Clinico-microbiological determinants of urinary tract abnormality following first culture proven urinary tract infection in children

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Abstract

Introduction: Clinico-microbiological factors would help clinicians in developing countries to optimize the use of radioimaging childhood urinary tract infection (UTI), especially in resource limited settings with financial constraints

Objective*:* To study the clinico-microbiological profile and determine the association of renal tract abnormalities in children with their first documented UTI and to find out the clinico-microbiological determinants of the anomalies.

Method: This prospective study was carried out over a period of two years in a tertiary care teaching hospital at Ahmedabad, Gujarat after obtaining permission from institutional review board. A total of 65 children up to 12 years of age with first culture proven UTI, were recruited from the paediatric outpatient department (OPD), paediatric ward and neonatal intensive care unit (NICU) after obtaining parental consent.

Results*:* Most (49.2%) patients belonged to the 1-5 year age group. There were 36 (55.4%) males. Fever (69.2%) was the commonest symptom followed by excessive crying (29.2%) and dysuria (27.7%). Of the 65 patients, 15.3% had complicated UTI, 29.2% required hospitalization and 4.6% had hypertension. Of male patients 91.7% were uncircumcised. Malnutrition was found in 57.9% of patients in the under 5 year age group. We found altered renal function tests (RFTs) in 6.1%, leucocytosis in 29.2% and pyuria in 35.2% patients. *Escherichia coli* caused 40% of the infections, followed by *Klebsiella* (29.2%). Renal abnormalities were found in 27 (41.5%) with statistically significant (p<0.05) correlation with young age, complicated UTI, haematuria, oliguria, hypertension, altered RFTs, malnutrition and non-*Escherichia coli* organisms. Ultrasonography (USG) detected abnormalities in 24/65 (36.9%), micturating cystourethrogram (MCUG) in 7/32 (21.8%) and DMSA revealed scar in 4/32 (12.5%) patients. USG had sensitivity of 88.8%.

Conclusions: *Escherichia coli* caused 40% of the UTI, followed by *Klebsiella* (29%). Renal anomalies were found in 41.5% with statistically significant correlation with young age, complicated UTI, haematuria, oliguria, hypertension, altered RFTs, malnutrition and non-*Escherichia coli.*

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(Keywords: Urinary tract infection, urine culture, renal tract abnormality, renal ultrasound, pyuria)

Introduction

The risk of having a UTI before the age of 14 years is approximately 1-3% in boys and 3-10% in girls[1]. Diagnosis of UTI is based on clinical symptoms in association with a positive urine culture [1-6]. Prompt evaluation and treatment is important to prevent renal parenchymal damage and renal scarring that can cause hypertension and progressive renal damage[1,3,4,5]. Abnormalities of the renal tract are identified in 10-75% of children following a UTI[5]. Based on the current guideline by the Indian Society of Paediatric Nephrologists (ISPN), all children with the first UTI should undergo radiological evaluation for underlying anomalies or voiding dysfunction with ultrasonography (USG), dimercaptosuccinic acid (DMSA) scan and/or micturating cystourethrogram (MCUG)[4]. Several recent evidence based guidelines either do not recommend routine renal tract imaging, or only recommend USG for primary screening following first UTI except in special circumstances based on age, atypical UTI or complex clinical situation[2,5,6]. Thus, clinico-microbiological factors would help clinicians in developing countries to optimize use of radioimaging especially in resource limited settings with financial constraints.

Objectives

- To study the clinico-microbiological profile and determine the association of renal tract abnormalities in children with their first documented UTI.

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- To find out the clinico-microbiological determinants of the renal tract anomalies.

Method

This prospective study was carried out over a period of two years in a tertiary care teaching hospital at Ahmedabad, Gujarat after obtaining permission from institutional review board. A total of 65 children up to 12 years of age with first culture proven UTI, were recruited from the paediatric outpatient department (OPD), paediatric ward and neonatal intensive care unit (NICU) after obtaining parental consent.

Selection of patients: The following groups of patients (*n=205*) were subjected to urine microscopy and urine culture.

