

## Urinary Tract Infections in Children: A Changing Paradigm

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### Abstract

**Purpose:** To review the changing paradigms in the diagnosis, investigation and management of Urinary Tract Infections (UTIs) in children beyond the neonatal period.

**Methods:** A literature search was done using PUBMED, EBSCO host database and GOOGLE SCHOLAR of all articles including reviews and guidelines on UTIs in children for the last ten years. A total of 2725 articles including review articles and guidelines published over the last 10 years were searched and reviewed.

**Results:** UTIs are the second most common cause of serious bacterial infections in early childhood, thus placing a huge financial burden on the health budget. Despite increasing resistance to several first-line antibiotics, appropriate antibiotic treatment has almost eliminated mortality.

Early guidelines advocated aggressive treatment and extensive imaging studies, particularly for the detection of serious ureteric reflex and kidney scarring. Treatment in the acute episode is aimed at eradication of bacteriuria and alleviation of symptoms. Long-term goals include prevention of recurrent attacks of UTIs, kidney scarring and correction of urological lesions that may predispose to recurrent infections. Although there is increasing evidence to show that long-term antimicrobial prophylaxis may be associated with a reduced risk of recurrent infection in selected groups of patients, but not renal scarring, more studies are needed to confirm this.

Surgical intervention is now restricted to cases with severe vesicoureteric reflux and failed medical management with endoscopic surgery being increasingly used in most centres compared to open surgery.

**Conclusion:** Following extensive research, a more tangible approach to UTIs is advocated providing for more judicious use of resources with reduced harm from procedures, without affecting outcome. This review addresses the diagnosis, management and treatment of UTIs in children beyond the neonatal period.

**Keywords:** Urinary tract infection; Children; Vesicoureteric reflux; Treatment; Prophylaxis

### Introduction

The introduction of vaccines especially those against *Streptococcus pneumoniae* and *Haemophilus influenzae type B*, has dramatically changed the epidemiology of serious bacterial infections in childhood, particularly in children younger than 36 months [1]. UTI in the first 3 months of life is more common in boys (3.7%) than in girls (2.0%) but thereafter this is reversed [2,3]. Urinary tract infections (UTIs) have now emerged as the most common serious bacterial infection in childhood with approximately 7 to 8% of females and 2% of males having UTIs during the first 8 years of life [4,5]. In children 3 to 36 months of age, UTIs following pneumonia, is the second most common cause of serious bacterial infections [6].

Following the increasing resistance of *Escherichia coli* and other bacteria to first line antibiotics such as penicillin and ampicillin, there has been a dramatic rise in the hospitalization rates of children with UTIs, particularly in those younger than 12 months [7]. Despite increasing resistance to first line antibiotics, appropriate antibiotic treatment of children with febrile UTIs has almost eliminated mortality from this condition that was in the region of 20% among hospitalized children with UTIs in the pre-antibiotic era [8].

In the early 1970s, vesicoureteric reflux (VUR) was linked to UTIs and late renal scarring and thus gave rise to the concept of reflux nephropathy [9]. As a result of this association, children with febrile UTIs were routinely evaluated for urinary tract abnormalities, and often-receiving long-term antibiotic prophylaxis and surgical correction of the VUR [10-12]. About a decade later studies comparing medical treatment with antibiotic prophylaxis to surgical correction of VUR showed similar results in both groups [13,14]. A study on

a prospective trial of operative versus non operative treatment of severe vesicoureteric reflux following two years of observation in 96 children showed a high prevalence of scarring (38%) prior to treatment compared to rates of new scarring (2%). Rates of new scarring and progression of existing scarring was low (2% vs. 9%) and were unrelated to persistent reflux or break through infections [13]. This established the important distinction between primary renal damage that precedes infection and that following UTIs. Primary kidney damage is linked to prior obstruction, genetic and developmental factors result in maldevelopment (hypodysplasia) of the urinary tract, or both. UTIs (pyelonephritis) however, produce an inflammatory process that may also lead to scarring.

Following the introduction of antenatal ultrasound to our screening armamentarium, there is frequent recognition of kidney and urinary tract abnormalities in-utero [15]. Population based studies in the present era using prenatal ultrasound are increasingly recognizing children with kidney abnormalities [16,17].

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Early guidelines for the management of UTIs that advocated aggressive treatment and extensive imaging studies to detect VUR and kidney scarring have in the last decade been replaced by using a more targeted approach to UTIs in children leading to more judicious use of resources with reduction of potentially harmful procedures and intervention, without affecting outcome [18]. This change in management strategy is based on recent studies that have questioned the casual relationship between UTIs-VUR and kidney scarring as well as concerns raised over unnecessary exposure to radiation, and invasiveness of some of the procedures with a potentially higher risk of infection [18,19]. Furthermore studies conducted in infants and young children with uncomplicated UTIs have shown that oral antibiotics were equally effective as intravenous antibiotics as there was no significant difference in the time to recovery or rates of kidney scarring, thereby allowing for potentially considerable cost savings [20-22]. This review addresses the diagnoses, management and treatment of UTIs in children beyond the neonatal period.

