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REGULAR ARTICLE

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A positive nitrite test was an independent risk factor for invasive bacterial infections in infants under 90 days of age with fever without source

Roberto Velasco[1] | Borja Gomez[2] | Mercedes de la Torre[3] | Javier Benito[2] | Santiago Mintegi[2] | on behalf of the Group of Study of Febrile Infant of the Spanish Pediatric Emergency Research Group

[1]Pediatric Emergency Department, Rio Hortega University Hospital, Valladolid, Spain
[2]Pediatric Emergency Department, Biocruces Bizkaia Health Research Institute, Hospital Universitario Cruces, University of the Basque Country, UPV/EHU, Bilbao, Spain
[3]Pediatric Emergency Department, Niño Jesús University Hospital, Madrid, Spain

Correspondence
Roberto Velasco, Pediatric Emergency Department, Rio Hortega University Hospital, C/Dulzaina, 2, Valladolid 47012, Spain.
Email: robertovelascozuniga@gmail.com

Abstract

Aim: This study analysed the association between a positive nitrite dipstick test and an invasive bacterial infection (IBI) in infants younger than 90 days of age with fever without source (FWS).

Methods: We performed a secondary analysis of data from a prospective multicentre study of infants up to 90 days of age with FWS undergoing care in 19 paediatric EDs between October 2011 and September 2013. Invasive bacterial infection was defined as a positive blood or cerebrospinal fluid culture.

Results: The dipstick urinalysis was positive for nitrite or leucocyte esterase in 766 (22.5%) of the 3401 infants we studied, and 270 (35.2%) had a dipstick test that was just positive for nitrite. Overall, 107 were diagnosed with an IBI (3.1%). The IBI prevalence was 2.2% among patients with a normal urine dipstick, 4.4% if they had positive leucocyte esterase test results, 8.3% where the nitrite test was positive and 10.6% when both tests were positive. After multivariate analysis, a positive nitrite test remained an independent risk factor for IBI (odds ratio 2.7, 95% confidence interval 1.4-4.9).

Conclusion: In infants under 90 days of age with FWS, a positive nitrite urine dipstick test was an independent risk factor for IBI.

KEYWORDS
bacteraemia, febrile infant, meningitis, nitrite test, urinary tract infection

1 | INTRODUCTION

A urinary tract infection (UTI) is the most common bacterial infection in febrile infants under 90 days of age, with a reported prevalence of 4-12%.[1-3] The American Academy of Pediatrics guidelines for the management of UTIs do not provide indications for patients under 2 months old. Most clinicians admit these infants for parenteral antibiotic treatment, due to the risk of complications, and one particularly severe example of this is a subsequent invasive bacterial infection (IBI).[4-6]

Urine dipsticks are widely used to identify infants with UTIs, as they provide rapid results and do not require microscopy.[4] Urine dipstick testing indicates the presence of leucocyte esterase, a surrogate

Abbreviations: CI, confidence interval; CSF, cerebrospinal fluid; ED, emergency department; FWS, fever without source; IBI, invasive bacterial infection; SD, standard deviation; UTI, urinary tract infection.

marker for pyuria, and urinary nitrites. After approximately 4 hours, this is converted from dietary nitrates in the presence of most Gram-negative enteric bacteria in the bladder.[7] However, as infants empty their bladders frequently and not all urinary pathogens reduce nitrate to nitrite, a nitrite test is not a sufficiently sensitive marker for UTI in infants.[4]

Some authors have developed predictive models that identify infants with a UTI who are at very low risk for adverse events and bacteraemia, thereby making them suitable for shorter inpatient stays or outpatient treatment with close follow-up.[3,6] However, when they evaluated the performance of the urine dipstick, these models did not assess the performance of leucocyte esterase and the nitrite test separately. The presence of a positive result for nitrite and leucocyte esterase on urinalysis has been proven to be an independent risk factor for bacteraemia in young febrile infants,[8-10] but little is known about the specific value of the nitrite test. One study showed that a model that included the urinary nitrite test may be useful for predicting bacteraemia among adult patients with pyelonephritis.[11] This suggests that this procedure could be used in the infant population.

The objective of our study was to analyse the association between a positive nitrite test using a urine dipstick and the presence of an IBI in infants younger than 90 days of age with fever without source (FWS).

Key notes

- We examined associations between positive nitrite tests and invasive bacterial infections (IBI) in 3401 infants aged under 90 days with fever without source.
- A positive result for nitrite and leucocyte esterase posed a higher risk of an IBI, and a test just positive for nitrite, rather than just leucocyte esterase, carried a 2.4-fold higher risk.
- After multivariate analysis, a positive nitrite test remained an independent risk factor for IBI

2 | METHODS

2.1 | Design of the study

This was a secondary analysis of data obtained from a prospective multicentre sample of infants younger than 90 days of age presenting with FWS to 19 paediatric emergency departments (ED) between October 2011 and September 2013. The hospitals were all members of the Spanish Pediatric Emergency Research Group of the Spanish Pediatric Emergency Society.[9] The institutional review board of each participating hospital provided approval for both the study and the sharing of data with the Rio Hortega Universitary Hospital, which coordinated the study. Parents or caregivers provide written informed consent before the infants were included in the study.