- Patients with acute voiding symptoms.
- Infants and children presenting with unexplained fever of 38°C or higher of at least 24 hours.
- Patients with failure to thrive in whom no apparent cause could be found.
- Neonates in NICU with one or more of the following: fever or temperature instability, vomiting, diarrhoea, lethargy, seizures, persistent jaundice or poor weight gain.

Criteria for diagnosis

- Significant pyuria: >10 leucocytes per cu mm in a fresh uncentrifuged sample, or >5 leucocytes per high power field (HPF) in a centrifuged sample.
- Significant bacteriuria: Presence of bacterial colony count of $>10^5$ CFU/ml of single species determined by quantitative culture.

Inclusion criteria: Patients having positive urine culture (*n=65*).

Exclusion criteria:

- Patients with confirmed past UTI.
- Antenatally diagnosed or history of past imaging for renal abnormality.
- Patients on prior antibiotics of more than 24 hours duration.
- Previous surgery of urinary tract, ano-rectal malformation or neural tube defect
- Patients infected with human immunodeficiency virus (HIV)

For each patient, a relevant detailed history was elicited focusing on risk factors and bowel-bladder habits. After initial stabilisation in hospitalised patients, and in all OPD patients, a thorough examination was carried out including blood pressure (BP) and nutritional assessment. BP was measured with a sphygmomanometer or non-invasive BP in young infants by paediatric resident with appropriate sized cuff using reference percentile charts. All details were recorded on pre-designed proforma. The need for hospitalization was decided according to departmental protocol.

Urine sample was collected before initiation of antibacterial therapy in all patients. The means of obtaining urine samples were clean catch mid-stream urine for toilet-trained children and urethral catheterisation using appropriate sized infant feeding tube for the rest. In none of the patients was urine collected by suprapubic aspiration. The parent or caretaker was informed about the correct method for clean catch midstream urine. The specimen was collected under supervision of medical/paramedical staff after washing the genitalia with soap and water. To avoid contamination of urine obtained by transurethral catheterization, the first few millilitres obtained by catheter were discarded (allowed to fall outside of the sterile container) and only the subsequent urine was cultured. Urine was processed in the laboratory within 30 minutes of voiding.

After 5 minutes of centrifugation, urine deposits were streaked on Nutrient agar and McConkey agar immediately. After overnight incubation at 37^0 C for 18-24 hours saline suspension of the colonies were plated on Mueller Hinton agar with lawn culture. Isolation and identification of the organisms were done by studying their motility, gram staining, colony characteristics and other relevant biochemical reactions. Drug sensitivity for isolated organism was performed by standard disc diffusion technique with antimicrobials. Complete blood counts and renal function tests were done for all patients. All were treated with appropriate antibiotics.

All patients were subjected to radioimaging as per ISPN 2011 guidelines for evaluation following initial UTI[4]. All patients had undergone USG of kidney, ureters and bladder (USG-KUB) using Toshiba Nemio XG machine with 3.75 mhz curved and 8 mhz linear probe by radiologist after 48 hours of diagnosis. MCUG and DMSA scan were done after 1 and 3 months respectively on follow up. Siblings of patients with VUR were also screened with USG. Patients were treated and counselled accordingly and appropriate referral was advised. Data were analysed using Chi-square test and Fisher Exact test; $p<0.05$ was considered significant.

Results

We analysed 65 patients with first culture proven UTI in whom imaging studies were systematically performed. The age and gender wise distribution is shown in Table 1.

Table 1: ***Age and gender wise distribution of study cases (n=65)***

Age	Female No. (%)	Male No. (%)	Total No. (%)	Female: male ratio
< 1 year	05.0 (07.7)	09.0 (13.8)	14.0 (21.6)	0.6
1 - 5 years	13.0 (20.0)	19.0 (29.2)	32.0 (49.2)	0.7
5 - 12 years	11.0 (16.9)	08.0 (12.3)	19.0 (29.2)	1.4
Total	29.0 (44.6)	36.0 (55.4)	65.0 (100.0)	0.8

The maximum number of cases was found between 1-5 years of age and female preponderance was seen in the 5-12 years age group. Age-wise urinary symptoms are depicted in Table 2. The common urinary symptoms were dysuria and increased frequency of micturition.