### Diagnosis of UTI

The diagnosis of UTI in children poses a major challenge as it varies

	Children with fever (5% baseline risk)		Children who have had 1 previous UTI (20% baseline risk)	
	Positive	Negative	Positive	Negative
	Post test probability of UTI		Post test Probability of UTI	
Dipstick				
Leucocyte esterase alone	24	2	72	9
Nitrite alone	56	3	91	18
Leucocyte esterase and nitrite	54	3	90	19
Leucocyte esterase or nitrite	18	1	64	6
Microscopy White cell count	22	2	69	11
Bacteria	37	1	82	5
Gram stained bacteria	55	0.3	90	19

UTI- Urinary Tract Infection.

Adapted with permission from Williams GJ et al. [23].

**Table 1:** Post-test probability of urinary tract infection with varying baseline risk of UTI for the common near patient tests.

Collection method	Colony forming units per litre	Number of bacterial species
	<b>Definite UTI</b>	
Voided samples Bag collection Midstream catch Clean catch	≥ 10 <sup>8</sup>	1
Catheter samples	≥ 10 <sup>7</sup>	1
Suprapubic bladder aspirate	Any number	1
	<b>Probable UTI</b>	
Voided samples		
Bag collection	≥ 10 <sup>7</sup>	1
Midstream catch	≥ 10 <sup>8</sup>	
Clean catch		
Catheter sample	≥ 10 <sup>6</sup> ≥ 10 <sup>7</sup>	1 2
Suprapubic bladder Aspiration	Any number	2

Adapted with permission from Williams GJ et al. [23].

**Table 2:** Microbiological Threshold for diagnosis of UTI.

depending on the method of collecting urine, number of bacterial species cultured and the clinical presentation [23-25]. Methods of urinary collection in children include midstream clean catch, catheterization, urine bag or pad, and suprapubic aspiration with or without ultrasound guidance. The method of urine collection is largely determined by whether the child can or cannot control urination as well as the level of training and resources available. In children who can control urination, a midstream clean catch urine sample is recommended. In children who do not have control of urination, the choice of technique will depend on the level of training and available resources as well as the patient's clinical status. It is advisable to use a technique of urine collection that minimizes the risk of certain contamination e.g. bladder catheterisation or suprapubic aspiration (best done using ultrasound guidance). These methods of urine collection are also used in children who have bladder control if clean catch fails or clinical status dictates its use. If a non-sterile technique is used for urine collection and the analysis shows contamination, this should be repeated using a technique that minimizes the risk of contamination [23].

An interpretation of the American Academy of Pediatrics Guidelines for use of post-test probability of urinary tract infection using dipsticks and microscopy published by Williams et al. for diagnosis of UTI is shown in (Table 1) [23]. In the guidelines above, a definite UTI using voided samples (clean catch, midstream, and bag) is defined as a pure growth of one bacterial species of ≥ 10<sup>8</sup> colony forming units per litre, a catheter sample of one bacterial species of ≥ 10<sup>7</sup> colony forming units per litre, or one bacterial species on any amount of urine on a suprapubic aspirate [23].

The *Clinical Evidence Handbook* of the United Health Foundation on the other hand defines UTIs by the presence of a pure growth of more than 10<sup>5</sup> colony-forming units of bacteria per ml of urine on a clear catch specimen. Lower bacterial counts may be considered clinically important, especially in boys and in specimens obtained by urinary catheterization, and if urine is obtained by suprapubic aspiration, any growth of a typical urinary pathogen is considered clinically important [2].

In children with prior antibiotic treatment, complete bilateral urinary tract obstruction or renal tract malformations such as an infected cyst with UTIs, urine culture may be negative [23]. The most common pathogens causing UTI in children include: *Escherichia coli* (accounting for over 85% of infections), with *Klebsiella*, *Proteus*, *Enterobacter* and *Enterococcus* species accounting for most of the rest of the UTIs. Organisms such as *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Group B streptococcus* are seen in patients with anatomical defects, following genitourinary surgery and bladder catheterisation [26,27]. Adenovirus and other viral infections may also cause UTI, usually cystitis.

Recent studies and guidelines indicate that the presence of bacteria is not required for the diagnosis of UTI [24,28,29]. The microbiological threshold for diagnosis of UTI according to the American Academy of Paediatrics Guidelines is shown in Table 2. Imirzalioglu et al. [30] have shown that a large fraction of fastidious and anaerobic bacteria may not be detected under culture conditions but only by using Polymerase Chain Reaction (PCR). These groups of bacteria evade the standard culture conditions used in routine diagnostic laboratories examining urine specimens. This molecular approach uses broad-range 16S rDNA PCR, denaturing high-performance liquid chromatography analysis, sequencing, and bioinformatic analysis to uncover these 'hidden' pathogens and is recommended in particular when examining leukocyte esterase-positive and culture-negative urinary tract specimens [30].

