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Tests for Early Detection of Paediatric Urinary Tract Infection

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Abstract: Urinary tract infection is the most common of all pediatric bacterial infections. This study aims to determine the efficacy of rapid diagnostic tests vs gram stain as against gold standard test (urine culture) and to find out the validity of each screening test for early detection of urinary tract infection in children. A cross-sectional study was conducted on children aged between 3-15 years of suspected urinary tract infections from August 2020 to January 2021. Data collection was facilitated by using a pre-designed checklist. The specimen was collected in a sterile, leak proof container by clean catch midstream technique and was subjected to urine microscopy, urine dipstick nitrite and leukocyte esterase, urine gram stain, and the gold standard test urine culture and sensitivity. Using the gold standard test, the sensitivity, specificity, positive predictive value, and negative predictive value of the other screening tests were determined. The patient's mean age was 5.16 ± 2.7 years, and half were in the age group 3-5 years. The majority of the patients were male (54%). Fever (64%) was the major symptom, followed by pain in the abdomen (52%) and dysuria (40%). Escherichia coli was the most common organism isolated (54%), followed by Klebsiella (22%). Urine gram stain has sensitivity and specificity of 95% and 100% respectively. Urinary tract infection is a common infection in children. Urine gram stain is a very sensitive and specific test for diagnosing urinary tract infections compared to other screening tests.

Keywords: Bacterial Infection, Gram Stain, Paediatric, Screening, and UTI

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1. INTRODUCTION

Urinary tract infection (UTI) is one of the most common serious bacterial infections in children. Urinary tract infection may involve the upper or lower tract depending on the infection in the kidney, bladder, and urethra[1]. Febrile UTIs are most common among boys and girls who are 2 to 24 months of age and occur in about 5% of children[2]. Although the incidence of UTI in the first few days is difficult to assess, it is reported up to 1.8% in developing countries[3]. UTI accounted for febrile presentations in 7.5% of 442 infants < 8 weeks, 5.3% of 945 infants < 1 year, 4.1% of 501 children < 2 years, and 1.7% of 664 children < 5 years[4]. With advancing age, the prevalence of UTI is declining, with a marked female predominance[5]. Infection in the urinary tract can progress to acute pyelonephritis, which in turn can lead to renal scarring, hypertension, or renal failure[6]. Early detection and appropriate management are essential to preserve renal function and prevent permanent renal damage. Accurate and timely diagnosis and treatment are important for the prevention of long-term morbidity and sequelae (e.g. hypertension, proteinuria, and chronic kidney disease[7]. The gold standard method in diagnosing urinary tract infection is the growth of a significant number of pathogenic bacteria in urine culture and sensitivity. To prevent delay in treatment, there are various rapid diagnostic tests available to diagnose urinary tract infections such as urine dipstick analysis for nitrite, leukocyte esterase (LE), urine microscopy, and urine gram stain[8]. Numerous studies and meta-analyses have examined the accuracy of the dipstick method using either nitrite or leukocyte esterase test to predict or exclude UTI in children with a specificity of 98% and 87% respectively[9]. However, these rapid diagnostic tests, conducted in pediatric and adult populations differ in their results frequently. A study by Lockhart et al[10] consisting of 207 febrile infants < 6 months of age concluded that the Gram stain has a sensitivity of 94% and specificity of 92%. Due to the non-specificity of the urinary symptoms in febrile children, it is pertinent for timely and appropriate detection of UTI; as the gold standard test (urine culture) takes a minimum of 48 – 72 hours to be reported. So, the dipstick and gram stain tests provide the primary care physician with early evidence of UTI in these children, enabling the initiation of appropriate treatment. Hence the purpose of this study was to compare the diagnostic effectiveness of urine microscopy, urine dipstick for nitrite, leukocyte esterase, urine gram stain, and urine culture and their validity in children with suspected urinary tract infection and to evaluate their advantage in diagnosing urinary tract infection.

2. MATERIALS & METHODS

This cross-sectional study was conducted at our institution between August 2020 and January 2021, with prior approval (SMC/IEC/2020/08/061) from the Institutional Review Board and Ethics Committee amongst pediatric patients (3 years to 15 years) admitted in the pediatric ward.

2.1 Inclusion and Exclusion Criteria

A total of 50 children were enrolled after written informed parental consent. Inclusion criteria were symptoms suggestive of urinary tract infection and children with fever without the focus of infection. Children with fever with a focus on infection other than the urinary tract and those with antibiotic coverage were excluded from the study.

2.2 Sample Size Calculation

Assuming a prevalence rate of 3.3%[11] of pediatric UTI, with a precision of 5%.
$N = Z^2pq/e^2$
N = sample size
Z = confidence level at 95%
PQ = variance of a population
e = allowable error (5%)
By substituting the above values in the said formula, the sample size was calculated to be 50.

