Urinary Tract Infection in Children : An Update

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Abstract

Background : *A large number of children with Urinary Tract Infection (UTI) are seen in the community by general practitioners , but there is frequently delay in treatment and not all are referred for further investigations. There is evidence that many cases are misdiagnosed. It is important to optimize diagnostic and management strategies.*

Result: *UTI is an important cause of acute illness, it may be a marker of underlying urinary tract abnormality. Bacteria causes the large majority of UTI in children- Escherichia coli is the most common (90%) bacterial cause . Urine culture & sensitivity is the gold standard for the diagnosis and mandatory for confirmation of UTI. On culture, a colony count of more than 10^5/ml organisms of a single species is considered confirmatory of UTI. But there is a strong recommendation that , presence of both pyuria and at least 50,000 Colony Forming Unit (CFU) / ml of a single uropathogen in an appropriately collected specimen makes the diagnosis . There is a recommended imaging schedule in childhood UTI to detect anatomical abnormality. Management depends on type of infection. There is no role of prophylactic antibiotics to prevent febrile recurrent UTI without VUR.*

Conclusion : *UTI is a very common disease and may be associated with renal abnormalities and long term squeale. There is debate about best investigation and management strategies. The greatest potential for prevention of renal damage lies in increased awareness, better diagnosis and management of young children with UTI in primary healthcare.*

Introduction :

Urinary Tract Infection (UTI) implies presence of actively multiplying organisms in the urinary tract[1]. UTI in childhood is a significant and common problem encountered by primary, secondary and tertiary healthcare professionals [2]. UTI is an important cause of acute illness, it may be a marker of underlying urinary tract abnormality also[2] .Review of the early literatures on this subject reveal that there has been an improvement in the outlook for children who have had UTI In the past[3]. Approximately 50 years ago many studies identified the relationship between UTI and renal parenchymal defects using Intravenous Urogram (IVU) and Micturating Cystourethrogram (MCUG) and a large series of patients have been described who at post mortem were found to have chronic infection and renal scarring due to pyelonephritis[3].

In addition to clinical observation, practice has been influenced by animal experiments, such as those by Ransley and Risdon20 who demonstrated that, in the presence of Vesico-Ureteric Reflux (VUR) and UTI, contrast and infected urine could enter the renal parenchyma in a retrograde direction via collecting ducts opening into compound papillae and cause renal scarring in the corresponding segments of renal cortex which drain into these ducts[3]. They demonstrated how the first infection could be devastating to the renal parenchyma of the mini-pig, and how early antibiotic treatment could prevent or attenuate the renal scarring. They also described a hypothetical process whereby progression of renal scarring might evolve following the first insult as a result of further infections. These animal studies tended to reinforce the importance of prompt diagnosis and treatment of the first infection as well as the importance of recognizing and treating recurrent infections[3].

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Since 1991 many Pediatricians and some general practitioners have adopted the guidance of the Working Group of the Research Unit of the Royal College of Physicians (RCP) who produced an opinion-based consensus statement on the diagnosis and management of a first UTI in childhood[3].

These guidelines advocate that UTI should be considered in every child with a fever or urinary symptoms, that the diagnosis should be confirmed by culture of a urine sample and that, following treatment of the acute illness, all infants and children younger than 7 years should have specific renal imaging and receive prophylactic antibiotics until these investigations have been completed . In the last 15 years there has been a plethora of publications exploring UTI as a common cause of morbidity, that , in association with abnormalities of the urinary tract ,contributes long term complications , including hypertension and chronic renal failure [3]. Prompt detection and treatment of UTI and complicating factors are of utmost importance[4].

