Febrile Young Infants With Altered Urinalysis at Low Risk for Invasive Bacterial Infection. A Spanish Pediatric Emergency Research Network's Study

Roberto Velasco, MD, Helvia Benito, MD,* Rebeca Mozún, MD,* Juan E. Trujillo, MD,* Pedro A. Merino, MD,† and Santiago, PhD,‡ on behalf of the Group for the Study of Febrile Infant of the RISeuP-SPERG Network*

Background: Urinary tract infection (UTI) is the most common serious bacterial infection (SBI) in infants younger than 90 days of age. Many physicians admit infants younger than 90 days old because of their greater risk of developing invasive bacterial infections (IBIs), secondary to UTI. The primary objective of this study was to design a prediction model to identify febrile infants younger than 90 days old with an altered urinalysis who were at low risk for IBI and suitable for outpatient management

Methods: Prospective multicenter study included 19 hospitals that are members of the Spanish Pediatric Emergency Research Group of the Spanish Society of Pediatric Emergencies. Febrile infants younger than 90 days old with altered urinalysis were included.

Results: A total of 766 (22.5%) infants with altered urine dipstick were analyzed. Fifty (6.5%) of them developed IBI, 39 (78.0%) secondary to UTI. Patients were at low risk for IBI if they were well appearing at arrival to the emergency department, were older than 21 days and had procalcitonin and C-reactive protein (CRP) blood values lower than 0.5 ng/mL and 20 mg/L, respectively. These factors were used to create a prediction model for IBI secondary to UTI, with a sensitivity of 100% (95% CI: 89.3–100) and a negative predictive value of 100% (95% CI: 97.5–100).

Conclusions: We have derived a highly accurate prediction model for IBI in febrile infants with altered urinalysis. Given these results, outpatient management might be suitable for 1 of each 4 infants diagnosed, with a considerable improvement in resource utilization.

Key Words: urinary tract infections, infants, bacteremia, meningitis, procalcitonin, C-reactive protein, emergency department, hospitalization

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Urinary tract infection (UTI) is the most common SBI in infants younger than 90 days of age. Depending on the series, 4–12% of febrile illnesses in patients of this age are caused by an UTI.[1–3] Clinical guidelines recommend outpatient treatment with oral antibiotics in patients older than>90 days of age, except when they appear toxic, are dehydrated with electrolyte disturbances, are suspected to have urologic malformation or are unable to take oral medications.[4] Many physicians admit infants younger than 90 days old to avoid complications.

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From the *Pediatrics Department and †Intensive Care Unit, Rio Hortega University Hospital, Valladolid, Spain; and ‡Pediatric Emergency Department, Cruces University Hospital, Barakaldo, Spain.

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Address for correspondence: Roberto Velasco, MD, Pediatrics Department, Rio Hortega University Hospital, C/Pisuerga, 7-3º B, Laguna de Duero, Valladolid 47140, Spain. E-mail: robertovelascozuniga@gmail.com.

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In recent years, several studies have suggested that the probability of complications in young infants without risk factors is as low as in older infants, establishing the option for outpatient treatment for selected patients as well.[3,5,6]

The objective of this study was to design a prediction model to identify febrile infants younger than 90 days old with an altered urinalysis who were at low risk for invasive bacterial infections (IBI) more suitable for outpatient management.

METHODS

Design of the Study

This is a multicenter observational prospective study to determine the risk of IBI in febrile infants younger than 90 days old with altered urinalysis according to their general appearance, age and laboratory tests. The participating centers included 19 hospitals that are members of the Spanish Pediatric Emergency Research Group of the Spanish Society of Pediatric Emergencies.[7] Approval for the study and for data sharing with the coordinating institution and with the centralized data center was granted by the institutional review board at each participating institution. Informed consent was requested to the parents or the caregivers of the patients before including them in the study.

