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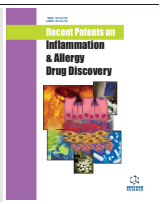
Recent Patents on Inflammation & Allergy Drug Discovery 2019, *13*, 2-18

REVIEW ARTICLE



Urinary Tract Infection in Children

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Abstract: ***Background***: Urinary Tract Infection (UTI) is a common infection in children. Prompt diagnosis and appropriate treatment are very important to reduce the morbidity associated with this condition.

Objective: To provide an update on the evaluation, diagnosis, and treatment of urinary tract infection in children.

Methods: A PubMed search was completed in clinical queries using the key terms "urinary tract infection", "pyelonephritis" OR "cystitis". The search strategy included meta-analyses, randomized controlled trials, clinical trials, observational studies, and reviews. The search was restricted to English literature and the pediatric age group. Patents were searched using the key terms "urinary tract infection" "pyelonephritis" OR "cystitis" from www.google.com/patents, http://espacenet.com, and www.freepatentsonline.com.

Results: *Escherichia coli* accounts for 80 to 90% of UTI in children. The symptoms and signs are nonspecific throughout infancy. Unexplained fever is the most common symptom of UTI during the first two years of life. After the second year of life, symptoms and signs of pyelonephritis include fever, chills, rigor, flank pain, and costovertebral angle tenderness. Lower tract symptoms and signs include suprapubic pain, dysuria, urinary frequency, urgency, cloudy urine, malodorous urine, and suprapubic tenderness. A urinalysis and urine culture should be performed when UTI is suspected. In the work-up of children with UTI, physicians must judiciously utilize imaging studies to minimize exposure of children to radiation. While waiting for the culture results, prompt antibiotic therapy is indicated for symptomatic UTI based on clinical findings and positive urinalysis to eradicate the infection and improve clinical outcome. The choice of antibiotics should take into consideration local data on antibiotic resistance patterns. Recent patents related to the management of UTI are discussed.

Conclusion: Currently, a second or third generation cephalosporin and amoxicillin-clavulanate are drugs of choice in the treatment of acute uncomplicated UTI. Parenteral antibiotic therapy is recommended for infants ≤ 2 months and any child who is toxic-looking, hemodynamically unstable, immunocompromised, unable to tolerate oral medication, or not responding to oral medication. A combination of intravenous ampicillin and intravenous/intramuscular gentamycin or a third-generation cephalosporin can be used in those situations. Routine antimicrobial prophylaxis is rarely justified, but continuous antimicrobial prophylaxis should be considered for children with frequent febrile UTI.

ARTICLE HISTORY

Received: August 29 2018
Revised: December 26, 2018
Accepted: December 26, 2018

DOI:
10.2174/1872213X13666181228154940

Keywords: Ampicillin, cephalosporin, cystitis, *Escherichia coli,* gentamycin, pyelonephritis, urinalysis, urine culture.

1. INTRODUCTION

Urinary Tract Infection (UTI) is one of the most common bacterial infections in childhood [1, 2]. The infection may affect the upper urinary tract (referred to as pyelonephritis) or the lower urinary tract (referred to as cystitis). Unfortunately, it may be difficult, if not impossible, to distinguish pyelonephritis from cystitis based on clinical symptoms and signs, especially in infants and young children [3, 4]. From a practical point of view, these two conditions are discussed together under the umbrella of UTI. The high incidence, tendency to relapse, associated morbidity, and problems with the collection of an uncontaminated urine specimen present significant challenges to the clinician [5, 6]. UTI is a signifi-

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2212-2710/19 $58.00+.00

cant concern for children, parents, and clinicians alike. Prompt diagnosis and appropriate treatment are very important to reduce the morbidity associated with this condition [7]. The purpose of this article is to familiarize physicians with an overview of the assessment and management of children with UTI.

2. PREVALENCE

During the first year of life, the incidence of UTI is approximately 0.7% in girls and 2.7% in uncircumcised boys [8, 9]. In febrile infants in the first two months of life, the incidence of UTI is approximately 5% in girls and 20% in uncircumcised boys [8, 9]. During the first 6 months, uncircumcised boys have a 10 to 12-fold increased risk of developing UTI [3, 8, 10]. In the neonatal period, UTI is more common in premature infants than term infants [11]. After one year of age, girls are much more likely than boys to develop UTI [11, 12]. UTI has a bimodal age of onset with one peak in the first year of life and another peak at between 2 and 4 years of age which corresponds to the age of toilet training [1, 2, 4]. It has been estimated that approximately 7.8% of girls and 1.7% of boys by the age of 7 years will have had a UTI [1, 13, 14]. By the age of 16 years, 11.3% of girls and 3.6% of boys will have had a UTI [1, 13, 14]. Hispanic and white children have a two- to-four fold higher prevalence of UTI than do black children [3, 15-17]. Generally, recurrence rates are 30 to 50% [2, 13]. Recurrence of UTI is especially common in girls [18]. Approximately 75% of Caucasian and 50% of African American school-aged girls in the United States with UTI have at least one recurrence of UTI [11, 13].

3. ETIOLOGY

The most common causative organisms are from the intestinal flora; *Escherichia coli* accounts for 80 to 90% of UTI in children [2, 11, 17, 19, 20]. Other organisms include *Enterobacter aerogenes, Klebsiella pneumoniae, Proteus mirabilis, Citrobacter*, *Pseudomonas aeruginosa*, *Enterococcus* spp., and *Serratia* spp. [3, 10, 17, 20-24]. *Proteus mirabilis* is more common in boys than in girls [14, 18]. *Streptococcus agalactiae* is relatively more common in newborn infants [4]. *Staphylococcus saprophyticus* is very common in sexually active female adolescents, accounting for ≥ 15% of UTI [11]. In children with anomalies of the urinary tract (anatomic, neurologic, or functional) or compromised immune system, *Staphylococcus aureus, Staphylococcus epidermidis, Haemophilus influenzae, Streptococcus pneumoniae*, *Streptococcus viridians,* and *Streptococcus agalactiae* may be responsible [21, 23, 25-27]. Hematogenous spread of infection, an uncommon cause of UTI, may be caused by *Staphylococcus aureus*, *Streptococcus agalactiae*, *Proteus mirabilis, Pseudomonas aeruginosa*, and nontyphoidal *Salmonella* [3, 21, 23]. Rare bacterial causes of UTI include *Mycobacterium tuberculosis* and *Streptococcus pneumoniae* [28, 29].

Viruses such as adenoviruses, enteroviruses, echoviruses, and coxsackieviruses may cause UTI [11, 17]. The associated infection is usually limited to the lower urinary tract [11, 17]. In this regard, adenoviruses are known to cause hemorrhagic cystitis [30]. Fungi (e.g., *Candida* spp., *Cryptococcus neoformans*, *Aspergillus* spp.) are uncommon causes of UTI and occur mainly in children with an indwelling urinary catheter, anomalies of the urinary tract, long-term use of broad-spectrum antibiotic, or compromised immune system [17, 30].

4. PATHOGENESIS

The majority (91 to 96%) of UTI results from the ascent of bacteria from the periurethral area, migrating in a retrograde fashion via the urethra to reach the bladder and potentially the upper urinary tract [4, 8, 17, 31]. Periurethral colonization with uropathogenic bacteria is considered an important factor [32]. The increased susceptibility of girls to UTI might be explained by the relatively shorter length of the female urethra and the regular heavy colonization of the perineum by enteric organisms [8]. Factors that increase colonization of the female perineum include high vaginal pH, increased adhesiveness of bacteria to vaginal cells, and diminished cervicovaginal antibody [5, 6]. The preputial space is a potential reservoir of bacterial pathogens in boys. Bacteria may also be introduced into the urinary tract via instrumentation such as catheterization [4]. Hematogenous spread can also occur and is more common in the first few months of life [33, 34]. Suffice to say, the majority of UTI occurs in the lower urinary tract [20] Only a minority results in pyelonephritis [20]. Invasion of the kidney by pathogens generates an intense inflammatory response which may lead to renal scarring [17].

4.1. Virulence Factors of Pathogens

Virulence factors of pathogens increase the likelihood that a specific bacterial strain will colonize and subsequently invade the urinary tract. These factors include α-hemolysin, M hemagglutinin, endotoxin, cytotoxic necrotizing factor 1, K capsular antigen, a rigid cell wall, serum resistance ability due to the outer membrane protein TraT, aerobactin which supports growth by chelating iron, and adhesive capacity [35, 36]. The three different types of adhesins identified on uropathogenic *E. coli* include type 1 pili (or fimbriae), P-fimbriae and X-adhesins [6, 35]. These adhesins facilitate adherence of the bacteria to mucosal receptors in the uroepithelium in spite of the flushing action of urine flow [20, 21]. Once the uroepithelium is invaded, an intracellular biofilm is formed [20]. The biofilm can protect the uropathogenic *E. coli* from the host immune system [20].

