Importance of Urine Dipstick in Evaluation of Young Febrile Infants With Positive Urine Culture

A Spanish Pediatric Emergency Research Group Study

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Background and Objectives: Guidelines from the American Academy of Pediatrics define urinary tract infection (UTI) as the growth of greater than 50,000 ufc/mL of a single bacterium in a urine culture with a positive urine dipstick or with a urinalysis associated. Our objective was to evaluate the adequacy of this cutoff point for the diagnosis of UTI in young febrile infants.
Methods: Subanalysis of a prospective multicenter study developed in RISeuP-SPERG Network between October 11 and September 13. To carry out the study, it was performed a comparison of analytical and microbiological characteristics of patients younger than 90 days with fever without focus, taking into account the results of urine dipstick and urine culture.
Results: Of a total of 3333 infants younger than 90 days with fever without focus which were included in the study, 538 were classified as UTI in accordance with American Academy of Pediatrics' guidelines. These patients were similar to those who had a positive urine dipstick and a urine culture yielding of 10,000 to 50,000 ufc/mL, and they were different from those who had a normal urine dipstick and a urine culture >50,000 ufc/mL, being focused on the isolated bacteria and blood biomarkers values. Forty-five invasive bacterial infections were diagnosed (5.9% of the 756 with a urine culture >10,000 ufc/mL). Half of the infants with a normal urine dipstick diagnosed with invasive bacterial infections were younger than 15 days.
Conclusions: It might be inadequate to use a threshold of 50,000 cfu/mL to consider a urine culture as positive in young febrile infants given the fact that it would misdiagnose several UTIs.

Key Words: bacteremia, febrile infants, urinary tract infections, urine dipstick

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Urinary tract infection (UTI) is the most common serious bacterial infection (SBI) in febrile infants less than 90 days of age. Depending on the series, 4% to 12% of febrile illnesses in patients of this age are UTI.[1–3]

American Academy of Pediatrics' Guidelines established the diagnosis of UTI on infants older than 2 months as the combination of a urine culture growing more than 50,000 cfu/mL and a positive urinalysis.[4] This urinalysis may be either a positive urine dipstick result (positive leukoesterase [LE] or nitrituria [NT] test in the urine) or the presence of leukocytes or bacteria in a microscopy examination of the urine sample.[5–8]

In 2011, a unique center study published by Mintegi et al[9] showed that patients with positive urine culture and positive urine dipstick test occurs more commonly altered blood biomarkers than those with a positive urine culture and a normal urine dipstick. The latter ones (positive urine culture and normal urine dipstick) showed the same inflammatory response as patients without any SBI.

Currently, it is not clear how to combine the results of urine dipstick and urine culture to get the best way to diagnose UTI in febrile young infants. If the dipstick is negative, and the urine culture has less than 10,000 cfu/mL, a UTI is unlikely. If the dipstick is positive, and the urine culture has more than 50,000 cfu/mL, then a UTI is more likely. In this article, we examine the less clear combinations of dipstick and urine culture, specifically (1) urine culture with 10,000 to 50,000 cfu/mL with or without a positive dipstick and (2) negative dipstick with urine culture more than 50,000 cfu/mL. This is done by comparing organisms grown, frequency of invasive bacterial infections (IBI), and levels of serum inflammatory markers to see whether infants with these unclear dipstick and urine culture combinations more closely resemble to those with or without UTI.

METHODS

Design of the Study

This is a subanalysis of a multicenter observational prospective study. The original objective was to determine the risk of IBI in febrile infants younger than 90 days with positive urinalysis according to their general appearance, age, and laboratory tests.[10] Centers participating included 19 hospitals members of the Spanish Paediatric Emergency Research Group of the Spanish Society of Paediatric Emergencies (RISeuP-SPERG). The study included all infants less than 90 days old attended in any participant pediatric emergency departments (PEDs) with fever without focus (FWS) between October 1, 2011, and September 30, 2013. All patients of the study were managed following the national guidelines, which recommended to obtain blood and urine culture in every infant younger than 90 days with FWS. Also, blood and urine samples were obtained for biomarkers determination (white blood cell count, C-reactive protein [CRP]) and urine dipstick test, respectively. Procalcitonin was not determined in every patient, depending on whether the test was available at that moment in the hospital or not. Examination of urine samples under microscope was not routinely made in the participant hospitals, so these data were not collected. Lumbar puncture was made under physician's criteria.

