Urinary tract infection and vesicoureteric reflux

Article · January 2017

DOI: 10.4103/jina.jina_6_17

CITATIONS
0

READS
141

3 authors, including:

Nitin Sharma
All India Institute of Medical Sciences, Raipur, India
36 PUBLICATIONS **126** CITATIONS
SEE PROFILE

Atul Jindal
All India Institute of Medical Sciences, Raipur, India
34 PUBLICATIONS **36** CITATIONS
SEE PROFILE

Review Article

Urinary Tract Infection and Vesicoureteric Reflux

Snehamayee Nayak, Nitin Sharma[1], Atul Jindal

Departments of Pediatrics and [1]Pediatric Surgery, All India Institute of Medical Sciences, Raipur, Chhattisgarh, India

Abstract

Urinary tract infection (UTI) is one of the common causes of hospital visit in infants and children. Vesicoureteral reflux (VUR) predisposes to UTI and renal scarring. VUR is usually diagnosed after an episode of UTI. VUR is the most common underlying etiology responsible for febrile UTIs or pyelonephritis in children. Along with the morbidity of pyelonephritis, long-term sequelae of recurrent renal infections include renal scarring, proteinuria, and hypertension. Treatment is directed toward the prevention of recurrent infection through the use of continuous antibiotic prophylaxis during a period of observation for spontaneous resolution or by surgical correction. In children, bowel and bladder dysfunction (BBD) plays a significant role in the occurrence of UTI and the rate of VUR resolution. Effective treatment of BBD leads to higher rates of spontaneous resolution and decreased risk of UTI.

Key words: Bowel bladder dysfunction, pyelonephritis, Urinary tract infection, vesicoureteral reflux

INTRODUCTION

Urinary tract infection (UTI) is one of the common causes of hospital visit in infants and children. The overall incidence of childhood UTI in girls and boys is 8% and 1%–2%, respectively.[1] The incidence is >2% in adolescent girls and young adults. In neonates and infants, the clinical features of UTI are usually nonspecific and require early diagnosis and prompt management as the risk of renal parenchymal damage is higher in them. Whereas in older children, usually specific symptoms of UTI appear and they can be diagnosed and managed early. Vesicoureteral reflux (VUR), a common urologic disorder, is usually diagnosed after an episode of UTI. In some cases, it is diagnosed by antenatal ultrasonography or by sibling screening.

Address for correspondence: Dr. Atul Jindal,
Department of Pediatrics, All India Institute of Medical Sciences,
Raipur - 492 099, Chhattisgarh, India.
E-mail: dratuljindal@gmail.com

Access this article online	
Quick Response Code:	Website: www.journal-ina.com
	DOI: 10.4103/jina.jina_6_17

DEFINITION

UTI is defined as significant growth of a single pathogenic species in urine culture in the presence of symptoms. The diagnosis of UTI is made on the basis of quantitative urine culture results in addition to evidence of pyuria and/or bacteriuria. In most instances, an appropriate threshold to consider bacteriuria "significant" in infants and children is the presence of at least 50,000 colony-forming units (CFUs)/mL of a single urinary pathogen.[2] Diagnosis of positive urine culture results also varies according to the method of collection. Any growth of pathogen in suprapubic aspiration (SPA) sample has the probability of 99% of UTI. Similarly 50,000 CFU/mL in urethral catheterization and 100,000 CFU/mL in midstream clean catch sample suggest UTI.

PATHOGENESIS

Escherichia coli is the predominant pathogen in childhood UTI, identified in 90% of girls and in 80% of boys at the first

How to cite this article: Nayak S, Sharma N, Jindal A. Urinary tract infection and vesicoureteric reflux. J Integr Nephrol Androl 2017;4:39-46.

episode of UTI.[3-5] The most prevalent pathogens in several recent pediatric studies were *E. coli* (54%–67%), *Klebsiella* (6%–17%), *Proteus* (5%–12%), *Enterococcus* (3%–9%), and *Pseudomonas* (2%–6%).[6,7] In uncircumcised boys, the prepucial area is colonized by non-*E. coli* Gram-negative bacilli such as *Klebsiella*, enterococci, and *Proteus*. Hence, in males, the prevalence of these organisms is higher. CONS, Haemophilus influenza, and Group B streptococcus can cause UTI in children with renal anomalies or compromised immune system. Children with foreign bodies in urinary system can have *Candida* UTI. Uropathogenic *E. coli* (UPEC) has the ability to attach to urinary epithelium, invade it, release toxins, and cause inflammation. Moreover, it also impairs flushing action. UPEC forms bacterial colonies inside uroepithelium and hence not invaded by host immune system and antibiotics resulting in recurrent UTI in the host. Normally, bacteria in the bladder are cleared within 2–3 days by antimicrobial action of urine, intrinsic mucosal defense, and proper voiding. As far as host immunity is concerned, urinary proteins such as mucin and Tamm–Horsfall protein trap the microbe and prevent adhesion. Risk of UTI increases when bladder emptying is inadequate, increased bladder pressure or intrinsic/extrinsic obstruction is present. When the pathogen adheres to mucosal epithelium and invades it, host inflammatory response is activated by cytokines such as interleukin (IL)-1, tumor necrosis factor-α, IL-6, and IL-8 produced by activation of toll-like receptors. In pyelonephritis, renal damage occurs more by host inflammatory response and to some extent direct injury by pathogen.