4.2. Host Defense Mechanisms

Although bacteria regularly ascend into the bladder, UTI is not inevitable. Local bladder-wall defense mechanisms, such as through the production of mucous and secretion of antimicrobial peptides by the uroepithelium, restrict attachment of bacteria to uroepithelial cells such as through the production of mucous and secretion of antimicrobial peptides by the uroepithelium [2]. In addition, the uroepithelium expresses toll-like receptors with the capacity to recognize pathogen-associated molecule patterns [37]. Engagement of Toll-like receptors can lead to uroepithelial cell activation and production of inflammatory mediators such as cytokines which generate a local inflammatory response to facilitate eradication of the invading bacteria [2, 37]. Additionally,

regular voiding with the antegrade flow of urine and complete bladder emptying minimize the opportunity for attachment [2, 8]. The urethral flora includes anaerobic bacteria; however, the growth of these micro-organisms is inhibited by low urine pH, soluble IgA, polymorphonuclear cells, lactoferrin, lipocalin, Tamm-Horsfall glycoprotein, and a high organic acid or urea concentration in the urine [6, 8, 11].

4.3. Host Compromising Factors

Conditions that interfere with the uni-directional flow of urine increase susceptibility to UTI. This occurs with vesicoureteric reflux and obstruction [31]. Vesicoureteric reflux, the most common urologic anomaly in children, allows bacteria to ascend from the bladder to the kidney, and also leads to post-void residual urine [38, 39]. Vesicoureteric reflux can be primary or secondary to the posterior urethral valve, ectopic ureter, or prune belly syndrome [11]. It is an important risk factor for recurrent UTI and renal scarring [40]. Vesicoureteric reflux occurs in 25 to 30% of children who have had a UTI [41]. Primary vesicoureteric reflux often resolves spontaneously while secondary vesicoureteric reflux only resolves with correction of the underlying cause [11].

Anatomic obstruction with resultant stasis of urine can occur due to phimosis, meatal stenosis, labial fusion, posterior urethral valves, urethral strictures, ureteroceles, ureterovesical or ureteropelvic junction obstruction, renal stone, or extrinsic mass (e.g., fecal impaction, tumor, cyst) [2, 8,31, 42-45]. These may predispose the child to UTI. In this regard, uncircumcised febrile male infants have a four- to-eight fold higher risk of UTI than circumcised ones [17, 46]. In spite of the higher risk, most uncircumcised males do not develop UTI [17].

A foreign body, such as a catheter or stone, predisposes to UTI by providing a nidus for bacterial growth [47, 48]. Urge syndrome and dysfunctional voiding are associated with post-void residual urine, which predisposes to UTI [49, 50]. Voiding postponement and infrequent voiding are other risk factors [51]. Other adverse host factors include parenchymal renal anomalies, dysfunctional bladder emptying, detrusor muscle instability, constipation, diabetes mellitus, immunodeficiency, obesity, and vitamin D deficiency [51-60].

Infants, especially neonates, are at a higher risk for UTI, presumably due to their incompletely developed immune systems [52]. Sexual intercourse is an important risk factor in female adolescents [8, 13, 52, 61]. Recent studies have shown that children and adolescents with psychosis are more prone to UTI [62, 63].

4.4. Genetic Factors

There is a genetic predisposition to recurrent UTI and renal scarring [64-69]. Genes that have been shown to predispose patients to recurrent UTI and renal scarring include *Angiotensin-Converting Enzyme Insertion/Deletion* (*ACE I/D*) gene, *Interleukin (IL)-8 receptor CXCR1* and *CXCR2* genes, *IL-10-1082 A/G* gene, *heat shock protein 72* (*HSPA1B*) gene, *Transforming Growth Factor* (*TGF*)-*β1* gene, *Toll-Like Receptor* (*TLR*) *pathway* genes, and *Vascular Endothelial Growth Factor* (VEGF) *gene* [64-69].

5. CLINICAL MANIFESTATIONS

In the neonatal period, the symptoms and signs are nonspecific. A neonate might present with signs of sepsis, such as temperature instability, peripheral circulatory failure, lethargy, irritability, apnea, seizure, or metabolic acidosis [6, 12]. Alternatively, a neonate might present with anorexia, poor sucking, vomiting, suboptimal weight gain, or prolonged jaundice [12, 21]. Foul-smelling urine is an uncommon, but more specific symptom of UTI [6]. Septic shock is unusual unless the patient is compromised or obstruction is present [2, 9, 25]. In neonates with UTI, there is a high probability of bacteremia, suggesting hematogenous spread of the bacteria [21].

The symptoms of UTI usually remain nonspecific throughout infancy. Unexplained fever is the most common during the first two years of life [9, 11, 21, 70]. In fact, it may be the only presenting symptom of UTI in this age group. In general, the prevalence of UTI is greater in infants with temperatures $\geq$ 39°C than those with temperatures $<$ 39°C [71]. Other nonspecific manifestations include irritability, poor feeding, anorexia, vomiting, recurrent abdominal pain, and failure to thrive [6, 8, 72, 73]. Specific symptoms and signs include increased or decreased number of wet diapers, malodorous urine, and discomfort with urination [5, 74]. A weak or dripping urinary stream suggests a neurogenic bladder or obstruction in the low urinary tract such as posterior urethral valves in boys [21]. Constant dripping of urine or wetting of diapers may suggest the presence of an ectopic ureter, a predisposing factor to UTI.

After the second year of life, the symptoms and signs of UTI are more specific. Symptoms and signs of pyelonephritis include fever, chills, rigor, vomiting, malaise, flank pain, back pain, and costovertebral angle tenderness [2, 6]. Lower tract symptoms and signs include suprapubic pain, abdominal pain, dysuria, urinary frequency, urgency, cloudy urine, malodorous urine, daytime wetting, nocturnal enuresis of recent onset, and suprapubic tenderness [2, 6, 11, 50, 74-76]. Urethritis without cystitis may present as dysuria without urinary frequency or urgency [13].

6. LABORATORY INVESTIGATIONS

A urinalysis and urine culture should be performed when UTI is suspected. This applies to children $<$ 3 years of age with unexplained fever and children $\geq$ 3 years of age with suprapubic pain, dysuria, urinary frequency, urgency, malodorous urine, and new-onset daytime wetting [10]. Quantitative urine culture is the gold standard for the diagnosis of UTI [77]. In infants, a voided urine specimen can be collected by attaching a sterile bag to the perineum. The advantages of this procedure are that it is non-invasive and easy to obtain [22, 30]. However, a “bagged” specimen is susceptible to contamination by periurethral flora, especially in girls and uncircumcised boys [9, 32]. A positive culture from a bagged specimen has a false positive rate of 30 to 75%; therefore, it requires a subsequent confirmation of the culture with a urine specimen collected by clean-catch, catheterization or suprapubic aspiration [15, 22, 30, 78]. On the other hand, the absence of significant bacterial growth from a bagged specimen is strong evidence against UTI [4, 8, 10, 22, 25]. The "bagged" method of urine collection in infants

is the technique most often used in daily practice, especially in primary care settings [9].

A clean-catch midstream urine specimen obtained after proper cleansing of the external genitalia is satisfactory for most diagnostic purposes in children who can void on demand [25, 77-80]. During cleansing and voiding, the risk of contamination can be minimized by having young girls sitting backward on the toilet seat and gently spreading the labia in girls and in uncircumcised boys retracting the foreskin [6, 79].

Catheterization of the urinary bladder to obtain a urine specimen for culture is not routinely recommended. Catheterization is associated with discomfort for the child, emotional stress for both the child and the parents, significant trauma with consequent dysuria and hematuria, and potential introduction of infection into the bladder [5].

Suprapubic aspiration is a useful method to obtain a clean urine sample from infants, as well as from those children who are incontinent or acutely ill [25, 81, 82]. The procedure is contraindicated in children with coagulopathy or an abdominal wall defect. Since most failures are caused by the absence of urine in the bladder, a suprapubic tap should not be performed in an infant who has recently voided. The success rate is higher when ultrasonographic guidance is used to ensure the bladder is adequately full and allow visualization of structures between the abdominal wall and the bladder [4, 9, 25]. Complications of suprapubic aspiration include transient gross hematuria and the rare inconsequential puncture of other abdominal viscera. Suprapubic aspiration should be reserved for situations in which a clean-catch or catheter specimen is not otherwise readily available or when the time is of essence.

Currently, there is no consensus regarding the best method for urine collection in children who are not toilet trained. The American Academy of Pediatrics recommends that the urine specimen needs to be obtained through suprapubic aspiration or catheterization only [81, 82]. Unfortunately, suprapubic aspiration and catheterization are invasive, stressful, and may not be feasible in a primary care setting [52]. On the other hand, the National Institute for Health and Clinical Excellence (NICE) and the Italian Society of Pediatric Nephrology (ISPN) recommend the clean-catch method as the method of choice for urine collection, reserving suprapubic aspiration or catheterization for specific situations such as a febrile child in poor general health or appears severely ill [83, 84]. The Canadian Paediatric Society recommends leaving the child with the diaper off and obtaining a clean-catch urine sample when the child voids [10]. If the urinalysis is abnormal, urine collection by catheterization or suprapubic aspiration would be in order [10]. For children who are toilet trained, a clean-catch midstream urine specimen should be obtained after proper cleansing of the external genitalia [10].

