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Research Article

URINALYSIS AS A PREDICTOR FOR URINARY TRACT INFECTION: AN OBSERVATIONAL STUDY

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ABSTRACT

Objectives: The aims and objectives of the study are to find the usefulness of urine dipstick and urinalysis in children with an intention to identify the parameters which most likely point toward the presence of urinary tract infection (UTI), whether a combination of the parameters analyzed rather than single parameter is useful in suggesting the presence or absence of UTI.

Methods: The study was a prospective observational study done in 401 children below 16 years of age with clinically suspected UTI.

Results: The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of dipstick leukocyte esterase (LE) and nitrite were 85%, 93.1%, 75.6%, 96.1% and 51.2%, 99.1%, 93.2%, 89.1%, respectively. In urine microscopic analysis, the sensitivity, specificity, PPV, NPV of bacteria were 68.5%, 96.9%, 84.6%, and 92.6% and those of pus cells were 80%, 93.1%, 74.4%, and 94.9%.

Conclusion: Combination of parameters, i.e., LE, nitrite, and bacteria or LE, nitrite, and pus cells are good screening tools to predict and rule out UTI. Of the individual parameters analyzed, negative nitrites in dipstick and absence of bacteria in urine microscopy almost rule out UTI caused by most uropathogens.

Keywords: Urinary tract infection, Leukocyte esterase, Nitrite, Urine dipstick, Pus cells.

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INTRODUCTION

Acute febrile illnesses are common in children worldwide, especially in those under 5 years of age. Infections leading to these febrile episodes are responsible for the majority of under-5 mortality and morbidity [1]. Urinary tract infection (UTI) is one of the most common genitourinary diseases in pediatric practice. It accounts for 0.7% of outpatient visits and 5–14% of emergency department visits by children annually [2].

Diagnosis and management of UTI is a matter of concern in hospital settings and at community level. The accurate and timely diagnosis of UTI in children is important to alleviate short-term suffering and prevent the long-term consequences such as renal scarring, impaired renal growth, recurrent pyelonephritis, impaired glomerular function, hypertension, and end-stage renal failure [3-5]. The clinical diagnosis of UTI is difficult, due to non-specific or vague symptom spectrum seen in children. Often, clinical diagnosis needs to be supported with confirmatory tests such as urine culture, which guides in the treatment of the infection.

The use of rapid diagnostic tests such as urine dipstick and microscopy has helped us initiate the treatment early without waiting for a confirmation by way of urine cultures thereby avoiding serious systemic sequelae. Many studies have reported high specificity and sensitivity of dipstick tests when used in combination with urine microscopy. The American Academy of Pediatrics (AAP) states that if urinalysis is negative, UTI is unlikely (<0.3%). According to AAP guidelines for UTI, a diagnosis of UTI is done by both abnormal urinalysis results and positive culture results [6].

Although pediatric studies have been done to evaluate the performance characteristics of these rapid diagnostic tests in diagnosing a UTI, there is a lack of sufficient studies and paucity of data on these in developing countries like India. This study focuses on the reliability of urine dipstick and microscopy in early detection of childhood UTI and the current status of urine analysis as an effective screening tool in an Indian setup. This study looks at the single as well as combination of parameters that provide maximum sensitivity and specificity, providing a better diagnostic criterion in detecting an underlying urinary infection.

METHODS

Study design
Prospective observational study.

Study center
Apollo Hospitals, Chennai, Tamil Nadu, India.

Duration of study
1 year (September 2017–August 2018).

Sample size
A minimum of 370 cases.

Sample size justification
Since the primary objective of the study is to see the sensitivity of dipstick in identifying positivity of UTI, we kept the least sensitive non-invasive tool (nitrite) of 41% sensitivity based on Hay *et al.* [7] study, for the workup of sample size calculation. We took the least sensitive among the 2 tools to have a better precision of the study. Substituting this p-value in the equation for sample size calculation

$n = z^2pq/d^2$

Where z = Standard normal value (1.96) 95% confidence interval.
p = sensitivity of nitrite = 41%
q = 100- p = 59%
d = clinically allowable error (5%).
n = sample size.

Substituting these values in the above equation: n=(1.96×1.96×41×59)/25 =370.

Inclusion criteria
All children below 16 years of age with clinically suspected UTI.

Exclusion criteria
1. Children with ureteric stents, with indwelling urinary catheters and whose urine samples have been collected from vesicostomies and ureterostomies
2. Children who had received antibiotics already and those with immunodeficiency disorders and nephritic syndrome.