2.2 | Inclusion and exclusion criteria

We included Infants who were younger than 90 days of age when they presented to a participating paediatric ED with FWS and underwent urine dipstick testing and urine culture under sterile conditions and blood cultures.

We excluded patients if any past history and, or, physical examination suggested the source of the fever. They were also excluded if they were afebrile on arrival at the paediatric ED, but with no temperature readings of ≥38°C before arrival that confirmed the fever reported by the parents or caregivers. The other exclusion criteria were that the parent or caregiver refused to participate or there was telephone follow-up contact achieved 1 month after inclusion in the study.

2.3 | Data collection

Combur-test strips (Roche Diagnostics) were used for the urine test, and the urine dipstick results were read by trained nurses in the ED. All the samples were obtained by sterile methods, namely urethral catheterisation or suprapubic aspiration. The leucocyte esterase test results were considered to be positive if a result of more than trace values was shown by the urine dipstick. Similarly, all positive results for nitrite were considered to indicate altered nitrite levels on the dipstick analysis.

A standardised form containing the following data categories was completed for every infant, including their age and sex. We used this form to record the highest temperature measured at home and on arrival in the paediatric ED, the time between detecting the fever and arriving at the paediatric ED and the appearance of the patient when they arrived. It also detailed the patient's medical history, the physical examination and any laboratory and microbiological test results carried out and the final diagnosis and disposition of the patient. The parents or caregivers of each patient were contacted by telephone to inquire about any previously unrecorded adverse event 1 month after inclusion in the study. In addition, each investigator reported the total number of febrile infants seen in his or her hospital every month. These data were sent to the principal investigator using an online form.

2.4 | Definitions

Fever without source was defined as an axillary or rectal temperature ≥38°C (100.4°F) recorded either at home or in the paediatric ED in patients with a normal physical examination. They had no catarrhal or other respiratory signs or symptoms, such as tachypnoea, or diarrhoea.

Well-appearing was defined by a normal paediatric assessment triangle in those health centres that systematically recorded this data in the paediatric medical records.[12] In all other facilities, well-appearing was based on the criteria of the attending physician.

Invasive bacterial infection was isolation of a bacterial pathogen in a blood or cerebrospinal fluid culture. The following were considered indicative of the presence of contaminants: isolation of *Staphylococcus epidermidis*, *Propionibacterium acnes*, *Streptococcus viridans* or *Diphtheroids* in immunocompetent patients without cardiac disease, a ventriculoperitoneal shunt, a central catheter or another indwelling device.

Positive urine culture was defined as a growth of ≥1000 CFU/mL of a single pathogen in a urine culture collected by suprapubic aspiration or a growth of ≥10 000 CFU/mL in a urine culture collected by urethral catheterisation.

The gold standard for the diagnosis of a UTI was a positive urine culture in patients with positive findings on a urine dipstick: either more than trace levels of leucocyte esterase or the presence of nitrite.[6]

Invasive bacterial infection secondary to UTI was isolation of the same pathogen in the urine culture plus either the blood or CSF culture.

Pleocytosis was indicated by a microscopic examination that showed a CSF cell count of ≥25 cells/mm^3 in infants ≤28 days of life or ≥10 cells/mm^3 in those older than 28 days. For the purpose of this study, all white blood cells—neutrophils and lymphocytes—were counted.

2.5 | Outcome

The outcome of this secondary analysis was the diagnosis of an IBI.

2.6 | Statistical analysis

Quantitative variables are expressed as means and standard deviations (SD). These were compared using the t test for independent samples or ANOVA test when more than two categories of data were used. The chi-square test was used to compare categorical data. Statistical significance was set at $P < .05$.

A bivariate analysis was used for the objective of the study and this analysed the association between the result of the urine dipstick and the prevalence of IBI by means of a chi-square test. Logistic regression was used for the multivariate analysis, with the development of an IBI as the outcome. The model included the result of the nitrite test and other variables that displayed a statistically significant association during the univariate analysis. The model was adjusted for the presence of a positive leucocyte esterase test and other potential confounders such as age, sex, previous genitourinary malformations, maximum temperature, appearance, absolute neutrophils count, C-reactive protein and procalcitonin. As patients were recruited in 19 clusters, one for each of the participating EDs, this variable was included in the multivariate analysis as a potential confounder. The data were analysed with Stata 14 (StataCorp).

3 | RESULTS

Figure 1 is a flow chart of the participants and this shows that 19 hospitals participated in the study over a 2-year period. They recorded 4008 episodes affecting infants <90 days of age with FWS. We included 3401 (84.8%) of these episodes in the study as they were followed by a urine dipstick, urine culture and blood culture.