The urine should be collected in a sterile container, and the specimen should not be allowed to stand in room air because the number of bacteria will double every 30 minutes [5]. If the urine cannot be examined microscopically or plated within a short period, the specimen can be refrigerated at 4^{o}C for up to 4 hours, with minimal alteration in the results of the colony count [11, 16].

Microscopy should be performed to detect bacteriuria and pyuria [13, 25]. The presence of crystals or a significant number of urothelial cells, vaginal cells, red blood cells or white blood cells can mask the presence of bacteria in the urine. Gram stain of a urine specimen has a sensitivity of 81% and a specificity of 83% [3, 81, 82]. If a Gram stain of uncentrifuged urine specimen shows one or more bacteria per oil immersion field, there is an 80 to 95% correlation with a colony count of $>10^5$cfu/ml [6].

The presence of $\geq$ 5 white blood cells per high power field in centrifuged urine or $\geq$ 10 white blood cells as detected by hemocytometer in uncentrifuged urine, respectively, is the gold standard for pyuria [11, 13, 22, 77, 79]. However, pyuria is not diagnostic of UTI [85, 86]. Pyuria has a specificity of approximately 81% and sensitivity of 73% [81]. Sterile pyuria can be associated with infection due to anaerobic bacteria, tuberculosis, viral pathogens, chemical or allergic inflammation, cervical or vaginal secretion, Kawasaki disease, crystalluria, appendicitis, regional enteritis, glomerulonephritis, and interstitial nephritis [6, 11]. Conversely, the absence of pyuria on a single specimen does not rule out UTI [86]. Serial urinalysis in patients with UTI eventually shows pyuria.

Dipstick tests are inexpensive, convenient, readily available, and useful for diagnosis of UTI. The leukocyte esterase dipstick test demonstrates the presence of pyuria by histochemical methods that detect this enzyme in neutrophils [87, 88]. Leukocyte esterase is also present even if leukocytes are lysed [20]. On the other hand, a positive leukocyte esterase dipstick test is not diagnostic as leucocytes may be present in the urine in other conditions such as Kawasaki disease, hypercalciuria, gastroenteritis, and appendicitis [2, 15, 77]. The leukocyte esterase dipstick test may be falsely negative if leukocytes are present in low concentration [10]. The test has a specificity of approximately 78% and a sensitivity of 83% [81]. Application of the nitrite test is based on the principle that dietary nitrate in the urine will be reduced to nitrite if large numbers of nitrate-reducing bacteria (e.g., *E. coli*, *Klebsiella* species, *Proteus* species) are present and sufficient time is available to complete the reaction [87, 89]. The nitrite test has a specificity of approximately 98% and a sensitivity of 53% [77, 81]. False-negative reactions can result from inadequate dietary nitrate, inadequate time (< 4hr) for the conversion of nitrate into nitrite due to frequent emptying of the bladder, infection caused by non-nitrate-reducing bacteria (e.g., *Pseudomonas* spp., *Enterococcus* spp., *Staphylococcus saprophyticus*), antimicrobials that inhibit bacterial metabolism, a large volume of dilute urine, or ascorbic acid in the urine [15, 22, 88].

Williams *et al*. performed a meta-analysis on 95 studies involving 95,703 children to determine the absolute and relative accuracy of rapid urine tests (microscopy for bacteria and white blood cells and dipsticks for leukocyte esterase and nitrites) for UTI [90]. Summary estimates for specificity and sensitivity for microscopy for Gram-stained bacteria were 96% (95% confidence interval: 92 to 98) and 91% (95% confidence interval: 80 to 96), for unstained bacteria were 92% (95% confidence interval: 84 to 96) and 88% (95% confidence interval: 75 to 94), for urine white blood cells were 86% (95% confidence interval: 82 to 90) and 74%

(95% confidence interval: 67 to 80), for leukocyte esterase or nitrite positive dipstick were 79% (95% confidence interval: 69 to 87) and 88% (95% confidence interval: 82 to 91), and for nitrite-only positive dipstick were 98% (95% confidence interval: 96 to 99) and 49% (95% confidence interval: 41 to 57) [90]. The authors conclude that microscopy for bacteria with Gram stain had higher accuracy than other laboratory tests. Rapid urine tests have a false negative rate of approximately 10% and therefore cannot replace urine culture in the diagnosis of UTI [90, 91]. Nevertheless, rapid urine tests are good screening tests which when used in conjunction with urine culture can increase its diagnostic accuracy [92].

Urine culture remains the gold standard for diagnosing UTI [13]. Bacteria are usually evident in properly plated urine specimens by about 24hr and sensitivity results are usually available within 48hr. When a routine culture is negative, but the child is symptomatic or the Gram stain demonstrates bacteria, an anaerobic culture should be obtained. If the urine culture yields unusual bacteria or multiple bacteria in an uncontaminated urine specimen, immunodeficiency and malformation of the kidney and urinary tract should be excluded.

Neutrophilia, elevated erythrocyte sedimentation rate, elevated serum C-reactive protein, and white blood cell casts in the urinary sediment are suggestive of acute pyelonephritis [89, 93]. These tests, however, have low specificity and cannot accurately differentiate lower UTI from acute pyelonephritis [94]. Children with very high serum procalcitonin levels during UTI are more likely to have acute pyelonephritis [94-97]. A meta-analysis of 18 studies involving 831 children with acute pyelonephritis and 651 children with lower UTI were analyzed [94]. The authors found that a serum procalcitonin cutoff value of 1.0ng/ml provides a good diagnostic value for discriminating acute pyelonephritis from lower UTI. Because of the marked heterogeneity between studies, more intensive studies are necessary before this test can be routinely recommended in the evaluation and management of a child with UTI.

Serum creatinine should be considered in children treated with aminoglycosides > 48hr, with recurrent or complicated UTI, and suspected renal scarring [10, 77]. Blood culture is usually not necessary unless the child has suspected bacteremia or urosepsis, is toxic looking, or hemodynamically unstable [10].

7. DIAGNOSTIC IMAGING STUDIES

In the work-up of children with UTI, physicians must judiciously utilize imaging studies to minimize exposure of children to radiation. Renal and bladder ultrasonography is the method of choice to image the urinary tract [6]. Ultrasonography is noninvasive, safe, easy to perform, and radiation-free [77]. With renal and bladder ultrasound, hydration is essential to sufficiently fill the bladder filling. In toilet-trained children, a post-void evaluation is essential [98]. A renal and bladder ultrasound can define the kidney size, shape and position, echotexture of the renal parenchyma, the presence of duplication and dilatation of the ureters, obstructive uropathy, and structural abnormality of the bladder [9, 16]. The degree of echogenicity and the sharpness of the corticomedullary differentiation provide clues to the presence of generalized renal disease or local damage [99]. Renal ultrasonography can also identify renal or perirenal abscess or pyonephrosis [41]. Renal and bladder ultrasonography should be considered in children < 2 years of age with a febrile UTI, children of any age with recurrent UTI, and children with palpable abdominal mass, abnormal voiding, hypertension, hematuria, no response to standard antimicrobial treatment, and family history of renal or urological disease [9, 41, 70]. Ultrasonography is not a sensitive study to localize the infection or to detect a duplicated collecting system or vesicoureteric reflux [1, 7, 9]. It is, however, useful in predicting the risk of renal scarring [41]. For acutely sick children and children who do not respond to standard antimicrobial treatment, renal and bladder ultrasonography should be performed as soon as possible to rule out urinary tract obstruction or renal abscess [3, 41]. Otherwise, the procedure should be performed 1 to 2 weeks later to reduce the risk of false positive results secondary to renal inflammation [3, 41].

Renal imaging with ^{99m}Tc-Dimercaptosuccinic Acid (DMSA) can be used to detect acute pyelonephritis and renal scarring [4, 36, 100, 101]. Decreased renal uptake of the isotope suggests acute pyelonephritis or renal scarring [31, 41]. In addition, a DMSA renal scan can detect majority (> 70%) of children with moderate to severe vesicoureteric reflux [41, 102]. The routine uses of this imaging modality is not generally recommended due to the radiation hazard and the cost involved [20]. The NICE guidelines recommend DMSA renal scan 4 to 6 months after atypical UTI in children under 3 years of age and recurrent UTI in children of any age [84]. It has been suggested that a normal DMSA renal scan may obviate the need for voiding cystourethrogram in children with recurrent UTI [102]. If a DMSA renal scan has to be performed, it should be performed in the acute phase to detect acute pyelonephritis or 4 to 6 months later to assess for renal scarring [2].