Classifications of UTIs	Definition
Asymptomatic bacteraemia	Is defined as a growth of a significant number of an isolated organism [usually >100,000 colony-forming units (CFU/ml) from urine culture found in children without symptoms with no pyuria. This should not be treated as the inappropriate use of antibiotics may promote antibiotic resistance leading to symptomatic disease and does not confer any long-term benefit [100,101].
Cystitis	Is defined as infection limited to the urethra and bladder; symptoms include frequency, urgency, dysuria, lower abdominal discomfort or pain and or cloudy urine.
Acute pyelonephritis	Is defined as the presence of high $\geq 38.5^{\circ}\text{C}$ and/or systemic involvement, except in some very young infants [102,103].
Simple UTI	Denotes features of lower urinary tract involvement. These children have only mild pyrexia, but are able to take fluids and oral medication. They are only slightly or not dehydrated and generally have good compliance with medication [3].
Severe UTI	Is defined as the presence of fever of $\geq 39^{\circ}\text{C}$ , the feeling being ill, persistent vomiting, and moderate or severe dehydration. When a child with a simple UTI has a low level of compliance, such a child should be managed as one with a severe UTI [3].
Uncomplicated UTI	Is defined as the invasion of a structurally and functionally normal urinary tract by a non-resident infectious organism [104].
Complicated UTI	Refers to the occurrence of infection in Patients with an abnormal structural or functional urinary tract, or both, that involves the upper urinary tract and thus manifests as pyelonephritis.
Recurrent UTI	Is defined as the following: $\geq 2$ episodes of UTI with acute pyelonephritis plus one episode of UTI with acute pyelonephritis plus one or more episodes of UTI with cystitis or lower UTI or three or more episodes of UTI with cystitis or lower UTI [28].
Atypical UTIs	Are defined as those that fail to respond after 48 hours of appropriate antibiotic treatment, have poor urine flow, abnormal kidney function, bladder or abdominal mass, infection by an organism other than <i>E.coli</i> and onset of septicaemia.
Relapsing UTI	Is defined as a prompt recurrent infection with the same organism that occurs following treatment and implies there has been failure to eradicate the infection [105].
Acute lobar nephronia (acute lobar nephritis)	(is defined as a renal mass caused by focal infection with liquefaction and may lead to the development of a renal abscess later on [28].

UTIs- Urinary Tract Infection

**Table 3:** Definitions used in the classification of UTIs in children.

## Classification of UTIs

UTIs can be grouped into asymptomatic bacteriuria or depending on the site of infection: urethritis, cystitis, or pyelonephritis and by severity (simple, uncomplicated, complicated, recurrent, or relapsing). The various classifications used to define UTIs in children are shown in Table 3.

To date there are no clinical or laboratory tests that accurately localizes the site of UTI in children with suspected or confirmed UTIs i.e. differentiating lower UTI from upper UTI (acute pyelonephritis). Suspected acute pyelonephritis is diagnosed in the presence of high fever  $>38.5^{\circ}\text{C}$  and/or systemic involvement with the following laboratory findings (high acute phase reactants [C-Reactive Protein (CRP)  $>20$  ug/ml and/or procalcitonin (PCT)  $\geq 0.5$  ng/mL]), especially the latter; interleukin-6 (IL-6)  $>15$  pg/ml in the urine and a defect in renal concentrating ability i.e., reduced maximum urine osmolality checked by an appropriate diagnostic test [31]. Symptoms associated with acute pyelonephritis include fever, abdominal pain, headache, vomiting and, at times, dehydration. Young infants with acute pyelonephritis may present with fever with no localizing signs of infection.

## Screening for UTIs

Screening tests for the diagnosis of UTIs include urinary dipsticks analysis and microscopy. A urinary dipstick has best discriminatory power when interpreted as positive if either leucocyte esterase or nitrite are positive [23]. However dipstick testing for nitrite and leucocyte esterase is most useful when results are concordant but false negatives and false positives occur frequently so that a urine culture is always required if a UTI is suspected. Microscopy for bacteria has much greater diagnostic discrimination and when combined with a gram stain, a positive result gives a 55% probability of UTI and a negative result reducing the probability of UTI to 0.3% [23]. Urinary N-acetyl-b-glucosaminidase that is a marker of tubular injury is increased in febrile UTIs. It is also elevated in VUR and therefore presently is not advocated as a reliable diagnostic marker for UTIs in children [32].

## Pathogenesis of UTIs

The pathogenesis of UTIs reflects a complex interaction between

virulence factors of the microorganism and the host defense [33]. Shortly after birth, the peri-urethral area and distal urethra are colonized with anaerobic and anaerobic microorganisms from the gastro intestinal tract that competitively inhibits colonization by potential pathogenic bacteria. If there is disturbance of this normal peri-urethral area as may occur with the use of broad-spectrum antibiotics, there is colonisation of the peri-urethral area by pathogenic bacteria that ascend into the urinary tract [34,35]. Ascent of bacteria into the urinary tract is enhanced by patients with soiling around the perineum, presence of urinary catheters, adolescent females using spermicidal agents [36].

Almost all UTIs are ascending in origin and infection of the kidney through systemic spread of bacteria is uncommon except in immunocompromised patients in whom the renal parenchyma may be breached. In these patients UTIs due to *Staphylococcus aureus* or *Candida fungaemia* originating from the oral mucosa has been incriminated as the source of infection [37]. Lymphatic spread of bacteria is rare except in patients with retroperitoneal abscesses and severe bowel infections [38].