Definitions

- **Fever without source (FWS):** axillary or rectal temperature ≥ 38°C (100.4°F) registered either at home or at the Pediatric Emergency Department (PED), without catarrhal or other respiratory signs/symptoms (such as tachypnoea) or a diarrheal process in patients who had a normal physical examination.
- **Pathological background:** a patient was considered "not previously healthy" because having a history of prematurity (gestational age < 37 weeks), prior admissions in the hospital, chronic diseases, immunosuppression or previous administration of antibiotics.
- **Altered urinalysis:** presence of leukocyturia and/or nitrituria in urine dipstick.
- **Well Appearing:** defined by a normal pediatric assessment triangle in those centers in which these data are systematically recorded in the pediatric medical records.[8] For the other centers, infants were considered to be not well appearing under criteria of the attending pediatric physician.
- **IBI:** isolation of a bacterial pathogen in a blood or cerebrospinal fluid (CSF) culture. Isolation of *Staphylococcus epidermidis*, *Propionibacterium acnes, Streptococcus viridans or Diphtheroides* in inmunocompetent patients without cardiac disease, ventriculoperitoneal shunt, central catheters or other indwelling devices were considered contaminants.
- **SBI:** this definition includes, besides all the IBIs, also UTI, acute gastroenteritis with isolation of bacteria in stool, and isolation of a single pathogen in other sterile locations, as pleural effusion or intraarticular fluid.

- **UTI:** growth of ≥100 cfu/mL of a single pathogen in a urine culture collected by suprapubic aspiration, or ≥50,000 ufc/mL in a urine culture collected by urethral catheterization, or growth of ≥10,000 ufc/mL in a urine culture collected by urethral catheterization if presence of leucocyturia and/or nitrituria in urine dipstick was detected.
- **Possible UTI:** growth of 10,000–50,000 ufc/mL of a single pathogen in a urine culture collected by urethral catheterization if urine dipstick analysis was normal, or mixed growth of ≥50,000 ufc/mL of more than one pathogen if leucocyturia and/or nitrituria in urine dipstick was detected.
- **IBI secondary to UTI:** isolation of the same pathogen in blood or CSF culture than in urine culture.
- **Pleocytosis:** counting at CSF microscopical exam of ≥ 25 cells/mm^3 in infants ≤ 28 days old, or ≥ 10 cells/mm^3 in infants older than 28 days of age.

Epidemiologic, clinical and microbiological data of every infant younger than 90 days old attended in the participant PED with FWS between January 10, 2011 and September 30, 2013 were collected.

Inclusion Criteria

Infants younger than 90 days old presenting with FWS to the PED who had CRP, white blood cell (WBC) count, urine dipstick, urine and blood culture performed when admitted to the evaluation were included in the study.

Exclusion Criteria

We excluded patients for any of the following: (1) no collection of urine and blood culture by sterile method, (2) no determination of WBC or CRP values, (3) patients in whom the history and/or the physical examination suggested the source of the fever and (4) afebrile patients at arrival at PED who had not any measured temperature ≥ 38°C at home, no matter that parents or caregivers complaint of fever, (5) parental refusal to participate and (6) no phone contact to follow-up 1 month after their inclusion in the study.

Data Collection

A standardized form with the following data was filled for every patient included in the study: demographics (age, sex), highest temperature measured at home and at arrival to PED, time between fever was detected and the arrival to the PED, appearance of the patient when arrival to the PED, medical history, physical examination, results of the laboratory and microbiological tests and the final diagnosis and destination of the patient. A phone call was made to every patient's parent to check any unnoticed adverse event 1 month after the inclusion in the study. Also, every month, each investigator had to send the total number of patients and febrile infants attended in its hospital. Data were sent to main investigator using an online formulary of Google Drive platform.

Outcomes

Main outcome of the study was the development of an IBI (see Definitions).

Statistical Analysis

Normally distributed data were expressed as mean (SD); nonnormally distributed data were expressed as median and interquartile range; categorical variables were reported as percentages. For nonnormally 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.

For quantitative variables, as ancillary test values, several cutoff points were studied with univariate analysis, choosing the most discriminative one for each variable.

Variables that showed a P value lower than 0.3 in univariate analysis were included in multivariate analysis to build the predictive model. Multivariate analysis was made using logistic regression, and forward and backward stepwise method was used to select the variables included in final model.

