multicentre study.

Setting The derivation set in a single paediatric emergency department (ED) between 2003 and 2017. The validation set in 21 European EDs between December 2017 and November 2019.

Patients Two sets of well-appearing febrile infants aged ≤90 days with an abnormal urine dipstick (either leucocyte esterase and/or nitrite positive test).

Main outcome Prevalence of IBI in low-risk infants according to the RISeuP score.

Results We included 662 infants in the derivation set (IBI rate:5.2%). After logistic regression, we developed a score (RISeuP score) including age (≤15 days old), serum procalcitonin (≥0.6 ng/mL) and C reactive protein (≥20 mg/L) as risk factors. The absence of any risk factor had a sensitivity of 96.0% (95% CI 80.5% to 99.3%), a negative predictive value of 99.4% (95% CI 96.4% to 99.9%) and a specificity of 32.9% (95% CI 28.8% to 37.3%) for ruling out an IBI. Applying it in the 449 infants of the validation set (IBI rate 4.9%), sensitivity, negative predictive value and specificity were 100% (95% CI 87.1% to 100%), 100% (95% CI 97.3% to 100%) and 29.7% (95% CI 25.8% to 33.8%), respectively.

Conclusion This prediction rule accurately identified well-appearing febrile infants aged ≤90 days with an abnormal urine dipstick at low risk of IBI. This score can be used to guide initial clinical decision-making in these patients, selecting infants suitable for an outpatient management.

What is already known on this topic?

- Risk of invasive bacterial infection (IBI) in febrile young infants with an abnormal urine dipstick is high, and inpatient treatment is usually recommended.

What this study adds?

- This prediction rule accurately identified febrile infants aged ≤90 days with abnormal urine dipstick at low risk of IBI. Infants with a score of 0 may be suitable for an outpatient management.

INTRODUCTION

Urinary tract infection (UTI) is the most common serious bacterial infection in febrile infants younger than 3 months of age, occurring in 4%–20% of these infants.[1–3] Most children with UTIs have a benign clinical course if they are treated appropriately.[4 5] However, bacteraemia is associated with UTI in 4%–10% of febrile infants younger than 3 months, placing these infants at risk of dissemination to the central nervous system.[6–8] In fact, febrile infants under 2 or 3 months of age with a UTI are very likely to be admitted for parenteral antibiotic.[2 9]

Diagnosis of UTI is based on urine culture. Urine culture results, however, are not available for at least 24 hours. Thus, there is considerable interest in alternative testing methods such as the urine dipstick, which may anticipate the results of the urine culture and enable presumptive therapy to be initiated in the emergency department (ED).[10 11] In addition, the presence of leucocyte esterase and urinary nitrite is a risk factor for invasive bacterial infection (IBI) in young febrile infants.[12]

Clinical prediction rules support clinical decision-making and can reduce variation in care and limit unnecessary interventions. Certain subjective clinical findings and laboratory markers, such as serum procalcitonin (PCT) or C reactive protein (CRP), have been used to risk stratify febrile infants with leucocyturia.[13 14] Nevertheless, further assessment is necessary to identify optimal thresholds and to evaluate their utility.

A prediction rule to stratify febrile infants with leucocyturia by risk level can be used to guide initial

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clinical decision-making in these patients, identifying infants suitable for outpatient management.[14]

The aims of this study were to devise and to validate a score to safely identify well-appearing febrile infants aged ≤90 days with an abnormal urine dipstick at low risk of IBI.

METHODS

Multicentre collaborative research network

The RESeuP-Spanish Paediatric Emergency Research Group and the Research in European Paediatric Emergency Medicine network approved the study.

Study design, setting and population

This was an ambispective, multicentre study including infants aged ≤90 days with a temperature of ≥38°C (100.4°F) measured either at home or in the ED and an abnormal urine dipstick (either a positive leucocyte esterase or nitrite test). In order to avoid bias, since few participant centres had an analyst available all day to perform a microscopic analysis of the urine, only patients with an altered urine dipstick were included.

Derivation sample

The derivation sample was obtained from a prospective paediatric ED registry that includes all infants aged less than 90 days with fever without a source (FWS) starting in September 2003. This paediatric ED is in a tertiary hospital with around 55 000 ED episodes corresponding to children ≤14 years of age annually, including 200–250 infants ≤90 days of age with FWS. The hospital's protocol recommends obtaining blood and urine cultures for all febrile infants aged ≤90 days regardless of urine dipstick and blood test results. Cerebrospinal fluid (CSF) exam and admission for antibiotics are recommended for high-risk infants according to established clinical and laboratory criteria. The database used in this prospective registry has been described elsewhere.[15–17] For the purposes of this study, we analysed those infants seen until August 2017.