Turbulent urine flow during normal voiding, as in patients with voiding dysfunction or instrumentation results in pathogenic bacteria gaining access to the distal urethra with subsequent ascending infection [39]. In patients with urinary tract obstruction, the obstructive process results in mucosal defense mechanism being disrupted due to the epithelial lining being over-distended and the pooling of urine facilitates bacterial growth and proliferation [40]. Urinary catheters, particularly in patients with high residual volumes, are also ideal media for uropathogens to colonise the urinary tract and fistulae can facilitate direct access into the genitourinary tract via the gastro-intestinal system [41].

A genetic predisposition to UTIs has been demonstrated in children with defect in the CXCR1 receptor [42]. Bacterial virulence factors determine whether organism will invade the urinary tract and the level of infection [43,44]. Once adherent to the urinary tract mucosa, an inflammatory response is triggered that alters the function of the ureter, permitting ascent of bacteria to the kidneys [45]. There is evidence that renal parenchymal infection, rather than VUR, is responsible for acquiring renal scarring in patients with unobstructed urinary tracts [46].

It has been shown that both cell-mediated immunity and humoral arms of the immune system are activated with invasion of the urinary tract by bacteria [47]. Additionally, sensitized B lymphocytic cells migrate to the lamina propria from the lymphatics and differentiate into IgA-secreting cells. These antibodies inhibit bacterial colonisation by lowering the bacterial adhesion to mucosa or assist in opsonisation by white blood cells. These mechanisms work together in warding off invading pathogens and eradicating UTIs.

### Clinical presentation of UTI

Although a definitive diagnosis of UTI is made on the basis of positive urine analysis and quantitative urine culture from samples obtained appropriately according to age, certain signs and symptoms may suggest a diagnosis of UTI depending on the age of the child [48].

Fever is the most common symptom and although appropriately treated, may take several days to resolve [49]. A clinically significant fever in children younger than 36 months is a rectal temperature of at least 38°C [1]. Non-febrile UTIs occur predominantly in female older than 3 years whilst febrile UTIs have their highest incidence during the first year of life in both sexes.

Malodorous urine has been reported in 29 to 18% of children with UTI [50]. A more recent study found that although malodorous urine reported by parents increases the likelihood of UTI among young children, the association was not strong enough to definitely rule out a diagnosis of UTI [51]. Forty percent of children with UTI in this study did not have malodorous urine and >30% of parents whose children did not have a UTI reported this symptom.

Beyond the neonatal period, older infants with UTI often also present with feeding problems, failure to thrive, diarrhoea and vomiting. Additional findings that may be present include dribbling, a weak urinary stream, or prolonged voiding. Clinical examination may reveal abdominal and/or suprapubic tenderness, pallor, lethargy, and irritability.

In older children the classic manifestation of UTI are more common. Clinically, cystitis presents with enuresis, frequency, dysuria, hesitancy, and suprapubic discomfort. Acute pyelonephritis has more severe manifestations with fever, chills, malaise, nausea and vomiting, and flank pain. Other physical findings that one must look for on examination include hypertension, abdominal or flank masses, a palpable bladder, neurological deficits, abnormal genitalia and abnormal urinary stream. In all children presenting with UTI a concerted effort must be made to rule out sexual abuse, particularly in female patients.

In those patients in whom urine analysis does not confirm a UTI, the differential diagnosis includes urethritis, lichen sclerosus, hypercalcaemia, viral cystitis, sexual molestation, masturbation, use of bubble baths, pinworm, and in patient with haematuria, hemorrhagic cystitis [52].

### Impact of Vesicoureteric reflux in Urinary tract Infections in Children

VUR is defined as the retrograde flow of urine from the bladder into the ureter and renal pelvis. The exact prevalence of VUR in children has not been determined but has been reported to be between 1-6% [53]. Presently available options of management include observation, continuous antibiotic prophylaxis or surgical correction. The latter is either open or endoscopic surgery.

VUR by itself is not a disease and has few long-term effects, however when combined with UTIs, there can be more serious consequences.

Recurrent UTIs occur in 30-40% of children and VUR is diagnosed in about a third of children presenting with the first episode of UTI [54]. The primary goal therefore in diagnosing and treating VUR is to prevent UTIs. In children with VUR it is important to differentiate between those with febrile UTI (temperature >38.5°C) from those with non-febrile UTIs as the former is usually a sign of acute pyelonephritis and more likely to have long-term sequelae with subsequent scarring in 10-40% of children [49,55].

Age impacts morbidity with children <1 year of age being more likely to suffer significant morbidity than older children and less likely to communicate their symptoms [56] with recurrent pyelonephritis occurring in up to 40% of these patients [57]. Predictors of recurrent febrile UTI include age less than 6 months, female gender, bladder and bowel dysfunction, and dilating reflux [58,59]. It is important to note that renal damage in children following UTI is rare without reflux [60]. In the presence of reflux it can occur in up to 6% of children, particularly females, and is directly related to the severity of reflux [54,61,62]. Male children often have congenital abnormalities of the kidney and urinary tract (hypoplasia/dysplasia) that can be found in approximately 1 in 500 prenatal ultrasounds with or without UTI that develop a high incidence of chronic kidney diseases and will gain little benefit from intervention [63,64].

### Management of UTI

The management of UTIs in children is empirically divided between those under 3 month of age and those over 3 months. Evidence based treatment in the very young is lacking as very young children are usually excluded from randomized controlled trials.