Table 2: ***Age wise urinary symptoms (n=65)***

Age group	< 1 year No. (%)	1 - 5 years No. (%)	5 - 12 years No. (%)	Total No. (%)
Frequency	02 (03.1)	03 (04.6)	08 (12.3)	13 (20.0)
Urgency	0 (0)	0 (0)	01 (01.5)	01 (01.5)
Dysuria	0 (0)	10 (15.4)	08 (12.3)	18 (27.7)
Poor stream	01 (01.5)	06 (09.2)	01 (01.5)	08 (12.3)
Altered colour of urine	01 (01.5)	03 (04.6)	01 (01.5)	05 (07.7)
Foul smelling urine / discharge	0 (0)	03 (04.6)	01 (01.5)	04 (06.2)
Straining	02 (03.1)	07 (10.8)	03 (04.6)	12 (18.5)
Dribbling	0 (0)	01 (01.5)	01 (01.5)	02 (03.1)
Haematuria	0 (0)	03 (04.6)	01 (01.5)	04 (06.2)
Reduced urine output	02 (03.1)	02 (03.1)	0 (0)	04 (06.2)

**Patients had more than one symptom*

Non-urinary complaints are presented in Table 3, of which fever was the commonest symptom followed by excessive crying and poor weight gain. Neonates presented with fever, poor weight gain, lethargy and decreased urine output.

Table 3: ***Age wise non-urinary symptoms (n=65)***

Age group	< 1 year No. (%)	1 - 5 years No. (%)	5 - 12 years No. (%)	Total No. (%)
Fever	09 (13.8)	23 (35.4)	13 (20.0)	45 (69.2)
Frequency of stool	02 (03.1)	01 (01.5)	02 (03.1)	05 (07.7)
Vomiting	03 (04.6)	01 (01.5)	09 (13.8)	13 (20.0)
Abdominal pain	0 (0)	03 (04.6)	08 (12.3)	11 (16.9)
Poor weight gain	05 (07.7)	03 (04.6)	02 (03.1)	10 (15.4)
Decreased oral intake	06 (09.2)	09 (13.8)	02 (03.1)	17 (26.2)
Excessive crying /irritability	07 (10.8)	12 (18.5)	0 (0)	19 (29.2)
Jaundice	01 (01.5)	0 (0)	01 (01.5)	02 (03.1)
Periorbital oedema	0 (0)	03 (04.6)	01 (01.5)	04 (06.2)
Febrile seizure	0 (0)	03 (04.6)	0 (0)	03 (04.6)
Peri-genital redness	01 (01.5)	0 (0)	0 (0)	01 (01.5)

**Patients had more than one symptom*

Of the total 65 patients, 10 (15.3%) had complicated UTI[4] and 55 (84.7%) had uncomplicated UTI. Nineteen (29.2%) patients required hospitalisation. Hypertension was detected in 3 (4.6%). Of the 36 males, 33 (91.7%) were uncircumcised. Other risk factors included wiping from back to front in females (n=16/29, 55.2%), pinworm infestations (12.4%), constipation (3.07%) and instrumentation (1.5%).

According to the IAP classification, in the 6 month to 5 year age group (n=38), nutritional status was normal in 16 (42.1%) and the rest fell into protein energy malnutrition (PEM) I (2, 5.3%), II (11, 28.9%), III (7, 18.4%) and IV (2, 0.3%). In the 5 to 12 year age group (n=19), 6 (31.5%) had normal body mass index (BMI), while 13 (68.5%) patients were undernourished. We found altered renal function tests (RFTs) in 4 (6.1%), leucocytosis in 19 (29.2%) and pyuria in 23 (35.2%) patients. The pathogens that grew on urine culture are shown in Table 4. Figure 1 represents the age group wise algorithm for radiological investigations as per ISPN[4].

