

## REGULAR ARTICLE

# Using a urine dipstick to identify a positive urine culture in young febrile infants is as effective as in older patients

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## Keywords

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## ABSTRACT

**Aim:** There is limited evidence about the diagnostic value of urine dipsticks in young febrile infants. The aim of this study was to determine whether urine dipsticks would identify positive urine cultures in febrile infants of less than 90 days of age.

**Methods:** This study was a subanalysis of a prospective multicentre study developed in 19 Spanish paediatric emergency departments belonging to the Spanish Paediatric Emergency Research Network. It focused on febrile infants of less than 90 days of age admitted between October 2011 and September 2013. A positive urine culture was defined as the growth of  $\geq 50\,000$  cfu/mL of a single pathogen collected by a sterile method.

**Results:** We included 3401 patients, and 176 (12.8%) female patients and 473 (23.3%) males had a positive urine culture. The leucocyte esterase test showed a mean sensitivity of 82.1% and a mean specificity of 92.4%, with a greater mean negative predictive value for females than males (97.8 versus 94.1%) and a greater mean positive predictive value for males than females (79.4% versus 58%).

**Conclusion:** The leucocyte esterase test showed the same accuracy in young febrile infants as previously reported findings for older children. It predicted positive urine cultures and also revealed important gender differences.

## INTRODUCTION

Urinary tract infection (UTI) is the most common serious bacterial infection in febrile infants less than 90 days of age. Depending on the series, 4–12% of febrile patients in this age group are diagnosed with an UTI (1–3).

The gold standard for diagnosing an UTI is a quantitative urine culture, but it has a handicap that its result is not available in the first 48 h. When a patient is evaluated in a paediatric emergency department, a suspicion diagnosis has to be made as accurately as possible. Several methods have been used, such as urine examination under microscopy or Gram stain, with different results (4,5). However, the most comprehensive method for screening the UTI is the detection of the presence of leucocyte esterase or nitrites in urine, with a urine dipstick analysis (6). Several studies have analysed the accuracy of the urine dipstick for diagnosis of

UTI (4,7–12), but most of them include patients older than 2 months of age. The American Academy of Pediatrics' guidelines describe sensitivity and specificity values of 93% and 72% for either the presence of leucocyte esterase or nitrites in the urine dipstick in febrile infants between 2 and 24 months of age (7).

The primary objective of the study was to determine the accuracy of urine dipstick to identify febrile infants of less than 90 days of age with a positive urine culture.

## Key notes

- There is limited evidence about the diagnostic value of urine dipsticks in young febrile infants, and we explored whether they would identify positive urine cultures in those under 90 days of age.
- We studied 3401 patients seen in 19 Spanish paediatric emergency departments and the leucocyte esterase test showed the same accuracy in young febrile infants as previously reported in older children.
- The test predicted positive urine cultures and revealed important gender differences.

## Abbreviations

CFU, Colony-forming units; FWS, Fever without source; LR, Likelihood ratio; NPV, Negative predictive value; PPV, Positive predictive value; UTI, Urinary tract infection.

## METHODS

### Design of the study

This is a subanalysis of a multicentre observational prospective study designed to determine the risk of invasive bacterial infection (IBI) in febrile infants of less than 90 days of age with altered urinalysis according to their general appearance, age and laboratory tests (13).

Approval for the study and data sharing with the coordinating institution was granted by the institutional review board at each participating institution. Informed consent was obtained from the parents or caregivers of the patients before including them in the study.

### Definitions

We used the following definitions. Fever without source (FWS) was defined as axillary or rectal temperature  $\geq 38^{\circ}\text{C}$  ( $100.4^{\circ}\text{F}$ ) registered either at home or at paediatric emergency department, without catarrhal or other respiratory signs/symptoms (such as tachypnoea) or a diarrhoeal process in patients who underwent a normal physical examination. A leucocyte esterase test was considered as altered if a positive result ( $>1+$ ) of a leucocyte esterase test on the urine dipstick was found. Also, a nitrites test was defined as altered when a positive result of a nitrite test on the urine dipstick was found. The threshold for considering a urine culture as positive was the growth of  $\geq 50\,000$  cfu/mL of a single pathogen in a urine culture collected by a sterile method (urethral catheterization, suprapubic aspiration) (6). Finally, an IBI was defined as the isolation of a bacterial pathogen in blood or cerebrospinal fluid culture. Isolation of *Staphylococcus epidermidis*, *Propionibacterium acnes*, *Streptococcus viridans* or *Diphtheroides* in immunocompetent patients without cardiac disease, ventricle-peritoneal shunt, central catheters or any other indwelling devices that were considered contaminants.