The characteristics of study participants are shown in Table 1. This shows that 107 (3.2%) of the 3401 infants were diagnosed with an IBI, with a 95% confidence interval (95% CI) of 2.6-3.8. Of these, 89 (2.6%) patients had a positive blood culture, seven (0.2%) had a positive CSF culture and 11 (0.3%) had positive results for both of their blood and CSF cultures. Overall, *Escherichia coli* was the bacterium most frequently isolated in the blood and CSF cultures.

Of the 3401 infants, 766 (22.5%, 95% CI 21.1-23.9) had a positive dipstick test: positive leucocyte esterase in 496 (64.8%, 95% CI 61.3-68.1), positive nitrites in 24 (3.1%, 95% CI 2.1-4.6) and positive tests for both in 246 (32.1%, 95% CI 28.9-35.5). Among the 766 infants with a positive dipstick urinalysis for nitrite and leucocyte esterase, 607 (79.2%) had a positive urine culture and 50 (6.5%) had an IBI. We noted that 39 (78%) of these IBIs were secondary to a UTI. Patient characteristics according to urine dipstick results are shown in Table 2. This shows that 158 (6.0%) of the 2635 infants with a normal urine dipstick also had a positive urine culture.

Infants with a positive nitrite test, with or without a positive leucocyte test, (241/270, 89.3%) were more likely to have a urine culture growth of more than 50 000 CFU/mL than those with only a positive leucocyte test (304/496, 61.3%, $P < .01$). Of the 270 infants with a positive nitrite test, 26 (9.6%, 95% CI 6.7-13.7) were diagnosed with bacteraemia and two (0.7%, 95% CI 0.2-2.7) were found to have meningitis.

The prevalence of IBI according to all the urine dipstick results is shown in Figure 2. Table S1 shows the performance of the urine dipstick in predicting a positive urine culture and the presence of an IBI.

The results of the multivariate analysis revealed that a positive nitrite test in the urine dipstick was an independent risk factor for IBI (odds ratio 2.7; 95% CI 1.4-4.9). This association remained (odds ratio 2.4; 95% CI 1.20-4.95) when only patients with a positive dipstick urinalysis for nitrite and leucocyte esterase were analysed (Table 3).

4 | DISCUSSION

This sub-study of data obtained from a large multicentre prospective sample showed that a positive urinary nitrite test was an independent risk factor for IBI in young febrile infants. This was regardless of the presence or absence of a positive leucocyte test. Similar results were obtained in an adult study.[11]