CLINICAL FEATURES

Clinical presentations of UTI are variable, hence a strong suspicion of UTI should be kept in mind while managing febrile infant and children. In neonates, UTI is usually a part of septicemia and presents with fever, vomiting, lethargy, jaundice, and seizures. In infants and young children, it may present as recurrent fever, diarrhea, vomiting, abdominal pain, and poor weight gain. Older children and adolescents present with dysuria, frequency, urgency, enuresis, pain abdomen, and flank pain. Presence of high fever, vomiting, and systemic toxicity usually indicates upper UTI and warrants prompt treatment.

DIAGNOSIS

Both urine microscopy and urine culture are indicated in the diagnosis of UTI. Leukocyte esterase test and nitrite test are the other modalities to detect UTI.

Sample collection

Midstream clean catch sample after washing the genital area with soap and water is acceptable in toilet-trained children for culture. Urine sample should be processed immediately, and if delay in processing is anticipated, it should be stored in refrigerator and transported in an ice pack. In infants and young children, catheterized specimen, SPA specimen, should be used for culture.

Urine microscopy

The standard method of assessing pyuria is centrifugation of the urine and microscopic analysis, with a threshold of 5 WBCs per high-power field. In uncentrifuged urine, 10 WBC per μl is sufficient to diagnose pyuria.[8] Urinalysis cannot substitute for urine culture to document the presence of UTI but needs to be used in conjunction with culture. Absence of pyuria in UTI is rare. However, the reverse can be true in glomerulonephritis, high fever, physical exercise, renal calculi, and foreign body in urinary tract. Significant bacteriuria in the absence of pyuria can occur in asymptomatic bacteriuria, contaminated specimen. Presence of pyuria distinguishes true UTI from asymptomatic bacteriuria. The presence of bacteria in a fresh, Gram-stained specimen of uncentrifuged urine correlates with 10^5 CFUs per mL in culture.[9] "Enhanced urine analysis" comprising pyuria detected by 10 WBC in uncentrifuged urine with Gram staining of fresh uncentrifuged sample showing at least 1 Gram-negative rod in 10 oil immersion fields has greater sensitivity, specificity, and positive predictive value than standard urinalysis.[6]

Urine dipstick test

At present, two rapid diagnostic tests having clinical significance in UTI are urine leukocyte esterase test and urinary nitrite test. The sensitivity of leukocyte esterase test is 83% (67%-94%) and specificity is 78% (64%-92%).[10] Urinary nitrite test detects nitrites released by Gram-negative enteric bacteria from dietary nitrates in urine. Conversion of dietary nitrates into nitrites by pathogens requires at least 4 h of contact period in urinary bladder. Sensitivity of this test is 53% (15%-82%) and specificity is 98% (90%-100%).[10] The performance characteristics of both leukocyte esterase and nitrite tests vary according to the definition used for positive urine culture results, the age and symptoms of the population being studied, and the method of urine collection.

Urine culture

Midstream clean catch urine sample in toilet-trained children and catheterized sample or SPA sample in infants are accepted for urine culture. Cultures of urine specimens collected in a bag applied to the perineum have an unacceptably high false-positive rate and are valid only when they yield negative results. Urine culture should be sent in febrile infants before starting antibiotics.

If a clinician has a high suspicion of UTI in febrile infant, urine sample (catheterized or SPA) should be collected and

empirical antibiotic should be started. Another option is to collect urine in most convenient way possible (bag attached to perineal area) and send urine analysis. If fresh urine analysis suggests UTI (by microscopy, leukocyte esterase, and nitrite test), catheterized/SPA sample should be collected for culture and antibiotics should be started. If urine analysis is negative for UTI, invasive procedures could be avoided.[10]

TREATMENT

All neonates and infants <3 months with suspected UTI should be treated with intravenous antibiotics pending culture reports. Antibiotics should be administered as per the local prevalence of pathogens and their antibiotic sensitivity. Final antibiotic choice should be based on culture and sensitivity results. Pediatric data from North America and Europe show significant antimicrobial resistance rates for *E. coli*: ampicillin (38%–65%), amoxicillin/clavulanic acid (7%–43%), and cotrimoxazole (8%–35%).[7] For older children, and those with uncomplicated UTI, oral antibiotic for 7–10 days is sufficient. However, a Cochrane systematic review shows that for acute cystitis, short-course (2–4 days) oral antibiotic is also effective.[11]

