Review Article

Urinary tract infection in pediatric patients – Recent updates

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ABSTRACT

In children, urinary tract infection (UTI) is a common condition. Prompt identification and treatment are critical for reducing morbidity associated with this illness. Throughout infancy, the symptoms and indications remain nonspecific. During the first 2 years of life, the most prevalent sign of UTI is unexplained fever. Symptoms and indicators of pyelonephritis after the 2nd year of life include fever, chills, rigor, flank discomfort, and costovertebral angle tenderness. Suprapubic pain, dysuria, urinary frequency, urgency, murky urine, malodourous urine, and suprapubic tenderness are examples of the lower tract symptoms and indicators. When UTI is suspected, a urinalysis and urine culture should be conducted. In the treatment of acute uncomplicated UTI, second or third-generation cephalosporin and amoxicillin-clavulanate are currently the medications of choice. Parenteral antibiotic therapy is advised for infants under 2 months of age and any child who seems toxic is hemodynamically unstable, is immunocompromised, is unable to tolerate, or is not responding to oral medication. This study focuses on the most recent updates about UTIs in children and provides a comprehensive overview of the subject.

Key words: Children, Pediatrics, Pyelonephritis, Urinary tract infection

One of the most prevalent bacterial diseases in children is urinary tract infections (UTIs). The infection can affect either the upper urinary tract (pyelonephritis) or the lower urinary tract (cystitis) [1]. UTIs are a major source of concern for children, parents, and physicians alike. Prompt identification and treatment are critical for reducing morbidity associated with this disease [2].

Although the diagnosis and treatment of UTI may appear straightforward, they are among the most disputed events in pediatrics. The absence of traditional clinical symptoms, improper urine specimen collection, changing urinary tract imaging recommendations, and different treatment and prevention efforts all contribute to the problems related to adequate address of UTIs. UTI diagnostic and management options have been clarified by recently published guidelines and big clinical trials. This article provides an overview of pediatric UTIs, including current breakthroughs and evidence updates.

ETIOLOGY

The most prevalent organisms that cause UTIs in children are from the intestinal flora; *Escherichia coli* accounts for 80–90% of UTIs in children. *Enterobacter aerogenes*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Citrobacter*, *Pseudomonas aeruginosa*, *Enterococcus* spp., and *Serratia* spp. are among the other species that cause UTI [3]. *P. mirabilis* affects boys more than girls. *Streptococcus agalactiae* is more frequent in newborn infants. *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Streptococcus viridians*, and *S. agalactiae* may be responsible in infants with urinary tract defects (anatomic, neurologic, or functional) or an impaired immune system. *S. aureus*, *S. agalactiae*, *P. mirabilis*, *P. aeruginosa*, and *nontyphoidal Salmonella* may induce hematogenous dissemination of infection, a rare cause of UTI. *Mycobacterium tuberculosis* and *S. pneumoniae* are two uncommon bacterial causes of UTI [4].

UTI can be caused by viruses such as adenoviruses, enteroviruses, echoviruses, and coxsackieviruses. In most cases, the accompanying infection is restricted to the lower urinary tract. Adenoviruses are known to induce hemorrhagic cystitis in this context. Fungi (e.g., *Candida* spp., *Cryptococcus neoformans*, and *Aspergillus* spp.) are infrequent causes of UTI and are most common in children with an indwelling urinary catheter, urinary tract abnormalities, long-term use of broad-spectrum antibiotics, or a damaged immune system [5,6].

Access this article online

Received- 19 July 2023
Initial Review- 29 July 2023
Accepted- 10 August 2023

DOI: 10.32677/ijch.v10i8.4202

Quick Response code

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PATHOGENESIS

Except for the distal section of the urethra, the urinary system is typically sterile. Bowel bacteria can be found in the periurethral region. *E. coli* is the most common bacteria in healthy young girls, but *P. mirabilis* predominates in boys after the first 6 months of life. Bowel bacteria, on the other hand, are not typically seen in the periurethral flora of older children. It should be noted, however, that Gram-negative bacterial colonization often precedes the incidence of UTI [7]. In certain cases, broad-spectrum antibiotics prescribed for other illnesses may cause alterations in the natural flora.