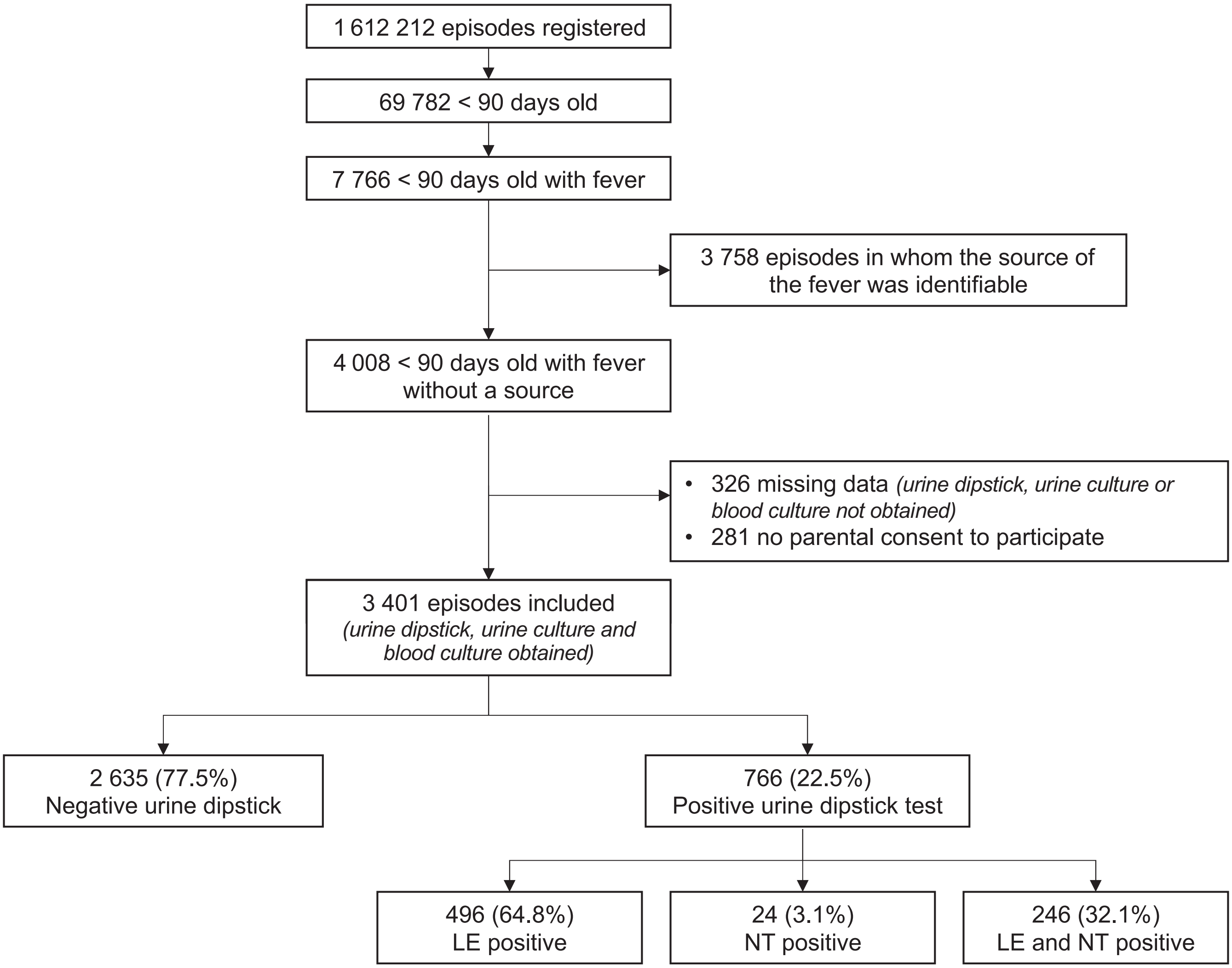

FIGURE 1 Flow chart of the study. LE, leucocyte esterase test; NT, nitrite test

UTI is the most common serious bacterial infection in febrile young infants.[1,2] A definitive diagnosis of UTI is based on a positive urine culture result.[4] Culture-based confirmation of a suspected UTI can take 24 hours or more, and, as a result, empiric therapy is usually commenced in the ED based on clinical findings and screening test results.[4] Direct observation of the urine under microscopy has been proven to be a highly accurate method, but the need for an analyst makes this method quite expensive and not very feasible.[13] Physicians usually use a urine dipstick as a screening method, as it has sufficient accuracy to predict a UTI, even in younger patients.[14,15] The urinary nitrite test has the highest positive predictive value for UTI.[14]

Urinary tract infection is the main cause of bacteraemia in febrile infants,[16] and positive dipstick urinalysis has been proven to be a risk factor for bacteraemia.[8] The nitrite test offers greater specificity when diagnosing UTI than the leucocyte esterase test,[14] making it a good predictor of IBI in these patients.

Contrary to prior studies,[8] a positive leucocyte esterase was not an independent risk factor for IBI in our sample. This may be due to the design of the multivariate analysis used. We included blood biomarkers and urine nitrites and positive leucocyte esterase separately. The results suggest that further research is warranted to better identify febrile young infants with dipstick results indicating nitrite and leucocyte esterase at risk for bacteraemia. In fact, current clinical guidelines for the management of the febrile infant consider a positive urine dipstick as a risk factor, as it indicates the presence of a positive test for leucocytes and, or, nitrites.[17,18] However, when we limited our analysis to patients with positive dipstick results for nitrite and leucocyte esterase, those with a positive nitrite test had a 2.4-fold higher risk of an IBI, while a positive leucocyte esterase test alone was not independently associated with the diagnosis of an IBI. If these results are confirmed, the value of the urine dipstick for classifying young febrile infants at high or low risk of IBI should be reconsidered to include a positive nitrite test as a risk factor for invasive infection.

Current guidelines recommend inpatient treatment for infants younger than 2-3 months of age with a suspected UTI due to the higher risk of complications, mainly bacteraemia.[4] Prior research

TABLE 1 Characteristics of the patients, tests performed and management

Age (days) mean (SD)	46.6 (23.6)
Gender (male) n (%)	2029 (59.7)
Previously diagnosed urogenital malformation n (%)	104 (3.1)
Not-well appearance on arrival to the ED n (%)	367 (10.8)
Hours of fever mean (SD)	9.9 (13.5)
Maximum temperature (°C) mean (SD)	38.6 (0.46)
Urine dipstick and urine culture performed n (%)	3401 (100)
Method of urine culture collection	
Urethral catheterisation n (%)	3336 (98.1)
Suprapubic aspiration n (%)	65 (1.9)
Blood tests performed	
White blood cell count n (%)	3401 (100)
Absolute neutrophils count n (%)	3401 (100)
C-reactive protein n (%)	3398 (99.9)
Procalcitonin n (%)	2806 (82.5)
Blood culture n (%)	3401 (100)
CSF examination and culture performed n (%)	877 (25.8)
Positive urine culture n (%)	764 (22.5)
Patients with an invasive bacterial infection n (%)	107 (3.2
Positive blood culture only n (%)	89 (2.9)
Positive CSF culture only n (%)	7 (0.2)
Both positive blood and CSF culture n (%)	11 (0.3)
Admitted	
To ward n (%)	1836 (54.0)
To intensive care unit n (%)	53 (1.6)

Abbreviations: CSF, cerebrospinal fluid; IQR, interquartile range.

has aimed to define a group of patients at low risk for IBI, making them suitable for outpatient treatment.[3,9,19] However, none of these models include the nitrite test as an item. Our results suggest that patients with a positive nitrite test are at higher risk for an IBI. In the light of this, clinical prediction models may be revised to consider infants with a positive nitrite test as candidates for more conservative management, than those patients with just a positive leucocyte esterase test.

