

Do all Pediatric Urine Specimens Need to Go to the Laboratory?

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Abstract: *Objective:* This study aimed to evaluate the accuracy of the urine dipstick in diagnosing UTIs in children at a tertiary care centre in Pakistan.

Methods: 72 inpatients at the Aga Khan Hospital pediatric ward, getting laboratory urinalysis due to UTI suspicion, were included. Dipstick tests were done on the urine samples being sent to the lab for microscopy. The sensitivity, specificity and likelihood ratios (LRs) of dipstick LE, and pyuria and bacteriuria on microscopy were calculated and compared, using urine culture results as the gold standard for diagnosis.

Results: The specificity of dipstick LE, pyuria and bacteriuria were 77%, 77% and 90% respectively, while the positive likelihood ratios were 28%, 44% and 49% respectively. Urine cultures were done for 58 patients, with 5 positive cultures, so plausible estimates of sensitivity were not made.

Conclusions: Urine microscopy is a more accurate screening test for ruling in UTIs than the dipstick. Keeping in mind its diagnostic limitations, the dipstick can be used to help rule in a UTI, although confirmation by cultures is recommended. Further studies are needed to validate these results in children and to evaluate the dipstick's sensitivity for ruling out disease.

Keywords: Urinary tract infection, pediatric, dipstick, urinalysis, accuracy.

INTRODUCTION

Urinary tract infections (UTIs) are a common pediatric problem in Pakistan. The prevalence of UTIs in children reported worldwide varies from 3-73% [1]. In Pakistan, the prevalence of urinary tract infections in febrile children is estimated to be 12% [2].

Unlike adults, children with UTIs have a variety of signs and symptoms in children. Clinical features which suggest a UTI in infants include a history of prior UTI, temperature greater than 39°C or 40°C, temperature lasting more than 24 hours, suprapubic tenderness, and lack of circumcision; while vomiting, diarrhea, irritability and poor feeding are not useful for screening for UTIs [3]. Furthermore, presence of another source of fever reduces the probability of a UTI by only a small extent. In older children, a UTI is likely in the presence of abdominal pain, back pain, dysuria, frequency and incontinence [3]. Circumcised male children, have a very low likelihood of a UTI. Overall, due to the lack of reliability of clinical features, it is preferred that any child presenting with fever without a localizing source should undergo workup for a UTI.

The definitive diagnosis of a UTI in children requires documentation of bacterial pathogen growth on urine culture, with a sample obtained preferably by

suprapubic aspiration [1]. However, culture reporting delays diagnosis by approximately 24-72 hours. This delay in initiation of antimicrobial therapy increases the risk of renal scarring from the UTI [3]. On the other hand, initiation of empiric antibiotic treatment based on clinical suspicion of UTI alone promotes the development of antibiotic resistance, as not all such patients actually have a bacterial infection [4].

Thus, rapid urine screening tests are frequently used to determine the probability of a UTI. Rapid tests include urine microscopy for pyuria and bacteriuria (with or without Gram staining), and the urine dipstick test for leukocyte esterase (LE) and nitrites. The most sensitive and specific rapid method for diagnosing UTI is urine microscopy for bacteriuria and pyuria [5]. The urine dipstick LE and nitrite tests have debatable accuracy [4]. Urine microscopy requires more time and equipment and is more costly, than the dipstick test. Furthermore, the several-hour delay in obtaining microscopy results encourages physicians to initiate empiric antibiotics without obtaining better evidence of an infection, while the dipstick provides results within a few minutes.

