Revised Statement on Management of Urinary Tract Infections

INDIAN SOCIETY OF PEDIATRIC NEPHROLOGY

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Justification: In 2001, the Indian Pediatric Nephrology Group formulated guidelines for management of patients with urinary tract infection (UTI). In view of emerging scientific literature, the recommendations have been reviewed.

Process: Following a preliminary meeting in November 2010, a document was circulated among the participants to arrive at a consensus on the evaluation and management of these patients.

Objectives: To revise and formulate guidelines on management of UTI in children.

Recommendations: The need for accurate diagnosis of UTI is emphasized due to important implications concerning evaluation and follow up. Details regarding clinical features and diagnosis, choices and duration of therapy and protocol for follow up are discussed. UTI is diagnosed on a positive culture in a symptomatic child, and not merely by the presence of leukocyturia. The need for parenteral therapy in UTI in young infants and those showing toxicity is emphasized. Patients with aysmptomatic bacteriuria do not require treatment. The importance of bowel bladder dysfunction in the causation of recurrent UTI is highlighted. Infants with the first UTI should be evaluated with micturating cystourethrography. Vesicoureteric reflux (VUR) is initially managed with antibiotic prophylaxis. The prophylaxis is continued till 1 year of age in patients with VUR grades I and II, and till 5 years in those with higher grades of reflux or until it resolves. Patients and their families are counselled about the need for early recognition and therapy of UTI. Children with VUR should be followed up with serial ultrasonography and direct radionuclide cystograms every 2 years, while awaiting resolution. Siblings of patients with VUR should be screened by ultrasonography. Children with renal scars need long term follow up on yearly basis for growth, hypertension, proteinuria, and renal size and function.

Key words: *Child, India, Prevention, Urinary tract infections, Vesicoureteric reflux.*

Urinary tract infection (UTI) is a common bacterial infection in infants and children. The risk of having a UTI before the age of 14 years is approximately 1-3% in boys and 3-10% in girls [1,2]. The diagnosis of UTI is often missed in infants and young children, as urinary symptoms are minimal and often non-specific. Rapid evaluation and treatment of UTI is important to prevent renal parenchymal damage and renal scarring that can cause hypertension and progressive renal damage [3]. Pediatricians should be aware of the clinical features, diagnosis, management and evaluation of children with UTI. Even a single confirmed UTI should be taken seriously, especially in young children, due to the potential for renal parenchymal damage.

An Expert Group Meeting of the Indian Society of Pediatric Nephrology was held on 12th November, 2010 in Kolkata to review the guidelines published in *Indian Pediatrics* in 2001 [4]. New evidence was analyzed, with an aim to update and revise the guidelines. The revisions are highlighted in ***Table* I**.

Definitions

Infection of the urinary tract is identified by growth of a significant number of organisms of a single

species in the urine, in the presence of symptoms. The diagnosis of UTI should be made only in patients with a positive urine culture, since this has implications for detailed evaluation and follow up. Recurrent UTI, defined as the recurrence of symptoms with significant bacteriuria in patients who have recovered clinically following treatment, is common in girls. Recurrent UTI add to parental anxiety, medical costs and the risk of renal parenchymal damage in young infants.

Clinical Features

UTI is an important cause for fever without a focus, especially in children less than 2 years old [5,6]. In neonates, UTI is usually a part of septicemia and presents with fever, vomiting, lethargy, jaundice and seizures. Infants and young children present with recurrent fever, diarrhea, vomiting, abdominal pain and poor weight gain. Older children show fever, dysuria, urgency, frequency and abdominal or flank pain. Adolescents may have symptoms restricted to the lower tract, and fever may not be present.

The distinction between upper and lower UTI is difficult and not necessary. In view of risks of renal parenchymal damage associated with delayed treatment, UTI in children is considered to involve the upper tract and should be treated promptly. Patients with features of systemic toxicity are considered as having complicated UTI, while those without these features are referred to as simple UTI (***Table* II**) [4]. This distinction has implications for therapy, as is discussed later.

Diagnosis

The diagnosis of UTI is based on positive culture of a properly collected specimen of urine. While urinalysis enables a provisional diagnosis of UTI, a specimen must be obtained for culture prior to therapy with antibiotics [7].