Several hypotheses can be advanced regarding the relationship between a positive urine nitrite test and diagnosis of an IBI. First, some authors have suggested that, as it takes around 4 hours for the urinary bacterium to reduce the urine nitrates into nitrites. This means that a positive nitrite test may reflect a longer incubation time of nitrite-producing bacteria in urinary tracts,[20] thereby increasing the probability of subsequent bacteraemia development. *Escherichia coli* and other species of *Enterobacteriaceae* bacteria can reduce urine nitrates to nitrite, but the urine must remain in the bladder long enough for this transformation to happen and infants void frequently so they tend to get flushed out of the bladder.[21] In our study, the rate of patients with more than 50 000 CFU/mL in the urine culture was higher in those infants with a positive urine nitrite test (89.3% vs 61.3% in the group of infants with just a positive leucocyte test ($P < .01$). This could possibly indicate a larger bacterial upload or a longer period of incubation. Secondly, plasma levels of nitrites are elevated in paediatric sepsis.[22] Several animal and human studies have proven that in septic shock excessive nitric oxide production, due to activation of inducible nitric oxide synthase, is associated with elevated nitrite and nitrate levels in the circulation.[23] This increased plasma level could subsequently lead to a higher nitrite concentration in the urine. Regarding this, it should be noted that five patients in our study who tested positive for the nitrite test were diagnosed with an IBI that was not secondary to a UTI. These included the two patients with a positive nitrite test without associated positive leucocyte test. There were three patients with bacteraemia caused by a bacterium—*Staphylococcus aureus*, *Klebsiella pneumoniae* and *Neisseria meningitidis*—other than the one that grew in the urine culture (*E coli*). In addition, we found one infant with a negative urine culture and *Streptococcus agalactiae* isolated by blood culture and a fifth patient was diagnosed with bacterial meningitis caused by *Staphylococcus aureus* and a concomitant UTI by *Klebsiella pneumoniae*.

This study had several limitations. Firstly, it was a post hoc sub-study, so the sample size was not specifically designed for this aim. In addition, the number of patients with an isolated positive nitrite test was relatively small. Nevertheless, the multivariate analysis showed the highest odds ratio for IBI in infants who did not appear well and those with a positive nitrite test. Also, in the original study, the results of the leucocyte esterase test were only recorded as a positive, indicating more than trace amounts, or negative result. This meant that it was not possible to study whether there was an association between the degree of positivity of this test and the IBI diagnosis.

A second limitation concerns the fact that only patients without any source of fever after the physical examination were included. Patients with upper airway symptoms were excluded and no data on these infants were obtained, since routine management of these patients calls for observation with no further laboratory testing.

Thirdly, the issue of the optimal threshold of CFU/mL in a urine culture for the diagnosis of a UTI is controversial.[15] In our study, we chose the 10 000 CFU/mL cut-off point for samples obtained by urethral catheterisation and 1000 CFU/mL when obtained by suprapubic aspiration, based on prior research.[24] In any case, as the objective of the study was to analyse the relationship between a positive nitrite test and the diagnosis of an IBI, rather than a UTI, we considered that this issue would not affect the validity of our results.

Finally, in our study, the positive predictive value of just a positive nitrite test for a positive urine culture was lower than previously published, which was 89.3%,[14] as we recorded a false-positive rate of 12/24 (50.0%) in this study (Table 2). We think that this might have been due to the small number of patients with just a positive nitrite test. When all the patients in this study with a positive nitrite