Sensitivity, specificity, positive and negative likelihood ratios (LRs) for the predictive model and their 95% confidence intervals were calculated. Data were analyzed with Stata 12 (Stata Corp., College Station, TX).

RESULTS

Nineteen hospitals participated in the study. Over the 2-year period of study 1,612,210 patients were admitted in the PED of the participant hospitals, including 4008 (0.25%) infants younger than 90 days old with FWS (see Definitions). After applying the exclusion criteria, 3401 (84.9%) infants were finally included. Urinalysis was altered in 766 (22.5%) of the patients. Flowchart of patients is shown in Figure 1. Characteristics and laboratory test results of all the patients with altered urinalysis are shown in the Table, Supplemental Digital Content 1, http://links.lww.com/INF/B958. Urine culture confirmed the diagnosis of UTI in 607 (79.2%) of the patients. Fifty (6.53%) patients with altered dipstick developed IBI. There were 47 bacteremias, 38 of them were secondary to UTI (36 due to *Escherichia coli*, 1 to *Enterobacter cloacae* and 1 to *Staphilococcus aureus*) and 3 meningitis, 1 of them secondary to UTI, due to *E. coli*. Characteristics of patients with and without IBI are shown in Table 1.

Procalcitonin (PCT) blood value was determined in 597 (77.9%) patients. There were no significant differences between the patients with and without PCT blood value determined on age, appearance, hours of fever, CRP blood value or proportion of patients with IBI.

CSF exam was performed in 195 (25.5%) of the patients with altered urine dipstick. Forty-one (21.0%) patients showed pleocytosis. In 1 of them, the same bacteria grew in the CSF and urine cultures (*E. coli*). In the other 2 cases, *S. aureus* grew only in the CSF culture, both of them were considered true pathogens.

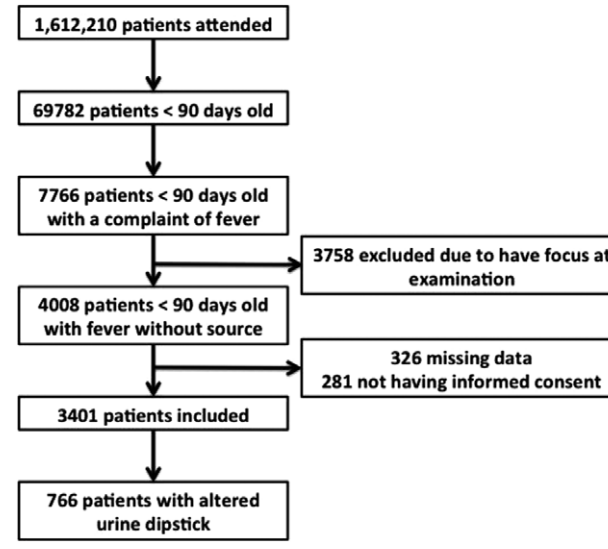

FIGURE 1. Study flow chart.

TABLE 1. Prevalence of IBI Based on the Presence of Each Risk Factor

	IBI	*P* Value
Age		0.005
≤21 days	17/145 (11.72%)	
>21 days	33/621 (5.31%)	
Sex		n.s.
Male	32/496 (6.45%)	
Female	18/270 (6.67%)	
Pathological background		0.007
Yes	1/117 (0.85%)	
No	49/649 (7.55%)	
Urogenital malformation previously diagnosed	1/42 (2.38%)	n.s.
Yes	49/724 (6.77%)	
No		
Irritability		n.s.
Yes	16/176 (9.09%)	
No	34/590 (5.76%)	
Not-well appearance		0.011
Yes	11/85 (12.94%)	
No	39/681 (5.73%)	
WBC		n.s.
≤15,000 cells/mL	26/411 (6.33%)	
>15,000 cells/mL	24/355 (6.76%)	
ANC	33/568 (5.81%)	n.s.
≤10000 cells/ml	17/198 (8.59%)	
>10000 cells/ml		
CRP		<0.001
≤20 mg/L	7/304 (2.30%)	
>20 mg/L	43/462 (9.31%)	
PCT		<0.001
≤0.5 ng/mL	9/368 (2.45%)	
>0.5 ng/mL	30/229 (13.10%)	

ANC, absolute neutrophil count.