In approximately 75% of children whose first infection occurs during infancy, and in about 40% of girls and 30% of boys presenting after 1 year, recurrent UTI may develop.[12] Risk factors for recurrence of UTI are presence of dilating VUR, family history of UTI, infrequent voiding, and inadequate fluid ingestion. Long-term antibiotic prophylaxis has been recommended to prevent recurrent UTI in high-risk conditions such as high-grade VUR. A Cochrane database systematic review published in 2011 included 12 studies and concluded that long-term antibiotics appear to reduce the risk of repeat symptomatic UTI in susceptible children, but the benefit is small and must be considered together with the increased risk of microbial resistance.[12] Multiple studies on the effect of long-term antibiotic prophylaxis on the prevention of recurrent UTI in VUR have been done. The Swedish reflux trial compared the effect of antibiotic prophylaxis, endoscopic injection, and no prophylaxis in 203 children with a median age group of 21 months and concluded that antibiotic prophylaxis reduced the rate of UTI recurrence and renal scarring in girls only.[13,14] The RIVUR study enrolled 607 children with a median age of 12 months, with VUR Grade I-V, and a follow-up period of 2 years concluded that the proportion of symptomatic febrile UTI rate is reduced in prophylaxis group compared to placebo group with a relative risk of 0.55% (0.38–0.78). However, the frequency of renal scarring is same in both groups.[15,16]

Imaging in urinary tract infection

Protocol for imaging after an episode of UTI is a very controversial topic and has been discussed many a times by various authors. The aim of imaging is to detect treatable conditions early, intervene quickly, and to prevent long-term sequelae. Imaging can provide information on potential urinary tract malformations, Vesicoureteral reflux (VUR), or obstructive uropathies such as pelvic-ureteric junction obstruction, megaureter, and posterior urethral valve. It also helps in detecting the potential damage occurring in kidneys following an episode of UTI.

As per the National Institute for Health and Clinical Excellence (NICE) guidelines, following are the risk factors for having major malformation and resultant renal damage following UTI,[17] and these features are suggestive of atypical UTI.

i. Children with recurrent UTI
ii. Impaired urine flow
iii. Palpable mass in the abdomen
iv. Serious septic presentation
v. Bacteremia
vi. Increased serum creatinine
vii. Slow response to treatment – no notable improvement within 48 h
viii. Infection with non-*E. coli* bacteria
ix. Any prenatal urinary tract finding.

According to the NICE guidelines, for infants below 6 months with first episode of UTI, renal bladder ultrasonography (RBUS) should be done within 6 weeks of infection. Those with atypical or recurrent UTI, along with RBUS during acute infection, voiding cystourethrogram (VCUG) and Tc-99 m dimercaptosuccinic acid (DMSA) scan should be done 4–6 months after infection. For children in the age group of 6 months–3 years with first episode of UTI, no investigations are indicated. For those children with recurrent and atypical UTI, RBUS should be done within 6 weeks followed by DMSA scan in 4–6 months. Table 1 shows various imaging to be carried out in children as per the NICE guideline.

The American Academy of Pediatrics (AAP) recommends RBUS in all febrile infants with first episode of UTI. RBUS should be done within 2–3 days if disease severity is more or responding poorly to treatment. If response to treatment is good, RBUS can be done within 6 weeks to avoid false-positive reporting of hydronephrosis during acute infection. VCUG is indicated if RBUS 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.[10]

Table 1: Imaging to be carried out in children as per the National Institute for Health and Clinical Excellence guideline

Age	<6 months			6 months-3 years			>3 years		
	Typical responsive UTI	Atypical UTI	Recurrent UTI[a]	Typical responsive UTI	Atypical UTI	Recurrent UTI	Typical responsive UTI	Atypical UTI	Recurrent UTI
RBUS	Within 6 weeks	Acute infection	Acute infection	No	Acute infection[c]	Within 6 weeks	No	Acute infection	Within 6 weeks
VCUG	No[b]	Yes	Yes	No	No	No	No	No	No
DMSA	No	Yes	Yes	No	Yes	Yes	No	No	Yes

[a]Recurrent UTI - two or more episodes of UTI with acute pyelonephritis/upper UTI OR one episode of UTI with acute pyelonephritis/upper UTI plus one or more episode of UTI with cystitis/lower UTI OR three or more episodes of UTI with cystitis/lower UTI, [b]VCUG is indicated if RBUS is abnormal, [c]In an infant with non-E. coli UTI responding well to antibiotics and with no other features of atypical infection, RBUS can be requested within 6 weeks. RBUS: Renal bladder ultrasonography, VCUG: Voiding cystourethrogram, DMSA: Dimercaptosuccinic acid, E. coli: Escherichia coli, UTI: Urinary tract infection

The European Association of Urology (EAU) and European Society of Pediatric Urology (ESPU) guidelines recommend that, in febrile infants with UTI, VCUG should be done in addition to RBUS.[18]

In contrast, the European Society of Pediatric Radiology has recommended a "top-down approach," i.e., in children with UTI, initial evaluation should be done by RBUS and DMSA scan. If renal involvement is identified, VCUG is performed.[19] Advantages of this approach include decreased urethral catheterizations, decreased ionizing radiation to the gonads, and decreased detection of "clinically insignificant" VUR not involving the kidneys. However, a recent meta-analysis has shown that DMSA is less effective in detecting high-grade VUR, with sensitivity and specificity of only 79% and 53%, respectively.[20]