E. coli causes 80–90% of community-acquired acute pyelonephritis episodes, particularly in children. *P. mirabilis*, *Klebsiella* spp., and *Staphylococcus saprophyticus* are less prevalent uropathogenic bacteria [8]. The infectious agents of UTI acquired when hospitalized are affected by the hospital environment as well as underlying host characteristics. Bacterial virulence factors and innate host immune systems may both play a role in the occurrence and severity of UTI [9].

UTI can occur in two ways – hematogenic or ascending. The hematogenic pathway is common in infants, but the ascending route develops beyond the neonatal period. In infants, UTI can cause sepsis, characterized by nonspecific clinical symptoms such as anorexia, vomiting, poor sucking, irritability, lethargy, convulsions, pallor, hypothermia, and, in rare cases, jaundice [10]. As with other infections, there is a high risk of bacteremia and a high chance of mortality (about 10%) in this age group due to infection spreading to other areas, such as meningitis. Uropathogenic bacteria migrate, fixate, and multiply in the urinary system via the ascending pathway. Uropathogenic bacteria can live in the gastrointestinal tract for long duration before moving to the periurethral area. Bacteria ascend the urinary tract against urine flow after spreading from the perineum to the periurethral area and establishing infection through a variety of processes. Fimbriae that increase attachment to urothelial cells, flagella-mediated movement, resistance to antibacterial defenses, and other adaption techniques are among the key processes [11].

During the acute phase of the disease, host resistance to UTI is primarily dependent on innate immune defenses. The response to uropathogenic *E. coli* is triggered by P-fimbriae-mediated adhesion to glycolipid receptors, which activates TLRs, the most important of which is TLR4 [12]. When TLR4 signaling is activated, transcription factors such as IRF3 are released, causing neutrophil recruitment and cytokine synthesis to destroy germs. These mechanisms are responsible for the symptoms and indications of UTI. Interleukin-8 (IL-8) is produced by urothelial cells and draws neutrophils to the urinary tract, resulting in pyuria. Infection stimulates neutrophil recruitment and activation by increasing the expression of IL-8 receptors. Urothelial cells also release Interleukin-6 (IL-6). IL-6 promotes the development of mucosal IgA and activates the creation of C-reactive protein [11]. Antimicrobial peptides, which are natural antibiotics produced by practically all organisms, are another source of innate immune defense.

Although normal architecture is more common, UTIs may be the sentinel event for underlying congenital abnormalities of the kidney and urinary tract (CAKUT). UTI might be the first symptom of CAKUT in 30% of children. The upper urinary tract may be harmed if pediatricians fail to detect patients at risk of CAKUT [13]. Anatomical or functional changes in normal urine flux may surely predispose to UTI episodes, which most often occur in neonates or early babies. In this regard, vesicoureteral reflux (VUR) has been linked to around 20% of neonatal cases of UTI, although the incidence of VUR does not change significantly by gender, birth weight, gestational age, or mode of delivery [8].

CLINICAL MANIFESTATIONS

Symptoms and indications are nonspecific during the early days of life period. Temperature instability, peripheral circulatory failure, lethargy, irritability, apnea, seizure, or metabolic acidosis are all indications of sepsis in a neonate. A neonate may also present with anorexia, poor sucking, vomiting, inadequate weight gain, or persistent jaundice. A foul-smelling urine is a rare yet distinct symptom of UTI [14]. Septic shock is uncommon unless the patient is compromised or there is an obstruction. There is a substantial likelihood of bacteremia in neonates with UTI, indicating hematogenous spread of the bacteria. UTI symptoms are typically nonspecific throughout infancy. During the first 2 years of life, unexplained fever is the most common. It could be the only sign of UTI in this age range. UTI is more common in newborns with temperatures above 39°C than in those with temperatures below 39°C [15,16].