A voiding cystourethrogram is the preferred screening test for vesicoureteric reflux [15, 36-39, 41]. This study accurately grades vesicoureteric reflux; identifies posterior urethral valves, ureteroceles, obstructive uropathies, and other abnormalities of the urethra, ureter, and bladder (e.g., bladder diverticuli or trabeculations); and provides clues to the presence of urge syndrome and dysfunctional voiding [16, 30]. It has been shown that 25 to 30% of children with UTI have vesicoureteric reflux [41]. The procedure is invasive and costly and exposes the child to radiation [41]. A voiding cystourethrogram does not need to be performed after the first febrile UTI unless renal and bladder ultrasonography reveals scarring, hydronephrosis, or other findings suggestive of high-grade vesicoureteric reflux or obstructive uropathy. The voiding cystourethrogram is also not required after the first febrile UTI in other atypical or complex clinical circumstances such as poor growth, hypertension, and a combination of high fever (temperature ≥ 39°C) and a pathogen other than *E. coli* [9, 15, 41, 81, 82]. This is because only a small number of children with vesicoureteric reflux ultimately require medical or surgical treatment for the vesicoureteric reflux [52]. Otherwise, the procedure should be performed if the child has 2 or more febrile UTI [15, 41]. Traditionally, a voiding cystourethrogram is usually scheduled several weeks after the febrile UTI. It is now recognized

that the procedure may be performed as long as the patient is asymptomatic [41]. The risk of post-procedural UTI after a voiding cystourethrogram is very low [103].

The nuclear cystogram is a sensitive test for the detection of vesicoureteric reflux but does not detect intrarenal reflux, delineate the degree of reflux, or provide a detailed image of the urethra and ureters [1, 16]. Thus, posterior urethral valves can be missed. The advantages of a nuclear cystogram are the low radiation dose and high sensitivity [1]. A nuclear cystogram is useful to screen siblings of patients who have vesicoureteric reflux and to follow children who have vesicoureteric reflux [36]. This test requires the child be toilet-trained [100].

Some authors suggest that imaging studies are indicated only for children at risk of developing renal damage [100]. A child is considered at risk of subsequent complications if the following features are present: clinical signs such as high fever, toxicity, poor urinary stream, palpable kidneys; unusual organism isolated in urine culture (other than *E. coli*); failure to respond to antibiotic treatment within 48hr, and recurrent UTI [100, 104].

Cystoscopy is indicated in children with severe vesicoureteric reflux, moderate vesicoureteric reflux unresponsive to conservative treatment, suspected duplicated collecting system, ureterocele, urethral obstruction, or neurogenic bladder.

8. DIAGNOSIS

According to the American Academy of Pediatrics (AAP) clinical practice guidelines, the diagnosis of UTI in children 2 to 24 months requires positive dipstick test (leukocyte esterase and/or nitrite test), microscopy positive for pyuria or bacteriuria, and the presence of ≥ 50,000cfu/ml of a uropathogen in a catheterized or suprapubic aspiration specimen [81, 82]. According to the Canadian Paediatric Society (CPS) guidelines, a positive dipstick test (leukocyte esterase and/or nitrite) and a positive urine culture of a single uropathogen (≥ 100,000cfu/ml in a midstream urine specimen, ≥ 50,000cfu/ml in a catheterized specimen, and any organism in a suprapubic aspiration specimen) are required for the diagnosis of UTI [10]. The European Association of Urology (EAU) / European Society for Paediatric Urology (ESPU) guidelines state that growth of 10,000 or even 1,000cfu/ml of a uropathogen from a catheterized specimen or any counts from a suprapubic aspiration specimen is sufficient to diagnose a UTI [25]. In toilet-trained children, a clean-catch midstream urine specimen rather than a catheterized or a suprapubic aspiration specimen should be submitted for urinalysis and urine culture [10].

Clinical judgment is important as UTI can occur, though rarely, in the absence of pyuria and that urine culture can be negative in children with UTI if a bacteriostatic/bactericidal antimicrobial agent is present in the urine or if there is ureteric obstruction preventing discharge of bacteria from the kidney to the bladder [77]. UTI with low bacterial count is not uncommon if the infection is caused by non-*E. coli* species [105].

9. DIFFERENTIAL DIAGNOSIS

Asymptomatic bacteriuria refers to colonization of the urinary tract by nonvirulent bacteria that are incapable of mounting a symptomatic response or inflammation [25]. The condition occurs in approximately 1% of children with a predominance in girls [77]. Children with underlying genitourinary abnormalities have a higher chance of asymptomatic bacteriuria. Asymptomatic bacteriuria is present when a urine culture is positive, but there are no symptoms to suggest UTI and the urine does not contain an abnormal number of white blood cells.

A urine culture that yields multiple microorganisms suggests contamination rather than UTI, unless the patient is immunocompromised or if there is a malformation of the kidney and urinary tract.

Failure to spread the labia with voiding can lead to urine flow into the vagina, contamination of the urine with vaginal bacteria and an erroneous diagnosis of UTI. Vulvovaginitis can cause dysuria, and often co-exist with UTI. Prepubertal girls may have urethritis with resulting dysuria from poor hygiene or exposure to irritants such as bubble bath or harsh soap per se and not from UTI [10, 79].

Urge syndrome and dysfunctional voiding may present with a frequency of micturition, urgency, daytime wetting, and nocturnal enuresis. Although UTI is more common in these children, the voiding dysfunction symptoms are present in the absence of UTI. When these symptoms persist after successful treatment of a culture-proven UTI, urge syndrome or dysfunctional voiding should be considered.

Other differential diagnoses include viral infection, post-vaccination fever, urinary calculi, vaginal foreign body, orchitis, urethritis secondary to a sexually transmitted disease, Kawasaki disease, appendicitis, group A streptococcal infection, and, in the adolescent female, pelvic infection [3, 77]. The distinctive features of each condition allow a straightforward differentiation from UTI.

10. COMPLICATIONS

UTI distresses the child, concerns the parents and is a common cause of discomfort, in addition to missed school and work. The condition may adversely affect the quality of life of the child or parents, especially if the UTI is recurrent or causes permanent renal damage [106, 107]. UTI in infancy is a risk factor for recurrent abdominal pain in childhood [108].

Bacteremia is not uncommon [21]. In one study, bacteremia occurred in 5.6% of children with UTI [109]. Risk factors for bacteremia include prematurity, young age (< 1 year), and high serum creatinine at presentation [109]. Late-onset sepsis due to UTI is not uncommon in infants with a gestational age of less than 32 weeks [110]. Febrile convulsion may occur in young children with high fever from pyelonephritis [111, 112].

Renal insufficiency is a well-known complication, either from pyelonephritis per se, a preexisting congenital renal anomaly which predisposes the child to UTI, or from the use of nephrotoxic antibiotics [4]. Electrolyte and acid-base disturbance may occur. In one prospective cross-sectional study, electrolyte and an acid-base disturbance occurred in 59 (74%) of 80 children with acute pyelonephritis [113]. Fifty children had hyponatremia, 18 had hypobicarbon-

atemia, 14 had hyperkalemia, 6 had hyperbicarbonatemia, 3 had hypochloremia, 3 had hypokalemia, and 1 had hyperchloremia [113].

The most important cause of renal scarring is renal hypodysplasia which is often congenital in origin [2, 20]. Renal scarring can also be associated with urinary tract anomalies such as high-grade vesicoureteric reflux or urinary tract obstruction [2, 20]. Nevertheless, a renal scar develops in up to 5% of girls and 13% of boys after their first symptomatic episode of pyelonephritis [6, 18, 31]. Other factors that predispose to renal scarring include pyelonephritis in infancy, increased number of pyelonephritic attacks, delay of antibiotic treatment, bacterial virulence, and individual susceptibility [17, 36, 41, 75, 114]. The first two years of life are considered an especially vulnerable time for scarring, with diminishing risk until about eight years of age, beyond which the risk is much reduced [6]. Predictors of renal scarring after a first URI include temperature $\geq 39^{\circ}C$, vesicoureteric reflux (especially high-grade), abnormal renal/bladder ultrasonography, increased absolute neutrophil count, increased serum procalcitonin, C-reactive protein > 40mg/l, and *VEGF*, *ACE I/D* and *TGF-β1* gene polymorphisms [11, 17, 69, 114, 115].

Approximately 10% of children with a renal scar will develop hypertension in adolescence or early adulthood [8, 101]. Females with a renal scar are at increased risk for toxemia in pregnancy. Renal insufficiency and end-stage renal disease is a possible consequence of renal scarring from pyelonephritis [8, 34].

Complications such as renal abscess, pyonephrosis, emphysematous pyelonephritis, and xanthogranulomatous pyelonephritis are rare in the post-antibiotic era [4, 41].

11. TREATMENT

Children should be instructed to void about every 1.5 to 2hr and never to hold the urine to the last minute. With voiding, children should be encouraged to use optimal posture and take time to completely empty themselves. Meticulous genital hygiene and adequate fluid intake should be encouraged. Underlying conditions such as constipation, dysfunctional voiding should be treated [116, 117].