VESICOURETERAL REFLUX

VUR is the abnormal retrograde flow of urine from bladder to one or both ureters and kidneys due to abnormality in the submucosal ureteric tunnel and ureterovesical junction. According to the International Reflux Study, VUR is classified into five grades depending on the degree of reflux into ureters and kidneys. The incidence of VUR is estimated to be 0.4%–1.8% of the pediatric population who have not presented with UTI, and 10%–40% in patients who have presented with UTI.[21] VUR can be primary or secondary to increased pressure in the bladder. Primary VUR can be explained by abnormal ureteric budding, dysfunctional interaction between the ureteric bud and metanephric mesenchyme, or both. There is a genetic basis of primary VUR and the nonsyndromic primary VUR gene locus localized to chromosome 1.[22] In asymptomatic screening studies, approximately 30%–35% of siblings were found to have VUR, and the incidence of VUR in offspring of parents with the condition was 35.7%.[23] Secondary reflux occurs when there is an anatomical defect and/or an imbalance in pressure on either side of vesicoureteric junction, which is seen in conditions such as voiding dysfunction, posterior urethral valves, ureteral diverticulum, and neurogenic bladder.

NATURAL HISTORY OF VUR

Low-grade primary VUR and VUR with nondilated ureters may resolve spontaneously without treatment. In a prospective 5-year follow-up study of children younger than 5 years of age who had primary VUR and radiographically normal kidneys, Grade I VUR resolved in 82%, Grade II in 80%, and Grade III in 46% of the ureters.[24] The resolution rates for Grade IV and V VUR over a 5-year period were approximately 30% and 13%, respectively.[25] Grades I through III VUR resolved at a rate of 13%/year for the first 5 years of follow-up and 3.5% per year during subsequent years; Grades IV and V VUR resolved at a rate of 5% per year.[26] The major complication associated with VUR is reflux nephropathy and renal scarring that later on may result in proteinuria, hypertension, and eventually end-stage renal disease. Hence, the purpose of diagnosis and treatment of VUR is prevention of renal scarring. UTI predisposes to acute pyelonephritis in cases of VUR and may result in renal scarring. In few cases, renal scarring may be noticed at the time of diagnosis of VUR without UTI. Such cases are usually dysplastic kidneys, and the VUR may not have any role in renal tissue damage.

DIAGNOSIS OF VUR

VUR is commonly diagnosed among infants with UTI (10%–40%). In cases where prenatal hydronephrosis is identified by ultrasonography, the prevalence of VUR is 16% (7%–35%).[23] Thorough history including family history, assessment of bowel and bladder dysfunction (BBD), blood pressure measurement, urinalysis and urine culture, and measurement of serum creatinine level should be evaluated in patients with bilateral renal parenchymal abnormality and suspected VUR. VCUG is the diagnostic modality of choice for VUR. Various imaging modalities and their use for diagnosis of VUR in cases of febrile UTI have been discussed

previously. Recommendation by the NICE, AAP, European Urological Association, and European Society of Paediatric Research has been discussed. Depending on the degree of suspicion, availability of tests, and interpretation of tests, imaging modality should be chosen. Another imaging test that has been used to diagnose VUR is voiding urosonography (VUS), which entails the intravesical administration of US contrast agents such as Levovist microbubbles.[27] VUS may be useful for follow-up examinations and for screening high-risk patients.[28] Whenever VUR is diagnosed, a baseline DMSA scan should be done for comparison with successive scans for follow-up.

Magnetic resonance urography is another imaging modality to detect renal scarring with the advantage of providing a full anatomical description of the urinary tract and no risk of radiation exposure during recurrent scanning in follow-up.

RBUS is advised for screening of siblings of an index case of VUR, and depending on RBUS findings, further workup is planned.

TREATMENT OF VUR

The primary aim of treatment of VUR is preservation of renal function by preventing pyelonephritis and to minimize morbidity. Three modalities of treatment advocated for VUR are as follows:

i. Conservative approach
ii. Surgical approach
    - Endoscopic surgery
    - Conventional surgery.

Conservative approach

Conservative approach includes watchful waiting with intermittent or continuous antibiotic prophylaxis (CAP), bladder rehabilitation, and bowel management in children with BBD.

Continuous antibiotic prophylaxis

Multiple randomized controlled trials have been done to find the effect of antibiotic prophylaxis on the prevention of recurrent febrile UTI in VUR. In the PRIVENT study, 576 children were randomized to receive trimethoprim-sulfamethoxazole or placebo. Investigators found a 6% absolute reduction in UTI in those receiving prophylaxis (39% relative reduction; 95% confidence interval [CI], 7–60) irrespective of patient's gender, age, and severity of VUR.[29] In the Swedish reflux trial as described previously, those children who did not receive antibiotic prophylaxis had 3 times more chance of developing febrile UTI, and CAP was found to be more effective in girls and those with higher grades of reflux.[13,14] Garin *et al.* studied 113 children with VUR who were randomized to prophylaxis with trimethoprim-sulfamethoxazole/nitrofurantoin and no prophylaxis group. There was no difference in new renal scarring.[30] Roussey-Kesler *et al*. also found similar results in their randomized controlled trial.[31] Montini *et al*. and Pennesi *et al*. followed up 128 and 100 children, respectively, with VUR and found no significant difference in the occurrence of recurrent febrile UTI and renal scarring.[32,33] However, in the above studies, the sample size was small, and in most cases, low-grade VUR was present. The RIVUR study involved 607 children (558 girls and 49 boys) with Grade I–IV vesicoureteric reflux. Recurrent UTIs developed in 39 (13%) of 302 children who received prophylaxis compared with 72 (24%) of 305 who received placebo (relative risk 0.55, 95% CI 0.38–0.78). However, the rate of renal scarring was not different in both groups (12% *vs*. 10%). Hence, antibiotic prophylaxis may reduce the risk of recurrent febrile UTI with a slight risk of UTI by resistant organisms in children with higher grades of reflux.

