Management of Urinary Tract Infections and Vesicoureteric Reflux: Key Updates from Revised Indian Society of Pediatric Nephrology Guidelines 2023

Abstract

Non-specific symptoms and difficulty in collecting urine specimens make diagnosis of urinary tract infection (UTI) challenging in young children. However, timely diagnosis and initiation of therapy are essential to prevent complications. Children with recurrent UTIs require detailed evaluation and follow-up for optimal management. We report key updates from revised evidence-based practice guidelines of the Indian Society of Pediatric Nephrology for urinary tract infections and primary vesicoureteric reflux.

Keywords: *Antibiotic prophylaxis, Acute pyelonephritis, Children, Vesicoureteral reflux*

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Introduction

Urinary tract infection (UTI) is a common bacterial infection in childhood affecting 1.7% of boys and 8.4% of girls before the age of 7 years.[1] UTI may be associated with acute discomfort, fever, and long-term complications such as hypertension and kidney scarring.[2] The diagnosis of UTI in infants and young children is difficult. Primary vesicoureteric reflux (VUR) and bladder-bowel dysfunction (BBD) are the two most common risk factors for the recurrence of UTI. Almost 20%-30% of children with the first episode of febrile UTI may have an underlying congenital anomaly. Therefore, prompt evaluation and treatment are important for managing acute and long-term complications associated with UTI. The last guidelines by the Indian Society of Pediatric Nephrology (ISPN) on this topic were published in 2011.[3] Because of significant new evidence that has emerged in the last decade, the Indian Society of Pediatric Nephrology (ISPN) has recently revised and published evidence-based guidelines with a robust methodology.[4] This article highlights the key updates in the recent guidelines [Table 1 and Figure 1]. Box 1 describes the various definitions used in this review.

Materials and Methods

These guidelines were developed using international standards for developing good-quality clinical practice guidelines. Initially, six working groups and an evidence review group were formed, following which questions were developed in PICOM (population, intervention, control, outcome, methods) format, a detailed systematic literature search was performed, and used the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) approach[5] to assess the quality of evidence and strength of recommendations. While recommendations are based on evidence generated through systematic review and meta-analysis, clinical practice points are drafted chiefly based on limited literature or expert opinions. For detailed methodology, one may refer to the original manuscript.[4]

Diagnosis

The emphasis on urine dipstick for making a presumptive diagnosis of UTI

Diagnosis of UTI in children should be based on the significant growth of single uropathogens in urine culture in an appropriate clinical context. The presence of leukocyturia is not necessary. Growth of single bacterial species $\geq 10^3$, $\geq 10^4$, and $\geq 10^{4-5}$ (CFU/mL) in urine obtained by suprapubic aspiration, catheterization, and clean-catch, respectively, is considered significant. The previous threshold of $\geq 10^5$ CFU/mL has been lowered in the present guideline due to many studies that suggest true UTI may be missed with this strict definition, especially in infants. Collecting an optimal urine specimen is challenging. In

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Table 1: Summary of key recommendations and clinical practice points for management of urinary tract infections and vesicoureteric reflux