Combur-test<sup>®</sup> strips (Roche Diagnostics, Basel, Switzerland) were used for the urine test. Urine dipsticks were read by trained nurses in the emergency department.

### Inclusion criteria

Following local protocols, blood and urine samples were obtained from all infants younger than 90 days of age admitted to the paediatric emergency department with FWS. Those who had received tests for C-reactive protein, a white blood cell count, urine dipstick, urine and blood culture during the initial evaluation were included in the study.

### Exclusion criteria

We excluded patients for any of the following reasons: (i) no collection of urine or blood culture by sterile method, (ii) no determination of white blood cells count or C-reactive protein values, (iii) patients in whom the anamnesis and/or the physical examination made by an expert paediatrician suggested the source of the fever, (iv) afebrile patients who arrived at the paediatric emergency department who had no registered temperature  $\geq 38^{\circ}\text{C}$  at home, despite parents or caregivers complaining of fever, and (v) parental refusal to participate.

### Data collection

The following data were collected for every patient included in the study: demographics (age, sex), highest temperature measured at home and on arrival at the paediatric emergency department, duration of the fever before arriving to the paediatric emergency department, appearance of the patient in the initial evaluation, medical history, physical examination, results of laboratory and microbiological tests, and the final diagnosis and destination of the patient. A phone call was made to every patient's parent to confirm any unnoticed adverse event. Each investigator also supplied monthly figures on the number of patients and febrile infants who were treated at their hospital. Data were sent to the lead investigator using an online Google Drive<sup>®</sup> platform.

### Outcomes

The main outcome of the study was the detection of a positive urine culture (see *Definitions*).

### Statistical analysis

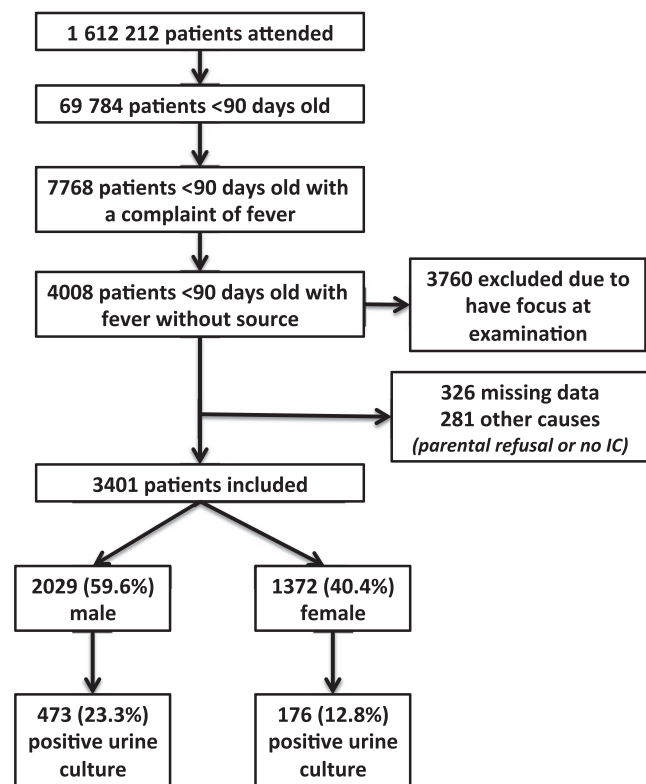
Normally distributed data were expressed as means and standard deviations (SD), non-normally distributed data were expressed as medians and interquartile ranges, and categorical variables were reported as percentages. To compare accuracy of the urine dipstick in young febrile infants, 95% confidence intervals were found and compared with those published in the literature for older patients. To analyse differences between genders, a comparison was performed employing the Mann-Whitney U-test for non-normally distributed data and independent samples t-tests for normally distributed data. The chi-squared test was used for categorical data. Parameters displaying  $p < 0.05$  were considered statistically significant. Data were analysed with Stata 12 (Stata Corp., College Station, TX, USA).

## RESULTS

Over the 2-year period of the study, 1 612 210 patients were admitted to the paediatric emergency department of the participant hospitals. A flow chart of patients is shown in Figure 1.