Prompt antibiotic therapy is indicated for symptomatic UTI based on clinical findings and positive urinalysis while waiting for the culture results to eradicate the infection and improve clinical outcome [5, 7,25, 31, 77, 118] Asymptomatic bacteriuria, on the other hand, does not need to be treated [6, 30, 119]. The empiric antibiotic chosen should provide adequate coverage for Gram-negative rods notably *E. coli* and Gram-positive *Cocci* [7]. The ideal antibiotic should be easy to administer, achieve a high concentration in the urine, have minimal or no effect on the fecal or vaginal flora, have a low incidence of bacterial resistance, have minimal or no toxicity, and have a low cost [6, 31]. The least broad-spectrum antibiotic should be used [10]. Empiric antimicrobials that have been used in the treatment of acute uncomplicated UTI in children include cephalosporins such as cefixime (Suprax), cefdinir (Omnicef), ceftibuten (Cedax), cefpodoxime (Vantin), cefuroxime (Ceftin), and cefprozil (Cefzil), fluoroquinolones such as ciprofloxacin (Cipro, Ciloxan, Neofloxin), nitrofurantoin (Macrobid, Macrodantin), trimethoprim-sulfamethoxazole (TMP-SMX), ampicillin (Ampi, Omnipen, Principen, Penglobe), amoxicillin (Amoxil, Moxatag, Trimox, Wymox), and amoxicillin-clavulanate (Clavulin, Augmentin) (Table **1**) [10, 36, 41, 87, 116, 120]. The choice of antibiotics should take into consideration local data of antibiotic resistance patterns [7, 13, 52, 119]. The antibiotic may have to be adjusted based on the response to treatment and sensitivity testing of the isolated uropathogen [6]. In recent years, resistance to antimicrobials is increasing as extended spectrum beta-lactamase-producing organisms are emerging [119, 121]. In one study, of the 584 UTI cases caused by *E. coli* or *Klebsiella* spp., 91 (15.5%) cases were

Table 1. Oral Antimicrobial Agents for Pediatric Urinary Tract Infection.

Medication	Dosage (mg/kg/day)	Doses/day
Cefixime	8	1
Cefdinir	14	1
Ceftibuten	9	1
Cefpodoxime	10	2
Cefuroxime	30	2
Cefprozil	30	2
Ciprofloxacin	30	2
Nitrofurantoin	5-7	4
TMP–SMX	6 TMP and 30 SMX	2
Ampicillin	50	4
Amoxicillin	50	3
Amoxicillin-clavulanate	40*	3

*Dose for amoxicillin component.

caused by spectrum beta-lactamase-producing organisms [121]. A significant linear increase in resistance to all generations of cephalosporins ($r^2 = 0.442$) and fluoroquinolones ($r^2 = 0.698$) were found. Currently, a second- or third-generation cephalosporin and amoxicillin-clavulanate are drugs of choice [7, 13, 41]. Resistance to fluoroquinolones is rare; however, widespread use may lead to increase bacterial resistance [4, 116]. Therefore, fluoroquinolones should not be used as a first-line agent except for UTI caused by *Pseudomonas aeruginosa* or other multidrug-resistance, Gram-negative bacteria [41]. Antibiotic resistance to nitrofurantoin is low [4]. However, the inability to achieve high tissue levels limits its use in infants and young children with febrile UTI in whom renal involvement is likely [4, 41]. Likewise, trimethoprim-sulfamethoxazole should be used with caution, especially when pyelonephritis is suspected because of the high rates of resistance to this medication in some communities [41]. Nitrofurantoin or trimethoprim-sulfamethoxazole should be considered in sexually active females with UTI caused by *Staphylococcus saprophyticus* [120]. Ampicillin and amoxicillin are not ideal medications either for empiric treatment of UTI because of a high rate of resistance of *E. coli* to these medications [41]. Rather, ampicillin or amoxicillin should be used when enterococcal UTI is suspected or confirmed [41].

The American Academy of Pediatrics guidelines state that initiating antibiotics orally or parenterally is equally efficacious in the treatment of UTI (both cystitis and acute pyelonephritis) [81, 82]. Parenteral antibiotic therapy is recommended for infants ≤ 2 months and any child who is toxic-looking, hemodynamically unstable, immunocompromised, unable to tolerate oral medication, or not responding to oral medication [6, 41]. A combination of intravenous ampicillin 100 to 200mg/kg/day in divided doses every six hours and intravenous or intramuscular gentamycin 5 mg to 7.5mg/kg/day in divided doses every eight hours is recommended [6]. Gentamycin levels and serum creatinine should be obtained in any child treated with gentamycin for more than 48 hours. Alternatively, ampicillin in combination with a third-generation cephalosporin, such as cefotaxime 100 to 150mg/kg/day in divided doses every eight hours intravenously, ceftriaxone 50 to 75mg/kg/day in divided doses every 12hr intravenously or intramuscularly, or cefepime (Maxipime) 100mg/kg/day in divided doses every 12hr intravenously or intramuscularly can be used because they are less nephrotoxic than gentamycin [8, 10, 41, 87] (Table **2**). Ampicillin is important to cover Enterococcus. The drug of choice should be adjusted when culture and sensitivity results are available.

The optimal duration of treatment of UTI is controversial [25]. A 2003 Cochrane systematic review of 10 randomized and quasi-randomized controlled studies involving 652 children with lower UTI found no significant difference between 2 to 4 days and 7 to 14 days of oral antibiotic therapy in terms of frequency of positive urine cultures, development of resistant organisms, or recurrence of UTI [122]. A 2012 Cochrane systematic review of 16 randomized and quasi-randomized controlled studies involving 1,116 children with lower UTI found that 10 days of antibiotic treatment is more likely to eliminate bacteria from the urine than single-dose therapy [71]. There is also evidence that treatment ≤ 3 days duration is less than desirable [81, 82]. We take the middle of the road approach and suggest a duration of treatment for 5 to 7 days for lower (afebrile) UTI, depending on the age of the child, risk factors, clinical severity, and response to treatment unless further studies and more updated systematic review show it otherwise.

A 2007 Cochrane review of 23 randomized and quasi-randomized controlled studies involving 3,295 children with acute pyelonephritis found no significant difference between oral antibiotic therapy (10 to 14 days) and intravenous antibiotic therapy (3 days) followed by oral antibiotic therapy (10 days) in terms of duration of fever and subsequent persistent renal damage [123]. Similarly, there was a significant difference between intravenous antibiotic therapy (3 to 4 days) followed by oral antibiotic therapy and intravenous antibiotic therapy (7 to 14 days) in terms of persistent renal damage [123]. A more recent 2014 Cochrane database systematic review of 27 randomized and quasi-randomized controlled studies involving 4,452 children with acute pyelonephritis showed that a short course of intravenous antibiotic therapy (2 to 4 days) followed by oral antibiotic therapy is as effective as a longer course (7 to 14 days) of intravenous antibiotic therapy [124]. We and other investigators suggest a course of therapy of 7 to 10 days for febrile (upper) UTI [6, 7, 83, 90, 124]. For patients who are initially treated with parenteral antibiotics, oral antibiotics can be used to complete the course of therapy if the child can tolerate oral medications and has been afebrile for 24 hours [41].

12. ADJUNCTIVE THERAPIES

Phenazopyridine hydrochloride (Pyridium) may be considered for the symptomatic treatment of severe dysuria in adolescents [16, 125]. The recommended dose is 4mg/kg

Table 2. Parenteral Antimicrobial Agents for Pediatric Urinary Tract Infection.

Medication	Dosage (mg/kg/day)	Doses/day
Ampicillin	100-200	4
Gentamycin	5-7.5	3
Cefotaxime	100-150	3
Ceftriaxone	50-75	2
Cefepime	100	2

three times a day for up to 2 days [16]. Phenazopyridine when excreted into the urine, has a local analgesic effect. It is often used to alleviate the pain, irritation, discomfort, or urgency caused by UTI. The medication typically turns the urine dark orange to bright red.

Sweazy and Sweazy disclosed a pharmaceutical composition that they claimed is effective in the treatment of UTI which consists of a combination of nitrofurantoin, an analgesic (preferably phenazopyridine), and a pharmaceutically acceptable carrier [126]. The invention is predicated on the discovery that the co-administration of the antibiotic nitrofurantoin and an analgesic for the treatment of UTI results in an unexpected, significantly improved patient compliance with prescribed drug dosing regimens. It is believed that the alleviation of the pain associated with UTI by the analgesic co-administered with the antibiotic functions to relieve the anxiety suffered by patients over the length of treatment regimens, thereby ensuring better patient compliance.

It has been shown that cytokines play an important role in the formation of renal scar following febrile UTI [127, 128]. Of 54 children with a diagnosis of first-time acute pyelonephritis, Sharifian *et al*. treated 34 children with ceftriaxone and dexamethasone and 20 children with ceftriaxone alone [128]. The authors found that urinary cytokines (IL-6 and IL-8) concentrations were significantly lower in children treated with ceftriaxone and dexamethasone versus those children with ceftriaxone alone ($p < 0.05$), suggesting the use of corticosteroids may prevent the formation of renal scar following acute pyelonephritis. Huang *et al*. randomly assigned 84 children with a diagnosis of first-time acute pyelonephritis and at high risk of renal scar formation to receive either antibiotics plus methylprednisone (n = 19) or antibiotics plus placebo (n = 65) [129]. The authors found that treatment with antibiotics plus methylprednisone significantly reduced renal scar formation at 6 months post-UTI (33% versus 60%; $p < 0.05$). Because of the study's small sample size, further well-designed, large-scale, randomized, double-blind, placebo-controlled studies are needed to confirm these findings before corticosteroids can be recommended in the treatment of febrile UTI to reduce the risk of scarring.