Methodology and sampling
This prospective study was done in our tertiary care center after approval by our institutional Ethical Committee and also with informed consent from parents and caretakers in emergency room, out-patient, and in-patient department, Apollo Hospitals, Chennai, Tamil Nadu, India. The urine samples for our study were collected with aseptic precautions (i.e.) mid-stream urine for toilet-trained children and urinary catheter specimen for non-toilet trained children. All samples were sent to the clinical pathology and microbiology laboratory within 2 h of collection. Dipstick was done with Clinitek dipstick method, using Siemens Multistix reagent strips for urinalysis. Results were read after 30 s.

For microscopic features of urinalysis, 5 mL of urine was taken and it was centrifuged at 3000 rbm for 7 min. This centrifuged urine was examined with automated and manual microscope. Culture reports were obtained according to growth on MacConkey agar and Blood agar after 24 h of incubation period. The results obtained from the urinalysis which includes both urine dipstick and microscopy were compared with the urine culture. Parameters such as nitrite, leukocyte esterase (LE), red blood cell (RBC), bacteria, and pus cells were compared with urine culture.

Criteria for positive and negative parameters:
a. Nitrite: clear positive or negative
b. LE: Trace, +1, +2, +3 taken as positive and negative is negative
c. Bacteria: presence of bacteria is positive and absence of bacteria is negative
d. Pus cells: >4 cells/HPF taken as positive [6,8] and recategorized as 5–20 cells/HPF and plenty cells and HPF <4 is taken as negative.

As for red cells in urine, there were not published evidence for a nomogram for RBCs in urine except one by Smith *et al*. [9] who took any RBCs as positive and analyzed for UTI, and we had done the same, along with another analysis with <4 RBC being normal and >4 as significant as in the case of pus cells. We had taken a positive culture as 50,000 colony counts based on the AAP guidelines [10]. These data were then corroborated statistically to find which of the tests are most likely to associate with the presence of culture-positive UTI.

Statistical analysis
All the continuous variables were represented by mean±standard deviation. All the categorical variables were represented by percentages. Comparison of categorical variables was done by Chi-square test. Kappa values were computed to know the agreement between test and gold standard. Sensitivity, specificity, PPV, and NPV were computed. Data entry was done in MS Excel spreadsheet. Data analysis was done by SPSS Version 25.0. All $p<0.05$ were considered as statistically significant.

RESULTS AND DISCUSSION

In our study, we included 401 children who were suspected to have UTI. Statistical analysis was performed as mentioned above. Out of these, 231 (58%) were boys and 170 (42%) were girls. Fever was the most common (92%) presenting feature in our study.

Urine culture which is gold standard for diagnosing UTI was positive in 80 (20%) samples. The urine culture positivity varied from 2.2% to 29% in various studies, and study done by Ramlakhan *et al*. [11] had the closest positive culture rate to our study (Table 1).

Table 1: Percentage of positive culture in various other studies along with our study statistics

Author	Total urine culture available	Positive urine culture number	Percentage
Duty study [7]	2,740	60	2.2
Ojha and Aryal [12]	110	32	29
Glissmeyer *et al*. [13]	6394	770	12
Ramlakhan *et al*. [11]	321	78	24.3
Smith *et al*. [9]	500	77	15
Our study.	401	80	20

Comparison of different parameters with gold standard

LE versus gold standard

Dipstick LE was positive in 90 samples, i.e., 22.4% out of which 68 were culture positive and 22 were culture negative. Total LE negative was 311, i.e., 77.6% out of which 12 were culture positive and 299 were culture negative. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of LE were 85%, 93.1%, 75.6%, and 96.1% in our study (Table 2); this was higher than other studies we reviewed, like in the case of Ojha and Aryal [12] where similar parameters showed 84%, 55%, 43%, and 89%. The absence of LE seems to indicate more likelihood of a negative culture in our study, but nitrite which is discussed below had an even higher specificity. Of all the single parameters we analyzed, LE had the highest sensitivity in predicting UTI.

Nitrite versus gold standard

Nitrite in dipstick was positive in 44 samples (11%) out of which 41 were culture positive and 39 were culture negative. Total nitrite negative was 357 (89%) out of which 318 were culture negative and 39 were culture positive. The sensitivity, specificity, PPV, and NPV were 51.2%, 99.1%, 93.2%, and 89.1% (Table 2). The specificity of nitrites was almost 100%. This makes nitrite a good-negative screening test. The absence of nitrites in a child with UTI might signify a less common uropathogen which does not produce nitrite [14]. Having said that Gram-negative enteric organisms which produce nitrite represent the most common uropathogen causing UTI.