Epidemiology :

Prevalence rates of UTI varied by age, gender, race,and circumcision status [5]. Knowledge of the prevalence of UTI among different subgroups of children can assist clinicians in selecting children who would benefit from further diagnostic testing. Using prevalence rates as an estimate of the prior probability of disease is the first step in evidence-based practice. In 2007, a meta-analysis was carried out to determine the pooled prevalence of urinary tract infection (UTI) in children by age, gender, race, and circumcision status. Here , among infants presenting with fever, the overall prevalence of UTI was 7.0% (CI: 5.5– 8.4).The pooled prevalence rates of febrile UTIs in female aged 0–3 months, 3–6 months, 6–12 months, and more than 12 months was 7.5%, 5.7%, 8.3%, and 2.1% respectively. Among febrile male infants less than 3 months of age, 2.4% (CI: 1.4 –3.5) of circumcised males and 20.1% (CI: 16.8 –23.4) of uncircumcised males had a UTI. UTI rates were higher among white infants , 8.0% (CI: 5.1–11.0) than among black infants 4.7% (CI: 2.1–7.3). Among older children (>9 years) with urinary symptoms, the pooled prevalence of UTI (both febrile and afebrile) was 7.8% (CI: 6.6–8.9)[5].

In Indo-Pak sub-continent, UTI is a common bacterial infection in children occurring in 3-5% of girls and 1% of boys[4]. Commonest age for 1st symptomatic UTI is the first year of life in both sexes [4] The Incidence in the term neonate is approximately 1% & in the preterm 3%, both with male preponderance (male to female ratio is 5:1).During infancy, risk of developing UTI is equal in boys and girls and thereafter higher in girls [4]. Obstructive lesions may be found in 10% of boys investigated for UTI & 30-40% show vesicoureteric reflux (VUR).The risk of UTI is higher in children with malnutrition and chronic diarrhea[4] . Pediatric urinary tract infections (UTI) account for 0.7% of physician office visits and 5–14% of emergency department visits by children annually.[5]

Etiology :

Bacteria causes the large majority of UTI in children[6]. Viral infection of bladder are less common, while fungal infections are rare and occurs most commonly in immuno- compromised individuals (those with HIV/ AIDS, chemotherapy recipients etc) [6].

Escherichia coli is the most common (90%) bacterial cause of UTI in children [7] .Other gram-negative bacteria includes Klebsiella, Psuedomonas , Proteus, Enterobacter, and Citrobacter. Gram-positive bacteria includes Staphylococcus saprophyticus, Enterococcus, and, rarely, Staphylococcus aureus. Some viruses are also responsible for the development of UTI. These are adenovirus, enteroviruse, Coxsackievirus and echovirus. Among fungi, Candida spp , Aspergillus spp, Cryptococcus neoformans, endemic mycoses may cause UTI as opportunistic pathogen in immunocompromized patients[7]. Study conducted In a tertiary level hospital in Bangladesh showed the growth of E.coli in maximum (70%) patients [8].

Risk Factors

A variety of conditions lead to an increase predisposition to UTI[4]. These include female gender as they have short urethra which is in close proximity with anus and wiping from back to front [4]. Uncircumcised male have 4-20 times more chance of developing UTI[9]. Other risk factors include obstructive uropathy , urolithiasis , voiding dysfunction , lack of toilet training , urethral instrumentation ,tight clothings, pinworm infestation, constipation, labial adhesion, neuropathic bladder, sexual activity[4] etc. In Bangladesh [8], a study conducted in a tertiary level hospital showed the commonest age of first symptomatic UTI is less than one year (32%) with female preponderance (Male to Female ratio is 1: 1.3) [8]

Pathogenesis

In the neonatal period , renal parenchymal infection is due to hematogenous spread[4] .At all other ages, bacteria reaches urethra and bladder through the ascending route and ureter and kidney through VUR . Bacteria under the prepuce in boys reach the bladder by ascending through the urethra . However, development of UTI depends upon presence of risk factors, lack of host defense mechanism and bacterial virulence[4].

Bacteria that reach the urinary bladder are expelled with micturition [4]. Because of rapid bacterial multiplication in UTI , normal voiding cannot eliminate all bacteria. A small number may remain in a moist film lining the bladder mucosa , and are destroyed by the intrinsic defense of bladder epithelial cells. Other defense mechanisms include secretory IgA in urine and blood group antigens in secretions that impede bacterial adhesion. Breastfeeding has been found to protect infants against UTI during first 6 months of life. Human milk provides antiadhesive factors in urine and stabilizes intestinal flora with less pathogenic enteropathogens[4].

