Urinary tract infection in children younger than 5 years. *Etiology and associated urological anomalies*

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ABSTRACT

Objectives: To investigate the most common underlying organisms, and associated urological anomalies in children presenting with urinary tract infection (UTI).

Methods: Retrospectively, all children with confirmed UTI between October 2013 and February 2014 were evaluated at King Abdulaziz University Hospital, Riyadh, Kingdom of Saudi Arabia. The electronic files of 279 children presenting with UTI, aged less than 5 years were reviewed.

Results: A total of 153 patients (85 males) with a mean (SD) age of 15 (19.86) months were included in the study. Recurrent UTI was present in 45.1%. Urine collection in children less than 2 years of age was through trans-urethral catheterization in 69.4%, while midstream urine was the main method in those above 2 years (78.6%). *Escherichia coli (E. coli)* was the causative organism in 41.2% of first UTI. The second most common organism was *Klebsiella Pneumoniae*, seen in 19.6%. Urological anomalies were found in 28.1% of the overall study population. Ninety percent of those with single UTI did not have anomalies. However, urological anomalies were reported in 50.7% of those with recurrent episodes of UTI (p<0.005). Non-*E. coli* cases were associated with a higher percentage of abnormal renal ultrasonography results (p=0.006).

Conclusion: *Escherichia coli* was the most common causative organism for UTI, and a single episode of UTI signified normal urological anatomy.

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Urinary tract infection (UTI) is common in children. Early diagnosis and management is essential to minimize the acute morbidity and prevent the long-term complications associated with UTI, which include hypertension and renal scarring. However, considerable controversy prevails in the diagnosis and management of UTI in children.[1] Major changes have also been presented in recent treatment guidelines.[2,3] Blood investigations such as leukocyte count with urine analysis and inflammatory markers such as C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR), might indicate the presence of an infection, but confirmation is only by urine culture. Midstream urine is the standard method in older children, but in young children selecting the best-suited method of urine collection is crucial to avoid false positive results. Using urine bags for collecting specimens for culture is discouraged as it increases the possibility of false positive results.[4] Urinary tract infection is associated with renal anomalies in children,[1] and investigation of affected children is recommended to diagnose renal anomalies. An ultrasound study is recommended by both the American Academy of Pediatrics,[2] as well as the National institute of Clinical Excellence (NICE)[3] as initial screening. Voiding cystourethrogram (VCUG) is used to detect vesicoureteral reflux, and DMSA (dimercaptosuccinic acid) scan to detect renal scars.[1-3] The DMSA scan is recommended before VCUG by NICE in children aged 6 months to 3 years.[3] The DMSA scan could replace VCUG as the first line procedure, and this approach is recommended by many investigators.[5] In Saudi Arabia, due to a high rate of consanguinity,[6] the risk of renal anomalies looms large; it is believed that up to 70% of renal anomalies in children can be attributed to an underlying genetics cause.[7] In this study, we aimed to detect abnormal renal US findings in children aged <5 years with a UTI, and compare the etiology of infection and abnormal US finding in cases with first episode of infection with those with recurrence of infection.

Methods. A retrospective review was conducted, inclusive of all children who had UTI confirmed by urine culture and who presented to King Abdulaziz University Hospital, Jeddah, Saudi Arabia between October 2013 and February 2014. We reviewed electronic files of 279 children aged less than 5 years of age. Urinary tract infection was defined as bacterial growth of 10^5 CFU/ML. Patients with a colony count