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. Before including patients in the study, an informed consent was requested to parents or caregivers.

Definitions

- FWS: axillar or rectal temperature of 38°C (100.4°F) or higher registered either at home or at the PED, without catarrhal or

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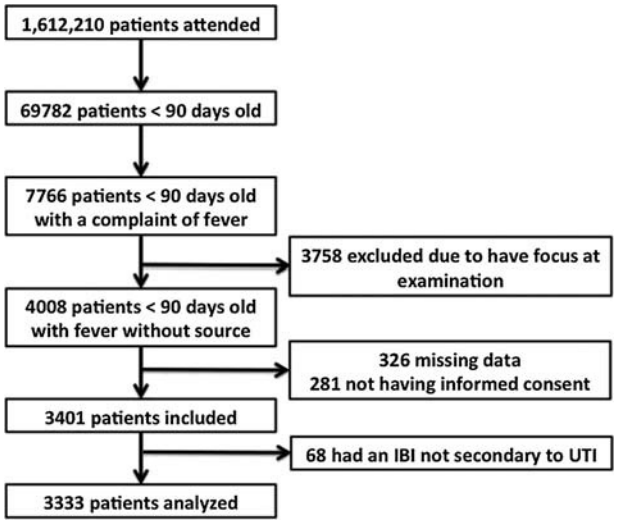


FIGURE 1. Study flowchart.

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 Pediatric Assessment Triangle in those centers in which these data are systematically recorded in the pediatric medical records.[11] For the other centers, infants were considered to be not well-appearing under criteria of an expert pediatrics physician.
- Positive urine dipstick: presence of positive LE and/or NT test in urine dipstick.
- Positive urine culture: culture growing > 10,000 cfu/mL of a single organism in a urine culture collected by a sterile method. The cultures are divided in those growing 10,000 to 50,000 cfu/mL and those growing greater than 50,000 cfu/mL.
- IBI: isolation of a bacterial pathogen in a blood, cerebrospinal fluid culture or other sterile locations, as pleural effusion or intraarticular fluid. Isolation of *Staphylococcus epidermidis*, *Propionibacterium acnes*, *Streptococcus viridans,* or *Diphtheroides* in immunocompetent patients without cardiac disease, ventricle-peritoneal shunt, central catheters, or other indwelling devices were considered contaminants.
- SBI: this definition includes, besides all the IBIs, also UTI, and acute gastroenteritis with isolation of pathogenic bacteria in stool.
- IBI secondary to UTI: isolation of the same pathogen in blood or cerebrospinal fluid culture than in urine culture.

Epidemiologic, clinical, and microbiological data of every infant younger than 90 days attended in the participant PED with FWS between October 1, 2011, and September 30, 2013, were collected.

Inclusion Criteria

The study included all infants younger than 90 days who were seen at the PED presenting with FWS who had CRP, white blood cell count, urine dipstick, urine and blood culture performed when admitted to the evaluation.

Exclusion Criteria

The study exclude *any* of the following patients: (a) no collection of blood culture, (b) no collection of urine culture by urethral catheterization or suprapubic aspiration, (c) afebrile patients which arrive at PED and had not measured temperature of 38°C or higher at home, even if parents or caregivers complain of fever, and (d) parental refusal to participate.

For the purpose of this substudy, patients with an IBI *not* secondary to a UTI were also excluded, considering that they could suppose a bias, because they could have elevated blood biomarkers due to their IBI, not to the UTI.

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 PED arrival, time between fever was detected and when arrives to PED, appearance of the patient when arrives 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 1 month after the inclusion in the study to check any unnoticed adverse event. Also, every month, each investigator had to send the total number of patients and febrile infants that have attended in its hospital. Data have been sent to the main investigator by using an online formulary of Google Drive platform.