Validation sample

The validation sample was prospectively recruited in 21 European paediatric EDs between December 2017 and November 2019. Patients aged ≤90 days managed for FWS with a positive urine dipstick were recruited and managed in accordance with the protocols of each hospital. We monitored the progress of the patients by telephone within a month of discharge.

Exclusion criteria

We excluded patients who had received antibiotics in the previous 72 hours, when the urine sample was not collected using a sterile method; patients in whom caregivers refused to sign the consent; and infants lacking for the value of any of the biomarkers included in the score. Finally, as appearance has been proven as a risk factor for IBI and given that it seems unreasonable to discharge a febrile infant who appears unwell regardless of any other clinical or laboratory findings, we also excluded from the analysis those patients who were classified as not well appearing. For patients receiving medical attention on two occasions due to the same episode, only those data pertaining to the first care encounter were collected.

Definitions

- Fever without a source: axillary or rectal temperature of ≥38°C (100.4°F) measured either at home or in the ED in an infant in whom after medical history and physical exam it is not possible to identify the source of the fever.
- Previously healthy infant: born at term, not treated for unexplained hyperbilirubinemia, not hospitalised longer than the mother, not currently or previously receiving antimicrobial therapy, no prior hospitalisation, and no chronic or underlying illness.
- Well appearing: normal findings according to the Paediatric Assessment Triangle (appearance, work of breathing and circulation to skin)[18] as assessed by a physician within an hour of arrival to the ED.
- Abnormal urine dipstick: presence of a positive leucocyte esterase and/or nitrite test in urine samples collected by a

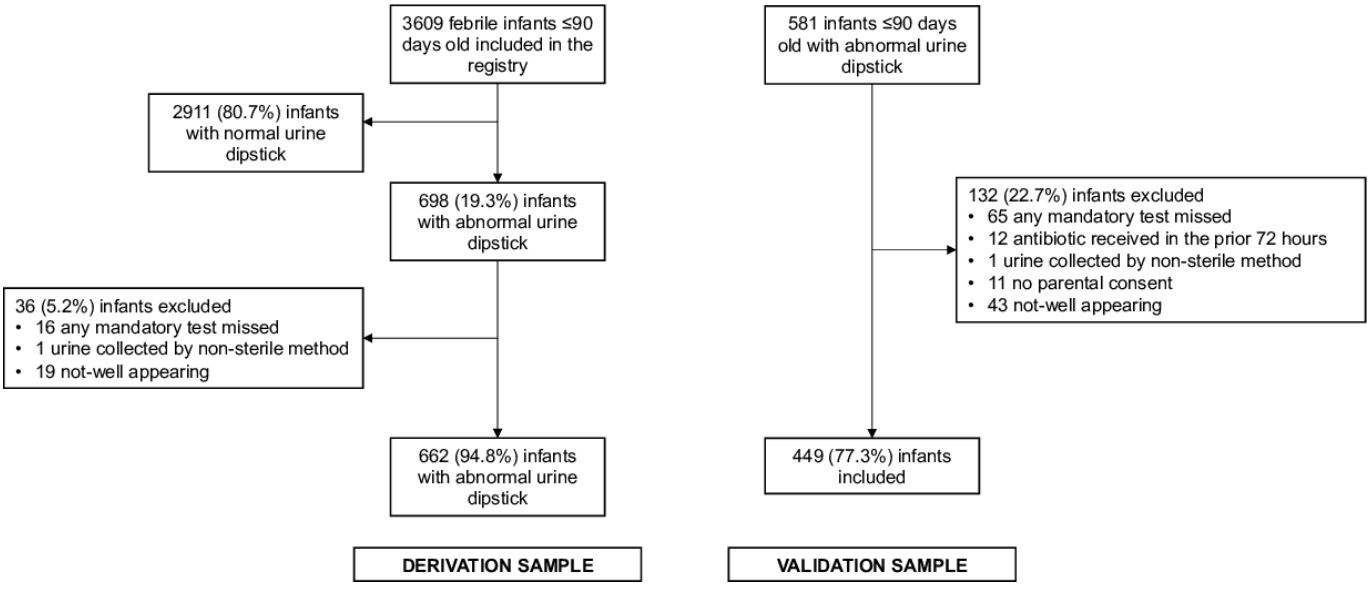

Figure 1 Derivation and validation sample flowchart. Note: urine dipstick results were considered abnormal in cases where a leucocyte esterase and/or nitrite test was positive.

sterile method (urethral catheterisation, suprapubic aspiration or clean-catch technique[19 20]).