Six hundred and ninety-two (90.3%) of patients with a positive urine dipstick were admitted, 9 (1.3%) of them in the pediatric intensive care unit, with a median length of hospitalization of 5 days (interquartile range: 4–7 days).

After multivariate analysis was made, the following remained as risk factors for IBI: not-well appearance at arrival to the PED, the age of 21 days old or younger, a CRP blood value higher than 20 mg/L and a PCT blood value higher than 0.5 ng/mL (Table 2). Those factors were used to create a predictive model for IBIs (Figure 2). As shown in Figure 2, there was no patient who developed an IBI being classified in the low-risk group by the predictive model, showing a sensitivity value of 100% (95% CI: 91.0–100) and a negative predictive value for IBI of 100% (95% CI: 97.5–100).

As PCT remain as risk factor after multivariate analysis, only patients with PCT blood value determined were included in the model. There were 11 IBI in patients excluded of the model because of not having PCT determined. Two of them had an altered Pediatric Assessment Triangle at arrival at the Emergency Department (1 of them was also younger than 21 days old) and 8 of the other 10 had a CRP value higher than 20 mg/L.

TABLE 2. Risk Factors for Developing IBI After Multivariate Analysis

Risk Factor	Odds Ratio	95% CI
Age ≤ 21 days old	2.42	1.18–4.96
Not well appearing	1.82	0.79–4.96
CRP > 20 mg/L	3.82	1.27–11.42
PCT > 0.5 ng/mL	3.32	1.46–7.56

DISCUSSION

UTI is the most common SBI in infants.[9–12] Spanish clinical guidelines recommend inpatient treatment in infants younger than 90 days old[4;] meanwhile, The American Academy of Pediatrics' guidelines set the cutoff age in 60 days.[13] One of the main reasons for this recommendation is the greater risk of developing bacteremia or meningitis secondary to the UTI.[10–14] But not all infant had the same risk of developing an IBI.[15–18] This is the reason several approaches had been taken, trying to select within febrile infants younger than 90 days old a group of patients with low risk of adverse events, that might be suitable for outpatient management.[19,20] This same approach has been taken for febrile infants with an UTI,[3] with a very good sensitivity and negative predictive value for predicting adverse events, but with a rate of false negatives of almost 23% when predicting bacteremia. For this reason, another predictive model was developed including CRP,[21] improving its accuracy, but still having near to 10% of patients with IBI that were not detected by the model.

Recent studies have demonstrated the great value of PCT in diagnosis of IBI in febrile infants,[17,22,23] so it seemed necessary to include it in the model.

Moreover, it has been proven that leukocyturia is a risk factor of IBI.[9] For this reason, our model includes patients with altered urinalysis, not only confirmed UTI, which is the main difference in comparison to other models previously published.[3,21] When a febrile infant is attended in the PED, the physician is only able to make a suspicion diagnosis of UTI, and the purpose of this model is to help to decide which patients could be discharged safely.

All the variables that showed statistical significance as predictors of IBI in the multivariate analysis were incorporated to the predictive model.

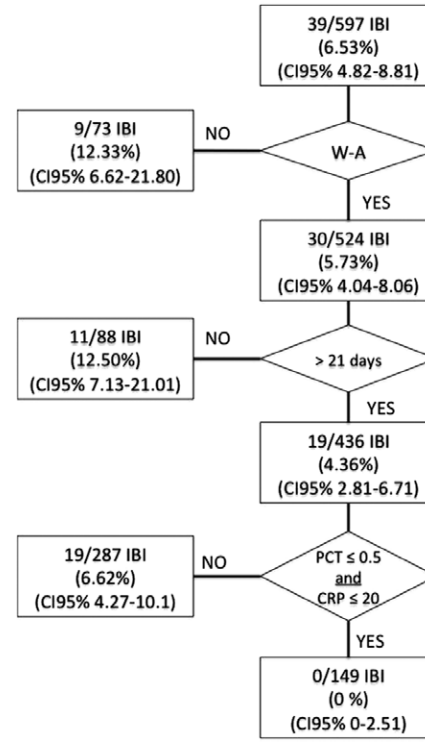

FIGURE 2. Application of the predictive model to patients with altered urine dipstick in studied population. Only patients with altered urine dipstick and PCT value determined are included (n = 597).