Despite the presence of these studies comparing the dipstick and microscopy, awareness and use of the urine dipstick as an alternative screening modality to evaluate UTIs remains limited among medical professionals in Pakistan. Urine microscopy is the preferred rapid test to investigate a very common febrile illness, which generates enormous workloads for

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laboratories. Local professionals tend to dismiss the possible benefits of using the dipstick, due to the lack of international rock-solid evidence in its favor. This is largely due to a complete absence of any local studies to evaluate the accuracy of the dipstick for pediatric UTIs. A study in Karachi in the Emergency Department setting in adults found the sensitivity of the dipstick LE plus nitrites test to be 94%, and specificity 50% [6]. No similar study has been done to evaluate the same for children. Such a study is sorely needed to shed light on the relevance and role of the urine dipstick when suspecting a UTI in a febrile child. Evaluating the accuracy of the dipstick in our population and identifying situations where the dipstick can give reliable results, could help reduce the costs and antibiotic overuse associated with the diagnosis of UTIs in children.

Thus, our study aimed to evaluate the accuracy of the urine dipstick, and to compare it with microscopy as a screening test for pediatric inpatients suspected of having a UTI. Our hypothesis was that the urine dipstick leukocyte esterase and nitrite tests would have accuracy comparable to urine microscopy for pyuria and bacteriuria. Through the results, this study aimed to promote the awareness and use of the urine dipstick, and help reduce the cost of diagnosing UTIs as well as antibiotic overuse in this developing country.

METHODS

This was a prospective cross-sectional study carried out on patients admitted to the pediatric ward of Aga Khan University Hospital between September 2009 and May 2011. Data was collected from total 72 subjects. The inclusion criteria specified inpatients, aged 1 month to 14 years, who had a laboratory urinalysis as part of their initial workup ordered by the attending physician to determine to the presence of a UTI. Only inpatients were included, as they constitute a sicker group of patients for whom early initiation of antibiotic therapy is of concern. They were admitted for the investigation and treatment of presenting complaints suggestive of a UTI, including fever, abdominal pain, vomiting, and/or urinary complaints (burning micturition and incontinence).

The nursing staff in the pediatric ward, which was pre-trained in using urine dipsticks (Multistix 10 SG, Bayer Diagnostics Manufacturing Ltd, UK), was instructed to perform a dipstick test on urine samples collected from inpatients that were being sent to the laboratory for urinalysis. The results of the dipstick test

were noted in a questionnaire. The noted dipstick findings included: (1) Leukocyte Esterase: Negative/ 1+ (small)/ 2+ (moderate)/ 3+ (large); (2) Nitrite: Negative/ Positive; (3) Blood: Negative/ 1+ (small)/ 2+ (moderate)/ 3+ (large). Findings for protein and nitrites were also noted. Urine cultures were sent only for subjects if the attending physician deemed it required.

Laboratory urinalysis and culture was performed per routine practice by AKU laboratory technologists. Specimens were sealed and sent in sterile containers to the laboratory and examined within two hours of collection. At our center, the urinalysis has three components: (1) Physical appearance (color, consistency), (2) Biochemistry (using Bayer Multistix 10 SG reagent strips, results quantified with Clinitek-500 automated dipstick reader for specific gravity, proteins, ketones, nitrites and hemoglobin in mg per mL of urine); and (3) Microscopy (of specimen centrifuged at 3000 rpm for 3 minutes, supernatant discarded, and pellet used to make the slide) for red and white blood cells count, bacteria (without Gram staining), yeasts, casts and crystals. The threshold for pyuria was > 5 white cells / high power field (HPF). Bacteria visualized were reported as 'none', 'few', 'moderate' or 'numerous'.

Urine culture was performed using a 0.01 ml calibrated loop to inoculate CLED media, with incubation of plates at 37°C for growth detection every 24 hours for a maximum of 48 hours. Colony counts were reported as number of colonies per mL of urine. A positive urine culture was defined as 10^5 or more colonies / mL of urine at 24 or 48 hours, of uropathogens. A negative urine culture was reported as 'no growth', 'no uropathogens isolated', 'normal microbial flora' or growth of less than 10^5 colonies / mL of a pathogenic species.

As the dipstick test was not part of the clinician's investigations ordered for the patient, the cost of the dipstick test was borne by the study investigators.