Patient characteristics are listed in Table 1. Urine dipstick results were altered in 766 patients (22.5%): 496 had exclusively altered leucocyte esterase tests (14.6%), 24 had exclusively altered nitrites tests (0.7%), and 246 had alterations of both leucocyte esterase and nitrites in their test results (7.2%). Only 14 samples (1.8%) were collected by suprapubic aspiration, while the rest were collected by urethral catheterisation.

The urine culture was positive in 649 (19.1%) of the patients: 473 (23.3%) of the males and 176 (12.8%) of the females. *Escherichia coli* was the most frequently isolated bacteria, growing in 550 (84.8%) of the urine cultures. In Table 2, the results of the urine cultures are shown, stratified by gender. Only 34 infants with previously diagnosed urological abnormalities had a positive urine culture. *Escherichia coli* was the isolated bacteria in 20



**Figure 1** Study flow chart.

(58.8%) of these cultures, and this difference showed a statistical significance when compared with urine cultures of infants without malformations ( $p < 0.001$ ).

Sensitivity, specificity, positive and negative predictive values (PPV/NPV) and positive and negative likelihood ratios (LR+/LR-) of urine dipstick for the prediction of a positive urine culture are listed in Table 3. The same results are listed in Table 4, but stratified by gender.

**DISCUSSION**

Our study is, as far as we know, the first one to analyse the accuracy of a urine dipstick to diagnose a positive urine culture using the American Academy of Pediatrics’ threshold of 50 000 cfu/mL. Given our results, urine dipsticks should be considered an accurate screening test for UTI in young febrile infants, as already demonstrated in older patients.

UTI is the most common serious bacterial infection in febrile infants of less than 90 days of age (1–3). Moreover, the risk of developing an IBI, mainly bacteraemia, secondary to UTI is higher in these patients (13–15). The gold standard for the diagnosis of UTI is the growth of a single pathogen in a urine culture (6). But the result of a urine culture usually takes about 48 h, so the emergency physician needs some other tool to make a primary diagnosis of UTI. Several guidelines recommend using urinalysis, with observation of the urine sample under microscopy (16), or a

**Table 1** Characteristics of the patients

Age in days mean (SD)	46.6 (23.6)
Male sex n (%)	2029 (59.6)
Previously healthy† n (%)	2940 (86.4)
Urogenital malformation previously diagnosed n (%)	104 (3.1)
Well appearing n (%)	3035 (89.2)
Hours of fever median (IQR)	5 (10)
Maximum temperature at home mean (SD)	38.4 (0.49)
Maximum temperature at ED mean (SD)	38.1 (0.73)
WBC median (IQR)	10 500 (7080)
CRP median (IQR)	7.3 (17.1)
PCT median (IQR)	0.13 (0.19)
IBI n (%)	107 (3.2)
Final diagnose	
Fever without source	2048 (60.2)
UTI	704 (20.7)
Possible UTI	43 (1.3)
Meningitis	
Bacterial	17 (0.5)
Viral	106 (3.1)
Inespecific	48 (1.4)
Occult bacteraemia	31 (0.9)
Sepsis	19 (0.6)
Pneumonia	12 (0.4)
Flu	95 (2.8)
Others	278 (8.2)

CRP, C-reactive protein; ED, emergency department; IBI, invasive bacterial infection; IQR, interquartile range; PCT, procalcitonin; UTI, urinary tract infection; WBC, white blood cell count.

†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.

**Table 2** Result of urine cultures stratified by gender

	All	Male	Female
<i>Escherichia coli</i>	550 (84.8)	397 (83.9)	153 (86.9)
<i>Klebsiella pneumoniae</i>	36 (5.6)	30 (6.3)	6 (3.4)
<i>Enterococcus faecalis</i>	24 (3.7)	17 (3.6)	7 (4)
<i>Enterobacter cloacae</i>	8 (1.2)	6 (1.3)	2 (1.1)
<i>Streptococcus agalactiae</i>	1 (0.2)	0 (0)	1 (0.6)
<i>Klebsiella oxytoca</i>	7 (1.1)	6 (1.3)	1 (0.6)
Others†	23 (3.5)	17 (3.6)	6 (3.4)

†*Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Citrobacter freundii*, *Enterobacter aerogenes*, *Proteus mirabilis*.