- Positive urine culture: growth of (1) ≥1000 cfu/mL of a single pathogen in a urine culture collected by suprapubic aspiration or (2)>10 000 cfu/mL of a single pathogen in a urine sample collected by urethral catheterisation or clean-catch technique. The perineal bag was not considered a valid method to collect the samples.
- Serious bacterial infection.
  - Invasive bacterial infection: bacterial meningitis or bacteraemia.
    - Bacteraemia: isolation of a bacterial pathogen in a blood culture. Bacteria reported to consistently cause disease in children were considered true bacterial pathogens. Isolation of *Staphylococcus epidermidis*, *Propionibacterium acnes*, *Streptococcus viridans*, or *diphtheroids* in immunocompetent patients without heart disease, ventriculo-peritoneal shunt, central catheters, or another indwelling device were considered contaminants. When any doubt was raised, it was solved with the main investigator.
    - Bacterial meningitis: detection of a bacterial pathogen in CSF (with or without associated pleocytosis).
  - Urinary tract infection: patients with positive findings on urine dipstick (either leucocyte esterase or nitrite test) and positive urine culture.
  - IBI secondary to UTI: isolation of the same bacterium in urine culture and in blood and/or CSF culture.

Statistical analysis

We carried out a descriptive statistical analysis for all collected variables. We summarised continuous data as mean and SD and reported categorical variables as percentages. Normal distribution of data were evaluated using the Shapiro-Wilk test. For non-normally distributed data, comparison was performed with the

Table 1 Characteristics of the included patients

	Derivation sample (n=662)	Validation sample (n=449)	P value
Age (days)			0.16
≤28, n (%)	133 (20.1)	101 (22.5)	
29–60 n (%)	245 (37.0)	181 (40.3)	
>60 n (%)	284 (42.9)	167 (37.2)	
Gender (male), n (%)	454 (68.6)	310 (69.0)	0.87
Highest registered temperature (°C), mean (SD)	38.8 (0.56)	38.7 (0.54)	0.02
Duration of fever prior to ED visit (hours), median (IQR)	5 (2–15)	6 (2–14)	0.44
Urine dipstick collection method, n (%)			<0.01
Urethral catheterisation	648 (97.9)	365 (81.3)	
Suprapubic aspiration	0 (0)	3 (0.7)	
Clean-catch technique	14 (2.1)	81 (18.0)	
Urine dipstick result, n (%)			0.02
LE+	402 (60.7)	307 (68.4)	
NT+	9 (1.4)	9 (2.0)	
LE+ and NT+	251 (37.9)	133 (29.6)	
WBC (cells/µL), median (IQR)	15 400 (11 100–19450)	14 550 (10 620–19 500)	0.17
ANC (cells/µL), median (IQR)	7800 (5100–10 800)	7100 (4500–10 450)	0.05
CRP (mg/L),* median (IQR)	31.0 (110–71.7)	29.9 (12.0–62.1)	0.67
PCT (ng/mL),* median (IQR)	0.3 (0.18–1.1)	0.37 (0.13–1.5)	0.2
Positive urine culture, n (%)	562 (84.9)	417 (92.9)	<0.01
Escherichia coli	511 (90.9)	365 (87.5)	
Klebsiella pneumoniae	16 (2.8)	20 (4.8)	
Proteus mirabilis	7 (1.2)	0 (0)	
Enterococcus faecalis	6 (1.1)	14 (3.4)	
Other	22 (3.9)	18 (4.3)	
Positive blood culture, n (%)	34 (5.1)	22 (4.9)	0.86
E. coli	28 (82.4)	19 (86.4)	
Staphylococcus aureus	2 (5.9)	0 (0)	
K. pneumoniae	1 (2.9)	1 (4.6)	
E. faecalis	1 (2.9)	2 (9.1)	
Pseudomonas aeruginosa	1 (2.9)	0 (0)	
Streptococcus pneumoniae	1 (2.9)	0 (0)	
Lumbar puncture performed, n (%)	99 (15.0)	88 (19.6)	0.04
Positive CSF culture, n (%)	1 (0.15)	0 (0)	0.35
E. coli	1 (100)	0 (0)	
IBI secondary to UTI, n (%)	31 (91.2)		