The results of the dipstick test and laboratory urine microscopy were recorded in questionnaires. For laboratory urinalysis, this included white blood cell (WBC) count, red blood cell count, bacteriuria, and presence and quantity of proteins and nitrites. The subjects' presenting symptoms, urine collection technique, diagnosis at discharge, and results of urine culture - if done - were also noted. Information for the latter categories was obtained from medical records.

Table 1: Demographic Details of Study Subjects (n=72)

Demographic		Frequency (%)
Age	1 month – 1 year	19 (26.4%)
	1 -14 years	53 (73.6%)
Gender	Male	40 (55.6%)
	Female	32 (44.4%)
Clinical Symptom	Fever	59 (82%)
	Vomiting	30 (42%)
	Abdominal Pain	8 (11%)
	Urinary symptoms (Dysuria, incontinence)	2 (2.7%)
	Non-UTI symptoms (e.g seizures, sore throat, loose stools)	26 (36%)

Ethical approval for conducting this study was obtained from the hospital's Ethics Review Committee before initiation. Direct informed consent from the patients' parents/guardians was not required.

SPSS v. 17.0 software was used for data analysis. Pretest probability of a UTI for each subject was determined using the prevalence of UTIs found in the study. Using urine culture results as the criteria for diagnosis of UTI, the sensitivity and specificity of the dipstick LE and nitrite tests, as well as predictive values and likelihood ratios were calculated. These calculations were also made for urine microscopy findings for pyuria.

RESULTS

72 questionnaires were completed for this study. The participants' age ranged from 1 month to 14 years, with mean age 4.8 months, including 19 infants (Table 1). The patients' presenting symptoms (Table 1) included fever in 59 cases (82%), vomiting and abdominal pain. A significant number also had symptoms suggesting a non-UTI source of fever.

The type of urinary collection was urinary bag or clean catch specimen. Suprapubic aspiration was not performed for any case.

Urine cultures were performed for 27 (37.5%) of the cases, among which 5 (6.9%) were positive, and 22 (30.6%) were negative. The prevalence of UTIs in our study population of febrile children was 18%. The clinical features of the 5 patients with a positive urine culture included fever (4), vomiting (2), and, in one case, loose stools and febrile seizures. Urine cultures were not obtained for the remaining patients as the attending physician deemed it unnecessary.

The results of the dipstick LE, microscopy (for pyuria and bacteriuria) and urine culture are shown in Table 2. All of the dipstick nitrite tests were reported negative. The sensitivity of the dipstick was therefore, analyzed using LE results only. The sensitivity of the dipstick LE calculated against urine culture results as gold standard, was 40% (95% confidence interval 7-82%), with a specificity of 77% (95% confidence interval 54-91%). Positive predictive value for LE was 0.28 (95% confidence interval 0.05-0.69), and the negative predictive value was 0.85 (95% confidence interval 0.61-0.96). Positive likelihood ratio (LR+) was 1.76 (95% confidence interval 0.46-6.59), and the negative likelihood ratio (LR-) was 0.77 (95% confidence interval 0.37-1.63).

Analysis of urine microscopy pyuria revealed a sensitivity of 80% (95% confidence interval 29-98%),

Table 2: Results of Dipstick Tests, Urine Microscopy and Urine Culture for our Sample Patients

Test Result	Frequency (%)			
	Dipstick LE	Pyuria	Bacteriuria	Urine Culture
Negative	53 (73.6%)	58 (80.6%)	66 (91.7%)	22 (81%)
Positive	19 (26.4%)	14 (19.4%)	6 (8.3%)	5 (18%)
Total	72	72	72	27

and specificity of 77% (95% confidence interval 54% - 91%). The positive predictive value of microscopy was 0.44 (95% confidence interval 0.15-0.77), and the negative predictive value was 0.94 (95% confidence interval 0.70-0.99). The positive likelihood ratio (LR+) was 3.52 (95% confidence interval 1.45-8.54), and the negative likelihood ratio (LR-) was 0.26 (95% confidence interval 0.043-1.53).