Statistical Analysis

Normally distributed data were expressed as mean and SD; non-normally distributed data were expressed as median and interquartile range; categorical variables were reported as percentages. Continuous variables within non-normal distribution were transformed to achieve normality. Comparison of normally distributed data was performed by using analysis of variance test. Linear regression was made to analyze differences in continuous variables between groups, adjusting by potential confounders as age, appearance, and hours of fever. For categorical data, the χ^2 test was used. Parameters displaying values less than 0.05 were considered statistically significant. Data were analyzed with Stata 12 (Stata Corp, College Station, Tex).

RESULTS

Over the 2-year period of the study, 1,612,210 patients were admitted in the PED of the participant hospitals, including 4008 (0.25%) infants younger than 90 days with FWS. After applying the exclusion criteria, 3401 (84.9%) infants were included in the original study. For this subanalysis, 68 (2.0%) were excluded because they have an IBI not secondary to UTI. Finally 3333 patients were included for this substudy. Flowchart of the patients is shown in Figure 1.

TABLE 1. Bacteria Isolated in the Urine Cultures in Young Febrile Infants With a Growth ≥50,000 cfu/mL in the Urine Culture With and Without Altered Urine Dipstick

	UD− (n = 154)	UD + (n = 605)
E. coli	85 (55.2)	540 (89.3)
K. pneumoniae	18 (11.7)	27 (4.5)
E. faecalis	26 (16.9)	8 (1.3)
E. cloacae	4 (2.6)	6 (1.0)
P. aeruginosa	1 (0.7)	5 (0.8)
K. oxytoca	9 (5.8)	3 (0.5)
Other*	11 (7.1)	16 (2.6)

*Other bacteria are *C. freundii*, *S. aureus*, *P. mirabilis*, *S. agalactiae*, *E. asburiae*, *S. marcescens*, *M. morganii.*

TABLE 2. Microbiological Characteristics of Patients Depending on the Result of Urine Dipstick and Urine Culture

Urine Dipstick	Negative (n = 2582)			Positive (n = 751)		
Urine culture, cfu/mL	<10,000 (n = 2,426)	10,000-50,000 (n = 52)	>50,000 (n = 104)	<10,000 (n = 151)	10,000-50,000 (n = 62)	>50,000 (n = 538)
E. coli, %	—	26 (50)	58 (55.8)	—	51 (82.3)	484 (90)
Median CRP (IQR), mg/L	5.6 (2.3-12)	6.35 (2-19.2)	6.65 (4.6-24.6)	7.4 (3-24)	33.8 (11-64)	37 (14-75.3)
Median PCT (IQR), ng/mL	0.12 (0.1-0.2)	0.1 (0.08-0.2)	0.14 (0.09-0.3)	0.11 (0.09-0.38)	0.5 (0.16-1.2)	0.41 (0.17-1.7)
IBI secondary to UTI, %	—	3 (5.8)	3 (2.9)	—	1 (1.6)	38 (7.1)

IQR, interquartile range.

Mean age was 46.8 (SD, 23.6) days, 1985 (59.7%) being male patients. Urine dipstick results were positive in 754 (22.6%) patients: LE test positive, 489 (64.9%); NT positive, 22 (2.9%); both LE and NT positive, 243 (32.2%). Only 64 (1.9%) urine samples were collected by suprapubic aspiration, the being rest collected by urethral catheterization.

Urine culture growth greater than 50,000 cfu/mL in 648 (19.4%) patients, and between 10,000 and 50,000 cfu/mL in 110 (3.3%). *Escherichia coli* was the most frequently isolated bacteria, growing in 625 (82.4%) of the urine culture, with a higher proportion in those patients with a positive urine dipstick. Bacteria isolated in urine culture of patients with and without a positive urine dipstick are shown in Table 1.

In Table 2, blood levels of biomarkers and percentage of either urine culture positive to *E. coli* are shown and IBI on each group of patients depending on the result of the urine dipstick test and the number of colony form units isolated in the urine culture. Most of the patients with IBI are included in the group with positive urine dipstick and urine culture growing greater than 50,000 cfu/mL. Characteristics of patients with negative urine dipstick who developed an IBI are described in Table 3. Boxplot showing distribution of values of CRP and procalcitonin (PCT) of each group of patients are shown in Figures 2 and 3. Values of these variables were transformed to achieve normal distribution. After adjusting by age, appearance, and hours of fever, patients with positive urine dipstick and urine culture with greater than 10,000 cfu/mL had significant higher values than the other ones.