A preliminary study showed that vitamin E supplementation has a significant effect on ameliorating symptoms and signs of UTI [130]. Yousefichaijan *et al*. randomly assigned 152 girls aged 5 to 12 years with first-time acute pyelonephritis to receive a 14-day treatment with vitamin E and antibiotics (n = 76) or antibiotics alone (n = 76). The authors found that the mean frequency of fever ($p = 0.01$), urinary urgency (n = 0.003), frequency ($p = 0.001$), dribbling ($p = 0.001$), and urinary incontinence ($p = 0.006$) were significantly lower in children treated with vitamin E and antibiotics compared to those treated with antibiotics alone [130]. It is speculated that vitamin E, an antioxidant, exerts its effect through inhibition of prostaglandin caused by an infectious process, thereby triggering host defense mechanisms [130]. Further studies are needed to confirm or refute these findings.

Another preliminary study showed that zinc supplementation has a significant effect in ameliorating dysuria, urinary frequency, and urgency of UTI [131]. Yousefichaijan *et al*. randomly assigned 200 children hospitalized for UTI to receive a 14-day treatment with oral zinc sulfate syrup and intravenous ceftriaxone (n = 100) or intravenous ceftriaxone alone (n = 100) [131]. The authors found that the number of days with dysuria ($p = 0.01$), urinary frequency ($p = 0.004$), and urgency (n = 0.003) were significantly lower in children treated with zinc sulfate and antibiotics compared to those treated with antibiotics alone. Further studies are needed to confirm or refute these findings before zinc supplementation can be recommended.

13. PROPHYLAXIS

Recurrences of UTI are often the result of noncompliance, inadequate antimicrobial therapy, bacterial resistance, urinary stasis, or host susceptibility, notably vesicoureteric reflux [29, 132, 133]. Recurrent UTI usually does not lead to renal scarring in children with no structural renal anomaly [134]. As such, routine antimicrobial prophylaxis is rarely justified as the number needed to treat (16 children on antimicrobial prophylaxis for 1 year) to prevent one episode of UTI is too high, taken into consideration the adverse events and the emergence of antimicrobial resistance associated with such antimicrobial prophylaxis [7, 79, 135, 136]. A 2017 systematic review of 7 randomized, controlled trials involving 1,427 children with symptomatic or febrile UTI showed no significant influence of antibiotic prophylaxis in the prevention of renal scarring (pooled risk ratio: 0.83; 95% confidence interval: 0.55 to 1.26) as did a sub-analysis limited to those children with vesicoureteric reflux (pooled risk ratio: 0.79; 95% confidence interval: 0.51 to 1.24) [137]. The use of prophylactic antibiotics in recurrent UTI is less clear as several large-scale studies have demonstrated a statistically beneficial effect of antibiotic prophylaxis in children with recurrent UTI [2]. The present consensus is that continuous antimicrobial prophylaxis should be considered for children with frequent febrile UTI regardless of the presence of urinary tract abnormalities [79]. Some authors consider continuous antimicrobial prophylaxis to children with grade IV or V vesicoureteric reflux or a major urological anomaly after a UTI [134]. In such cases, the benefits and risks of antimicrobial prophylaxis should be discussed with the child/parents before the prophylaxis is implemented [134].

Continuous prophylaxis with either low-dose nitrofurantoin (1 to 2mg/kg) or TMP-SMX (1 to 2mg of TMP and 5 to 10mg of SMX/kg) once a day orally is effective in the prevention of UTI in children with severe vesicoureteric reflux or frequent recurrences [7, 36, 87]. As nitrofurantoin and TMP-SMX are not recommended in infants younger than 6 weeks, a first-generation cephalosporin such as cephalexin 10mg/kg orally may be given until the infant reaches 6 weeks of age. Breakthrough infections should be treated with another antibiotic based on culture and sensitivity.

Parents and children should be instructed on proper perineal hygiene, including wiping from the anterior perineum towards the anal region and regular rinsing of the perineum in girls and the foreskin and glans in boys [2]. Although uncircumcised male infants are at higher risk for UTI, routine circumcision in the neonatal period is not recommended as 110 to 140 male infants would have to be circumcised to prevent one episode of UTI [30, 85]. Circumcision, or even better, topical application of corticosteroid to the distal

stenotic portion of the prepuce, may be considered in boys with recurrent UTI [85, 138]. Normal bowel and bladder habits must be established and constipation, if present, should be properly treated [2, 6, 117, 134]. Parents should be informed of the symptoms and signs of a recurrence and to seek medical attention when suspicion arises [134].

It has been shown that cranberry products are effective in the prevention of adhesion of bacteria to the uroepithelium [139]. Cranberry products have been used with increasing frequency to prevent UTI [139, 140]. Common cranberry products include cranberry juice, cranberry capsules, gelatinized products, and fresh, whole cranberries [7]. A 2017 meta-analysis of 7 randomized controlled studies conducted in 1,498 women aged ≥ 18 years with a history of UTI showed that cranberry reduced the risk of UTI by 26% (pooled risk ratio: 0.74; 95% confidence interval: 0.55 to 0.98) [141]. The benefit of cranberry products for the prevention of recurrent UTI in children is less clear. Moreover, long-term, regular consumption of cranberry products can be difficult, especially for young children [7].

Probiotics have been used for the prevention of UTI in children and adults [52, 142, 143]. A 2017 Cochrane meta-analysis of 6 randomized and quasi-randomized controlled studies involving 352 children and adults with UTI found no significant reduction in the risk of recurrent UTI between patients treated with probiotics and placebo (risk ratio: 0.82; 95% confidence interval: 0.60 to 1.12) with wide confidence intervals [143]. The authors commented that a benefit cannot be ruled out as the data were few and derived from small studies with poor methodological reporting.

14. PROGNOSIS

Children with a functional or anatomic abnormality of the urinary tract or immunodeficiency are prone to UTI [120]. The prognosis of UTI in the absence of vesicoureteric reflux and renal scarring is usually good and not associated with long-term sequelae [1, 144]. Recent studies have shown that much of the renal scarring previously attributed to acute pyelonephritis is related to congenital renal dysplasia, high-grade vesicoureteric reflux, or urinary tract obstruction [20]. Nevertheless, it has been proven beyond doubt that delay in treatment of febrile UTI or recurrent febrile UTI may lead to renal scarring [120].

CONCLUSION

Management of UTI in children can be challenging because symptoms can be vague and nonspecific in young children. A high index of suspicion is essential. UTI should be considered in any child < 2 years presenting with fever. On the one hand, over-diagnosis may lead to unnecessary and potentially invasive testing, unnecessary treatment, and the emergence of bacterial resistance to antibiotics. On the other hand, under-diagnosis and delayed treatment may lead to recurrence and risk for renal scarring which may lead to hypertension and chronic renal failure. Timely and accurate diagnosis and appropriate treatment are therefore essential.

CURRENT & FUTURE DEVELOPMENTS

There is an urgent need to develop non-invasive methods and devices for urine collection that are relatively free from contamination in non-toilet trained children. Automated urine analyzers have been developed in the screening of urine samples to determine the need for urine culture [145, 146]. SediMAX (also known as Urised) is an automated walk-away analyzer which uses digital imaging and an automatic image module to detect, count, and classify urine particles and reports quantitative results [146]. SediMAX has a false negative rate of 2.4% and a positive rate of 27.6%. By employing the automated urine analyzer SediMAX, 54% of the investigated samples could have avoided urine culture. Sysmex UF-1000i is another urine particle analyzer which uses flow cytometer to determine cell counts and incorporates bacteria morphology distinction [145]. The analyzer has a negative predictive value of 97 and only 1.17% diagnostic error. The diagnostic error can be reduced to 0.4% when contaminated samples are excluded.

There is a continuing need for identifying more specific biomarkers to improve the diagnostic accuracy of UTI. Accurate diagnosis and efficient treatment can improve the outcome of children with UTI. Promising results have been published on urinary Neutrophil Gelatinase-Associated Lipocalin (NGAL) in identifying children with UTI, especially acute pyelonephritis [147-149]. Barasch and Paragas pointed out that in response to UTI caused by enterochelin-dependent uropathogenic bacteria, epithelial cells of the genitourinary tract secrete NGAL [150]. Urinary NGAL has a sensitivity of 93 to 96% and a specificity of 95 to 100% for diagnosing UTI which are considerably higher than those of leukocyte esterase dipstick test and the nitrite test [147,149]. The test has similar specificity compared to Gram stain of a urine specimen but has higher sensitivity [147]. It has also been shown that plasma NGAL is a sensitive predictor for identifying acute pyelonephritis and can be used to monitor its treatment response [151-153]. Plasma NGAL is more useful than serum procalcitonin, serum C-reactive protein, and white blood cells levels [151-153].