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of less than 10^5 CFU/ML were excluded, as well as those with bag urine collection. Methods of urine collection (midstream urine, catheter, or suprapubic aspiration), causative organisms, urine analysis, and all radiological investigations were analyzed. Data from the patients' files were collected on an Excel sheet. The causative organisms were also mapped for each patient included in the study. Data on infection indices were collected including white blood cell (WBC) count, neutrophils count, ESR, and CRP. Renal function was estimated by documenting plasma creatinine and blood urea nitrogen (BUN). The study patients were divided into 2 groups; those with a single episode, and those with repeated episodes of UTIs. Study patients were also categorized as per their age into 2 groups; namely, those below 2 years of age and those in the age group of 2-5 years. Patients' radiological investigations were also documented while eliciting data on urological anomalies. These radiological investigations included ultrasound, VCUG, Tc99m-DTPA (diethylene triamine pentaacetic acid) scan, and DMSA scan. We follow the modified NICE recommendations for radiological investigations.[3] A renal US for all babies aged less than one year, and only for those with recurrent UTI or with atypical presentation for children aged above one year (severe infection with bacteremia, not responding to antibiotics after 48 hours, poor urinary flow, palpable abdominal mass, history of abnormal antenatal renal scan and non-*E. coli* pathogen). We performed VCUG for children with atypical or recurrent UTI aged less than one year,[3] and for those with abnormal DMSA scan in the older age group. The DMSA scan was carried out after at least 3 months from clearing the UTI in the first episode for infants, and after the second episode in older children (**Table 1**). We defined secondary vesicoureteral reflux (VUR) as raised vesicular pressures associated with obstruction, which distorts the ureterovesical junction. The obstructions may be anatomical, such as posterior urethral valve (PUV), or functional, such as neurogenic bladder.

We searched for similar and related studies using PubMed and Medline searching engines. The study design was carried out in accordance with the Principles of the Helsinki Declaration. The ethical approval was obtained for this study from the Biomedical Ethics department at King Abdulaziz University, Faculty of Medicine.

Statistical analysis. All data were entered and saved to the Excel software of Microsoft windows 8. Statistical analysis was carried out using the IBM SPSS Statistics software version 22 (IBM Corp, Armonk, NY, USA) and data cleaning was carried out by a professional statistician. Baseline demographic, clinical, and laboratory data were summarized in the form of mean±standard deviation (SD) or median (range) for continuous variables, and numbers, and percentages for categorical variables wherever appropriate. Chi-squared test was used for the categorical variables. For all the statistical tests, a $p<0.05$ was considered statistically significant.

Table 1 - Recommended imaging schedule for infants and children younger than 5 years with recurrent urinary tract infection.

Test	Responds well to treatment within 48 hours	Atypical UTI	Recurrent UTI
Infants younger than one year			
Ultrasound during the acute infection	No	Yes	Yes
Ultrasound within 6 weeks	Yes	No	No
DMSA 4-6 months following the acute infection	No	Yes	Yes
MCUG	No	Yes	Yes
Children one year or older, but younger than 5 years			
Ultrasound during the acute infection	No	Yes	No
Ultrasound within 6 weeks	No	No	Yes
DMSA 4-6 months following the acute infection	No	Yes	Yes
MCUG	No	No	No

UTI - urinary tract infection, MCUG - micturating cystourethrogram, DMSA - dimercaptosuccinic acid

Results. Table 2 summaries the demographic and clinical data of the included children. A total of 111 (72.5%) of the involved children were under 2 years of age, and the remaining 42 (27.5%) patients were above 2 years. In patients less than 2 years, urine collection through trans-urethral catheterization was used in 77 patients (69.4%), while midstream urine was the main method in those above 2 years, employed in 33 out of 42 (78.6%), $p<0.005$. The UTI was recurrent in 69 patients (45.1%), while the remaining 84 patients (54.9%) had only one episode of UTI. In patients with a single episode of UTI, *E. coli* was the causative organism in 36 out of 84 (42.9%) patients, while non-*E. coli* organisms caused the UTI in the remaining 48 patients. The second common causative organism in single episode

Table 2 - Demographic, clinical and radiological data of the studied children with urinary tract infection (N=153).