Treatment of bowel and bladder dysfunction

BBD may increase the chance of recurrent UTI and reduce the probability of resolution of VUR. Hence, it should be managed aggressively. Although no prospective randomized trial has shown any benefit in VUR, it has theoretical benefit in conservative management of VUR. Possible options include behavioral therapy, biofeedback (particularly for school-age children), anticholinergic medications, alpha blockade, and treatment of constipation.

Surgical treatment

Surgical treatment includes ureteric reimplantation or injection of bulking agent below ureteric orifice.

Endoscopic treatment

Endoscopic injection of periurethral bulking agents was first described by Matouschek in 1981.[34] In 1991, O'Donnell and Puri endoscopically injected Polytef (50% suspension of Teflon particles in glycerol) for the treatment of VUR.[34] However, the adverse effects associated with it were migration of Teflon particles into lymph nodes, spleen, lungs, cerebral hemispheres, etc., which resulted in its replacement by other agents. Macroplastique is another endoscopic injectable agent composed of 40% vulcanized polydimethylsiloxane particles in a 60% water-soluble carrier medium containing low molecular weight polyvinylpyrrolidone.[35] Advantage of Macroplastique is chance of migration is less as it contain less amount of smaller particles. The subureteric Teflon injection by O'Donnell and Puri was supplanted by the hydrodistention implantation technique by Kirsch *et al*. in 2004.[36] At present, the most commonly used Food and Drug Administration-approved agent for endoscopic injection is dextranomer/hyaluronic

(Dx/HA) acid. Elder *et al*. analyzed the data of 5527 patients with VUR and demonstrated that, following single treatment, the reflux resolution rate (by ureter) for Grades I and II reflux was 78.5%, Grade III was 72%, Grade IV was 63%, and Grade V was 51%.[37] A meta-analysis by Routh *et al*. concluded that the overall per-ureter Dx/HA success rate was 77% after 3 months, although success rates varied widely among studies.[38] Increased VUR grade negatively affected success rates, whereas patient age and injected Dx/HA volume were not significantly associated with treatment outcome after adjustment for VUR grade.[39] Although the short-term follow-up following endoscopic injection shows favorable results, long-term follow-up may differ in outcome as there are chances of recurrence of VUR. Verma *et al*. have studied the plasma renin activity (PRA) that correlates with persistence/recurrence of VUR and found that, in Grades I and II, VUR level of PRA remains persistently low, whereas in higher grades of VUR after endoscopic injection, its level falls, reaches a nadir, and then increases indicating recurrence.[40] Studies have shown the various risk factors for recurrence of VUR following endoscopic injection as history of BBD, previous recurrent UTI prior to treatment, and presence of renal scarring prior to injection.[41] The Swedish reflux trial has compared antibiotic prophylaxis, endoscopic treatment, and regular surveillance of patients without treatment. No significant differences could be found between the Dx/HA acid group and either the antimicrobial prophylaxis or surveillance groups for recurrent febrile UTIs or further renal scarring after 2 years. Since there is a high level of heterogeneity in studies evaluating the efficacy of endoscopic injection, its use is controversial.

Conventional surgical treatment

The surgical management of VUR is ureteric reimplantation. This aims at progressing the ureteric orifice in the bladder to a new space with creation of a subcutaneous tunnel. The size of the ureter determines the need for tapering which can be done by imbrications or excision. Various approaches are available which include open surgery, laparoscopic surgery, and robotic surgery. It is the most effective modality of treatment with resolution rate as high as 95% and reduces the risk of febrile UTI by 57%.[42] Surgical reimplantation of ureters is reserved for high-grade reflux, failure of previous endoscopic corrections, and complex cases.

The EAU[18] and ESPU recommend children <1 year of age with Grades I to III VUR without febrile UTI should be under regular follow-up without antibiotic prophylaxis. Infants without a history of febrile UTI and VUR Grades IV and V should receive CAP, and surgical intervention should be considered if breakthrough UTI occurs. Children between 1 and 5 years of age with/without febrile UTI with any grade of VUR should receive CAP. BBD should be managed appropriately in children with lower urinary tract symptoms. In children aged 1–5 years with febrile UTI and Grades IV-V VUR, surgery may be considered as the first line of treatment. Persistent VUR and breakthrough UTI are indications for surgery in this age group. Children >5 years of age with any grade of VUR without febrile UTI should be on CAP and surgery is indicated in cases of persistent VUR and breakthrough UTI. If febrile UTI occurs in children aged >5 years, surgery may be considered as the first line of treatment. EAU guideline has been summarized in Table 2.