Björck *et al*. disclosed that urinary level of Heparin Binding Protein (HBP) increases in individuals with UTI [154]. HBP (CAP37, Azurocidin) is a glycosylated, single chain, positively charged 37kDa inactive serine protease homologue exhibiting 44% sequence identity with human neutrophil elastase. The three-dimensional structure of HBP is contained in the azurophilic granulae and secretory vesicles of human neutrophils. It is a multifunctional protein that has been shown to induce vascular leakage by altering the calcium balance of the blood vessel cytoskeleton.

Antimicrobial peptides Human α-Defensin 5 (HD5) and Human Neutrophil Peptides (HNP)1-3 are other urinary biomarkers. Schwaderer *et al*. patented a kit for diagnosing UTI using antibodies specific for HD5 and HNP1-3 [155]. The kit includes a first antibody or binding fragment thereof specific for HD5 and/or a second antibody or binding fragment thereof specific for HNP1-3, reagents for conducting the diagnosis, and a package for holding the antibodies and the reagents. In some embodiments, the kit also includes a third antibody or binding fragment thereof specific for leukocyte esterase.

YKL-40, also referred to as Chitinase-3-Like-1 (CH13L1) or cartilage glycoprotein-39 is another novel useful urinary biomarker [156-158]. Novel urinary biomarkers useful in diagnosing acute renal injury and predicting subse-

quent renal scarring include Kidney Injury Molecule-1 (KIM-1) and angiotensiogen [159, 160]. Further studies are warranted to investigate the pathophysiological role of these biomarkers, ways to improve their sensitivity and specificity, and cost-effectiveness analysis of these biomarkers in the diagnosis of UTI.

Very recently, Swiss *et al*. disclosed compositions, methods, and kits that are directed to detection of UTI caused by urease-producing bacteria such as *Proteus* spp., *E. coli*, *Enterococcus* spp. [161]. The composition comprises of urine and a solid support comprises of a plurality of fissile ester bonds; each fissile bond is linked to a label so as to provide for a pro-label. Each fissile bond is stable in the urine from a patient not suffering from UTI but the fissile bond is cleaved by urease in the urine from a patient suffering UTI. The urease converts the pro-label to a label capable of generating a distinct label which will produce a distinct detectible signal indicative of a UTI. The signal generated by the UTI can be amplified by including urea particles such as microparticles in the chamber. Such microparticles, in the presence of any urease, will generate additional ammonia in the urine. The resulting ammonia will enhance the early detection of UTI that expresses urease. The amplification of signal also allows for the detection of incipient UTI. This invention is directed especially to UTI associated with the use of urinary catheters.

Newer non-invasive imaging modalities are being investigated in the work-up of children with UTI. Recently, non-enhanced magnetic resonance imaging has been investigated as a modality for the detection of renal scarring [162, 163]. An important advantage of non-enhanced magnetic resonance imaging over DMSA renal scan is that it can distinguish an area of inflammation and an area of scarring whereas both types of areas might be interpreted as scarring on DMSA renal scan [163]. In addition, non-enhanced magnetic resonance imaging is radiation free, requires no intravenous route for administration, and takes only 20 minutes to perform. In contrast, DMSA renal scan exposes the child to radiation, requires intravenous route for administration of the radioactive nuclide, and takes several hours to perform [163].

Superb microvascular imaging is a new ultrasound Doppler technique that enables ultrasound imaging of low-velocity flow that is non-invasive, radiation free, and without intravenous contrast [164]. The procedure can detect the direction of the urinary flow. The presence of reversed urinary flow at the distal ureter and/or renal pelvis or swirling at the renal pelvis correlates with high-grade vesicoureteric reflux [164]. It is hoped that superb microvascular imaging can replace other imaging techniques in the detection of vesicoureteric reflux.

Worldwide, the frequency of UTI caused by extended-spectrum beta-lactamase-producing organisms is increasing [165]. Antibiotics effective in the treatment of UTI caused by extended-spectrum beta-lactamase-producing organisms include aminoglycosides, fluroquinolones, piperacillin/tazobactam (Tazocin, Zosyn), and carbapenems [119, 165-167]. Carbapenems are the treatment of choice for severe infections caused by extended-spectrum beta-lactamase-producing organisms [119]. To minimize the emergence of carbapenemase-producing strains, the use of carbapenems should be reserved for severe UTI caused by multidrug resistant strains, in which there is only one treatment choice [119]. A preliminary study showed that 14 of 15 extended-spectrum beta-lactamase-producing *E. coli* isolates were susceptible to cefmetazole (Zefazone), fosfomycin (Monurol), flomoxef (Flumarin, Efmox), and imipenem/cilastatin (Primaxin) [165]. This new finding warrants further investigations in randomized, placebo-controlled trials to further elucidate the clinical efficacy of these medications in the treatment of UTI caused by extended-spectrum beta-lactamase-producing organisms.

Recently, Loutit *et al*. disclosed a composition comprising a cyclic boronic acid ester vaborbactam or a pharmaceutically acceptable salt thereof in combination with meropenem for the treatment of complicated UTI [168]. Meropenem-vaborbactam is a beta-lactam antibiotic combination of the approved carbapenem, meropenem, and a new novel chemical class of a beta-lactamase inhibitor, vaborbactam. Meropenem is a broad-spectrum, injectable, carbapenem antibiotic. The authors claimed that the invention is efficacious, safe, and well tolerated. Meropenem' s spectrum of activity includes many Gram-positive bacteria, Gram-negative bacteria, and anaerobic bacteria. Vaborbactam is a beta-lactamase inhibitor from a new novel chemical class that was optimized for potent inhibition of class A serine carbapenemases.

Bentley *et al*. disclosed an invention comprising finafloxacin (Xtoro) or a pharmaceutically acceptable salt, derivative, enantiomer, or hydrate thereof [169]. A preferred salt in embodiments of the present invention is finafloxacin monohydrochloride. Finafloxacin is a novel fluoroquinolone that has good activity against Gram positive, Gram negative and anaerobic pathogens and eradicates uropathogens more quickly than other fluoroquinolones currently used for the treatment of UTI. Finafloxacin is an antibiotic of the class of the quinolone carboxylic acids of the following formula: 8-cyano-1-cyclopropyl-6-fluoro-7-[(4aS,7aS)-hexahydropyrrolo [3,4-B]-1,4-oxazin-6(2H)-yl]-4-oxo-1,4-dihydroquinoline-3-carboxylic acid. Due to the efficacy of finafloxacin and reduced treatment durations without increasing the daily dosage, the use of finafloxacin would improve patient convenience and significantly lower the costs of hospitalization and treatment. The inventive treatment regimens comprise an oral finafloxacin administration for 1 to 5 days for uncomplicated UTI and a parenteral finafloxacin administration for 1 to 5 days for use in the treatment of pyelonephritis. The increased activity of finafloxacin in an acidic environment is found to be exactly opposite to that of all marketed quinolones. Therefore, finafloxacin appears to be an excellent medication in all indications associated with a low pH environment.

Shapland *et al*. patented a pharmaceutical composition for the prevention and/or treatment of UTI [170]. The said composition comprises of one or more oligomeric tannins, selected from proanthocyanidins and/or hydrolysable tannins, wherein the said pharmaceutical composition can be administered intraurethrally and/or intravesically. The pharmaceutical composition forms a protective barrier on the epithelial surfaces of the urogenital tract, thereby promoting

uroepithelial impermeability to bacterial adherence or bacterial invasion.

Raduti disclosed a composition comprising 0.1 to 2g of a pH increasing agent, 0.1 to 2g of a pH decreasing agent, and 0.5 to 4g of mannose and/or an analogue thereof, claimed by the author to be useful in the treatment and/or prevention of UTI [171]. The pH increasing agent and the pH decreasing agent are provided to be alternately administered orally to the subject together with mannose and/or an analogue thereof. The pH increasing agent is selected from a group consisting of a carbonate, a lactate, a hydroxide, an amine, an amide, an ammonium salt, ammonium, alanine, and pyridine, or any mixture thereof. The pH decreasing agent is selected from a group consisting of citric acid, a straight-chain, saturated carboxylic acid, lactic acid, ascorbic acid, tartaric acid, mandelic acid, acetylsalicylic acid, benzoic acid, boric acid, ethylenediaminetetraacetic acid, carbonic acid, maleic acid, hydrochloride, hypochlorous acid, a hypochlorite, and/or any mixture thereof.

