

Leading Article

Urinary Tract Infection in Children: Importance of Proper Diagnosis and Management

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Urinary Tract Infection (UTI) is a common bacterial infection causing illness in infants and children and recurrent UTI is known as one of the major factors for renal scarring. It may be difficult to recognize UTI in children because the presenting symptoms and signs are non-specific, particularly in infants and children younger than 3 years. It can be associated with long-term sequelae of renal scarring, which may cause hypertension, proteinuria, pregnancy-related complications, or even progressive renal failure¹. The risk of recurrent UTI in children has been estimated to be 12-30% in the first 6-12 months after the initial UTI². Predisposing factors for recurrence include vesico-ureteral reflux and dysfunctional voiding problems³. In infants with normal urinary system, age less than 6 months, non-retractile prepuce and Acute Pyelonephritis (APN) in male infants are the most important risk factor for recurrent UTI⁴.

Escherichia coli remains the most common organism causing UTI in children (60-92%). Other common organisms include *Klebsiella*, *Proteus*, *Enterococcus* and *Enterobacter Spp.*^{5,6}. Less common organisms such as *Pseudomonas*, Group B *Streptococcus* and *Staphylococcus aureus* are seen with increased frequency in patients with anatomical defects, kidney stones, following genitourinary surgery or bladder catheterization and following repeated courses with antibiotic treatments.^{5,7} The mechanism of pathogenesis in UTI is thought to be an ascending infection from periurethral organisms in children older than the neonatal period. UTI in neonatal period mostly presents as a part of generalized septicaemia.

Clinical manifestations of UTI are also age dependent. Older children may present with dysuria, urinary frequency or hesitancy, low-grade abdominal pain apart from fever and flank pain when there is APN. Infants and younger children may present with a combination

of symptoms that include fever, irritability, excessive crying, diarrhoea and poor feeding. In infants and younger children, fever is an important clinical marker of renal parenchymal involvement (pyelonephritis). American Academy of Pediatrics (AAP) acknowledges the presence of high fever ($> 39^{\circ}\text{C}$) with clinical diagnosis of UTI as an important indicator of pyelonephritis compared with no fever ($\leq 38^{\circ}\text{C}$) in those with cystitis⁸.

Although urine culture remains the gold standard for diagnosis of UTI, it requires appropriate collection of uncontaminated urine sample. The technique of obtaining urine can affect sample quality. Urine collected by 'clean catch method' is most appropriate in children who can respond to command or toilet trained. In infant and younger children, urine should be obtained by urinary catheterization or suprapubic aspiration. Collection of urine with adhesive bags to the perineal area has limited role in diagnosing UTI due to high risk of contamination. To get the result of urine culture, it requires a minimum of 18 hours and some rapid tests are often needed to guide the initial management. Urine dipstick is an inexpensive and readily available technique. The presence of either leukocyte esterase (LE) and/or nitrite is interpreted as a positive dipstick test⁹ whereas RBC and proteins are poor indicators of UTI. Urine microscopy is performed to look for the presence of WBC or bacteria and its sensitivity and specificity are better with uncentrifuged urine and Gram staining of the sample. Pyuria is defined by the presence of > 10 WBC/mm³ in uncentrifuged urine sample and bacteriuria by the presence of any bacteria per 10 oil-immersion field of Gram-stained smear.

Asymptomatic bacteruria:

An important cause of bacteruria in the absence of pyuria is asymptomatic bacteruria (ABU). This is defined as the growth of a significant number of a single organism ($\geq 100,000$ cfu/ml) from a urine sample of an asymptomatic child with no pyuria. It is often an

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incidental finding and can be demonstrated on repeat urine cultures. The bacteruria isolated is most often an E.coli of low virulence that colonizes the urinary tract and does not have significant ability to damage the kidneys¹⁰, ABU is also observed in children with neurogenic bladder, particularly if the patient is on intermittent catheterization. Antibiotics should not be given to eradicate ABU, because studies suggest that antimicrobial treatment may do more harm than good¹¹. The key to distinguish true UTI from asymptomatic bacteruria is the presence of pyuria.

UTI Treatment

It is believed that prompt antibiotic treatment of UTI diminishes the risk of renal scarring. Although there are conflicting reports that early initiation of treatment (<1 day of fever) and delayed starting (after 24 hours) had no significant benefit^{12,13}, it is not advisable to delay treatment of a sick child when UTI is suspected. Patients with APN can have complications other than scarring when treatment is delayed, such as sepsis and abscess formation. Empiric therapy for UTI should be initiated after appropriate urine specimen has been obtained.

A Cochrane review of 23 randomized controlled studies showed no significant difference in persistent kidney damage at 6-12 months between orally administered antibiotic therapy for 10-14 days and intravenously administered (iv) antibiotic therapy for 3 days followed by oral therapy for 10 days¹⁴. However most of these studies excluded high risk children such as infants age less than 3 months, those with significant renal scarring or genitourinary abnormalities. These high risk children need to be identified and might benefit from initial parenteral therapy. Indications for hospitalization of any child with UTI include clinical urosepsis, laboratory evidence of bacteriuria, immunocompromised patient, intolerance to oral intake, lack of adequate outpatient follow-up or failure to respond to outpatient therapy. Thorough septic work-up should be done in patients less than 1 month of age because UTI is most often secondary to haematogenous seeding rather than ascending infection at this age.