Topics	Description	Strength of recommendation*
Diagnosis		
CPP	The guidelines suggest using the clean-catch method for urine collection in toilet-trained children. For non-toiled trained stable children, clean-catch should be attempted initially; if unsuccessful, the urine sample may be collected by catheterization or suprapubic aspiration.	Not graded
	For sick infants, catheterization and suprapubic aspiration are the preferred methods for urine collection.	
Recommendation	The guidelines suggest using the urine dipstick (leukocyte esterase and nitrite combination) as a first-line screening test for UTI.	2⊕⊕◯◯
Recommendation	Urine microscopy (for bacteriuria and leukocyturia) in a freshly voided sample can be used as an alternative to the dipstick for screening for UTI.	2⊕⊕◯◯
CPP	Diagnosis of UTI should be based on positive urine culture in the presence of symptoms suggestive of UTI. The growth of single uropathogenic bacteria $\geq 10^3$, $\geq 10^4$, and $\geq 10^{4-5}$ (CFU/mL) in urine obtained by suprapubic aspiration, catheterization, and clean-catch, respectively, are highly suggestive of UTI.	Not graded
Treatment		
CPP	Antibiotic therapy should be initiated as early as possible, preferably within 48–72 hours of the onset of fever.	Not graded
Recommendation	The guidelines suggest using third-generation cephalosporins or co-amoxiclav as initial empirical antibiotic therapy in children with suspected febrile UTIs.	2⊕◯◯◯
Recommendation	The guidelines suggest first-generation cephalosporin (cephalexin, cefadroxil) or co-amoxiclav as initial empirical therapy in adolescents with cystitis.	2⊕◯◯◯
Recommendation	The oral route is preferred over intravenous for the administration of antibiotic therapy for the treatment of acute febrile UTI in all patients except (i) infants less than 2 months of age, (ii) severely ill patients, and (iii) patients who are unable to ingest oral antibiotic.	2⊕◯◯◯
CPP	The guidelines suggest changing initial antibiotic therapy only in patients with clinical treatment failure regardless of antibiotic sensitivity patterns.	Not graded
CPP	The guidelines suggest 7–10 days of therapy with the antibiotic in children with acute symptomatic UTI.	Not graded
Recommendation	The guidelines recommend that 3–7 days of oral antibiotic therapy in children with cystitis.	1⊕⊕◯◯
CPP	Antibiotics should not be used for the treatment of asymptomatic bacteriuria. Urine cultures should not be performed in asymptomatic children.	Not graded
Imaging		
CPP	An ultrasound scan of the urinary tract should be performed after an episode of UTI in all children.	Not graded
CPP	The guidelines suggest performing micturating cystourethrography in children with one of the following: (a) UTI caused by non-*E.coli* uropathogens in children less than 2 years, (b) abnormal ultrasound scan, or (c) history of recurrent UTI.	Not graded
Recommendation	The guidelines suggest that an acute-phase DMSA scan should not be performed in children with febrile UTIs.	2⊕◯◯◯
CPP	Late-phase DMSA scan can be done to assess kidney scarring in children with recurrent UTI or high-grade VUR.	Not graded
Prevention of UTI		
Recommendation	The guidelines suggest against using antibiotic prophylaxis for the prevention of UTI in patients with a normal urinary tract and absence of bladder-bowel dysfunction.	2⊕◯◯◯
Recommendation	The guidelines suggest using antibiotic prophylaxis for the prevention of recurrent febrile UTIs in patients with high-grade (grades 3–5) VUR.	2⊕⊕◯◯
CPP	Antibiotic prophylaxis may be considered in preference to surveillance in patients presenting with recurrent febrile UTIs and bladder-bowel dysfunction, irrespective of the presence or absence of primary VUR.	Not graded

Continued.

Table 1: Continued

Topics	Description	Strength of recommendation*
Recommendation	The guidelines suggest against using antibiotic prophylaxis for the prevention of symptomatic UTI in children with antenatally detected hydronephrosis while awaiting evaluation.	2⊕◯◯◯
Recommendation	Cotrimoxazole or nitrofurantoin should be used as the first-line antibiotic for prophylaxis in children older than 3 months.	2⊕⊕◯◯
Recommendation	The guidelines suggest discontinuing antibiotic prophylaxis in children older than 2 years of age if they satisfy all three criteria: (i) toilet training, (ii) absence of BBD, and (iii) no febrile UTI in the preceding 1 year.	2⊕◯◯◯
Recommendation	Circumcision can be considered one of the interventions for the prevention of UTI in children at risk (high-grade VUR or recurrent UTI) of recurrence.	2⊕⊕⊕◯
Recommendation	The guidelines suggest cranberry products can be used for the prevention of UTI in children with recurrent UTI and normal urinary tract.	2⊕⊕◯◯
CPP	All toilet-trained children with UTI should be evaluated for bladder-bowel dysfunction.	Not graded
Recommendation	The guidelines recommend that all children with bladder-bowel dysfunction should be managed with urotherapy for the prevention of UTI recurrence.	1⊕⊕◯◯
Management of primary VUR		
Recommendation	The guidelines suggest that surgical reimplantation can be considered in patients with high-grade VUR with recurrent breakthrough febrile UTIs on antibiotic prophylaxis.	2⊕⊕⊕◯
CPP	In children with high-grade VUR, surgical intervention may be an alternative for parenteral hesitancy to use antibiotics. When surgical intervention is indicated, patients may be given the option of endoscopic injection of a bulking agent as initial therapy with guidance from a physician about its minimally invasive nature but lower success rate as compared to ureteric reimplantation.	Not graded
CPP	Children with high-grade VUR and reflux nephropathy need periodic follow-up to detect long-term complications: their growth, blood pressure, proteinuria, and kidney function are checked during each hospital visit.	Not graded
CPP	Ultrasound is suggested to be performed periodically to monitor kidney growth in children with persistent high-grade VUR.	Not graded
CPP	The guidelines suggest that DMSA scintigraphy can be repeated during follow-up only in children with recurrence of UTI.	Not graded
CPP	We suggest that repeat cystography for documenting the resolution of reflux is not required; however, it may be performed after 4–8 years following the initial diagnosis if deemed necessary by treating physicians in children with high-grade VUR.	Not graded
CPP	We suggest screening siblings (aged less than 3 years) of children with primary VUR with an ultrasound scan.	Not graded