Table 4: ***Age wise pattern of urinary isolates (n=65)***

Urinary isolate	< 1 year No. (%)	1 - 5 years No. (%)	5 - 12 years No. (%)	Total No. (%)
E. Coli	06 (09.2)	12 (18.5)	08 (12.3)	26 (40.0)
Klebsiella	03 (04.6)	09 (13.8)	07 (10.8)	19 (29.2)
Proteus	02 (03.1)	06 (09.2)	0 (0)	08 (12.3)
Pseudomonas	0 (0)	02 (03.1)	02 (03.1)	04 (06.2)
Staph. Aureus	01 (01.5)	0 (0)	01 (01.5)	02 (03.1)
Enterococcus faecalis	0 (0)	01 (01.5)	01 (01.5)	02 (03.1)
Citrobacter	01 (01.5)	0 (0)	0 (0)	01 (01.5)
Candida	01 (01.5)	02 (03.1)	0 (0)	03 (04.6)

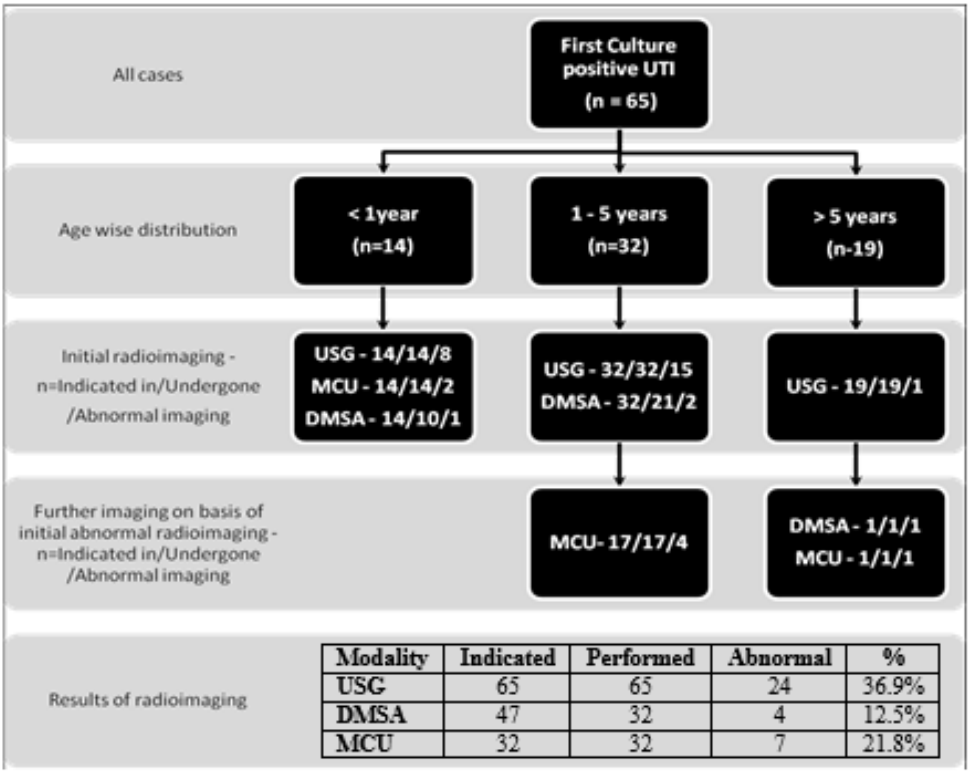

Figure 1: ***Age group wise algorithm for radioimaging as per ISPN***

USG (n=65) and MCUG (n=32) were done in all indicated patients. DMSA scan was done in 32 out of 47 indicated patients as our hospital does not have an in-house facility for DMSA and a few patients had financial constraints. Radioimaging detected renal tract abnormalities in 27/65 (41.5%) patients, with male preponderance (66.6%) which was statistically insignificant (p=0.12). The age wise proportion of abnormalities was 9/14 (64.3%) in the <1 year age group, 17/32 (53.1%) in the 1-5 year age group and 1/19 (5.2%) in the >5 year age group respectively which was highly significant (p=0.0004). Other statistically significant determinants for abnormalities were complicated UTI (p=0.001), haematuria (p=0.025), decreased urine output (p=0.025), hypertension (p=0.05) malnutrition (p=0.004) and altered RFT (p=0.025). Poor urinary stream showed no association (p=0.70). Renal tract abnormalities were detected in 21/39 (53.8%) patients with non E-coli organism versus 6/26 (23%) with E-coli isolates, which was statistically significant (p=0.02). USG showed abnormality in 24/65 (36.9%) and MCUG in 7/32 (21.8%). Two children with grade I/II VUR and one with renal scar had a normal USG finding which was picked up by MCUG and DMSA scan. USG had sensitivity of 88.8% and specificity of 100% to detect renal abnormality. The sensitivity increased to 96.2% if combined with MCUG. DMSA revealed renal scar in 4/32 (12.5%) patients.