Significant pyuria is defined as >10 leukocytes per mm^3 in a fresh uncentrifuged sample, or >5 leukocytes per high power field in a centrifuged sample. Leukocyturia might occur in conditions such as fever, glomerulonephritis, renal stones or presence of foreign body in the urinary tract. The detection of leukocyturia in absence of significant bacteriuria is not sufficient to diagnose a UTI. Rapid dipstick based tests, which detect leukocyte esterase and nitrite, are useful in screening for UTI. A combination of these tests has moderate sensitivity and specificity for detecting UTI, and is diagnostically as useful as microscopy [1].

TABLE I MAJOR REVISIONS IN THIS DOCUMENT

- The importance of urine culture on a correctly collected specimen is reemphasized. The diagnosis of urinary tract infection (UTI) must be based on a positive urine culture.
- Patients with UTI should be evaluated for the presence of complications, underlying anomalies or voiding dysfunction.
- Recommendations on imaging following the first episode of UTI are revised. Detailed investigations are done in infants. In older children, micturating cystourethrography is done in those who show abnormalities on ultrasonography and DMSA scintigraphy.
- Patients with recurrent UTI and/or vesicoureteric reflux should be evaluated for bowel bladder dysfunction.
- Patients with grades I and II reflux should receive antibiotic prophylaxis till they are 1 year old. Those with higher grades of reflux are given prophylaxis till 5 years of age, or longer in case of bowel bladder dysfunction or breakthrough UTI.

TABLE II DEFINITIONS

Significant bacteriuria	Colony count of $>10^5$/mL of a single species in a midstream clean catch sample.
Asymptomatic bacteriuria	Significant bacteriuria in the absence of symptoms of urinary tract infection (UTI).
Simple UTI	UTI with low grade fever, dysuria, frequency, and urgency; and absence of symptoms of complicated UTI.
Complicated UTI	Presence of fever >39ºC, systemic toxicity, persistent vomiting, dehydration, renal angle tenderness and raised creatinine.
Recurrent infection	Second episode of UTI.

Collection of specimen for culture

A clean-catch midstream specimen is used to minimize contamination by periurethral flora. Contamination can be minimized by washing the genitalia with soap and water. Antiseptic washes and forced retraction of the prepuce are not advised. In neonates and infants, urine sample is obtained by either suprapubic aspiration or transurethral bladder catheterization. Both techniques are safe and easy to perform [7].

The urine specimen should be promptly plated within one hour of collection. If delay is anticipated, the sample can be stored in a refrigerator at 4ºC for up to 12-24 hours. Cultures of specimens collected from urine bags have high false positive rates, and are not recommended.

A urine culture should be repeated in case contamination is suspected, *e.g.*, mixed growth of two or more pathogens, or growth of organisms that normally constitute the periurethral flora (lactobacilli in healthy girls; enterococci in infants and toddlers). The culture should also be repeated in situations where UTI is strongly suspected but colony counts are equivocal. The number of bacteria required for defining UTI depends on the method of urine collection **(*Table* III)** [2,4,5].

Initial Evaluation

The patient is examined for the degree of toxicity, dehydration and ability to retain oral intake. The blood pressure should be recorded and history regarding bowel and bladder habits elicited. The child is examined for features that suggest an underlying functional or urological abnormality **(*Tables* IV** and **V).** Complete blood counts, serum creatinine and a blood culture should be done in infants and children with complicated UTI.

TABLE III CRITERIA FOR THE DIAGNOSIS OF UTI

Method of collection	Colony count	Probability of infection
Suprapubic aspiration	Any number of pathogens	99%
Urethral catheterization	$>5 \times 10^4$ CFU/mL	95%
Midstream clean catch	$>10^5$ CFU/mL	90-95%

CFU: colony forming units.

Immediate Treatment

The patient's age, features suggesting toxicity and dehydration, ability to retain oral intake and the likelihood of compliance with medication(s) help in deciding the need for hospitalization. Therapy should be prompt to reduce the morbidity of infection, minimize renal damage and subsequent complications.