*GRADE approach was used to determine the strength of the recommendation. CPP: clinical practice point, DMSA: dimercapto succinic acid, UTI: urinary tract infection, VUR: vesicoureteric reflux, CFU: colony forming units, BBD: Bladder bowel dysfunction.

the revised guidelines, we suggest that clean-catch should be the preferred method for urine collection, except in sick young infants where catheterization or suprapubic aspiration should be used to avoid delay in sending the specimen for urinalysis and culture. Timely initiation of antibiotic therapy is crucial to avoid kidney damage; hence, rapid screening tests are needed to make a presumptive diagnosis of UTI. While bacteriuria is the best screening test on urinalysis for presumptive diagnosis of UTI, it is cumbersome and not feasible everywhere. Leukocyturia alone has lower sensitivity (76%) but good specificity (80%). While leukocyte esterase alone has good specificity (90%) with only moderate sensitivity (79%), the combination of leukocyte esterase or nitrite provides good sensitivity (84%) and specificity (88%).[4] Hence, the guidelines suggest that a urine dipstick (combination of nitrite and leukocyte esterase) can be used as an alternative to urine microscopy for the presumptive diagnosis of UTI in children.

Treatment: Initiation of prompt antibiotic therapy

Since the delay in initiating antibiotic therapy has been shown to increase the risk of kidney scarring the guidelines suggest that treatment should be commenced within 48–72 hours of the onset of fever. Third-generation cephalosporins or co-amoxiclav should be used as first-line antibiotics in children with febrile UTI; first- or second-generation cephalosporin can be used in adolescents for cystitis.

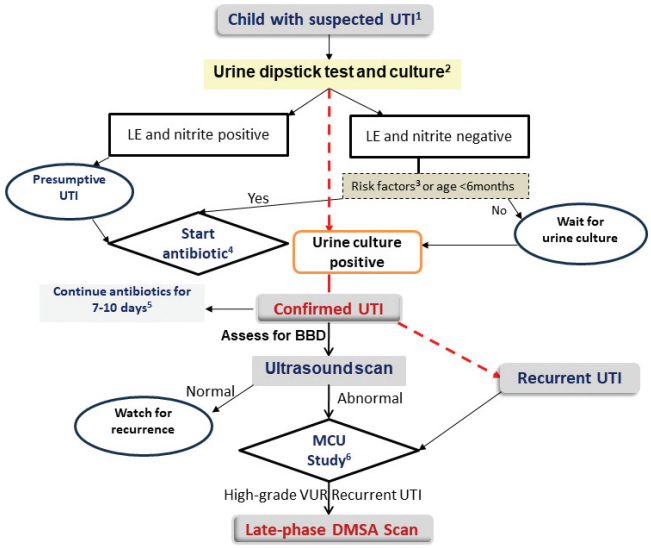

Figure 1: Approach to a child with suspected urinary tract infection (UTI). 1. Fever (>48 h) without focus in children less than 24 months or with specific urinary symptoms in older children; 2. If feasible to perform urine microscopy (leukocyturia and bacteriuria) can be used as an alternative to the dipstick; 3. Risk factors: bladder-bowel dysfunction, primary vesicoureteric reflux, previous history of UTI; 4. Oral route is preferred over IV except in infants less than 2 months, sepsis, and inability to take oral medications; 5. In adolescents where it is feasible to make the diagnosis of cystitis oral antibiotic therapy of 3–7 days is sufficient; 6. MCU study can also be considered in children with UTI due to non-*E.coli* uropathogens.[11] LE: Leukocyte esterase, DMSA: Dimarcapto succinic acid scintigraphy, VUR: vesicoureteric reflux, BBD: bladder bowel dysfunction.

Oral antibiotic therapy is preferred over intravenous in all children with febrile UTI except in the following settings: (i) infants less than 2 months, (ii) severely ill children, and (iii) those who are unable to tolerate oral medications. The guidelines recommend using 7–10 days of antibiotic therapy for febrile UTI, and a shorter course of 3–7 days for cystitis. Patients not responding to initial empirical antibiotic therapy should be evaluated with an ultrasound scan of kidneys, ureters, and bladder and might require a change of therapy as per the sensitivity of the uropathogens. Patients showing clinical response to initial therapy do not require a change of antibiotic therapy as considerable discrepancy in in-vivo susceptibility and in-vitro clinical response has been reported. Response to therapy is chiefly determined based on the resolution of symptoms and urine culture need not be repeated to document response. The guidelines reemphasized that asymptomatic bacteriuria should not be treated with antibiotics.