Bacterial adhesion mediated by fimbriae (pili) leads to activation of cytokines, production of adhesion molecules and chemotaxis of Leukocytes[4] . Once bacterial adhesion has taken place , their persistence and multiplication depend upon the formation of biofilm on epithelial surface[4] .

Classification:

It is helpful to classify children with UTI into subgroups for clinical as well as for scientific purpose[10]. UTI may be classified on presence of anatomical abnormality as primary (uncomplicated) or secondary to anatomical abnormality of urinary tract (complicated)[11]. UTI can also be classified on severity of symptoms which includes acute cystitis, acute pyelonephritis and covert or asymptomatic bacteruria[11]. Acute cystitis is the inflammation of urinary bladder[1]. Pyelonephritis indicates bacterial involvement of renal parenchyma which may result in renal injury termed as pyelonephritic scarring[12]. Asymptomatic bacteruria is a benign condition where there is a positive urine culture without any manifestation of infection. It does not cause any renal injury[12].

Recurrent infections are common , occurring in 60 percent of girls and 20 percent of boys[13]. Recurrent UTI has a pragmatic definition of 2 proven episodes within 6 months or 3 within a year[14] and are classified according to aetiology into persisting , relapsing infection and reinfection[11]. In childhood , most recurrent infections are due to reinfection[13]. Risk factors for recurrent UTI include voiding dysfunction ,constipation, underlying anatomical abnormality etc[12].

Clinical Presentation

Clinical presentation depends on age , site of infection and severity.[12]Newborns may show non specific symptoms such as poor feeding , irritability and weight loss[4]. Older boys may have urethral discharge and adolescent girls may experience vaginal irritation and symptoms like pelvic inflammatory disease.[15] Clinical pyelonephritis is characterized by any or all of the following : abdominal or flank pain, chills & rigors, fever , malaise, vomiting, and occasionally diarrhea.[4] Symptoms of Cystitis include dysuria , urgency ,frequent voiding , suprapubic pain ,incontinence and malodorous urine[4]. Sometimes patients experience urethritis and present with dysuria, reluctance to void , perineal discomfort, erythema etc [4]. In Bangladesh [8], a study conducted in a tertiary level hospital which showed fever (82%) as the commonest presentation.

Laboratory Evaluation

Patients should be advised to test urine when there is symptoms and signs of UTI , Unexplained fever of 38°C or higher and patients with an alternative site of infection but who remain unwell[15].

Urine specimens can be collected in four ways[4] - midstream clean catch specimen , suprapubic aspiration from the bladder ,from bag applied to the perenium and temporary transurethral catherization.[4]A midstream clean catch specimen is most widely used in toilet trained older children. Early morning urine samples harbor greater bacterial count. in neonate and infants, suprapubic aspiration from the bladder gives the most reliable result with high sensitivity and specificity .Bag specimens have unacceptably high contamination rate[4].

The specimen should be transported to the laboratory within 30 minutes to two hours or stored at 4^0C[4]. Urine collected in this way is used for dipstick , microscopy and for culture and sensitivity test[14].

Newer Tests :

Urine dipstick is appealing as they provide rapid result, do not require microscopy. It is convenient, inexpensive, and requires little training[7] . Production of esterase by neutrophils or conversion of nitrate to nitrite can be detected as color change on chemically coated paper strips[4].

Dipstick tests for UTI include leukocyte esterase, nitrite, blood, and protein[16]. Leuko-cyte esterase is the most sensitive single test in children with a

suspected UTI. The test for nitrite is more specific but less sensitive. A negative leukocyte esterase result greatly reduces the likelihood of UTI, whereas a positive nitrite result makes it much more likely; the converse is not true, however. Dip-stick tests for blood and protein have poor sensitivity and specificity in the detection of UTI and may be misleading. Accuracy of positive findings is as follows: (a) Nitrite: 53 percent sensitivity, 98 percent specificity, 75 percent probability of UTI (b) Leukocyte esterase: 83 percent sensitiv-ity, 78 percent specificity, 30 percent prob-ability of UTI[16] .