Children less than 3 months of age and those with complicated UTI should be hospitalized and treated with parenteral antibiotics. The choice of antibiotic should be guided by local sensitivity patterns. A third generation cephalosporin is preferred **(*Table* VI).** Therapy with a single daily dose of an aminoglycoside may be used in children with normal renal function [8]. Once the result of antimicrobial

TABLE IV FEATURES SUGGESTING UNDERLYING STRUCTURAL ABNORMALITY

Distended bladder
Palpable, enlarged kidneys
Tight phimosis; vulval synechiae
Palpable fecal mass in the colon
Patulous anus; neurological deficit in lower limbs
Urinary incontinence
Previous surgery of the urinary tract, anorectal malformation or meningomyelocele

TABLE V FEATURES SUGGESTIVE OF BOWEL BLADDER DYSFUNCTION

Recurrent urinary tract infections
Persistent high grade vesicoureteric reflux
Constipation, impacted stools
Maneuvers to postpone voiding (holding maneuvers, *e.g.*, Vincent curtsy, squatting)
Voiding less than 3 or more than 8 times a day
Straining or poor urinary stream
Thickened bladder wall >2 mm
Post void residue >20 mL
Spinning top configuration of bladder on micturating cystourethrogram

sensitivity is available, the treatment may be modified. Intravenous therapy is given for the first 2-3 days followed by oral antibiotics once the clinical condition improves.

Children with simple UTI and those above 3 months of age are treated with oral antibiotics (***Table* VI**). With adequate therapy, there is resolution of fever and reduction of symptoms by 48-72 hours. Failure to respond may be due to presence of resistant pathogens, complicating factors or noncompliance; these patients require re-evaluation.

TABLE VI ANTIMICROBIALS FOR TREATMENT OF UTI

Medication	Dose, mg/kg/day
Parenteral	
Ceftriaxone	75-100, in 1-2 divided doses IV
Cefotaxime	100-150, in 2-3 divided doses IV
Amikacin	10-15, single dose IV or IM
Gentamicin	5-6, single dose IV or IM
Coamoxiclav	30-35 of amoxicillin, in 2 divided doses IV
Oral	
Cefixime	8-10, in 2 divided doses
Coamoxiclav	30-35 of amoxicillin, in 2 divided doses
Ciprofloxacin	10-20, in 2 divided doses
Ofloxacin	15-20, in 2 divided doses
Cephalexin	50-70, in 2-3 divided doses

Duration of Treatment

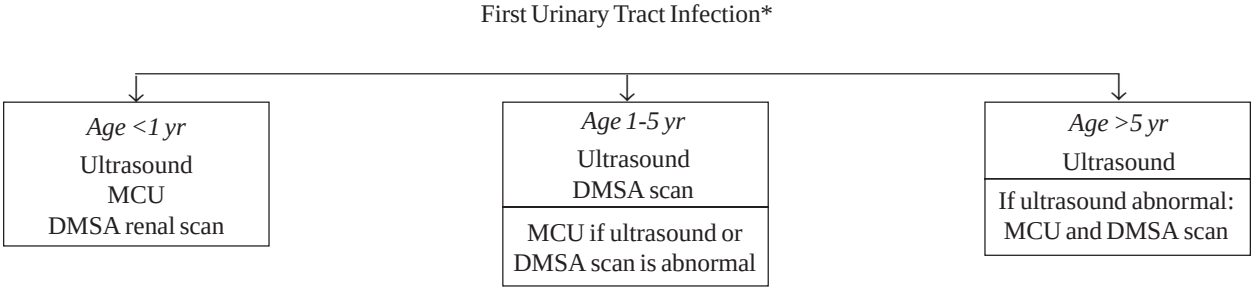
The duration of therapy is 10-14 days for infants and children with complicated UTI, and 7-10 days for uncomplicated UTI [4, 5]. Adolescents with cystitis may be treated with shorter duration of antibiotics, lasting 3 days [1]. Following the treatment of the UTI, prophylactic antibiotic therapy is initiated in children below 1 year of age, until appropriate imaging of the urinary tract is completed.