Age group wise renal tract abnormalities are shown in Table 5. Hydronephrosis with obstruction and VUR predominated in the <1 year age group while calculi with hydronephrosis predominated in the 1-5 year age group. All 4 patients with vesicoureteral reflux (VUR) were below 5 years. USG in siblings of four VUR patients did not reveal any abnormality.

Table 5: ***Age group wise renal tract abnormality on radioimaging (n=65)***

Abnormality/Age group	< 1 year No. (%)	1 - 5 years No. (%)	5 - 12 years No. (%)	Total No. (%)
Calculi	0 (0)	06 (09.2)	01 (01.5)	7 (10.8)
Hydronephrosis	02 (03.1)	07 (10.8)	01 (01.5)	10 (15.4)
Pelvi-ureteric junction obstruction	02 (03.1)	0 (0)	0 (0)	02 (03.1)
Posterior urethral valves	01 (01.5)	02 (03.1)	0 (0)	03 (04.6)
Vesicoureteral reflux	02 (03.1)	02 (03.1)	0 (0)	04 (06.2)
Cortical scar	01 (01.5)	02 (03.1)	01 (01.5)	04 (06.2)
Cystitis	01 (01.5)	03 (04.6)	01 (01.5)	05 (07.7)
Solitary kidney	01 (01.5)	02 (03.1)	0 (0)	03 (04.6)
Cross-fused kidney	0 (0)	02 (03.1)	0 (0)	02 (03.1)
Small kidney	0 (0)	01 (01.5)	01 (01.5)	02 (03.1)
Pyelonephritis	0 (0)	02 (03.1)	0 (0)	02 (03.1)

**Patients had more than one finding*

Discussion

There is a paucity of epidemiological data and associated renal tract anomalies after first culture proven UTI from India, especially western India. Out of 205 clinically suspected UTI cases, 65 (31.7%) had positive urine culture, which was close to other studies ranging from 35% to 45%[7,8,9]. Out of 65 patients, 21.6% were below 1 year of age, matching with observations of other researchers[10,11,12]. Though the commonest age for the first symptomatic UTI is the first year of life in both genders, the reason the for the low number could be the small sample size and nonspecific complaints leading to under-diagnosis at this age[3,4]. Maximum cases (49.2%) were in age group of 1-5 years as in other studies[8,9,10,12]. Males outnumbered females by a smaller proportion except in the 5-12 year age group with a male: female ratio of 1:1.3. The predominance of males in our study was not consistent with many previous reports where females, except during infancy, were more affected than the males[9,13-16]. Reasons may be the smaller sample size and increased preference for seeking treatment for only the male child in certain communities.

After fever (69.2%) and excessive crying/ irritability (29.1%), urinary symptoms like dysuria (27.7%) and increased frequency of micturition (27.7%) predominated. Other studies also indicated high association between fever and UTI[8-13,15-17]. According to the World Health Organisation (WHO), fever as a marker of UTI has a sensitivity of 80% and specificity of 40%[18]. Many studies have shown significant proportion of patients presenting with dysuria[8-10,13,15-17,19]. Straining and poor urinary stream were found mostly in male patients. Increased frequency of micturition[12,16,19] and haematuria[12,19] have been also reported. Poor weight gain[9,10,15,19], febrile seizure[15,19], vomiting[8-10,15,16], diarrhoea[10,13,15] and abdominal pain[8,9,13,15,16] were documented by other studies. There was a poor relationship between urine colour and odour, similar to earlier reported studies[9,13].