Imaging: A less aggressive approach for detecting VUR and kidney scarring

Imaging following UTI has traditionally been targeted at detecting underlying anomalies and kidney damage. However, none of the existing interventions can effectively reduce the risk of kidney scarring and do not improve long-term outcomes. Hence, the updated guidelines suggest a conservative approach for imaging, primarily aimed at diagnosing high-grade VUR [Table 2]. All children with a UTI should be evaluated with an ultrasound scan of the kidneys, ureters, and bladder. A good quality ultrasound can detect congenital anomalies of the urinary tract or provide a clue for bladder-bowel dysfunction. We suggest performing micturating cystourethrography (MCU) any time after UTI has been treated as per the convenience of the patient and physician (generally after 2–3 weeks) in children with recurrent UTI, abnormal ultrasound scan, and those younger than 2 years with UTI caused by non-*E. coli* uropathogens. Limiting MCU study to the above indications increases diagnostic yield and avoids unnecessary radiation to many children where the probability of detecting high-grade VUR is low. Acute-phase dimercapto succinic acid (DMSA) scintigraphy has low specificity in detecting high-grade VUR and does not differentiate between permanent kidney scarring and acute pyelonephritis. The guidelines emphasize that acute-phase DMSA scintigraphy should be avoided. The clinician should perform a DMSA scan 4–6 months after an episode of UTI to detect permanent kidney scars. The probability of developing kidney scarring is highest in children with high-grade VUR and recurrent UTI hence we suggest that late-phase DMSA scans should be restricted to these categories of patients [Table 2].

Table 2: Imaging following urinary tract infections

Imaging modality	Indications	Advantage	Limitations
Ultrasound scan	All patients	Non-invasive No radiation exposure Provides dynamic images	Operator dependent
Micturating cystourethrography	Patients with abnormal ultrasound scan Patients aged less than 2 years with non-*E. coli* UTI Patients with recurrent UTI	Enable grading of VUR Provide detailed anatomic delineation of the urinary tract	Radiation exposure Invasive; needs catheterization Risk of UTI
Late-phase DMSA scintigraphy	Recurrent UTI High-grade VUR	The Gold standard for detecting kidney scars	Radiation exposure Invasive Accessibility

DMSA: dimercaptosuccinic acid; UTI: urinary tract infection; VUR: vesicoureteric reflux.

Prevention: Antibiotic prophylaxis is limited to high-grade VUR and for shorter duration

Primary VUR and BBD are the two most important risk factors for recurrent UTIs in children.[6] Prevention of febrile UTIs is essential as the risk of kidney scarring increases with the higher number of febrile UTIs.[7] Low-dose antibiotic prophylaxis has been considered as a first-line strategy for the prevention of UTI in at-risk children. However, recent evidence raised concerns about the efficacy as well as safety of this intervention. The pooled data that included recent studies suggests that antibiotic prophylaxis is not effective in children with normal urinary tract and low-grade VUR. The revised ISPN guidelines recommend giving antibiotic prophylaxis only to children with high-grade (Grade 3–5) VUR [Table 3]. Recent data also suggest that antibiotic prophylaxis is effective in preventing the recurrence of UTI in children with BBD.[8] Considering the importance of BBD in patients with recurrent UTI, we therefore suggest that patients with VUR should be evaluated carefully for the presence of BBD. Patients with BBD should optimally be managed with urotherapy and laxatives to reduce the risk of recurrent UTIs.[9] We do not advise using antibiotic prophylaxis in children detected to have antenatal hydronephrosis while awaiting evaluation including MCU study. Co-trimoxazole and nitrofurantoin are the two most commonly used antibiotics for prophylaxis in children older than 3 months; cephalexin being preferred for young infants. Clinicians should avoid using broad-spectrum antibiotics such as co-amoxiclav for prophylaxis as this practice increases the risk of antimicrobial resistance. Once initiated, antibiotic prophylaxis may be discontinued in toilet-trained children without BBD and no febrile UTI in the preceding 1 year. Recent evidence suggests that cranberry products can be used for the prevention of UTI in children with normal urinary tract, however, data for this intervention in children with primary VUR is still limited.[10] Considering multiple and long-term benefits, the guidelines suggest that circumcision may be advised as a potential intervention to reduce the risk of recurrent febrile UTIs in children.[11]