Variables	n (%)
Age (months)	
Mean ± SD	15 ± 19.86
Median (range)	5 (0.1 - 60)
Gender	
Boys	85 (55.6)
Girls	68 (44.4)
Urine collection	
Trans-urethral catheterization	86 (56.2)
Mid-stream urine	65 (42.5)
Suprapubic aspiration	2 (1.3)
Causative organism	
Escherichia coli	63 (41.2)
Klebsiella Pneumonia	30 (19.6)
Urine nitrite, n=45	
Positive	11 (24.4)
Leukocyte esterase, n=45	
Positive	23 (51.1)
Renal ultrasound	
Normal	100 (65.3)
Unilateral hydronephrosis, hydroureter or pelvic dilation	25 (16.3)
Bilateral hydronephrosis, hydroureter or pelvic dilation	24 (15.7)
Nephrocalcinosis	
Multicystic dysplastic kidney and other minor findings	3 (2.0) 1 (0.7)
Voiding cysto-urethrogram	48 (31.3)
Normal	19 (39.6)
Vesicoureteric reflux	29 (60.4)
Neutrophil count in the peripheral blood (K/UL), mean ± SD	5.6 ± 6.06
Serum creatinine (Umol/L), mean ± SD	35.6 ± 62.9
Erythrocyte sedimentation rate, mean ± SD	26.06 ± 21.7
C-reactive protein (mg/l), mean ± SD	29.5 ± 60.6

UTI was *Klebsiella pneumonia (K. pneumonia)* (20.2%). The most common causative organism in patients with repeated UTI was also *E. coli* (40%) followed by *K. pneumonia* (19%). **Table 3** provides a summary between boys and girls regarding the causing organism, and associated urological abnormalities in the US and VCUG. Of the 48 patients with VUR, 16 (55.2%) were primary while the remaining 13 (44.8%) were secondary. Among those with secondary VUR, PUV was involved in 8 patients (61.5%) and neurogenic bladder was the causal factor in the other 5 patients (38.5%). Most of the reflux was grade 4 (37.9%), followed by grade 5 in (24.1%). One reflux was documented in 17.2%; and grade 2 and 3 contributed to 10.3% each. Dimercaptosuccinic acid scan (DMSA) was carried out in 11 patients (7.2%), with abnormalities

Table 3 - The difference between boys and girls among children with urinary tract infection.

Urological abnormalities	Boys	Girls	*P*-value
E. coli as causing organism	54.4	30.6	0.003
Abnormal ultrasound	34	18	0.230
Abnormal VCUG	17	4	0.598

E. coli - Escherichia coli, VCUG - voiding cystourethrogram

detected in 7 of them (63.6%). Diethylene triamine pentaacetic acid (DTPA) was carried out in 27 patients (17.65%), which showed reduction in the glomerular filtration rate (GFR) with abnormal perfusion and initial uptake in a considerable number of them, except one patient who had a normal renal function. The median (range) of GFR was 53 (5-188) ml/min/1.73 m^2. Renal ultrasound was carried out in 104 patients. Abnormal findings were found in 53 patients (51%). Non-*E. coli* organisms were implicated as the causative pathogens, 73.6% of patients with abnormal findings on ultrasonographic examination; while *E. coli* was involved in 26.4% cases. The distribution of *E. coli* (49%), and non-*E. coli* (51%) in patients with normal ultrasound was comparable (p=0.006). No anatomical, or functional renal anomalies were detected in 110 patients, while patients (28.1%) suffered anomalies. Ninety percent of patients with single UTI not have renal anomalies. Renal anomalies were found in 50.7% of those with recurrent episodes of UTI (p<0.005).

Discussion. The findings of this study indicate that UTI is more common in children less than 2 years (72%) with a mean age of 15 months. This observation is similar to the worldwide data. A meta-analysis in 2008 showed that uncircumcised males less than 3 months, and females less than 12 months of age had the highest baseline prevalence of UTI.[8] Most male patients in this study were circumcised. However, UTI seems higher in the younger age group, even in circumcised males. Studies from UK,[9] Iran,[10] and Nigeria also revealed a higher prevalence among children less than 2 years of age.[9] An observation from Sudan showed that 74% of affected children with UTI were less than 5 years, and 35% were infants.[11] In Saudi Arabia, Al-Ibrahim et al[12] from the central province described UTI and VUR in Saudi children; wherein 71% were between the age of 1-5 years, 18% were between 0-1 year, and 11% were more than 5 years of age.