The American Urological Association (AUA) recommends CAP in children <1 year of age with a history of febrile UTI and any grade of VUR.[43] In infants diagnosed by family screening of VUR or antenatal USG without febrile UTI and Grades I or II VUR, antibiotic prophylaxis may be offered, but for those with Grade III to V VUR, antibiotic prophylaxis is recommended. Circumcision may be considered in boys to avoid the risk of recurrent UTI. In children older than 1 year of age with febrile UTI and BBD, BBD should be managed first along with CAP before any endoscopic treatment or surgical intervention. For those children with febrile UTI without BBD, CAP may be offered. Observational management without CAP, with prompt initiation of sensitive antibiotic therapy for UTI, may be considered for children over 1 year of age with VUR in the absence of BBD, recurrent febrile

Table 2: The European Association of Urology guidelines regarding the management of vesicoureteral reflux as per grades

Age (years)	Febrile UTI	VUR grade	LUTS	Treatment	Indication of surgery
<1	No	I-III	Not applicable	Observation	Breakthrough UTI
	No	IV-V		CAP	
	Yes	I-V		CAP	
1-5	Yes/no	I-V	No	CAP	Persistent VUR and breakthrough UTI
	Yes	I-III	Yes	CAP + management of BBD	
	Yes	IV-V	Yes	CAP *vs*. surgery and management of BBD	
>5	No	I-V	No	CAP	
	Yes	I-V	Yes/no	CAP *vs*. surgery and management of BBD	

UTI: Urinary tract infection, VUR: Vesicoureteral reflux, LUTS: Lower urinary tract symptoms, CAP: Continuous antibiotic prophylaxis, BBD: Bowel and bladder dysfunction

UTIs, or renal cortical abnormalities. Surgical intervention in infants is indicated in breakthrough UTI episodes. In older children, surgical intervention may be considered as an initial mode of treatment.

FOLLOW-UP OF CASES WITH VUR

Children with VUR irrespective of age and severity of VUR should be monitored regularly by growth monitoring, blood pressure measurement, clinical examination, and laboratory investigations with urine analysis, serum creatinine level, and appropriate mode of renal imaging. The goal of monitoring is to identify UTI and early signs of renal impairment. This monitoring should continue till VUR resolves or becomes clinically insignificant. In children with VUR, general evaluation, BP monitoring, and growth evaluation with urine analysis should be done yearly. Ultrasonography is recommended for every 12 months to monitor renal growth and detect any parenchymal scarring.[43] VCUG or radionuclide cystogram should be done for every 12–24 months, and longer interval should be preferred in higher grades of reflux as chances of spontaneous resolution are less in these patients. DMSA scanning is indicated in children with VUR who have abnormal renal ultrasound, higher probability of renal scarring due to breakthrough UTI, or elevated level of serum creatinine.

Breakthrough UTI (BT-UTI) may be expected in up to 20% of children with VUR on CAP. Occurrence of BT-UTI indicates ineffectiveness of current treatment and need for upgrading treatment. Based on grade of VUR, risk of renal scarring, presence of BBD, and parental preference surgical modality can be opted for treatment. The AUA recommends that patients receiving CAP with a febrile BT-UTI should be considered for open surgical ureteral reimplantation or endoscopic injection of bulking agents for intervention with curative intent. In patients receiving CAP with a single febrile BT-UTI and no evidence of preexisting or new renal cortical abnormalities, changing to an alternative antibiotic agent is an option prior to intervention with curative intent. If those patients not on CAP develop UTI, CAP should be initiated.

After endoscopic injection of bulking agent, VCUG should be done to look for persistent VUR. Ultrasonography is advised after both endoscopic injection and open surgery to rule out postoperative complications such ass obstruction of ureters. Growth monitoring and measurement of blood pressure and urine analysis are recommended annually after definitive surgical/endoscopic treatment till adolescence in children who had renal cortical abnormality and it is optional in children who had normal renal ultrasound and DMSA scan. After definitive surgical management, if BT-UTI occurs, clinicians should look for recurrence of reflux and BBD and manage accordingly.

VUR may be present in 8%–38% of patients diagnosed with unilateral or bilateral antenatal hydronephrosis (ANH).[44] A systematic review by Phan *et al*. suggests that severity of ANH does not correlate with the degree of reflux, and severe VUR may have normal postnatal USG.[45] VCUG is recommended at 4–6 weeks' age in cases of moderate-to-severe ANH (SFU Grade 3–4 or renal APD > 10 mm) with dilated ureters after ruling out lower urinary tract obstruction.[46] As per the ISPN recommendation, all infants diagnosed with VUR detected by ANH should be on CAP. The preferred antibiotic for prophylaxis is cephalexin during the first 3 months of life and cotrimoxazole and nitrofurantoin later on. Decision regarding further intervention and surgical management would depend on follow-up clinical presentations, laboratory findings, and results of sequential ultrasonography.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

