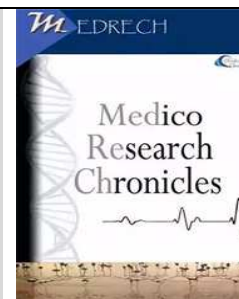




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### UTILITY OF SIMPLE DIPSTICK TEST IN DIAGNOSING URINARY TRACT INFECTION IN CHILDREN PRESENTING WITH FEVER: A PROSPECTIVE OBSERVATIONAL STUDY

Dr. Vivek Gupta<sup>1</sup>, Dr. K M Adhikari<sup>2</sup>, Dr. Manish Kumar<sup>3</sup>

1. Assistant Professor, Department of Pediatrics, Command Hospital, Southern Command, Pune, Maharashtra, India – 411040

2. Professor, Head of Department, Department of Pediatrics, Armed Forces Medical College, Pune, Pune, Maharashtra, India - 411040

3. Associate Professor, Department of Pediatrics, Armed Forces Medical College, Pune, Pune, Maharashtra, India – 411040

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**Corresponding author**  
Dr. Manish Kumar\*

#### ABSTRACT

**Background:** Urinary tract infection (UTI) in children continues to be under-diagnosed, despite its association with renal scarring, hypertension, renal failure, and other sequelae. To avoid these preventable complications, we should treat UTIs in children at the earliest. A simple, reliable, bedside test could solve this problem.

**Methods:** The study was conducted in a tertiary care hospital as a prospective observational study. The study included 534 children until 12 years of age (excluding neonates), presented with fever without focus or fever with urinary complaints. The Rapid diagnostic urine test was performed with a urine dipstick (Combur 10 test®), for urine nitrite, leukocyte esterase and protein determination. Simultaneously urine culture was also sent. Sensitivity, Specificity, Positive Predictive Value, Negative Predictive Value and diagnostic accuracy were calculated. **Observations:** Urine culture was found positive in 80 cases (14.9 %). When all the three tests were positive, diagnostic accuracy was maximum (90.7%). The diagnostic accuracy of the nitrite test was also > 90%. Furthermore, all three tests have very high negative predictive values (> 87%). **Conclusion:** If all the three tests are positive or only nitrite is positive antibiotic should be started and given a full course of treatment irrespective of the urine culture report. All three tests have very high negative predictive values, which excludes UTI. The rapid diagnostic dipstick will reduce the workload of the laboratory. This may guide the clinician in managing OPD as well as inpatient empirical therapy, as delay or untreated UTI can have long-term future implications.

#### ORIGINAL RESEARCH ARTICLE

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## INTRODUCTION

A Urinary Tract Infection (UTI) is defined as colonization of a pathogen occurring anywhere along the urinary tract: kidney, ureter, bladder, and urethra. Urinary tract infection in infancy continues to be underdiagnosed, despite its association with renal scarring, hypertension, renal failure, and other sequelae.

Children with complicated UTI (i.e., pyelonephritis) are at risk for irreversible renal parenchymal damage evidenced by renal scarring. It is noted in 10% to 30% of children after UTI<sup>1</sup>. The incidence of hypertension in adulthood after urinary infection ranges from 7% to 17%<sup>2</sup>. To avoid these preventable complications one must treat UTI in children at the earliest. There is an urgent requirement to diagnose UTI rapidly and start the empirical therapy, before urine culture report is available. A simple, reliable, bedside test could solve this problem.

This novel study is aimed to use rapid diagnostic test kit, in early diagnosis of UTI in children presenting with fever without focus or fever with urinary symptoms. To determine if rapid diagnostic test can decrease the time to diagnose UTI in children so that early treatment can be initiated.

## MATERIALS & METHODS

This prospective observational study was conducted in a tertiary care hospital for one year. The study group comprised of infants and children until 12 years of age (excluding neonates), presenting with fever without focus or fever with urinary complaints. Patients with evidence of infection at any other site and patients who have received empirical antibiotics before presentation to this hospital were excluded from the study group. A total number of 560 children were enrolled and out of them, 26 children were excluded within 72 hours once alternate diagnoses were made. Rest 534 children were finally studied.