Only 2 children had their urine collection through suprapubic aspiration (SPA). The SPA is known to be

the gold standard method for obtaining urine culture. However, it is invasive and therefore the least preferred method by most clinicians and families.[2] A total of 56.2% had their urine collected by trans-urethral catheterization, and 42.5% patients by mid-stream urine. This indicates the accuracy in diagnosing UTI in the study cohort. This distribution was closely related to the age of the patient; as transurethral catheterization was used in 69.4% of patients less than 2 years, while in children above 2 years, 78.6% had mid-stream urine. It is recommended to obtain urine through trans-urethral catheterization or SPA, because the diagnosis of UTI cannot be established reliably through culture of urine collected in a bag.[2]

The *E. coli* species was found to be the most common pathogen in our study accounting for 41.2% of UTI cases in the study patients; followed by *K. pneumonia* recorded in 19% of cases. This is similar to previous studies from the central province of KSA.[13] Similarly, *E. coli* was the predominant causative agent worldwide.

The radiological investigations carried out in the study patients were requested by different pediatricians working at KAUH. All children have renal US carried out. However, the NICE recommendations state that a renal US be carried out for all babies aged less than 6 months, and only for those with recurrent UTI or with atypical presentation for children aged above 6 months.[3] The American Academy of Pediatrics (AAP) recommendation is to carryout renal US for febrile infants with UTI.[2]

Patients with documented abnormal findings on renal ultrasound suffered from recurrent UTI. Around 50% of those with abnormal ultrasound had multiple episodes of UTI (p<0.005). It is noteworthy in this regard that abnormal findings on renal ultrasound are associated with non-*E. coli* pathogens (p=0.006). This is similar to previous reports, and therefore NICE considered non-*E. coli* as a typical feature with the recommendation to investigate children with non-*E. coli UTI*.[3]

The AAP recommends that VCUG is indicated if the renal ultrasound reveals hydronephrosis, scarring or other findings that would suggest either high-grade VUR or obstructive uropathy; as well as in other atypical or complex clinical circumstances.[2] The NICE recommends VCUG for children with atypical or recurrent UTI aged less than 6 months,[3] and for those with abnormal DMSA scan in the older age group. The VCUG was conducted in 31.3% of our patients, and VUR was detected in 60.4% of those (18.9% of total patients). The most common abnormality detected in imaging studies in children with UTI was VUR. Also, the severity of VUR is a significant risk factor for renal scarring.[14] The VUR was reported in previous studies to be present in 30% of children with UTI.[1] However, a higher incidence of around 50% was noted in children younger than one year of age.[14] Hoberman et al[15] showed that 39% of the children who underwent VCUG had VUR.[15]

In KSA, VUR was found in 41.5% and 50% of patients with UTI in 2 studies from the central province.[12,13] In studies from other Arab countries, a lower percentage of VUR of 10-20% was reported in children with UTI.[11] This difference in the incidence of VUR between KSA and other Arab nations is perhaps attributable to the variability in demography and the underlying genetics; which is affected by the prevalence of consanguinity between parents.

During the course of the study, the authors came across an interesting finding from the diagnostic point of view. When patients' records were checked retrospectively for this study, it was noted that the DMSA scan was performed in a relatively small number of patients. This conflicts with the recommendations provided by clinical practice guidelines, and reflects a need to sensitize pediatricians in the region to ensure complete adherence to widely accepted treatment guidelines.

Our study has several limitations, including the retrospective nature of the study, and the small study population.

In conclusion, *E. coli* was the most commonly implicated pathogens leading to UTI. Non-*E. coli* UTI and recurrent episodes of UTI represent a significant risk factor for renal anomalies secondary to UTI. Children with recurrent UTI had 5-fold increased risk of associated urological abnormalities compared with those with single UTI.

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