2.3 Demographic Data and Specimen Collection Technique

Registration data, data on age, sex, symptoms of UTI, and physical examination findings were recorded on a standardized data collection form and then entered into a database. Complete blood count, C-reactive protein, renal function tests, serum electrolytes, and ultrasound abdomen were done for all patients. Under strict aseptic precautions, clean catch midstream urine of 5ml was collected in a sterile container. The collected sample was transported to the Central Microbiology Laboratory in our hospital and processed immediately. Intravenous fluids, intravenous empirical antibiotics (as per hospital guidelines), and antipyretics were administered.

2.4 Diagnosis of Urinary Tract Infection

The midstream urine specimen was collected in sterilized tubes from study subjects in the age group of 3 – 15 years with clinical symptoms suggesting UTI. All the urine samples were processed by centrifugation at 3000rpm for 15 minutes. Centrifuged samples were submitted for urine dipstick, urinary gram stain, and urine culture. Dipstick urinalysis was done using Siemens multistix 10 SG[12] and clinitek advantus analyzer[13]. The reagent strip contains test pads for protein, blood, leukocyte, nitrite, glucose, ketone, pH, specific gravity, bilirubin, and urobilinogen. In our study, the parameters considered in dipstick analysis were nitrites and leukocyte esterase. Uncentrifuged urine was inoculated on Nutrient agar and Cystine-Lactose-Electrolyte-Deficient (CLED) agar[14] procured from HiMedia labs, India by standard loop technique and semi-quantitative method on Mac Conkey agar for culture and sensitivity. Cultures were considered positive if the cultures yielded ≥10⁵ bacterial colonies[15].

3. STATISTICAL ANALYSIS

Data was entered in MS Excel and Statistical Package for the Social Sciences (SPSS) program for Windows (SPSS Inc, Chicago, version 20.0) was used for analysis. Demographic variables were presented in the form of frequencies and percentages. Using the quantitative urine culture and sensitivity as the gold standard, the sensitivity, specificity, positive (PPV), and negative predictive values (NPV) of the screening tests were determined and compared for the diagnostic yield of UTI. A p-value of ≤ 0.05 was considered statistically significant.

4. RESULTS

A total of 50 children were enrolled in the study. The mean age of children enrolled in the study was 5.16 ± 2.7 years (range 3 - 15 years); with 26 (52%) patients between 3 and 5

years of age (Table1). There were no significant differences between the mean ages of boys and girls (p = 0.284). The study population comprised 27 (54%) male and 23 (46%) female children, giving a male-to-female (M: F) ratio of 1.2:1 (Fig 1). Fever (64%) was the most common presentation, followed by pain in the abdomen (52%), dysuria (40%), vomiting (32%), hematuria (14%), and increased frequency of urination (8%). The clinical profile is represented in Fig 2. *Escherichia coli* (n = 27, 54%) was the most common organism isolated followed by

Klebsiella spp. (n = 11, 22%), *Proteus spp.* (n = 8, 16%) and *Enterococcus* (n = 4, 8%). The details of the organism profile are depicted in Fig 3. Test results of urine microscopy, nitrite test, leukocyte esterase test, and urine gram stain were compared with the gold standard quantitative urine culture (Table2). With urine culture as the gold standard, the sensitivity, specificity, PPV, and NPV of urine microscopy, dipstick tests, and the gram stain was calculated (Table3).

Table1: Demographic characteristics of Study Population			
Age	**Male n(%)**	**Female n(%)**	**Total n(%)**
3 – 5 years	17(34)	9(18)	26(52)
6 – 8 years	8(16)	5(10)	13(26)
9 – 15 years	2(4)	9(18)	11(22)
Total	27(54)	23(46)	50(100)

The above table depicts males were more affected than females; with the majority of them belonging between 3 and 5 years of age.

Table2: Comparison of urine culture with other tests			
Parameters		**Urine culture**	
		Positive	Negative
Urine microscopy	Positive	17	3
	Negative	23	7
Nitrite test	Positive	22	3
	Negative	18	7
Leukocyte esterase test	Positive	24	2
	Negative	16	8
Gram stain	Positive	38	0
	Negative	2	10

Amongst the screening tests done, urine gram stain provided the maximum detection rate as evidenced by 100% confirmation with urine culture in all cases of gram stain positivity

Table3: Statistical indicators of efficacy of Rapid Diagnostic tests for UTI					
Test	**Sensitivity (%)**	**Specificity (%)**	**PPV(%)**	**NPV(%)**	**Efficacy(%)**
Urine microscopy	42.5	70	85	23.3	48
Nitrite test	55	70	88	28	58
Leukocyte esterase test	60	80	92.3	33.3	64
Gram stain	95	100	100	83.3	96