Demographic profiles of patients were recorded. History of fever with or without urinary symptoms and any previous history of urinary tract infection noted. Physical examination to find out the focus of fever was done. Screening tests done to find out the other causes of fever were Complete blood count, peripheral blood smear and Immunochromatography for malaria. The random Urine sample was collected by the patients in a clean test tube. At the same time, mid-stream sample for the urine culture was also collected in a sterile container as per the guidelines given by Indian Society of Pediatric Nephrology in 2011<sup>3</sup>.

Rapid Diagnostic urine test was done with the help of a multi parameter urine dipstick, Combur 10 test ® (Pack of 100 urine test strips, Roche Diagnostics GmbH, Germany) (Fig 1). This test strip can be used for testing 10 parameters of the urine. In this study semi quantitative determination of leukocytes, nitrite and protein in the urine was done. Colour coded label over the box was used for the specific parameter.

Uncentrifuged fresh urine sample was used. Most of the time the test was performed immediately but when it was delayed due to any reason (eg. OPD patients brought the sample from their home), performed within 2 hours of collection as recommended. The test strip was dipped into the urine for 1 second. After 60 – 120 seconds the reaction colors of the test area were compared with the colors on the label and assigned the value of the nearest color block (Fig 2). If the rapid test result showed it negative, then it was repeated on the next day on an early morning urine sample.

Results of the dipstick test were interpreted visually according to standard color charts. The leukocyte esterase measurement was read at 60 – 120 sec and recorded as negative, 1+ (10-25 leukocytes/mcl), 2+ (75 leukocytes/mcl), or 3+ (500 leukocytes/mcl). The nitrite measurement was read at 60 seconds and recorded as

negative or positive. The protein measurements were also recorded at 60 seconds as negative, 1+ (30 mg/dl), 2+ (100 mg/dl) or 3+ (500 mg/dl). Urine culture was considered a gold standard test. Urine dipstick and urine culture were performed on all the patients.

A midstream urine sample was collected for urine culture. Urine culture was considered positive if  $>10^5$  cfu/ml were present. A urine culture was repeated in case contamination was suspected. The culture was also repeated in situations where UTI was strongly suspected (children with urinary symptoms) but colony counts were equivocal. The child was not started on any antibiotic till the urine culture report was positive. The results obtained by the dipstick were compared with the urine culture reports. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and diagnostic accuracy for the tests were calculated.

## RESULTS

A total number of 560 children were considered for the study. But 26 of them were excluded within 72 hours when we find a focus of infection other than UTI present in them. The rest of the 534 children were taken for the study.

Urine culture was found positive ( $>10^5$  colony forming units/ml) in 80 cases (14.9%) out of total 534 cases. The organisms isolated included *Escherichia coli* (78.8%), *Citrobacter* (7.5%), *Proteus* (6.3%), *Klebsiella* sp (2.5%), *Pseudomonas* sp. (1.3%), *Enterobacter* (1.3%), *Acinetobacter* sp (1.3%) and *Staphylococcus aureus* (1.3%).

Results in the form of sensitivity, specificity and diagnostic accuracies of urine dipstick nitrite, leukocyte esterase and protein alone and their various combination tests are shown in fig 3-5. Leukocyte Esterase with protein, nitrite with protein and nitrite with leukocyte esterase test were taken in combination for calculating the above

parameters. Then any one of the three tests vis nitrite or leukocyte esterase or protein (N or LE or P) positive is taken as a positive result and compared with a urine culture. Finally, all the three test positive (N+LE+P) is taken as a positive result and compared with urine culture and further parameters calculated. Furthermore, all the tests have very high negative predictive value, which ranges from 87.6% for nitrite and protein to 99.7% when nitrite, leukocyte esterase, or protein is taken alone into consideration and can exclude UTI confidently if test results are negative (Table 1).