Table-I

Actions to be taken on dipstick reports[17]

Urine dipstick	Nitrite Positive	Nitrite Negative
Leukocyte Positive	treatment required	treatment required on clinical grounds
Leukocyte Negative	treatment required	No treatment required

In most cases of symptomatic UTI, microscopic examination of fresh urine shows a large number of bacteria and neutrophils[4]. Presence of five or more neutrophil per high power field (HPF) of centrifuged urine , or ten or more neutrophils per HPF of an uncentrifuged sample indicates pyuria [4]. Bacteriuria implies presence of bacteria in any number per HPF[7]. Urine microscopy may also reveal hematuria , mild proteinuria and WBC cast[4].

Table-II

Actions to be taken on Urine Microscopy reports[17]

Microscopy	Pyuria Positive	Pyuria Negative
Bacteriuria Positive	Treatment needed	Treatment needed
Bacteriuria Negative	Treatment needed on clinical grounds	No treatment needed

Urine culture & sensitivity is the gold standard for the diagnosis of UTI[7]. It is mandatory for confirmation of UTI [7]. The presence of even a few bacteria on suprapubic specimen is diagnostic[4] . On culture, a colony count of more than 10^5/ml organisms of a single species is considered confirmatory of UTI[4]. Counts between 10^4 to 10^5/ml require re-evaluation [4].Bacterial counts less than 10^5/ml are significant if symptomatic[4]. But there is a strong recommendation that , presence of both pyuria and at least 50,000 Colony Forming Unit (CFU) / ml of a single uropathogen in an appropriately collected specimen makes the diagnosis [9].

In acute pyelonephritis, there is a neutrophilic leukocytosis[4]. Raised level of ESR (> 30 mm in 1st hr) and C-Reactive Protein (>20 mg/dl) indicates host inflammatory response[4]. Bacteremia occurs in 4-9 % of infants with UTI [7]. Approximately 1 % of infants with UTI may also have meningitis, so, lumbar puncture should be done [7]. In Fungal UTI , pseudohyphae is found in urinary sediment[4] .Ultrasonography (USG) & other imaging should be done to detect obstruction by fungal ball , upper urinary tract dilatation and post voidal residue [4] .

Leukocytosis and white cell cast in urine indicates renal parenchymal involvement[4].

Sensitivity Pattern In Bangladesh :

In Bangladesh [8], a study was conducted in a tertiary level hospital which showed presence of pyuria in nearly all patients (92%). Urine culture revealed growth of E.coli in a good number of (70%) patients and maximum (80%) sensitivity was for Ceftriaxone , Amikacin , Nitrofurantoin and Levofloxacin[8] .

Imging in UTI

The goal of imaging studies in children with UTI is to identify anatomic abnormalities that predispose to infection[12]. Recommended imaging schedule[3] in childhood UTI is as follows-

Table-III

Recommended imaging schedule in Infants < 6 months[3]

Test	Responds well to treatment within 48 hours	Atypical UTI	Recurrent UTI
Ultrasoundduring acute infection	No	Yes	Yes
Ultrasoundwithin 6 weeks	Yes	No	No
Dimercaptosuccinic Acid(DMSA) Scan4–6 months following acute infection	No	Yes	Yes
Micturating Cystourethrogram (MCUG)3 - 4 wks following acute infection	No	Yes	Yes

Table -IV

Recommended imaging schedule in children aging 6 months to 3 years[3]

Test	Responds well to treatment within 48 hours	Atypical UTI	Recurrent UTI
Ultrasound during the acute infection	No	Yes	No
Ultrasound within 6 weeks	No	No	Yes
DMSA4–6 months following the acute infection	No	Yes	Yes
MCUG3 - 4 wks later	No	No	No

Table-V

Recommended imaging schedule in children aging 3 years and older[3]

Test	Responds well to treatment within 48 hours	Atypical UTI	Recurrent UTI
Ultrasound during the acute infection	No	Yes	No
Ultrasound within 6 weeks	No	No	Yes
DMSA 4–6 months following the acute infection	No	No	Yes
MCUG 3 - 4 wks later	No	No	No

So, from above schedules it can be said that ,MCUG should not be performed routinely after the first febrile UTI[9]; MCUG is indicated if 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.[9]

Management

The goal of management of UTI in children is to resolve acute symptoms ,to eliminate infection, to prevent urosepsis and recurrence and long-term complications also[7] .