Comparing the validity of the various screening tests, gram stain had the maximum sensitivity (95%) and specificity (100%) with an efficacy of 96%
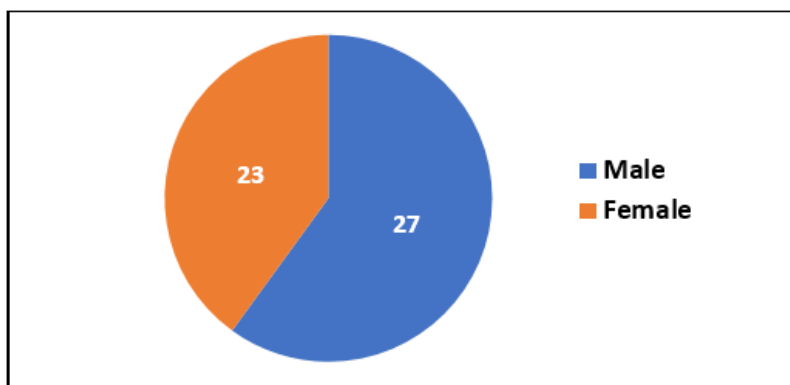

Fig 1: Gender Distribution of Study Population

The study population comprised 54% male and 46% female children, with a ratio of 1.2:1; nearly equal numbers in each gender category
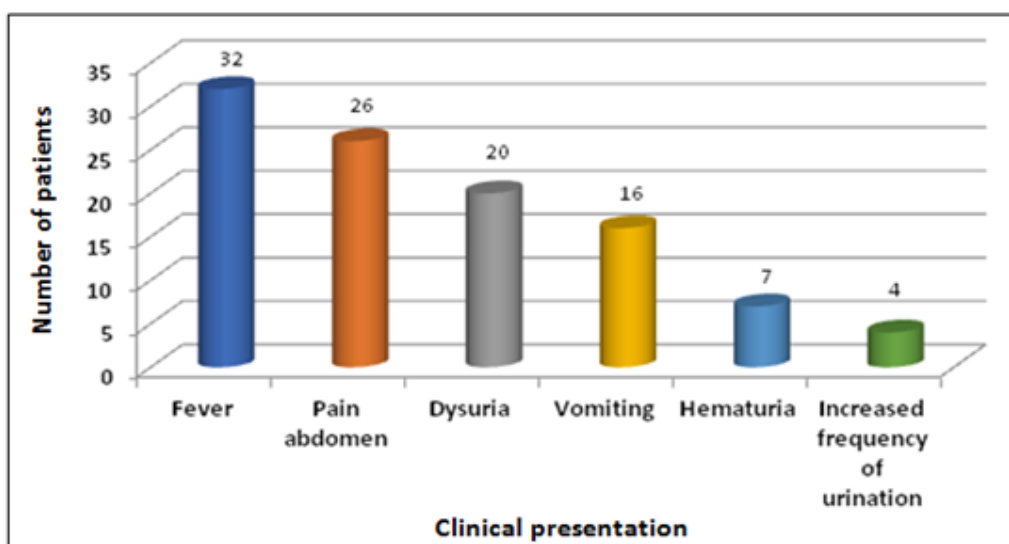
Fig 2: Clinical Profile of Study Population

Clinical manifestations were in the order of fever, abdomen pain, dysuria, vomiting, and hematuria. Barring dysuria and hematuria, other symptoms are non–specific to UTI
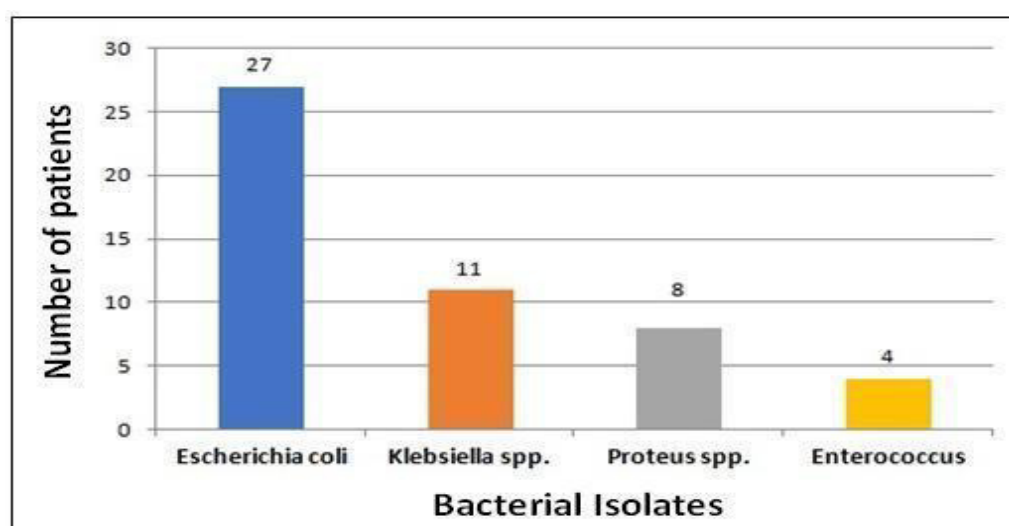

Fig 3: Bacterial isolates Profile of Study Population

The most common bacterial isolate from urine culture specimens was E. Coli followed by klebsiella spp.