TABLE 2 Characteristics of patients according urine dipstick result

	Normal (n = 2635)	LE+ (n = 496)	NT+ (n = 24)	LE+ and NT+ (n = 246)
Age in days mean (SD)	46.9 (23.3)	49.1 (24.7)	47.5 (20.5)	48.6 (25.4)
Male sex n (%)	**1533 (58.2)**	315 (63.5)	16 (66.7)	165 (67.1)
Previously diagnosed urogenital malformation n (%)	**62 (2.4)**	**29 (5.9)**	0 (0)	13 (5.3)
Not-well appearance n (%)	282 (10.7)	51 (10.3)	5 (20.8)	29 (11.8)
Maximum temperature in °C mean (SD)	38.6 (0.44)	38.6 (0.51)	38.5 (0.47)	38.7 (0.56)
Hours of fever mean (SD)	**9.2 (12.4)**	12.2 (17.7)	11.7 (16.0)	12.0 (14.8)
White blood cell count mean (SD)	**10 510.8 (4795.5)**	15 225.1 (6162.5)	13 112.9 (5175.5)	15 668.3 (6423.1)
Absolute neutrophil count mean (SD)	**4464.0 (3148.2)**	7723.7 (4561.8)	6677.3 (3447.0)	8373.6 (4382.9)
C-reactive protein (mg/L) mean (SD)	**11.3 (17.9)**	41.7 (50.9)	42.6 (58.6)	**61.8 (58.1)**
Procalcitonin (ng/mL) mean (SD)	**0.44 (2.62)**	**1.83 (5.56)**	**3.16 (7.44)**	**5.49 (15.4)**
Urine culture n (%)				
Negative	**2477 (94)**	**144 (29.0)**	**12 (50)**	**3 (1.2)**
10 000-50 000 cfu/mL	**53 (2.0)**	**49 (9.9)**	**1 (4.2)**	**13 (3.5)**
>50 000 cfu/mL	**105 (4.0)**	**303 (61.3)**	**11 (45.8)**	**230 (93.5)**
Urine culture bacteria n (%)				
Escherichia coli	**86 (54.4)**	**301 (85.5)**	**11 (91.7)**	**230 (94.7)**
Klebsiella pneumoniae	**18 (11.4)**	**20 (5.7)**	**1 (8.3)**	**7 (2.9)**
Enterococcus faecalis	**27 (17.1)**	**8 (2.3)**	**0 (0)**	**0 (0)**
Other	**27 (17.1)**	**23 (6.5)**	**0 (0)**	**6 (2.5)**
Invasive bacterial infection n (%)	**57 (2.2)**	**22 (4.4)**	**2 (8.3)**	**26 (10.6)**
Secondary to urinary tract infection	**0 (0)**	**16 (72.7)**	**0 (0)**	**23 (88.5)**
Blood culture bacteria n (%)	**53 (2.0)**	**21 (4.2)**	**2 (8.3)**	**24 (9.8)**
Escherichia coli	**9 (17.0)**	**15 (71.4)**	**0 (0)**	**22 (91.7)**
Streptococcus agalactiae	**23 (43.4)**	**0 (0)**	**1 (50)**	**0 (0)**
Klebsiella pneumoniae	**1 (1.9)**	**0 (0)**	**0 (0)**	**1 (4.2)**
Enterococcus faecalis	**4 (7.6)**	**1 (4.8)**	**0 (0)**	**0 (0)**
Streptococcus pneumoniae	**5 (9.4)**	**1 (4.8)**	**0 (0)**	**0 (0)**
Neisseria meningitidis	**1 (1.9)**	**0 (0)**	**1 (50)**	**0 (0)**
Staphylococcus aureus	**3 (5.7)**	**3 (14.3)**	**0 (0)**	**1 (4.2)**
Other	**7 (13.2)**	**1 (4.8)**	**0 (0)**	**0 (0)**
CSF culture bacteria n (%)	15 (0.6)	1 (0.2)	0 (0)	2 (0.8)
Escherichia coli	6 (40)	0 (0)	0 (0)	1 (50)
Streptococcus agalactiae	3 (20)	0 (0)	0 (0)	0 (0)
Enterococcus faecalis	0 (0)	0 (0)	0 (0)	0 (0)
Streptococcus pneumoniae	3 (20)	0 (0)	0 (0)	0 (0)
Listeria monocytogenes	1 (6.7)	0 (0)	0 (0)	0 (0)
Staphylococcus aureus	0 (0)	1 (100)	0 (0)	1 (50)
Other	2 (13.3)	0 (0)	0 (0)	0 (0)

Note: (Comparisons between groups were made using ANOVA test for quantitative variables and chi-square test for categorical variables. Results with significance level <.05 appear in bold).

Abbreviations: CSF, cerebrospinal fluid; LE, leucocyte esterase test; NT, nitrite test.

test were analysed as a whole, regardless the presence of a positive leucocyte esterase test, the false-positive rate was 15/270 (5.6%) (Table 2), with a positive predictive value of 94.4% and this was consistent with previous literature.[14]

5 | CONCLUSION

In infants younger than 90 days of age with FWS, obtaining a positive nitrite test using urine dipstick was an independent risk factor