Analysis of bacteriuria results showed a sensitivity of 40% and a specificity of 90.1%. The positive predictive value was 50% (CI 9.1% - 90.9%), and the negative predictive value was 87% (CI 65.3% - 9.5%). The positive likelihood ratio was 4.4 (CI 0.80 - 24.1), while the negative likelihood ratio was 0.66 (CI 0.32 - 1.36).

Post-test probabilities for the three tests are given Table 3. These were estimated with the Bayes' nomogram, assuming the pre-test probability to be the prevalence of UTIs found in our study (18%). The post-test probability of the dipstick LE test in our study was 28%. The post-test probability of pyuria on microscopy was higher at 44%. Thus, our results show that in a child with clinical features raising suspicion of a UTI, the likelihood of a UTI is about 18%, a positive dipstick test would indicate that the likelihood is increased to 28%, while urinalysis positive for pyuria on microscopy would increase the likelihood to 44%, and positive bacteriuria on microscopy would increase the likelihood to 49%.

DISCUSSION

The accurate diagnosis of UTIS in children has always had strings attached. The prevalence of UTIs in febrile children reported in Pakistan is 12% [2]. In our study, which included febrile and non-febrile children suspected of having a UTI, the prevalence was 18%. A likely reason for this higher prevalence in our study is that the urine culture was performed for patients with a positive urinalysis for confirmation, while many patients

with negative urinalysis were never subjected to a urine culture.

Several systematic reviews and meta-analyses have attempted to conclude as to which rapid test would most accurately diagnose a UTI, however, no universal opinions exist. Sheikh *et al.*, [3] concluded that febrile infants and children, or those with one or more other features suggestive of a UTI, have a high pretest probability of the disease - more than 2% - and should be subjected to a rapid screening test to determine the likelihood of having a UTI. They reported microscopic urinalysis to be the most sensitive and specific urinalysis method.

A more recent meta-analysis by Williams *et al.*, [7] reported that the most accurate rapid test for diagnosing a UTI was urine microscopy for bacteriuria on Gram staining, with a sensitivity of 91% and specificity 96%. Direct visualization and quantification of bacteria on microscopy without Gram staining was slightly less accurate. Even Gram staining had a relatively high false negative rate of 9%, allowing many patients with a UTI to be missed. They recommended that for very high pre-test probabilities - in other words, for a patient who has more than two clinical features suggesting a UTI - a urine culture should be obtained even if the rapid test is negative. They recommended that due to the ease of use and faster results, the urine dipstick test should not be replaced entirely by urine microscopy for bacteriuria. Furthermore, they reported the accuracy of the dipstick LE test to be comparable to urine microscopy for pyuria - sensitivity 79% and 74% respectively, and specificity 87% and 86% respectively. They suggested pyuria by microscopy could be abandoned in favor of Gram staining for pyuria or the dipstick LE. Moreover, a positive nitrite test was found to make the dipstick result more specific. Our results are concordant with these recommendations as far as the specificity is concerned - which was 77% for both the urine dipstick test and urine microscopy for pyuria, and 91% for bacteriuria. The sensitivity of the urine

Table 3: Likelihood Ratios and Corresponding Post-Test Probabilities for Dipstick LE and Microscopy for Pyuria and Bacteriuria

	Dipstick LE	Pyuria	Bacteriuria
Positive likelihood ratio	1.76	3.52	4.4
Post-test probability	28%	44%	49%
Negative likelihood ratio	0.77	0.26	0.66
Post-test probability ^a	14%	5%	13%

^aThe pre-test probability used for the estimation of post-test probability was 0.18 - the prevalence of UTIs found in our study.

dipstick and bacteriuria was low in our study – at 40%, while the sensitivity of pyuria by microscopy was 80%. However, the results for sensitivity cannot be generalized, as they involved only 5 positive cases of urine culture.