Diagnostic accuracies of more than 90% were noted when the combination of all three tests vis nitrite, leukocyte esterase and protein or nitrite test alone found positive (Fig 5).

## DISCUSSION

Detection of urinary nitrites has been used as a screening test for urinary tract infections. We compared urine nitrite results with urine culture, the gold standard for the detection of bacteriuria. For specimens having colony counts of  $>10^5$  cfu/ml, we found the sensitivity, specificity and predictive values similar to those reported by Lohr<sup>4</sup>, Shaw<sup>5</sup>, Goldsmith<sup>6</sup> and Bagga<sup>7</sup> (Table 2).

The utility of the nitrite test in clinical practice is limited by its low sensitivity. However, its high specificity allows it to be used in a few clinical situations. First, the test is likely to be useful when symptoms of UTI are not very definite. A positive result may enhance the number of urine cultures sent by the clinicians and start treatment with antibiotics presumptively. Similarly, if the nitrite test is positive in a patient with fever without localization, the clinician may avoid unnecessary evaluation for other infections. Third, in clinical settings where culture facilities are not available, this test may serve as a possible substitute.

As the sensitivity of the nitrite test is low, this test alone has limitations as a

screening test. Certain reasons can result in a lower sensitivity. The causes for low sensitivity are low colony counts, frequent bladder emptying in children<sup>8</sup>, high specific gravity and low nitrates in the diet. A negative nitrite test may correctly predict the absence of UTI (negative predictive value) in situations where the possibility of UTI is low.

Leukocyte esterase (LE) is specific to host's inflammatory response in the genitourinary tract and is not affected by conditions that cause nitrite tests to be false negative. It is suggested that a combination of both nitrites and leukocyte esterase can increase the sensitivity to reach nearly 100%. Dipstick LE and nitrites are commonly used to identify pediatric patients with positive urine cultures. A study by Oneson et al suggests that routine use of dipstick tests could result in substantial cost saving by decreasing the need for more expensive microscopic urinalysis and culture<sup>9</sup>.

In a meta-analysis<sup>10</sup>, overall, the sensitivity of the urine dipstick test for nitrites was low (45-60% in most situations) with higher levels of specificity (85-98%). A study by Mustafa et al, showed the urine dipstick test for nitrites had 61.7% sensitivity, 96.9% specificity, 95.2% PPV and 71.7% NPV<sup>11</sup>. Results of our study are similar to previous studies. Leukocyte esterase measurement has been shown to give an accurate estimate of the number of leucocytes present<sup>12</sup>. The urine dipstick test for leukocyte esterase and nitrite continues to be a low-cost excellent screening test for UTI<sup>13</sup>. Of all the tests studied, it is the only one not requiring Clinical Laboratory Improvement Amendments certification and can be performed by the bedside nurse or physician. The strategy of urine dipstick and culture tests for patients for whom a UTI is considered is less costly, identifies patients with UTI, and allows one to screen which patients should begin presumptive treatment.

In another meta-analysis by Williamms et al<sup>14</sup>, Data from 95 studies in 95,703 children

were analyzed. Summary estimates for sensitivity and specificity for leucocyte esterase or nitrite positive dipstick were 88% (82—91) and 79% (69—87), and for nitrite-only positive dipstick were 49% (41—57) and 98% (96—99).

As per the European Association of Urology Guidelines 2006, the nitrite test has a sensitivity of only 45-60%, but a very good specificity of 85-98%. The test for leukocyte esterase has a sensitivity of 48-86% and a specificity of 17-93%<sup>14</sup>. The dipstick test has become useful to exclude rapidly and reliably the presence of a UTI, provided both nitrite and leukocyte esterase tests are negative. If the tests are positive, it is better to confirm the results in combination with the clinical symptoms and other tests<sup>15</sup>.