Gram stain of the urine sample. However, both of these methods need the presence of an analyst in the hospital, which makes them more expensive and increases the time needed for diagnosis. This is why most hospital physicians use the urine dipstick as a screening method for UTI (4–6). This method detects the presence of leucocyte esterase in the urine, an enzyme released from leucocytes associated with an inflammatory reaction secondary to the UTI, and the presence of nitrites, as a product of the transformation of nitrates in the diet by the bacteria. Several studies have

**Table 3** Diagnostic performance of leucocyte esterase and/or nitrites on urine dipstick testing for urine cultures with more than 50 000 cfu/mL

Test	n	UC +	UC -	Sn (CI 95%)	Sp (CI 95%)	PPV (CI 95%)	NPV (CI 95%)	LR+ (CI 95%)	LR- (CI 95%)
LE+	742	533	209	82.1 (79–85)	92.4 (91.4–93.4)	71.8 (69–74.5)	95.6 (94.9–96.3)	10.8 (9.5–12.4)	0.19 (0.16–0.23)
NT+	270	241	29	37.1 (33.4–41)	98.9 (98.5–99.3)	89.3 (85.1–92.4)	87 (86.3–87.6)	35.2 (24.2–51.3)	0.64 (0.60–0.67)
LE+ or NT+	766	544	222	83.8 (80.8–86.6)	91.9 (90.9–92.9)	71 (68.3–73.6)	96.0 (95.3–96.6)	10.4 (9.1–11.8)	0.18 (0.15–0.21)
LE+ and NT+	246	230	16	35.4 (31.8–39.3)	99.4 (99.1–99.7)	93.5 (89.7–95.9)	86.7 (86.1–87.4)	61 (37–100)	0.65 (0.61–0.69)

LR, likelihood ratio; LE, leucocyte esterase; NPV, negative predictive value; NT, nitrites; PPV, positive predictive value; Sn, sensitivity; Sp, specificity; UC, urine culture.

**Table 4** Diagnostic performance of leucocyte esterase and/or nitrites on urine dipstick testing for urine cultures with more than 50 000 cfu/mL. Highlighted in bold typing are values with statistical significant differences between genders

Test	Gender	n	Sn (CI 95%)	Sp (CI 95%)	PPV (CI 95%)	NPV (CI 95%)	LR + (CI 95%)	LR - (CI 95%)
LE+	Male	480	80.5 (76.7–84)	93.6 (92.3–94.8)	<b>79.4 (76–82.4)</b>	<b>94.1 (92.9–95)</b>	12.7 (10.4–15.4)	0.21 (0.17–0.25)
	Female	262	86.4 (80.4–91.1)	90.8 (89–92.4)	<b>58 (53.4–62.5)</b>	<b>97.8 (96.9–98.5)</b>	9.4 (7.8–11.3)	0.15 (0.10–0.22)
NT+	Male	181	34.5 (30.2–38.9)	98.8 (98.2–99.3)	90.1 (84.9–93.6)	<b>83.2 (82.3–84.1)</b>	29.8 (18.5–47.9)	0.66 (0.62–0.71)
	Female	89	44.3 (36.8–52)	99.1 (98.4–99.5)	87.6 (79.4–92.9)	<b>92.4 (91.4–93.2)</b>	48.2 (26.2–88.8)	0.56 (0.49–0.64)
LE+ or NT+	Male	496	82.2 (78.5–85.6)	93.1 (91.8–94.3)	<b>78.4 (75.1–81.4)</b>	<b>94.5 (93.4–95.4)</b>	12 (9.9–14.4)	0.19 (0.16–0.23)
	Female	270	88.1 (82.3–92.5)	90.4 (88.6–92)	<b>57.4 (52.9–61.8)</b>	<b>98.1 (97.2–98.7)</b>	9.2 (7.6–11)	0.13 (0.09–0.2)
LE + and NT +	Male	165	32.8 (28.6–37.2)	99.4 (98.8–99.7)	93.9 (89.2–96.7)	<b>82.9 (82–83.8)</b>	51 (27.1–95.8)	0.68 (0.64–0.72)
	Female	81	42.6 (35.2–50.3)	99.5 (98.9–99.8)	92.6 (84.7–96.6)	<b>92.2 (91.2–93)</b>	84.9 (37.5–192)	0.58 (0.51–0.66)

LR, likelihood ratio; LE, leucocyte esterase; NPV, negative predictive value; NT, nitrites; PPV, positive predictive value; Sn, sensitivity; Sp, specificity.

evaluated the accuracy of a urine dipstick for diagnosis of UTI, but most of them included few patients younger than 90 days of age (6,17). The only study that we found that analysed diagnostic performance of urine dipstick in patients younger than 60 days of age used a cut-off point of 10 000 colony-forming units (CFU) to consider a urine culture as positive. Given the fact that American Academy of Paediatrics' Guidelines accept a threshold of 50 000 cfu/mL, the diagnostic values in that study are barely useful (6,18). It is quite controversial to establish the cut-off point for a positive urine culture, but for our study, we used the definition of the American Academy of Pediatrics (6).