Bacteria versus gold standard

Bacteria were present in 65 (16.2%) urine samples out of this 55 were culture positive and 10 were culture negative. Bacteria negative in 336 samples (83.8%) out of which 311 were culture negative and 25 culture positive. The presence of bacteria in urine had the sensitivity, specificity, PPV, and NPV of 68.8%, 96.9%, 84.6%, and 92.6% (Table 2). The sensitivity and specificity of the presence of any bacteria in urine in the study done by Schroeder *et al*. [15] were 92% and 66.1%, respectively. AAP in the review of literature published by their subcommittee shows an average sensitivity of 81 which is higher than our study and specificity of 83% which is lower than our study [10]. In our study, the presence of bacteria does seem to increase a likelihood of getting a positive culture but had a lower negative likelihood ratio, i.e., in the absence of a bacteriuria, a UTI cannot be ruled out convincingly.

Pus cells versus gold standard

We had taken pus cells >4 cells as positive in our study. Pus cells were positive in 86 samples out of 401 urine samples, i.e., 21.4% out of this, 64 culture positive and 22 were culture negative. Pus cells were negative in 315 samples (78.6%) out of this 299 were culture negative and 16 were culture positive. The sensitivity, specificity, PPV, and NPV were 80%, 93.1%, 74.4%, and 94.9% in our study (Table 2). The sensitivity and specificity of pyuria were higher in our study than previous studies. In their study, Tsai *et al*. [8] mentioned the sensitivity and specificity as 74% and 86%. In the AAP subcommittee review, the average sensitivity and specificity were 73% and 81% both of which were lower than our results [9]. Nevertheless, results from our study

Table 2: Summary of results with different parameters tested

Parameter tested	Sensitivity	Specificity	PPV	NPV	Positive likelihood ratio (95% CI)	Negative likelihood ratio (95%CI)	Kappa value
Leukocyte esterase	85	93.1	75.6	96.1	12.4 (8.2–18.7)	0.16 (0.1–0.27)	0.746
Nitrite	51.2	99.1	93.2	89.1	54.84 (17.43–72.5)	0.49 (0.39–0.62)	0.60
Bacteria	68.85	96.9	84.6	92.6	20.64 (10.94–38.92)	0.37 (0.27–0.51)	0.706
Pus cells	80	93.1	74.4	94.9	11.67 (7.69–17.73)	0.21 (0.14–0.33)	0.71
RBC (any RBC)	60	85.7	51.1	48.9	4.19 (3.03–5.78)	0.47 (0.36–0.61)	0.429
RBC (>4)	10.4	87	45.5	48.2	0.8 (0.26–2.44)	1.03 (0.89–1.19)	-
LE and nitrite	90	92.2	74.2	97.4	11.56 (7.88–16.96)	0.11 (0.06–0.21)	0.761
LE, nitrite, and bacteria	92.5	90	69.8	98	9.28 (6.64–12.97)	0.08 (0.04–0.18)	0.736
LE, nitrite, and pus cells	91.3	90	69.5	97.6	9.15 (6.54–12.8)	0.10 (0.05–0.20)	0.727
LE, nitrite, bacteria, and pus cells	92.5	88.2	66.1	97.9	7.81 (5.76–10.6)	0.09 (0.04–0.18)	0.701

RBC: Red blood cell, PPV: Positive predictive value, NPV: Negative predictive value, LE: Leukocyte esterase

suggest a good likelihood in the presence of pus cells (>4/HPF) ruling in and the absence of pus cells ruling out a positive urine culture.

RBC versus gold standard

Total RBC positive were 94 (when the presence of any RBC taken as positive), i.e., 23.4% out of which 48 were culture positive and 46 were culture negative. RBC negative in 307 samples, i.e., 76%, out of this 275 were culture negative and 32 were culture positive.

RBC (>4 cells) versus gold standard

When RBC >4 cells/HPF taken as positive, 11 samples were positive for RBC, out of which 5 were culture positive and 6 were culture negative. RBC negative (<4 cells/HPF) in 83 samples, out of which 43 were culture positive and 40 were culture negative.

We also looked and compared the sensitivity and specificity of RBC to predict UTI in children. When the presence of any RBC has taken as positive, 94 (23.4%) samples were positive for RBC, which had the sensitivity, specificity, PPV, and NPV of 60%, 85.7%, 51.1%, and 48.9% (Table 2). The sensitivity and PPV were higher than that of one previous study by Smith *et al*. [9] and specificity and NPV were lower than the same study. If >4 RBCs are taken as positive in our study, except the specificity which slightly increased, the rest of the parameters such as the sensitivity and PPV became lot lower 10.4%, 45.5% and a similar NPV compared to when any RBCs were taken as positive, 48.2%. The negative likelihood ratio is 1.03 (95% CI: 0.89–1.19) and a positive likelihood ratio is 0.8 (95% CI: 0.26–2.44). From these analyses, we conclude that hematuria is a poor indicator to predict the presence of UTI.