The accuracy of the urine dipstick in our study was lower than that reported in the meta-analysis by Williams *et al.*, [7]. This discrepancy can be attributed to several factors, including small sample size and wide confidence intervals. Yet, it would be reasonable to conclude that based on the results of our study and prior literature, the urine dipstick is at least as specific as urine microscopy for pyuria in the diagnosis of UTIs. On the other hand, the low sensitivity of the urine dipstick found in our study is in contrast to a majority of the reported literature from other regions, and further studies using an adequate number of positive urine cultures, are needed to make a definite conclusion regarding the sensitivity in our setting.

Gram staining of urine samples with microscopy is not routinely performed at our center, and bacteriuria is reported on visualization of bacteria on a sample wet prep. The interpretation of this test is limited, as samples have a significant likelihood of contamination by vaginal and external meatus during urine collection by midstream and bag methods. In our study, interpreting 'few' bacteria seen on microscopy as negative but 'moderate' and 'numerous' as positive, revealed a specificity as high as 91%, which is consistent with the conclusions of Williams *et al.*, [7].

At least two reviews have concluded that the urine dipstick has a high sensitivity at 68 to 88%, and can be reliably used to rule out urinary tract infection [4,8]. Our results cannot corroborate these conclusions. In contrast, another recent review by Mori *et al.*, [9] concluded that the urine dipstick was more accurate for ruling in infections, while pyuria on microscopy was more accurate for ruling out infections in children over the age of 2. In children under 2 years of age, they recommended using urine microscopy over the dipstick test.

Likelihood ratios (LRs) are used for determining the accuracy of screening tests. They have more clinical relevance than the sensitivity and specificity as they allow a clinician to determine the probability of a disease in an individual patient [10]. A positive LR larger than 2.0 implies a high likelihood of disease, supporting the decision to treat, while a negative LR lower than 0.1 implies a very low likelihood of disease

so that treatment is not needed [4]. The Bayes' theorem is used to determine disease post-test probability using the LR and the pre-test probability (taken to be the disease prevalence) [10].

We found a much higher LR+ with correspondingly higher post-test probabilities for pyuria and bacteriuria on microscopy (44% and 49% respectively) than for the dipstick LE test (28%). Similarly, LR-and its corresponding post-test probability and was lower for the microscopy tests than for dipstick LE. Microscopy appears to be a better rule-in as well as rule-out strategy based on these results, which are not entirely concordant with reported reviews elsewhere. Mori *et al.*, [9] found a higher LR+ for the dipstick than microscopy (6.24 vs. 1.63 in young children, and 27.1 vs. 1.69 in older children), while microscopy had a slightly lower LR- than the dipstick (0.27 vs. 0.31). Whiting *et al.*, [1] found it impossible to make reliable pooled estimates of likelihood ratios of dipstick LE and microscopy due to the heterogeneity between studies' methodologies and results.

The nitrite test in our study was negative for all cases, both for the dipstick test in the ward and the laboratory urinalysis strip test. Although a positive nitrite test is very specific for a UTI, false negatives can occur if the urine has not been incubating in the bladder for at least 4 hours, as time is needed for the bacteria to produce nitrites [11]. Thus, unless a first morning urine sample is taken, the nitrite test cannot yield much information.

LIMITATIONS

The limitations of our study include a small sample size, and a small number of urine cultures done. This restricted the analysis and interpretation of results. It was assumed that all sample male patients were circumcised, and that they had an equal pretest probability of a UTI. However, this may not necessarily have been true.

CONCLUSIONS

Our study demonstrated that the urine dipstick LE has a similar specificity to urine microscopy pyuria as a rapid test for detecting UTIs. However, bacteriuria has a higher specificity than both. Also, the positive likelihood ratios of microscopy tests – pyuria and bacteriuria -are higher than those for dipstick LE. Keeping in mind its limitations, the urine dipstick test may be used to rule in UTIs in combination with the

pretest probability, based on international recommendations, and where time and cost are significant issues. However, confirmation with a culture is recommended while the patient is started on empiric antibiotics. Further studies are needed to establish the pretest probability of UTIs, and to evaluate the sensitivity of the dipstick and its role in ruling out UTIs in children.

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