REFERENCES

1. Hellström A, Hanson E, Hansson S, Hjälmås K, Jodal U. Association between urinary symptoms at 7 years old and previous urinary tract infection. Arch Dis Child 1991;66:232-4.
2. Hoberman A, Wald ER, Reynolds EA, Penchansky L, Charron M. Pyuria and bacteriuria in urine specimens obtained by catheter from young children with fever. J Pediatr 1994;124:513-9.
3. Mårild S, Jodal U. Incidence rate of first-time symptomatic urinary tract infection in children under 6 years of age. Acta Paediatr 1998;87:549-52.
4. Hay AD, Whiting P, Butler CC. How best to diagnose urinary tract infection in preschool children in primary care? BMJ 2011;343:d6316.
5. Zorc JJ, Kiddoo DA, Shaw KN. Diagnosis and management of pediatric urinary tract infections. Clin Microbiol Rev 2005;18:417-22.
6. Gökçe I, Alpay H, Biyikli N, Ozdemir N. Urinary tract pathogens and their antimicrobial resistance patterns in Turkish children. Pediatr Nephrol 2006;21:1327-8.
7. Zhanel GG, Hisanaga TL, Laing NM, DeCorby MR, Nichol KA, Palatnick LP, *et al*. Antibiotic resistance in outpatient urinary isolates: Final results from the North American Urinary Tract Infection Collaborative Alliance (NAUTICA). Int J Antimicrob Agents 2005;26:380-8.
8. Hoberman A, Wald ER, Reynolds EA, Penchansky L, Charron M. Is urine culture necessary to rule out urinary tract infection in young febrile children? Pediatr Infect Dis J 1996;15:304-9.
9. Wald ER, Feigin RD, Chery JD, Demmier GJ. Cystitis and pyelonephritis. Textbook of Pediatric Infectious Diseases. Philadelphia, PA: Saunders; 2004. p. 541-55.
10. Subcommittee on Urinary Tract Infection, Steering Committee on Quality Improvement and Management, Roberts KB. Urinary