In a study by Joseph et al<sup>16</sup>, the rapid diagnostic urinary nitrite test showed sensitivity of 50(16-72) % and specificity of 98(95-100) %, leukocyte esterase test with a sensitivity of 83(64-89) % and specificity of 84(71-95) % and either leukocyte esterase or nitrite showed the sensitivity of 88(71-100) % and specificity of 93(76-98) %. Our study also shows the results which are similar to the above studies.

There are few drawback points of the study. The urine sample required for the test should have a long (4 – 6 hrs.) retention time in the bladder. Mostly early morning urine specimen has to be taken. This type of urine sample collection has poor compliance.

This study does not substantiate the definite role of urine culture in the diagnosis of UTI. The study results corroborate with other pieces of evidence in the literature regarding the utility of dipstick in early diagnosis of UTI which has both short and long-term implications for early treatment and prevention of long-term complications.

## CONCLUSION

When all the three tests vis nitrite, LE and protein are positive diagnostic accuracy was maximum (90.7%). Diagnostic accuracy

of nitrite test alone was also > 90%. Therefore, if all three tests are positive or only nitrite is positive antibiotic should be started and given a full course of treatment irrespective of the urine culture report, if the patient is symptomatic. All three tests have very high negative predictive values, which excludes UTI if all test results are negative.

### RECOMMENDATIONS

Rapid diagnostic urine dipstick test should form an important component of pediatric care both in OPD and inpatient setup. All the suspected cases of UTI should undergo Rapid diagnostic dipstick test to enable early initiation of therapy. Later therapy can be modified as per urine culture reports. When all the three tests are positive together or nitrite test positive alone antibiotic should be started and given as a full course of treatment irrespective of the urine culture report if patient is symptomatic. In case any other than the above test (leukocyte esterase alone, proteins alone, combination of leukocyte esterase and proteins, leukocyte esterase and

nitrite, proteins and nitrite) is positive on urine dipstick in a symptomatic patient, antibiotic should be started empirically but if urine culture is negative antibiotic should be stopped. All three tests have very high negative predictive values, which excludes UTI if all test results are negative. Though more studies will help in rationalizing OPD management of approach to UTI, the rapid diagnostic dipstick test is a useful test to detect urinary tract infection in children and initiate early treatment. Rapid diagnostic dipstick could be a useful point of care test for primary rural setup, where culture facilities are not available or, if available, to reduce the workload, one should be provided with the Rapid diagnostic dipstick test kits. In hospitals, it will reduce the workload of the laboratory. In both setups it will guide the clinician for empirical therapy as delay or untreated UTI can have long-term future implications. This urine dipstick multi-parameter test strip is easily available everywhere, even at small places.

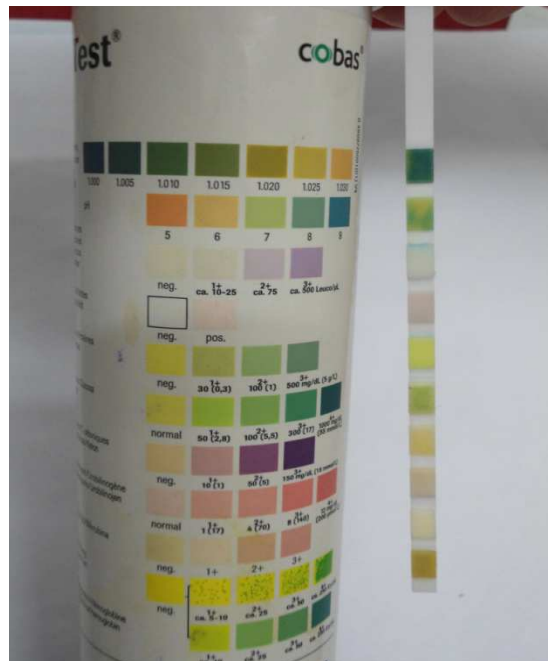
**Table 1** – shows sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy of nitrite, leukocyte esterase and protein test by dipstick, alone and their various combinations.