In infants under 3 months diagnosed with UTI, treatment is usually intravenous antibiotics initially until systemic signs have resolved followed by oral antibiotics for a period of 7-14 days of total treatment [23]. The choice of initial intravenous antibiotic therapy is based on the probability of a high rate of concomitant bacteremia of about 10% and the risk of uropathology (e.g. posterior urethral valves, obstructed symptoms) [65,66]. The most likely pathogens in this age group are *Escherichia coli* and *Enterococcus faecalis* and hence these patients are usually treated empirically with a beta-lactam antibiotic and aminoglycoside e.g. ampicillin and gentamycin.

In children >3 months of age good evidence from three randomized trials with oral antibiotics of 960 children has shown that oral antibiotics are as effective as intravenous treatment and the former mode of treatment is now recommended [67]. Intravenous antibiotic therapy is limited to those that are seriously ill with a septic appearance or those children with persistent vomiting. There is no strong evidence to support the optimal duration of treatment but based on the National Institute for Health and clinical Excellence guidelines, clinical practice is to give between 7-10 days of oral antibiotics [23]. In children <3 years of age, who have difficulty taking oral medication, the Guidelines on Urological Infections 2014 state that parenteral treatment for 7-10 days seems advisable, with similar results to those with oral treatment [3]. Limited data report intramuscular antibiotic treatment, but suggest no difference between oral treatments and intramuscular combined with oral treatment [67]. In children over 3 months with cystitis and no evidence of pyelonephritis cumulative evidence has shown that shorter courses of oral antibiotic treatment (3-4 days) is as effective as standard therapy (7-14 days) in eradicating urinary tract bacteria [23,68,69]. According to the Guidelines on Urological Infections 2014 uncomplicated UTIs can be treated using oral antibiotics for 5-7 days. A single parenteral dose may be used in cases of doubtful compliance

Antimicrobial agent	Dosage	Common adverse effects
Parenteral		
Amoxicillin/clavulanate (>3 months)	60-100 mg/kg body weight 8 hourly	Gastrointestinal upsets, urticaria, pruritis, stomatitis, oral and perineal candidiasis, elevated liver enzymes, anaphylaxis.
Astreonom (>3 months)	50-100 mg/kg daily	Phlebitis, gastrointestinal upsets, elevated liver enzymes, eosinophilia, nephrotoxicity.
Ceftriaxone	75 mg/kg, every 24 h	Eosinophilia, elevated liver enzymes, thrombocytosis, leukopenia, diarrhoea
Cefotaxime	150 mg/kg per day, divided every 6-8 hours	Rash, pruritis, fever, eosinophilia, fever
Ceftazidime	100-150 mg/kg per day, divided every 8 hours	Gastrointestinal upsets, rash, pruritis, headaches, elevated liver enzymes, nephrotoxicity
Gentamicin	5 mg/kg per day. (8 or 24 hourly >12 months)	Nephrotoxicity, dizziness, vertigo, tinnitus, hearing loss
Tobramycin	5 mg/kg per day, divided every 8 hours	Same as gentamycin Same as gentamycin
Piperacillin	300 mg/kg per day, divided every 6-8 hours	Gastrointestinal upsets, cardiac disturbances, central nervous system effects, allergic reactions, micturition disorders.
Oral		
Amoxicillin clavulanate	20-40 mg/kg per day in three doses	Diarrhea, nausea/vomiting, rash
Trimethoprim sulfamethoxazole	6-12 mg/kg trimethoprim and 30-60 mg/kg sulfamethoxazole per day in two doses	Diarrhea, nausea/vomiting Photosensitivity rash
Sulfisoxazole	120-150 mg/kg per day in four doses	
Cefixime	8 mg/kg per day in one dose	Abdominal pain, diarrhea, Flatulence,rash
Cefpodoxime	10 mg/kg per day in two dose	Abdominal pain, diarrhea, nausea, rash
Cefprozil	30mg/kg per day in two doses	Abdominal pain, diarrhea, elevated results on liver function tests, nausea
Cefuroxime axetil	20-30 mg/kg per day in two doses	Anaemia, eosinophilia, nephrotoxicity, diarrhoea, elevated liver enzymes
Cephalexin	50-100 mg/kg per day in two doses	Diarrhea, headache, nausea/ vomiting, rash

**Table 4:** Commonly used Antimicrobial agents for treatment of urinary tract infections.

and with a normal urinary tract. However if the response is poor, or the child develops complications, admission to hospital for parenteral treatment is advised [3].

Cephalosporin and amoxicillin-clavulanic acid are the oral antibiotics most often used [24,67]. The choice of intravenous antibiotics is usually a cephalosporin combined with an aminoglycoside although no particular antibiotic choice has been shown to be superior [15,67]. However, it must be noted that the best method of directing antibiotic choice will be based in resistance patterns in a given institution or region. Table 4 shows the most commonly used antibiotics, dosage and most common adverse effects used in the treatment of UTIs.

Early initiation of antibiotic treatment following suspicion of UTI is thought to decrease the risk of kidney scarring [24,70]. However the impact of early treatment (<1 day of fever) does not seem to impact the incidence of kidney scarring when compared to children treated after 24 hours [71,72]. Early and appropriate treatment during the first 24 hours after onset of symptoms however may diminish the likelihood of kidney involvement during the acute phase of the infection [72]. Delayed treatment may lead to complications such systemic sepsis and abscess formation. Thus early treatment is advised once UTI is diagnosed [73].