Combination of LE and nitrite versus gold standard

Total 97 samples were positive for LE and nitrite, out of these 72 were culture positive and 25 were culture negative. Total 304 samples were negative for LE and nitrite; in these, 8 were culture positive and 296 were culture negative.

When we combined dipstick LE and nitrite, sensitivity increased to 90%, specificity, PPV and NPV were 92.2%, 74.2%, and 97.4% (Table 2) and an accuracy of 91.77% (95% CI: 88.64–94.27%). These are higher in our study than that of Ojha and Aryal [12] study, in their study, sensitivity, specificity, PPV, and NPV were 86.3%, 83.3%, 73%, and 92.1%. It is clear from the above analysis that a combination of parameters was giving a better screening tool than individual parameters.

Combination of LE, nitrite, and bacteria versus gold standard

Combination of LE, nitrite, and bacteria was positive in 106 samples, in this 74 culture positive and 32 culture negative. These were negative in 295 samples, out of this 6 were culture positive and 289 were culture negative.

When the combination of LE, nitrite, and bacteria was analyzed, we found that the sensitivity and NPV were increased than that of individual parameters, the sensitivity, specificity, PPV, and NPV of this combination in our study were 92.5%, 90%, 69.8%, and 98% (Table 2).

Combination of LE, nitrite, and pus cells versus gold standard

Combination of LE, nitrite, and pus cells was positive in 105 samples, in this, 73 were culture positive and 32 were culture negative. This combination was negative in 296 samples, out of this, 7 were culture positive and 289 were culture negative.

The combination of LE, nitrites, and pus cells also increases the sensitivity than the individual parameters. The sensitivity, specificity, PPV, and NPV of the above-mentioned combination are 91.3%, 90%, 69.5%, and 97.6% (Table 2). The positive and negative likelihood ratios along with accuracy of LE, nitrites, and pus cells were similar when pus cells were substituted with bacteria; this suggests that any of the above two combinations are good predictor of UTI.

Combination of LE, nitrite, bacteria, and pus cells versus gold standard

Combination of these parameters is positive in 112 samples, out of this 74 were culture positive and 38 were culture negative. Combination of these was negative in 289 samples, of this 6 were culture positive and 283 were culture negative.

The sensitivity, specificity, PPV, and NPV of all these 4 parameters were 92.5%, 88.2%, 66.1%, and 97.9%, respectively (Table 2). The negative likelihood ratio of these parameters was 0.09 (95% CI: 0.04–0.18) and the accuracy value of 89.3% (95% CI: 85.55–91.91%) suggesting that a negative result in these parameters makes it very unlikely a positive urine culture can be got.

An ideal screening tool should have high specificity and sensitivity. The above discussion definitely points to a combination of parameters in dipstick and urinalysis being more useful with higher specificity than individual parameters in predicting UTI.

CONCLUSION

Combination of parameters, i.e., LE, nitrite, and bacteria or LE, nitrite and pus cells are good screening tools to predict and rule out UTI. Of the individual parameters analyzed, negative nitrites in dipstick and absence of bacteria in urine microscopy almost rule out UTI caused by most uropathogens. Individually dipstick parameters (LE, nitrite) are not highly sensitive markers for UTI but they have high specificity, i.e., absence of these parameters in dipstick almost rules out UTI. This study adds to the increasing evidence that more than one of the parameters discussed in our study being positive should trigger a suspicion of a UTI and a gold standard test, i.e., urine culture should be performed.

AUTHOR'S CONTRIBUTION

Protocol writing, data collection, and statistical analysis were done by SK, research reviewed and edited by SM, manuscript prepared by AU, RK, and manuscript edited, finalized by SB.

CONFLICTS OF INTEREST

None.

AUTHOR'S FUNDING

None.

What this study adds?

- Urine dipstick is a simple and fast method for initial screening of urinary tract infection in children.
- In any children with suspected urinary tract infection, initial tests such as dipstick and microscopic urinalysis should perform before starting antibiotic therapy and can proceed to do urine culture if any of these parameters pointing toward urinary tract infection.

Ethics registration number

ECR/37/Inst/TN/2013/RR-16.

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