tract infection: Clinical practice guideline for the diagnosis and management of the initial UTI in febrile infants and children 2 to 24 months. Pediatrics 2011;128:595-610.
11. Michael M, Hodson EM, Craig JC, Martin S, Moyer VA. Short versus standard duration oral antibiotic therapy for acute urinary tract infection in children. Cochrane Database Syst Rev 2003;1:CD003966.
12. Williams G, Craig JC. Long-term antibiotics for preventing recurrent urinary tract infection in children. Cochrane Database Syst Rev 2011;3:CD001534.
13. Brandström P, Esbjörner E, Herthelius M, Holmdahl G, Läckgren G, Nevéus T, *et al.* The Swedish reflux trial in children: I. Study design and study population characteristics. J Urol 2010;184:274-9.
14. Holmdahl G, Brandström P, Läckgren G, Sillén U, Stokland E, Jodal U, *et al.* The Swedish reflux trial in children: II. Vesicoureteral reflux outcome. J Urol 2010;184:280-5.
15. RIVUR Trial Investigators. Antimicrobial prophylaxis for children with vesicoureteral reflux. N Engl J Med 2014;2014:2367-76.
16. Carpenter MA, Hoberman A, Mattoo TK, Mathews R, Keren R, Chesney RW, *et al.* The RIVUR trial: Profile and baseline clinical associations of children with vesicoureteral reflux. Pediatrics 2013;132:e34-45.
17. Price E, Pallett A, Gilbert RD, Williams C. Microbiological aspects of the UK National Institute for Health and Clinical Excellence (NICE) guidance on urinary tract infection in children. J Antimicrob Chemother 2010;65:836-41.
18. Riedmiller H, Androulakakis P, Beurton D, Kocvara K, Gerharz E. EAU guidelines on pediatric urology. European Urology. 2001;40:589-99.
19. Riccabona M, Avni FE, Blickman JG, Dacher JN, Darge K, Lobo ML, *et al.* Imaging recommendations in paediatric uroradiology: Minutes of the ESPR workgroup session on urinary tract infection, fetal hydronephrosis, urinary tract ultrasonography and voiding cystourethrography, Barcelona, Spain, June 2007. Pediatr Radiol 2008;38:138-45.
20. Mantadakis E, Vouloumanou EK, Georgantzi GG, Tsalkidis A, Chatzimichael A, Falagas ME. Acute Tc-99m DMSA scan for identifying dilating vesicoureteral reflux in children: A meta-analysis. Pediatrics 2011;128:e169-79.
21. Sargent MA. What is the normal prevalence of vesicoureteral reflux? Pediatr Radiol 2000;30:587-93.
22. Feather SA, Malcolm S, Woolf AS, Wright V, Blaydon D, Reid CJ, *et al.* Primary, nonsyndromic vesicoureteric reflux and its nephropathy is genetically heterogeneous, with a locus on chromosome 1. Am J Hum Genet 2000;66:1420-5.
23. Skoog SJ, Peters CA, Arant BS Jr., Copp HL, Elder JS, Hudson RG, *et al.* Pediatric vesicoureteral reflux guidelines panel summary report: Clinical practice guidelines for screening siblings of children with vesicoureteral reflux and neonates/infants with prenatal hydronephrosis. J Urol 2010;184:1145-51.
24. Arant BS Jr. Medical management of mild and moderate vesicoureteral reflux: Follow up studies of infants and young children. A preliminary report of the Southwest Pediatric Nephrology Study Group. J Urol 1992;148:1683-7.
25. McLorie GA, McKenna PH, Jumper BM, Churchill BM, Gilmour RF, Khoury AE. High grade vesicoureteral reflux: Analysis of observational therapy. J Urol 1990;144:537-40.
26. Schwab CW Jr., Wu HY, Selman H, Smith GH, Snyder HM 3rd, Canning DA. Spontaneous resolution of vesicoureteral reflux: A 15-year perspective. J Urol 2002;168:2594-9.
27. Calliada F, Campani R, Bottinelli O, Bozzini A, Sommaruga MG. Ultrasound contrast agents: Basic principles. Eur J Radiol 1998;27 Suppl 2:S157-60.
28. Darge K. Voiding urosonography with US contrast agent for the diagnosis of vesicoureteric reflux in children: An update. Pediatr Radiol 2010;40:956-62.
29. Craig JC, Simpson JM, Williams GJ, Lowe A, Reynolds GJ, McTaggart SJ, *et al*. Antibiotic prophylaxis and recurrent urinary tract infection in children. N Engl J Med 2009;361:1748-59.
30. Garin EH, Olavarria F, Garcia Nieto V, Valenciano B, Campos A, Young L. Clinical significance of primary vesicoureteral reflux and urinary antibiotic prophylaxis after acute pyelonephritis: A multicenter, randomized, controlled study. Pediatrics 2006;117:626-32.
31. Roussey-Kesler G, Gadjos V, Idres N, Horen B, Ichay L, Leclair MD, *et al*. Antibiotic prophylaxis for the prevention of recurrent urinary tract infection in children with low grade vesicoureteral reflux: Results from a prospective randomized study. J Urol 2008;179:674-9.
32. Montini G, Rigon L, Zucchetta P, Fregonese F, Toffolo A, Gobber D, *et al.* Prophylaxis after first febrile urinary tract infection in children? A multicenter, randomized, controlled, noninferiority trial. Pediatrics 2008;122:1064-71.
33. Pennesi M, Travan L, Peratoner L, Bordugo A, Cattaneo A, Ronfani L, *et al.* Is antibiotic prophylaxis in children with vesicoureteral reflux effective in preventing pyelonephritis and renal scars? A randomized, controlled trial. Pediatrics 2008;121:e1489-94.
34. O'Donnell B, Puri P. Treatment of vesicoureteric reflux by endoscopic injection of Teflon. Br Med J (Clin Res Ed) 1984;289:7-9.
35. Soto Beauregard C, Rivilla Parra F, García Casillas J. Suburethral polydimethylsiloxane injection for the endoscopic treatment of vesicoureteral reflux. An Pediatr (Barc) 2005;62:543-7.
36. Kirsch AJ, Perez-Brayfield M, Smith EA, Scherz HC. The modified sting procedure to correct vesicoureteral reflux: Improved results with submucosal implantation within the intramural ureter. J Urol 2004;171:2413-6.
37. Elder JS, Diaz M, Caldamone AA, Cendron M, Greenfield S, Hurwitz R, *et al.* Endoscopic therapy for vesicoureteral reflux: A meta-analysis. I. Reflux resolution and urinary tract infection. J Urol 2006;175:716-22.
38. Routh JC, Inman BA, Reinberg Y. Dextranomer/hyaluronic acid for pediatric vesicoureteral reflux: Systematic review. Pediatrics 2010;125:1010-9.
39. Bajpai M, Verma A, Panda SS. Endoscopic treatment of vesico-ureteral reflux: Experience of 99 ureteric moieties. J Indian Assoc Pediatr Surg 2013;18:133-5.
40. Verma A, Panda SS, Bajpai M. Role of endoscopic treatment of vesico-ureteric reflux in downgrading renin angiotensin system activation. J Pediatr Urol 2014;10:386-90.
41. Sedberry-Ross S, Rice DC, Pohl HG, Belman AB, Majd M, Rushton HG. Febrile urinary tract infections in children with an early negative voiding cystourethrogram after treatment of vesicoureteral reflux with dextranomer/hyaluronic acid. J Urol 2008;180 4 Suppl:1605-9.
42. Elder JS, Peters CA, Arant BS Jr., Ewalt DH, Hawtrey CE, Hurwitz RS, *et al.* Pediatric vesicoureteral reflux guidelines panel summary report on the management of primary vesicoureteral reflux in children. J Urol 1997;157:1846-51.
43. Peters CA, Skoog SJ, Arant BS Jr., Copp HL, Elder JS, Hudson RG, *et al.* Summary of the AUA guideline on management of primary vesicoureteral reflux in children. J Urol 2010;184:1134-44.
44. Lee RS, Cendron M, Kinnamon DD, Nguyen HT. Antenatal hydronephrosis as a predictor of postnatal outcome: A meta-analysis. Pediatrics 2006;118:586-93.
45. Phan V, Traubici J, Hershenfield B, Stephens D, Rosenblum ND, Geary DF. Vesicoureteral reflux in infants with isolated antenatal hydronephrosis. Pediatr Nephrol 2003;18:1224-8.
46. Sinha A, Bagga A, Krishna A, Bajpai M, Srinivas M, Uppal R, *et al.* Revised guidelines on management of antenatal hydronephrosis. Indian J Nephrol 2013;23:83-97.