In our study 91.7% of males were uncircumcised. Meta-analysis on UTI prevalence by Sheikh *et al* found pooled prevalence of 20.1% in uncircumcised male as compared to 2.4% in circumcised male in <3 months of age[20]. According to the literature, there is a high incidence amongst uncircumcised male infants[1-4]. We found 15.3% complicated UTI similar (15%) to study by Gupta *et al*[7]. In our study, 57.9% patients had malnutrition which was comparable to other UTI studies[9,11]. According to WHO, in developing countries there is a higher UTI prevalence of 8-35% in malnourished children[18]. Leucocytosis had poor correlation as reported by another study[15]. We found pyuria in 35.2% of patients. Many studies and literature have shown its poor correlation with UTI[1-4,6]. For our study, the reason may be higher proportion of non–E coli uropathogens as non-E coli isolates are less frequently associated with pyuria than E coli[6].

In keeping with other studies, Gram negative organisms accounted for over 90% of the isolates with E. coli (40%) predominating[7,12,13,16,19,21]. Many studies[10,14,15,17,22] found E-coli in the range of 63-88%. This variation could be because of different microbial epidemiology, presence of associated risk factors, the number of UTI episodes and underlying renal tract abnormality. According to WHO, gram negative organisms, particularly E. coli are commonly associated with UTI in children in developing countries[18]. Klebsiella accounted for 29.2% which varied from 13-36.6% in other studies[13,15,16,19,22]. Different studies have shown the growth of uropathogens like Proteus[10,21,22], Pseudomonas[10,16,21], Citrobacter[10,16], Staphylococcus Aureus[10,11,22] & Candida[16] in the range close to our study. The growth of Candida found in one neonate and two patients with PEM IV in the 1-5 year age group signifies immunocompromised status.

Renal abnormalities were found in 41.5% with statistically significant ($p<0.05$) correlation with young age, complicated UTI, haematuria, oliguria, hypertension, altered RFT and malnutrition. Literature has shown its association with atypical and complex clinical presentation[2,5,6]. For malnutrition it could be cause and effect phenomenon for UTI and abnormalities. Though statistically non-significant, a higher proportion of renal abnormalities was detected in patients with poor urine stream. We found statistically significant abnormalities with non-E coli organism in UTI. As per NICE guidelines, if UTI is caused by a non-E coli coliforms or any other type of bacteria, there is an increased risk of serious underlying pathology[2].

USG showed abnormalities in 36.9% in our study but many researchers have reported them ranging from 12-17% in different age groups[14-16,19,23]. According to the literature, reported incidence of structural abnormalities detected by USG range between 10 and 75% (median around 30%) of children scanned after UTI and tend to be seen more often in younger children[5]. MCUG was positive in 21.8% whereas it ranged from 17-39% in other studies[14,16,19,23] and 30 and 40% in the literature[5]. Among the 46 indicated children, 32 underwent DMSA scan, of whom 4 (12.5%) had renal scars. A systematic review of the literature showed 15% (95% CI, 11-18%) of the children had evidence of renal scarring after the first UTI[24]. The NICE evidence concluded that 5% of children had renal parenchymal abnormalities and for other researchers it ranged from 7-25% after first UTI[5,14,16,23]. The exact proportion could not be derived from our study as DMSA could not be done in a few indicated patients.

USG had a sensitivity of 88.8% to detect renal tract abnormality. The main limitation of US is the lesser sensitivity for detecting low-grade VUR and renal scars[24]. The low-grade VUR is generally not considered of concern for renal damage[6]. Recent reaffirmation from the American Academy of Paediatrics (AAP) and American College of Radiology appropriateness criteria have recommended USG as a screening following first febrile UTI and MCUG only if USG shows some abnormality or in special circumstances to avoid unnecessary radiation exposure[6,24].

Though the study provides focused data exclusively on initial UTI and radio-imaging in a resource limited setting, the small sample size remains the limitation of our study. The knowledge of diverse clinical presentation of UTI and determinants of renal tract abnormalities help the paediatrician to optimize investigative approach in a resource limited setting. Renal USG is a highly sensitive, readily available, noninvasive imaging method that avoids the risk of ionizing radiation and should be recommended as a single screening modality after initial UTI.

Conclusions

Escherichia coli caused 40% of the UTI, followed by Klebsiella (29%). Renal anomalies were found in 41.5% with statistically significant correlation with young age, complicated UTI, haematuria, oliguria, hypertension, altered RFTs, malnutrition and non-*Escherichia coli.*

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