

Extended Abstract

Urinary Tract Infection in Children: what's updated

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Introduction:

Urinary tract infection is the most common bacterial infection in children. Urinary tract infection in pediatric patients can be the early clinical manifestation of congenital anomalies of the kidney and urinary tract (CAKUT) or be related to bladder dysfunctions.

E. coli is responsible for 80–90% of community-acquired acute pyelonephritis episodes, especially in children. Bacterial virulence factors and the innate host immune systems may contribute to the occurrence and severity of urinary tract infection. The clinical presentation of urinary tract infections in children is highly heterogeneous, with symptoms that can be quite obscure.

Magnitude Of the problem:

- Urinary tract infections (UTIs) are among the most common bacterial infections in children. Up to 8% of children will experience at least one UTI between the ages of 1 month and 11 years, and up to 30% of infants and children experience recurrent infections during the first six to 12 months after initial UTI.
- In the United States, there are about 1.5 million pediatric ambulatory visits annually for UTIs. The overall US health care costs for management and treatment of UTI in 2013 was \$630 million. UTIs cause short-term morbidity such as fever, dysuria, and flank pain, and may also result in long-term renal injury, such as permanent kidney scarring. (Arshad et al.,2015)
- Over the last two decades, the scenario of the management of children with a febrile UTI has changed. The old model proposed that all children with UTI were to be investigated using ultrasound (US), a micturition cystourethrogram (MCUG), and some form of nuclear imaging, such as dimercaptosuccinic acid (DMSA).

Etiology:

E.Coli is responsible for 80–90% of community-acquired acute pyelonephritis episodes, especially in children. Less common uropathogenic bacteria include *Proteus mirabilis*, *Klebsiella* spp., and *Staphylococcus saprophyticus*.

Infectious agents of UTI acquired during hospitalization depend on the hospital environment and underlying host factors. Bacterial virulence factors and the innate host immune systems may contribute to the occurrence and severity of UTI.

UTI may occur via two routes: hematogenic and ascendant. The hematogenic route is typical in newborns, while the ascendant route characteristically develops after the neonatal period. In newborns, UTI may manifest as sepsis, largely with nonspecific clinical features, including anorexia, vomiting, poor sucking, irritability, lethargy, convulsions, pallor, hypothermia and, sometimes, jaundice.

Clinical presentation

- The classic presentations of dysuria, frequency, and flank pain in adults are unreliable when applied to pediatric UTI, particularly in infants. The presenting complaints in children tend to be vague, including fever, irritability, lethargy, poor feeding, failure to thrive, and gastrointestinal complaints.
- Newborns and infants younger than 3 months may have, at onset, vague and nonspecific symptoms of illness that are difficult to interpret, including failure to thrive, diarrhea, irritability, lethargy, malodorous urine, hypothermia, fever, asymptomatic jaundice, and oliguria or polyuria.
- It has been recommended that testing for UTI be part of the evaluation of asymptomatic jaundice in infants younger than 8 weeks, especially those with elevated conjugated bilirubin levels.
- The American Academy of Pediatrics (AAP) recommends that infants with elevated direct bilirubin levels be screened for UTIs. Those with elevated unconjugated bilirubin levels should not be excluded, especially if other concerning clinical features are present.
- In infants between 3 months and 2 years old, fever is the main symptom, and often the only sign of infection. High temperatures associated with nonspecific manifestations like appetite loss, vomiting, abdominal pain, dehydration, and poor weight gain are commonly found in this age group. It can be rarely associated with specific signs or symptoms related to the urinary tract, such as urinary dysuria and foul-smelling urine.
- The pediatrician should consider investigating UTI in infants with unexplained fever. The prevalence of UTI in infants and young children with fever that is not localizable by history or physical examination is high.

According to the AAP guidelines, the presence of UTI should be considered in neonates and children between 2 months to 2 years of age with unexplained fever (with strong evidence). In the same guideline, the experts pointed out that the two sexes are not affected equally. The prevalence of UTI in febrile girls with 2 months to 2 years is more than twice that in boys (relative risk, 2.27).

The prevalence of UTI in girls younger than 1 year of age is 6.5%, while, in boys, it is 3.3%. The prevalence of UTI in girls between 1 and 2 years of age is 8.1%, whereas, in boys, it is 1.9%. In an updated guideline, the AAP recommended that if a clinician decides that a febrile infant with no apparent cause for the fever requires antimicrobial therapy to be administered because of ill appearance or another pressing reason, the clinician should ensure the collection of urine specimens for both culture and urinalysis before antibiotic administration. If a clinician assesses a febrile infant with no apparent source for the fever as not being so ill as to require immediate antimicrobial therapy, then the clinician should assess the likelihood of UTI.