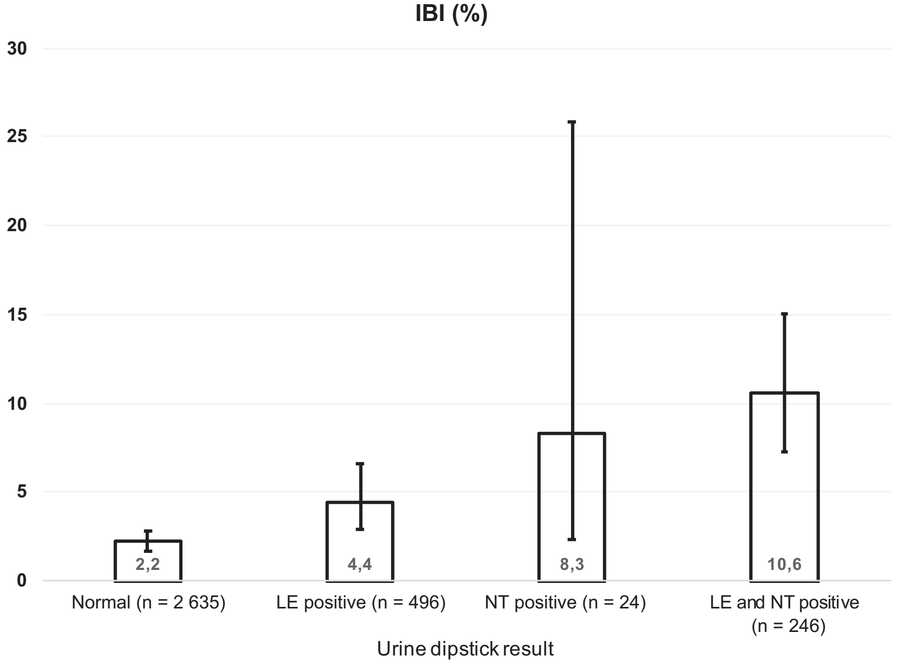

FIGURE 2 Prevalence of invasive bacterial infection according to the urine dipstick result. Note: bars are labelled with the percentage of IBI in each group and their 95% confidence intervals. IBI, invasive bacterial infection; LE, leucocyte esterase test; NT, nitrite test

TABLE 3 Factors associated with the diagnosis of an invasive bacterial infection in multivariate analysis for the whole sample and including only infants with positive dipstick urinalysis for nitrite/leucocyte

	Univariate analysis			Multivariate analysis	
Whole sample	**No IBI (n = 3294)**	**IBI (n = 107)**	***P***	**Odds ratio**	**95% CI**
Male sex n (%)	1955 (59.4)	74 (69.2)	.04	–	–
Not well appearing n (%)	335 (10.2)	32 (29.9)	<.01	2.69	1.57-4.59
Age (days) mean (SD)	46.9 (23.5)	36.7 (25.3)	<.01	0.98	0.97-0.99
Max. temperature (°C) mean (SD)	38.6 (0.46)	38.7 (0.57)	<.01	1.63	1.02-2.61
Hours of fever mean (SD)	9.9 (13.6)	9.3 (12.4)	.61	–	–
White blood cells (cells/mcl) mean (SD)	11 556.8 (5492.5)	12 604.5 (6451.2)	.10	–	–
Absolute neutrophil count (cells/mcl) mean (SD)	5172.6 (3733.8)	7245.9 (4498.4)	<.01	–	–
C-reactive protein (mg/L) mean (SD)	18.4 (31.5)	58.4 (67.2)	<.01	1.01	1.00-1.01
Procalcitonin (ng/mL) mean (SD)	0.75 (4.28)	8.94 (16.32)	<.01	1.04	1.02-1.07
Positive leucocyte esterase test n (%)	694 (21.1)	48 (44.9)	<.01	–	–
Positive nitrite test n (%)	242 (7.4)	28 (26.2)	<.01	2.67	1.45-4.92
	Univariate analysis			**Multivariate analysis**	
Dipstick urinalysis positive	**No IBI (n = 716)**	**IBI (n = 50)**	***P***	**Odds ratio**	**95% CI**
Male sex n (%)	464 (64.8)	32 (64.0)	.91	–	–
Not well appearing n (%)	74 (10.3)	11 (22.0)	.01	1.43	0.59-3.48
Age (days) mean (SD)	49.6 (24.6)	38.2 (24.7)	<.01	0.97	0.96-0.99
Max. temperature (°C) mean (SD)	38.6 (0.52)	38.9 (0.60)	<.01	2.28	1.17-4.44
Hours of fever mean (SD)	12.2 (16.9)	11.6 (14.9)	.82	–	–
White blood cells (cells/mcL) mean (SD)	15 323.0 (6256.0)	14 990.6 (5862.6)	.72	–	–
Absolute neutrophil count (cells/mcL) mean (SD)	7860.9 (4490.0)	8455.1 (4416.8)	.37	–	–
C-reactive protein (mg/L) mean (SD)	45.3 (51.4)	88.3 (75.4)	<.01	1.01	1.00-1.01
Procalcitonin (ng/mL) mean (SD)	2.40 (8.82)	11.8 (17.86)	<.01	1.02	1.00-1.04
Positive leucocyte esterase test n (%)	694 (96.9)	48 (96.0)	.72	–	–
Positive nitrite test n (%)	242 (33.8)	28 (56.0)	<.01	2.43	1.20-4.95

Note: (Univariate analysis was conducted using independent-sample t test for quantitative variables and chi-square testing for categorical variables. A logistic regression was used for multivariate analysis).

for IBI. Larger, prospective studies are required to confirm these results.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