Supportive Therapy

During an episode of UTI, it is important to maintain adequate hydration. A sick, febrile child with inadequate oral intake or dehydration may require parenteral fluids. Routine alkalization of the urine is not necessary. Paracetamol is used to relieve fever; therapy with non steroidal anti- inflammatory agents should be avoided. A repeat urine culture is not necessary, unless there is persistence of fever and toxicity despite 72 hours of adequate antibiotic therapy.

Evaluation after the first UTI

The aim of investigations is to identify patients at high risk of renal damage, chiefly those below one year of age, and those with VUR or urinary tract obstruction. Evaluation includes ultrasonography, dimercaptosuccinic acid (DMSA) renal scan and micturating cystourethrography (MCU) performed judiciously as shown in ***Fig.* 1**. An ultrasonogram provides information on kidney size, number and location, presence of hydronephrosis, urinary bladder anomalies and post-void residual urine. DMSA scintigraphy is a sensitive technique for detecting renal parenchymal infection and cortical scarring. MCU detects VUR and provides anatomical details regarding the bladder and the



**All patients with recurrent UTI need detailed evaluation with ultrasonography, DMSA scan and MCU.*

FIG. 1 *Evaluation following initial urinary tract infection.*
MCU: micturating cystourethrogram; DMSA dimercaptosuccinic acid.

urethra. Follow-up studies in patients with VUR can be performed using direct radionuclide cystography.

There is limited evidence that intensive imaging and subsequent management alters the long-term outcome of children with reflux nephropathy diagnosed following a UTI. With availability of antenatal screening, most important anomalies have already been detected and managed after birth. Therefore, there is considerable debate regarding the need and intensity of radiologic evaluation in children with UTI [1,9].

The Expert Group reviewed the current literature, keeping in view that in our country the diagnosis of UTI is often missed or delayed, and there are limitations of infrastructure and scarcity of resources for routine antenatal screening. Based on the above, it concluded that all children with the first UTI should undergo radiological evaluation. The detection of significant scarring, high grade VUR or obstructive uropathy might enable interventions that prevent progressive kidney damage in the long-term. Since infants and young children are at the highest risk for renal scarring, it is necessary that this group undergo focused evaluation.

It is recommended that all infants with UTI be screened by ultrasonography, followed by MCU and DMSA scintigraphy. Since older patients (1-5 year old) with significant reflux and scars or urinary tract anomalies are likely to show abnormalities on ultrasonography or scintigraphy, a MCU is advised in patients having abnormalities on either of the above investigations. Children older than 5 years are screened by ultrasonography and further evaluated only if this is abnormal.

It is emphasized that patients with recurrent UTI at any age should undergo detailed imaging with ultrasonography, MCU and DMSA scintigraphy.

Ultrasonography should be done soon after the diagnosis of UTI. The MCU is recommended 2-3 weeks later, while the DMSA scan is carried out 2-3 months after treatment. An early DMSA scan, performed soon after a UTI, is not recommended in routine practice. Patients showing hydronephrosis in the absence of VUR should be evaluated by diuretic renography using ^{99m}Tc-labeled diethylenetriamine-pentaacetic acid (DTPA) or mercaptoacetylglycine (MAG-3). These techniques provide quantitative assessment of renal function and drainage of the dilated collecting system.

PREVENTION OF RECURRENT UTI

General

Adequate fluid intake and frequent voiding is advised; constipation should be avoided [2,5]. In children with VUR who are toilet trained, regular and volitional low pressure voiding with complete bladder emptying is encouraged. Double voiding ensures emptying of the bladder of post void residual urine. Circumcision reduces the risk of recurrent UTI in infant boys, and might therefore have benefits in patients with high grade reflux [10,11].

Bowel bladder dysfunction

Children presenting with recurrent UTI or persistent VUR often have an associated voiding disorder, which are characterized by abnormal patterns of micturition in presence of intact neuronal pathways without congenital or anatomical abnormalities. Abnormal bladder pressure and urinary stasis predispose these children to recurrent UTI. There may be an abnormality either during the filling phase as in an overactive bladder, or the evacuation phase as in dysfunctional voiding [12]. Since constipation is often associated with a functional voiding disorder, the condition is referred to as Bowel bladder dysfunction (BBD). Children with recurrent UTI are likely to have dysfunctional voiding [5,13]. Features suggestive of voiding disorders are shown in ***Table* V**.