Irritability, poor eating, anorexia, vomiting, recurring stomach pain, and failure to flourish are some nonspecific signs. Specific symptoms and indicators include an increase or reduction in the amount of wet diapers, malodourous urine, and urination discomfort. A weak or leaking urine stream indicates a neurogenic bladder or a low urinary tract obstruction, such as posterior urethral valves in boys. Constant urination or diaper wetting may indicate the presence of an ectopic ureter, a risk factor for UTI. The symptoms and indicators of UTI become increasingly precise after the 2nd year of life. Fever, chills, rigor, vomiting, malaise, flank pain, back pain, and costovertebral angle discomfort are all symptoms and indicators of pyelonephritis. Suprapubic pain, abdominal pain, dysuria, urinary frequency, urgency, murky urine, daytime wetness, nocturnal enuresis of recent onset, and suprapubic tenderness are examples of lower tract symptoms and indicators. Urethritis without cystitis can cause dysuria in the absence of urine frequency or urgency [17].

LABORATORY INVESTIGATIONS

When UTI is suspected, a urinalysis and urine culture should be conducted. This applies to children under the age of three who have an unexplained fever, as well as children under the age of three who have suprapubic discomfort, dysuria, urinary frequency, urgency, malodourous urine, and new-onset daytime wetness [10]. The gold standard for diagnosing UTI is quantitative urine culture. A sterile bag attached to the perineum can be used to collect a voided urine specimen in infants. The benefits

of this process include its non-invasive nature and simple to obtain [10]. A "bagged" specimen, on the other hand, is vulnerable to contamination by periurethral flora, particularly in girls and uncircumcised boys. A positive culture from a bagged specimen has a false positive rate of 30 to 75%, necessitating confirmation with a urine specimen taken via clean-catch, catheterization, or suprapubic aspiration [18]. The absence of considerable bacterial growth from a bagged specimen, on the other hand, is solid proof against UTI [19]. The "bagged" method of urine collection in infants is the most commonly utilized approach in daily practice, particularly in primary care settings [14].

In children who can urinate on request, a clean-catch midstream urine specimen taken following sufficient washing of the external genitalia is adequate for most diagnostic purposes. The risk of contamination can be reduced during washing and voiding by having young females sit backward on the toilet seat and gently widening the labia in girls and retracting the foreskin in uncircumcised boys. Catheterization of the urinary bladder to obtain a urine specimen for culture is not indicated regularly. Catheterization causes discomfort for the kid, emotional stress for both the child and the parents, substantial trauma with subsequent dysuria and hematuria, and the possibility of infection entering the bladder [20].

Suprapubic aspiration is an effective way for obtaining a clean urine sample from infants, as well as children who are incontinent or critically unwell. The treatment is not recommended for children who have coagulopathy or an abdominal wall deformity [21]. Because the majority of failures are caused by a lack of urine in the bladder, a suprapubic tap should not be attempted on a newborn who has recently urinated. When ultrasonographic imaging is utilized to ensure the bladder is appropriately full and to allow visualization of tissues between the abdominal wall and the bladder, the success rate increases. Transient gross hematuria and penetration of abdominal viscera are complications of suprapubic aspiration. Suprapubic aspiration should be used only when a clean catch or catheter specimen is not readily available.

Bacteriuria and pyuria should be detected using microscopy. The presence of crystals or a large number of urothelial cells, vaginal cells, red blood cells, or white blood cells in the urine can hide the presence of germs. It is reported that the gram stain of urine has a sensitivity of 81% and a specificity of 83% [22]. Dipstick tests are affordable, simple, and widely available for the diagnosis of UTI. The leukocyte esterase dipstick test detects pyuria by histochemical methods that identify this enzyme in neutrophils.

Urine culture is still the gold standard for determining UTI. Bacteria are typically visible in adequately plated urine specimens within 24 h, and sensitivity data are typically available within 48 h. An anaerobic culture should be obtained if a regular culture is negative but the child is sick or the Gram stain shows bacteria. If a urine culture reveals uncommon bacteria or many bacteria in an uncontaminated urine specimen, immunodeficiency and kidney and urinary tract malformations should be ruled out [22].