*In the derivation sample, CRP and PCT serum levels were obtained in 660 and 494 patients, respectively.
ANC, absolute neutrophil count; CRP, C reactive protein; CSF, cerebrospinal fluid; ED, emergency department; IBI, invasive bacterial infection; LE, leucocyte esterase test; NT, nitrite test; PCT, procalcitonin; UTI, urinary tract infection; WBC, white blood cell count.

Table 2 Factors associated with the diagnosis of an IBI in the derivation sample

	Univariable analysis			Multivariable analysis	
	No IBI (n=628)	IBI (n=34)	P value	OR	95% CI
Male sex, n (%)	429 (68.3)	25 (73.5)	0.52	–	–
Not previously healthy, n (%)	118 (18.8)	4 (11.8)	0.30	–	–
Age (days), mean (SD)	54.4 (23.9)	39.0 (24.6)	<0.01	0.97	0.95 to 0.99
Maximum temperature (°C), mean (SD)	38.8 (0.55)	38.9 (0.62)	0.13	–	–
Hours of fever, mean (SD)	12.5 (20.0)	12.2 (18.0)	0.93	–	–
White blood cells (cells/µL), mean (SD)	15 882.8 (6486.9)	15 970.6 (6411.6)	0.94	–	–
Absolute neutrophil count (cells/µL), mean (SD)	8419.0 (4734.6)	8973.6 (4853.7)	0.51	–	–
C reactive protein (mg/L), mean (SD)	47.9 (58.7)	109.2 (86.8)	<0.01	1.01	1.00 to 1.01
Procalcitonin (ng/mL), mean (SD)	2.13 (7.58)	13.6 (23.1)	<0.01	1.03	1.00 to 1.06
Positive leucocyte esterase test, n (%)	619 (98.6)	34 (100)	0.48	–	–
Positive nitrite test, n (%)	243 (38.7)	17 (50)	0.19	–	–

IBI, invasive bacterial infection.

Mann-Whitney U test; comparison of normally distributed data were performed using the t-test for independent samples. For categorical data, the χ^2 test was used. We considered a p value of <0.05 statistically significant. CIs of proportions were built by the Wilson interval method.

To determine the independent risk factors, we conducted a logistic regression in the derivation set using the diagnosis of an IBI as the dependent variable and including all the variables that showed statistical significance on univariable analysis. For the continuous variables identified by the multivariable analysis and included in the prediction rule, we determined optimal cut-off points using Youden's index.[21]

Finally, to analyse the accuracy of the prediction rule, values of sensitivity, specificity, negative predictive value, positive predictive value and area under the curve (AUC) were calculated for these optimal cut-off points.

Data were analysed with STATA V.14.

RESULTS

We included 1111 patients (662 in the derivation set and 449 in the validation set). The study flowchart is shown in figure 1, and the characteristics of the included patients appear in table 1.

Table 3 Prevalence of IBI according to score, and diagnostic performance for IBI for scores ≥1

	Derivation sample (n=493*)	Validation sample (n=449)
Patients with IBI by score, n (%, 95% CI)		
0	1/155 (0.7, 0.1% to 3.6%)	0/125 (0, 0% to 3%)
1	7/184 (3.8, 1.9% to 7.6%)	2/145 (1.4, 0.4% to 4.9%)
2	11/135 (8.2, 4.6% to 14.0%)	18/156 (11.5, 7.4% to 17.5%)
3	6/19 (31.6, 15.4% to 54.0%)	2/23 (8.7, 2.4% to 26.8%)
Sensitivity (95% CI)	0.960 (0.805 to 0.993)	1.000 (0.867 to 1.000)
Specificity (95% CI)	0.329 (0.288 to 0.373)	0.297 (0.258 to 0.338)
Positive predictive value (95% CI)	0.071 (0.048 to 0.103)	0.068 (0.033 to 0.071)
Negative predictive value (95% CI)	0.994 (0.964 to 0.999)	1.000 (0.974 to 1.000)
Area under the curve (95% CI)	0.645 (0.601 to 0.687)	0.648 (0.605 to 0.689)
Positive likelihood ratio (95% CI)	1.431 (1.292 to 1.585)	1.422 (1.342 to 1.506)
Negative likelihood ratio (95% CI)	0.122 (0.018 to 0.833)	–

*Only patients for whom serum procalcitonin and C reactive protein levels were obtained were included.
IBI, invasive bacterial infection.