Classically, it has been considered that a urine dipstick have had a lower diagnostic value in young infants than in older children (4,7). In our study, we found sensitivity and specificity values of 82.1% and 92.4%, respectively, for the leucocyte esterase test and similar sensitivity values have been published for older patients, with even higher specificity values (6,19). Nitrites test do have lower sensitivity values than published, with the same specificity, but given that few patients exclusively show a positive nitrites test, it does not significantly affect global performance of the urine dipstick. LR+ and LR- for a positive urine dipstick (either leucocyte esterase or nitrites positive test) in our sample were 10.4 and 0.18, respectively, without significant differences when compared with those published by Mori et al. in infants less than 1 year old, and the same LR- showed by patients older than 1 year old (4). Taking into account that bacteraemia is more frequent in younger infants and leukocyturia has been proven a risk factor for developing bacteraemia, even without a positive urine culture (20), an

altered urine dipstick test seems to be at least as useful in this group of young patients as in older ones. In this way, the physician in charge should start antibiotics in any febrile young infant showing altered leucocyte esterase and, or, nitrites test. Not to initiate antibiotics should not be an acceptable strategy, although around three in each 10 patients would be a false positive. To reduce the proportion of false positives, blood biomarkers (C-reactive protein or procalcitonin) could be considered in the evaluation of these infants, but this subject is beyond the scope of this paper, and further research should be carried out on this topic (21–24). Nevertheless, the most important implication for a clinician is that our study confirms that a negative urine dipstick allows a physician to rule out an UTI in a young febrile infant safely, with a false-negative rate of 4%.

As far as we know, no previous study has analysed the accuracy of urine dipstick by gender in febrile young infants. In our study, we can see that negative predictive values for leucocyte esterase and nitrites in female patients were higher, while male patients had significantly higher positive predictive values leucocyte esterase test results. This is easily explainable due to the higher prevalence of UTIs in male patients (23.3% versus 12.8%).

However, despite the lack of statistical significance, we can see that the sensitivity of all the tests seemed to be higher in female patients. Moreover, the LR+ of leucocyte esterase test was higher in males. Given that sensitivity and specificity values and likelihood ratios are not influenced by prevalence (25), this may indicate that the performance of urine dipstick tests is different when it comes to gender. Although it is difficult to find an explanation for this, we

observed that the number of urine cultures growing unusual UTI pathogens, other than *E. coli*, was higher in male patients. These unusual pathogens are more common not only in patients with congenital deformity of the urinary tract, but also in uncircumcised patients (26). If only urine cultures growing unusual bacteria were analysed, excluding patients with previously diagnosed urological abnormalities (27), the sensitivity of the leucocyte esterase test would be only 49.4%. Higher rates of contaminated urine culture have been described in uncircumcised patients (28), and given that male neonates are not normally circumcised in Spain, the higher rate of unusual flora may indicate contamination of the urethral catheter by contact with the foreskin, which should explain the absence of alterations in the urine dipstick of these infants. This hypothesis could not be proved because there are few patients that had a urine sample collected by a method other than catheterisation, given that suprapubic aspiration is a method barely used in our environment and not routinely recommended by the AAP. This topic could be the subject of further research.

Our study has some limitations. First of all, this is a subanalysis of a sample collected for a prior study. For this reason, the sample was not calculated to obtain significant results and some of them only show a modest trend. Further investigation should be carried out to confirm these data. In addition, clinical outcome was not registered in every patient, so it cannot be evaluated without bias in the study. Nevertheless, no complication was detected in the follow-up of the infants with normal urine dipstick results and a positive urine culture. Second, we did not study diagnostic performance of haematuria or proteinuria. This was decided based on prior studies that referred to the poor accuracy of these tests for the diagnosis of UTI (7,29). Finally, our study only included febrile infants, so it is not possible to extrapolate diagnostic performance of a urine dipstick for the diagnosis of nonfebrile UTI.

## CONCLUSION

The leucocyte esterase test showed, at least, the same accuracy in predicting a positive urine culture in young febrile infants as the accuracy previously reported for older children. It also showed important gender differences.

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