DISCUSSION

Although American Academy of Pediatrics' guidelines for UTIs in patients older than 2 months only consider a urine culture as positive when growing greater than 50,000 cfu/mL,[4] several authors had proposed a more conservative threshold of 10,000 cfu/mL to consider a urine culture positive due to risk of misdiagnosing real UTIs.[8,9,12,13] Our study suggests that this threshold should not be extrapolated to younger patients. In fact, young febrile infants with a urine culture with a growth of 10,000 to 50,000 cfu/mL with associated altered urine dipstick have to be firmly considered to have a UTI. These patients did not show significant differences compared with those with a growth greater than 50,000 cfu/mL with associated altered urine dipstick related with the isolated bacteria and alterations of the biomarkers. Also, this study supports strongly to consider the value of altered urine dipstick in the final diagnosis of UTI in this population. On the other hand, febrile infants with a positive urine culture without an altered urine dipstick may represent, in a significant number of cases, asymptomatic bacteriuria.

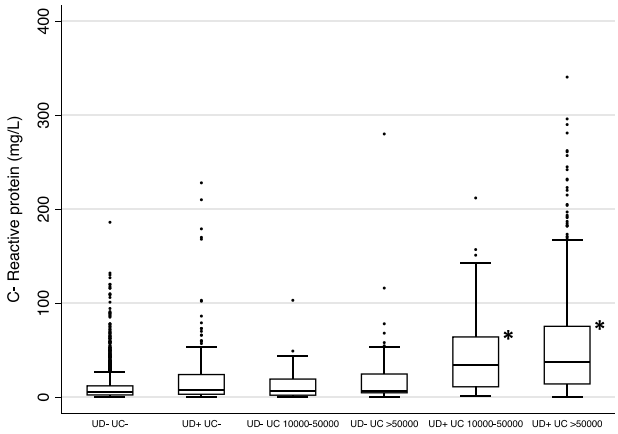
Spanish guidelines only take into consideration the number of colonies isolated in a urine culture to diagnose a UTI, regardless the result of the urinalysis.[14] However, Mintegi et al[9] published a study in 2011 showing that patients with a positive urine culture and an altered urinalysis presented higher level of blood biomarkers than those who have a positive urine culture and a normal urinalysis. The latest ones had the same inflammatory response as patients without any SBI. However, nevertheless, this study was unicenter with a limited number of patients included.

We have analyzed a large sample derived from a prospective multicenter study to create a predictive model of patients with suspected UTIs with low risk to develop IBIs.[10] The sample has been divided in 6 groups, based on the results of the urine dipstick (positive or negative) and the number of colonies growing in the urine culture. It has been observed that the proportion of urine bacterial culture grown different from *E. coli* is greater in patients with a normal urine dipstick test. Although these bacteria may cause UTI mainly in patients with urogenital abnormalities,[15] some of these positive urine culture might mean colonization of the urinary tract or contamination of the catheter.[16] Besides, our results show a higher inflammatory response in patients with a positive urine dipstick test and also show that patients with a positive urine culture and normal urine dipstick show the

TABLE 3. Characteristics of Patients Who Developed Invasive Bacterial Infection on Patients With Normal Urine Dipstick and Urine Culture With > 10000 cfu/mL

Patient	Age, d	Sex	W-A	Hours of Fever	CRP, mg/L	PCT, ng/mL	UC, cfu/mL × 10^3	Bacteria (Blood and Urine Culture)
1	6	Male	Yes	1	44	0.76	10-50	*E. coli*
2	11	Male	Yes	2	2	0.2	10-50	*E. coli*
3	34	Female	No	0.5	28	2	10-50	*S. agalactiae*
4	44	Male	Yes	12	27	0.13	>50	*E. coli*
5	67	Male	Yes	5	7	0.57	>50	*K. pneumoniae*
6	8	Male	Yes	2	48	—	>50	*E. faecalis*

W-A indicates well appearance; UC, urine culture.