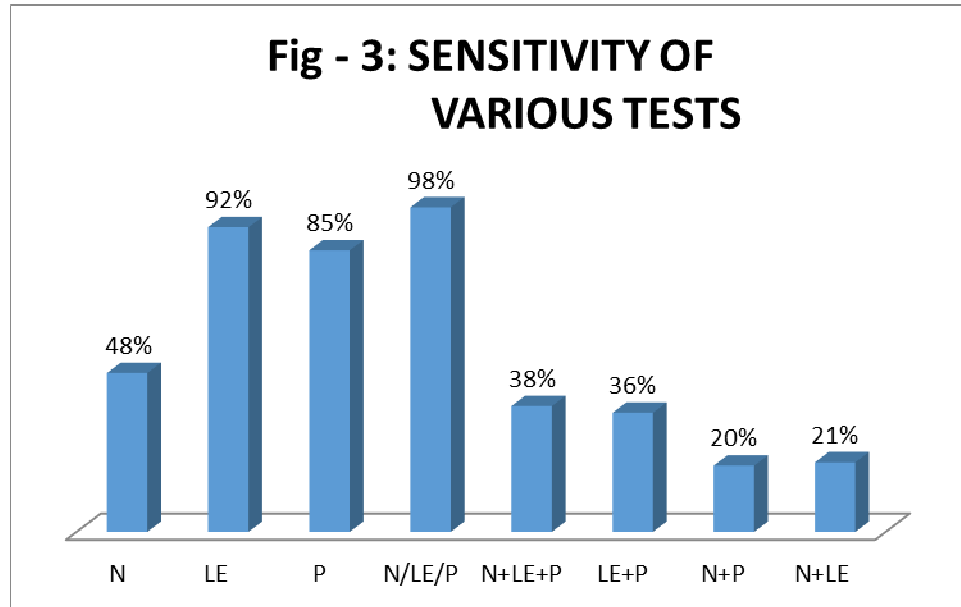
Urine dipstick parameter	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)	Diagnostic accuracy (%)
Nitrite (N)	48	97	80	91	90.4
Leukocyte Esterase (LE)	92	87	56	98	87.8
Proteins (P)	85	89.4	58	97	88.7
LE + P	36.3	97.8	74.3	89.6	88.5
N + P	20	99.7	94	87.6	87.8
N + LE	21.3	99.5	89.4	87.7	87.8
N or LE or P	98.7	77.7	43.8	99.7	80.9
N + LE + P	38.7	99.1	88.5	90.1	90.7

(N – Nitrite, LE – Leukocyte Esterase, P – Protein)