DIAGNOSTIC IMAGING STUDIES

Physicians must use imaging studies sparingly in the treatment of children with UTIs to avoid exposing youngsters to radiation. Renal and bladder ultrasonography is the preferred approach for imaging the urine tract. Ultrasonography is non-invasive, safe, simple to conduct, and free of radiation. Hydration is crucial while employing renal and bladder ultrasonography to adequately fill the bladder [23]. A post-void examination is necessary for toilet-trained children. A renal and bladder ultrasound can detect kidney size, shape, and location, echo texture of the renal parenchyma, ureter duplication and dilatation, obstructive uropathy, and bladder structural abnormalities. The degree of echogenicity and the sharpness of the cortico-medullary distinction indicate if generalized renal illness or local damage is present.

Renal ultrasonography can also detect abscesses, pyonephrosis, and renal or perirenal abscesses. Renal and bladder ultrasonography should be considered in children under the age of two who have a febrile UTI, children of any age who have recurrent UTIs, and children who have a palpable abdominal mass, abnormal voiding, hypertension, hematuria, no response to standard antimicrobial treatment, and a family history of renal or urological disease [1]. Ultrasonography is not a sensitive test for determining the location of an infection or detecting a duplicated collecting system or vesicoureteric reflux. It can, however, predict the probability of renal scarring. Renal and bladder ultrasonography should be conducted as soon as feasible in acutely ill children and children who do not respond to routine antibiotic treatment to rule out urinary tract obstruction or renal abscess [24].

The nuclear cystogram detects VUR but does not detect intrarenal reflux, characterize the degree of reflux, or offer a comprehensive image of the urethra and ureters. As a result, posterior urethral valves may be missed. The low radiation dose and high sensitivity of a nuclear cystogram are its advantages. A nuclear cystogram can be used to assess siblings of patients with VUR as well as to track children with VUR. This exam necessitates that the child be toilet-trained [25].

Cystoscopy is recommended for children who have severe VUR, moderate VUR that has not responded to conservative treatment, a suspected duplicated collecting system, ureterocele, urethral blockage, or neurogenic bladder [26].

DIFFERENTIAL DIAGNOSIS

When a urine culture is positive yet there are no symptoms of UTI and the urine does not contain an abnormal amount of white blood cells, this is referred to as asymptomatic bacteriuria. Asymptomatic bacteriuria is the colonization of the urinary system by nonvirulent bacteria that are incapable of causing symptoms or inflammation. The syndrome affects about 1% of children, with a female predominance. Asymptomatic bacteriuria is more common in children with underlying genitourinary disorders [10].

A urine culture that contains several microorganisms suggests contamination rather than UTI unless the patient

is immunocompromised or has a kidney and urinary tract malformation. Failure to spread the labia when voiding can result in urine flow into the vagina, urine contamination with vaginal germs, and an incorrect diagnosis of UTI. Vulvovaginitis can produce dysuria and is frequently associated with UTI. Prepubertal girls may experience urethritis with dysuria as a result of poor hygiene or exposure to irritants such as bubble baths or harsh soap, rather than UTI [27].

Urge syndrome and defective voiding can be characterized by frequent micturition, urgency, daytime wetting, and nocturnal enuresis. Although UTI is more common in these children, the signs of voiding dysfunction are evident even when UTI is not present. When these symptoms persist following therapy for a culture-proven UTI, urge syndrome or dysfunctional urination should be investigated.

Viral disease, post-vaccination fever, urinary calculi, vaginal foreign body, orchitis, urethritis owing to a sexually transmitted disease, Kawasaki disease, appendicitis, Group A streptococcal infection, and, in the adolescent female, pelvic infection are further differential diagnoses. The distinguishing characteristics of each illness allow for a clear distinction from UTI [2].

COMPLICATIONS

In addition to missed school and work, UTI distresses the youngster, concerns the parents, and is a common source of discomfort. The ailment may harm the child's or parent's quality of life, especially if the UTI is recurring or causes chronic kidney impairment. UTI in childhood is a risk factor for recurrent abdominal pain [28]. Bacteremia is rather prevalent. Prematurity, early age (<1 year), and high blood creatinine upon presentation are all risk factors for bacteremia [29]. In newborns with a gestational age of fewer than 32 weeks, late-onset sepsis owing to UTI is not uncommon. Febrile convulsions can develop in young infants with pyelonephritis and a high fever. Renal insufficiency is a common complication of pyelonephritis, a preexisting congenital renal defect that predisposes the kid to UTI, or the use of nephrotoxic medications. Electrolyte and acid-base disturbances are possible [30].