The North American Urinary Tract Infection Collaborated Trial reported *E.coli* resistance to B-lactam antibiotics as high as 37.7% and to trimethoprim-sulfamethoxazole as 21.3% [74], thus making these agents inadequate as first line treatment for UTI. Resistant *E.coli* are more commonly seen in children with VUR [75]. *E.coli* however remain sensitive to third generation cephalosporins, aminoglycosides and nitrofurantoin [73]. The final choice of antibiotic should be based on pathogen identification and sensitivity testing from urine culture. Fluoroquinolones have safety concerns in children and their use should be reserved for UTIs caused by *Pseudomonas aeruginosa* or other multi drug resistant organisms. When aminoglycosides are used, therapeutic

drug levels and kidney function must be monitored as these drugs are nephrotoxic.

Most children respond within 24-48 hours after initiation of antibiotic treatment. In those who have a worsening clinical condition (other than fever), further imaging to exclude urinary tract obstruction, abscess formation or calculi is needed. Repeated urine culture after treatment is not essential in children who respond to treatment [76,77]. Children on previous prophylaxis treatment usually have resistant organism [78-80]. Causative organisms such as *Pseudomonas aeruginosa*, *Group B streptococcus*, *Staphylococcus aureus*, or *Streptococcus epidermidis* are more likely to be found in children with anatomical defects, following genitourinary surgery, or repeated antibiotic treatment. These children may therefore not respond to initial empiric antibiotic treatment [73].

### Imaging for children with Urinary Tract infections

The rationale for performing imaging of the urinary tract in children with UTIs is to identify genitourinary tract abnormalities that can be modified to decrease the risks of recurrent UTI and prevent renal scarring. The evaluation of a child with its first attack of UTI has been summarised in Figure 1.

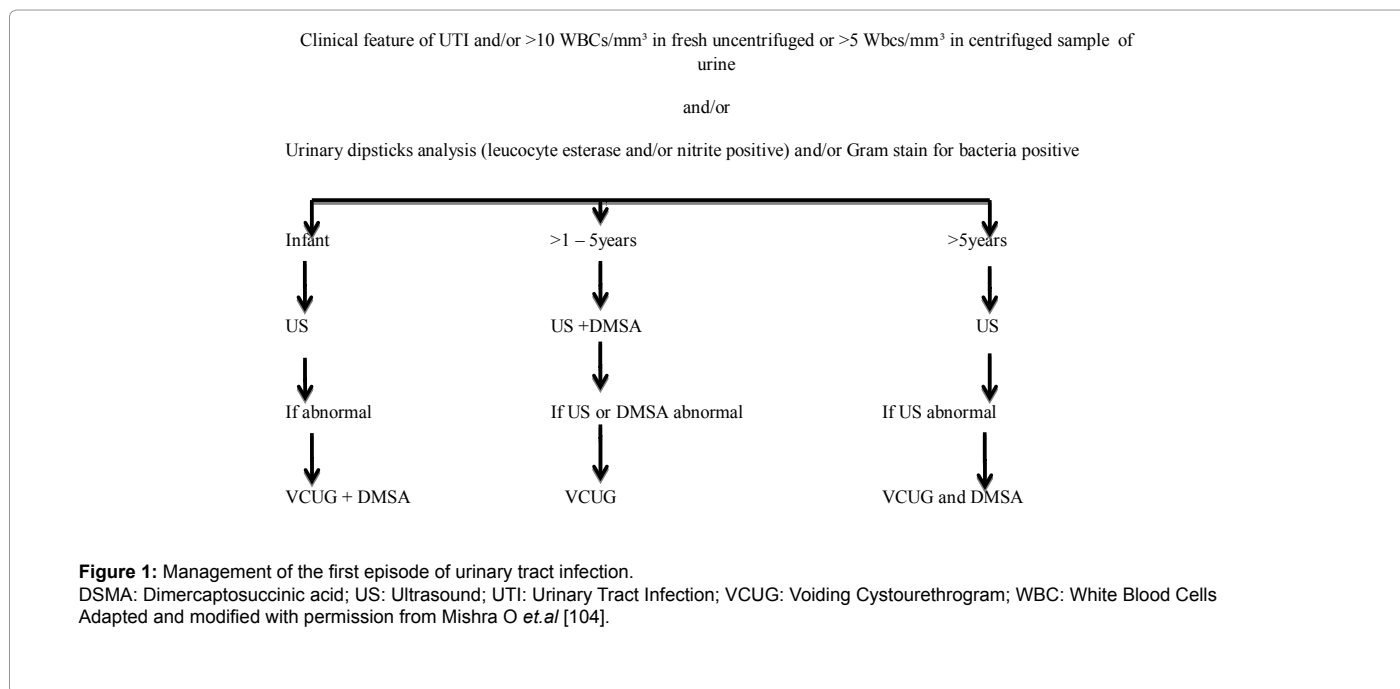
**Kidney ultrasound:** Ultrasonography is the most common and widely used imaging technique as it is free of side effects but is operator dependent. It is used to detect kidney abscesses, Congenital Abnormalities of the Kidney and Urinary Tract (CAKUT), hydronephrosis, calculi, and post-void residual urine.