Evaluation for a voiding disorder includes a record of frequency and voided volume and fluid intake for two to three days. It is useful to watch the urinary stream, and for post void dribbling in boys. Urodynamic studies are done in selected cases. The management of voiding disorders should be carried out in collaboration with an expert. This includes the exclusion of neurological causes, institution of structured voiding patterns and management of constipation. In patients with an overactive bladder, therapy with anticholinergic medications (*e.g.*, oxybutinin) is effective. Patients with bowel bladder

TABLE VII ANTIMICROBIALS FOR PROPHYLAXIS OF URINARY TRACT INFECTIONS

Medication	Dose, mg/kg/day	Remarks
Cotrimoxazole	1-2*	Avoid in infants <3 mo, glucose-6-phosphate dehydrogenase deficiency
Nitrofurantoin	1-2	May cause vomiting and nausea; avoid in infants <3 mo, G6PD deficiency, renal insufficiency
Cephalexin	10	Drug of choice in first 3-6 mo of life
Cefadroxil	5	An alternative agent in early infancy

Usually given as single bedtime dose; **of trimethoprin.*

dysfunction and large post void residues, benefit from timely voiding, bladder retraining, and clean intermittent catheterization.

Antibiotic Prophylaxis

Long-term, low dose, antibacterial prophylaxis is used to prevent recurrent, febrile UTI **(*Table* VII)**. The antibiotic used should be effective, non-toxic with few side effects and should not alter the growth of commensals or induce bacterial resistance [14].

Indications and Duration of Prophylaxis

The indications and duration of prophylaxis depend on patient age and presence or absence of VUR. Antibiotic prophylaxis is recommended for patients with *(i)* UTI below 1-yr of age**,** while awaiting imaging studies, (*ii*) VUR (see ***Table* VIII**), (*iii*) frequent febrile UTI (3 or more episodes in a year) even if the urinary tract is normal [14, 15]. Antibiotic prophylaxis is not advised in patients with urinary tract obstruction (*e.g.*, posterior urethral valves), urolithiasis and neurogenic bladder, and in patients on clean intermittent catheterization.

Breakthrough UTI on Prophylactic Antibiotics

Breakthrough UTI results either from poor compliance or associated voiding dysfunction. The UTI should be treated with appropriate antibiotics. A change of the medication being used for prophylaxis is usually not necessary. There is no role for cyclic therapy, where the antibiotic used for prophylaxis is changed every 6-8 weeks.

Asymptomatic Bacteriuria

Asymptomatic bacteriuria is the presence of significant bacteriuria in the absence of symptoms of UTI. Its frequency is 1-2% in girls and 0.2% in boys [1]. Asymptomatic bacteriuria is a benign condition, which does not cause renal injury and requires no treatment. The organism isolated in most instances is *E. coli*, which is of low virulence. Eradication of these organisms is often followed by symptomatic infection with more virulent strains. Therapy of asymptomatic bacteriuria or antibiotic prophylaxis is not required [1].

The presence of asymptomatic bacteriuria in a patient previously treated for UTI should not be considered as recurrent UTI**.**

Vesicoureteric Reflux

VUR is seen in 40-50% infants and 30-50% children with UTI, and resolves with age. Its severity is graded using the International Study Classification from grade I to V, based on the appearance of the urinary tract on MCU [16]. Lower grades of reflux (grade I-III) are more likely to resolve. Secondary VUR is often related to bladder outflow obstruction, as with posterior urethral valves, neurogenic bladder or a functional voiding disorder.

The presence of moderate to severe VUR, particularly if bilateral, is an important risk factor for pyelonephritis and renal scarring, with subsequent risk of hypertension, albuminuria and progressive kidney disease. The risk of scarring is highest in the first year of life [17]. The presence of intrauterine VUR has been associated with renal hypoplasia or dysplasia [18]**.**

Therapy for Primary VUR

Over the last decade it has been increasingly recognized that not all children with VUR benefit

from diagnosis or treatment. In some patients the reflux is innocuous and self limiting. In others, VUR is accompanied with renal damage that has an onset during the intrauterine period with dysplastic kidneys at birth, where the treatment of VUR will not change the long term outcome [18]. There is a subset of children who would benefit from treatment; however, identifying this group of patients remains a challenge.