The choice of empirical antibiotic should be guided by local sensitivity patterns but it must include the drugs which are effective against E.Coli, the most common infective organism causing UTI. E.Coli remains largely sensitive to third-generation

cephalosporin, aminoglycosides and nitrofurantoin¹⁵. Nitrofurantoin should not be used as an empirical antibiotic in a febrile child with UTI because parenchymal and serum concentration may be insufficient to treat pyelonephritis. It is very effective as prophylaxis because its urinary concentration remains high.

Final antibiotic choice should be based on pathogen identification and sensitivity from urine culture. In infants <1 months, the most likely pathogens are E.Coli and E. faecalis which require empiric therapy with a b - lactam antibiotic and an aminoglycoside.

Among oral antibiotics, second and third generation cephalosporins are appropriate for first line drugs for APN. Amoxycilin-clavulanate, trimethoprim-sulphamethoxazole can also be used. Ciprofloxacin should be reserved for UTI caused by P. aeruginosa or other multi-drug resistant organisms.

UTI & Renal imaging

Renal imaging is required to identify risk factors and abnormalities of genitourinary tract so that the chances of recurrent UTI and renal scarring could be reduced.

Renal ultrasound (RUS) is useful for detecting renal abscess, hydronephrosis, congenital abnormalities, post-voidal residual urine and sometimes stones. Ultrasound has limited influence for assessing the presence of renal scarring¹⁶

DMSA (dimercaptosuccinic acid) renal scan is the gold standard for diagnosing acute pyelonephritis (APN) and renal scars. DMSA scan cannot identify which lesions in APN will resolve spontaneously or which ones will result in scar formation. It also cannot differentiate between changes occurring due to APN and those due to pre-existing / congenital scars.

Voiding cystourethrogram (VCUG) is the most useful diagnostic modality for detecting vesico-ureteric reflux (VUR). It should not be done during acute infection because urinary catheterization is required to perform the procedure. It is better to do it after completion of antibiotic course when the patient is asymptomatic. VUR grading (from grade I to grade V) can be done by VCUG. Radionuclear cystography (RNC) may be done to identify VUR but because of its inability to grade VUR or renal anatomic defects, it is not used as an initial test to diagnose VUR.

There are plenty of controversies and debates regarding the necessity and timing of doing imaging

studies in children having UTI. In 2007 the National Institute for Health and Clinical Excellence (NICE) of United Kingdom published its recommendations as a selective approach for renal imaging after UTI¹⁷. They recommend RUS only in patients aged under 6 months if no other risk factors such as atypical UTI and recurrent UTI are present. The very selective imaging by NICE guidelines would have left a significant number of undiagnosed VUR and renal scars in infants and younger children¹⁸. The American Academy of Pediatrics (AAP) recommends RUS in all children from 2 months to 2 years of age after the first febrile UTI¹⁹.

AAP does not recommend VCUG after the first UTI. It is recommended when RUS 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. VCUG is also recommended by AAP in case of recurrent UTI.

One reasonable recommendation is that to screen high grade VUR in young infants with febrile UTI, RUS and DMSA scan could be performed first. VCUG is only indicated when abnormalities are apparent on either RUS or DMSA scan or both²⁰.

A recent study showed that the accuracy of USG in the diagnosis of VUR is higher in normal children and those with severe VUR. It is suggested that although VCUG is required for a definitive diagnosis of VUR, USG may be the first step to assess patients with suspected VUR, thereby reducing exposure to radiation²¹.

However, it should be kept in mind that the best strategy for preventing renal scar is not searching for VUR itself, rather prompt diagnosis and correct treatment of UTI. Another recent study strongly suggests that a diagnosis of APN with normal RUS does not require searching for VUR²². In fact, in future only DMSA will be necessary in febrile UTI follow-up and searching for VUR will probably become unnecessary.

Antimicrobial prophylaxis in UTI

Although long-term antimicrobial prophylaxis has been a standard practice for many decades to prevent recurrent UTI in children with or without VUR, there are many studies on the subject giving confusing results. However most of the reports showed no significant difference in recurrence of UTI between prophylaxis groups and control groups. Until more evidence based practices evolve, physicians should

give proper attention while treating children having risk factors for recurrent UTI, including VUR.

Antibiotics commonly used as prophylaxis include trimethoprim – sulphamethoxazol (TMP-SMX), nitrofurantion and first generation cephalosporin. Amoxicillin can be used in children <2months, because TMP-SMX is contra-indicated in this age group. Antimicrobial resistance is a major concern with antibiotic prophylaxis²³. Other problems with prophylaxis include compliance and parental concern over long-term antibiotic administration.

Parents of the infants and young children having risk factors like VUR, hydronephrosis should be reminded about early warning symptoms and risk of UTI, with routine review of signs and symptoms of UTI which would be an important approach to prevent late complications. It may be possible to substantially reduce renal scarring and chronic kidney disease in children and hence in the next generation of adults by early detection and prompt treatment of a febrile UTI. Considering the huge burden of management of a child or adult having chronic kidney disease upon the family as well as on the society in a developing country like Bangladesh, we should always keep in mind that 'prevention is better than cure'.

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