Ultrasonographic detection of VUR can only be done indirectly for grades III to V and rates of detection varies from 22%, when only dilatation of the urinary tract is defined as abnormal [81], to 67% and 86% [82], when other abnormalities (hydronephrosis, thickened bladder or pelvic wall, or signs of pyelonephritis) are present. Approximately 70% of CAKUT are detected with routine ultrasonography performed antenatally during the second and third trimesters of pregnancy [83,84].

Grade I	Reflux does not reach the renal pelvis; varying degrees of ureteral dilatation
Grade II	Reflux reaches the renal pelvis; no dilatation of the collecting system; normal fornices
Grade III	Mild or moderate dilatation of the ureter, with or without kinking; moderate dilatation of the collecting system; normal or minimally deformed fornices
Grade IV	Moderate dilatation of the ureter with or without kinking; moderate dilatation of the collecting system; blunt fornices, but impressions of the papillae still visible
Grade V	Gross dilatation and kinking of the ureter, marked dilatation of the collecting system; papillary impressions no longer visible; intraparenchymal reflux

VUR: Vesicoureteral Reflux; VCUG: Voiding Cystourethrography  
Adapted with permission from Lebowitz RL et al. [87].

**Table 5:** Grading system for VUR on VCUG, according to the International Reflux Study Committee.



Ultrasound has a lower sensitivity than Dimercaptosuccinic Acid (DMSA) scan for detection of pyelonephritis (22-69% vs. 40-92%) [85]. It is also less sensitive than DMSA in detecting renal scarring [86]. In infants presenting with prenatally diagnosed hydronephrosis, ultrasonography should be delayed the first week after birth because of early oliguria in the neonate, as it is essential to evaluate both bladder and kidneys. Characteristics of bladder wall thickness and configuration may be indirect signs of lower urinary tract disease and reflux [87].

All children should have an ultrasonographic evaluation done following an initial UTI, particularly if there is an atypical UTI. All children with recurrent UTI must have an ultrasound evaluation performed.

**Voiding cystourethrogram:** Voiding cystourethrogram (VCUG) is the main diagnostic modality used for detection of VUR. It can be done following completion of antibiotic therapy when the child is asymptomatic. This study involves instilling a radiopaque, radioactive, or echo contrast medium into the bladder through urethral catheterisation, followed by serial imaging during filling and voiding [88]. VUR has been graded by the International Reflux Study (IRS) into 5 grades as shown in Table 5 [89]. This grading system has been used to predict the outcome of children with different grades of reflux, standardize management, and compare outcomes of different management approaches.

Most controversy exists regarding when this imaging is indicated, as there is a strong association between the severity of reflux and the presence of kidney scarring and the ability to intervene either medically

or surgically. Most experts would agree that detecting reflux with associated dilatation of the urinary tract on ultrasound is mandatory [49,90,91].

Figure 1 shows when a VCUG is indicated after a first febrile UTI. All children with atypical UTIs or if the child with a repeat UTI did not undergo a VCUG after the initial attack of UTI, must undergo a voiding study [15]. This selective approach however may miss children with clinically important reflux until the next infection [15,92].

**Radionuclear cystography:** In order to reduce radiation exposure for children requiring follow-up VCUG after surgical correction of VUR or to verify resolution, Radionuclear Cystography (RNC) is used. The greatest limitation of this modality of imaging is inability to grade VUR or reveal anatomic defects and therefore it cannot be used as the initial test for VUR. Tailored low-dose fluoroscopic VCUG has comparable radiation exposure and is being increasingly used [74].

**Renal scintigraphy:** Renal scintigraphy using DMSA is the gold standard for diagnosing acute pyelonephritis and renal scars. Its use at the time of acute illness can help confirm acute pyelonephritis. However it does not distinguish between lesions that will spontaneously resolve from those that will progress to permanent kidney scarring. Also differentiating lesions secondary to acute pyelonephritis from those due to preexisting kidney scars is difficult [73]. It is also difficult to differentiate renal hypodysplasia from scars due to pyelonephritis. A small kidney, with uniform uptake of isotope suggests hypodysplasia of the kidney; if there are focal areas of reduced cortical uptake associated with loss of contours, or the presence of cortical thinning; this is most

likely due to scarring from pyelonephritis [81]. A delay of 4-6 months following acute pyelonephritis is required to allow for resolution of acute reversible kidney scars in order to diagnose permanent kidney scars using DMSA scars [81]. DMSA scan has limited ability to detect VUR and therefore cannot replace a VCUG for this purpose. Its indication for use in an initial attack of UTI is shown in Figure 1.

**Other imaging:** Computerized tomography and magnetic resonance imaging are used to detect renal abscesses or when there is a delayed response to antibiotic treatment [93]. Video urodynamic studies are important only in patients with secondary reflux as found in spina bifida patients, and in boys with posterior urethral valves [94]. Cystoscopy has a limited role in evaluating reflux except in patients with infravesical obstruction or urethral anomalies that may influence therapy.