The rate of IBI was 5.1% (95% CI 3.7% to 7.1%) in the derivation sample (33 cases of bacteraemia and one patient in whom an *Escherichia coli* strain was isolated in urine, blood and CSF cultures). Meanwhile, 22 (4.9%, 95% CI 3.3% to 7.3%) were diagnosed with an IBI in the validation sample, all presenting bacteraemia. The prevalence of IBI according to age was 9.0% (95% CI 5.9% to 13.3%) in patients aged <28 days, 4.9% (95% CI 3.2% to 7.4%) in patients aged 29–60 days and 3.1% (95% CI 1.9% to 5.1%) in patients aged >60 days.

There were 52 patients with an IBI secondary to UTI. The remaining four IBI were three bacteraemia in the derivation set (due to *Enterococcus faecalis*, *Streptococcus pneumoniae* and *Staphylococcus aureus*, respectively), and one *E. faecalis* bacteraemia in the validation set.

Table 2 shows the association between the different variables and the diagnosis of an IBI for the derivation set. Based on these data, a prediction rule (RISeuP score) was built using three items: age≤15 days, serum PCT level≥0.6 ng/mL and CRP level≥20 mg/L. Each item of the score had a value of 1 point. A RISeuP score of ≥1 predicted IBI with a sensitivity of 96.0% (95% CI 80.5% to 99.3%) and a specificity of 32.9% (95% CI 28.8% to 37.3%) values. The absence of any of these three risk factors identified patients in the derivation sample without an IBI with a negative predictive value of 99.4% (95% CI 96.4% to 99.9%). The only misclassified patient was an infant aged 52 days with *E. faecalis* bacteraemia and CRP=0.08 mg/L and PCT=0.05 ng/mL. The sensitivity and negative predictive value of the model in the validation sample were 100% (95% CI 85.1% to 100%) and 100% (95% CI 97.0% to 100%), respectively. The diagnostic value of the score is shown in table 3.

DISCUSSION

In this large prospective multicentre study, we calculated and validated a prediction rule to identify well-appearing febrile infants aged ≤90 days with an abnormal urine dipstick at low risk of IBI. The proposed score is based on objective findings and has a very high negative predictive value for identifying infants without IBI.

Recently, some authors have devised predictive models that identify infants with a UTI at very low risk of adverse events and bacteraemia, thereby making them suitable for shorter inpatient stays or outpatient management.[13 14] The first rule[13] showed excellent accuracy for adverse events, although it was unable to predict bacteraemia secondary to UTI. Furthermore, this clinical rule applies to febrile infants with a positive urine culture, which

may limit its feasibility in the ED, although it would facilitate earlier discharge of the infants. Years later, a new clinical rule[14] was designed, focusing on patients with abnormal urine dipstick, making this a more practical approach in the ED. Additionally, a positive leucocyte esterase or nitrite test with urine dipstick has been proven to be an independent risk factor for bacteraemia.[12 22] Though not prospectively validated, this clinical rule showed good accuracy.[14] However, the cut-off point of the variables included in this model were chosen based on the step-by-step approach and were not derived from an adequate statistical analysis.[23]

In our multivariable analysis, age and blood PCT and CRP were independent risk factors for IBI, with the adequate cut-off points being 15 days, PCT=0.6 ng/mL and CRP=20 mg/L, maximising the sensitivity of the model with the highest possible specificity. Regarding the age cut-off, values under 15 days were not considered, given that prior research had showed that infants under this age with abnormal urine dipstick are at higher risk of IBI, and the accuracy of biomarkers when ruling out an IBI was lower in the youngest patients.[17 24]