Bijno *et al*. disclosed an oral pharmaceutical composition or dietary supplement comprising as the active ingredients. The combination of D-mannose, proanthocyanidins, hydroquinone derivatives and zinc is claimed to be useful in the prophylaxis and/or treatment of bacterial UTI [172]. A cranberry extract is used as the proanthocyanidins source, preferably having a proanthocyanidins titre of 7.2%. An Arctostaphylos uva-ursi extract is used as the hydroquinone derivatives source, the extract being preferably a leaf extract and having preferably a hydroquinone derivatives titre of 20%. Zinc bisglycinate chelate is used as the zinc source. The pharmaceutical composition or dietary supplement, in a dosage form comprises of 450 to 550mg of D-mannose, preferably about 500mg of D-mannose; 200 to 300mg of cranberry extract, preferably about 250mg of cranberry extract; 100 to 150mg of Arctostaphylos uva-ursi extract, preferably about 125mg of Arctostaphylos uva-ursi extract; and 5 to 10mg of zinc, preferably 6.25mg of zinc. The composition according to the invention is designed to neutralize the adhesive capacity of the main uropathogens (including *E. coli*), characterized by the presence of mannose-sensitive and mannose-resistant fimbriae, and to eliminate the situation of bacteriuria that develops, by increasing the urinary flow. An important feature of the composition is the presence of zinc, which is indispensable for restoring the functions of the immune system, which has been compromised by the massive presence of pathogens in the case of infections. The compositions of the invention can be formulated in any form suitable for oral administration, for example, as hard or soft gelatin capsules, tablets, effervescent or chewable tablets, granules or powders in sachets, solid forms with controlled release, chewing gums and the like.

There is also the need for the development of new and effective antibiotics, particularly for UTI caused by multidrug resistance organisms. Well-designed, large-scaled, randomized, double-blind, and placebo-controlled studies should be done to compare the efficacy of new antibiotics/agents with the current ones that are known to work. The optimal dose and duration of treatment have to be determined.

The development of new vaccines or improvement of existing vaccines may be of potential use in the prevention of UTI. MV 140 (Uromune®) is a sublingual polyvalent vaccine composed of equal proportion of whole heat-inactivated bacteria including *E. coli*, *Enterobacter faecalis, Klebsiella pneumonia,* and *Proteus vulgaris* in a suspension of 10^9 inactivated whole bacteria/mL [173]. Lorenzo-Gómez *et al*. performed a retrospective record review of 669 women with recurrent UTI; 339 women had a 6-month prophylaxis with antibiotics (trimethoprim/sulfamethoxazole or nitrofurantoin) and 360 women had a 3-month prophylaxis with MV 140 daily [174]. The authors found that women in the antibiotic prophylactic group had a shorter time to first recurrence of UTI and women in the vaccine prophylactic group had an absolute risk reduction of 90.28% (95% confidence interval: 87.18 to 93.38). In a prospective study, 77 women with recurrent UTI were given Uromune® as a sublingual spray daily for 3 months [175]. Of the 75 women who successfully completed the study, 59 (78%) women were free of UTI recurrence during the treatment period and in the subsequent period of 12 months. These findings, though promising, need to be confirmed by randomized, double-blind, placebo-controlled trials.

OM-89 (Uro-Vaxom) is a lyophilised preparation of membrane proteins from 18 different uropathogenic *E. coli* [176]. The vaccine is given daily as an oral capsule for 3 months and, after a lapse period of 3 months, a booster dose of 10 capsules per month for an additional 3 months [176]. A 2016 systematic review and meta-analysis of 5 double-blind randomized trials (n = 392) showed a benefit in favor of the vaccine [177]. The authors commented that the studies were of low quality, limited to a follow-up period of 6 months only, and with variable definition of UTI. Also, no robust trial was identified, resulting in a high heterogeneity in the data analyzed.

ExPEC4V is a biconjugate vaccine that targets the 4 most common O-antigens of the lipopolysaccharide of extraintestinal pathogenic *E. coli* [176, 178]. In a randomized, single-blind, placebo-controlled phase1b trial, 188 women with recurrent UTI were randomized to receive a single injection of either ExPEC4V (n = 95) or placebo (n = 95) [178]. The vaccination was able to mount a robust response demonstrated by significant elevation of IgG titers to all 4 *E. coli* serotypes that persisted at 270 days. Unfortunately, the study was underpowered and no reduction in the incidence of UTI with $\geq 10^3$cfu/ml of vaccine-serotype *E. coli* was observed between the two arms. In post-hoc exploratory analysis of UTI with $\geq 10^5$cfu/ml, the number of vaccine serotype UTI did not differ significantly between the two groups. However, significantly fewer UTI caused by *E. coli* of any serotype were noted in the vaccine group compared with the placebo group. On the whole, the vaccine was well tolerated and no vaccine-related serious adverse events occurred. It is hoped that future, well-designed, large-scale, randomized, double-blind, placebo-controlled trials will provide more information on the efficacy and safety profile of this vaccine.

Urovac™ is a vaginal vaccine containing heat-killed bacteria from 10 human uropathogenic strains, including *E. coli*, *Enterobacter faecalis, Klebsiella pneumoniae, Proteus vulgaris,*and *Morganella morganii* combined in equal numbers (1×10^8 each) in a polyethylene glycol base to form suppositories [179, 180]. In three Phase 2 clinical trials comprising

220 women with ≥ 3 UTI in the previous year, all by the same group of investigators, placebo was compared with primary immunization [181] or with primary immunization with booster immunizations [179, 182]. Primary immunization consisted of three vaginal vaccine suppositories at weekly intervals. Booster immunization consisted of three additional vaginal vaccine suppositories at monthly intervals. The authors found that primary vaginal mucosal immunization alone did not reduce recurrence of UTI. On the other hand, booster vaginal mucosal immunization significantly reduced the rate of recurrence of UTI. The authors suggest that the vaccine may provide an alternate to long-term antibiotic prophylaxis for recurrent UTI in susceptible women [180].

Solco-Urovac® is another vaccine that can be used in the prevention of UTI [183]. The vaccine contains five strains of heat-killed uropathogens: *E. coli* (7.5×10^8), *Klebsiella pneumoniae* (1.5×10^8), *Proteus vulgaris* (7.5×10^7), *Morganella morganii* (7.5×10^7), and *Enterobacter faecalis* (2.5×10^7) [183]. The vaccine is given intramuscularly and has been shown to be effective in four Phase 2 clinical trials [183]. Kochiashvili *et al*. enrolled 115 patients who had more than one-year history of recurrent UTI and had already taken appropriate course of standard antibiotics into an open-label post-marketing trial [183]. There were 32 men and 18 women in the trial group and they were given three intramuscular injections of Solco-Urovac® at weekly intervals. In addition, the 32 men were also treated with standard antibiotics. Patients in the control group (n = 65) were treated with standard antibiotics without intramuscular injections of Solco-Urovac®. During the treatment and follow-up (minimum 6 months), improvement of symptoms in the trial group was 92% versus 74% in the control group. In the trial group, 28 men and 18 women did not have recurrence of UTI during the follow-up period.

Eldridge and Martin disclosed an invention relating to novel vaccine compositions and formulations to prevent UTI [184]. The invention describes novel adjuvant compositions and formulations with excellent stability at refrigerated and room temperatures and up to 37°C that can be produced at remarkably low costs. These novel adjuvant compositions and formulations are used in vaccines and exhibit superior properties of enhancing immune responses to antigens while causing less severe injection site and systemic reactions. The adjuvant formulations include one synthetically produced adjuvant PHAD, a buffer selected from the group consisting of citrate, succinate, and phosphate (preferably about 30 to 50mM). In 2018, the same investigators disclosed another invention which provides novel adjuvant compositions and formulations with excellent stability at refrigerated and room temperatures for about 60 or more days facilitating its shelf life during shipping and storage and lowering its delivery costs [184]. These novel adjuvant compositions and formulations are used in vaccines to treat UTI and exhibit superior properties of enhancing immune responses to antigens while causing less severe injection site and systemic reactions. The invention provides novel liquid adjuvant compositions and formulations which provides many unexpected and advantageous properties unknown in the art of adjuvant and pharmaceutical compositions. In one aspect of the invention, the composition comprises one synthetically produced adjuvant phosphorylated hexaacyl disaccharide or its derivative, 3-deacyl-phosphorylated hexaacyl disaccharide, and a buffer selected from the group consisting of citrate, succinate, and phosphate at 30 to 50mM.

Thus far, all the potential vaccines for the prevention of UTI target at adults, especially women. It is hoped that vaccines for the prevention of UTI also target at high-risk children. In terms of vaccines that are in routine clinical use for the prevention of UTI, we still do not have one.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

HUMAN AND ANIMAL RIGHTS

No Animals/Humans were used for studies that are the basis of this research.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

Not applicable.

FUNDING

None.

CONFLICT OF INTEREST

Professor Alexander Leung, Dr. Alex Wong, Dr. Amy Leung, and Professor Kam L. Hon disclose no relevant financial relationship. The authors confirm that this article content has no conflict of interest.

ACKNOWLEDGEMENTS

Professor Alexander Leung is the principal author. Dr. Alex Wong, Dr. Amy Leung, and Professor Kam L. Hon are the co-authors who contributed and helped with the drafting of this manuscript.

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