### Prevention of recurrent urinary tract infection

Large-scale prospective studies to identify children at risk for repeated UTIs are lacking. About 12% of children with first UTI experience a recurrence within 1 year [95,96]. Risk factors for recurrence of UTI include age of first UTI less than 6 months; grade 3-5 VUR and white race. Other factors include poor fluid intake, dysfunctional voiding, bladder instability, constipation, infrequent voiding and inadequate genital hygiene [97].

### Antibiotic prophylaxis

Six prospective, randomized, controlled trials that compared prophylaxis with no therapy were published between 2006 and 2010 [15]. The initial four studies were underpowered and unblinded [15,61,98,99]. All four studies showed there were no significant differences in the rates of recurrent, symptomatic UTIs in the groups with or without prophylaxis. Two of the studies showed that grade III reflux were associated with a trend towards an increased likelihood of recurrent UTIs in the group without prophylaxis; however, the studies were insufficiently powered for an analysis according to the grade of reflux [15,98]. Two of the studies showed 1.4% to 5.9% of children had scarring from recurrent infections [15,61].

In the Prevention of Recurrent Urinary Tract Infection in Children with Vesicoureteric Reflux and Normal Renal tract study (PRIVENT) [29], recurrent UTI was diagnosed in 13% of the antibiotic group and 19% of the placebo group. However, 17% of study participants were not evaluated for reflux, and 49% of those who were did not have reflux. The study was inadequately powered to evaluate the impact of the grade of VUR [29]. In the more recent Swedish Reflux Trial, females given antibiotic prophylaxis or those who received endoscopic treatment had lower rates of UTI recurrence (19% and 23% respectively) compared to those in the surveillance group (57%,  $p < 0.001$ ). The findings from this trial supported the role for prophylaxis in girls younger than 4 years old with grade III or IV reflux [28,59].

Based on the findings from these studies of a recurrence rate of infection of 3 to 8% per year with prophylaxis in children with no reflux or low grades of reflux (grade I and grade II), prophylaxis does not provide much benefit and should not be used. For children with higher grades of reflux (grade III to IV), particularly in female children, with a much higher rate of reinfection (28-37%) prophylaxis would seem appropriate. The most recent RIVUR trial investigated the use of antimicrobial prophylaxis using trimethoprim-sulfamethoxazole in preventing recurrences of UTI in children with VUR diagnosed after a first or second febrile or symptomatic UTI [78]. Prophylaxis reduced the risk of recurrences by 50% and was particularly effective in children

where index infection was febrile and in those with baseline bladder and bowel dysfunction. The occurrence of renal scarring did not differ significantly in the prophylaxis or placebo group (11.9% and 10.2%, respectively). It is important to note that among 87 children with a first recurrence caused by *Escherichia coli*, 63% of isolates in the prophylaxis group were resistant to trimethoprim-sulfamethoxazole compared to 19% in the placebo groups. These findings suggest that recurrence that did occur in children who received prophylaxis were more likely to have been caused by resistant pathogens.

Presently there is no data on the optimal duration of prophylaxis. However in most prospective trials the treatment period has been 1 to 2 years [15].

### Surgical correction of vesicoureteric reflux

VUR can be surgically corrected either by ureteric re-implantation or endoscopic injection of a bulking agent next to the vesicoureteric junction. The subureteral or intraureteral injection of dextranomer/hyaluronic acid copolymer (Deflux<sup>®</sup>) endoscopically as an alternative to surgical repair is increasingly being used [100].

Surgical intervention is nowadays reserved for children with higher grades of VUR (III-V) with breakthrough infection being treated with antimicrobial prophylaxis, non-compliance with prophylaxis, parental preference or in those children showing deteriorating kidney function [56,73,101]. The American Urology Association however gives the option of surgical intervention (open or endoscopic) at the time of initial diagnosis. The decision is affected by the patient's age, kidney status, grade of reflux, and parental preference [56]. Success rates for open surgery are approximately 98% and that for endoscopic intervention 83% [56]. Although endoscopic treatment leads to significantly higher resolution or downgrading of dilating VUR compared to prophylaxis or surveillance, there is a significant recurrence of VUR after 2 years necessitating repeating the procedure [29,73].

### Long-term follow-up

Patients with kidney scarring need long-term follow-up for recurrence of infection, monitoring growth, blood pressure and kidney function to determine the degree of renal impairment and its progression. Ultrasonography is used to determine kidney size and further imaging may be required if there is recurrent infections and depending on other underlying abnormalities [102].

### Conclusion

UTIs are common in childhood and require appropriate management of the acute episode as well as prevention to minimize the risk of kidney scarring and other long-term complications. Whilst ultrasonography is the most simple and cheapest modality for detection of congenital abnormalities that may require surgical intervention or increase the risk for recurrent infection, VCUG and DMSA remain the investigations of choice for diagnosing VUR and renal scarring respectively. Although there is increasing evidence to show that long-term antimicrobial prophylaxis may be associated with a reduced risk of recurrent infection in selected groups of patients, but not renal scarring, more studies are needed to confirm this. The need for surgical intervention in children with VUR is primarily based on age, grade of VUR, presence or absence of renal scarring, treatment of infections, and voiding dysfunction. Endoscopic surgery is now being increasingly used in most centres when surgery is warranted compare to open surgery.

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