5. DISCUSSION

UTI is the most common infection in the pediatric population. Due to its non-specific clinical presentations, early diagnosis and appropriate management are essential to prevent its complications. Urine culture and sensitivity is the gold standard test for detecting UTI. However various tests were proposed for screening and rapid diagnostic methods in UTI, our study aimed at evaluating Sensitivity, Specificity, Positive predictive value, and negative predictive value for Urine Microscopy, Urine Nitrite test, Leukocyte esterase (LE) test and Urine gram stain in diagnosing UTI. The ideal screening test for significant bacteriuria should be rapid, inexpensive, simple to use, and accurate. In our study, 27 (54%) were male and 23 (46%) were female with a little male predominance, which is consistent with the results of the study done by Vinod Kumar et al[16]. The mean age of patients was 5.16 ± 2.7 years; ages ranged from 3 years to 15 years with 26 (52%) patients between 3 and 5 years of age. This demographic profile is homogeneous with the results of the south Indian study by

Gupta et al[17]. Fever [32 (64%)] was the most common symptom presentation in our study, which is comparable to Mohammed et al[18], who found fever (63.82%) to be the most common presentation in their study. Analysis of our results found *Escherichia coli* [27 (54%)] being the most common uropathogen associated with pediatric UTI. The finding of our study is consistent with studies reported by Badhan et al[19] (42.3%) in India, Antonio Sorlozano-Puerto et al[20] (60.3%) in Spain, and Edlin et al[21] (79%) in the United States. In the present study, out of 40 urine culture-positive samples, urine microscopy was positive in 17 samples. Urine microscopy showed a sensitivity of 42.5%, specificity of 70%, Positive Predictive Value (PPV) of 85%, and Negative Predictive Value (NPV) of 23.3%. The efficacy of urine microscopic examination was 48%. Yildrim et al[22], in 2008, quoted similar validity figures with a sensitivity of 32%, specificity of 93.7%, PPV of 83.7%, and NPV of 58%. Our study results reveal that, out of 40 urine culture-positive samples, a urine gram stain was positive in 38 samples. Urine gram stain showed a sensitivity of 95%, specificity of 100%, PPV of 100%, and NPV of 83.3%, which is

similar to the results by Yodoshi et al[23] and Putri et al[24]. The efficacy of the urine gram stain was 96%. Gram-negative bacteria causing UTI can metabolize urinary nitrate to nitrite, therefore, detection of urinary nitrite can be a valuable rapid diagnostic test to identify significant bacteriuria. In our study, out of 40 urine culture-positive samples, the nitrite test was positive in 22 samples. The nitrite test showed a sensitivity of 55%, specificity of 70%, PPV of 88%, and NPV of 28%. The Efficacy of the Nitrite test was 58%. This result is consistent with the finding by Fidelia et al[25] and Taneja et al[26]. Leukocyte Esterase (LE) test detects the production of an esterase by neutrophils, when present in urine, indicative of inflammation. Using urine culture as the gold standard, the lone performance of the LE test showed a sensitivity of 60%, specificity of 80%, PPV of 92.3%, and NPV of 33.3%; which is comparable with the findings by Dadzie et al[27].

6. CONCLUSION

Urinary tract infection is one of the commonest infections that can be missed by the treating physician due to nonspecific symptoms in young children. With simple point-of-care screening tests, these infections can be diagnosed early in the course of the disease and appropriate management can be initiated. Urine culture is considered the gold standard diagnostic test. Urine gram stain has the highest sensitivity and specificity amongst the screening tests available for pediatric UTI. The utility of gram stain in primary care settings is beneficial for early diagnosis and appropriate treatment of pediatric UTIs.

7. ACKNOWLEDGEMENT

8. AUTHORS CONTRIBUTION STATEMENT

Dr. Melpakkam Venkatesan Srinath conceptualised and designed the study. Dr. Vidhyasagar prepared the methodology after discussion with Dr. Srinath. Data collection was done by both authors; faormal analysis wa s done by Dr. Srinath. The original draft written by Dr. Vidhyasagar was reviewed and edited by bith authors. Both authors contributed equally to the designing of the final manuscript.

9. CONFLICT OF INTEREST

Conflict of interest declared none.

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