ORCID

Roberto Velasco https://orcid.org/0000-0003-0073-2650

REFERENCES

1. Watt K, Waddle E, Jhaveri R. Changing epidemiology of serious bacterial infections in febrile infants without localizing signs. *PLoS ONE*. 2010;5(8):e12448.
2. Byington CL, Rittichier KK, Bassett KE, et al. Serious bacterial infections in febrile infants younger than 90 days of age: the importance of ampicillin-resistant pathogens. *Pediatrics*. 2003;111(5 Pt 1):964-968.
3. Schnadower D, Kuppermann N, Macias CG, et al. Febrile infants with urinary tract infections at very low risk for adverse events and bacteremia. *Pediatrics*. 2010;126(6):1074-1083.
4. Roberts KB. Urinary tract infection: clinical practice guideline for the diagnosis and management of the initial UTI in febrile infants and children 2 to 24 months. *Pediatrics*. 2011;128(3):595-610.
5. Spencer JD, Schwaderer A, McHugh K, Hains DS. Pediatric urinary tract infections: an analysis of hospitalizations, charges, and costs in the USA. *Pediatr Nephrol*. 2010;25(12):2469-2475.
6. Robinson JL, Finlay JC, Lang ME, Bortolussi R. Urinary tract infections in infants and children: diagnosis and management. *Paediatr Child Health*. 2014;19(6):315-325.
7. Kunin CM, DeGroot JE. Sensitivity of a nitrite indicator strip method in detecting bacteriuria in preschool girls. *Pediatrics*. 1977;60(2):244-245.
8. Gómez B, Mintegi S, Benito J, Egireun A, Garcia D, Astobiza E. Blood culture and bacteremia predictors in infants less than three months of age with fever without source. *Pediatr Infect Dis J*. 2010;29(1):43-47.
9. Velasco R, Benito H, Mozún R, Trujillo JE, Merino PA, Mintegi S. Febrile young infants with altered urinalysis at low risk for invasive bacterial infection. A Spanish Pediatric Emergency Research Network's Study. *Pediatr Infect Dis J*. 2015;34(1):17-21.
10. Velasco R, Gómez B, Hernández-Bou S, et al. Validation of a predictive model for identifying febrile young infants with altered urinalysis at low risk of invasive bacterial infection. *Eur J Clin Microbiol Infect Dis*. 2017;36(2):281-284.
11. Nakamura N, Uehara Y, Fukui S, Fujibayashi K, Yokokawa H, Naito T. Useful predictive factors for bacteremia among outpatients with pyelonephritis. *Intern Med*. 2018;57(10):1399-1403.
12. Dieckmann RA, Brownstein D, Gausche-Hill M. The pediatric assessment triangle: a novel approach for the rapid evaluation of children. *Pediatr Emerg Care*. 2010;26(4):312-315.
13. Mori R, Yonemoto N, Fitzgerald A, Tullus K, Verrier-Jones K, Lakhanpaul M. Diagnostic performance of urine dipstick testing in children with suspected UTI: a systematic review of relationship with age and comparison with microscopy. *Acta Paediatr*. 2010;99(4):581-584.
14. Velasco R, Benito H, Mozun R, et al. Using a urine dipstick to identify a positive urine culture in young febrile infants is as effective as in older patients. *Acta Paediatr*. 2015;104(1):39-44.
15. Tzimenatos L, Mahajan P, Dayan PS, et al. Accuracy of the urinalysis for urinary tract infections in febrile infants 60 days and younger. *Pediatrics*. 2018;141(2):e20173068.
16. Greenhow TL, Hung YY, Herz AM. Changing epidemiology of bacteremia in infants aged 1 week to 3 months. *Pediatrics*. 2012;129(3):e590-e596.
17. Kuppermann N, Dayan PS, Levine DA, et al. A clinical prediction rule to identify febrile infants 60 days and younger at low risk for serious bacterial infections. *JAMA Pediatr*. 2019;173(4):342-351.
18. Mintegi S, Bressan S, Gomez B, et al. Accuracy of a sequential approach to identify young febrile infants at low risk for invasive bacterial infection. *Emerg Med J*. 2014;31:e19-e24.
19. Velasco-Zúñiga R, Trujillo-Wurttele JE, Fernández-Arribas JL, Serrano-Carro B, Campo-Fernández N, Puente-Montes S. Predictive factors of low risk for bacteremia in infants with urinary tract infection. *Pediatr Infect Dis J*. 2012;31(6):642-645.
20. Lie JT. Evaluation of a nitrite test kit (Stat-test) for the detection of significant bacteriuria. *J Clin Pathol*. 1968;21(4):443-444.
21. Kahlmeter G. An international survey of the antimicrobial susceptibility of pathogens from uncomplicated urinary tract infections: the ECO.SENS Project. *J Antimicrob Chemother*. 2003;51(1):69-76.
22. Doughty L, Carcillo JA, Kaplan S, Janosky J. Plasma nitrite and nitrate concentrations and multiple organ failure in pediatric sepsis. *Crit Care Med*. 1998;26(1):157-162.
23. Sharawy N. Vasoplegia in septic shock: do we really fight the right enemy? *J Crit Care*. 2014;29:83-87.
24. Velasco R, Benito H, Mozun R, et al. Importance of urine dipstick in evaluation of young febrile infants with positive urine culture: a Spanish Pediatric Emergency Research Group Study. *Pediatr Emerg Care*. 2016;32(12):851-855.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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