Nearly 30% of the infants included had a RISeuP score of 0 and could have been managed safely as outpatients. It is noteworthy that among the 70% of infants not considered to be at low risk of IBI, the rate of IBI was 6.9%, with a false-positive rate of 68.8%. Applying higher cut-off points for age, PCT and CRP would increase the specificity though at the expense of sensitivity. Since our main objective was to develop a tool with which to safely identify patients at low risk of IBIs, and given the adverse outcomes that misdiagnosis could produce, we believe those items were optimal for the score, no matter the AUC value. However, it must be taken into account that in recent times the trend to manage patients aged >28 days on an outpatient basis has increased.[9] In line with this, in those centres with a higher rate of outpatient management, the use of this clinical rule might have the opposite effect to that desired, increasing the number of patients who would be admitted for antibiotic treatment. In any case, given that nowadays the rate of hospitalisation in these patients in most centres is high, we consider that the implementation of the RISeuP score in practice would mean a global benefit for patients. Furthermore, since the most used criteria to select patients at low risk of bacteraemia still underdiagnosed 3.2% of infants,[13] the use of a clinical tool with greater sensitivity should be an improvement for the clinician.

The lower prevalence of IBI among patients with a RISeuP score of 3 in the validation sample also merits commentary. Since there were no differences between the samples that could explain the elevated biomarker values in the derivation sample such as disparities in mean patient age, nor in the symptom duration, the only plausible explanation for this difference is the low number of patients with a score of 3. In any case, given that only those patients with a RISeuP score of 0 would be candidates for safe management on an outpatient basis, we do not believe that this lower prevalence invalidates our results.

Our study has several limitations. First, the derivation sample was obtained from a retrospective analysis conducted using a single-centre registry. Nevertheless, patients were recruited prospectively, and as all data were obtained from a single hospital, we are confident of their accuracy. Second, the samples differed in some aspects, such us age, maximum temperature and proportion of positive urine cultures. Despite this, we do not consider these differences to be clinically relevant and are unlikely to have biassed the results of the study. Third, we included only well-appearing infants. Not well-appearing infants are at higher risk of bacteraemia and meningitis,[12 15] and since the main goal of the rule was to determine a low-risk group of infants suitable for outpatient management, we decided to exclude not well-appearing patients. On the other hand, it should be underlined that we only had an infant with bacterial meningitis. This could limit the accuracy of this rule to identify well-appearing young infants with febrile UTI and associated bacterial meningitis, but, honestly, we do think that this reflects the low rate of bacterial meningitis in infants with febrile UTI after the neonatal period.[7 8] It is also true that only 16.8% of patients had a lumbar puncture performed, so it is not possible to be sure that no meningitis was missed. However, since a follow-up was made to all patients, and no adverse outcome was reported, it is unlikely that a patient was misdiagnosed.

Another possible limitation involves the use of a single urine dipstick test and the absence of routine microscopic analysis. Although the accuracy of urine dipstick is as good as microscopy testing for diagnosing UTI, it is likely to misdiagnose some patients with a suspected UTI.[25] Also, Mori *et al* proved that urine dipstick performed similarly to microscopy when attempting to rule out a positive urine culture,[10] and our clinical experience is consistent with this finding. Other possible limitation might be that peripheral bands were not analysed as a possible predictor of IBI. Although Schnadower *et al* found a statistically significant association between elevated peripheral band count and bacteraemia in febrile infants with UTI,[13] they are barely used in Europe. Also, the diagnostic value of this biomarker has been proven as moderate, as best.[26] Finally, another limitation might be the colony count threshold chosen to consider a urine culture as positive. Since it is controversial which ones are the optimal cut-off points,[27 28] some patients might be misdiagnosed as UTI. In any case, since the main objective of the score was to select a group of patients at low risk of IBI, we consider that that issue did not bias our results.

CONCLUSION

This prediction rule accurately identified well-appearing febrile infants aged ≤90 days with abnormal urine dipstick at low risk of IBI. The RISeuP score can be used to guide initial clinical decision-making in young febrile infants with abnormal urine dipstick without misclassifying children with IBI.

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Contributors RV conceptualised and designed the study, analysed the data, wrote the initial draft of the manuscript,and approved the final manuscript as submitted. AL collaborated in the data collection, revised multiple versions of the initial manuscript and critically reviewed the final manuscript. BG and MdlT collaborated in the design of the study and in the data collection, revised multiple versions of the initial manuscript and critically reviewed the final manuscript. ID, AC, DdlR, SMa, JR, AG, A-AL, AR, IM, CMA, SMi, SC, JA, PdR, ES, IRdO, IN and BV reviewed, made suggestions and approved the initial version of the protocol, collaborated in the data collection and reviewed, made suggestions and approved the final manuscript as submitted. SMi conceptualised and designed the study, revised multiple versions of the initial manuscript and approved the final manuscript as submitted. All authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.

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