**Table 2 – Comparison of Sensitivity, Specificity and Predictive Values of nitrite test (%).**

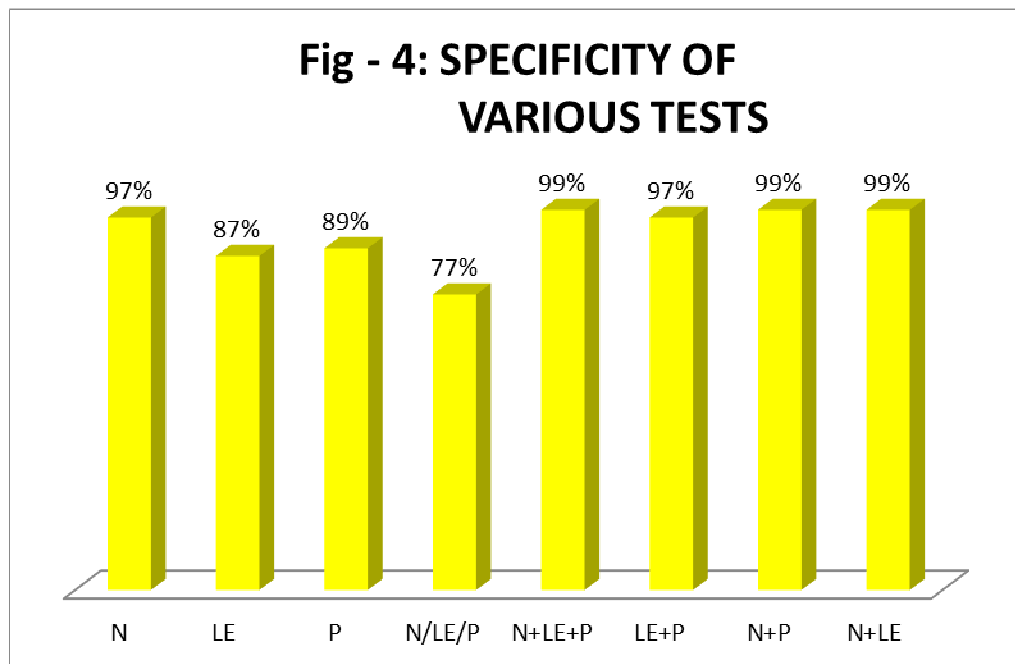
Author	Number of samples	Prevalence of UTI	Sensitivity (%)	Specificity (%)	Predictive value	
					Positive	Negative
Lohr	689	14.8	37.3	100	88	92
Shaw	491	9	50	85	–	–
Goldsmith	1010	10	21	99	88	
Bagga	1018	11	47	87	31	93
<b>Present study</b>	534	14.9	48	97	80	91

**Fig 1 – Urine dipstick container (Combur 10 test)****Fig 2 – Comparison of the dipstick with standard color-coding**



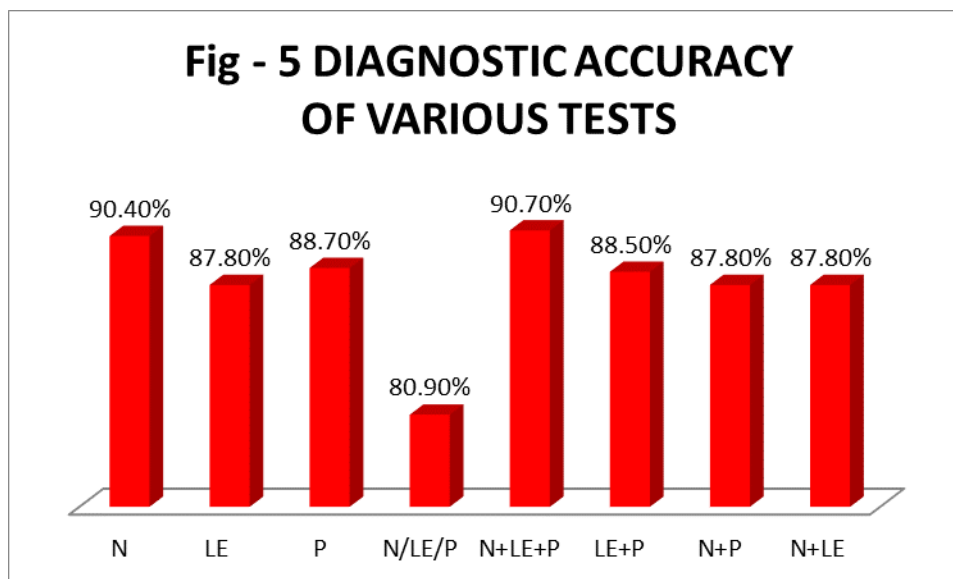
(N – Nitrite, LE – Leukocyte Esterase, P – Protein)

**Fig 3** – This shows the sensitivity of various tests alone and their combinations in a bar diagram.



(N – Nitrite, LE – Leukocyte Esterase, P – Protein)

**Fig 4** – Shows the specificity of various tests alone and their combinations.



(N – Nitrite, LE – Leukocyte Esterase, P – Protein)

**Fig 5** – Shows the Diagnostic accuracy of various tests alone and their combinations.

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