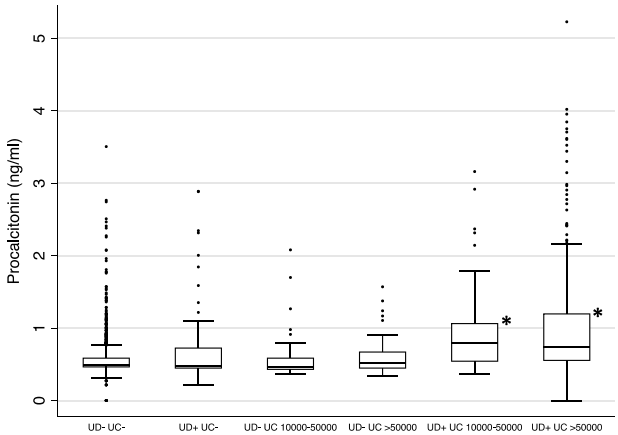
UC: urine culture; UD: urine dipstick
**: p<0.001 (after multivariate analysis)*

FIGURE 2. Values of C-reactive protein in each group.

same CRP and PCT blood values than patients with no SBI confirmed by culture. These data are consistent with the data presented by Mintegi et al[9] and suggest that patients with normal urine dipstick and positive urine culture might be asymptomatic bacteriuria, and the source of the fever could be a viral infection.

In our environment, there is still a wide variability in the management of patients with normal urine dipstick and positive urine culture, but there is a majority of physicians who tend to avoid treating patients with antibiotics if, by the time that the result of the urine culture is obtained, the patient is afebrile and well appearing. Unfortunately, our study's results do not allow us to make any recommendation about it, so future research should be made on this topic.

However, it is a remarkable fact that there are 6 IBIs secondary to UTI in patients with normal urine dipstick test und urine culture with greater than 10,000 cfu/mL. Three of them are younger than 15 days, this suggests that the youngest patients should be treated more aggressively, regardless of their results of ancillary tests, as suggested by other investigators.[12,17] The other 3 patients showed elevated values of PCT and CRP, suggesting that blood biomarkers might be a useful tool to determine whether a positive urine culture in a patient with normal urine dipstick could be a real UTI or not.[18]



UC: urine culture; UD: urine dipstick
**: p<0.001 (after multivariate analysis)*

FIGURE 3. Values of procalcitonin in each group (n = 2755).

It should be understood that the presence of these 6 patients, apparently in contradiction with the data shown above, is due to the fact that patients with negative urine dipstick and urine culture growing greater than 10,000 cfu/ml are not a homogeneous group. Probably, to define whether a patient with a positive urine culture has a UTI or not, blood biomarkers should be used, instead of urinalysis only. In fact, although there was a 3.8% of patients in the group with IBI and normal urine dipstick versus the 6.5% in the altered urine dipstick group, only patients older than 15 days with normal blood biomarkers levels (CRP < 20 mg/L and PCT < 0.5 ng/mL) were analyzed, and there was no IBI, which suggests that a proportion of these patients might be febrile infants with asymptomatic bacteriuria instead of a real UTI.

Our study has some limitations. First of all, some of the groups have few patients. Nevertheless, multivariate analysis showed significant differences between groups in CRP and PCT values. Second, patients that were excluded, because they have an IBI not secondary to UTI, had significant differences with the remaining patients. These patients presented a bacteraemia and/or meningitis caused by different germs than in UTI, their CRP and PCT values might be elevated, and it would have supposed a bias, so the investigators preferred to assume the limitation. Third, scintigraphy is not routinely performed on all patients, so it is not possible to determine which patients had real UTIs.[19] However, it has been proven that higher values of blood biomarkers, mainly PCT, are associated with renal parenchyma involvement.[18,20–23]

Considering the results of our study, we propose that thresholds given by the American Academy of Paediatrics' Guidelines for patients older than 2 months old should not be used for younger infants. Instead, young febrile infants with a urine culture growing more than 10,000 cfu/mL of a single pathogen with an altered urine dipstick should be considered as a UTI. Furthermore, for febrile infants older than 15 days, with a urine culture greater than 10,000 cfu/mL, negative urinalysis and normal blood CRP and PCT values might be managed individually, maybe with a conservative approach, because many of them may have an asymptomatic bacteriuria, although future research should be made on this point to confirm this hypothesis.

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