Mintegi et al[19] have proven accuracy of a sequential approach to febrile infant to identify patients with low risk of IBI, so this model was structured the same way. Following the "step-by-step" model, patients who are not-well appearing or are under 21 days old are not included in the low-risk group,[24] so inpatient treatment is recommended. In the rest of patients, there is still >4% of IBI. Biomarkers are useful at this point to select which patients are less likely to develop an IBI. Although PCT has shown better performance than CRP to rule in an IBI in several studies,[10,12,17,19,25] a substantial number of patients would be missed if only this biomarker were to be used, so both PCT and CRP have to be included in the model.

It might be possible to choose higher cutoff points, as published in recent studies,[26] but our model has been created trying to achieve maximum sensitivity and negative predictive values, looking for the safest approach. Limits of 0.5 ng/mL for PCT and 20 mg/mL for CRP were chosen, based on previous studies and statistical methods.[19] However, despite these conservative limits, one fourth of the patients are determined as low-risk and might be suitable for outpatient treatment.

The study has several limitations. First of all, appearance of the patient is an important item of the model. For this reason, its accuracy might not be extrapolated to places where patients are attended by less experienced personnel. As Pediatric Assessment Triangle was used in the study, we recommend a good knowledge of that tool before applying this model. Second, PCT values were not determined in all patients. Nevertheless, the main reason for not having PCT determined was that in some hospital, this test was not disposable sometimes, so this data has been considered as missing completely at random, and multivariate analysis has been made only with patients with PCT values determined, without introducing any bias in the results. Also, we can see that there were no significant differences between patients included or not, and the model would include almost all patients whom developed an IBI and without PCT determined in the not-low risk group because other risk factors. The only patient that would have been misdiagnosed by the model in absence of the PCT was a well-appearing 24-day-old girl, who presented in the PED after 2 hours of fever, with a CRP blood value of 2 mg/L, and had a *S. aureus* in the blood culture. It is, precisely, in patients with a few hours of fever in whom PCT has shown much better accuracy than CRP.[17] Nevertheless, as only 39 patients with IBI were finally included in the model, and the in the model were analyzed 5 variables, results could be overfitted, and type II error rate be increased, so the results of the model have to be tested in a different population before applying to practice.

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Members of the Group for the Study of Febrile Infant of the Spanish Pediatric Emergency Research Group of the Spanish Society of Pediatric Emergencies Network are: Catediano E. (Cruces University Hospital, Barakaldo, Spain), González A. (Basurto University Hospital, Bilbao, Spain), Fabregas A. (Vall d'Hebrón University Hospital, Barcelona, Spain), Durán I. (Carlos Haya University Hospital, Málaga, Spain), Moya S. (Parc Tauli Health Corporation, Sabadell, Spain), Herreros M. L. (Infanta Sofía hospital, Madrid, Spain), Rodriguez J. (Virgen de la Arrixaca University Hospital, Murcia, Spain), Montes D. (Fuenlabrada University Hospital, Madrid, Spain), Uribarri F. (San Rafael Hospital, Madrid, Spain), de la Zerda F. (Hospital de Nens, Barcelona, Spain), Garcia E. (Cabueñes Hospital, Gijón, Spain), Crespo E. (Virgen de la Salud University Hospital, Toledo, Spain), Plana M. (Arnau de Vilanova Hospital, Lleida, Spain), Moreno L. (Virgen de las Nieves University Hospital, Granada, Spain), Rivas A. (Gregorio Marañón University Hospital, Madrid, Spain), de la Torre M. (Niño Jesús University Hospital, Madrid, Spain), Manrique I. (Pediatric Institute of Valencia and Quirón Hospital, Valencia, Spain) and Rodriguez A. (Alto Deba Hospital, Arrasate, Spain).

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