Conventional therapy for VUR includes antibiotic prophylaxis and surgical intervention [11, 19, 20]. A recent systematic review on patients with dilating reflux concluded that the outcomes following surgical repair *versus* prophylaxis were similar in terms of the number of breakthrough UTI and risk of renal scarring [20]. Experts recommend that the management of patients with VUR should depend on the patient age, grade of reflux and whether there are any breakthrough infections [11].

The proposed guidelines for management of VUR are outlined in ***Table* VIII.** It is recommended that patients should initially receive antibiotic prophylaxis while awaiting spontaneous resolution of VUR. A close follow up is required for occurrence of breakthrough UTI. Repeat imaging is required after 18-36 months in patients with grade III-V VUR. Radionuclide cystogram, with lower radiation exposure, has higher sensitivity for detecting reflux and is therefore preferred for follow-up evaluation. Since the risk of recurrent UTI and renal scarring is low after 4-5 years of age [11, 21], it is advised that prophylaxis be discontinued in children older than 5 years with normal bowel and voiding habits, even if mild to moderate reflux persists.

TABLE VIII MANAGEMENT OF VESICOURETERIC REFLUX

VUR grade	Management
Grades I and II	Antibiotic prophylaxis until 1 yr old. Restart antibiotic prophylaxis if breakthrough febrile UTI.
Grades III to V	Antibiotic prophylaxis up to 5 yr of age. Consider surgery if breakthrough febrile UTI.
	Beyond 5 yr: Prophylaxis continued if there is bowel bladder dysfunction.

While evidence from few studies suggests that the strategy of prompt diagnosis and treatment of UTI might be as effective as antibiotic prophylaxis [1,22], this approach requires validation in controlled trials. The clinician should discuss the benefits and risks of withholding antibiotic prophylaxis with the parents [19, 20].

Patients with grade III to V reflux may be offered surgical repair if they have breakthrough febrile UTI, if parents prefer surgical intervention to prophylaxis, or in patients who show deterioration of renal function [20,21]. An evaluation for voiding dysfunction (based on history, voiding diary) should be done before surgery. Antibiotic prophylaxis is continued for 6 months after surgical repair.

The availability of dextranomer/hyaluronic acid copolymer (Deflux) endoscopic treatment has been proposed as an alternative to surgical repair for patients with VUR [23]. While results are satisfactory in surgeons experienced with the procedure, a significant proportion of patients, particularly those with bowel bladder dysfunction, may show persistence and/or recurrence of reflux and progressive renal damage [24,25]. In view of limited prospective randomized controlled trials, the use of endoscopic correction is currently not recommended as first line therapy [11].

Screening of siblings and offspring

Reflux is inherited in an autosomal dominant manner with incomplete penetrance; 27% siblings and 35% offspring of patients show VUR [26]. Ultrasonography is recommended to screen for the presence of reflux. Further imaging is required if ultrasonography is abnormal [11, 26].

Long Term Follow-up

Patients with a renal scar (reflux nephropathy) are counseled regarding the need for early diagnosis and therapy of UTI and regular follow up. Physical growth and blood pressure should be monitored every 6-12 months, through adolescence. Investigations include urinalysis for proteinuria and estimation of blood levels of creatinine. Annual ultrasound examinations are done to monitor renal growth.

TABLE IX INDICATION FOR REFERRAL TO A PEDIATRIC NEPHROLOGIST

- Recurrent urinary tract infections
- Urinary tract infections in association with bowel bladder dysfunction
- Patients with vesicoureteric reflux
- Underlying urologic or renal abnormalities
- Children with renal scar, deranged renal functions, hypertension

Indications for a referral to a Pediatric Nephrologist

UTI can be effectively managed by the primary care physician. However because of their potential for renal parenchymal damage, scarring and subsequent chronic kidney disease, patients having risk factors that increase the likelihood of complications should be managed in collaboration with an expert (***Table* IX**).

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