Renal hypodysplasia, which is commonly congenital, is the most common cause of renal scarring. Renal scarring can also be linked to urinary tract abnormalities including high-grade VUR or urinary tract blockage. Nonetheless, after their first symptomatic bout of pyelonephritis, up to 5% of girls and 13% of boys develop a kidney scar [31]. Other risk factors for renal scarring include pyelonephritis in childhood, an increase in the number of pyelonephritic bouts, a delay in antibiotic treatment, bacterial virulence, and individual sensitivity. Scarring is considered highly vulnerable during the first 2 years of life, with a decreasing risk until about 8 years of age, after which the risk is greatly reduced [32].

In adolescence or early adulthood, around 10% of children with kidney scars will develop hypertension. Females who have renal scar are more likely to develop toxemia during pregnancy. Renal insufficiency and end-stage renal disease are probable outcomes of pyelonephritic renal scarring. In the post-antibiotic period, complications such as renal abscess, pyonephrosis, emphysematous pyelonephritis, and xanthogranulomatous pyelonephritis are uncommon [33].

TREATMENT

Children should be trained to urinate every 1.5–2 h and to never retain their urine until the last minute. When urinating, children should be encouraged to utilize proper posture and to take their time. Proper genital hygiene and fluid consumption should be promoted. Underlying problems including constipation and inefficient urination should be addressed [34].

Prompt antibiotic therapy is recommended for symptomatic UTI based on clinical signs and a positive urinalysis while waiting for culture results to eliminate the infection and enhance clinical outcomes. Asymptomatic bacteriuria, on the other hand, is not a medical condition that requires treatment. The empiric antibiotic used should provide adequate protection against Gram-negative rods, particularly *E. coli*, as well as Gram-positive Cocci. The ideal antibiotic should be simple to give, attain a high concentration in urine, have little or no effect on fecal or vaginal flora, have a low rate of bacterial resistance, be non-toxic, and be inexpensive. Use the least broad-spectrum antibiotic possible [35].

Antibiotics should be chosen based on local data on antibiotic resistance tendencies. Antimicrobial resistance has been developing in recent years due to the emergence of extended-spectrum beta-lactamase-producing pathogens. Fluoroquinolone resistance is uncommon; nonetheless, widespread use may enhance bacterial resistance. Fluoroquinolones should not be utilized as first-line therapy for UTIs caused by *P. aeruginosa* or other multidrug-resistant Gram-negative bacteria. Nitrofurantoin has low antibiotic resistance. The failure to achieve high tissue levels, however, limits its usage in infants and young children with febrile UTIs who are likely to have renal involvement. Because of the high prevalence of E. coli resistance to these drugs, ampicillin and amoxicillin are not appropriate treatments for empiric therapy of UTI [36].

CONCLUSION

UTI management in children can be difficult since symptoms in young children might be vague and nonspecific. A significant level of suspicion is required. UTI should be considered in any child under the age of two who has a fever. On the one hand, over-diagnosis may result in unneeded and potentially intrusive testing, treatment, and the growth of antibiotic-resistant microorganisms. Underdiagnosis and delayed treatment, on the other hand, may result in recurrence and an increased risk of renal scarring, which can lead to hypertension and chronic renal failure. As a result, prompt and correct diagnosis and treatment are critical.

AUTHOR'S CONTRIBUTION

RA: Concept, interpretation of data and data analysis, drafting the article, literature review, and revising the article critically for important intellectual content. AA, JJM: Acquisition and interpretation of data, data analysis, drafting the article, and literature review; all the authors approved the final manuscript.

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Funding: None; Conflicts of Interest: None Stated.

How to cite this article: Agrawal R, Agrawal A, Mandumpala JM. Urinary tract infection in pediatric patients – Recent updates. Indian J Child Health. 2023; 10(8):98-102.