After 5 years, the classic urinary tract symptoms, including dysuria, frequency, suprapubic or flank discomfort, incontinence, and costovertebral angle tenderness are usually present. Less common signs such as secondary enuresis in a previously toilet-trained child or frank hematuria can also occur.

Adolescent girls are more likely to present with typical cystitis symptoms including frequency, urgency, dysuria, cloudy urine, hematuria, and lower abdominal discomfort. The prevalence of UTI among adolescent boys is very low. Adolescents are better able to provide history and participate in physical exams. Sexual activity is a special issue for this population that requires additional attention.

Examination of the external genitalia and perineum is important and may reveal the possible origin of symptoms like balanitis, meatal ulcer, or vulvovaginitis.

In summary, diagnosis of UTI in children, especially in younger infants, can be difficult and requires a high index of suspicion. Some key points must be considered by the pediatrician to prevent missing the diagnosis of UTI in children

- Any child and adolescent with urinary symptoms
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- Any child, especially infants, with an unexplained fever
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- Any newborn with signs or symptoms of bacteremia
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- Any newborn with elevated conjugated serum bilirubin
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- Any infant with unexplained failure to thrive

Box 1. Conditions to consider the investigation of urinary tract infection in children

- Structural urinary tract anomalies
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- Antenatal hydronephrosis
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- Bowel and bladder dysfunction
-
- Neurogenic bladder
-
- Immunocompromised states, including newborns
-
- Gender
-
- Sexual activity
-
- Indwelling catheter
-
- Uncircumcised boys

Box 2. Risk factors for urinary tract infection in children.

The main methods of urine collection include clean-catch, plastic bag, bladder catheterization, and suprapubic aspiration (SPA). These four methods have variable contamination rates and invasiveness.

International guidelines generally recommend that urine should be collected by bladder catheterization or SPA under ultrasound control

SPA is the most sensitive method for obtaining an uncontaminated urine sample. When urine is collected by SPA, any colony count is considered to represent significant bacteriuria. All other methods of urine collection (clean catch, bladder catheterization, and plastic bag collections) require passage of urine through the urethra

SPA is recommended for boys with severe phimosis, girls with tight labial adhesions, and in case of external genital infection or presence of complex genital abnormalities. Bladder catheterization is considered an alternative to SPA, although with higher rates of contamination

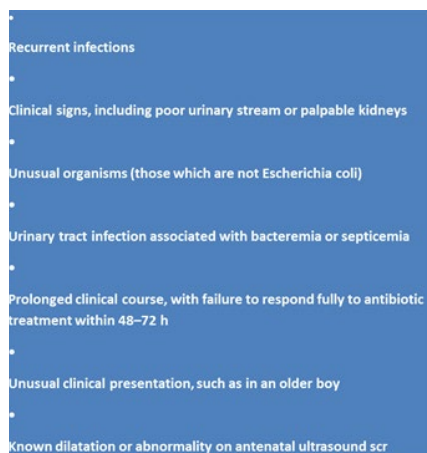
Urine culture

- Urine culture is still the gold standard for diagnosing UTI.
- In freshly voided urine, a growth of more than 10⁸ colony-forming units (CFU) per liter (10⁵ per mL) of a unique bacterium is regarded most frequently as the cutoff between contamination and UTI.