Table 3: Strategies for prevention of recurrence of UTI in children

Strategy	Indications
Antibiotic prophylaxis	High-grade VUR, recurrent UTI in patients with BBD
	Also, can be considered in infants with low-grade VUR
Surgical re-implantation	Recurrent febrile UTI despite antibiotic prophylaxis and adequate management of BBD
Cranberry products	Patients with recurrent UTI and normal urinary tract
	No data to support its use in patients with VUR
Urotherapy*	All patients with BBD
Circumcision	Can be suggested as an option in patients at risk of recurrence of UTI

*Urotherapy includes behavioral modifications (regular bladder and bowel habits, adequate fluid intake, optimal posture during voiding, etc.) information and demystification related to lower urinary tract symptoms, adequate intervals between urinations, documentation of voiding symptoms and systematic follow-up. BBD: bladder-bowel dysfunction; VUR: vesicoureteral reflux; UTI: urinary tract infection.

Box 1: Definitions

Leukocyturia

Presence of ≥10 leukocytes per mm^3 in a fresh uncentrifuged sample, or >5 leukocytes per high power field in a centrifuged sample.

Bacteriuria

Presence of one or more bacteria per oil immersion field in a freshly voided uncentrifuged sample.

Acute pyelonephritis

Bacterial infection involving the upper urinary tract (kidney parenchyma).

Cystitis

Bacterial infection localizing to the bladder, characterized by dysuria, frequency, urgency, and suprapubic tenderness.

Recurrent urinary tract infection

Two episodes of urinary tract infection during any time period in childhood.

Febrile urinary tract infection

Fever (temperature ≥38°C) with positive urine culture defined by the presence of significant colony count of a single uropathogens.

Primary vesicoureteric reflux (VUR)

The passage of urine from the bladder back into ureters and kidneys in the absence of obstructive uropathy and neurogenic bladder dysfunction.

Low-grade vesicoureteric reflux

Grade 1 and 2 vesicoureteric reflux on micturating cystourethrography.

High-grade vesicoureteric reflux

Grade 3 to 5 vesicoureteric reflux on micturating cystourethrography.

Reflux nephropathy

Abnormalities in the renal cortex associated with primary VUR (congenital dysplasia or acquired scarring).

Management of primary VUR

Antibiotic prophylaxis is the first line of management and surgical reimplantation only in patients with recurrent breakthrough febrile UTIs.

In patients with primary VUR, neither antibiotic prophylaxis nor surgical reimplantation is effective in reducing the risk of kidney scarring, although the latter is more effective in preventing febrile UTIs.[9] The revised guidelines suggest that surgical reimplantation should be reserved for patients with recurrent febrile UTIs despite antibiotic prophylaxis

and optimal management of BBD. Endoscopic injection of bulking agents has a lower success rate as compared to surgical reimplantation and hence, should be used after careful discussion with the caregivers.[10]

Children with primary VUR may have associated kidney damage termed as reflux nephropathy. Kidney damage in these patients is chiefly caused by congenital hypodysplasia but may also be due to kidney scars caused by febrile UTI. Patients with reflux nephropathy may develop proteinuria, hypertension, and rarely impaired kidney function in the long term. Hence, these patients require long-term follow-up and monitoring. An ultrasound scan can be used to assess the growth of kidneys. DMSA scan may be repeated in patients with a recurrence of febrile UTI. The median time to resolution is variable depending on the grade of VUR therefore, if felt necessary, repeat imaging for resolution of VUR may be done 4 to 8 years after initial diagnosis. Primary VUR is reported to be common in siblings, however, considering limited intervention to alter the long-term outcome, the guidelines suggest that screening should be done using an ultrasound scan only in siblings below 3 years of age. If the ultrasound scan is abnormal or the sibling develops febrile UTI, clinicians may consider MCU to confirm the diagnosis of VUR.

Conclusion

Timely diagnosis of UTI can be sometimes challenging but is necessary to reduce acute discomfort and long-term consequences. BBD and primary VUR, are two important risk factors for recurrence. These updated guidelines present evidence-based systematic and algorithmic guidance for optimal management of these disorders. Updated guidelines emphasize less aggressive approaches while evaluating shorter courses of treatment and briefer duration of antimicrobial prophylaxis to reduce the burden of antimicrobial resistance.

Conflicts of interest

There are no conflicts of interest.

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