Treatment should be started before investigation reports are available if age is less than 3 years, upper tract symptoms ,urine is positive for nitrite or leukocyte, child has known renal tract problem or if there is family history of VUR or renal scarring[18]. The child with UTI should be hospitalized if age is less than 2 months ,there is clinical urosepsis , potential bacteremia , immunocompromised patient ,vomiting , inability to tolerate oral medication ,lack of adequate outpatient follow-up or failure to respond to outpatient therapy[7].

Oral antibiotic treatment is as efficacious as sequential Intravenous (IV) /Oral antibiotic treatment in the prevention of renal scarring in children of acute pyelonephritis and scintigraphy documented acute lesion[9] .However IV antibiotics should be given in any person of any age who appears to be toxic clinically , patients having neutropenia, neonates until bacteremia, sepsis & meningitis are ruled out , children unable to tolerate oral antibiotics and immunocompromised patients[18].

Table-VI

Parenteral treatment of UTI[9]

Anti microbial agent	Dosage	
Ceftriaxone	75 mg/kg	Once daily
Cefotaxime	150 mg/kg	6-8 hourly
Ceftazidime	100-150mg/kg	8 hourly
Gentamicin	7.5 mg/kg	8 hourly
Tobramycin	5 mg/kg	8 hourly
Piperacillin	300 mg/kg	6-8 hourly

Oral antimicrobials can be prescribed when the child is non-toxic appearing and taking oral fluids and medications[18].

Table-VII

Oral Antimicrobial agent [8]

Oral Antimicrobial agent	Dosage	
Amoxicillin – Clavulanate	20-40 mg/kg	8 hourly
Trimethoprim- Sulfamethoxazole	T - 6-12 mg/kg ,S – 30-60 mg/kg	12 hourly
sulfisoxazole	120-150 mg/kg	6 hourly
Cephalosporin		
Cefixime	8 - 20mg/kg	12 hourly
Cefpodoxime	10 mg/kg	12 hourly
Cefprozil	30 mg/kg	12 hourly
Cefuroxime axetil	20-30 mg/kg	12 hourly
Cephalexin	50-100 mg/kg	6 hourly

Choice of antibiotics vary with age[15] , in neonates Ampicillin plus a second antibiotic (usually Gentamycin or Cefotaxime) is given usually to cover Group B Sterptococcus, Listeria as well as gram negative organisms[15].

Vancomycin may be indicated for toxic patients or those unresponsive to initial therapy[15] .In older infants and children, E. coli, Klebsiella & Proteus are among the most common organisms [15]. Here , treatment is based on resistance patterns in the community. Hospitals and the health department are good sources of information[15]. In Adolescents empiric therapy for STD should be strongly considered[15].

Duration of treatment is 7- 10 days for Uncomplicated infection and 10-14 days for Complicated infections[9] .There is no evidence of benefit from treatment of asymptomatic bacteruria in girls with normal urinary tract[2].

With appropriate treatment –Urine becomes sterile (no bacteriuria) after 24 hrs and symptoms disappear within 48 – 72 hrs[4]. Clinical response (afebrile) was noticed on the 5th day in the study conducted in a tertiary level hospital in Bangladesh[8].

In children with acute pyelonephritis, adjunct therapy with oral methyl-prednisolone for 3 days reduces the occurrence of renal scarring [19].