Imaging studies for urinary tract infections

- The National Institute of Health and Care Excellence (NICE) in the UK, from the AAP, and from the Italian Society of Pediatric Nephrology (ISPN) suggest limited investigations for children with UTI.
- The NICE guidelines provide imaging recommendations for children of all ages, whereas the AAP guidelines apply to children aged 2–24 months, and the ISPN guidelines refer to children aged 2–36 months. serious urinary tract abnormalities .69, 78
- The NICE guidelines recommend that children aged over 6 months with their first uncomplicated UTI require no investigations following the episode and that children under 6 months should have only RUS.
- The AAP and ISPN guidelines recommend that all infants aged 2–24 months with febrile UTIs should undergo RUS, although they recognize that prenatal US is likely to identify most serious urinary tract abnormalities.
- In a spite of the imaging protocol adopted, RUS is generally considered the first-line investigation for urinary tract malformations, since the method is noninvasive and can identify structural anomalies including obstructive uropathies, kidney hypodysplasia, and urinary tract dilatations.
- The main limitations of RUS are the dependence on the equipment and the operator, and the impossibility to obtain data on renal function.
- The termed 'bottom-up' approach is traditionally adopted for imaging evaluation of UTI. RUS and VCUG are recommended after the first episode of UTI in all pediatric patients despite sex and age group.
- VCUG is regarded as the reference standard for identifying VUR and for providing information on the bladder and urethra.
- Recently, it has been debated whether the presence and severity of VUR on VCUG might influence decisions on the management of VUR.
- The remaining clear indication for a VCUG is to evaluate the bladder and urethra in children suspected of having obstructive uropathy, such as posterior urethral valves(PUV).

• A recent line of investigation on the ideal imaging protocol is the use of machine learning algorithms to develop predictive models for the probability of recurrent UTI associated with VUR in children after first infection



Box 3. Features of high-risk children that warrant investigation for an abnormal urinary tract.

Treatment and chemoprophylaxis

Therapy of UTI eradication

• The aims of the management of children with UTI are (1) resolution of the acute symptoms of the infection; (2) prompt recognition of concomitant bacteremia, particularly in infants less than 2 months of age and (3) prevention of renal damage by eradication of the bacterial pathogen, identification of abnormalities of the urinary tract, and avoidance of recurrent infections.

Antibiotic	Dose: mg/kg/day	Interval
Ampicillin	100 mg	Every 6 h
Gentamicin	7.5 mg	Every 8 h
Ceftriaxone	50–100 mg	Every 12 h
Cefotaxime	100–200 mg	Every 8 h
Cefepime	100 mg	Every 12 h

Table 1. Parenteral antibiotics for treating acute pyelonephritis.

Treatment and chemoprophylaxis

• Recent guidelines, which recommend that oral antibiotics should be given for seven to ten days unless the child is seriously unwell or unable to take oral antibiotics, in which case intravenous antibiotics are indicated

• The initial choice of antibacterial therapy is preferably based on the knowledge of the predominant uropathogens in the patient's age group, antibacterial sensitivity patterns in the practice area, the clinical status of the patient, and the opportunity for close follow-up.

Antibiotic	Dose: mg/kg/day	Interval
Trimethoprim-sulfamethoxazole	40 mg (SMT)	Every 12 h
Cefadroxil	30–50 mg	Every 12 h
Cephalexin	50–100 mg	Every 6 h
Amoxicillin-clavulanate	40 mg (amoxicillin)	Every 12 h

Table 2. Orally administered antibiotics for acute urinary tract infection.

A common choice for treatment of UTI orally in the well-appearing child includes a sulfonamide-containing antimicrobial (trimethoprim-sulfamethoxazole [TMP-SMX]) or cephalosporin.

Food and Drug Administration (FDA) and the European Medicines Agency (EMA), have released warnings that fluoroquinolones should not be prescribed for patients who have other treatment options for infectious diseases, including uncomplicated UTIs, because the risks outweigh the benefits in these patients and other antibiotics to treat these conditions are available.

As regard treatment options of children and adolescents with afebrile cystitis, recent studies have shown that short duration therapy (three to four days) is as effective as standard therapy (seven to 14 days) in eradicating urinary bacteria.

The NICE guidelines recommend three days of treatment, with the choice of antibiotic directed by local guidelines.

Prevention of the recurrent UTI and antibiotic prophylaxis

- Recent studies have confirmed that nitrofurantoin, sulfonamides, and cotrimoxazole are effective in reducing the recurrence rate of infection in patients with normal urinary tracts as long as the drug is given
- Agents of choice for prophylaxis of recurrent UTI are nitrofurantoin and cotrimoxazole
- Nitrofurantoin was found to be superior to trimethoprim, but no different from cefixime in reducing the incidence of recurrent repeat-positive urine cultures.
- Nitrofurantoin was three times more likely to be discontinued because of the adverse effects such as of nausea, vomiting, or stomachache.

Complications and prognosis

- The involvement of renal parenchyma in UTI may lead to an inflammatory reaction with risk of permanent damage.
- The long-term consequences of such damage include hypertension and impaired renal function, but the frequency of these complications is still poorly

Conclusion

In conclusion, methods of urine collection in individual centers should be determined based on the accuracy of voided specimens.