In case of fungal UTI , if there is no systemic feature and negative fungal culture ,only bladder irrigation with Amphotericin B (50mg/L) for 7 days or continuous irrigation for 72 hours should be done[20]. In Candida cystitis, oral Fluconazole 5-10 mg/kg/day for 4 weeks is usually prescribed [21]. Surgical consultation should be taken if there is feature of obstruction by fungal ball , obstructive uropathy and VUR grade IV AND V [21].

Besides specific therapy , some general measures should be considered such as adequate fluid intake , regular bowel habit , avoidance of constipation and other risk factors, prompt correction of obstructive uropathy and complete bladder emptying[4].

Management of Recurrent UTI

Recurrent UTI must be treated cautiously as it may result in renal scarring , followed by hypertension and ultimately Renal failure[4]. Lifestyle should be modified considering underlying risk factors which may cause recurrence[4]. Long term low dose antibiotic prophylaxis is a widely used strategy to prevent UTI in clinical practice[4]. Antibiotic prophylaxis is given to children in VUR and those with recurrent febrile UTI even if the urinary tract is normal [4]. The ideal antibiotic for prophylaxis should have a broad spectrum of action and higher urinary concentration with minimal alteration of bowel flora , although the precise mechanism of action is not known[4]. Cotrimoxazole, Nitrofurantoin, Cephalexin, Cephadroxil, Cefaclor and Cefixime are used as prophylaxis at one third of the conventional dose at bed time as single dose[4]. But data from the most recent 6 studies do not support the use of antimicrobial prophylaxis to prevent febrile recurrent UTI without VUR[9].

Cranberry juice is a well known folk remedy in America which is effective in reducing the actual number of recurrences[22]. It decreases adherence of E. coli and as effective as prophylactic Cotrimoxazole[22]. Use of probiotic is emerging now a days as a measure to

prevent recurrent UTI [22]. Lactobacillus Acidophillus is used to restore commensal microflora.[23]

Prevention of UTI

Uncircumcised male infants appear to be at increased risk of UTIs. Circumcision diminishes that risk [24].Breast feeding protects against UTIs, both during the time the infant is receiving breast milk and for a period after breast feeding is discontinued, presumably by promoting a stable intestinal flora with fewer potentially pathogenic strains[25]. In the anatomically and neurologically normal child, voiding dysfunction is usually caused by persistence of an unstable urinary bladder, an important contributor to recurrent UTIs[26]. Recognition and management of voiding dysfunction is the area in which the physician can be most effective in the prevention of recurrent UTIs. Voiding dysfunction is treated with the use of a voiding retraining program that emphasizes good voiding technique, usually following a timed voiding schedule[26]. A relationship between constipation and UTIs is well known[27]. Effective treatment of the constipation results in normalization of bladder function and cessation of UTIs[27]. Perineal hygiene is regularly emphasized. For aesthetic reasons, it seems appropriate to instruct girls to wipe from front to back[28]. Besides , use of prophylactic antibiotics[4] in appropriate cases , cranberry juice and anti helminthes[22] can help in prevention of UTI.

Breakthrough UTI

The development of UTI during prophylaxis is called breakthrough UTI[4]. It is due to Poor drug compliance & bacterial resistance [4] . DMSA is indicated here[3]. Proper dose and regular intake of drug , change of drug if bacterial resistance and surgical correction of underlying abnormality are the mainstay of treatment[29].

Follow up

Follow up should be continued until imaging is normal[3]. If renal scar is present, long term follow up should be done 3-6 monthly up to adulthood to slow progression to CKD[3]. During each follow up, clinically - height, weight, anaemia , blood pressure , proteinuria and examination of kidney and urinary bladder should be considered[3]. Urine Analysis should be done 6 monthly , urine culture if symptomatic, renal function and USG yearly [3]. Asymptomatic bacteriuria does not require follow up[12].

Conclusion :

Urinary tract is a common site of bacterial infection in infancy and childhood with potentially important implications[11].UTI have been considered as an important risk factor for the development of renal insufficiency and end stage renal disease in children[4] . Better recognition of risk factors, prompt diagnosis and early intervention are sufficient enough to maintain normal renal function and healthy lifestyle[12].

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